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SYNTHESIS AND CHEMISTRY OF POLYNITROALKANES AND POLYNITROOLEFINS

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Final Report

October 1986

Clifford D. Bedford, Jeffery C. Bottaro, and Robert J. Schmitt

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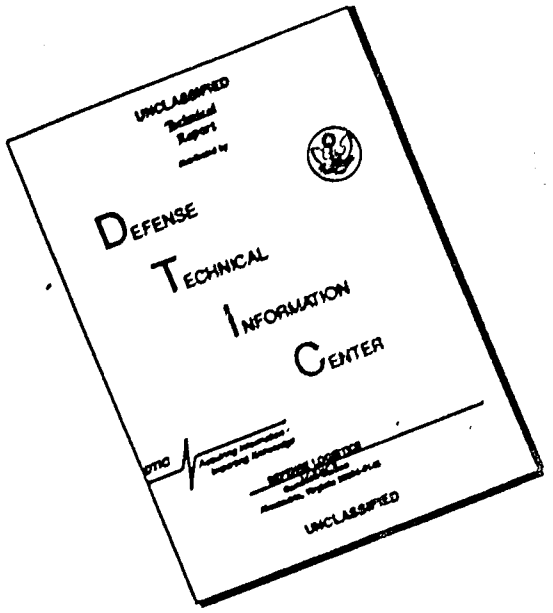

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The objective of the current study was to develop new methods for C-NO_2 and N-NO_2 bond formation. Below we summarize the results of three major research areas:

(1) Nonacidic Amine Nitration. Two new nonacidic nitrating agents were developed that proved to be effective in secondary nitramine synthesis; 2,2-bis(chloromethyl)propane-1,3-diol dinitrate and 2-trifluoromethyl-2-propyl nitrate. These two nitrating reagents give nitramines in 60-100% yield without nitrosamine by-product formation. The reaction scope of these new lipophilic nitrophores appears to be limited only by steric crowding of the amine substrate.

(2) Nitroacetylene Synthesis. A general method was developed and refined for nitroacetylene synthesis by treating substituted bis-trialkylsilyl acetylenes with either

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nitronium hexafluorophosphate or freshly triturated nitronium tetrafluoroborate in polar solvents such as nitromethane and acetonitrile. Using this procedure, we prepared several new nitroacetylenes in 30-70% yields. Preliminary experiments indicate that the electrophilic nitroacetylenes behave in an anticipated manner toward dienes, 1,3-dipolaraphiles, and general acetylenic addition reactions.

(3) Nitrodealumination. We examined the interactions between vinylaluminate salts and various nitrating agents. This effort culminated in nitroolefin preparation by treating vinylaluminium and vinylaluminate salts with tetranitromethane. Using this procedure, we converted several aryl and aliphatic acetylenes to the corresponding nitroolefin in low to moderate yields. (keywords:)

1st page

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COMPLETED PROJECT SUMMARY

TITLE: Synthesis and Chemistry of Polynitroalkanes and Polynitroolefins

PRINCIPLE INVESTIGATORS: Dr. Robert J. Schmitt and Dr. Clifford D. Bedford
SRI International
333 Ravenswood Avenue
Menlo Park, CA 94025

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SENIOR RESEARCH PERSONNEL: Dr. Jeffery C. Bottaro
Dr. Mitchel B. Halpern
Dr. Ripudaman Malhotra

PUBLICATIONS:

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"Synthesis of Nitroacetylenes," Robert J. Schmitt, Jeffery C. Bottaro, and Clifford D. Bedford, Presented at Working Group Meeting on Synthesis of High Energy Density Materials, ARDC, Dover, NJ (1986).

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"New Nitration Methods: Nitrodealumination," Clifford D. Bedford, Robert J. Schmitt, and Mitchell B. Halpern, Presented at 189th Am. Chem. Soc. Meeting, Paper No. 239 (1985).

"Nonacidic Amine Nitration and Nitrosation. Nitration of Secondary Amines with Tetranitromethane and Nitrosyl Chloride," Robert J. Schmitt, Clifford D. Bedford, and Mitchell B. Halpern, Presented at 189th Am. Chem. Soc. Meeting, Paper No. 249 (1985).

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"Nitroacetylene Synthesis and Chemistry," Robert J. Schmitt, Jeffery C. Bottaro, and Clifford D. Bedford, Presented at Working Group Meeting on Synthesis of High Energy Density Materials, ARDC, Dover, NJ (1985).

"New Nitration Methods: Nitrodealumination," Mitchell B. Halpern, Robert J. Schmitt, and Clifford D. Bedford, Presented at Working Group Meeting on Synthesis of High Energy Density Materials, ARDC, Dover, NJ (1984).

ABSTRACT OF OBJECTIVES AND ACCOMPLISHMENTS:

The synthesis of many desired energetic materials is severely hindered by the scarcity of good methods for introducing C-NO_2 and N-NO_2 functional groups into acid-sensitive high energy material precursors. Thus, the deveopment of new nonacidic synthesis methods for C-NO_2 and N-NO_2 bond-forming reactions is required.

Under this AFOSR contract, we have investigated the synthesis of C-nitro and N-nitro groups in nonpolar, aprotic solvent systems. Our goal has been to develop new methods for preparing nitro compounds in nonacid

solvent systems. The major accomplishments of the work performed over the past three years include

- A new preparative route to nitroacetylenes.
- A nonacidic neutral amine nitration/nitrosation nitrodesilylation reaction using P-block-protected amines.
- Development of neutral lipophilic nitrating agents for nitrating acid-sensitive amines.
- Discovery of a new nitrodealumination reaction for introducing nitro groups onto olefins.

In summary, we developed several new routes for forming $C-NO_2$ and $N-NO_2$ bonds. The discovery of the new routes for synthesizing nitroacetylenes opens up the posssiblity of direct synthesis of highly nitrated caged compounds through the cycloaddition of nitroacetylenes. The development of new nitrating agents and the nitrodesilylation reaction may lead to new routes for synthesis of acid-sensitive nitramines and other types of energetic materials that are otherwise unavailable.

AFOSR Program Manager: Dr. Anthony J. Matuszko

INTRODUCTION AND SUMMARY

Research programs in energetic materials synthesis and mechanisms have been hampered by the lack of general synthesis methods for introducing nitro/azido functional groups. Currently, the synthesis limitations facing energetic materials researchers forces many potential insensitive, high-density, high-energy compounds to be placed on a waiting list of wish compounds. The major obstacle is the lack of appropriate synthesis methodologies to bring about the chemical transformations required to prepare these target compounds. Our research program focuses on identifying and overcoming these research barriers. Basic questions concerning the nature of specific molecular requirements (reagents) and reaction conditions that give rise to mild nitration of organic materials in nonacidic media were investigated.

The objective of the current study was to develop new methods for $C-NO_2$ and $N-NO_2$ bond formation. Below we summarize the results of three major research areas: (1) the development and evaluation of new neutral lipophilic "nitrophores" for the preparation of nitramines free of nitrosamine contamination, (2) the synthesis and preliminary evaluation of the chemistry associated with trialkylsilyl nitroacetylenes, and (3) the nitrodealumination of vinylaluminate salts for the preparation of nitroolefins. Details of this work are presented in Appendices A through E.

(1) Nonacidic Amine Nitration. Two new nonacidic nitrating agents were developed that proved to be effective in secondary nitramine synthesis; 2,2-bis(chloromethyl)propane-1,3-diol dinitrate and 2-trifluoromethyl-2- propyl nitrate. These two nitrating reagents give nitramines in 60-100% yield without nitrosamine by-product formation. The reaction scope of these new lipophilic nitrophores appears to be limited only by steric crowding of the amine substrate.

(2) Nitroacetylene Synthesis. A general method was developed and refined for nitroacetylene synthesis by treating substituted bis-trialkylsilyl acetylenes with either nitronium hexafluorophosphate or freshly triturated nitronium tetrafluoroborate in polar solvents such as nitromethane and acetonitrile. Using this procedure, we prepared several new nitroacetylenes in 30-70% yields. Preliminary experiments indicate that the electrophilic nitroacetylenes behave in an anticipated manner toward dienes, 1,3-dipolaraphiles, and general acetylenic addition reactions.

(3) Nitrodealumination. We examine the interactions between vinylaluminate salts and various nitrating agents. This effort culminated in nitroolefin preparation by treating selected vinylaluminum and vinylaluminate salts with tetranitromethane. Using this procedure, we converted several aryl and aliphatic acetylenes to the corresponding nitroolefin in low to moderate yields.

RESULTS AND DISCUSSION

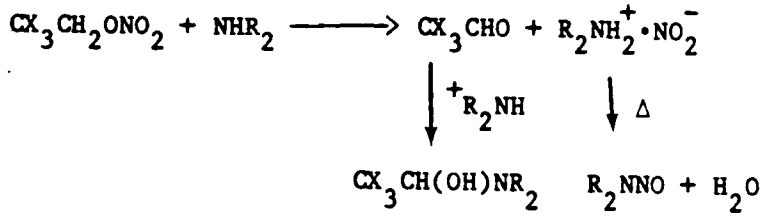
Nonacidic Amine Nitration (Appendices A and B)

The N-nitration of secondary amines under neutral conditions poses a problem of N-nitrosation as a competing side reaction. When nitrogen dioxide,[1] nitryl chloride, nitrogen pentoxide, nitryl fluoride,[2] nitronium fluoroborate,[3] and tetranitromethane[4] are used in the N-nitration of amines, they all result in substantial yields (> 30%) of nitrosamine side products, which are extremely toxic and difficult to separate from the target nitramine. Nitrosamines are produced as a result of the redox reaction between secondary amines and nitrating agent. To overcome the problems associated with N-nitrosation, we studied a series of novel covalent nitrating agents. The oxidizing power of the nitrating agent was attenuated by varying the electronegativity of the leaving group. Because ordinary nitrate esters fail to nitrate secondary amines and nitryl fluoride reacts rapidly even at -78°C, we concluded that the viable range of electronegativities for the nitro transfer reaction lay somewhere between alkoxide (the leaving group on a nitrate ester) and fluoride (the leaving group on nitryl fluoride). Thus, we examined a series of electron-deficient nitrate esters as our target category of neutral nitrating agents for secondary amines.

This approach was originally attempted by Emmonds and Freeman,[1] who studied electron-deficient nitrate esters and found that acetone cyanohydrin nitrate[2,5] does nitrate amines at elevated temperatures. Unfortunately, this reagent releases acetone and hydrogen cyanide, which react with amines to give aminonitriles, rendering this method low-yielding with respect to the amine substrate.

Our initial efforts to overcome this potential problem focused on the use of polyfluoroalkyl nitrates, such as hexafluoroisopropyl nitrate

and trifluoroethyl nitrate. These compounds were synthesized by direct nitration of the corresponding alcohols in fuming nitric/sulfuric acid. Treating these materials with piperidine yielded predominantly elimination products, Scheme I. In the case of trifluoroethyl nitrate, a small amount of nitramine was formed in competition with the elimination products. Only elimination products were detected in the case of hexafluoroisopropyl nitrate. Also detected were small amounts of nitrosation products resulting form the thermal decomposition of the nitrite salt.



SCHEME I. AMINE-INDUCED ELIMINATION OF NITROUS ACID

The trend established by these nitrate esters prompted us to design alkyl nitrates that were less electron-poor and, if possible, endowed with structural attributes that preclude the elimination reaction shown in Scheme I, which ultimately leads to nitrosation by self-condensation of the resulting nitrite salt. Candidates for a new generation of nitrate-transfer reagents are shown below. All these structures preclude the elimination side reaction shown in Scheme I.

1 2

The pentaerythritol nitrate derivative 2 has a high degree of steric hindrance to base attack on the protons alpha to the nitrate ester, and the fluorinated t-butyl nitrate, 1, is devoid of such protons entirely.

The new compounds were synthesized by direct nitration of the corresponding protic compound. Thus, compound 1, (2-trifluoromethyl-2-propyl nitrate) was synthesized by nitration of 2-trifluoromethyl-2-propanol in nitric acid/trifluoroacetic anhydride. Compound 2 (2,2-bis(chloromethyl)propane-1,3-diol dinitrate) was prepared by hydrolysis and nitration of 3,3-bis(chloromethyl)oxetane in nitric acid/oleum. Both compounds 1 and 2 nitrate secondary amines under mild conditions (room temperature to 55°C) without nitrosation, except in isolated cases. In general, 1 is a more convenient, cleaner, and efficient nitrating agent, which allows for a facile workup. The results obtained with selected amines for both reagents are shown in Table 1.

Nitroacetylene Synthesis (Appendices C and D)

The five previously reported nitroacetylenes[6-11] are thermally unstable. In an effort to uncover new synthesis routes to energetic materials precursors, we developed a general synthesis route to new 1-nitro-2- trialkylsilyl acetylenes, 3. The synthesis is achieved by treating a bis-substituted trialkylsilylacetylene with a nitronium ion source (i.e., nitronium tetrafluoroborate, nitronium hexafluorophosphate, or nitryl fluoride) and a fluoride soruce in acetonitrile or nitromethane, to give the desired nitroacetylenes in fair to excellent yields, equation (1).

$$R_3Si\text{-}C{\equiv}C\text{-}SiR'_3 \xrightarrow[\text{"}F^-\text{"}]{\text{"}NO_2^+\text{"}} R_3Si\text{-}C{\equiv}C\text{-}NO_2 \qquad (1)$$

CH_3CN/CH_3NO_2 ; 3

where R = alkyl, trimethylsilyl, $Si(CH_3)_2(t\text{-}Bu)$, $Si(CH_3)_2(i\text{-}Pr)$, $Si(i\text{-}Pr)_3$.

Reaction (1) is an improvement over our previously reported synthesis of nitro-trimethylsilyl acetylene[12] by the reaction of nitronium tetrafluoroborate with bis-trimethylsilylacetylene in methylene chloride. The best yields from reaction (1) (30-70%, see

Table 1

NITRATION OF SECONDARY AMINES WITH NITRATE ESTERS

Amine	2-Trifluoromethyl-2-propyl Nitrate		2,2-Bis(chloromethyl)propane-1,3-diol Dinitrate	
	Yield of Nitramine (%)	Yield of Nitrosamine (%)	Yield of Nitramine (%)	Yield of Nitrosamine (%)
Piperidine	75	0[a]	65	0
Morpholine	72	0	40	Trace[a]
Pyrollidine	100	0	86	0
Diethylamine[b]	58	0	17	4
N-Benzylmethyl-amine	75	0	42	6
Dimethylamine	—	—	55	0

[a]As detected by TLC.
[b]Probable loss of product during isolation due to high volatility.

Table 2) are obtained when R contains another silyl group, either trimethylsilyl, $Si(CH_3)_2(t\text{-}Bu)$, $Si(CH_3)_2(i\text{-}Pr)$, or $Si(i\text{-}Pr)_3$. Only the trimethylsilyl nitro acetylene was reported previously.

When R is an alkyl group, methyl, butyl, hexyl, or t-butyl, the yields are considerably lower. We estimate from qualitative measurements that the nitroacetylenes resulting from these mono-substituted trialkylsilyl acetylenes range from 2-10% yields. 1-Nitropropyne, 1-nitrohexyne, and 1-nitrooctyne are all new compounds (see Table 2).

Two products can result from the nitrodesilylation of bis-trialkylsilylacetylene substrates: one resulting from replacement of the trimethylsilyl group, the other from replacement of the more sterically crowded trialkylsilyl group. In general, the ease of desilylation and consequently the relative proportion of the two nitroacetylene products follow the order observed for the elimination of trialkylsilyl moieties[13]: $Si(CH_3)_3 > Si(CH_3)_2(i\text{-}Pr) > Si(CH_3)_2(t\text{-}Bu) > Si(i\text{-}Pr)_3$. This high degree of regioselectivity (entries 2-4, Table 2) result from the ease of attack by fluoride ion on the trialkylsilyl moiety. The steric crowding encountered in the triisopropylsilyl case resulted in exclusive fluoride-ion-assisted displacement of the trimethylsilyl group. Mixtures of nitroacetylenes were obtained when less bulky silyl substituents were studied.

The yield of the nitroacetylene is considerably enhanced when a bis-trialkylsilylacetylene is used as the acetylene substrate rather than a mono-trialkylsilylacetylene. The higher yields are attributed to the intrinsic properties of the silicon atom. Silicon generally stabilizes beta-carbonium ions better than carbon. Furthermore, silicon enhances alpha-carbonium ion stability due to hyperconjugation and induction. Consequently, any intermediate carbonium ion formed during the reaction of nitronium ion with a bis-trialkylsilyl acetylene is more stable than the corresponding carbonium ion generated from a mixed silyl-alkylacetylene. This extra stabization in the transition state of the bis-silylated acetylenes significantly improves the yield of the target nitro-trialkylsilylacetylene product.

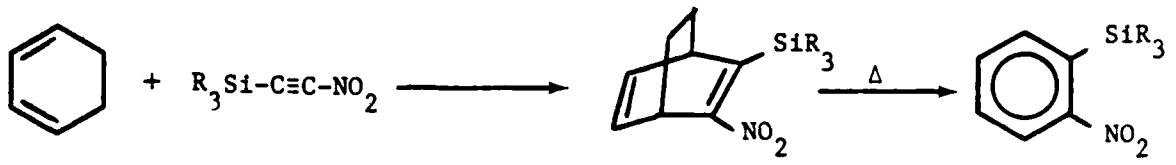
Table 2

NITROACETYLENES YIELDS

Starting Material	Nitronium Salt	Nitroacetylene Product	Yield (%)
TMS-C≡C-TMS	NTFB	TMS-C≡C-NO_2	70[a]
TMS-C≡C-$SiMe_2$(i-Pr)	NHFP	$SiMe_2$ i-Pr-C≡C-NO_2 TMS-C≡C-NO_2	34[b] 6[b]
TMS-C≡C-$SiMe_2$(t-Bu)	NHFP	$SiMe_2$ t-Bu-C≡C-NO_2 TMS-C≡C-NO_2	59[a] 29[a]
TMS-C≡C-Si(i-Pr)$_3$	NHFP	Si(i-Pr)$_3$-C≡C-NO_2 TMS-C≡C-NO_2	57[a] 0[b]
TMS-C≡C-CH_3	NHFP	CH_3-C≡C-NO_2	c,d
TMS-C≡C-$(CH_2)_4CH_3$	NHFP	$CH_3(CH_2)_4$-C≡C-NO_2	0
TMS-C≡C-t-Bu	NHFP	t-Bu-C≡C-NO_2	0
TMS-C≡C-C_6H_5	NHFP	C_6H_5-C≡C-NO_2	0
TMS-C≡C-$(CH_2)_4$-C≡C-TMS	NHFP	TMS-C≡C-$(CH_2)_4$-C≡C-NO_2	0

[a]Isolated yield.
[b]Yield determined from internal standard.
[c]Rapidly decomposes.
[d]Trace yield, observed by GC/MS.

The nitroacetylenes readily undergo Diels-Alder reactions with cyclopentadiene, cyclohexadiene, and furan, equation (2).

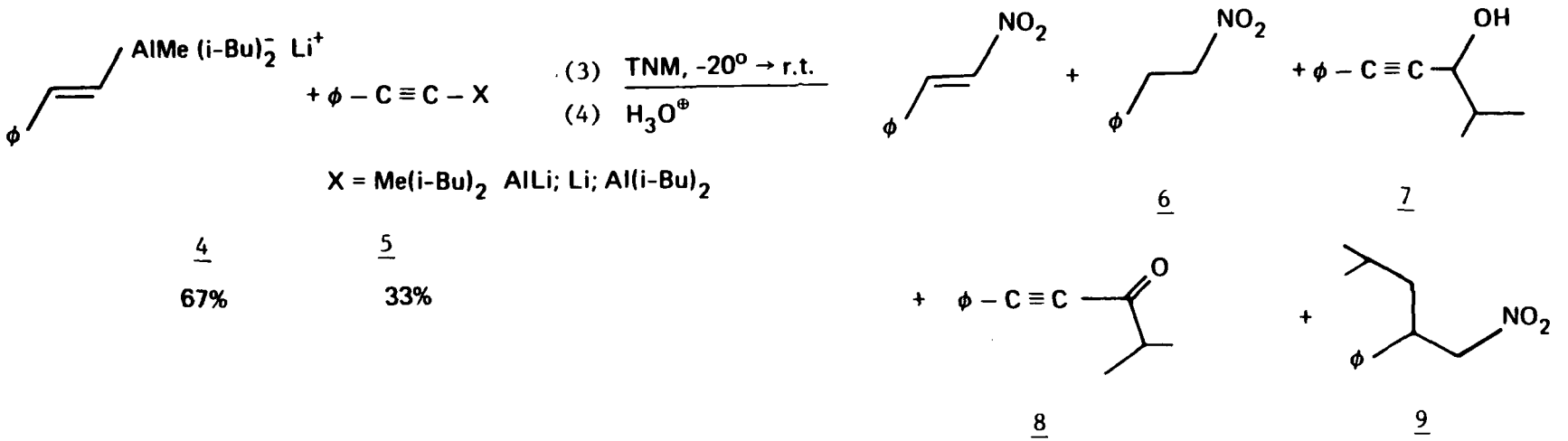


(2)

Nitrodealumination (Appendix E)

The nitrodemetallation of vinylaluminium compounds was investigated as a method for preparing electron-deficient olefins. The rationale for selecting this synthesis method is straightforward. Several methods exist for synthesizing vinylaluminum compounds with various substitution patterns around the double bond,[14] and geminal dialuminated olefins have been prepared[15] that could not lead to a general synthesis method for elusive gem-dinitroalkenes. Furthermore, vinylaluminium compounds and vinylaluminate salts react with various electrophiles to yield vinylhalides,[16] vinylnitriles,[17] trans-alkenes,[16] and other substituted olefins. By analogy, vinylaluminate salts should yield nitroolefins upon treatment with nitronium ion sources.

We prepared styrylaluminate 4 [equation (3)] via the procedure of Zweifel et al.[17] This procedure produces aluminum acetylide 5 as a side product in approximately 33% yield. Treatment of 4 with tetranitromethane (TNM) at -20°C yields less than 20% β-nitrostyrene. Although the reaction mixture is complex and difficult to separate, we have isolated compounds 6 through 9 in addition to β-nitrostyrene. Furthermore, a substantial amount of polymeric material was formed during the reaction. Compounds 6 through 9 result from nitrodealumination, hydroalumination, carboalumination, condensation, and/or radical coupling reactions.


AlMe (i-Bu)$_2^-$ Li$^+$
+ φ – C ≡ C – X
(3) TNM, -20° → r.t.
(4) $H_3O^⊕$
X = Me(i-Bu)$_2$ AlLi; Li; Al(i-Bu)$_2$
4
5
67%
33%
NO$_2$
NO$_2$
OH
+ φ – C ≡ C –
6
7
O
+ φ – C ≡ C
NO$_2$
8
9

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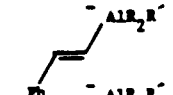
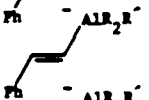
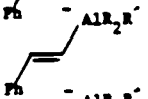
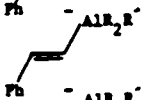
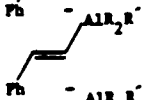
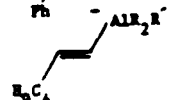
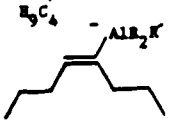
Simultaneous application of lower temperature, THF solvent, and inverse addition increased the yield of β-nitrostyrene to 33% and suppressed the formation of compounds 6, 7, and 9. Compound 8 appeared in increased yield along with several new products that were not characterized. The reaction failed if the temperature was lowered to -78°C.

The effect of other nitrating agents on the production of β-nitrostyrene was examined. Reaction of the vinylaluminate 4 with N_2O_5 in CH_2Cl_2, NOCl in CH_2Cl_2, and NO_2BF_4 in sulfolane did not yield β-nitrostyrene. The reaction of 4 with N_2O_4 yielded <1% of the nitroolefin. The failure of NO_2BF_4/sulfolane or TNM/DMSO to improve the nitrodealumination process is a strong indication that the process involves radical chemistry. The failure of N_2O_4, which is known to react as a radical, might be due to attack by the radical on the double bond of the vinylaluminate 4. In essence, N_2O_4 might be too vigorous an oxidant to be useful in the presence of double bonds or aromatic rings.

The hydroalumination/nitrodealumination sequence appears to be general for terminal and internal alkylacetylenes. 1-Hexyne and 4-octyne yield the corresponding nitroolefins in low yield, whereas trimethylsilyl acetylene does not yield 1-trimethylsilyl-2-nitro-ethylene. The lower yields observed in these cases may result from an increased susceptibility of the alkyl-substituted nitroolefins toward base-catalyzed polymerization. Alternatively, the intermediate aluminium species may be more susceptible to radical decomposition. The nitrodealumination results are summarized in Table 3.

Table 3

SUMMARY OF NITRODEALUMINATION RESULTS

Alkyne	Aluminate Salt	Mode of Addition	Conditions	Nitroolefin Yield
Ph-C≡CH		N	1	< 10%
Ph-C≡CH		N	2	11%
Ph-C≡CH		I	3	30%
Ph-C≡CH		I	4	41%
Ph-C≡CH		I	5	16%
n-C_4H_9-C≡CH		I	3	7.6%
n-C_3H_7-C≡C-nC_3H_7		I	3	15.5%

R = i-Bu; R'=Me

Key: N = normal addition; THM added neat to aluminate
I = inverse addition; aluminate added to THM solution

Conditions:
1 = -20° → room temp., water quench, solvents (hexane, Et_2O).
2 = -20°, 1/2 h, acid quench, solvents (hexane, Et_2O).
3 = -20°, 1/2 h, acid quench, THM dissolved in THF, aluminate in hexane/Et_2O.
4 = -20°, 1/6 h, acid quench, 2 equivalents of THM dissolved in THF, aluminate in hexane/Et_2O.
5 = -20°, 1/2 h, acid quench, THM dissolved in DMSO, aluminate in hexane/Et_2O.

CONCLUSIONS

Two new and effective reagents, 2-trifluoromethyl-2-propyl nitrate and 2,2-bis(chloromethyl)propane-1,3-diol dinitrate, were developed and shown to be effective in the nitration of secondary amines. The nitramine products are formed in high yield without contamination by nitrosamine side-products. The 2-trifluoromethyl-2-propyl nitrate can be applied more broadly because it reacts more cleanly and in higher yields for the nonacidic nitration of basic amines.

A general synthesis route to 1-nitro-2-trialkylsilylacetylenes was developed. The simple one-step reaction affords numerous new nitroacetylenes through the treatment of bis-trialkylsilylacetylenes with nitronium and fluoride ion sources to give excellent yields of the nitroacetylene products. The regioselectivity of the reaction depends on the trialkylsilyl moieties on the acetylene substrate, as does the chemical and thermal stability of the products.

Finally, through the nitrodealumination process we extended the concept of nitrodemetallation to include the cleavage of metal-carbon bonds other than tin and mercury. Although the reaction is of scientific interest, the moderate yields as well as the basic and radical nature of the reaction media make synthesis of the geminal dinitroolefins via a geminal dinitrodealumination process unlikely.

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Appendix A

NONACIDIC AMINE NITRATION AND NITROSATION. I. NITRATION OF SECONDARY AMINES WITH TETRANITROMETHANE AND NITRYL CHLORIDE

Robert J. Schmitt,* Mitchell B. Halpern, and Clifford D. Bedford*

Physical Organic Chemistry Department, SRI International, Menlo Park, California 94025

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ABSTRACT

Secondary N-nitramines and N-nitrosamines were prepared by treating secondary amines or their trimethylsilyl derivatives with tetranitromethane (TNM) or nitryl chloride. The reactions with TNM were found to depend on solvent, temperature, and stoichiometry, with the highest yield of N-nitramine product obtained in nonpolar solvents, at room temperature, and with a 1:1 ratio of amine to nitrating agent. The N-nitrations of all amines studied were accompanied by N-nitrosation arising from a proposed oxidation-reduction process between nitrating agent and the basic amine. A special feature of the reaction is the mild, neutral conditions used to bring about nitration/nitrosation, allowing for the preparation of numerous compounds not easily accessible by known preparative routes.

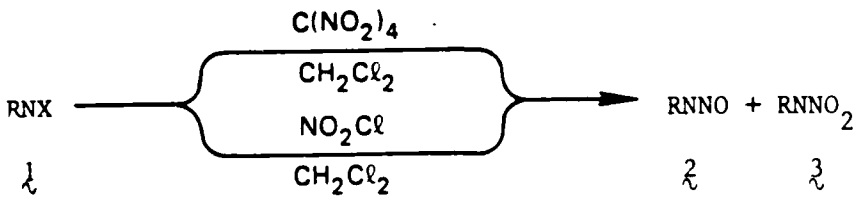
INTRODUCTION

As part of a study of new synthesis routes to introduce nitro functional groups on amines, this report describes the nitration and nitrosation of secondary amines in nonpolar organic media under neutral, aprotic reaction conditions. The nitration/nitrosation of secondary amines is generally conducted in highly acidic media such as nitric acid,[1] N_2O_5/nitric acid,[2] nitric-sulfuric acid mixtures,[3] nitric-acetic acid mixtures,[4] or with nitronium salts.[5] For these systems competition among nitration, nitrosation, and oxidative amine decomposition results in low yields, poor selectivity, and cumbersome isolation procedures.

RESULTS AND DISCUSSION

Recent synthesis programs in this laboratory have resulted in the facile preparation of nitrosamines (2) and nitramines (3) by treating secondary amines (1) or their trimethylsilyl (TMS) derivatives with either tetranitromethane (TNM) or nitryl chloride, Scheme I. The effects of solvent, temperature, and stoichiometry have been studied. A special feature of this synthesis is the introduction of nitroso/nitro functional groups under extremely mild and neutral reaction conditions, allowing for the preparation of numerous compounds not easily accessible by known preparative routes. A second feature of this system is the enhanced solubility in organic solvents imparted by the addition of a TMS group to the amine.

SCHEME I



1a, R = $-(CH_2)_5-$; X = H

b, R = $-(CH_2)_4-$; X = H

c, R = $-CH_2CH_2OCH_2CH_2-$; X = H

d, R = $-(CH_2)_5-$; X = TMS

e, R = $-(CH_2)_4-$; X = TMS

The synthesis approach is based on well-established experimental observations. First, treatment of secondary amines with nitronium ions leads to nitration and nitrosation,[5-10] and second, both TNM and nitryl chloride are known nitronium ion sources.[11-14] For the TMS protected amines, chloride, from nitryl chloride, or potentially fluoride from nitryl fluoride, are known TMS displacing agents, providing a driving force for the replacement of the TMS group by a nitro group.[15]

To establish the scope and limitations of this reaction with respect to amine substrate, we conducted several nitrations/nitrosations with piperidine (1a), pyrrolidine (1b), and morpholine (1c). We also examined the direct nitration/nitrosation of the TMS derivatives of piperidine (1d) and pyrrolidine (1e). The TMS group was used, to increase amine solubilities in organic media and to establish the nature of direct nitronium salt interactions with electrophilic substrates (the TMS moiety).

In the nitration reaction, the amine or TMS-amine was dissolved in an organic solvent. The nitrating agent TNM (1 equivalent) or nitryl chloride (5 equivalents) dissolved in the same solvent was then added, and the progress of the reaction was monitored by GC. The products were obtained as oils and purified by column chromatography. The results are summarized in Table I and indicate the versatility and ease of this method.

The reaction temperature has a considerable effect on the TNM nitration/nitrosation reaction. The yield of nitramine/nitrosamine decreased from 73 to near 0% by decreasing the temperature from 25 to -78°C (Table II). Nitration with nitryl chloride does not show this temperature dependence. For nitryl chloride all reactions were conducted at -78°C and appeared complete (as determined by GC) after 30 min.

The nature of the solvent was found to have a substantial influence on the reaction yield and on the nitramine to nitrosamine production ratio, Table III. For direct nitration/nitrosation of secondary amines or TMS-protected amine with TNM, the reaction yield tended to increase with increased solvent polarity (Figures 1 and 2). For this analysis the reaction yield is plotted versus E_T, a measure of the solvent polarity.[16] The nitration of 1a by TNM (Figure 1) shows a reasonable correlation of yield with increased solvent polarity for solvents other than the chloromethanes and hexane where no correlation is observed. For the reaction of TNM with 1d a good correlation is observed for all solvents except ethyl ether (Figure 2). Similar observations on the anomalous behavior of ether solvents when used in the production of nitrosamines and nitramines of highly basic amines has been noted.[5]

Unfortunately, when the ratio of nitramine to nitrosamine is plotted versus E_T, no correlation can be found for either substrates nitration by TNM. This is somewhat surprising given the correlation observed earlier. These observations are still not completely understood and further studies are under way to elucidate this behavior.

We also examined the effect of stoichiometry on the reaction pathway. As shown in Table IV, a four-fold increase in amine substrate resulted in complete inversion of nitramine to nitrosamine product distribution. This observation is consistent with the postulated electron transfer mechanism below. An increase in amine concentration is expected to enhance the conversion of NO_2^+ to NO_2 and thus increase the production of nitrosamine product. Increasing the amount of TNM relative to the amine had no effect on product composition, observations consistent with eq. (1).

Nitration and nitrosation by nitryl chloride was also examined. Nitryl chloride has low thermal stability and generally contains NO_2 or NOCl as impurities despite rigorous purification. We investigated the nitration of amines 1a, 1b, and 1c as well as the TMS-derivatives 1d and 1e with nitryl chloride (Table I). We found that the TMS-protected amines yielded a higher percentage of nitrosamine than nitramine. Additionally, the overall yield is higher when nitryl chloride is used as the nitrating/nitrosating agent than when TNM is used.

Comparing the results between reactions of amines and TMS-amines with nitryl chloride indicates that the overall mass balances are the same, but more nitramine is now obtained from the TMS-amine than from the free secondary amine. This is a complete inversion of the results

obtained in the TMN cases above. This difference in results can be partly explained by the large excess of nitryl chloride over substrate (approximately 5:1). Also, the NO_2Cl reactions are considerably faster, being completed within the first few minutes after mixing at -78°C.

Finally, we briefly examined the effect of solvent on the reaction of 1d with nitryl chloride (Table III). Only a narrow range of solvents was studied, and we found that the overall mass balance decreased with increasing solvent polarity. Moreover, nitrosamine formation increased with increasing solvent polarity, again supporting our postulation of increased NO_2 formation in more polar media.

We postulate that the nitration/nitrosation of the test amines, piperidine, pyrrolidine, or morpholine, by TNM can proceed via one of three possible mechanisms; a simple ionic mechanism, an electron transfer initiated mechanism, or by a free radical mechanism (Eq. 1-3). There is sufficient literature precedent to support our postulation that all three possible mechanisms may be operative in these reactions.[1-10] These mechanisms, lead to both nitration and nitrosation, are shown in Scheme II. The piperidine/trinitromethide salt shown in Eq. 1 was isolated as evidence of the ionic pathway.

For the TMS-protected amines, the nitration/nitrosation process differs from that of eq. (1). These reactions benefit from the cleavage of a relatively weak TMS-N bond (100 kcal/mole) and the formation of either a strong TMS-O (128 kcal/mole) or TMS-Cl (113 kcal/mole) bond,[17] Eq. (4).

$$RN\text{-}TMS + NO_2^+X^- \longrightarrow TMS\text{-}X + RNNO_2 \qquad (4)$$

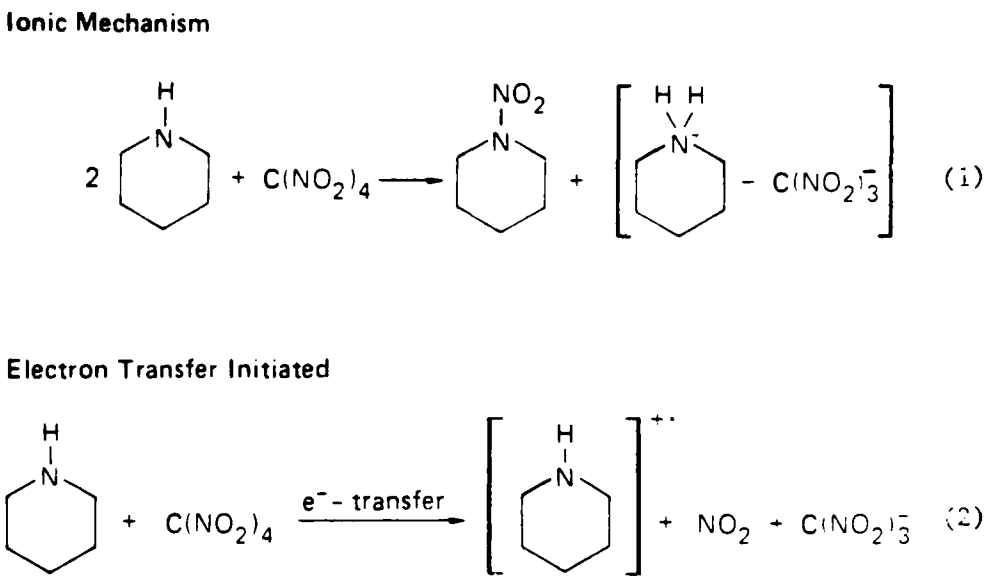
$$X = Cl;\ C(NO_2)_3$$

SCHEME II: PROPOSED MECHANISM FOR $C(NO_2)_4$ NITRATIONS

Ionic Mechanism

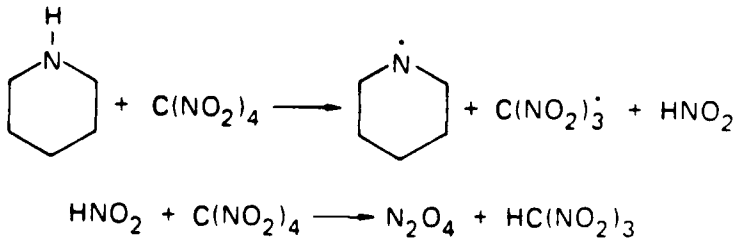
(1)

Electron Transfer Initiated



(2)

Free Radical



(3)

One possible drawback of the nitryl chloride nitrations is the presence of NOCl or N_2O_4 in the freshly prepared nitryl chloride or their formation during the course of the reaction. Either of these materials immediately react with either the amine or TMS-amine to give nitrosamine products accounting for some or all of the nitrosamine observed in these reactions. Additionally, the free radical or electron transfer mechanisms (Scheme II) may also be operative under these reaction conditions.

The formation of nitramine and nitrosamine products represents two independent parallel processes. It is not clear where the nitrosamine product comes from in the TNM reactions, but several possible sources exist. Either the electron transfer initiated (Eq. 2) or the free radical mechanism (Eq. 3) can lead directly to nitrosamine formation. Further, nitrosamine can result by the one electron reduction of NO_2^+ by electron transfer from the secondary amine to give nitrogen dioxide. This gives a convenient source of NO_2, a known amine nitrosating agent. We expected polar solvents to favor this reductive process, yet as can be seen in Figure 3 and 4 no correlation was found between product ratio and E_T. This lack of correlation with product ratios does not rule out oxidation/reduction processes, but it does diminish their likelihood as being the major factor determining the reaction pathway.

CONCLUSIONS

The scope of the new nitration synthesis of secondary amines is believed to be potentially large. A wide variety of dialkyl or alkyl/aryl secondary amines may be used. Primary amines, although not examined in the present study, are expected to react. It appears that this nitration process offers a unique, rapid, mild, and neutral method for converting secondary amines or their TMS-derivatives to N-nitramine and N-nitrosamine products.

EXPERIMENTAL SECTION

General Procedures. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates EM-360 or EM-390 spectrometer. Chemical shifts are reported in parts per million (δ) from an internal tetramethylsilane standard. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 1420 spectrophotometer. Analytical thin layer chromatography (TLC) was performed on Analtech Uniplate silica gel GF (scored 10 x 20 cm plates, 250 μm). Column chromatography was done on reagent silica gel (90–200 mesh) obtained from Accurate Chemical and Scientific Corporation.

Caution! All nitramine and nitrosamine compounds are considered toxic and potentially explosive and should be handled with appropriate precautions. Tetranitromethane in hydrocarbon solvents forms an extremely hazardous mixture. In scale-up examples, the organic extracts must be washed several times to remove the nitroform side products formed during the reaction. Insufficient washing may result in fumeoffs on concentration of the organic solvent.

Analysis. The crude reaction mixtures were analyzed on a Varian Associates 3700 gas chromatograph equipped with a FID detector and a 50 m x 0.25 mm fused silica polydiphenylvinyldimethylsiloxane SE-54 capillary column. The products were determined by comparison with known materials and the yields calculated from an internal standard of nitrobenzene. A measured response factor of 0.63 were used to calculate both nitramine and nitrosamine yields. Under the reaction conditions nitrobenzene did not react with starting materials or products. As

necessary GC/MS (HP 5970) and field ionization MS (FIMS) were conducted to verify products. FIMS were especially useful for product identification because a molecular ion is obtained and little or no fragmentation occurs.

Materials. The amines were obtained from Aldrich Chemical Company and distilled before reaction. TNM was also obtained from Aldrich. The trimethylsilyl derivatives of pyrrolidine and piperidine were obtained from Petrach Systems, Inc., and used without further purification.

Nitryl chloride was prepared by the method of Schecter et al.[18] Chlorosulfonic acid (20 mL) and NO_2 free 90% nitric acid (12 mL) were mixed at 0°C. The NO_2Cl bubbled out of the mixture and was condensed in a dry ice/acetone trap. All subsequent manipulations of NO_2Cl were done in a vacuum line to prevent reaction with water. Before use, the NO_2Cl was purified by freeze-thaw degassing several times and subsequently transferred to a clean dry flask to remove NOCl, N_2O_4, NO, HNO_3, or HCl that may have been trapped or formed from NO_2Cl decomposition.

General Reaction Condition for TNM with Amines or TMS-Amines. The reactions of TNM with amine or TMS-amine were generally done by the addition of one equivalent of TNM (usually 1.42×10^{-3}M) to one equivalent of the amine/TMS-amine in 10 mL of solvent. The reactions were sampled with time to monitor the course of the reaction. One equivalent of an internal standard, nitrobenzene, was added to all reactions and yields were calculated on the basis of [nitro]/[nitroso] products found versus [nitrobenzene].

General Reaction Conditions for Nitryl Chloride with Amines and TMS-Amines. The reactions of piperidine or TMS-piperidine with NO_2Cl were done by the transfer of a known amount of nitryl chloride on a vacuum line to a flask containing the amine and an internal standard. The receiver flask was cooled to -78°C to condense the nitryl chloride. All reactions were done at -78°C. Following a 1 minute reaction time, all reactions were over in one minute or less, the excess nitryl chloride was removed by evacuating the flask. The products were then analyzed by gas chromatography.

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Table I. Reaction of Secondary Amines or TMS-Derivatives With Nitronium Ion Sources

$$RN\text{-}X \xrightarrow{NO_2^+} RNNO + RNNO_2$$

compound[a,b]	X	Nitronium[c,d,e] Ion Source	Mass Balance, %	Product Distribution, % RNNO	Product Distribution, % $RNNO_2$	Ratio $RNNO_2$/RNNO	Reaction Time, hr
Piperidine	H	TNM	66	22.0	78.0	3.5	1.0
Pyrrolidine	H	TNM	43	29.8	70	2.4	1.0
Morpholine	H	TNM		57	43	0.76	6.0
Piperidine	TMS	TNM	55	65.0	35	0.54	2.0
Pyrrolidine	TMS	TNM	43	74.0	26	0.35	1.0
Piperidine	H	NO_2Cl	99	83.1	17	0.20	1.0
Pyrrolidine	H	NO_2Cl	99	83.2	17	0.20	1.0
Morpholine	H	NO_2Cl	98	82.9	17	0.21	1.0
Piperidine	TMS	NO_2Cl	99	55.0	45	0.82	1.0
Pyrrolidine	TMS	NO_2Cl	95	63.5	37	0.58	1.0
Piperidine	H	NO_2F	70.6	52.6	47.4	0.90	1.0
Piperidine	TMS	NO_2F	98.5	39	61.0	1.6	1.0

[a] See text for structures.
[b] All TNM reactions were conducted at 25°C; the NO_2Cl reactions were run at -78°C.
[c] Al:1 ratio TNM: Amine was used.
[d] For NO_2 reactions, 5 equivalents of NO_2Cl were used per equivalent of amine.
[e] For NO_2F reactions, excess NO_2F was used.

Table II

Effects of Temperature on TNM Nitration/Nitrosation of Piperidine[a]

Substrate	Temp.,	Mass Balance, %	Product Distribution, % RNNO	$RNNO_2$	Rate $RNNO_2$/RNNO
Piperidine	-78	18	52	48	0.93
Piperidine	0	58	50	50	1.00
Piperidine	25	51	22	78	3.61
Piperidine	40	67	29	71	2.50

[a]All reactions were conducted in CH_2Cl_2.

Tab III. Effects of Solvents on The Nitration/Nitrosation of Piperidine And TMS-Piperidine by TNM and NO_2Cl at 25°C

$$RNX \longrightarrow RNNO + RNNO_2$$

X	Solvent	Mass Balance, %[a]	Product Distribution, % RNNO	$RNNO_2$	Ratio $RNNO_2$/RNNO
TNM					
H	CH_2Cl_2[b]	67	22	78	3.5
H	$CHCl_3$	28	34	66	1.9
H	CCl_4	99	25	75	3.0
H	Hexane[b]	46	92	7	0.08
H	CH_3CN	99	67	33	0.49
H	Et_2O[2]	74	41	59	1.4
H	p-Dioxane	77	85	15	0.18
H	DMF	88	63	37	0.59
H	Pyridine	88	80	20	0.25
TMS	CH_2Cl_2[b]	52	65	35	0.54
TMS	$CHCl_3$	54	46	53.8	1.2
TMS	CCl_4[b]	37	69	31	0.45
TMS	Hexane[b]	33	82	18	0.22
TMS	CH_3CN	74	55	45	0.82
TMS	Et_2O[b]	74	56	44	0.79
TMS	p-Dioxane	48	91	9	0.10
TMS	DMF	75	66	34	0.52
TMS	Acetone[c]	(d)	97	3	0.03
NO_2Cl[e]					
TMS	CH_2Cl_2	99	55	45	0.82
TMS	THF	69	100	-	-
TMS	CH_3CN	56	95	5	0.05

[a]Mass balance calculated as RNNO + $RNNO_2$/internal standard in initial solution.
[b]A material precipitated from the reaction mixture (most likely the nitroform salt of piperidine) and was redissolved with acetone before analysis.
[c]Solvent may have contained water.
[d]Not determined.
[e]NO_2Cl reactions were conducted with 5 equivalents NO_2Cl per equivalent of amine.

Table IV. EFFECT OF PIPERIDINE:TNM RATIO ON PRODUCT COMPOSITION

Piperidine Equivalents	TNM Equivalents	Mass Balance, %[a]	Product Distribution, %		ratio $RNNO_2/RNNO$
			RNNO	$RNNO_2$	
1	1	67	22	78	3.5
2	1	77	52	48	0.9
4	1	52	71	39	0.5
1	2	64	24	76	3.2

[a]Mass balance was calculated as equivalents products/one equivalent of piperidine.

FIGURE 1: YIELD VERSUS E_T (SOLVENT POLARITY PARAMETER)

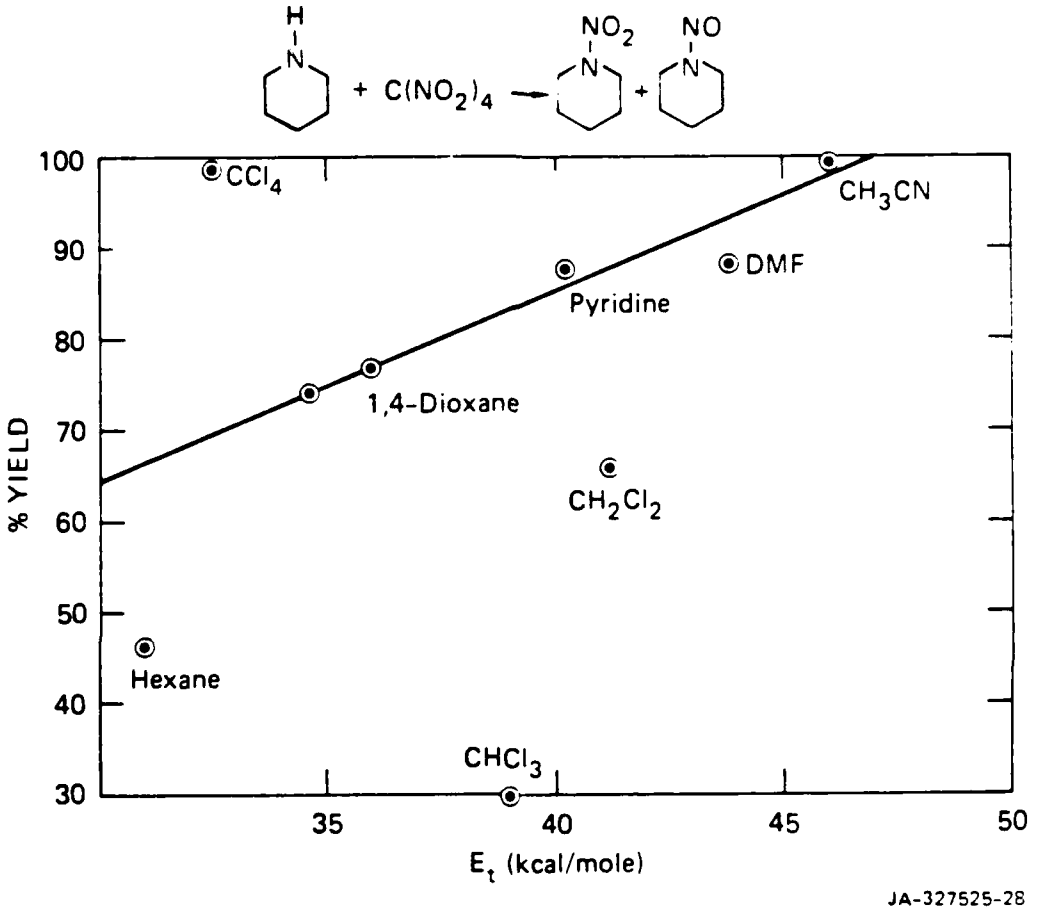


FIGURE 2: YIELD VERSUS E_T (SOLVENT POLARITY PARAMETER)

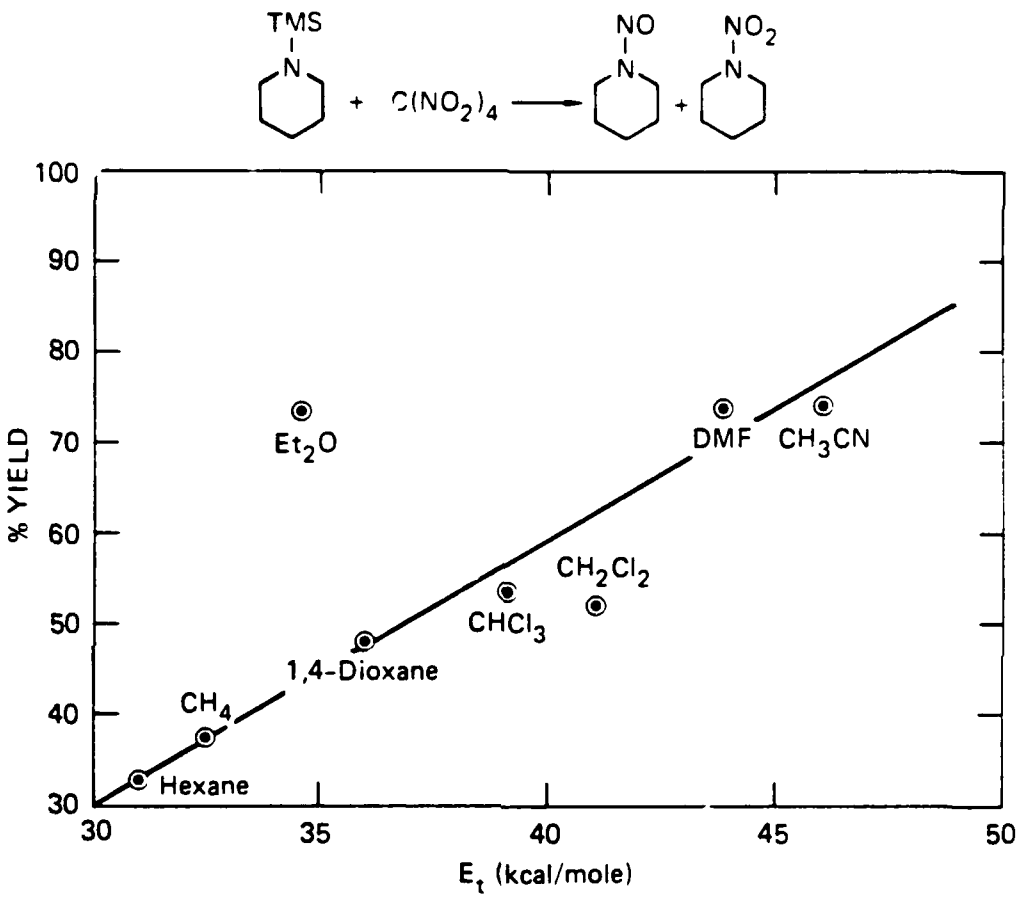


FIGURE 3: PRODUCT RATIO VERSUS E_T (SOLVENT POLARITY PARAMETER)

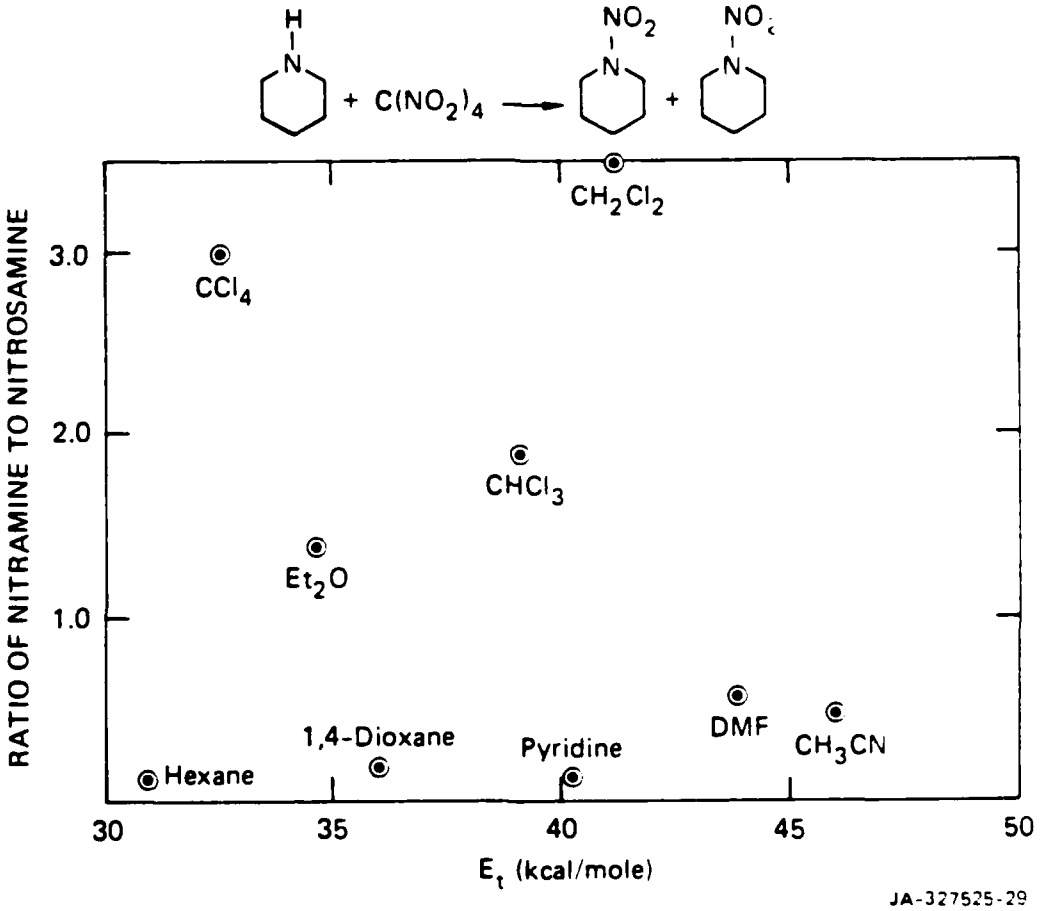
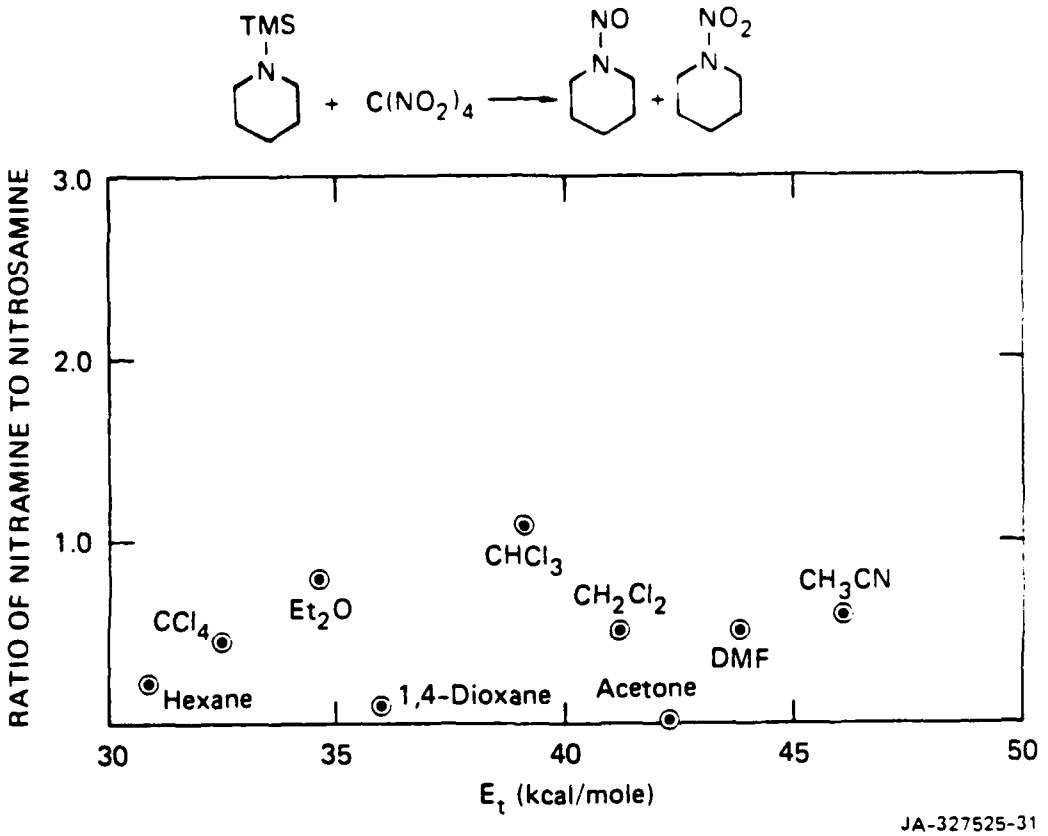


FIGURE 4: PRODUCT VERSUS E_T (SOLVENT POLARITY FACTOR)



Appendix B

NONACIDIC NITRATION OF SECONDARY AMINES

Jeffrey C. Bottaro*, Robert J. Schmitt, and Clifford D. Bedford

Organic Chemistry Program, Physical Organic Chemistry
Department, Chemistry Laboratory, Physical Sciences Division
SRI International, 333 Ravenswood Ave., Menlo Park, CA 94025

Abstract

The development of effective acyl-transfer agents that operate in the absence of acid is encumbered by side reactions when the acyl moiety is a nitro group. When secondary amines are the substrate for a prospective nitrating agent, nitrosation of the amine is a serious side reaction. Electron-poor nitrate esters, such as 2-trifluoromethyl-2-propyl nitrate and 2,2-bis(chloromethyl)propane-1,3-diol dinitrate, are effective nonacidic reagents developed for the transfer of a nitro group to an amine under neutral conditions, with suppression of any accompanying nitrosation.

The N-nitration of secondary amines under neutral conditions poses a unique problem of N-nitrosation as a competing side reaction. When nitrogen dioxide,[1] nitryl chloride,[2] nitrogen pentoxide, nitryl fluoride, nitronium fluoroborate,[3] and tetranitromethane[4] are used in the N-nitration of amines, they all result in substantial yields (> 30%) of nitrosamine side products, which are extremely toxic and difficult to separate from the target nitramines.

To overcome the problems associated with N-nitrosation, we studied a series of novel covalent nitrating agents and examined the effect of amine blocking groups on the outcome of the nitration reaction. The use of amine protecting groups on the nitro/nitrosamine product distribution proved futile. When the N-trimethylsilyl, N-trimethoxysilyl, N-trichlorosilyl, and N-difluoroboryl derivatives of piperidine, (our model amine substrate) were treated with the conventional nitrating agents mentioned above, they all produced products contaminated with nitrosamine by-products. Nitrations with nitryl fluoride were complicated by unavoidable contamination of NO_2F with NO_2, which occurred as a result of contact of NO_2F with glass, air, and organic solvents. This approach was abandoned in favor of developing novel nonacidic nitrating agents.

The production of nitrosamines is a result of the redox reaction between secondary amines and nitrating agent. We sought to attenuate the oxidizing power of the nitrating agent by varying the electronegativity of the leaving group. For example, when nitryl fluoride was reacted with secondary amines, it gave unacceptable yields of nitrosamines ($\approx$ 50%); in response to this problem, we chose to examine nitrating agents with leaving groups that were less electronegative than fluorine. Since ordinary nitrate esters failed to nitrate secondary amines at all, we concluded that the viable range of electronegativities for the nitro transfer reaction lay somewhere between alkoxide (the leaving group on a nitrate ester) and fluoride (the leaving group on nitryl fluoride). Thus, we examined a series of electron-deficient nitrate esters as our target category of neutral nitrating agents for secondary amines.

This approach was attempted by Emmonds and Freeman,[5] who studied some electron-deficient nitrate esters and found that acetone cyanohydrin

nitrate[6,7] does indeed produce the nitration of amines at elevated temperatures. Unfortunately, this reagent releases acetone and hydrogen cyanide, which react with amines to give aminonitriles, rendering this method low-yielding with respect to the amine substrate. The use of trichloroethyl nitrate[6] also did not solve this problem; the nitrate ester suffered an elimination of nitrous acid to give a mixture of dialkylammonium nitrite and trichloroacetaldehyde, which itself reacted with an equivalent of the amine to form the hemiaminal side product (Scheme I).

We sought to design nitrating agents that could achieve the desired acyl transfer (here, acyl = nitro) without any undesirable side reactions. Our initial efforts focused on the use of polyfluoroalkyl nitrates. Hexafluoroisopropyl nitrate and trifluoroethyl nitrate were synthesized by direct nitration of the corresponding alcohols in fuming nitric/sulfuric acid. Treating these materials with piperidine, our preliminary test amine, yielded predominantly elimination products as depicted in Scheme I. In the case of trifluoroethyl nitrate, a small amount of nitramine was formed in competition with the elimination products. Only elimination products were detected in the case of hexafluoroisopropylnitrate. Also detected were small amounts of nitrosation products resulting from the thermal decomposition of the nitrite salts.

The trend established by hexafluoroisopropyl nitrate (no nitration) and trifluoroethyl nitrate (low yield of nitration) prompted us to design alkyl nitrates that were less electron-poor and, if possible, endowed with structural attributes that precluded the elimination reaction shown in Scheme I, which ultimately leads to nitrosamines by self-condensation of the resulting nitrite salts.

Candidates for this new generation of nitrate-transfer reagents are shown in Table I. All these structures preclude the elimination side reaction shown in Scheme I. The pentaerythritol nitrate derivative $\underset{\sim}{1}$ has a high degree of steric hindrance to base attack on the protons α to the nitrate ester, and the fluorinated t-butyl nitrates, $\underset{\sim}{2}$ through $\underset{\sim}{4}$, are devoid of such protons entirely. The N-nitro pyrazole, $\underset{\sim}{5}$, also enjoys an immunity to elimination reactions.

Compounds 1, 2, and 5 were synthesized by direct nitration of the corresponding protic compound. Compound 3 could not be prepared by nitration of hexafluoro-t-butanol, and the synthesis of compound 4 was not attempted because of the failures experienced in the attempted synthesis of of 3. Compound 2 (2-trifluoromethyl-2-propyl nitrate) was synthesized by nitration of 2-trifluoromethyl-2-propanol in nitric acid/trifluoroacetic anhydride. Compound 1 (2,2-bis(chloromethyl)propane 1,3-diol dinitrate)[8] was prepared by hydrolysis and nitration of 3,3-bis(chloromethyl)oxetane in nitric acid/oleum.

Both compounds 1 and 2 nitrate secondary amines under mild conditions (room temperature to 55°C) without nitrosation, except in isolated cases. In general, 2 is a more convenient, cleaner, and efficient nitrating agent, which allows for a facile workup. The results obtained with selected amines for both reagents are shown in Tables II and III. N-nitropyrazole, 5, failed to transfer its nitro group to diethylamine even when refluxed in a solution with diethylamine as solvent. This compound was abandoned as a nitrating agent.

Attempts to nitrate primary amines and ethylenediamine derivatives met with difficulty. For example, attempted dinitration of piperazine with 2 resulted in a low yield of N-nitroso-N'-nitro piperazine. The same result was obtained with N,N'-dimethylethylenediamine, giving mixed nitro and nitroso compounds in poor yields. Furthermore, the nitration of 3-methyl-3-(N-ethylaminomethyl)-oxetane, a highly hindered amine, gave only a poor yield of nitramine, with no nitrosation. Finally, nitrations of benzylamine and phenethylamine gave low yields of corresponding primary nitramines, which could not be purified to analytical specifications. Evidently, amines of diminished nucleophilicity due to inductive or steric encroachments yield nitrosation products through the decomposition of the nitrating agent. The poor performance of compound 2 in N-nitration of primary amines is probably due to decomposition of the product under the prolonged heating necessary to drive the nitro transfer reaction.

In conclusion, we have developed two effective reagents, 2-trifluoromethyl-2-propyl nitrate and 2,2-bis(chloromethyl)propane 1,3-diol dinitrate, for the neutral nitration of secondary amines. These materials have complementary properties, the first being useful for volatile substrates and the second for nonvolatile substrates. The 2-trifluoromethyl-2-propyl nitrate will enjoy a broader application in synthesis because it reacts more cleanly and in higher yield than 2,2-bis(chloromethyl) propane 1,3-diol dinitrate for the nonacidic nitration of basic amines.

Scheme I: Amine Induced Elimination of Nitrous Acid

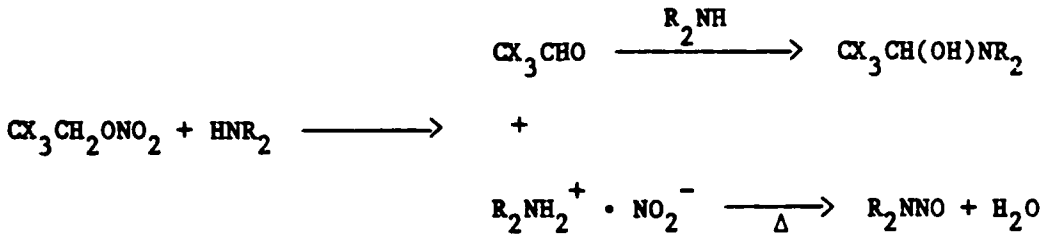
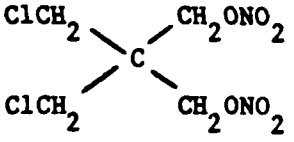
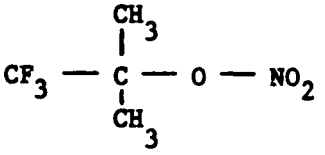
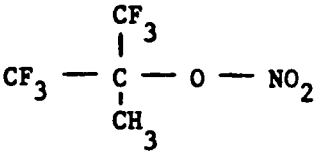
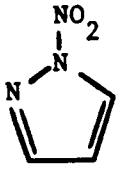


Table I

CANDIDATE NITRATE-TRANSFER REAGENTS

Compound	Structure	Yield	Properties
1		5%	m.p. 62°C decomp. > 150°C
2		60%	bp 98°C slight decomp. at bp
3		Not synthesized	
4	$(CF_3)_3CONO_2$	Not synthesized	
5		80%[a]	mp 93°C

[a] Ref. 9.

TABLE II

NITRATION OF AMINES
WITH 2-TRIFLUOROMETHYL-2-PROPYL NITRATE

Amine	Yield of Nitramine (%)	Yield of Nitrosamine (%)
Piperidine	75	0[a]
Morpholine	72	0
Pyrollidine	100	0
Diethylamine	58	0
Benzyl methyl-amine	75	0

[a]As detected by TLC.

Table III

NITRATION OF AMINES WITH 2,2-BIS(CHLOROMETHYL) PROPANE-1,3-DIOL DINITRATE

Amine	Yield of Nitramine (%)	Yield of Nitrosamine (%)
Piperidine	65	0
Morpholine	40	Trace
N-Benzylmethylamine	42	6
Dimethylamine	55	0
Pyrollidine	86	0
Diethylamine[a]	17	4

[a]Probable loss in isolation due to high volatility.

EXPERIMENTAL SECTION

General Methods

^1H NMR spectra were determined on a Varian T-60 NMR spectrometer as solutions in $CDCl_3$ or CCl_4. IR spectra were determined on a Perkin-Elmer 1420 IR spectrophotometer.

Synthesis of Hexafluoroisopropyl Nitrate

Oleum (100 g of 30% SO_3) was cooled to 0°C under argon and treated with 25 mL of 90% nitric acid (Caution! Exotherm!) followed by addition of hexafluoroisopropanol (35 g, 210 mmol). The reaction was stirred under argon for 1 hour, warming to room temperature over that time. The crude product was distilled out of the biphasic reaction mixture at ~30 torr, trapping the product in a dry-ice/acetone bath. The crude product was stirred over 4 g Na_2CO_3, treated with 2 mL H_2O, and decanted. It contained some free alcohol and was stored at 0°C. Even at 0°C, it slowly decomposed, giving off NO_2 gas. ^1H NMR (CCl_4): δ 5.8, septet, J = 6 Hz.

Synthesis of Trifluoroethyl Nitrate

Oleum (360 g of 30% SO_3) was cooled to 0°C under argon, and was carefully treated with 80 mL of 90% nitric acid. After this mixture had cooled, trifluoroethanol (77 g, 0.77 mole) (Aldrich) was added, and the reaction mixture was allowed to warm to room temperature over 1 hour. The resulting biphasic reaction mixture was then distilled, under an aspirator vacuum, into a dry-ice cooled receiver, neutralized by stirring over 2 g Na_2CO_3/4 mL H_2O, followed by addition of 5 g Na_2CO_3 to remove H_2O. The supernatant liquid was decanted and found to be sufficiently pure for synthesis. The yield of clear colorless liquid was 101 g (85%). ^1H NMR (CCl_4) δ 4.9 (quart., J = 8 Hz). IR (neat) 1400, 1430, 1680 cm^{-1}.

Synthesis of 2-(Trifluoromethyl)-2-propyl Nitrate

Trifluoroacetic anhydride (16 g, 75 mmol) was cooled to 0°C with stirring under argon, in a 50-mL round-bottomed flask. Nitric acid (4.5 g, 75 mmol) was carefully added over 5 min to avoid excessive heating. After the addition was complete, the mixture was stirred for 20 min at 0°C, 2-trifluoromethyl-2-propanol (6.5 g, 50 mmol) was added, and the reaction mixture was stirred for an additional 30 min. The reaction mixture was diluted with 25 mL of dichloromethane, extracted with 100 mL of ice-water, dried over Na_2CO_3, and distilled at ~400 torr. The yield of clear, colorless liquid was 5.3 g (62%), bp 60°/400 torr ^1H NMR (CCl_4, 60 MHz): δ 1.7 (s) IR (Neat) 1660 cm^{-1}. The neat compound slowly decomposed at room temperature upon storage. At low temperatures, (0°C) no decomposition has been observed.

Reaction of 1,1,1-Trifluoroethyl Nitrate with Piperidine

Piperidine (4.3 g, 50 mmol) was dissolved in 50 mL of diethyl ether, and treated with trifluoroethyl nitrate (9 g, 60 mmol). An exotherm ensued, causing the solvent to reflux. After 1 hour, the exotherm had subsided, and a solid had precipitated from the reaction mixture. The solid was isolated by filtration, and the filtrate was freed of acidic and basic compounds by extraction with aqueous base and acid, respectively. The ether layer was found to contain approximately 600 mg (~ 10% yield) of N-nitropiperidine, as determined by IR, NMR, and TLC in comparison with an authentic sample. The solid (2.3 g) was unstable, degrading to N-nitrosopiperidine on standing. The solid had an NMR spectum identical to piperidine • HNO_3, but its IR spectrum was different as compared with authentic sample. On this basis, and due to its tendency to degrade to N-nitrosopiperidine, the solid proved to be piperidine • HNO_2.

Reaction of 2-Trifluoroethyl-2-propyl Nitrate with Secondary Amines

The secondary amine (1 mmol) was mixed with 2-trifluoromethyl-2-propyl nitrate (250 mg, 1.5 mmol) and kept at 50°C for 7 d. Volatiles were evaporated in vacuo, and the crude product was filtered through a short plug of silica gel to give pure N-nitramines. The products were identical

to known materials in their spectroscopic and physical properties. The yields were not further optimized, (see Table II).

Synthesis of 2,2-Bis(chloromethyl)propane 1,3-Diol Dinitrate

Fuming nitric acid (90%) (100 mL) was saturated with $NaNO_3$ at room temperature. Next, 3,3-bis(chloromethyl) oxetane (20 g, 130 mmol) was added. A mild exotherm was observed, and ice-cooling was applied. The mixture was stirred at 0°-15°C for 5 hours, with gradual warming from 0° to 15°C over that interval. The reaction mixture was cooled to 0°C and was carefully treated with 40 mL of 30% fuming H_2SO_4, stirring and adding the acid in 2-mL aliquots. The resulting mixture was warmed to room temperature over 15 minutes and poured over ice, giving a white solid. The solid was collected by filtration, dissolved in 150 mL of warm carbon tetrachloride, and crystallized to give 25 g (73%) of large, colorless prisms, mp 63°C. Anal. Calcd for $C_5H_8Cl_2N_2O_6$: C, 22.8; H, 3.0; N, 10.6; Cl, 26.9. Found: C, 22.9; H, 3.0; N, 10.6; Cl, 26.8. ^1H NMR ($CDCl_3$, TMS) δ 3.7 (s); δ 4.6 (s). IR (CCl_4 smear) ν_{max} 1670, 1300 cm^{-1}.

Reaction of 2,2-Bis(chloromethyl)-propane-1,3-Diol Dinitrate with Secondary Amines

The amine (10 mmol) was mixed with 2,2-bis(chloromethyl)propane-1,3-diol dinitrate (1.3 g, 5 mmol) and heated in a sealed vial at 55°C for 3 days. Unreacted nitrate ester was destroyed by adding 5 mL of ethyl alcohol and 2 mL of hydrazine, and heating at 80°C for 1 h. The reaction mixture was partitioned between 100 mL of ether and 100 mL of water. The ether layer was concentrated and chromatographed, eluting chloroform over silica gel, yielding the pure nitramines, which were visualized by UV. The products were chromatographically and spectroscopically identical to known samples of the target compounds, (see Table III).

ACKNOWLEDGMENTS

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Appendix C

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SYNTHESIS

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Synthesis of Nitro-trimethylsilyl-acetylene

Robert J. SCHMITT*, Clifford D. BEDFORD

Physical Organic Chemistry Department, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025, U.S.A.

A practical, one step, high yield synthesis of nitro-trimethylsilyl-acetylene (**1**), by treating bis[trimethylsilyl]acetylene with nitronium tetrafluoroborate in dichloromethane is described. Compound **1** was also obtained (in low yield) when bis-trimethylsilylacetylene was treated with nitryl fluoride in dichloromethane; the major reaction products resulted from addition of nitryl fluoride across the triple bond.

We report a mild, facile, one-step synthesis of nitro-trimethylsilyl-acetylene (**1**) from bis[trimethylsilyl]acetylene and nitronium tetrafluoroborate.

$(H_3C)_3Si-C\equiv C-NO_2$

1

A few nitroacetylenes have been synthesized by treating trimethylstannylacetylenes with nitronium tetrafluoroborate or nitrogen pentoxide in an inert solvent[1-5]. Other routes to nitroacetylenes are the displacement of an acetylenic trialkylstannyl group or the addition of nitryl iodide followed by base-catalyzed hydrogen iodide elimination[6]. Yields ranging from 40% to 70% can be obtained using these previously reported methods [Reactions *(1)* and *(2)*].

(1) $R-C\equiv C-Sn(CH_3)_3 + NO_2^{\oplus}BF_4^{\ominus} \xrightarrow{\text{inert solvent}} R-C\equiv C-NO_2$

(2) $R-C\equiv C-Sn(CH_3)_3 + N_2O_5 \xrightarrow{\text{inert solvent}} R-C\equiv C-NO_2$

$R = n\text{-}C_3H_7,\ i\text{-}C_3H_7,\ t\text{-}C_4H_9,$ $, (H_3C)_3Si$

In the literature, however, no yield was reported for the synthesis of nitro-trimethylsilyl-acetylene. Furthermore, the most general preparative route requires the acetylenic stannyl derivative prepared from trimethylchlorostannane, a known toxic material[7].

The procedure described in this report uses commercially available, nontoxic bis[trimethylsilyl]acetylene as starting material for the synthesis of compound **1**. Compound **1** was synthesized in 70% yield by treating bis[trimethylsilyl]acetylene with nitronium tetrafluoroborate [Reaction *(3)*].

(3) $(H_3C)_3Si-C\equiv C-Si(CH_3)_3 + NO_2^{\oplus}BF_4^{\ominus}$

$\xrightarrow[CH_2Cl_2,\ r.t.,\ 2h]{CsF/(n\text{-}C_4H_9)_4N^{\oplus}BF_4^{\ominus}/}$ (70%) $(H_3C)_3Si-C\equiv C-NO_2$

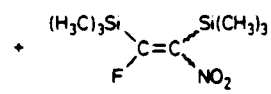
1

This reaction is driven by the formation of a strong SiF bond (SiF = 130 kcal/mol)[8]. Apparently, sufficient fluoride ion concentration is produced from the tetrafluoroborate counter ion to assist the displacement reaction. The choice of dichloromethane as a solvent for nitronium tetrafluoroborate reaction is unusual as such reactions are usually conducted in acetonitrile or sulfolane to increase nitronium tetrafluoroborate solubility. In acetonitrile, however, only a 10% yield of the nitroacetylene **1** was obtained, demonstrating an unusual solvent dependency.

The reaction rate appears to depend on fluoride ion sources. A combination of added tetrabutylammonium tetrafluoroborate and cesium fluoride increases the nitration rate fourfold. A consistent 70% yield of the desired nitro-trimethylsilyl-acetylene was obtained from several reactions, making this a rapid, clean methodology for preparing this elusive compound.

Alternatively, compound **1** was prepared in low yield by treatment of bis[trimethylsilyl]acetylene with nitryl fluoride in dichloromethane at −78 °C. The major reaction product resulted from addition of nitryl fluoride across the triple bond [Reaction *(4)*].

(4) $(H_3C)_3Si-C\equiv C-Si(CH_3)_3 + NO_2F \xrightarrow{CH_2Cl_2,\ -78°C,\ 30\,min}$

$(H_3C)_3Si-C\equiv C-NO_2$ + 

1 (10%) (50%)

However, the nitroacetylene was also obtained in low yield. Subsequent attempts to catalyze the elimination of fluorotrimethylsilane from the adduct were of limited success.

The structure of compound 1 was determined by G.C./F.T.I.R. (Digilab FTX 90) and G.C./M.S. (HP 5970). All synthesis steps were conducted at room temperature or slightly below since nitroacetylenes are thermally unstable. The reaction progress was monitored by gas chromatography, using a Varian model 3700 equipped with a SE-54, 50-meter capillary column. Because of the thermal sensitivity of compound 1, no satisfactory microanalysis could be obtained.

Nitro-trimethylsilyl-acetylene (1) using Nitronium Tetrafluoroborate: Nitronium tetrafluoroborate (1.6 g, 12 mmol), tetra-*n*-butylammonium tetrafluoroborate (3.9 g, 12 mmol), and cesium fluoride (1.8 g, 12 mmol) are added to a stirred solution of bis[trimethylsilyl]acetylene (1.0 g, 6 mmol) in dry dichloromethane (25 ml). After 2 h, the mixture is filtered, poured into water (100 ml), stirred, and washed three times with water. (Caution! The addition of sodium hydrogen carbonate or brine solutions causes immediate decomposition of the nitro-trimethylsilyl-acetylene; furthermore, the nitroacetylenes slowly decompose upon standing, even when frozen.) The dichloromethane/nitroacetylene solution is dried with magnesium sulfate and filtered, and the dichloromethane is removed under vacuum at low temperature to give the product 1; yield: 70%. Gas chromatographic analysis shows this material to contain a small amount (less than 5%) of a *cis/trans* mixture of 1,2-bis[trimethylsilyl]-1-fluoro-2-nitroethylene.

I.R. (gas phase): ν = 2980 (C—H stretch); 2250 (C≡C stretch); 1520, 1348 (NO_2 stretch); 1260 (Si—CH_3 stretch); 860 cm^{-1} (Si—CH_3 stretch).

M.S. (70 eV): *m/e* = 143 (M^+, low); 128 ($M^+ - 15$, major); 97 [$(H_3C)_3Si—C≡C^+$], 73 [$CH_3C)_3Si^+$], 70 [$O_2N—C≡C^+$]; isotopic peaks are observed for M − 15 + 1 (obs. 10.0, calc. 10.6) and M − 15 + 2 (obs. 4.0, calc. 3.5)[9].

Nitro-trimethylsilyl-acetylene (1) using Nitryl Fluoride: All experiments with nitryl fluoride are conducted in clean, dry Teflon reaction vessels to avoid nitryl fluoride decomposition. Nitryl fluoride is prepared by the reaction of NO-free nitrogen dioxide with fluorine[10]. Before use, the nitryl fluoride is checked by I.R. for the presence of NO, NO_2, or NOF.

Bis[trimethylsilyl]acetylene (1.0 g, 6 mmol) in dichloromethane (50 ml) is cooled to − 78 °C Nitryl fluoride (excess) is bubbled into the solution which is then allowed to stand at this temperature for 30 min. The crude mixture is then slowly warmed to room temperature, and residual nitryl fluoride is removed by flushing with argon. The reaction products are analyzed as above by G.C., G.C./M.S., and G.C./F.T.I.R. The yield of nitro-trimethylsilyl-acetylene is approximately 10%, and a mixture of *cis/trans*-1,2-bis[trimethylsilyl]-1-fluoro-2-nitroethylene is formed in about 50% yield. Other products resulting from further additions of nitryl fluoride to either acetylene or ethylene compounds are also detected but not characterized.

cis/trans-1,2-Bis[trimethylsilyl]-1-fluoro-2-nitroethylene: M.S. (70 eV): *m/e* = 235 ($M^+—CH_3$); 175 ($M^+—CH_2—NO_2$, major); 77 [$F—Si—CH_3]^+$; isotopic peaks are observed for M − 15 + 1 (obs. 20.9, calc. 19.0) and M − 15 + 2 (obs. 9.3, calc. 9.2)[9].

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A Facile Synthesis of α-Amino Esters via Reduction of α-Nitro Esters Using Ammonium Formate as a Catalytic Hydrogen Transfer Agent[1]

Siya RAM, Richard E. EHRENKAUFER*

Cyclotron/PET Facility, Division of Nuclear Medicine, The University of Michigan Medical Center, Ann Arbor, Michigan 48109, U.S.A.

Various nitroesters 3 were selectively and rapidly reduced to their corresponding amino esters 4 in very good yield using anhydrous ammonium formate as a catalytic hydrogen transfer agent.

Radiolabelled α-amino acids have been used to investigate amino acid metabolism in the brain and other organs, e.g. DL-[^{11}C-carboxyl]-tryptophan[2], DL-[^{11}C-carboxyl]-valine[2] and L-[^{11}C-methyl]-methionine[3] as pancreatic imaging, and 1-aminocyclopentane-1-[^{11}C]-carboxylic acid and 1-aminocyclobutane-1-[^{11}C]-carboxylic acid as tumor imaging[4] have been developed. Besides these, several other α-amino acids such as 1-aminocyclopropane-1-carboxylic acid[5,6] and 2,6-diaminopimelic acid[7,8] have considerable biological importance.

As a continuation of our ongoing program, we were interested in the radioisotopic synthesis of ^{11}C-α-amino acids (^{11}C-half-life = 20.4 min) especially ^{11}C-leucine for the tomographic measurement of protein synthesis in the human brain. For this purpose, we required α-nitro esters as intermediates, which could be rapidly reduced to the corresponding α-amino esters. In general the traditional syntheses[9-14] of α-nitro esters (except carboxylation procedures) are not applicable for the preparation of ^{11}C-α-nitro esters, due to limitation of short half-life and easy availability of the desired ^{11}C-precursors[15-18]. Further, reduction of α-nitro esters to α-amino esters is carried out either by catalytic hydrogenation[10,12,15,16,19-22] at high pressure/atmospheric pressure or by chemical reduction[10,18,23]. Catalytic hydrogenations usually require longer times, while chemical reductions, which are less studied in amino acid literature, provide poor yield of the desired product.

Recently ammonium formate has been successfully employed as catalytic hydrogen transfer agent in peptide chemistry for deprotection[24,25] in place of cyclohexene. Reduction of azides[26] and the cyano group[27] to corresponding amines and methyl group respectively has also been reported. We reported earlier[1] a general procedure for reduction of aliphatic and substituted aromatic nitro compounds to the corresponding amino derivatives using ammonium formate as a catalytic hydrogen transfer agent. We now report an extension of this new method for the efficient and rapid chemical reduction of α-nitro esters 3 to the corresponding α-amino esters 4 with ammonium formate.

Appendix D

Nitroacetylenes: Synthesis of 1-Nitro-2-Trialkylsilylacetylenes via Nitrodesilylation of Bis-Silylacetylenes

Robert J. Schmitt*, Jeffery C. Bottaro, and Clifford D. Bedford

Energetic Materials Program,
Physical Organic Chemistry Department,
Chemistry Laboratory,
SRI International,
333 Ravenswood Ave.,
Menlo Park, CA 94025

ABSTRACT

A general synthesis route to 1-nitro-2-trialkylsilylacetylenes has been developed. Treatment of bis-trialkylsilylacetylenes with nitronium and fluoride ion sources gives excellent yields of the nitroacetylene product. The regioselectivity of the reaction depends on the trialkylsilyl moieties on the acetylene substrate, as does the chemical and thermal stability of the products.

INTRODUCTION

As part of a study to develop new synthesis routes to nitroacetylenes, this report describes a general synthesis of 1-nitro-2-trialkylsilylacetylenes, 1.

$$R_3Si\text{-}C{\equiv}C\text{-}NO_2$$

1

The method involves direct reaction between a nitronium ion source [i.e., nitronium tetrafluoroborate (NTFB), nitronium hexafluorophosphate (NHFP), or nitryl fluoride], bis-trialkylsilylacetylene, and a fluoride ion source. Only five nitroacetylenes have been reported previously,[1-6]

and all are reported to be thermally unstable. The synthesis routes to known nitroacetylenes are shown in equations (1) and (2):

$$R\text{-}C{\equiv}C\text{-}SnMe_3 + N_2O_5 \xrightarrow{\text{Inert Solvent}} R\text{-}C{\equiv}C\text{-}NO_2 \qquad (1)$$

where R = phenyl, trimethylsilyl (TMS), n-propyl, i-propyl;

$$R\text{-}C{\equiv}C\text{-}H + NO_2I \rightarrow R(I)C{=}C(H)NO_2 \xrightarrow{\text{Base/Heat}} R\text{-}C{\equiv}C\text{-}NO_2 \qquad (2)$$

where R = t-butyl. We report here a general synthesis method for preparing 1-nitro-2-trialkylsilylacetylenes. This unique one-step procedure allows for the preparation of numerous nitroacetylenes not accessible through the known synthesis methods.

RESULTS AND DISCUSSION

Recently, we reported[7] an improved, one-step synthesis of 1-nitro-2-trimethylsilylacetylene by treating bis-trimethylsilylacetylene with NTFB in methylene chloride:

$$TMS\text{-}C{\equiv}C\text{-}TMS + NO_2BF_4 \xrightarrow{CH_2Cl_2} TMS\text{-}C{\equiv}C\text{-}NO_2 \qquad (3)$$

When freshly recrystallized NTFB is used, a 70% yield of the nitroacetylene is obtained. The effects of alkyl substituents on both the acetylene and silyl substrate, the nitronium ion source, and reaction solvents have been studied. A special feature of this one-step nitrodesilylation reaction is the regioselectivity observed with bis-(trialkylsilyl)acetylene substrates, allowing for the preparation of numerous 1-nitro-2-trialkylsilylacetylenes, not easily accessible by known preparative routes.

One aspect of the synthesis study centered on generalizing the reaction of 1-alkyl substituted silylacetylenes with nitronium ion sources. Initial studies showed that treatment of 1-trimethylsilyl substituted acetylenes with NTFB in methylene chloride gave no appre-

ciable quantities of the desired nitroacetylene product. Substituting dry acetonitrile as the solvent and NHFP as the nitronium ion and fluoride ion source yielded several new nitroacetylenes, although in extremely low yields, Table I. Recrystallized NTFB in anhydrous acetonitrile or nitromethane and methylene chloride solvents also proved to be an effective medium for the nitrodesilylation reaction, giving the 1-alkyl-2-nitroacetylene compounds in low yield. Treatment of 1-phenyl-2-trimethylsilylacetylene with nitronium ion sources failed to yield the desired nitroacetylene product.

NTFB can be used in this reaction sequence if it is throughly purified before use. Many of the original difficulties encountered with the nitrodesilylation reaction were due to the impurities in the NTFB, presumably nitric acid and hydrofluoric acid. Samples of NTFB as received from the manufacturer (Aldrich) were so badly contaminated that they were totally unusable for nitrodesilylation of acetylenes. Reactions with either freshly purified NTFB or NHFP could be conducted in dry acetonitrile or nitromethane without product degradation. However, the nitronium salt does not have to be dissolved in the reaction solvent as demonstrated by the successful preparation of 1-nitro-2-trimethylsilylacetylene using NTFB in methylene chloride.

Good to excellent yields of nitroacetylenes were obtained when the R of equation (4) was a trialkylsilyl group. The presence of a silicon

$$R\text{-}C{\equiv}C\text{-}TMS \xrightarrow[\text{Nitromethane}]{\text{NTFB/NHFP}} R\text{-}C{\equiv}C\text{-}NO_2 \qquad (4)$$

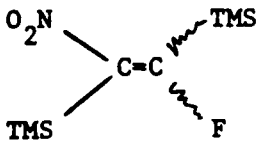
atom alpha to the triple bond provides extra stabilization to the nitronium ion/acetylene transition state. Table I gives the yield of nitroacetylenes from the various bis-trialkylsilylacetylene substrates. Note that particularly high yields of the nitroacetylene products were obtained when bis-trialkylsilylacetylene substrates were used compared with the low nitroacetylene yields for the monosilylacetylene substrates.

Two products can result from the nitrodesilylation of bis-trialkylsilylacetylene substrates: one resulting from replacement of the TMS group, the other from replacement of the more sterically crowded trialkylsilyl group, equation (5).

$$TMS\text{-}C{\equiv}C\text{-}SiRR'R'' \xrightarrow{NHFP/CH_3CN} NO_2\text{-}C{\equiv}C\text{-}SiRR'R'' + TMS\text{-}C{\equiv}C\text{-}NO_2 \qquad (5)$$

In general, the ease of desilylation, and consequently the relative proportion of the two nitroacetylene products, follow the order generally observed for elimination of trialkylsilyl moieties:[8] TMS > Me_2iPrSi > Me_2tBuSi > $(i\text{-}Pr)_3Si$. This high degree of regioselectivity (entries 2-4) results from the ease of attack by fluoride ion on the trialkylsilyl moiety. The steric crowding encountered in the triisopropylsilyl case results in exclusive fluoride-ion-assisted displacement of the TMS group, whereas mixtures of nitroacetylenes were obtained when less bulky silyl substituents were studied entries 2 and 3, Table I.

In addition to the target nitroacetylene compounds, two other minor products were isolated from many of these nitrodesilylation reactions. They resulted from cis and trans addition of NO_2F across the triple bond, 2



2

Presumably, the NO_2F resulted from slight decomposition of the nitronium ion salt, either NTFB or NHFP.

The nitroacetylenes were characterized by a combination of GC/MS and GC/FTIR observations (Tables II and III). All nitroacetylenes show the characteristic acetylene stretching frequency band between 2150 and 2250 cm^{-1} in the infrared. Furthermore, in all compounds the charac-

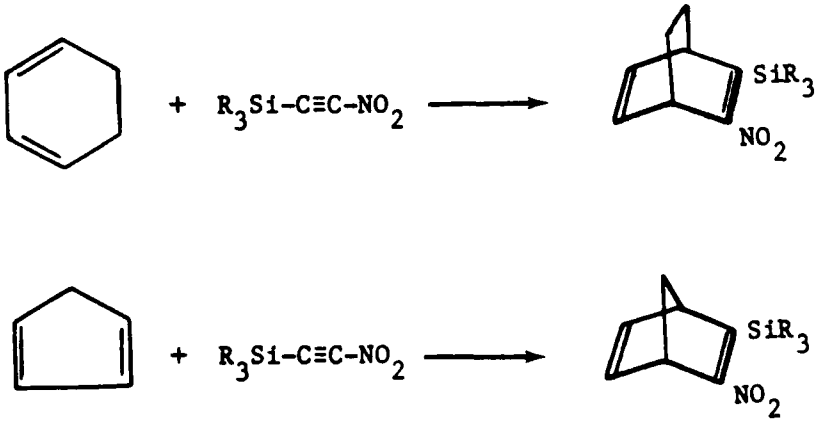
teristic asymmetric and symmetric NO_2 streching frequencies were observed in the infrared spectra near 1525 and 1350 cm^{-1}, respectively.

The 1-nitro-2-trialkylsilylacetylenes frequently gave a molecular ion ($M^{+\cdot}$) under electron impact mass spectrometry (70 eV). Other characteristic fragmentations are loss of an alkyl group from the silyl moiety ($M-R^+$) and complete loss of the silyl group ($M-SiR_3^+$).[8] The general fragmentation pathways for nitroacetylenes are shown in equation (7).

$$R_3Si\text{-}C{\equiv}C\text{-}NO_2 \xrightarrow{e^-} \begin{array}{l} [R_3Si\text{-}C{\equiv}C\text{-}NO_2]^{+\cdot} \ (M^{+\cdot}) \\ [R_2Si\text{-}C{\equiv}C\text{-}NO_2]^{+} + R^{\cdot} \ \ (M^{+}\text{-}R) \\ [C{\equiv}C\text{-}NO_2]^{\cdot} + R_3Si^{+} \\ R_3Si\text{-}C{\equiv}C^{+} + NO_2 \ \ (M^{+}\text{-}NO_2) \end{array} \qquad (7)$$

Additional simple fragmentations are observed from the alkyl or other functional groups.

The nitroacetylenes readily undergo Diels-Alder reactions with various cyclic dienes, equation (8)

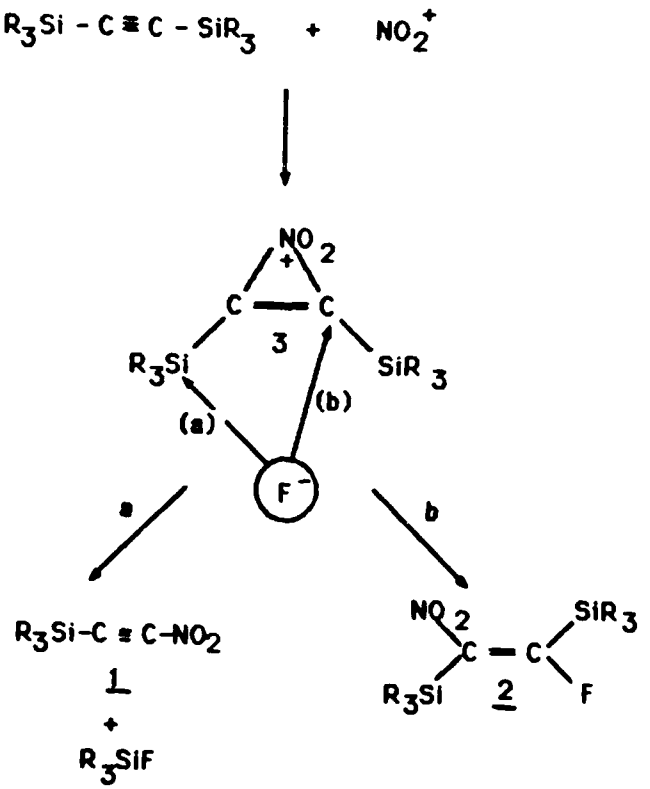


(8)

The structures of these products were confirmed by a combination of field ionization mass spectrometry, ^1H NMR, infrared, and elemental analysis.

Two possible mechanisms may account for the dramatic differences in the yields of nitroacetylenes formed when bis-silyl and mono-silyl acetylene substrates are used in the nitrodesilylation reaction. The first results from electrophilic attack of nitronium ion on the triple bond, followed by fluoride attack at silicon or carbon to give silyl-fluoride and nitroacetylene or cis/trans fluoronitroolefin products. The second mechanism arises from initial fluoride displacement of the silyl group to give silylfluoride and the acetylide anion, followed by nitronium ion addition to the carbanion, Schemes I and II, respectively.

Scheme I: Cyclic Nitronium Ion Intermediate



Scheme II: Acetylide Ion Intermediate:

$$TMS\text{-}C{\equiv}C\text{-}R + F^- \rightarrow R\text{-}C{\equiv}C^- + TMS\text{-}F$$

$$R\text{-}C{\equiv}C^- + NO_2^+ \rightarrow R\text{-}C{\equiv}C\text{-}NO_2$$

The driving force for either mechanism is the formation of the strong Si-F bond resulting from attack of fluoride ion at silicon.[9]

We postulate that the first mechanism is the most probable. The contrast in reactivity between mono- and bis-silylacetylenes is due to the ability of silicon to stabilize the carbonium ion intermediates over that of carbon.[10-13] Silicon is known to stabilize β-carbonium ions through hyperconjugation significantly better than alkyl groups. A second factor support the first mechanism is the observation of the small amounts of NO_2F addition products that would not be expected from the second reaction mechanism. Third, alkyl groups more readily undergo carbonium ion rearrangements, for example, to give a tertiary carbonium ion, than do silicon systems. This propensity of carbonium ions to rearrange may in part explain why we cannot synthesize t-butyl-nitro-acetylene from t-butyl-TMS-acetylene. Finally, addition of nitronium ion salts to a lithio-acetylene does not give any nitroacetylene product.

EXPERIMENTAL SECTION

CAUTION! All nitroacetylene compounds are considered toxic and potentially explosive and should be handled with appropriate precautions.

Materials

Nuclear magnetic resonance spectra were recorded on a Varian Associates EM-360 or a JOEL FXQ-90. Infrared spectra were obtained on a Digilab-20 GC/FTIR (HP5980 GC). Mass spectra were obtained on a HP mass selective detector 5790B with gas chromatographic separation on a HP5970 GC. The reaction progress was monitored by gas chromatography using a Varian model 3700 equipped with a SE-54, 50-meter capillary column. High quality NHFP and NTFB were obtained from Ozark-Mahoning. NHFP was used as obtained. NTFB was purified by dissolving NTFB in nitromethane, separating away the residual nitric acid components; and then rotovaccing away the nitromethane. This step was repeated several times, resulting in NTFB free of acidic impurities. The silicon compounds were generally obtained from Petrarch Systems, Inc., or from Aldrich Chemical Co.

General Synthesis Procedure for the Synthesis of Nitroacetylenes Using Nitronium Hexafluorophosphate or Nitronium Tetrafluoroborate

One equivalent of NHFP or purified NTFB dissolved in anhydrous acetonitrile, nitromethane, or nitromethane/methylene chloride was added to one equivalent of the TMS-acetylene in acetonitrile, nitromethane, or nitromethane/methylene chloride with rapid stirring for 1 h at room temperature. The crude nitroacetylenes were purified by simple column chromatography using a silica gel column and chloroform as the eluting solvent. The reaction mixture was quickly passed through a chloroform-saturated plug of silica-gel, applying suction at the effluent port and rinsing with 100 mL of chloroform. The effluent was typically

concentrated to 10 mL in vacuo and quickly utilized in subsequent synthetic transformations. NOTE: Do not wash with brine or bicarbonate solutions; they cause rapid decomposition of the nitroacetylenes. Nitroacetylenes will generally decompose rapidly if concentrated and allowed to stand. Decomposition can be slowed by addition of an inert solvent and storing in a freezer. However, both (tri-isopropyl)silyl-nitroacetylene and (dimethyl-t-butyl)silyl-nitroacetylene are stable for a few hours at room temperature when concentrated. The stability of the nitroacetylenes goes up dramatically with increasing size of the silyl group attached to the nitroacetylene. For example, we find no decomposition of tri-isopropylsilyl or dimethyl-t-butylsilyl-nitroacetylenes when dissolved in methylene chloride at room temperature over several weeks. Compound characterization of a new nitroacetylenes are shown in Tables II and III.

2-Nitro-3-(triisopropylsilyl)bicyclo[2.2.1.]hepta-2,5-diene. Tri-isopropylsilyl-nitroacetylene (70 mg, 0.4 mmol, with 30 mg of tri-isopropylsilylacetylene as impurity) was dissolved in 10 mL of CCl_4 and treated with cyclopentadiene (300 mg, 5 mmol). This mixture was stirred for 3 days at room temperature, concentrated, and chromatographed over silica gel, eluting with 90% heptane/10% dichloromethane to give 70 mg (75%) of the expected adduct, an oil. ^1H NMR (CCl_4) δ: 1.07 (d, 18H, CH_3), 1.32 (m, 3H, CH), 2.15 (m, 2H, CH_2), 4.10 (m, 2H, CH), and, 6.90 ppm (m, 2H, CH). IR: (Neat) 2925, 2850, 1500, 1465, 1340 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 65.90; H, 9.35; N, 4.82. Found: C, 65.41; H, 9.54; N, 4.73.

2-Nitro-3-(trimethylsilyl)bicyclo[2.2.2.]octa-2,5-diene. Nitronium fluoroborate (1.3 g, 10 mmol) was suspended in 10 ml of nitromethane and stirred under argon at 0° with ice-cooling. Bis-(trimethysilyl)-acetylene (1.7 g, 10 mmol) was then added, and the reaction became homogeneous and amber in color. The entire reaction was filtered through a 3" x 1" plug of chloroform-saturated silica-gel and was eluted with 150

mL of chloroform, using a vacuum aspirator to hasten elution rate. The product was concentrated to 10 mL, treated with 1,3-cyclohexadiene (2 g, 25 mmol) and allowed to stand at room temperature overnight. The reaction mixture was then chromatographed over silica-gel, eluting with 1:1 hexane/chloroform, collecting the Rf = 0.5 material. Concentration of the effluent in vacuo yielded 600 mg (27% overall, from bis(trimethylsilyl)acetylene of yellow crystals, mp 53-55°, IR: (CCl_4 smear) 3085; (w, vinyl C-H), 2960 (m, C-H); 1520 (S, NO_2); 2360 (S, NO_2) cm^{-1}. ^1H NMR (CCl_4) δ: 1.4 (m, 4H, CH_2); 4.1 (m, 1H, CH); 4.6 (m, 1H, CH); 6.3-6.6 (m, 2H, CH). Anal. Calcd. for $C_{11}H_{17}NO_2Si$: C, 59.19; H, 7.62; N, 6.28. Found: C, 59.14; H, 7.45; N, 6.28.

2-Nitro-3-(trimethylsilyl)norbornadiene. The reaction of nitronium fluoroborate and bis-trimethylsilylacetylene was carried out exactly as described in the previous sequence involving cyclohexadiene. The resulting 10 mL of solution containing trimethylsilyl nitroacetylene was treated with 5 mL of cyclopentadiene, and was stored under argon for 15 hours. The reaction mixture was concentrated and chromatographed over silica gel, eluting with chloroform, collecting the Rf = 0.7 material. The effluent was concentrated and distilled in vacuo to give 1.0 g (50%) of yellow oil, bp 44°, 0.1 torr. IR: (Neat Smear) 3080 (w, vinyl C-H); 2960 (m, C-H); 1505 (s, nitro); 1350 (s, nitro) cm^{-1}. ^1H NMR (CCl_4) δ: 2.2 (m, 2H, CH_2); 4.0 (m, 2H, CH) 6.8 (m, 1H, CH); 7.1 (m, 1H, CH). Anal. calcd. for $C_{10}H_{15}NO_2Si$: C, 57.42; H, 7.18; N, 6.70. Found: C, 56.73; H, 7.43; N, 6.39.

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Table I: Nitroacetylene Yields

Starting Material	Nitronium Salt	Nitroactylene Product	Yield (%)
TMS-C≡C-TMS	NTFB	TMS-C≡C-NO_2	70[a]
TMS-C≡C-$SiMe_2$iPr	NHFP	$SiMe_2$i-Pr-C≡C-NO_2	34[b]
		TMS-C≡C-NO_2	6[b]
TMS-C≡C-$SiMe_2$t-Bu	NHFP	$SiMe_2$t-Bu-C≡C-NO_2	59[a]
		TMS-C≡C-NO_2	29[a]
TMS-C≡C-Si(i-Pr)$_3$	NHFP	Si(i-Pr)$_3$-C≡C-NO_2	57[a]
		TMS-C≡C-NO_2	0[b]
TMS-C≡C-CH_3	NHFP	CH_3-C≡C-NO_2	c,d
TMS-C≡C-t-Bu	NHFP	t-Bu-C≡C-NO_2	0
TMS-C≡C-C_6H_5	NHFP	C_6H_5-C≡C-NO_2	0
TMS-C≡C-$(CH_2)_4$-C≡C-TMS	NHFP	TMS-C≡C-$(CH_2)_4$-C≡C-NO_2	0

[a] Isolated yield.
[b] Yield determined from internal standard.
[c] Rapidly decomposes.
[d] Trace yield, observed by GC/MS.

Table II: Infrared Absorbances (cm^{-1}) for TMS-acetylenes and Nitroacetylenes

Compound	C≡C	NO_2	NO_2	C-H	Other
TMS-C≡C-TMS	-	-	-	-	-
NO_2-C≡C-TMS	2250	1531	1265	2970 2936	1265/895/865 795
TMS-C≡C-CH_3	2187	-	-	2967	1258/1050/849/764
NO_2-C≡C-CH_3	2264	1543 1526	1342	2950	822/833
TMS-C≡C-Si(i-$PrMe_2$)	-	-	-	2960 2900 2880	1250/860/820/760
NO_2-C≡C-Si(i-$PrMe_2$)	2160	1533	1325	2965 2900 2880	1251/880/810
TMS-C≡C-Si(i-Pr_3)	2120	-	-	2950 2860	1250 950/880 680
NO_2-C≡C-Si(i-Pr_3)	2150	1520	1325	2940 2860 2850	950/880/680
TMS-C≡C-Si(t-$BuMe_2$)	-	-		2968 2940 2905 2870	1265/829/760
NO_2-C≡C-Si(t-$BuMe_2$)	2175	1531	1327	2963 2943 2870	1261/961/829/783

Table III: Fragmentation Patterns for Nitroacetylenes and TMS-Acetylenes

Compound	m/e Value	Assignment
TMS-C≡C-TMS	170	$M^{+\cdot}$
	155	$M-Me^+$
	97	$M-TMS^+$
	73	TMS^+
NO_2-C≡C-TMS	143	$M^{+\cdot}$ (small)
	128	$M-Me^+$
	129	$M+1-Me^+$ (Obs. 10.0, Calc. 10.6)
	130	$M+2-Me^+$ (Obs. 4.0, calc. 3.5)
	97	$M-NO_2^+$
	70	$M-TMS^+$
	73	TMS^+
TMS-C≡C-Me	112	$M^{+\cdot}$
	97	$M-Me^+$
	73	TMS^+
NO_2-C≡C-Me	85	$M^{+\cdot}$
	39	$M-NO_2^+$
	46	NO_2^+
TMS-C≡C-Si(i-Pr_3)	254	$M^{+\cdot}$
	211	$M-i-Pr^+$
	73	TMS^+
NO_2-C≡C-Si(i-Pr_3)	227	$M^{+\cdot}$
	184	$M-i-Pr^{+\cdot}$
TMS-C≡C-Si(i-PrMe_2)	198	$M^{+\cdot}$ (small)
	155	$M-i-Pr^+$
	73	TMS^+

NO_2-C≡C-Si(i-PrMe_2)	171	$M^{+\cdot}$
	128	M-i-Pr^+
	129	M+1-i-Pr^+ (obs. 10.2, calc. 9.9)
	130	M+2-i-Pr^+ (obs. 3.9, calc. 3.2)
TMS-C≡C-Si(t-BuMe_2)	212	$M^{+\cdot}$
	213	$M+1^{+\cdot}$ (obs. 22.6, calc. 22.9)
	214	$M+2^{+\cdot}$ (obs. 9.1, calc. 10.8)
	197	$M-15^+$
	156	M+H-t-Bu^+
	155	M-t-Bu^+
	73	TMS^+
	57	t-Bu^+
NO_2-C≡C-Si(t-BuMe_2)	185	$M^{+\cdot}$ (small)
	57	t-Bu^+
	128	M-t-Bu^+
	139	M-NO_2^+

Appendix E

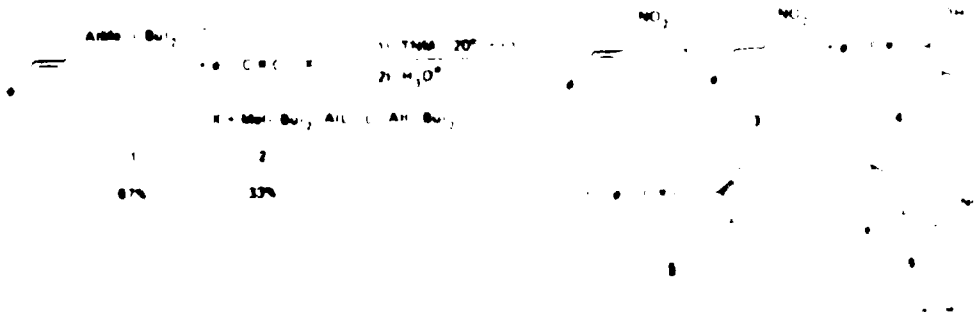
NEW NITRATION METHODS: NITRODEALUMINATION

Mitchell B. Halpern, Robert J. Schmitt, and Clifford D. Bedford*
Department of Physical Organic Chemistry, SRI International
Menlo Park, California, USA 94025

Abstract: The reaction of vinylaluminate salts with tetranitromethane gives the corresponding nitroolefins in moderate yield and is sensitive to solvent, temperature, mode of reagent addition, reaction time, and nitronium ion source.

The nitrodemetallation of vinylaluminum compounds was investigated as a method for preparing electron-deficient olefins. The rationale for selecting this synthetic method is straightforward. A number of methods exist for the synthesis of vinylaluminum compounds with various substitution patterns around the double bond,[1] and geminal dialuminated olefins have been prepared[2] that could lead to a general synthesis method for gem-dinitroalkenes. Furthermore, vinylaluminum compounds and vinylaluminate salts react with various electrophiles to yield vinylhalides,[3] vinylnitriles,[4] trans-alkenes,[3] and other substituted olefins. By analogy, vinylaluminate salts should yield nitroolefins upon treatment with nitronium ion sources.

We prepared styrylaluminate 1 via the procedure of Zweifel, et al.[4] This procedure produces aluminum acetylide 2 as a side product in approximately 33% yield. Treatment of 1 with tetranitromethane (TNM) at -20°C yields β-nitrostyrene in less than 10% yield. Although the reaction mixture is complex and difficult to separate, we have isolated compounds 3 to 6 in addition to β-nitrostyrene. Furthermore, a substantial amount of polymeric material was formed during the reaction.



Compounds 3-6 result from nitrodealumination, hydroalumination, carbodealumination, condensation, and/or radical coupling reactions.

Initial vinylaluminate reactions were conducted in a mixture of hexane and diethyl ether. To increase the yield of the process, we conducted the reaction at lower temperatures while adding styrylaluminate 1 to TNM in tetrahydrofuran (THF). Lowering the temperature of the reaction should suppress both polymer formation and secondary reactions. Since the use of THF should increase the amount of NO_2^+ in solution,[5] we observed increased rates

of the nitroolefin if the reaction occurs via an electrophilic mechanism. If the reaction occurs via a radical mechanism,[6] inverse addition of styrylaluminate 1 to TNM in THF should also result in increased formation of β-nitrostyrene because the aluminate 1 would encounter an excess of an NO_2· source in solution.

Simultaneous application of these conditions (i.e., lower temperature, THF solvent, inverse addition) increased the yield of β-nitrostyrene to 33% and suppressed the formation of compounds 3, 4, and 6. Compound 5 appeared in increased yield along with several new products that have not been characterized. The reaction failed if the temperature was lowered to -78°C.

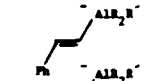
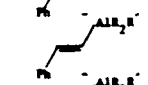
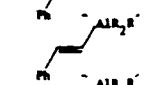
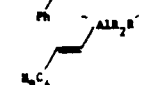
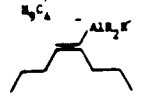
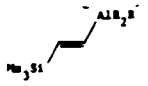
We conducted the above reaction in DMSO to clarify the effect of solvent on this process. In DMSO, TNM is almost completely dissociated into NO_2^+ and $^-C(NO_2)_3$.[5] If nitration occurred via an ionic electrophilic cleavage, the yield should increase. This was not observed and only a 16% yield of β-nitrostyrene was obtained.

The effect of other nitrating agents on the production of β-nitrostyrene was examined. Reaction of the vinylaluminate 1 with N_2O_5 in CH_2Cl_2, NO_2Cl in CH_2Cl_2, and NO_2BF_4 in sulfolane did not yield β-nitrostyrene. The reaction of 1 with N_2O_4 yielded only a small (<1%) amount of the nitroolefin. The failure of NO_2BF_4/sulfolane or TNM/DMSO to improve the nitrodealumination process is a strong indication that the process involves radical chemistry. The failure of N_2O_4, which is known to react as a radical, might be due to attack by the radical on the double bond of the vinylaluminate 1. In essence, N_2O_4 might be too vigorous an oxidant to be useful in the presence of double bonds or aromatic rings.

Finally, the effect of reaction time was investigated. The yield was influenced by the length of reaction preceding quenching with weak acid. Thus, using 2 equivalents of TNM and the standard reaction conditions described above, 41% β-nitrostyrene could be obtained after 10 minutes. After 30 minutes only 30% β-nitrostyrene was recovered, whereas after 60 minutes less than 10% β-nitrostyrene could be isolated. We postulate that the decrease in β-nitrostyrene results from increased polymerization and side product formation.

The hydroalumination/nitrodealumination sequence appears to be general for terminal and internal alkylacetylenes. 1-Hexyne and 4-octyne yield the corresponding nitroolefins in low yield, whereas trimethylsilyl acetylene does not yield 1-trimethylsilyl-2-nitroethylene. The lower yields observed in these cases may result from an increased susceptibility of the alkyl-substituted nitroolefins toward base-catalyzed polymerization. Alternatively, the intermediate aluminum species may be more susceptible to radical decomposition. The nitrodealumination results are summarized below.

Through the nitrodealumination process, we have extended the concept of nitrodemetallation to include the cleavage of metal-carbon bonds other than tin[7] and mercury.[8] Based on product analysis, the effect of experimental conditions, the failure of NO_2^+ sources to effect nitration, and the success of the highly oxidizing tetranitromethane, we postulate

Alkyne	Aluminate Salt	Mode of Addition	Conditions	Nitroolefin Yield
Ph-C≡CH		N	1	< 10%
Ph-C≡CH		N	2	11%
Ph-C≡CH		I	3	30%
Ph-C≡CH		I	4	41%
Ph-C≡CH		I	5	16%
n-C_4H_9-C≡CH		I	3	7.6%
n-C_3H_7-C≡C-nC_3H_7		I	3	15.5%
Me_3Si-C≡CH		I	3	0%

R = t-Bu; R'=Me Key: N = normal addition; THH added neat to aluminate
I = inverse addition; aluminate added to THH solution

Conditions: 1 = -20° → room temp., water quench, solvents (hexane, Et_2O).
2 = -20°, 1/2 h, acid quench, solvents (hexane, Et_2O).
3 = -20°, 1/2 h, acid quench, THH dissolved in THF, aluminate in hexane/Et_2O.
4 = -20°, 1/6 h, acid quench, 2 equivalents of THH dissolved in THF, aluminate in hexane/Et_2O.
5 = -20°, 1/2 h, acid quench, THH dissolved in DMSO, aluminate in hexane/Et_2O.

that the nitrodealumination reaction proceeds via radical species. Although the reaction is of scientific interest, the moderate yields as well as the basic and radical nature of the reaction media make synthesis of the geminal dinitroolefins via a geminal dinitrode alumination process unlikely.

Acknowledgments

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