ANHYDROUS NITRONIUM TRIFLATE NITRATION OF AROMATIC and HETEROAROMATIC COMPOUNDS: CONVENTIONAL BENCHTOP & MICROWAVE-ASSISTED CONDITIONS

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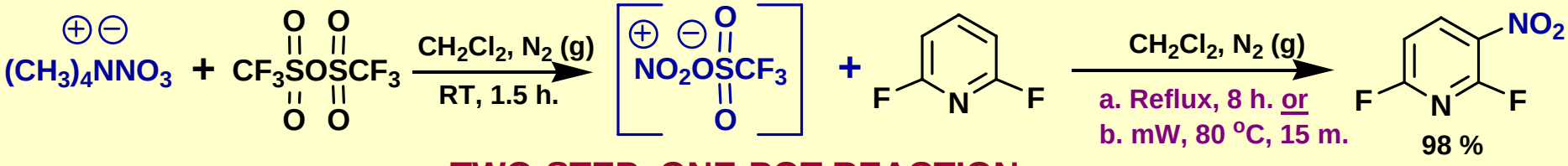

TWO-STEP, ONE-POT REACTION

POSTPRINT

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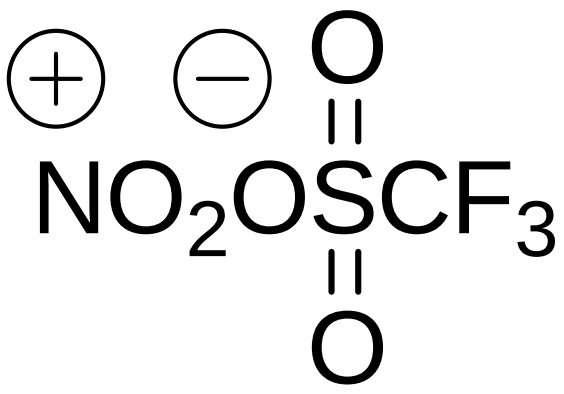
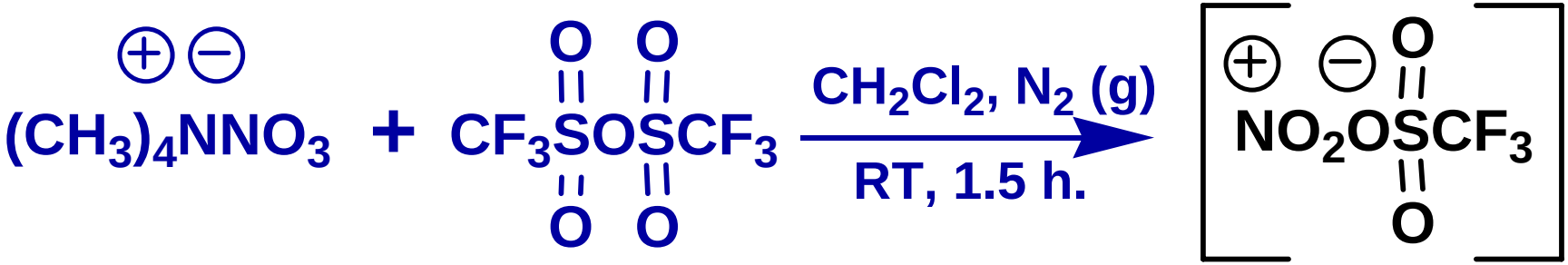
ANHYDROUS NITRONIUM TRIFLATE NITRATION



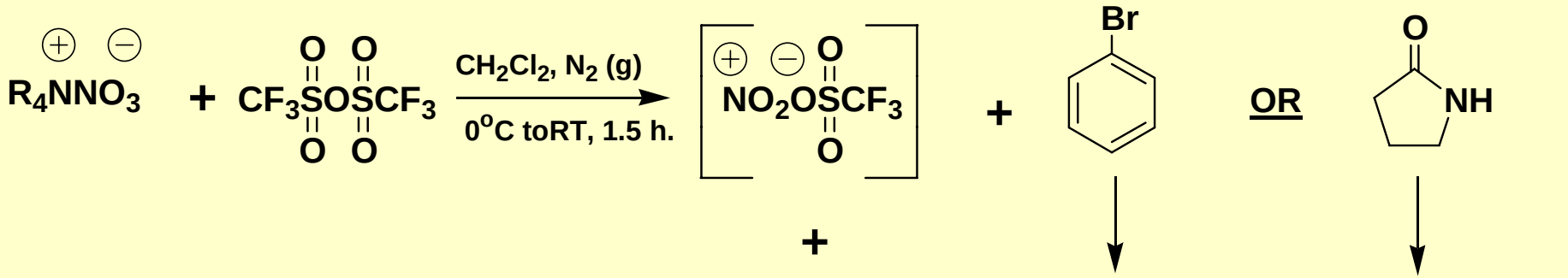
CONVENIENT IN-SITU GENERATION



OVERVIEW

- IMPROVED $NO_2OSO_2CF_3$ NITRATING REAGENT *IN-SITU* FORMATION
  - $(n\text{-Bu})_4NNO_3$ GENERATED REAGENT
  - $(CH_3)_4NNO_3$ GENERATED REAGENT
- CONVENTIONAL BENCHTOP & MICROWAVE-ASSISTED $NO_2OSO_2CF_3$ NITRATION RESULTS
  - CONVENTIONAL BENCHTOP LIMITATIONS
  - MICROWAVE-ASSISTED EXTENTIONS
- PRELIMINARY MICROWAVE-ASSISTED $NO_2OSO_2CF_3$ NITRATION SCREENING REACTIONS
  - DIRECTIONAL EFFECTS OF 5-MEMBERED HETEROAROMATICS
  - POSITIONAL NITRATION REACTIVITY

ANHYDROUS NITRONIUM TRIFLATE NITRATION



R = -*n*-Bu
-CH_2CH_3

CH_2Cl_2 SOLUBLE
COLUMN CHROMATOGRAPHY [1,2]

R = $-CH_3$

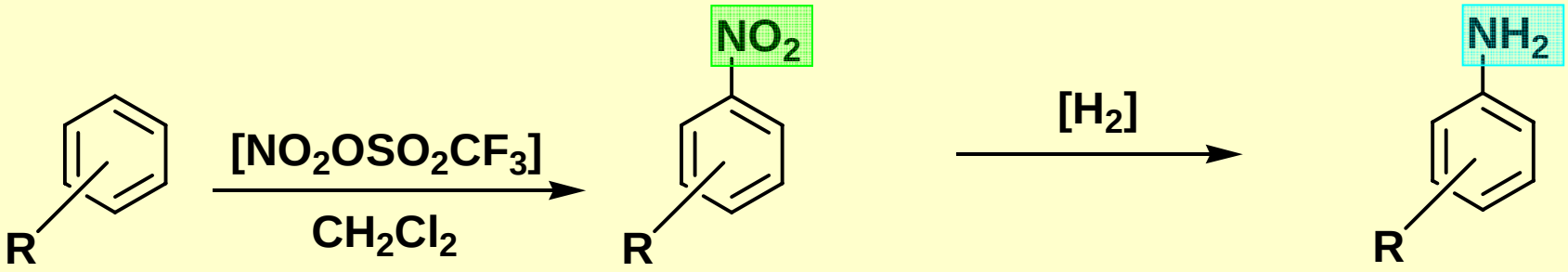
H_2O SOLUBLE
AQUEOUS WORK-UP ONLY

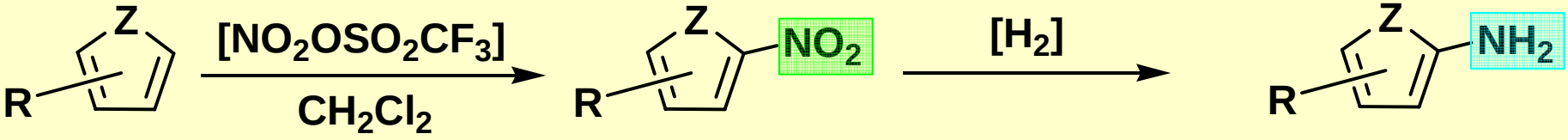
H_2O SOLUBLE

1. Shackelford, S. A.; Adams, C. M.; Sharts, C. M. 11th Rocky Mountain Region ACS Mtg., Albuquerque, NM, 10-12 Jul 1992.
2. Adams, C. M.; Sharts, C. M.; Shackelford, S. A. *Tetrahedron Lett.* **1993**, *34*, 6669-6671.

ANHYDROUS NITRONIUM TRIFLATE NITRATION

OBJECTIVE: NEW AROMATICS & HETEROAROMATICS



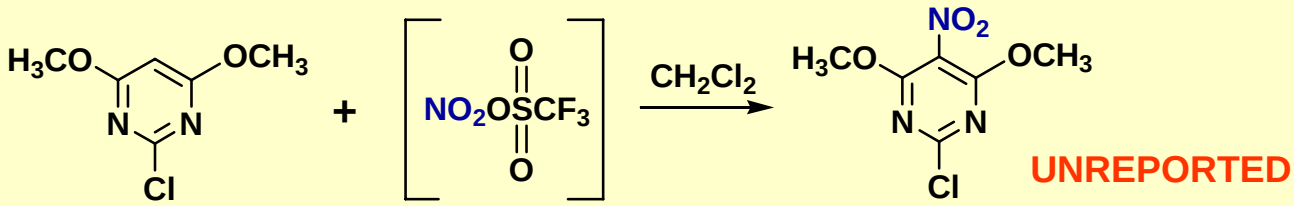


Z = C, O, N, S

NEW NITRATED COMPOUNDS

NEW AMINO-SYNTHONS

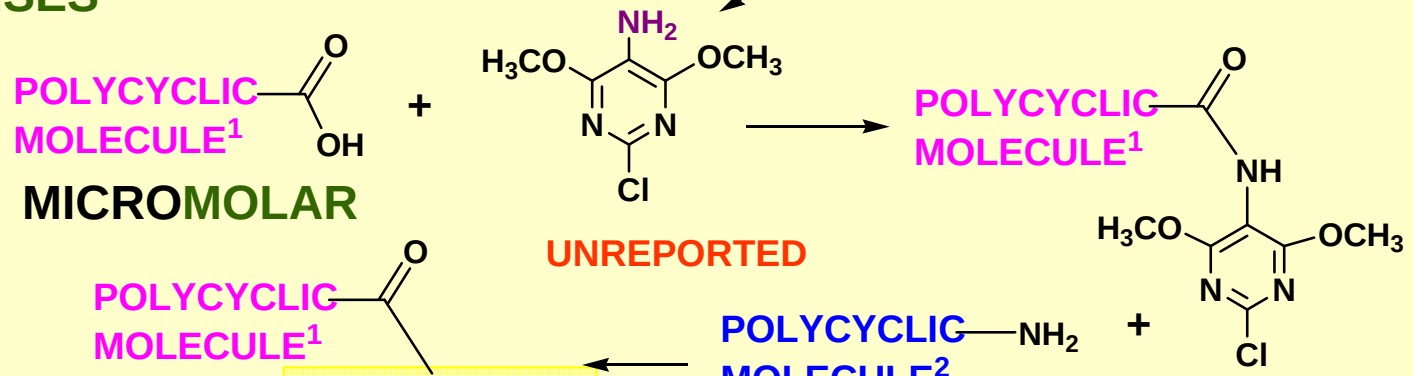
ANHYDROUS NITRONIUM TRIFLATE NITRATION



UNREPORTED

BIOASSY RESPONSES

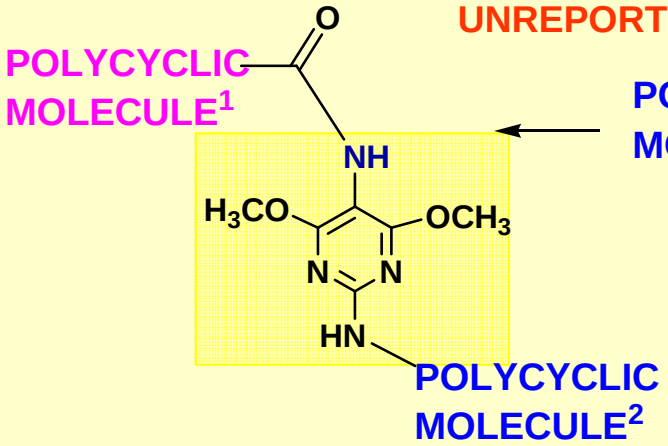
$[H_2]$



MICROMOLAR

UNREPORTED

NANOMOLAR

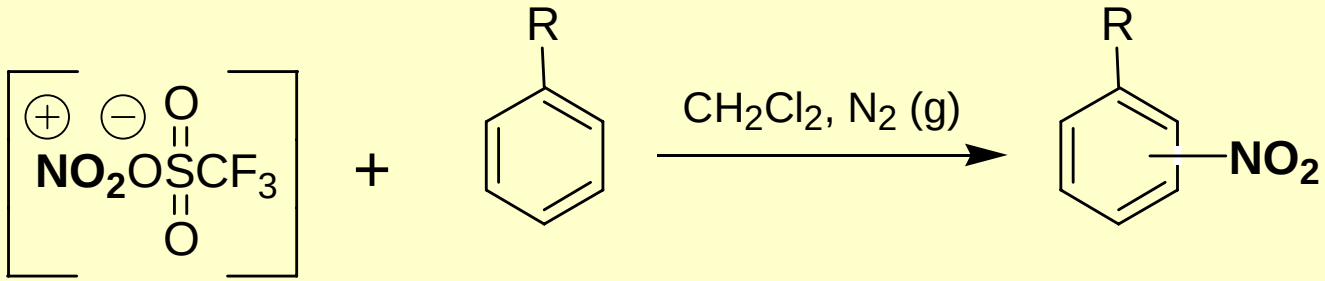


PICOMOLAR

7 PHARMACEUTICAL CANDIDATES

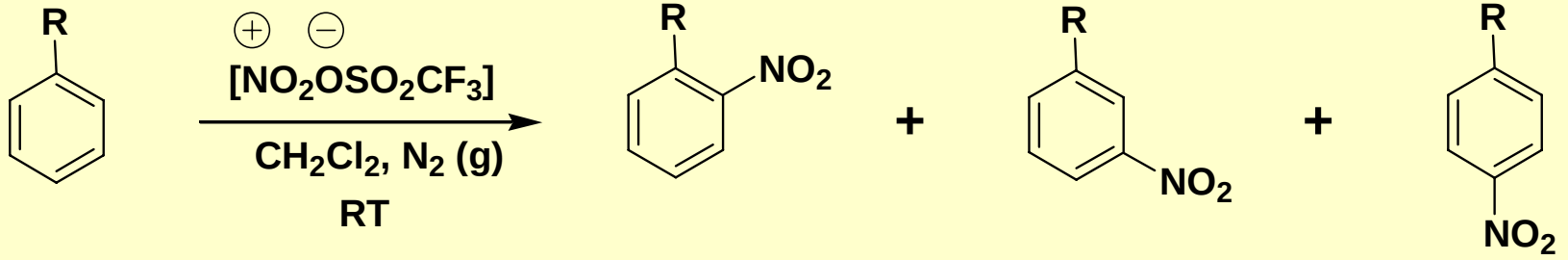
ANHYDROUS NITRONIUM TRIFLATE NITRATION

➢ NITRATION CONDITIONS:

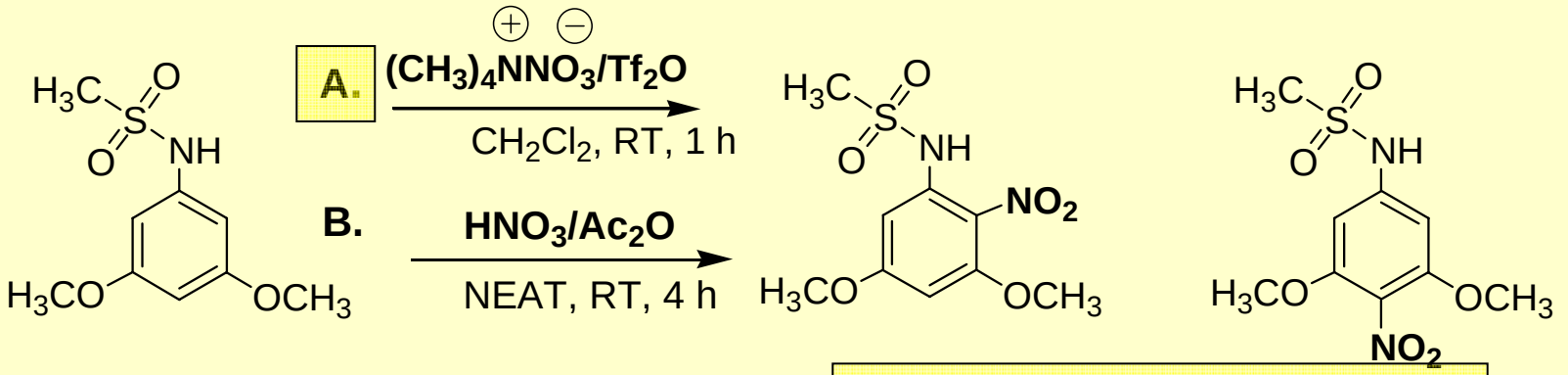


	EQUIVALENTS	CONCENTRATION	TEMPERATURE	METHOD
DILUTE:	1.05 to 1.7	0.2 to 0.3M	-78 °C to RT	CONVENTIONAL BENCHTOP
CONC.:	1.5 to 2.0	1.1 to 3.6M	RT to >REFLUX	CONVENTIONAL BENCHTOP & MICROWAVE-ASSISTED

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION



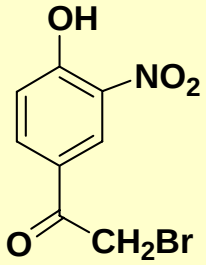
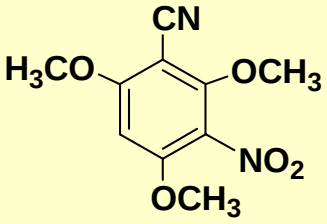
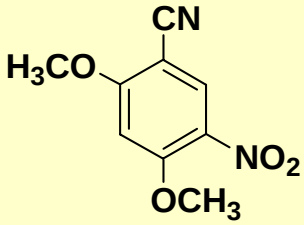
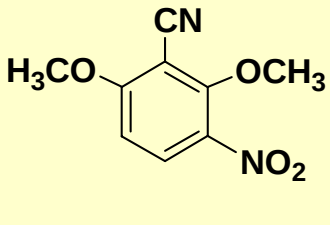
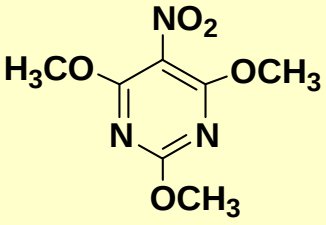
R =	-ortho	-meta	-para
$-OCH_3$	63%	5%	32%
-OH	90	0	10
$-CH_3$	62	0	38
-Br	33	0	67
$-CO_2H$	16	78	6
$-CF_3$	8%	88%	4%



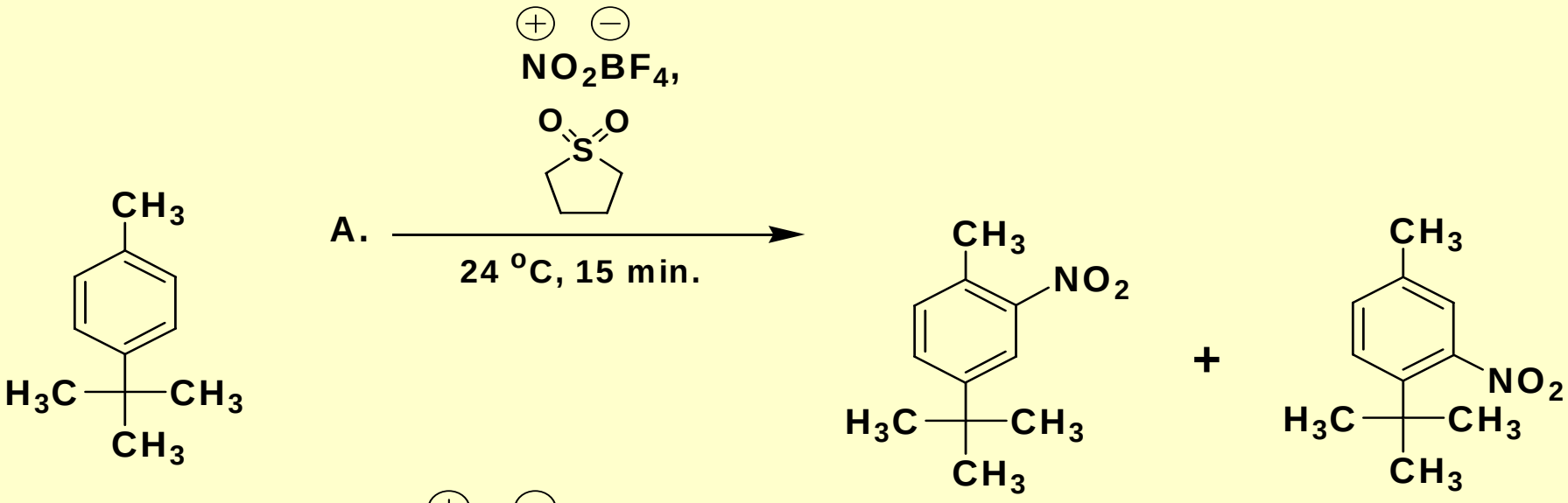
	ortho	para
A.	95%	5%
B.	0%	100%

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

➢ NITRATION RESULTS:

PRODUCT:					
		UNREPORTED	ONLY ISOMER		DIRECT NITRATION
SCALE (mmol):	8 93	8 100	100	100	371
ISOLATED YIELD:	94% 91%	86% 82%	91%	100%	82%
PURITY:	91% 88%	95% 95%	82%	97%	98%

➢ NITRATION SELECTIVITY (82 mmol):

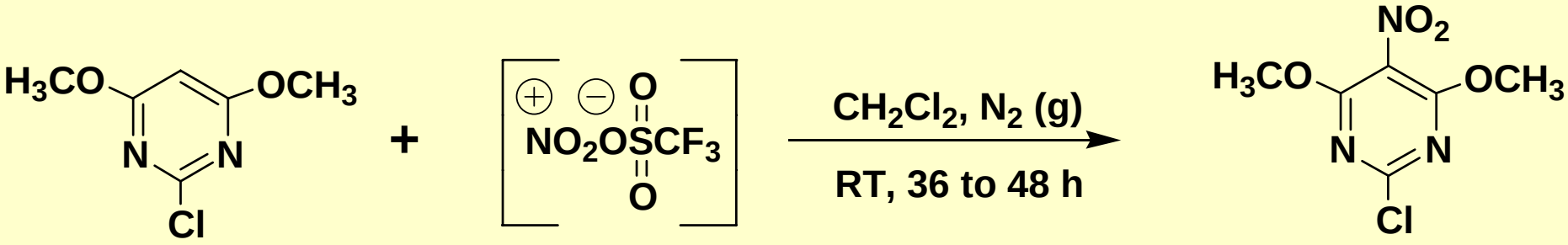


A.	95%	5%*
B.	100%	0%
B.	YIELD = 94% PURITY = 93%	

* Olah, G. A.; Kuhn, S. *J. Am. Chem. Soc.*, **1964**, *86*, 1067-1070.

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

➢ $NO_2OSO_2CF_3$ EQUIVALENTS & NITRATION SCALE-UP:



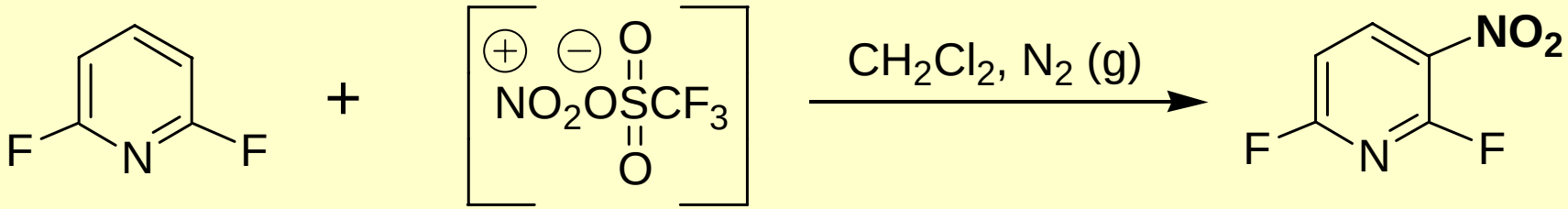
UNREPORTED

CONDITIONS	SCALE (mmol)	$NO_2OSO_2CF_3$ EQUIV.	% CONVERTED	ISOLATED YIELD.	PURITY
[0.2M], 48 h	8	1.05	68	---------	68%
	8	1.25	88	---------	88%
	8	1.50	100	98%	99%*
[3.6M], 36 h	2864	1.5	100	94%	>95%

*ANALYTICALLY PURE BY C, H, Cl, and N, ELEMENTAL ANALYSES

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

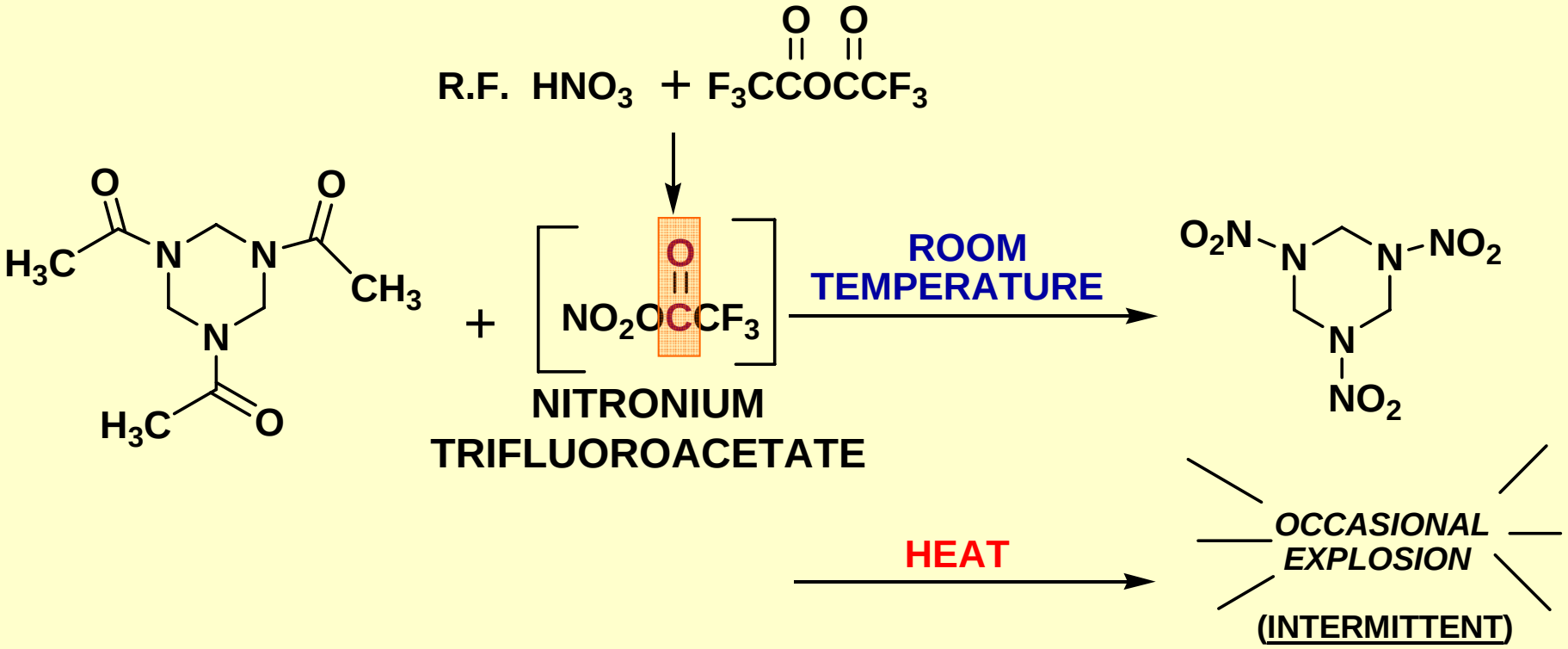
➢ NITRATION REACTIVITY:



CONDITIONS	$NO_2OSO_2CF_3$ EQUIV.	[REACTANT CONC.]	% CONVERTED	ISOLATED YIELD	PURITY
RT, 42 h	1.6	0.25M	69%	--------	<69%
RT, 24 h	1.5	1.09M	78%	--------	78%

CONVENTIONAL BENCHTOP NITRONIUM TRIFUOROACETATE NITRATION

➢ OTHER NITRATION REAGENT REACTIVITY:



MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

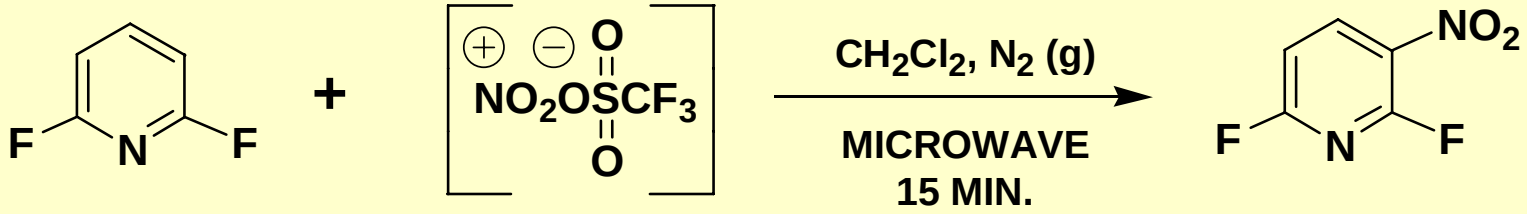
- **ORIGINAL MICROWAVE INSTRUMENTS EMPLOYED:**
  - **PERSONAL MICROWAVE™**
  - **MILESTONE ETHOS™**

SMALL SCALE REACTIONS
3.4 mmol (0.5 gram)

LARGER-SCALE REACTIONS
54.5 mmol (10 grams)

MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

➢ MICROWAVE TEMPERATURE SCREENING:



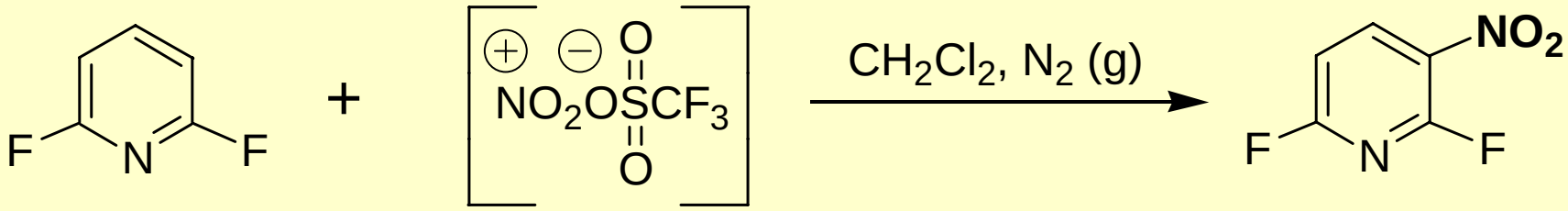
RUN NO.	$NO_2OSO_2CF_3$ EQUIV.	TEMP (°C)	% CONVERTED	ISOLATED YIELD	PURITY
1	1.3	60	91	-------	-------
8	1.5	60	96	85%	-------
5	1.5	110	100	91%	98%
7	1.5	100	100	91%	98%
9	1.5	80	100	94%	100%*

*ANALYTICALLY PURE BY C, H, F, & N ELEMENTAL ANALYSIS

- INCREASED $NO_2OSO_2CF_3$ EQUIVALENTS IMPROVE REACTANT CONVERSION (RUNS 1 & 8)
- INCREASED TEMPERATURE RAISES REACTANT CONVERSION (RUN 5)
- MINIMUM TEMPERATURE (80 °C) EXISTS FOR COMPLETE REACTION (RUN 9)

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

➢ REFLUX TEMPERATURE NITRATION:

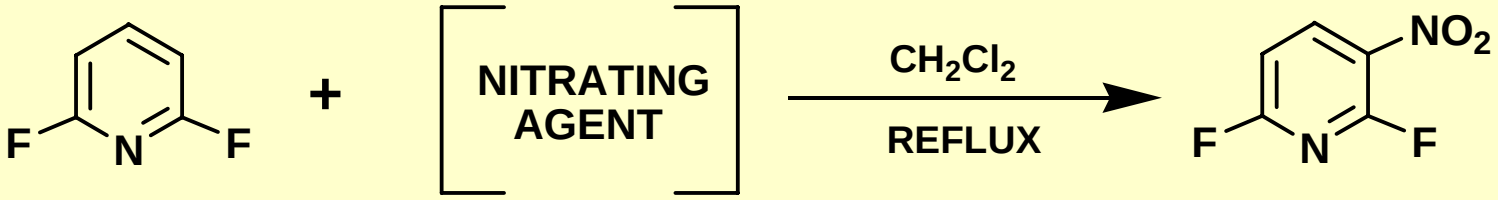


CONDITIONS	$NO_2OSO_2CF_3$ EQUIV.	[REACTANT CONC.]	% CONVERTED	ISOLATED YIELD	PURITY
RT, 42 h	1.6	0.25M	69%	--------	<69%
RT, 24 h	1.5	1.09M	78%	98%	78%
REFLUX, 8 h	1.5	1.09M	100%	98%	99%*

*ANALYTICALLY PURE BY C, H, F, and N, ELEMENTAL ANALYSES

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

➢ $NO_2OSO_2CF_3$ NITRATION EFFECTIVENESS:



	TIME (h)	ISOLATED YIELD	PURITY
[NO_2BF_4 [A]]	24	20%	------
[$NO_2OSO_2CF_3$]	8	98%	99%*

*ANALYTICALLY PURE BY C, H, F, and N ELEMENTAL ANALYSES

[HNO_3 (100%) / H_2SO_4 [B]]	23	78%[C]	------

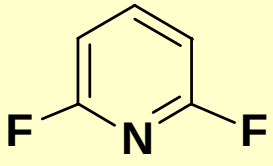
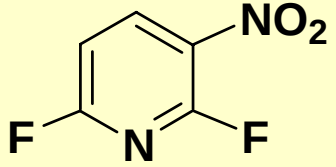
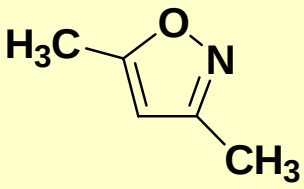
[B] NEAT, 0 °C to RT [C] DISTILLED YIELD

A. Duffy, J. L.; Laali, K. K. *J. Org. Chem*. **1991**, *56*, 3006-3009.

B. Mutterer, F.; Weiss, C. D. *Helv. Chem. Acta* **1976**, *59*, 229-235.

CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

➢ REFLUX REACTION TIMES:

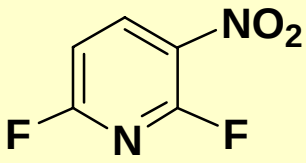
REACTANT	TIME (h)	ISOLATED YIELD	PURITY	PRODUCT
	8*	98%	99%**	
	24	94%	99%**	
	3.5	92%	95%	
	16	90%	95%	

* MINIMUM REACTION TIME

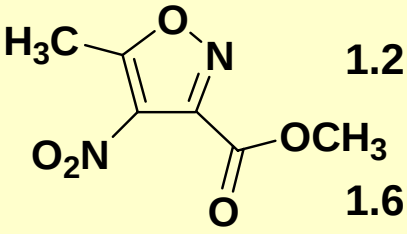
**ANALYTICALLY PURE BY C, H, F, and N ELEMENTAL ANALYSES

CONVENTIONAL VS. MICROWAVE $NO_2OSO_2CF_3$ NITRATION COMPARISON

➢ COMPARATIVE PRODUCT RESULTS:



CONC.	CONDITIONS	SCALE (mmol)	ISOLATED YIELD	PURITY
1.2M	PERSONAL MICROWAVE 80 ^{0}C, 15 min.	3.4	94%	100%*
1.3M	MILESTONE MICROWAVE 80 ^{o}C, 15 min.	54.5	98%	98%*
1.1M	CONVENTIONAL BENCHTOP REFLUX, 8 h	16.4	98%	99%*



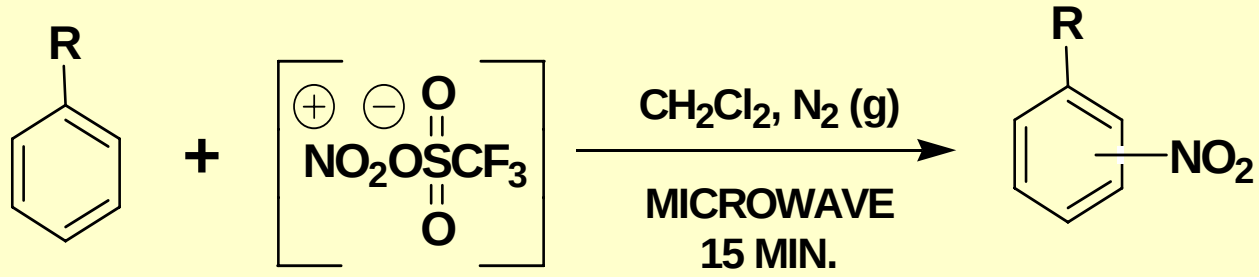
UNREPORTED

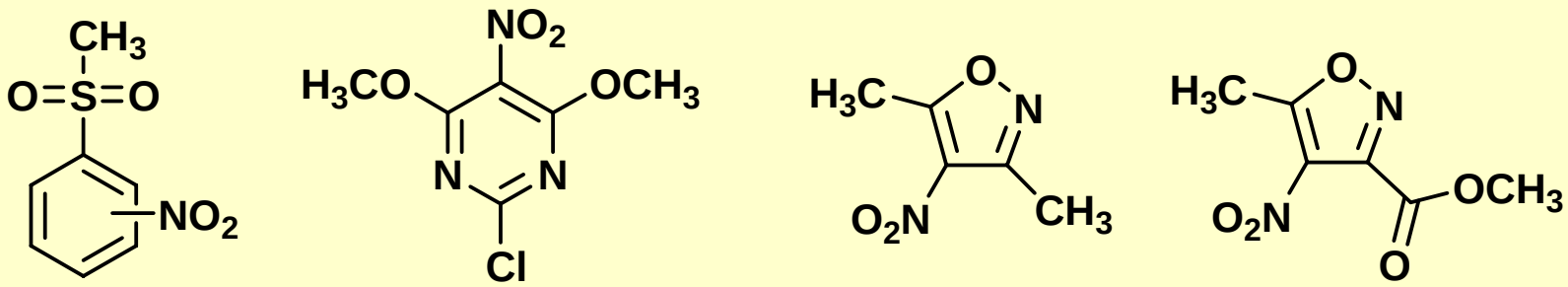
1.2M	PERSONAL MICROWAVE 60 ^{o}C, 15 min.	3.4	100%	99%*
1.6M	MILESTONE MICROWAVE 60 ^{o}C, 15 min.	27.0	100%	99%*
1.2M	CONVENTIONAL BENCHTOP REFLUX, 24 h	17.2	100%	99%**

*ANALYTICALLY PURE **ELEMENTAL ANALYSIS NOT CONDUCTED

MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

➢ MICROWAVE-ASSISTED PRODUCT RESULTS:



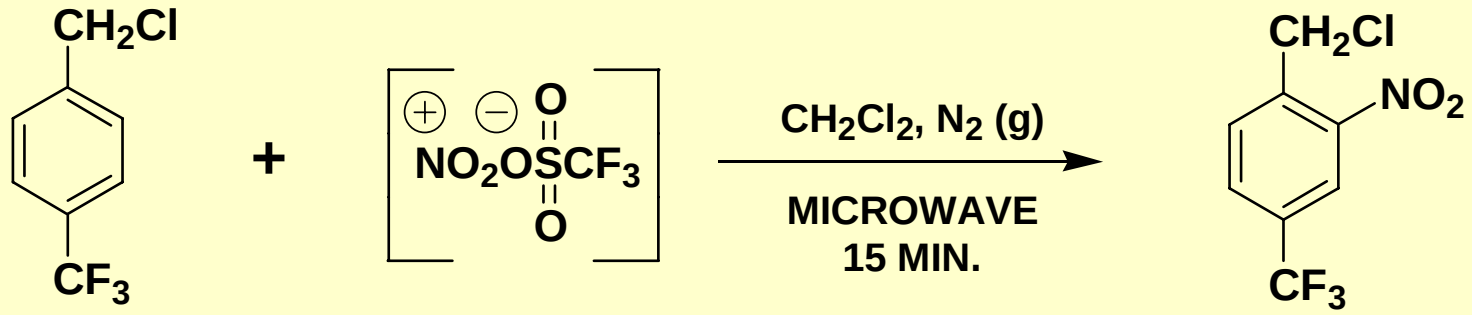


TEMP.(°C)	80	60	60	60
ISOLATED YIELD	94% (*O/M/P* = 17/79/4)	91%	92%	100%
PURITY	100%*	100%**	100%**	100%**

*ISOMERIC MIXTURE ANALYTICALLY PURE **ANALYTICALLY PURE

MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

➢ MICROWAVE-ASSISTED PRODUCT RESULTS:

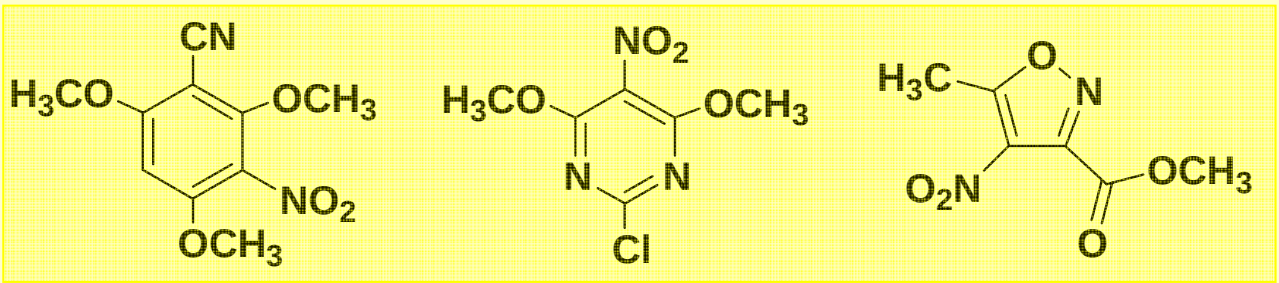


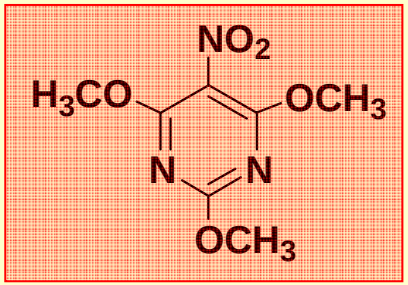
RUN NO.	$NO_2OSO_2CF_3$ EQUIV.	TEMP (°C)	% CONVERTED	ISOLATED YIELD	PURITY
1	1.5	80	82	-------	-----
2	1.5	100	82	-------	-----
3	2.0	80	100	98%	95%

- MINIMUM CONVERSION TEMPERATURE AT LEAST 80 °C (RUNS 1 & 2)
- $NO_2OSO_2CF_3$ EQUIVALENT INCREASE NEED FOR COMPLETE CONVERSION (RUN 3)

MICROWAVE & CONVENTIONAL $NO_2OSO_2CF_3$ NITRATION

- **$(CH_3)_4NNO_3$ BASED NITRONIUM TRIFLATE NITRATION:**
  - **SIMPLE & CONVENIENT REACTION METHOD**
    - ✓ ONE-POT REACTION
    - ✓ EASY AQUEOUS WORK-UP
    - ✓ ISOMERIC SELECTIVITY
    - ✓ EXCELLENT PRODUCT YIELDS
    - ✓ HIGH (ANALYTICAL) "CRUDE" PRODUCT PURITY
    - ✓ DIRECTLY SCALEABLE
  - **NEW COMPOUNDS & NEW SYNTHESIS ROUTE (DIRECT NITRATION)**





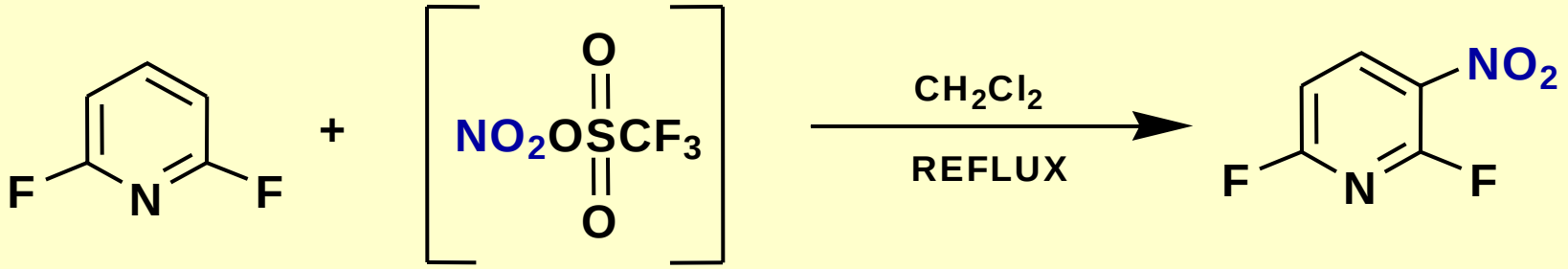
Shackelford, S. A.; Anderson, M. B.; Christie, L. C.; Goetzen, T.; Guzman, M. C.; Hananel, M. A.; Kornreich, W. D.; Haitao, L.; Pathak, V. P.; Rabinovich, A. K.; Rajapakse, R. J.; Truesdale, L. K.; Tsank, S. M.; Vazir H. N.
J. Org. Chem., **2003,** *68*, 267-275.

MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

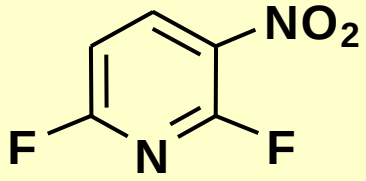
BIOTAGE MICROWAVE INITIATOR™

MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

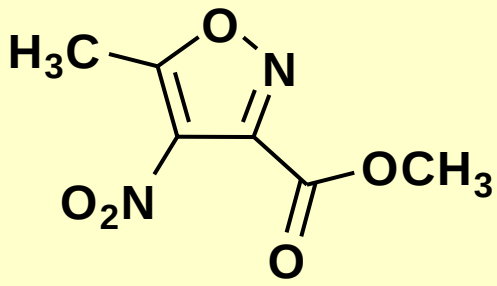
➢ MINIMUM NITRATION REACTION TIME:



TEMP.	TIME (MIN)	PRODUCT CONVERSION
MW SET	2	79%
= 80°C	3	98% (2 RUNS)
ACTUAL	4	100%
= 98-80°C		



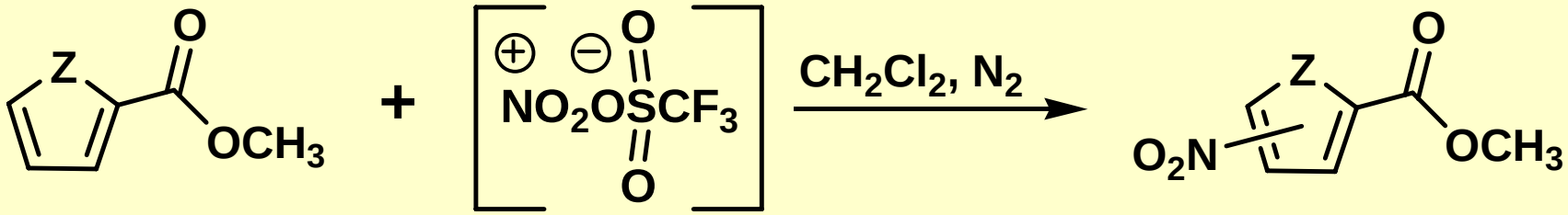
MW SET	3	93%
= 60°C	5	100%
ACTUAL		
= 68-60°C		

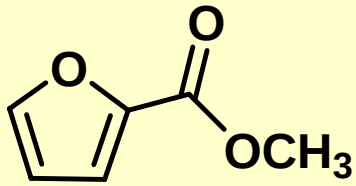


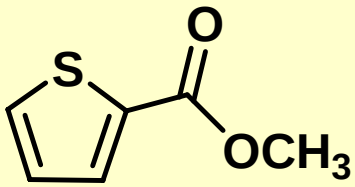
MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

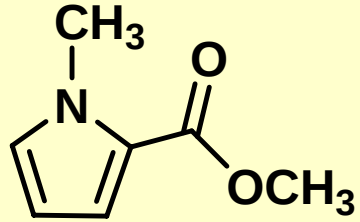
➢ 5-MEMBERED HETEROAROMATICS (ONE HETEROATOM)

- **DIFFERENT HETEROCYCLE REACTIVITY (Z = O, S, N)**





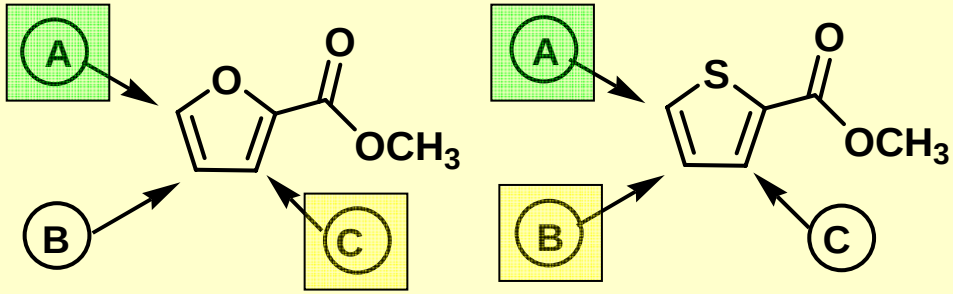


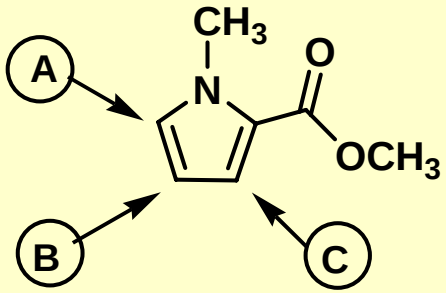


REACTIVE AT RT	**----------**	**VERY REACTIVE AT RT**
NON-REACTIVE AT -78°C	**NON-REACTIVE AT -78°C**	**VERY REACTIVE AT -78 °C**

MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

- **HETERO-RING DIRECTING EFFECTS**





CONDITIONS	A	B	C	A	B	C
RT to 60°C MICROWAVE 1.1 M (5 MIN)	95%	0%	5%	----	----	----
-78°C to 60°C MICROWAVE 0.7M (5 MIN)	94%	0%	6%*	59%	36%	5%(?)
	*2% UNREACTED			62%	38%	----
-78°C to RT CONVENTIONAL 0.7M (3 HR)	97%	0%	3%	----	-----	----
-78°C to RT CONVENTIONAL 0.09M (27-48 HRS)	91-92%	0	9-8%	62%	38%	0%

NO NITRATED PRODUCT

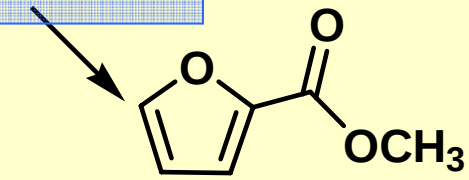
FURAN: SLIGHT CONC. EFFECT

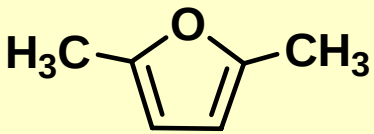
THIOPHENE: SLIGHT HEAT and./or CONC. EFFECT

MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

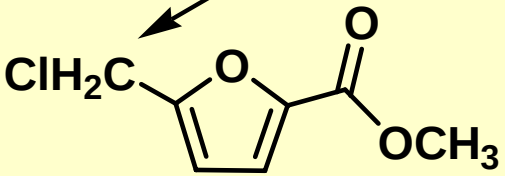
- **RING POSITIONAL REACTIVITY**

SELECTIVE -NO_2 POSITION



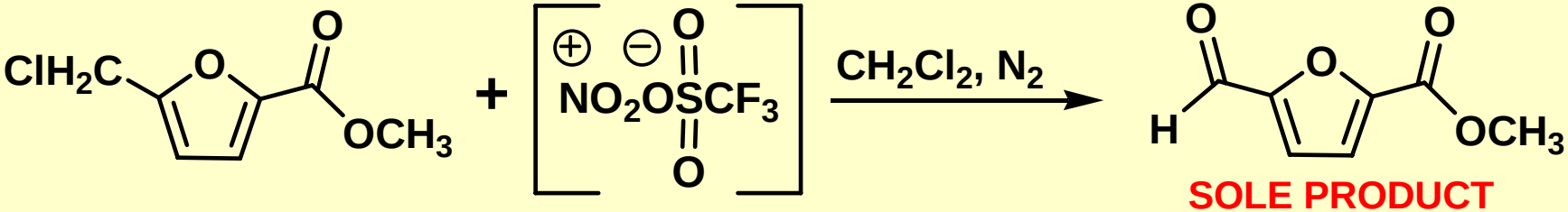


BENZYLIC-LIKE POSITION



VERY REACTIVE AT RT & -78°C, **NO** PRODUCT

NON-REACTIVE AT -78°C



CONVENTIONAL [0.19M, -78°C to RT, 76 HR]:

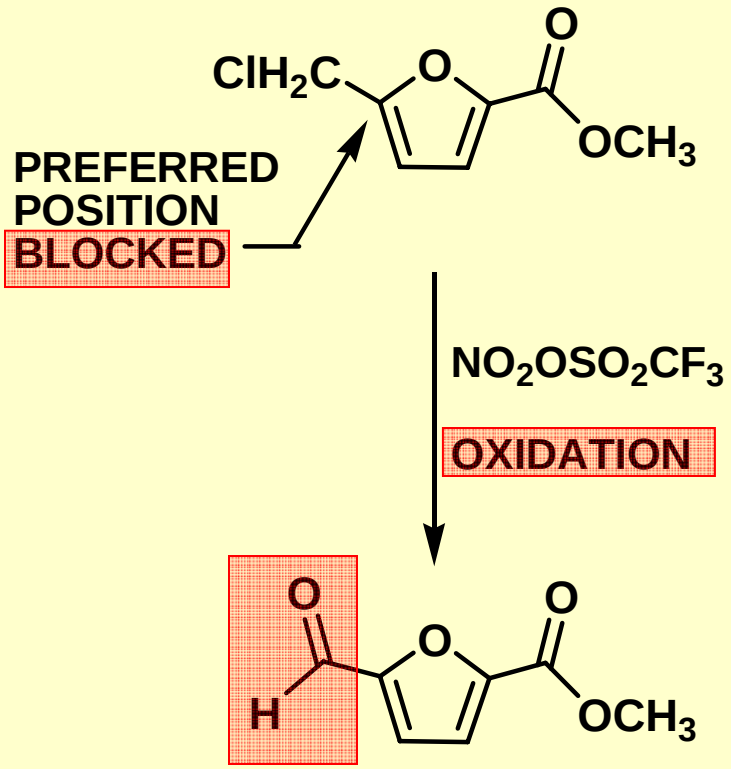
71% CONVERSION (NOT ISOLATED)

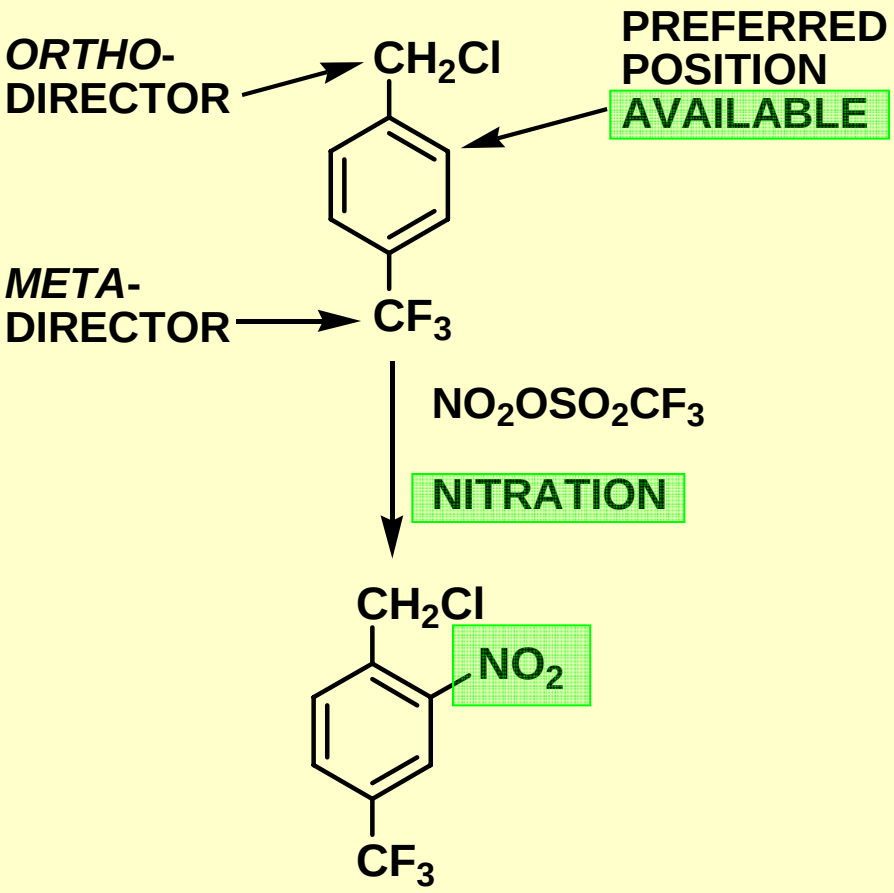
MICROWAVE [0.7M, -78°C to 70°C, 10 MIN]:

100% CONVERSION
64% YIELD (NMR PURE)
LT. YELLOW SOLID

MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

- **RING POSITION REACTIVITY**

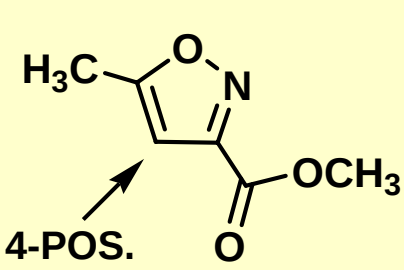




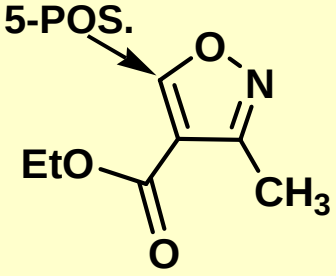
MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

➢ 5-MEMBERED HETEROAROMATICS (TWO HETEROATOMS)

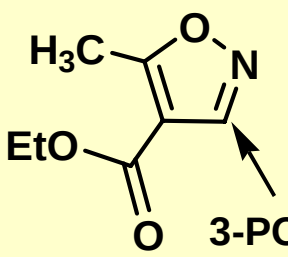
- 3,4,5-POSITION REACTIVITY PREFERENCE



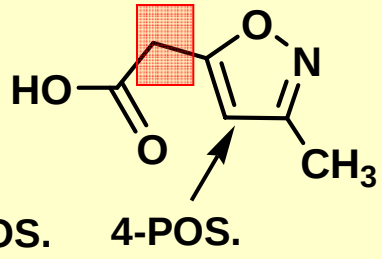
NON-REACTIVE AT RT
HIGH YIELD NITRATION
60°C, 5-15 MIN



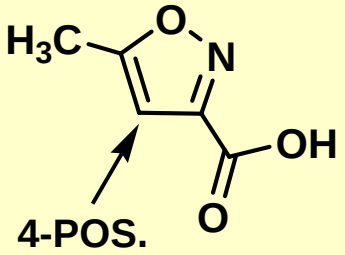
NON-REACTIVE AT RT
POSSIBLE TRACE NITRATON,
60-100°C, 6-10 MIN



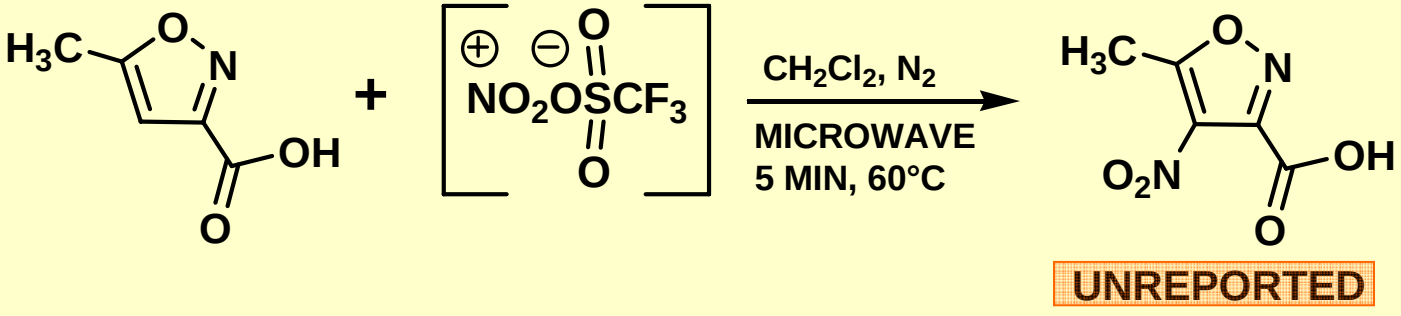
VERY REACTIVE AT RT
NON-REACTIVE AT -78°C
NO NITRATION



VERY REACTIVE AT -78°C
NO NITRATION OBSERVED



SEE BELOW



UNREPORTED

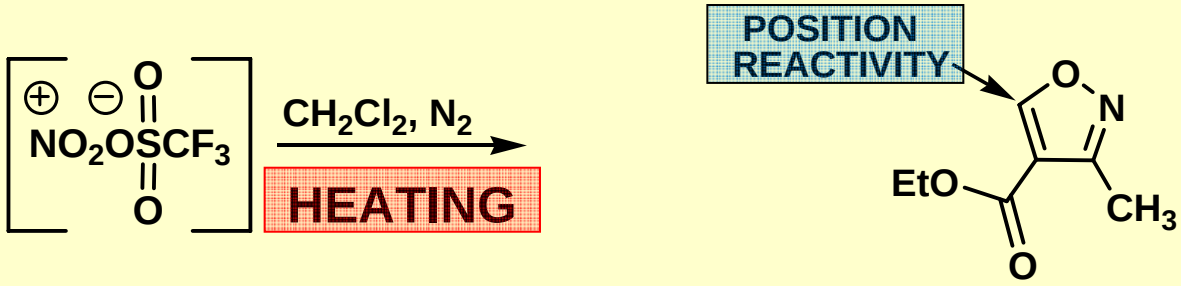
YELLOW SOLID
20+% CRUDE YIELD
NMR PURE

RECRYST. HOT CH_2Cl_2
WHITE SOLID

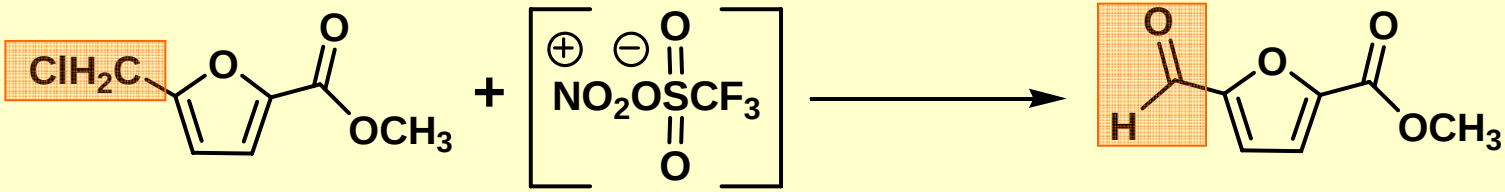
SUMMARY

➢ MICROWAVE-ASSISTED SYNTHESIS A USEFUL TOOL

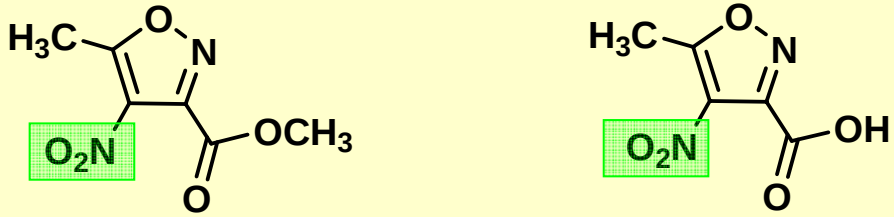
- **SCREENING NITRONIUM TRIFLATE NITRATION SAFETY / REACTIVITY**



- **COMPLETING NEW NITRONIUM TRIFLATE REACTION PATHWAY**



- **OBTAINING NOVEL NITRO-HETEROAROMATICS w. NITRONIUM TRIFLATE**



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