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Elaboration of Aldehydes/Ketones into Homologated α,β -Unsaturated Esters via β -Hydroxy Esters"

Tetrahedron Letters
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(Statement A)

New Application of Bromotrimethylsilane: Elaboration of Aldehydes/Ketones into Homologous α,β -Unsaturated Esters via β -Hydroxy Esters

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Abstract: α,β -unsaturated ester is formed when β -hydroxy-ester is reacted with bromotrimethylsilane generated from chlorotrimethylsilane-lithium bromide in acetonitrile.

The α,β -unsaturated ester is one of the important chemical functionalities that are encountered very commonly in organic synthesis. The standard method of introducing two carbon homologated α,β -unsaturated esters involves Horner-Wadsworth-Emmons¹ (HWE) modification of Wittig-olefination or Peterson-olefination² of aldehyde/ketone.

As a part of synthetic project, the conversion of β -hydroxy-ester to the corresponding β -bromo-ester was required. There is plethora of reagents³ to transform directly/indirectly alcohol into the corresponding bromo- derivative. Bromotrimethylsilane⁴ (TMSBr) was made the reagent of choice for converting hydroxy- ester to bromo- ester because of its weak electrophilicity and its inertness towards dealkylative transformation of esters, ethers, or carbamates under mild condition. Although many methods have been reported for the generation of bromotrimethylsilane, we generated bromotrimethylsilane *in situ* using chlorotrimethylsilane-lithium bromide⁵ (TMSCl-LiBr) in dry acetonitrile. In an effort to convert β -hydroxy-ester to β -bromo-ester using TMSCl-LiBr, we have observed the formation of α,β -unsaturated ester. To the best of our knowledge this type of chemical transformation by TMSBr has not been reported earlier. Herein, we report two-carbon homologation of aldehyde/ketone to α,β -unsaturated esters via β -hydroxy-ester.

To determine the generality of bromotrimethylsilane assisted chemical transformation of β -hydroxy-ester to α,β -unsaturated ester, a number of two-carbon homologated β -hydroxy-ester **8-13** were prepared from corresponding aldehyde/ketone **1-7** (TABLE-1) using lithio-

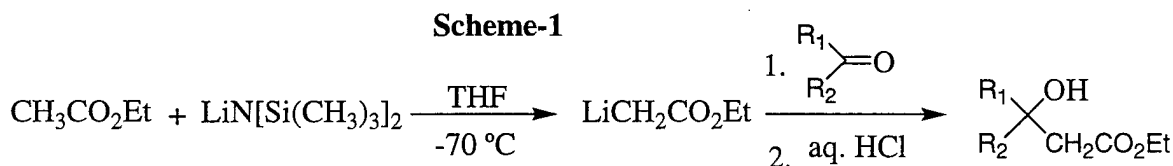


TABLE-1

Aldehyde/ketone	β -Hydroxy Ester (% Yield)	α,β -Unsaturated Ester (% Yield) ^{a,b}
Ph-CHO 1	Ph-CH(OH)CH ₂ CO ₂ Et 8 ⁶ (82)	 15 ⁷ (76) ^a
 2	 9 (92)	 16 ⁷ (73) ^a
 3	 10 ⁶ (76)	 17a (85) ^a 17b (3) ^a
 4	 11 (81)	 18 (84) ^a
 5	 12 (95)	 19 (60) ^a
 6	 13 ⁶ (50)	 20a (29) ^b 20b ⁷ (45) ^b 20c (18) ^b
 7	 14 ⁶ (70)	 21a (45) ^b 21b ⁷ (9) ^b 21c (16) ^b

a: Isolated yield; b: The yield is based on GC-Mass analysis

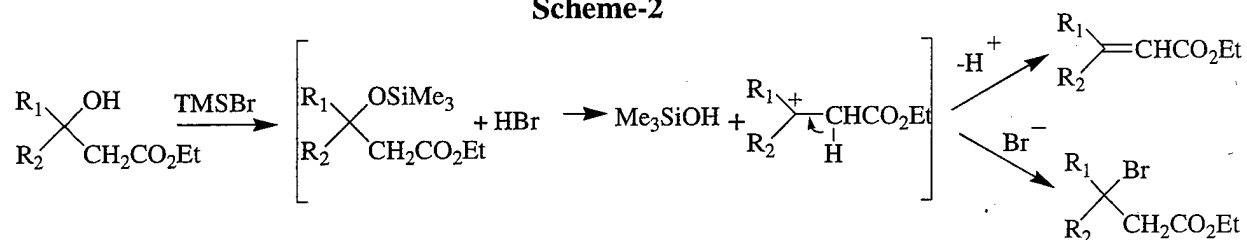
ethylacetate⁶ that is generated by addition of dry ethylacetate to a THF solution of lithium bis-trimethylsilylamide at $-70\text{ }^{\circ}\text{C}$ (**Scheme-1**). Thus, benzaldehyde (**1**), benzophenone (**2**), cinnamaldehyde (**3**), p-methylacetophenone (**4**), norbornan-2-one (**5**), cyclopentanone (**6**), and cycloheptanone (**7**) furnished ethyl-3-hydroxy-3-phenylpropionate (**8**)⁶, ethyl-3-hydroxy-3,3-

diphenylpropionate (**9**), ethyl-3-hydroxy-5-phenyl-pent-4-enoate (**10**)⁶, ethyl-3-hydroxy-2-*p*-tolyl butyrate (**11**), ethyl-(2-hydroxy-bicyclo[2.2.1]hept-2-yl)acetate (**12**), ethyl-(1-hydroxy-cyclopentyl)-acetate (**13**)⁶ and ethyl-(1-hydroxy-cyclohexyl)acetate (**14**)⁶ respectively in respectable yield.

When an acetonitrile solution of chlorotrimethylsilane-lithium bromide was treated with hydroxy esters **8**, **9** and **10**, only ethyl-(*E*)-cinnamate (**15**)⁷ and ethyl-5-phenyl-penta-2(*E*),4(*E*)-dienoate (**16**)⁸ and ethyl-3,3-diphenyl-2-propenoate (**17**)⁷ were formed respectively. Whereas, exposure of **11** to TMSBr furnished separable mixture of ethyl-3-*p*-tolyl-but-2(*E*)-enoate (**18**)⁹. Treatment of 2-ethylacetyl-norbornan-2-ol (**12**) with TMSBr furnished a non-separable (*E/Z*) isomer mixture of ethyl-2-norbornylidene **19**. The presence of isomeric mixture was reflected by the ¹³C NMR data¹⁰ of **19**. The hydroxy ethyl esters **13** & **14** gave mixture of unsaturated esters **20/21** (a-b) and bromo-esters **20/21**(c) respectively. It was observed by GC-mass and ¹³C NMR that the mixture **20/21** (a-c) collapsed to **20/21** (a-b) when refluxed with DBU. It was also observed that the reaction took place at room temperature in case of aromatic hydroxy esters (**8-11**) whereas it required refluxing for aliphatic hydroxy esters (**12-14**).

The chemical transformation can be rationalized by assuming silylation of β -hydroxy ester with TMSBr to furnish alkoxytrimethylsilane that in turn is hydrolyzed by *in situ* generated HBr to yield carbonium ion (Scheme-2). Elimination of proton (H^+) leads to α,β -unsaturated ester and trapping of carbonium ion by a bromo nucleophile (Br^-) furnishes corresponding bromo-compound.

Scheme-2



In conclusion, we have demonstrated a new application of bromotrimethylsilane by converting β -hydroxy ester to α,β -unsaturated esters. The above results illustrate the efficacy of TMSBr reaction with aromatic/aliphatic β -hydroxy esters having secondary and tertiary alcohol

group. This methodology could be an alternative for HWE method for the preparation of two carbon homologated α,β -unsaturated esters from aldehyde/ketone.

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10. ^{13}C NMR (CDCl_3) data of **19**: δ 171.28, 170.14, 167.02, 109.89, 108.92, 59.58, 47.24, 42.98, 41.10, 40.01, 39.46, 39.15, 36.42, 35.59, 32.65, 31.11, 28.82, 28.58, 27.91, 27.73, 14.57.