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A NEW METHOD FOR THE HYDROXYMETHYLATION OF CARBONYL COMPOUNDS

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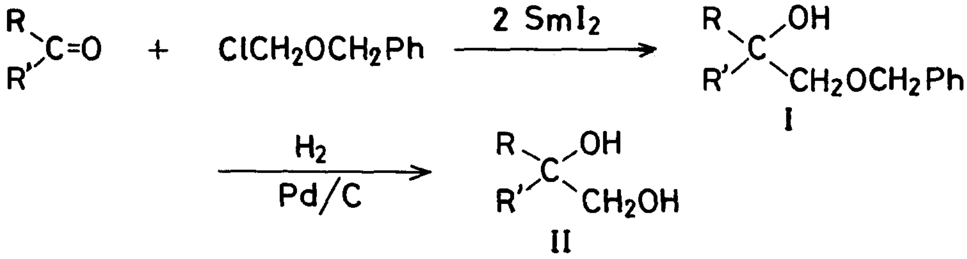
Summary: Benzyl chloromethyl ether reacts with carbonyl compounds in the presence of SmI_2 to afford alcohols (I), which are subsequently subjected to hydrogenolysis to yield diols (II).

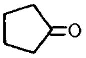
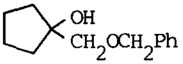
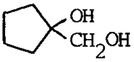
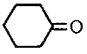
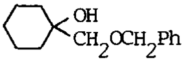
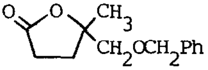
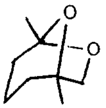
The nucleophilic hydroxymethylation is of potential utility in synthetic organic chemistry and several methods have been devised, particularly for the substitution of halogen atom of vinylic or alkyl halides for hydroxymethyl group.1) However, the hydroxymethylation of carbonyl group has only been described in a few papers.2,3) We report herein a new approach for the hydroxymethylation of carbonyl compounds. The overall sequence is shown as follows:



Our first trial was conducted with the reaction of simple aliphatic ketones (1 mmol) with benzyl chloromethyl ether (1.1 mmol) in the presence of $SmI_2$4) (3 mmol) in tetrahydrofuran (THF). The reaction proceeded rapidly at room temperature, and the addition products (I) were isolated in good yields.5) However, the reaction of aldehydes resulted in the formation of pinacols in 80-90% yields rather than expected alcohols.6) These pinacol formations could be suppressed by the prior addition of an equimolar amount of tetraethylene glycol dimethyl ether to the reagent SmI_2 solution,7,8) and the adducts (I) were produced in moderate yields. Next, some of the products (I) were subjected to hydrogenolysis on Pd/C, and the desired diols (II) were obtained. The results are summarized in Table 1.

It is noted that, frontalin, a pheromone of Dendroctonus bark beetles, was prepared via a short route from 2,6-heptadione.9) Another feature is that readily enolizable 1,3-diphenyl-2-propanone was hydroxymethylated in satisfactory yield by this procedure. This method may be useful for organic synthesis, particularly for the syntheses of natural products.

Table 1. Hydroxymethylation of Carbonyl Compounds

RCOR'	Conditions[a]	Product (I) (Yield, %)[b]	Product (II) (Yield, %)[b]
$(PhCH_2)_2CO$	2 h	$(PhCH_2)_2C(OH)CH_2OCH_2Ph$ (87)	$(PhCH_2)_2C(OH)CH_2OH$ (96)
$n\text{-}C_6H_{13}COCH_3$	2 h	$n\text{-}C_6H_{13}C(OH)(CH_3)CH_2OCH_2Ph$ (84)	
	1 h	 (57)	 (95)
	1 h	 (75)	
$Cl(CH_2)_3COCH_3$	1 h	$Cl(CH_2)_3C(OH)(CH_3)CH_2OCH_2Ph$ (82)	
$CH_3CO(CH_2)_2COOCH_3$	1 h	 (53)	
$CH_3CO(CH_2)_3COCH_3$	4 h[c]	$CH_3CO(CH_2)_3C(OH)(CH_3)CH_2OCH_2Ph$ (56)	 (91)
$n\text{-}C_3H_7CHO$	1 h[d,e]	$n\text{-}C_3H_7CHOHCH_2OCH_2Ph$ (46)	
$PhCH_2CH_2CHO$	1 h[f]	$PhCH_2CH_2CHOHCH_2OCH_2Ph$ (66)	$PhCH_2CH_2CHOHCH_2OH$ (90)

a) All reactions were carried out at room temperature unless otherwise stated. b) Isolated yield. c) At 0 °C. d) Benzyl iodomethyl ether was used in place of benzyl chloromethyl ether. e) The reaction was carried out in the presence of tetraethylene glycol dimethyl ether. f) The reaction was carried out in the presence of tetraethylene glycol dibenzyl ether.

References and Notes

1) K. Tamao, N. Ishida, and M. Kumada, J. Org. Chem., 48, 2120 (1983), and references cited therein. 2) N. Meyer and D. Seebach, Chem. Ber., 113, 1290 (1980). 3) P. Beak and B. G. McKinnie, J. Am. Chem. Soc., 99, 5213 (1977). 4) Samarium diiodide, which is conveniently generated by the reaction of samarium metal with 1,2-diiodoethane in THF, is a useful one-electron transfer reagent; P. Girard, J. L. Namy, and H. B. Kagan, J. Am. Chem. Soc., 102, 2693 (1980); H. B. Kagan, J. L. Namy, and P. Girard, Tetrahedron Supplement, 37, 175 (1981). 5) Chloromethyl methyl ether and chloromethyl methoxyethyl ether also reacted with simple ketones in the presence of SmI_2 to give the corresponding products in good yields. 6) Divalent samarium-induced pinacolic coupling of carbonyl compounds has been reported; J. Souppe, L. Danon, J. L. Namy, and H. B. Kagan, J. Organomet. Chem., 250, 227 (1983). 7) When tetraethylene glycol dimethyl ether was added to the solution of SmI_2 in THF, the characteristic green color immediately turned to purple. 8) These results can be explained by assuming the complex formation of SmI_2 with tetraethylene glycol dimethyl ether. The complex still displays strong reducing power but has less affinity for carbonyl oxygen, and thus pinacol coupling is suppressed. 9) The syntheses of frontalin including asymmetric synthesis have been reported; Y. Sakito and T. Mukaiyama, Chem. Lett., 1979, 1027, and references cited therein.

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