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A NEW ALDOL REACTION: A METHOD FOR THE GENERATION OF VINYLOXYBORANES BY THE ACYLATION OF BORON-STABILIZED CARBANIONS

Teruaki MUKAIYAMA, Masahiro MURAKAMI, Takeshi ORIYAMA,
and Masahiko YAMAGUCHI
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Phenyl-substituted vinyloxyboranes are generated by the acylation of boron-stabilized carbanions with methyl benzoate. Vinyloxyboranes thus generated further react with aldehydes to give the corresponding cross-aldols in good yields.

Recently, much attention has been focussed on the cross-aldol reaction,1),2) one of the most useful means for the stereoselective construction of acyclic compounds containing multiple chiral centers. It is demonstrated that an excellent diastereoselection can be attained in the formation of erythro and threo aldols by the utilization of vinyloxyboranes.2) Concerning the generation of vinyloxyboranes, several methods have been reported; namely a) using trialkylboranes and diazoketones;3) b) a 1,4-addition of trialkylboranes to α,β-unsaturated ketones;4) c) an addition of dialkylalkylthioboranes to ketene;5) d) from ketones and trialkylboranes using diethylboryl pivalate as a catalyst;6) e) using dialkylboryl triflates, ketones, and tertiary amines;7) f) from silyl enol ethers and dialkylboryltriflate.8) However, it still seems quite valuable to develop a new method for the generation of vinyloxyboranes, a key intermediate for the aldol reaction.

Now we wish to report a novel and useful procedure for the generation of phenyl-substituted vinyloxyboranes ($\underline{7}$) by the acylation of boron-stabilized carbanions ($\underline{4}$), prepared from 1-alkynes ($\underline{1}$), with methyl benzoate and its application to the cross-aldol reaction.

It is known that the treatment of 1,1-diborylalkanes ($\underline{2}$) easily prepared by the dihydroboration of 1-alkynes ($\underline{1}$), with alkyllithium affords boron-stabilized carbanions ($\underline{4}$) and that they further react with appropriate electrophiles such as alkyl halides and aldehydes giving alcohols and olefins respectively.9) We assumed that the reaction of boron-stabilized carbanions ($\underline{4}$) with acylating reagents would give α-borylketones ($\underline{6}$) which immediately isomerise to form vinyloxyboranes ($\underline{7}$). Based on the consideration, 1-hexyne was treated with 9-borabicyclo-[3,3,1]nonane (9-BBN) and methyllithium, and the resulting boron-stabilized carbanion was allowed to react with various benzoic acid derivatives. The desired product, 1-phenyl-1-heptanone, was isolated in yields varying from 20 to 50% after the usual workup. When reactive acylating reagents such as benzoyl chloride, benzoic anhydride, and S-(2-pyridyl)benzenecarbothioate were used, the formation of a considerable amount of the enol ester, resulting from O-acylation of the vinyloxyborane (7), was observed by IR. Contrary to these results, when methyl benzoate was employed, the pure sample of the ketone was obtained and the enol ester was not detected. A further screening of the reaction conditions using methyl benzoate as an acylating reagent revealed that the temporary evaporation of the solvent after treatment of 1-hexyne with 9-BBN raised the yield of the ketone to 73%. In addition, it was found that the utilization of 2.5 equivalents of methyllithium to 1-alkyne (1) gave the best result as shown in Table I.[10)] The tertiary alcohol, resulting from the addition of the nucleophile (4) to the α-borylketone (6), was not detected.

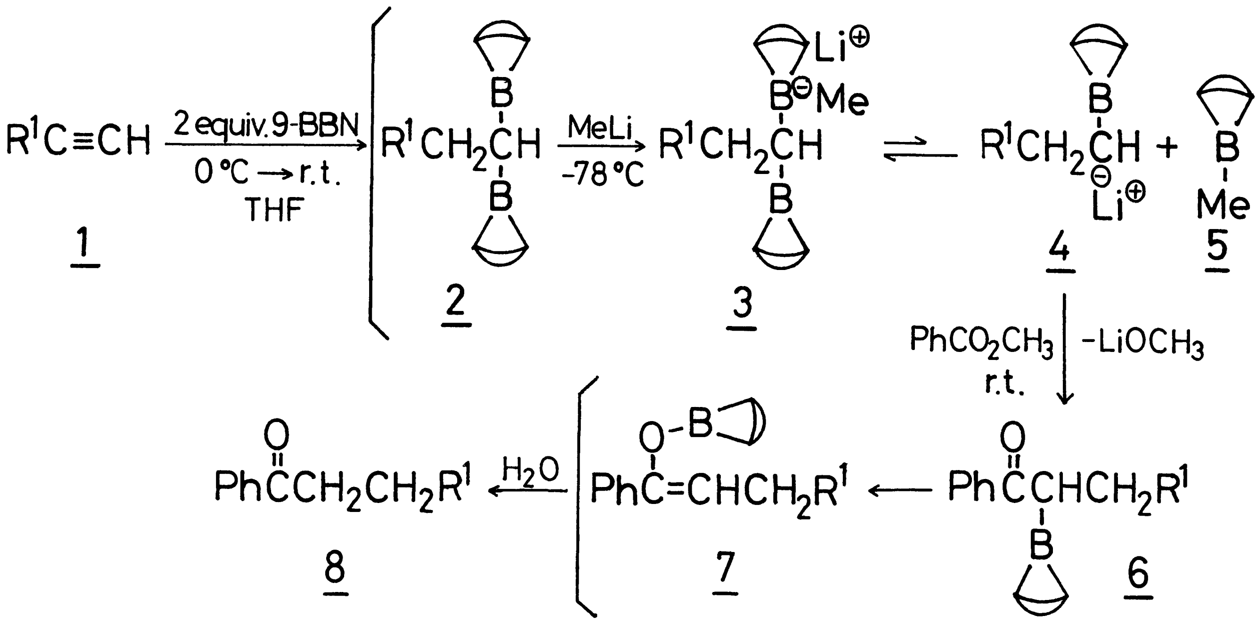

Table I. Synthesis of Ketones

R	Molar ratio of MeLi per 1	Yield of 8 (%)[1)]
n-C_5H_{11}	1.0	72
	2.0	80
	2.5	93
	3.0	80
n-C_4H_9	1.2	73
	2.5	83
n-C_6H_{13}	2.5	93

1) Yields were based on methyl benzoate. All compounds gave satisfactory spectral data (NMR and IR).

Next, a synthesis of cross-aldols (9) was attempted by the treatment of the vinyloxyboranes (7), generated in situ as mentioned above, with aldehydes. The corresponding cross-aldols (9) were obtained in good yields[11)] as summarized in Table II. A small amount of ketones (8), resulting from the hydrolysis of vinyloxyboranes (7), was isolated along with the cross-aldols (9). It was also found that threo isomer (9b) was predominantly formed when benzaldehyde was used (entry 1,2,4). But low diastereoselectivity was observed in the cases of propanal and 3-phenylpropanal (entry 3,5).

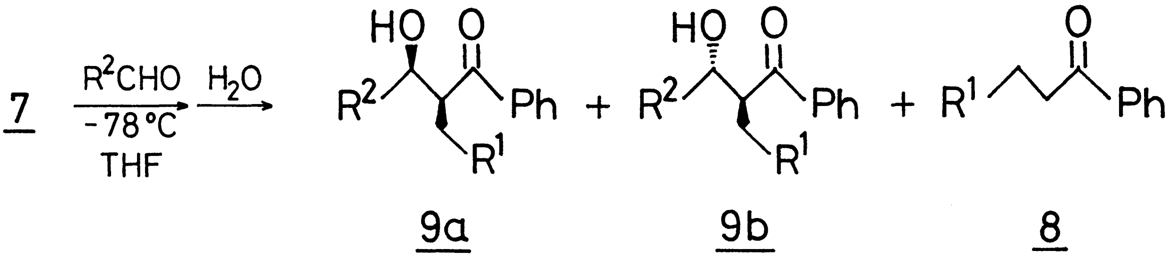

Table II. Cross-aldol Reaction

Entry	R^1	R^2	Yield of 9 (%)[1]	9a : 9b[2]	Yield of 8 (%)[1]
1	n-C_4H_9	Ph	86	22 : 78[3]	5
2	n-C_5H_{11}	Ph	80	16 : 84[3]	4
3	n-C_5H_{11}	Et	80	40 : 60[4]	9
4	n-C_6H_{13}	Ph	85	20 : 80[3]	14
5	n-C_6H_{13}	Ph$(CH_2)_2$	77	46 : 54[4]	10

1) Yields were based on methyl benzoate. All compounds gave satisfactory spectral data (NMR and IR).

2) The ratio was determined by HPLC analysis.

3) The configurational assignment was based on the NMR spectra.

4) The configurational assignment is tentative.

A typical procedure is described for the synthesis of 2-hydroxyphenylmethyl-1-phenyl-1-nonanone: To a tetrahydrofuran (THF, 1 ml) solution of 1-octyne (67 mg, 0.61 mmol) was added a THF (2.4 ml) solution of 9-BBN (1.2 mmol) at 0°C under argon atmosphere, and the mixture was stirred for 3 h at room temperature for the completion of the dihydroboration. Then the solvent was evaporated under reduced pressure and to the resulting viscous oil was again added 1 ml of THF. Next, an ether (0.89 ml) solution of methyllithium (1.5 mmol) was added at -78 °C, and after 10 min the temperature was allowed to warm up to room temperature. The boron-stabilized carbanion thus obtained was treated with a THF (1 ml) solution of methyl benzoate (55 mg, 0.41 mmol), and the pale yellow solution was stirred for 3 h at room temperature. Finally the aldol reaction was performed by the addition of a THF (1 ml) solution of benzaldehyde (48 mg, 0.45 mmol) at -78 °C and the continuous stirring for 22 h at that temperature. The reaction was quenched by the addition of phosphate buffer solution (pH 7, 3 ml), methanol (7 ml), and 28% H_2O_2 (2 ml). After stirring for 30 min at room temperature, the mixture was concentrated under reduced pressure in order to remove most of methanol, and the organic materials were extracted with ether. The ethereal layer was sequentially washed with water and a saturated solution of NaCl, and dried over $MgSO_4$. 2-Hydroxyphenylmethyl-1-phenyl-1-nonanone (112 mg, 85%) and 1-phenyl-1-nonanone (13 mg, 14%) were isolated by thin layer chromatography (silica gel). NMR(CCl_4)

δ 0.6-1.9 (15H, m), 2.9-3.3 (1H, m), 3.3-3.8 (1H, m), 4.71 and 4.80 (1H, d, J=8 Hz and 5 Hz respectively), 6.9-7.4 (8H, m), 7.6-7.9 (2H, m); IR (neat) 3460, 1675, 760, 700 cm^{-1}.

It should be noted that phenyl-substituted vinyloxyboranes (7) generated by the acylation of boron-stabilized carbanions (4) with methyl benzoate, reacted with aldehydes to afford cross-aldols (9) in good yields. The present method provides a novel one-pot procedure for the cross-aldol reaction consisted of two continuous carbon-carbon bond-formations.

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9) a) G. Cainelli, G. D. Bello, G. Zubiani, Tetrahedron Lett., 1965, 3429, 1966, 4315; b) G. Zweifel and H. Arzoumanian, ibid., 1966, 2535; c) G. Zweifel, R. P. Fisher, and A. Horng, Synthesis, 1973, 37; d) H. C. Brown and S. P. Rhodes, J. Am. Chem. Soc., 91, 4306 (1969).

10) It seemed that two equivalents of methyllithium were sufficient for the completion of the reaction. However, after screening of the various reaction conditions, it was shown that the utilization of 2.5 equivalents of methyllithium gave the maximum yield.

11) When ethyl propionate was used as an acylating reagent, the desired cross-aldol was obtained in only a 10% yield and the β-hydroxyester formed by the reaction of the enol borinate of the ester and an aldehyde was isolated in a 34% yield. In this case, the enolization of the ester proceeded prior to the nucleophilic addition of the boron-stabilized carbanion.

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