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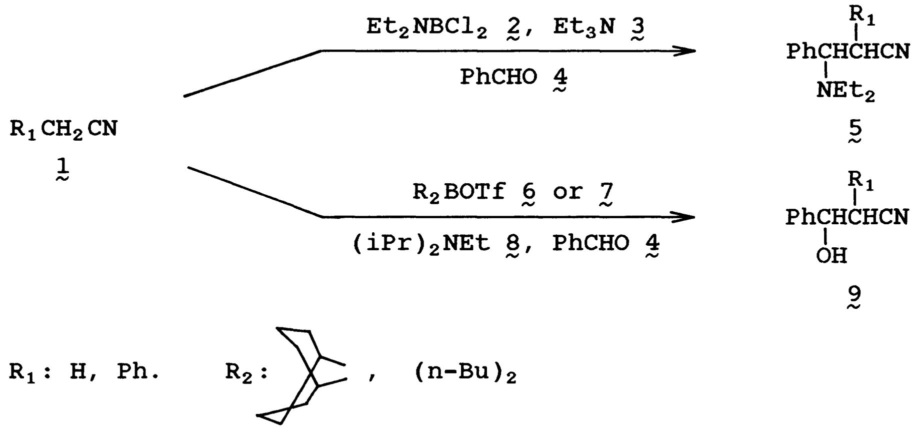
AN ALDOL-TYPE REACTION OF ACETONITRILES USING DIALKYLBORYL TRIFLATE

Hiroshi HAMANA* and Tsutomu SUGASAWA
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553

Acetonitriles and benzaldehydes react in the presence of dialkyl boryl triflate and diisopropylethylamine in dichloromethane to give the corresponding aldol-type products in good yields under mild conditions.

In general, aldol-type reactions of acetonitriles 1 proceed only in the presence of strong base such as alkyl lithium or alkali amide at low temperature.[1)] We previously reported that much milder reactions condition using diethylaminodichloroborane 2 and triethylamine 3 in dichloromethane make possible an aldol-type condensation of 1 and benzaldehydes 4 with unexpected introduction of the diethylamino group, giving 3-phenyl-3-diethylaminopropionitriles 5.[2)]

We report here the use of 9-BBN triflate 6 or di-n-butylboryl triflate 7[3)] and diisopropylethylamine 8 instead of 2 and 3 to obtain the desired aldol product, 3-phenyl-3-hydroxypropionitriles 9.

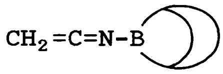


A solution of 6 and 1 (R_1 = H) (1:1.2) in dichloromethane was treated with 4 and 8 (1:1) at -20°C for 6 h under a stream of argon. Work-up by addition of pH 7 phosphate buffer, methanol and 30% H_2O_2 followed by purification with SiO_2-chromatography gave 9 (R_1 = H)$^{1)}$ in 58% yield (Run 1).

Investigation of the reaction conditions showed that those for Runs 3 to 8 in the table (ca. 40-fold excess of 1 in molar ratio, -78°C, 20 h) gave the preferable results. Use of 7 instead of 6 gave better results without a large excess of 1 as shown for Runs 9 to 17. Use of 7 made possible a preferable work-up, because the product containing the di-n-butylboryl moiety decomposed more easily than that derived from 6. Attempts to apply this reaction to aliphatic aldehyde were less satisfactory, giving the aldol product in moderate yield (Run 15).

Use of ether, tetrahydrofurane or dimethoxyethane as solvent and triethylamine or lutidine instead of 8 as base did not give favorable results.

As described above, the use of dialkylboryl triflate 6 or 7 with diisopropylethylamine 8 made possible the aldol-type reaction of acetonitriles 1 with mainly benzaldehydes 4 under very mild conditions. But the reaction species remains unclear,$^{2)}$ because in an ethereal solution of 1 (R_1 = H), 6 and 8, reasonable ^{1}H-NMR signals for the expected reaction species like 10 were not observed after removal of the diisopropylethylammonium triflate.



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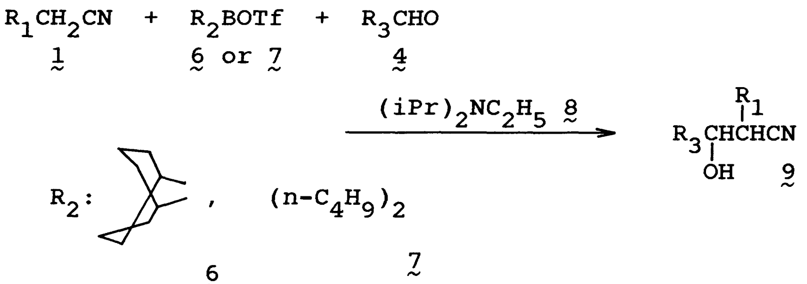
The following is a typical procedure. To a solution of acetonitriles (2 mmol) in dichloromethane (2 mL), di-n-butylboryl triflate (2 mmol) was added at -78°C under argon. After the solution was stirred for 30 min, a solution of benzaldehydes (1 mmol) and diisopropylethylamine (1.2 mmol) in dichloromethane (2 mL) was added and the mixture was stirred at -78°C for 20 h. Next, pH 7 phosphate buffer (6 mL) was added and the mixture was warmed up to 0°C under stirring. The organic layer was separated and the water layer was extracted with dichloromethane. The combined dichloromethane extract was stirred with 30% H_2O_2 (2 mL) in methanol (6 mL) at room temperature for 2 h. After evaporation of methanol under reduced pressure, the mixture was extracted with ether. The ether phase was washed successively with 5% $NaHCO_3$ and H_2O and the combined ether layer was dried ($MgSO_4$) and concentrated. The residue was purified by chromatography ($SiO_2$60, Pre-packed column A, Merck A.G.; benzene:ethyl acetate, 10:1).

Aldol-type Reaction of Acetonitriles with Aldehydes



$$\underset{\mathbf{1}}{R_1CH_2CN} + \underset{\mathbf{6}\ \text{or}\ \mathbf{7}}{R_2BOTf} + \underset{\mathbf{4}}{R_3CHO} \xrightarrow{(iPr)_2NC_2H_5\ \mathbf{8}} \underset{\mathbf{9}}{R_3\underset{OH}{C}H\overset{R_1}{C}HCN}$$

R_2: 6, $(n\text{-}C_4H_9)_2$ 7

Run	R_1	R_2BOTf	R_3	% yield of 9[a]
1	H	6	Ph	$58^{b)}$
2	H	6	Ph	$75^{c)}(14)^{d)}$
3	H	6	Ph	$82^{e)}\ (6)^{d)}$
4	H	6	p-NO_2-Ph	$54^{e,f)}$
5	H	6	p-CH_3O-Ph	$79^{e)}$
6	H	6	p-Cl-Ph	$91^{e)}$
7	H	6	o-Cl-Ph	$88^{e)}$
8	H	6	Ph-CH=CH-	$80^{e)}\ (20)^{g)}$
9	H	7	Ph	90
10	H	7	p-CH_3-Ph	83
11	H	7	p-CH_3O-Ph	53
12	H	7	p-$(CH_3)_2N$-Ph	32
13	H	7	o-Cl-Ph	66
14	H	7	m-Cl-Ph	55
15	H	7	C_2H_5	35
16	Ph	7	Ph	$100^{h)}$
17	CH_3CH=CH-	7	Ph	$82^{i)}$
18	CH_3	7	Ph	$90^{j)}$

a) Isolated yield based on aldehydes used. All products were oily, except that of Run 4, and their IR, NMR and mass spectra showed reasonable data for the structures assigned.

b) A solution containing 1 (2.4 mmol), 6 (2 mmol), 4 (2 mmol) and 8 (2 mmol) in dichloromethane (4 mL) was treated in the typical procedure and work-up (see text) analogous to those for Run 9 to 17. Changes involved stirring for 6 hr at -20°C.

c) A 4 molar excess of 1 was used and the reaction was carried out analogously to that in Run 1.

d) Yield of diastereoisomeric mixture of $(PhCHOH)_2CHCN$.

e) A 40 molar excess of 1 was used and the reaction was carried out at -78°C for 20 hr instead of 20° and 6 hr in Run 1.

f) Mp 119-121° (i-PrOH); $C_9H_8NO_3$ (C, H, N).

g) Crude yield of the diastereoisomeric mixture of

$(PhCH{=}CHCHOH)_2CHCN$.

h) Yield of the diastereoisomeric mixture, erythro-/threo-isomer = 1.

i) Yield of $PhCHOHCH_2CH{=}CHCN$.

j) A 40 molar excess of C_2H_5CN was used and the reaction was carried out as described in the typical procedure. Yield of the diastereoisomeric mixture, erythro-/threo-isomer = 1.

References

1) E. M. Kaiser and C. R. Hauser, J. Org. Chem., 33, 3402 (1968).

2) T. Sugasawa and T. Toyoda, Synth. Commun., 9, 553 (1979).

3) T. Inoue, T. Uchimaru and T. Mukaiyama, Chem. Lett., 1977, 153.

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