CHEMISTRY LETTERS, pp. 333-336, 1983. © The Chemical Society of Japan 1983

AN ALDOL-TYPE REACTION OF ACTIVE METHYL GROUPS OF NITROGEN-CONTAINING HETEROAROMATIC COMPOUNDS

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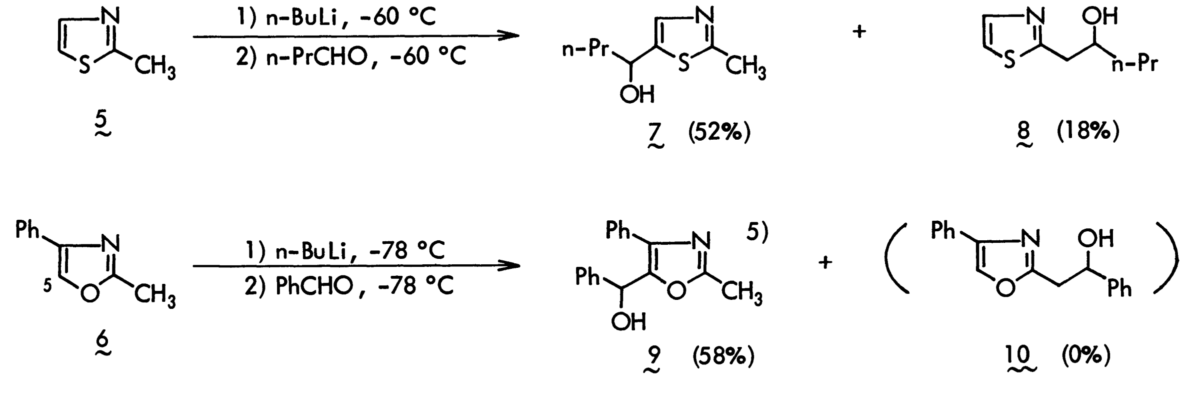
Active methyl groups of nitrogen-containing heteroaromatic compounds react with benzaldehydes in the presence of 9-BBN triflate and diisopropylethylamine in dichloromethane to give the corresponding aldol-type products under mild conditions.

Aldol-type reactions of "active methyl groups" of nitrogen-containing six-membered heteroaromatic compounds such as 2-picoline **1** with benzaldehyde **2** proceed by heating with water in sealed tubes at 140 °C1) or in the presence of strong base like organolithium compounds,2) giving 2-methylpyridylphenyl carbinols **4**. Furthermore, since metalation of five-membered heteroaromatic compounds such as 2-methylthiazol **5**3) and 2-methyl-4-phenyloxazole **6**4) with n-butyllithium proceed predominantly at the C-5 position, corresponding aldol-type products like **8** and **10** are difficult to obtain under these conditions (Scheme). We report here the reaction of these active methyl groups of hetero-

Scheme

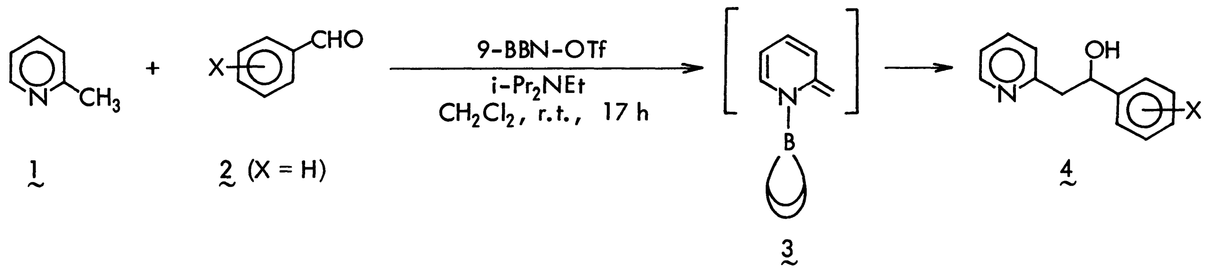


aromatic compounds with benzaldehydes in the presence of 9-BBN triflate[6)] and diisopropylethylamine in dichloromethane to give the corresponding aldol products.

In the typical procedure for the reaction of 2-picoline **1** and benzaldehyde **2**, 9-BBN triflate (1.0 mmol) and a solution of **2** (1.0 mmol) in dichloromethane (2.0 ml) containing diisopropylethylamine (1.2 mmol) were added successively to a stirred solution of **1** (1.0 mmol) in dichloromethane (2.0 ml) at -78 °C under argon. After the solution had been stirred at 20 °C 17 h, pH 7 phosphate buffer (3.0 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 (1.0 ml) in methanol (3.0 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 saturated brine, and the 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) giving 2-methylpyridylphenyl carbinol **4**, X = H, (78%).

Details of the reaction of **1** with benzaldehydes are given in Table 1. Benzaldehydes having electron-withdrawing groups gave better yields (Runs 2 to 5) than those having electron-donating groups (Runs 6 to 8). Similar reactions of active methyl groups of various nitrogen-containing heteroaromatic compounds with **2** were carried out as shown in Table 2. The sharp contrast between Runs 2 and 3 may be attributable to apparent double bond fixation[7)] of the starting materials. The clear distinction from the reaction using strong base arises with 2-methylthiazol **5** and 2-methyl-4-phenyloxazole **6** (Runs 4 and 5). Namely, whereas the reactions of **5** and **6** with **2** in the presence of n-butyllithium occur predominantly at the C-5 position, those of **5** and **6** with **2** using 9-BBN triflate and diisopropylethylamine occur exclusively at the 2-methyl groups to give aldol-type products such as **8** and **10** (Scheme). The results of the reactions of six-membered heteroaromatic compounds containing two nitrogens with benzaldehyde **2** are described in Runs 8 to 10. In this series, 2 mol equivalents of 9-BBN triflate is necessary to complete the reaction. In the case of 3-methylpyridazine, the negative result may be due to the steric hindrance of the 3-methyl group and alkyl substituents of 9-BBN triflate first attached to the N-1 position.

Table 1. Aldol-type Reaction of 2-Picoline with Benzaldehydes[a)]

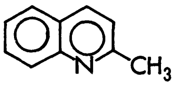
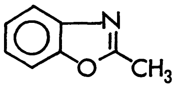
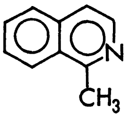
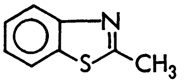
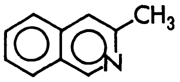
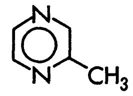
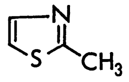
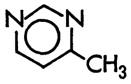
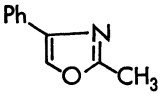
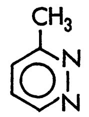


1 2 (X = H) 3 4

Run	X	Yield (%)	Mp (°C)	Run	X	Yield (%)	Mp (°C)
1	H	78	110	5	p-Cl	61	135
2	p-NO_2	54	168	6	p-CH_3	51	93
3	o-Cl	85	95.5[b)]	7	p-OCH_3	14	103
4	m-Cl	69	102	8	p-$N(CH_3)_2$	0	

a) All products exhibited spectral data and elementary analysis in accord with the assigned structures. b) Mp of p-nitrobenzoyl derivative.

Table 2. Aldol-type Reaction of Nitrogen-Containing Heteroaromatics with Benzaldehyde[a)]

Run	Heteroaromatic	Yield (%)	Mp (°C)	Run	Heteroaromatic	Yield (%)	Mp (°C)
1		88[b)]	127	6		85	161
2		79	113	7		83	155
3		0		8		54[d,e)]	89
4		77	104[c)]	9		89[d)]	91
5		70	112.5	10		0	

a) All products exhibited spectral data and elementary analysis in accord with the assigned structures. b) Contained the dehydrated aldol (15%). c) Mp of p-nitrobenzoyl derivative. d) 2 mol equivalent of 9-BBN-OTf was used. e) Contained the dehydrated aldol (59%).

In summary, our method offers an aldol-type reaction of active methyl groups of nitrogen-containing heteroaromatic compounds with benzaldehydes which proceeds under very mild conditions, although the reaction intermediate including the aminoboran moiety like 3 could not be verified spectrometrically or by isolation. Attempt to apply this reaction to aliphatic aldehyde or ketone was unsuccessful.

References

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(Received December 21, 1982)