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STEREO- AND REGIO-SELECTIVE ALDOL-TYPE REACTIONS OF ALKYLPYRIDINES WITH BENZALDEHYDE

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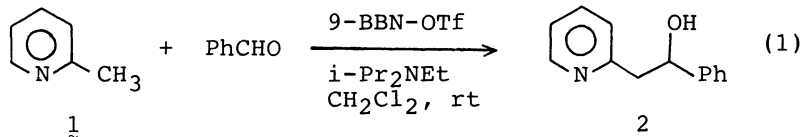
Stereo- and regio-selectivity in the reaction of alkylpyridines with benzaldehyde were studied. Erythro-selectivity could be obtained in the reaction of 2-alkylpyridine with benzaldehyde in the presence of dialkylboryl triflate and triethylamine. Substitution at the 2- or 4-position of 2,4-lutidine could be controlled by the combination of dialkylboryl triflate and an aliphatic tertiary amine. The steric effect had an important role in the reaction of 4-picoline and lepidine.

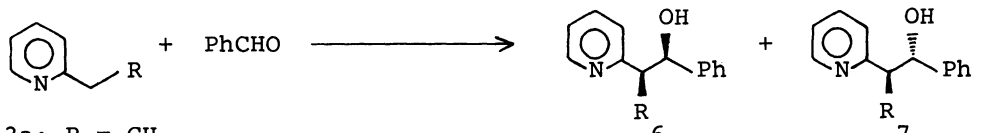
Recently, we reported an aldol-type reaction of α-active methyl groups of nitrogen-containing heteroaromatic compounds with benzaldehydes in the presence of 9-BBN triflate and diisopropylethylamine[1] (Eq. 1). This time we wish to report investigations on the stereo-selectivity of 2-alkylpyridine (3a and 3b) and the regio-selectivity of 2,4-lutidine 8 with benzaldehyde. The procedure was similar to that reported for the reaction of 2-picoline 1 with benzaldehyde.[1]



1 2 (1)

The erythro-selectivity obtained in the reaction of 3a and 3b with benzaldehyde when dialkylboryl triflate was used with triethylamine instead of LDA (Table 1) suggests that the reaction proceeds through the chairlike transition state proposed for the aldol reaction.[2] When diisopropylethylamine, as in the

Table 1.



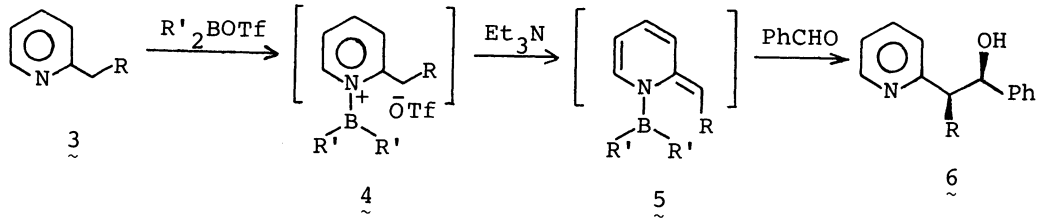
3a: R = CH_3
b: R = C_6H_5

6 erythro 7 threo

Run	R	Reaction conditions	Yield/%	6/7[a]
1	CH_3	i) LDA/THF/-78 °C → rt ii) PhCHO/-78 °C → rt	78	26:74
2	CH_3	i) n-Bu_2BOTf/CH_2Cl_2/-78 °C ii) PhCHO, Et_3N/rt, 17 h	50	94:6
3	CH_3	i) 9-BBN-OTf/CH_2Cl_2/-78 °C ii) PhCHO, Et_3N/rt, 17 h	76	84:16
4	C_6H_5	i) LDA/THF/-78 °C → rt ii) PhCHO/-78 °C → rt	84	77:23
5	C_6H_5	i) 9-BBN-OTf/CH_2Cl_2/-78 °C ii) PhCHO, Et_3N/rt, 17 h	66	100:0

a) Products were isolated by chromatography (SiO_2,60-Pre-packed column A. Merk A. G.: benzene:ethyl acetate = 10:1) and identified by IR and NMR spectra and elemental analysis.[6,7]

reaction of 2-picoline 1,[1] was used instead of triethylamine, the reaction scarcely proceeded and the starting material was recovered. These findings indicate that the steric effect plays an important role in the deprotonation process from the ate complex 4 and 4 reacts with benzaldehyde perhaps via the Z-form 5 to give the erythroisomer (Eq. 2).

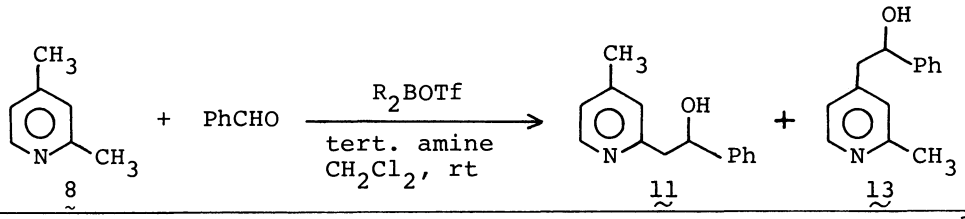


3 4 5 6 (2)

In the reaction of 2,4-lutidine 8, we expected an exclusive reaction of the 2-methyl group of 8, since neither diisopropylethylamine nor triethylamine could deprotonate the 4-methyl group of 4-picoline 14 in the presence of 9-BBN triflate (Eq. 4). Surprisingly, however, regio-selective reaction of the 2- or 4-methyl group of 8 occurred when a combination of dialkylboryl triflate and aliphatic tertiary amine was properly selected. Nemely, in the presence of di-n-butylboryl triflate and triethylamine, the 2-methyl group of 8 excusively reacted with benzaldehyde giving compound 11.[3] In contrast, with 9-BBN triflate and diiso-

propylethylamine, the reaction took place only at the 4-methyl group probably via the linear transition state, giving compound 13[4] (Table 2). The reason for this

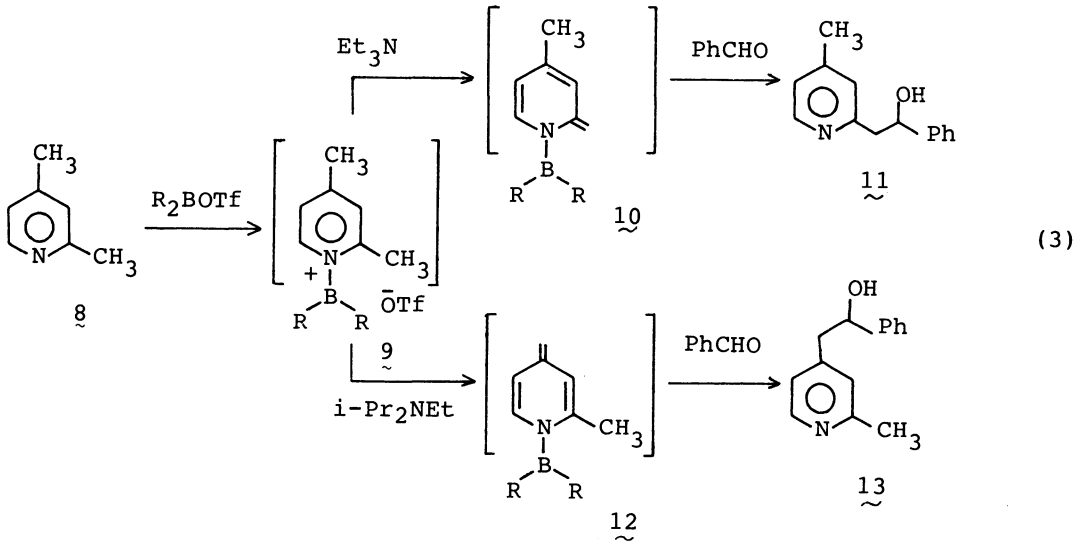
Table 2.



Run	R_2BOTf	Tert. amine	Yield/%	11/13[a]
1	n-Bu_2BOTf	Et_3N	68	100:0
2	"	i-Pr_2NEt	53	23:77
3	9-BBN-OTf	Et_3N	47	64:36
4	"	i-Pr_2NEt	73	0:100

a)Products were isolated by chromatography (SiO_2, 60-Pre-packed column A. Merck A. G.: gradient system benzene to ethyl acetate).

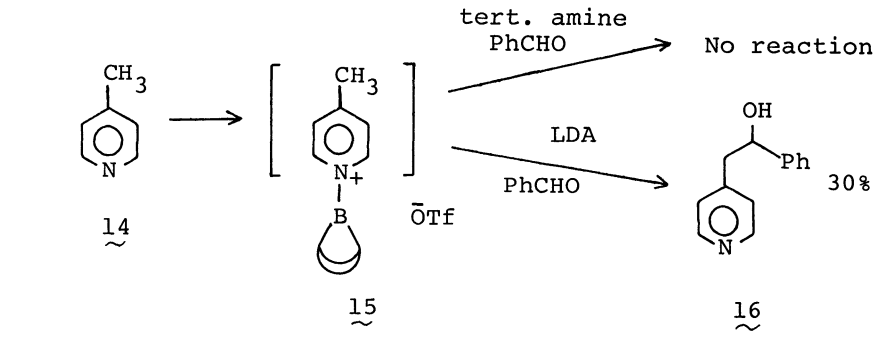
sharp difference has not been fully elucidated. It may be due to the fact that the selection of deprotonation from the 2- or 4-methyl group is delicately influenced by the mutual bulkiness of attacking tertiary amine and R group attached to the boron. Triethylamine tends to deprotonate the 2-methyl group, while diisopropylethylamine preferentially deprotonate the 4-methyl group (Eq. 3). This

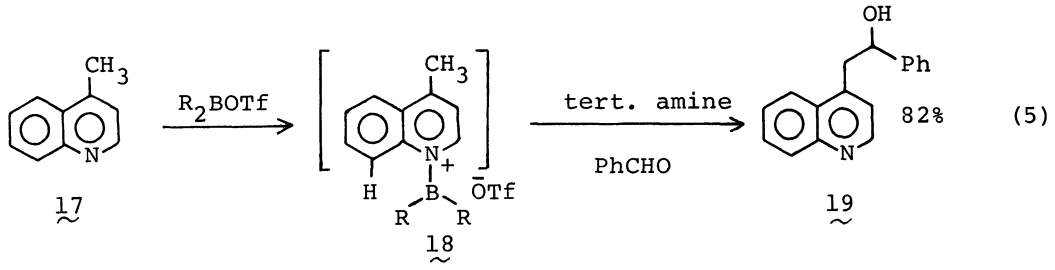


(3)

finding and the results shown in Eq. 4 suggests that the 2-methyl group may enhance the reactivity of the 4-methyl group by causing instability of the borate 9.

Similar treatment of lepidine 17 smoothly gave the corresponding product 19





(Eq. 5) unlike the case of 4-picoline 14. This difference may have arisen because compound 14 formed the completely stable borate 15, which was inert to the aliphatic tertiary amine. Even treatment of 15 with LDA and benzaldehyde gave the product 16 in only 30% yield (Eq. 4). In contrast, the borate 18 was comparatively unstable due to the steric influence of the 8-proton (peri position) and gave the product in the presence of aliphatic amine and benzaldehyde.

References

1) H. Hamana and T. Sugasawa, Chem. Lett., 1983, 333.
2) D. A. Evans, J. V. Nelson, and T. R. Taber, Topics in Stereochemistry, 13, 1 (1982); T. Mukaiyama, Org. Reac., 28, 203 (1982).
3) A. D. Cale, Jr., R. W. McGinis, Jr., and P. C. Teague, J. Org. Chem., 25, 1507 (1960).
4) Compound 13 was prepared by the method of E. M. Kaiser[5] and identified by comparison with spectral data.
5) E. M. Kaiser, G. J. Bartling, W. R. Thomas, S. B. Nichols, and D. R. Nash, J. Org. Chem., 38, 71 (1973).
6) 6a; mp 109-110 °C (p-nitrobenzoyl deriv.): 7a; mp 100-101 °C (p-nitrobenzoyl deriv.): 6b mp 123 °C: 7b; mp 151-152 °C.
7) The stereochemistry of 6 and 7 was determined from NMR spectra. ^{1}H NMR ($CDCl_3$), 6a; 7.07-8.57 (9H, aromatic), 5.20 (1H, d, J = 3 Hz, erythro-CHOH-5.17 (1H, bs, -OH), 3.13 (1H, dq, J = 3 Hz, J = 7.5 Hz, $-CHCH_3-$), 1.14 (3H, d, J = 7.5 Hz, $-CH_3$): 7a; 6.90-8.50 (9H, aromatic), 5.30 (1H, bs, -OH), 4.90 (1H, d, J = 7 Hz, threo-CHOH-), 3.17 (1H, dq, J = 7 Hz, $-CHCH_3$), 1.27 (3H, d, J = 7 Hz, $-CH_3$): 6b; 7.00-8.67 (14H, aromatic), 5.90 (1H, bs, -OH), 5.65 (1H, d, J = 3 Hz, erythro-CHOH-), 4.22 (1H, d, J = 3 Hz, $-CHC_6H_5$): 7b; 7.00-8.67 (14H, aromatic), 5.90 (1H, bs, -OH), 5.45 (1H, d, J = 7.5 Hz, threo-CHOH-), 4.32 (1H, d, J = 7.5 Hz, $-CHC_6H_5$).

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