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Syntheses of Aromatic Mannich Bases Involving Nitrogen Heterocycles by Means of Amine-exchange Reaction

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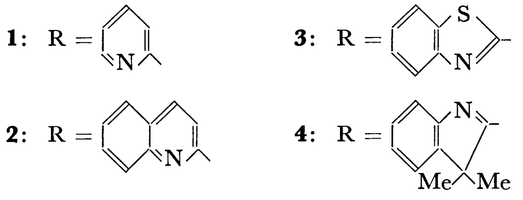
Synopsis. Amine-exchange reactions of aliphatic Mannich bases involving nitrogen heterocycles, such as 2-(2-dimethylaminoethyl)-substituted pyridine, quinoline, benzothiazole, and 3,3-dimethyl-3*H*-indole, with arylamines readily provided the corresponding aromatic Mannich bases which are otherwise hardly accessible.

A few amine-exchange reactions involving aliphatic Mannich bases and arylamines have been reported.[1,2] In spite of their expected usefulness in organic synthesis, however, the results so far reported have been limited only to those for Mannich bases containing ketone carbonyls.

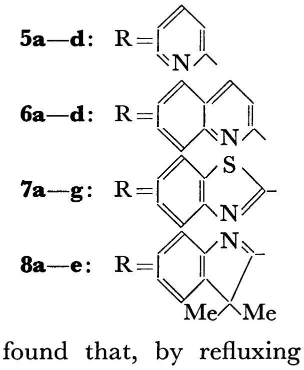
In the course of the synthetic studies of the polymerizable Mannich bases containing aromatic functional groups,[3] we have successfully attempted the amine-exchange reactions of aliphatic Mannich bases involving nitrogen heterocycles with arylamines; thereby we have isolated, in reasonable yields, the aromatic Mannich bases, which could not be synthesized directly from the corresponding 2-methyl-substituted nitrogen heterocycles, formalin, and arylamines.

Amine-exchange reactions take place as follows.

$$\underset{\mathbf{1-4}}{RCH_2CH_2NMe_2} + ArNH_2 + HCl$$



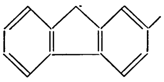
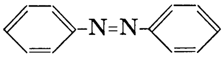
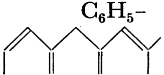
$$\longrightarrow RCH_2CH_2NHAr + Me_2NH \cdot HCl$$



It has been found that, by refluxing the ingredients in ethanol–water for 4—25 h, exchange reactions take place readily to afford the corresponding products (**5**—**8**). Table 1 gives the results obtained.

It may be seen that from this table that good nucleophiles, such as *p*-anisidine and *p*-toluidine generally provided better yields of the exchange products than poor nucleophiles such as *p*-nitroaniline and *p*-aminobenzoic acid. *p*-Nitroaniline, a poor nucleophile, failed even to react with 2-(2-dimethylaminoethyl)-substituted pyridine (**1**), and quinoline (**2**). Moreover, the reactivity of the Mannich base in the exchange reaction is considerably affected by the cyclic portion of the molecule, providing this decreasing order of reactivity: **3**, **4**, **2**, and **1**. The most reactive Mannich base, **3**, reacted successfully with all the arylamines employed.

Table 1. Amine-exchange reactions of Mannich bases

No.		Ar	Yield, %	Mp, °C
1→	**5a**	p-$OCH_3 \cdot C_6H_4$-	37.2a)	Oily product
	5b	p-$CH_3 \cdot C_6H_4$-	34.0a)	
	5c	C_6H_5-	30.3a)	
	5d	p-$NO_2 \cdot C_6H_4$-	0a)	
2→	**6a**	p-$OCH_3 \cdot C_6H_4$-	39.1b)	Oily product
	6b	p-$CH_3 \cdot C_6H_4$-	35.9b)	
	6c	C_6H_5-	31.0b)	
	6d	p-$NO_2 \cdot C_6H_4$-	0b)	
3→	**7a**	p-$OCH_3 \cdot C_6H_4$-	58.0b)	80—82
	7b	p-$CH_3 \cdot C_6H_4$-	60.6b)	85—88
	7c	C_6H_5-	32.4c)	Viscous mass
	7d		48.2b)	151—154
	7e		57.5b)	89—92
	7f	p-$NO_2 \cdot C_6H_4$-	41.3b)	85—90
	7g	p-$COOH \cdot C_6H_4$-	27.7b)	70—73
4→	**8a**	p-$OCH_3 \cdot C_6H_4$-	44.1b)	91—93
	8b	p-$CH_3 \cdot C_6H_4$-	62.2b)	103—105
	8c	C_6H_5-	40.9b)	128—131
	8d		73.7b)	119—122
	8e	p-$NO_2 \cdot C_6H_4$-	Traceb)	—

a) 25 h refluxing in $EtOH/H_2O$ (1/1). b) 4 h refluxing in $EtOH/H_2O$ (1/1). c) With tar.

Although the mechanism of the reaction is not exactly known, the fact that amine-exchange reactions also took place readily between aliphatic Mannich bases containing a *β*-dimethylaminoethyl group attached to a nitrogen heterocycle and arylamines indicates that the synthetic procedure for aromatic Mannich bases by amine-exchange reaction is generally applicable to Mannich bases containing a *β*-alkylaminoethyl group.

Experimental

The infrared, ^1H-NMR, and mass spectra were recorded on a Hitachi 215 spectrophotometer, a JNM-PMX 60 spectrometer, and a Hitachi RMU-6 MG spectrometer, respectively, all under standard measurement conditions. The elemental analyses were carried out using a Perkin-Elmer

250 instrument.

Syntheses of Starting Mannich Bases. A conventional procedure[4] was employed. Thus, in a typical example, for obtaining 2-(β-dimethylaminoethyl)-3,3-dimethyl-3*H*-indole (**4**), 9.5 g (60 mmol) of 2,3,3-trimethyl-3*H*-indole, 4.9 g (60 mmol) of dimethylamine hydrochloride, and 6 ml (60 mmol) of 37% formalin in 30 ml of ethanol were refluxed for 4 h. The resulting dark red solution was diluted with water and extracted with ether three times. The dark aqueous layer was then basified with aqueous sodium hydroxide, and the resulting orange oil was extracted with ether, followed by washing with water, drying over anhydrous sodium sulfate, and evaporation *in vacuo* to leave a red viscous mass, which was subsequently recrystallized from ethanol–water to afford light orange crystals (mp 58—60 °C) in a 33% yield. Found: C, 77.59; H, 9.42; N, 12.99%. Calcd for $C_{14}H_{20}N_2$: C, 77.78; H, 9.26; N, 12.96%. IR(CCl_4): 2970—2860 (CH_2, CH_3), 2820, 2760 (NMe_2), 1600 (aryl), 1450 cm^{-1}. NMR(CCl_4): δ 1.3 (m, 6H, 2Me), 2.2 (s, 6H, NMe_2), 2.4—4.0 (m, 4H, $2CH_2$), 6.8—7.8 (m, 4H, ArH) ppm. Mass (*m/e*) 216(M^+).

2-(β-Dimethylaminoethyl)-pyridine (**1**), -quinoline (**2**), and -benzothiazole (**3**) were obtained in similar manners in 44% (oil), 42% (oil), and 40% (oil) yields, respectively, their analytical and spectral data also being satisfactory.

Amine-exchange Reactions. In a typical example, 0.52 g (2.5 mmol) of **3**, 0.36 g (2.5 mmol) of *p*-toluidine hydrochloride, and 10 ml of ethanol–water (1/1 v/v) were refluxed for 4 h. The resulting yellow solution, with the red oil separated, was extracted with ether and water; the yellow organic layer was then dried over anhydrous sodium sulfate and evaporated *in vacuo* at 50 °C to leave a red viscous mass, which was subjected to silica gel-column chromatography to collect benzene–ether elutes. Recrystallizations from benzene provided orange-yellow crystals (**7b**) (mp 85—88 °C) in a 60.6% yield. Found: C, 71.51; H, 6.00; N, 10.37%. Calcd for $C_{16}H_{16}N_2S$: C, 71.64; H, 5.97; N, 10.45%. IR(CCl_4): 3390 (NH), 3000—2860 (CH_3, CH_2), 1600 (aryl), 1430 cm^{-1}. NMR (CCl_4): δ 2.2 (s, 3H, CH_3), 3.0—5.0 (m, 5H, NH+$2CH_2$), 6.3—8.3(m, 8H, ArH) ppm. Mass(*m/e*): 268(M^+, 20), 120 (100).

The reactions for the other combinations in Table 1 were carried out in similar manners, the identifications of the products by CHN analyses and the infrared, NMR, and mass spectra being satisfactory.

References

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