Acyclic Tertiary Amines as Nucleophiles in Substitution Reactions of Aromatic and Heteroaromatic Halides

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Even acyclic tertiary amines such as triethylamine, tri-n-propylamine and tri-n-butylamine, which have been believed to be inert to aromatic and heteroaromatic halides, underwent S_NAr reactions with aromatic and heteroaromatic halides to give the dialkylamino derivatives; in the case of monocyclic amines like *N*-methylpyrrolidine and *N*-methylpiperidine, the dealkylation being regioselective.

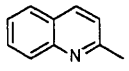
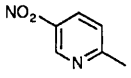
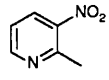
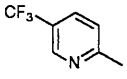
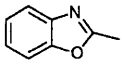
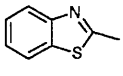
There have been extensive investigations of the scope, synthetic applications, and the kinetics and mechanism of the nucleophilic substitution reactions of aromatic halides.[1] Aminolysis of 'activated' aromatic and heteroaromatic halides (ArX) by nucleophilic aromatic substitution (S_NAr) reactions with primary and secondary amines are well known.[2] Usually, the addition–elimination mechanism of S_NAr reactions of ArX with amines involves formation of a Meisenheimer adduct followed by proton transfer or proton loss (*e.g.* elimination of HX) in the later stage of the reaction. Conceptually, acyclic tertiary amines can undergo addition to ArX giving a Meisenheimer type intermediate which would formally lose alkyl halide to afford the substitution product. However, to the best of our knowledge, such overall conversion has not been reported,[3,4] probably because of the extremely low reactivity of tertiary amines due to steric hindrance and partly because of difficulty in alkyl transfer as compared with proton transfer. Indeed, it has been reported that even triethyl amine did not react with ArX.[3,4]

We now report the first examples of S_NAr reactions of aromatic and heteroaromatic halides with acyclic tertiary amines in which the reactions were performed at 0.8 GPa (8 kbar) and 100 °C, and took 4 days.[5] For example, reaction of triethylamine with a variety of aromatic and heteroaromatic halides produced the corresponding diethylamino derivatives [see eqn. (1)]. The results are summarized in Table 1. It is surprising that the yields were practical in most cases where ArX are heteroaromatic halides. Naturally, this reaction is very sensitive to steric hindrance; therefore, the aromatic halides possessing an *ortho* substituent (even if it is an activating one) give rise to low yields of the products. In other words, the heteroaromatic halides are activated by the ring nitrogen towards S_NAr reactions with little steric hindrance when there is no substituent at the α-position.

$$ArX + Et_3N \rightarrow ArNEt_2 + Et_4N^+X^- \quad (1)$$

The reaction is not limited to triethylamine (Table 2). For instance, tri-n-propylamine **2a** and tri-n-butylamine **2b** underwent S_NAr reactions with 2-chlorobenzothiazole **1** to give the corresponding 2-dialkylaminobenzothiazoles **3a** and **3b** in 95 and 90% yields, respectively. The reaction is also possible with monocyclic tertiary amines; *N*-methylpyrrolidine **2c** and *N*-methylpiperidine **2d** with **1**, produced 2-pyrrolidino- and 2-piperidino-benzothiazole **3c** and **3d** in 96 and 92% yields, respectively. This demethylation–arylation (and possibly debenzylation–arylation) is potentially of synthetic value since unsubstituted cyclic amines are often not directly available as starting materials for aminolysis.†

Table 1 Reactions of aromatic and heteroaromatic halides with triethylamine at 0.8 GPa and 100 °C for 4 days[a]

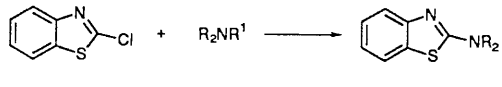
Ar	X	Yield (%)
4-$NO_2C_6H_4$	Cl	8
2,4-$(NO_2)_2C_6H_3$	Cl	11[b]
2-CF_3-4-$NO_2C_6H_3$	Cl	19
	Cl	10
	Cl	51
	Cl	82
	Cl	31
	Cl	68
	Cl	58
	Cl	18
	Br	93
	Cl	96
	Cl	98

[a] Isolated yield. Reaction conditions were not optimized. All the products gave satisfactory C, H, N and/or exact mass analyses along with ^1H and ^{13}C NMR spectra. [b] A considerable amount of insoluble black material was obtained.

Table 2 Reactions of 2-chlorobenzothiazole **1** with tertiary amines **2**

Amine **2**	R or RR	R^1	Yield of **3**[a] (%)
2a	Pr^n	Pr^n	95
2b	Bu^n	Bu^n	90
2c	$-(CH_2)_4-$	Me	96
2d	$-(CH_2)_5-$	Me	92

[a] Isolated yield. Reaction conditions were not optimized. All products gave satisfactory C, H, N analyses together with ^1H and ^{13}C NMR spectra.



1 **2** **3**

† For example, *N*-unsubstituted hexahydro-*s*-triazine is not available and most *N*-unsubstituted azacrown ethers are obtainable only after debenzylation.

At present, it is not clear whether the alkyl transfer takes place from a Meisenheimer adduct or from a quaternary ammonium halide.‡ In connection with this, the regioselective aspect of the dealkylkation process will be a subject of a future communication.

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‡ Attempts to isolate an aromatic quaternary halide from acyclic tertiary amines have so far been unsuccessful.

References

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5 The overall volume of activation of S_NAr reactions is found to be negative, -10 to -30 cm^3 mol^{-1}; K. R. Brower, *J. Am. Chem. Soc.*, 1959, **81**, 3504.