

Selectivity in the Consecutive S<sub>N</sub>Ar-Dequaternization Reactions of  
Heteroaromatic Chlorides with Tertiary Amines under High Pressure

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Consecutive S<sub>N</sub>Ar-dealkylation reactions of heteroaromatic chlorides such as 2-chloro-5-trifluoromethylpyridine and 2-chlorobenzothiazole with tertiary amines took place under high pressure in a highly selective fashion; some synthetic potential of the title reaction was exemplified.

Aminolysis of aromatic and heteroaromatic halides (ArX) with acyclic tertiary amines is generally a difficult reaction probably because of steric hindrance<sup>1)</sup> in transition state.<sup>2-5)</sup> Since Ibata et al.<sup>6)</sup> and ourselves<sup>7)</sup> have shown that S<sub>N</sub>Ar reactions of ArX with primary and secondary amines are highly accelerated by application of pressure, it would be worthwhile to clarify some synthetic potential of acyclic tertiary amines in high pressure aminolysis of heteroaromatic chlorides.

We now report on the selectivity of dealkylation<sup>8)</sup> in S<sub>N</sub>Ar reactions of heteroaromatic halides with tertiary amines where 2-chloro-6-trifluoromethylpyridine (**1a**), 4-chloro-2,6-bis(trifluoromethyl)pyridine (**1b**), 2-chlorobenzoxazole (**1c**) and 2-chlorobenzothiazole (**1d**) were selected as representative heteroaromatic halides. The reactions were carried out at 0.8 GPa (8 kbar) and 100 °C.<sup>9)</sup> The results are summarized in Table 1. The

yields were excellent in most cases. Inspection of Table 1 reveals that the reaction of *N,N*-dimethylalkylamines **2** (alkyl ≠ benzyl) with **1** undergoes selective demethylation to give the corresponding 2-(methylalkylamino) derivatives **3** along with a small amount of 2-(dimethylamino) derivatives **4**.

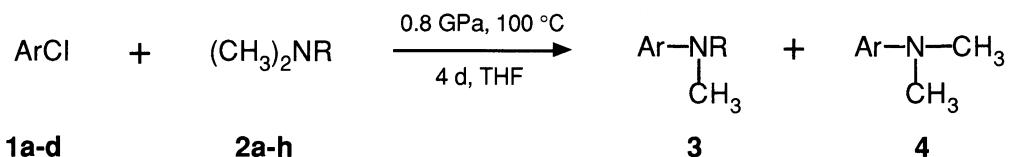


Table 1. Selectivity **3** / **4**<sup>a)</sup> in Consecutive  $\text{S}_{\text{N}}$  Ar-Dealkylation Reaction of **1** with **2**<sup>b)</sup>

R	ArCl				
	<b>1a</b>	<b>1b</b>	<b>1c</b>	<b>1d</b>	
<b>2a</b>	Et	73/ 3	93/ 7	—	94/ 5.5
<b>2b</b>	n-Hex	—	83/<1	—	—
<b>2c</b>	n-Oct	—	82/<1	—	97/ 3
<b>2d</b>	(CH <sub>2</sub> ) <sub>17</sub> CH <sub>3</sub>	74/ 2	76/<1	94/ 5	—
<b>2e</b>	i-Pr	69/13	73/13	65/32	79/20
<b>2f</b>	c-Hex	97/ 2	69/ 2	86/14	94/ 4
<b>2g</b>	Benzyl	2/96	0/90	1/89	2/98
<b>2h</b>	Ph	—	—	92/ 0	8/ 0

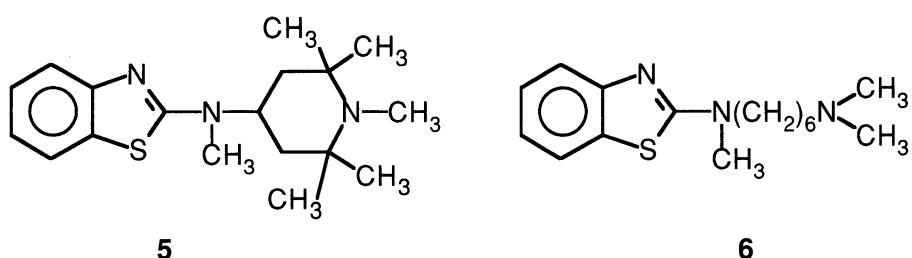
a) Isolated yield. All the compounds were characterized by <sup>1</sup>H and <sup>13</sup>C NMR as well as elemental analyses.

b) Reaction conditions were not optimized.

2-Chlorobenzoxazole (**1c**) was reactive enough even toward aromatic tertiary amines such as *N,N*-dimethylaniline (**2h**) giving **3** in 92% yield. The decreased selectivity generally observed in the reactions of **1c** is in

agreement with reactivity-selectivity relationship. In contrast, N,N-dimethylbenzylamine (**2g**) with **1** underwent a facile debenzylation to afford **4**. Thus, N,N-dimethylbenzylamine serves as a dimethylamino equivalent.

Since most of the previous methods for dealkylation were based on quaternary ammonium iodides<sup>8a,d,e,g,h)</sup> and quaternization of aromatic and heteroaromatic halides with tertiary amines is generally difficult,<sup>2-6)</sup> the present procedure provides a useful method for preparation of tertiary amines that are otherwise difficult in availability. For example, reactions of **1d** with 4-(dimethylamino)-1,2,2,6,6-pentamethylpiperidine and 1,6-bis(dimethylamino)hexane afforded the corresponding tertiary amines **5** and **6** in 95% and 91% yields respectively.



Clearly, high pressure is responsible to the acceleration of  $S_NAr$  reactions because the overall volume of activation of  $S_NAr$  reactions is found to be negative,  $-10$  to  $-30$   $cm^3 mol^{-1}$ .<sup>10</sup> Pressure effects on selectivity of dealkylations are a subject of further communications.

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- 9) General procedure: A mixture of the pyridine **1** (6 mmol) and the amine **2** (15 mmol) was diluted with tetrahydrofuran in polytetrafluoroethylene tube (8 ml) which was compressed to 0.8 GPa (8 kbar) and heated to 100 °C for 4 days. After cooling and depressurization, most of the excess amine was removed in vacuo and the residue was subjected to chromatography on silica gel, using benzene/hexane as eluent.
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