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Selectivity in Consecutive S_NAr-Dequaternization Reactions of Chlorodiazines with Tertiary Amines

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SYNTHETIC COMMUNICATIONS, 22(5), 787-792 (1992)

SELECTIVITY IN CONSECUTIVE S_NAr-DEQUATERNIZATION REACTIONS OF CHLORODIAZINES WITH TERTIARY AMINES

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ABSTRACT: Consecutive S_NAr-dealkylation reactions of chlorodiazines such as 2-chloropyrimidine and 3,6-dichloropyridazine with tertiary amines took place in a highly selective fashion.

Aminolysis of aromatic and heteroaromatic halides (ArX) with acyclic tertiary amines is generally a difficult reaction probably because of steric hindrance[1] in transition state.[2-4] Recently, we have disclosed that even acyclic tertiary amines such as triethylamine, tri-n-propylamine, and tri-n-butylamine underwent aromatic nucleophilic substitution (S_NAr) reactions with ArX at 0.8 GPa and 100°C to give the dialkylamino derivatives.[5,6] Specifically, diazines were particularly

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reactive toward tertially amines. Since the selective dealkylation of quaternary ammonium salts has been of perennial problem,[7] it is desirable to clarify selective aspects of consecutive S_NAr and dequaternization reactions of tertiary amines with chloroazines which are activated by the ring nitrogen towards S_NAr reactions with little steric hindrance.

We now report on the selectivity of dealkylation in S_NAr reactions of 2-chloropyrimidine (**1**) and 3,6-dichloropyridazine (**5**) with tertiary amines. The reactions were performed at 0.8 GPa (8 kbar) and 100°C. The results are summarized in Table.[8] The yields were excellent in most cases. Inspection of Table reveals that N, N-dimethylalkylamines **2** (alkyl≠benzyl) with **1** undergo selective demethylation to give the corresponding 2-methylalkylamino derivatives **3** along with a small amount of 2-dimethylamino derivatives **4**. 2-Chloropyrimidine also reacted with aromatic tertiary amines such as N,N-dimethylaniline (**2**) giving **3d** in 62% yield. In contrast, N,N-dimethylbenzylamine (**2e**) and bis(dimethylamino)methane (**2f**) with **1** afforded **4** in good yields. Thus, N,N-dimethylbenzylamine and bis(dimethylamino)methane serve as a dimethylamino equivalent. Analogous results were obtained in the reactions of **5** with **2** (Table).

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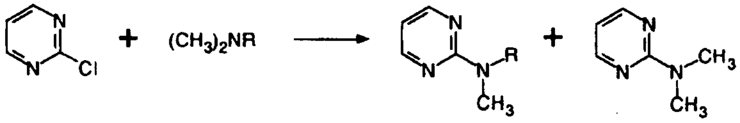
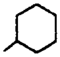
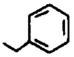
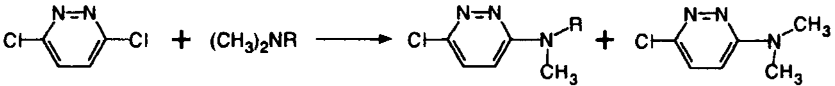
Table. Selectivity in S_NAr-Dequaternization Reaction of Diazines

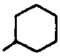
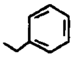


1 **2a~f** **3** **4**

2	R	Yield/% 3	4
a		96	~1
b	n-Oct	97	2
c	i-Pr	90	6
d		62	<1
e		<1	85
f	$(CH_3)_2NCH_2$-	0	92



5 **2a~c,e,f** **6** **7**

2	R	Yield/% 6	7
a		96	<1
b	n-Oct	38	<1
c	$(CH_3)_2CH_2$-	82	6
e		2	98
f	$(CH_3)_2NCH_2$-	0	95

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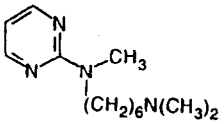
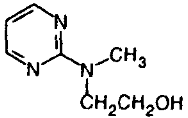
Although it is not yet clear whether the dealkylation proceeds through an aromatic quaternary ammonium chloride or directly via Meisenheimer complex, the present reaction provides some synthetic potential in those cases where an appropriate secondary amine is not readily available. For example, reactions of 1 with bis(dimethylamino)hexane and (dimethylamino)ethanol gave the corresponding tertiary amines 8 and 9 in 43 and 51% yields, respectively.



8



9

EXPERIMANTAL

General procedure- A mixture of the diazine (7 mmol) and the tertiary amine (17.5 mmol) was diluted with tetrahydrofuran in polytetrafluoroethylene capsule (8 ml) which was compressed to 0.8 GPa (8 kbar) and heated for 100 °C for 4 days. After cooling and depressurization, most of the excess amine was removed in vacuo and the residue was chromatographed on silica gel using hexane/benzene and benzene/ethyl acetate. Typical examples of the spectroscopic data of the products are

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following. **3a**: oil; ^{1}H-NMR($CDCl_3$) 0.80-1.93(m, 10H), 2.97(s, 3H), 4.56(m, 1H), 6.30(t, J=4.5 Hz, 1H), 8.19(d, J=4.5 Hz, 2H); ^{13}C-NMR($CDCl_3$) 25.7(t), 25.9(t), 28.6(q), 30.0(t), 53.7(d), 108.6)d), 157.4(d), 161.6(s). **3c**: oil; ^{1}H-NMR($CDCl_3$) 1.17(d, J=7.0 Hz, 6H), 2.98(s, 3H), 5.05(heptet, J=7.0 Hz, 1H), 6.32(t, J=5.0 Hz, 1H), 8.20(d, J=5.0 Hz, 2H); ^{13}C-NMR($CDCl_3$) 19.2(q), 27.0(q), 44.9(d), 108.5(d), 157.1(d), 161.4(s). **8**: oil; ^{1}H-NMR($CDCl_3$) 1.15-1.85(m, 8H), 2.18(m, 8H), 3.08(s, 3H), 3.58(t, J=7.5 Hz, 2H), 6.32(t, J=5.0 Hz), 8.20(d, J=5.0 Hz, 2H); ^{13}C-NMR($CDCl_3$) 26.6(t), 27.0(t), 27.1(t), 27.4(t), 34.9(q), 45.2(q), 48.8(t), 59.5(t), 108.4(d), 157.2(d), 161.6(s).

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8. Isolated yields. Reaction conditions were not optimized.

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