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A Convenient Synthesis of Tertiary Amines by Alkylation of Secondary Amines with Alkyl Halides in the Presence of Potassium Hydride and Triethylamine

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N-Alkylation of secondary amines with alkyl halides in the presence of potassium hydride and triethylamine gave corresponding tertiary amines in satisfactory yields.

Keywords direct *N*-alkylation; tertiary amine; potassium amide; alkyl halide scavenger; alkyl halide

Direct *N*-alkylation reaction of amines with alkyl halides is attractive as a synthetic method for tertiary amines. However, the method is severely limited in the case of amines with a bulky alkyl substituent, since further alkylation with alkyl halides generally gives a mixture of a tertiary amine and a quaternary ammonium salt, together with the starting secondary amine. Generally, a high yield of tertiary amine calculated from alkyl halide is possible only when a large excess of secondary amine over alkylating agent (10 : 1 or larger) is used.[1]

There are several reports on the reaction of *N*-anions of amines and alkyl halides to form tertiary amines. Puterbaugh and Hauser[2] reported that the reaction of lithium diethylamide and *n*-octyl bromide selectively gave *N*,*N*-diethyloctylamine in 89% yield, but in this case, 2 eq of the lithium reagent were required to avoid over-alkylation, furnishing a quaternary ammonium salt. Suga *et al.*[3] used lithium naphthalenide for selective *N*-alkylation of primary and secondary amines by alkyl halides. In this paper, we describe a new modification of the selective *N*-alkylation reaction of secondary amines with alkyl halides, which provides a convenient general synthetic method for tertiary amines from secondary amines.

We considered that the reaction of alkyl halides with the *N*-anions formed from secondary amines, when carried out in the presence of a suitable tertiary amine, would selectively form the desired *N*-alkylated products (tertiary amines), since the tertiary amine initially added may act as a scavenger of excess halides. Thus, we investigated the *N*-alkylation reaction of secondary amines *via* their metal amides with alkyl halides in the presence of triethylamine.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**) was converted to the corresponding potassium amide (**2a**) by treatment with potassium hydride (KH, 1.5 eq) in the presence of triethylamine (10 eq) in 1,2-dimethoxyethane (DME) at 0 °C, then treated with iodomethane (1.5 eq) to afford the *N*-methyl derivative (**3a**) in 70% yield, after solvent extraction and chromatography of the product on alumina (entry 1). Table I indicates that the presence of triethylamine is a critical factor; it presumably acts as a scavenger of excess alkyl halide. Formation of the triethylmethylammonium salt together with a small

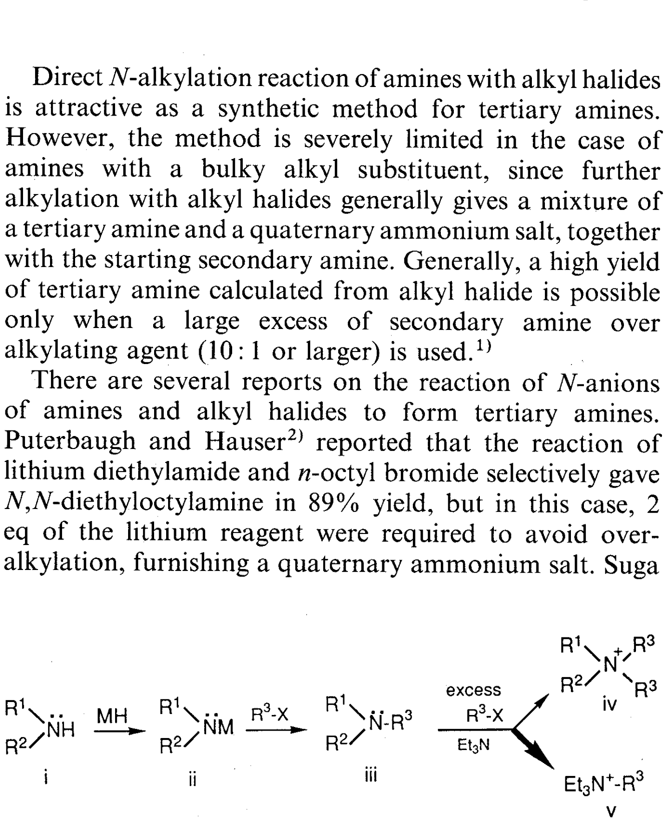

Chart 1

TABLE I. *N*-Alkylation of 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**)

Entry	RX	Conditions				Product (yield %)[a]	
		Solvent	Base	Scavenger	Time (h)[b]	**3**	Recovery of **1**
1	MeI	DME	KH	Et_3N	2	70	
2	MeI	DME	KH	Pyridine	2	10	30
3	MeI	DME	KH	None	2	21	30
4	MeI	THF	KH	Et_3N	2	40	10
5	MeI	DME	NaH	Et_3N	2	60	
6	MeI	DME	*n*-BuLi	Et_3N	12	67	
7	MeI	DME	None	None	2	18	26
8	EtI	DME	KH	Et_3N	12	74	
9	EtI	DME	*n*-BuLi	Et_3N	12	54	
10	$PhCH_2Br$	DME	KH	Et_3N	12	92	
11	$PhCH_2Br$	DME	KH	None	12	18	
12	$PhCH_2Br$	DME	None	None	12	27	

a) Isolated yield after solvent extraction and chromatography on alumina. *b*) Stirred at room temperature after addition of the alkyl halide.

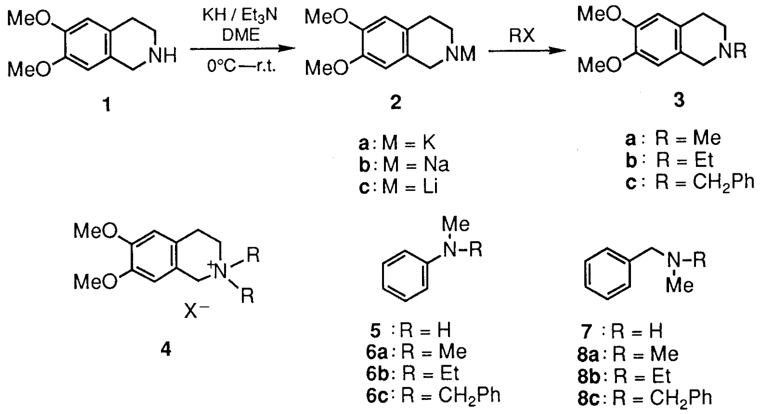

Chart 2

TABLE II. *N*-Alkylation of *N*-Methylaniline (**5**) and *N*-Methylbenzylamine (**7**) with RX (1.5 eq) in the Presence of KH (1.5 eq) and Triethylamine (10 eq) in DME

Starting material	RX	Time (h)	Product	Yield (%)
5	MeI	12	**6a**[a]	63
5	EtI	12	**6b**[b]	77
5	$PhCH_2Br$	12	**6c**[a]	69
7	MeI	12	**8a**[a]	65
7	EtI	12	**8b**[c]	68
7	$PhCH_2Br$	12	**8c**[a]	70

a) G. W. Gribble, C. F. Nutaitis, *Synthesis*, **1987**, 709. *b*) J.-B. Baudin, S. A. Julia, O. Ruel, *Tetrahedron*, **43**, 881 (1987). *c*) G. W. Gribble, J. M. Jasinski, J. T. Pellicone, J. A. Panetta, *Synthesis*, **1978**, 766.

amount of the quaternary salt (**4**) was demonstrated by its isolation as the iodide. For comparison, the amine **1** was directly alkylated with iodomethane to give **3a** in 18% yield (entry 7). When **2a** was alkylated with iodomethane without triethylamine, the yield of **3a** was only 21% (entry 3).

Alkylation of the *N*-sodium and *N*-lithium derivatives, **2b** and **2c**, with iodomethane proceeded as smoothly as in the case of the *N*-potassium salt to give **3a** in comparable yields (entries 5, 6). For solvents, DME was preferable, since methylation of the potassium derivative (**2a**) in tetrahydrofuran (THF) gave **3a** in lower yield (40%) (entry 4). Pyridine was not a suitable scavenger in this reaction (entry 2). Similarly, alkylations of the potassium amide (**2a**) with iodoethane and benzyl bromide proceeded smoothly to give **3b** and **3c** in yields of 74% and 92%, respectively (entries 8, 10).

The above-described alkylation reaction was applied to *N*-methylaniline (**5**) and *N*-methylbenzylamine (**7**). A solution of the potassium amide prepared from **5** with potassium hydride in the presence of triethylamine in DME at 0 °C was treated with iodomethane to give an *N*,*N*-dimethylaniline (**6a**) in 63% yield. Similar alkylations of the above potassium amide with iodoethane and benzyl bromide proceeded smoothly to give the *N*-ethyl and *N*-benzyl derivatives, **6b** and **6c**, in yields of 77% and 69%, respectively. Similarly, alkylations of the *N*-potassium amides of *N*-methylbenzylamine with iodomethane, iodoethane and benzyl bromide proceeded to give the tertiary amines, **8a**, **8b** and **8c** in satisfactory yields (65%, 68% and 70%, respectively). These results are summarized in Table II.

The above results indicate that *N*-alkylation of secondary amines with alkyl halides in the presence of potassium hydride and triethylamine is one of the most widely applicable methods for selective *N*-alkylation to produce tertiary amines.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were determined on Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer, and are given in cm^{-1}. ^1H-NMR spectra were recorded on a Hitachi R-600 (60 MHz) or a JEOL JNM-EX90 (90 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and are given in δ. High-resolution mass spectra (HRMS) were determined with a JEOL JMS D-300 spectrometer and M^+ is given in *m*/*z*.

***N*-Alkylation of Secondary Amines (General Procedure)** Et_3N (10 eq) and KH (35 weight % dispersion in mineral oil, 1.5 eq) were added to a solution of an amine (1—2 mmol) in 1,2-dimethoxyethane (5—10 ml) under argon at 0 °C, and the mixture was stirred for 0.5 h at 0 °C. Alkyl halide (1.5 eq) was added and the whole was allowed to warm to room temperature and stirred for a further 2—12 h with occasional monitoring of the progress of the reaction by TLC. After addition of saturated NH_4Cl solution and basification with 5% NaOH, the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by Al_2O_3 column chromatography with AcOEt–hexane to yield tertiary amines.

2-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3a) 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**, 386 mg, 2 mmol) was treated as described in the general procedure with Et_3N (2.8 ml, 20 mmol) and KH (342 mg, 3 mmol), then with iodomethane (426 mg, 3 mmol) for 2 h to give **3a** (290 mg, 70%), mp 63—64 °C (lit. mp 65 °C).[4] IR (KBr): 1620. ^1H-NMR: 6.60 (1H, s, ArH), 6.52 (1H, s, ArH), 3.84 (6H, s, 2 × OMe), 3.60 (2H, s, $ArCH_2N$), 2.87—2.71 (4H, br s, $ArCH_2CH_2N$), 2.51 (3H, s, NMe).

Detection of Quaternary Salts The above reaction mixture from 193 mg of **1** was quenched with saturated KI solution and concentrated *in vacuo*. The residue was purified by Al_2O_3 column chromatography with AcOEt–hexane to obtain the tertiary amine **3a** (145 mg). Elution was further conducted with AcOEt and then with MeOH. The MeOH eluate gave a 3 : 1 mixture (188 mg) of triethylmethylammonium iodide and the quaternary iodide **4**. The ratio was calculated from the ^1H-NMR spectrum. [Triethylmethylammonium iodide: 3.57 (q, J = 7 Hz, $C\underline{H}_2CH_3$), 3.21 (s, ^+N-CH_3), 1.41 (t, J = 7 Hz, $CH_2C\underline{H}_3$). The quaternary iodide **4**: 6.74 (s, ArH), 6.69 (s, ArH), 4.75 (s, $ArCH_2N$), 4.03—3.96 (m), 3.88 (s, OMe), 3.87 (s, OMe), 3.50 [s, $^+N(CH_3)_2$, 3.39—3.05 (m)].

2-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3b) Compound **1** (193 mg, 1 mmol) was treated with Et_3N (1.4 ml, 10 mmol), KH (171 mg, 1.5 mmol), and iodoethane (233 mg, 1.5 mmol) as described above to give **3b** (164 mg, 74%) as an oil. IR (neat): 1620. ^1H-NMR: 6.59 (1H, s, ArH), 6.52 (1H, s, ArH), 3.83 (6H, s, 2 × OMe), 3.55 (2H, s, $ArCH_2N$), 2.90—2.65 (6H, m, $ArCH_2CH_2N$), 2.57 (2H, q, $J=7$ Hz, $NC\underline{H}_2CH_3$), 1.18 (3H, t, $J=7$ Hz, $NCH_2C\underline{H}_3$). ^{13}C-NMR: 147.5 (s), 147.2 (s), 126.6 (s), 126.1 (s), 111.4 (d), 109.6 (d), 55.9 (2×q), 55.2 (t), 52.0 (t), 50.6 (t), 28.6 (t), 12.3 (q). HRMS Calcd for $C_{13}H_{19}NO_2$: 221.1416. Found: 221.1444.

2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3c**) Compound **1** (193 mg, 1 mmol) was treated with Et_3N (1.4 ml, 10 mmol), KH (171 mg, 1.5 mmol), and benzyl bromide (257 mg, 1.5 mmol) as described above to give **3c** (261 mg, 92%), mp 73—75 °C. IR (KBr): 1620. ^{1}H-NMR: 7.37 (5H, br s, ArH), 6.65 (1H, s, ArH), 6.55 (1H, s, ArH), 3.84 (3H, s, OMe), 3.73 (3H, s, OMe), 3.61 (2H, s, $ArCH_2N$), 2.83 (4H, br s, $ArCH_2CH_2N$). ^{13}C-NMR: 147.5 (s), 147.2 (s), 138.4 (s), 129.1 (2×d), 128.2 (2×d), 127.0 (d), 126.7 (s), 126.2 (s), 111.5 (d), 109.5 (d), 62.7 (t), 55.9 (2×q), 55.7 (t), 50.8 (t), 28.7 (t). HRMS Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1584.

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