Secondary Amines from the Iron(II) Ion-Catalyzed Reaction of Amine Oxides: A General Method for the Dealkylation of Tertiary Amines

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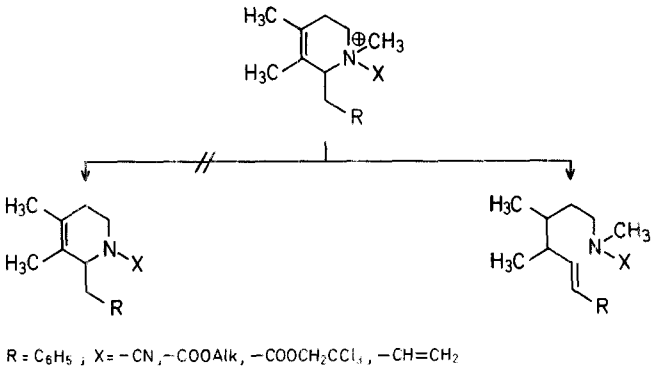
There are a number of general methods for the dealkylation of tertiary amines described in the literature. The classical von Braun reaction[2] using cyanogen bromide is the most frequently used. The use of alkyl carbonochloridates[3,4,5] has often been found to complement cyanogen bromide. Several other reagents such as azidocarboxylic esters, nitrous acid, and potassium chromate have also been described[6] and amine oxides have been shown to degrade to amides (Polonovsky reaction[7]) when treated with acid anhydrides.

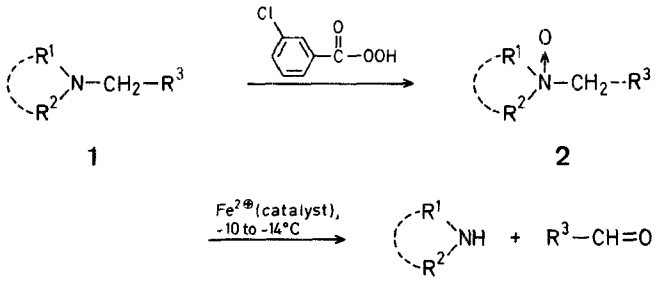
In the course of our studies on the total synthesis of morphinans and benzomorphans, it was often desirable to have an alternative method for the dealkylation of tertiary amines which did not require protection of functional groups such as hydroxy and primary or secondary amine and which would not involve quaternary ammonium intermediates associated with the von Braun reaction. The latter often leads to undesirable reaction pathways, particularly in the case of substituted tetrahydropyridines as shown in Scheme **A**.



Scheme **A**

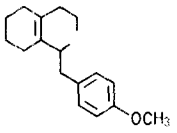
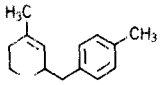
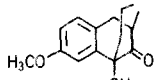
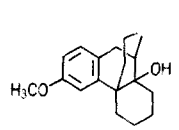
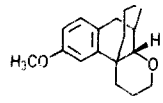
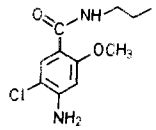
Our attention focused on an iron(II) ion-catalyzed rearrangement[8] of amine oxides to aldehydes and secondary amines involving the amminium radical ion intermediate $>\dot{N}^{\oplus}$ and the $Fe^{2\oplus}/Fe^{3\oplus}$ redox system. Although this reaction has been known for a number of years, it has not found synthetic application apart from several examples in which reactive intermediates are captured intramolecularly to give cyclization products[9,10,11].

We now describe a simple, one-pot method for the dealkylation of tertiary amines under mild, virtually neutral reaction conditions based on the iron(II) ion-catalyzed rearrangement of amine oxides as illustrated in Scheme **B**.



Scheme **B**

Table. Dealkylation of Tertiary Amines **1** by Iron(II)Chloride-Catalyzed Rearrangement of Amine Oxides **2** (Scheme **B**)

Amine No.	R^1	R^2	R^3	Product	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or Lit. Data
1a		H		**3a**	56	Characterized as cyclobutanecarboxamide: 190–200°/0.3	$C_{22}H_{29}NO_2$ (339.5)
1b		H		**3b**	54	Oxalate salt: 162–163°	$C_{14}H_{19}NO \cdot C_2H_2O_4$ (403.4)
1c		H		**3c**	68[b]	Characterized as cyclopropanecarboxamide: 108–110°	$C_{18}H_{21}NO_3 \cdot 0.25\ i\text{-}C_3H_7OH$ (314.4)
1d				**3d**	80	208–211°	214–217°[17]
1e				**3e**	89	[b]	
1f		C_2H_5	CH_3	**3f**	63[c]	142–143°	$C_{12}H_{18}ClN_3O_2$ (271.7)
1g				**4g**	67	176–182[d]/760	178–184°/760

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.33, Cl ± 0.20, N ± 0.41.

[b] Viscous oil isolated by chromatography on silica gel; identical with an authentic sample[18].

[c] Reaction at room temperature because of poor solubility of intermediate **2**. Product isolated by chromatography on deactivated silica gel eluting with dichloromethane/methanol/ammonia and recrystallized from dichloromethane/*n*-pentane; m.p. 142–143°C.

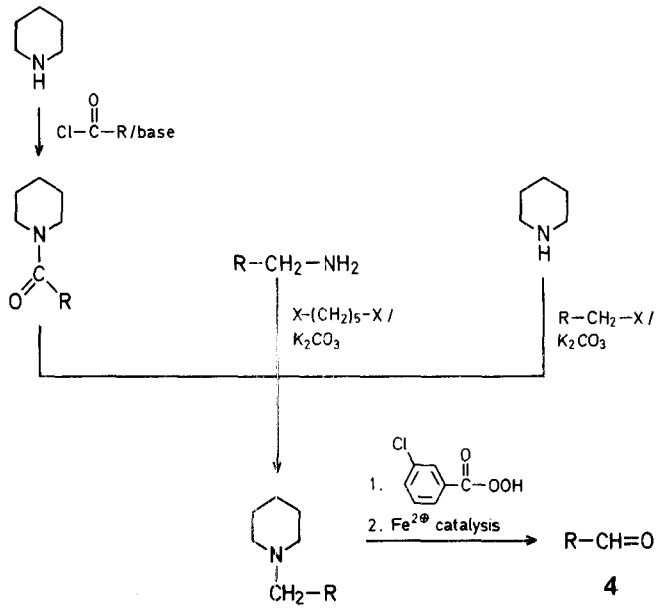
[d] Benzaldehyde (**4g**) isolated by partitioning the reaction mixture between ether and aqueous hydrochloric acid. The organic layer is washed with sodium hydrogen carbonate solution, dried, and distilled to give **4g**.

The method is particularly suitable for the dealkylation of substituted piperidines, benzomorphans, and morphinans and is also useful for the open-chain nitrogen compounds as shown in the Table.

The method consists of the addition of *m*-chloroperbenzoic acid to a solution of the amine[12] **1** in dichloromethane followed by addition with stirring of a catalytic amount of iron(II) chloride as a molar aqueous solution. The reaction is monitored by T.L.C. or H.P.L.C. and the secondary amine **3** isolated by standard procedures. In certain cases, strong complexation of iron ions to the amine requires additional attention. Thus, in the course of isolation of **3a** and **3b**, we have added an excess of ethylenediamine; others have shown that hydrogen sulfide can serve the same purpose[9].

A variety of functional groups (ketone, aniline, allylamine, alcohol) have been shown to be compatible with the reaction conditions. Compounds **1a** and **1b** are particularly sensitive to cyanogen bromide and alkyl carbonochloridates, giving the ring-opened products as shown in Scheme **A**.

It has been shown[8] that the other product of this reaction is the aldehyde **4** as shown in Scheme **B**. Since our efforts, with one exception [benzylpiperidine **(1g)** → benzaldehyde **(4g)**], were directed toward isolation of secondary amines **3**, a potential for the synthesis of aldehydes **4**, as indicated in Scheme **C**, remains to be investigated.



Scheme **C**

The yields shown in the Table were not optimized. We have attempted to maximize the yield only in the case of the demethylation of commercially available (+)-octahydroisoquinoline **(1a)**[13] because the nor-product **3a** is an intermediate in the total synthesis of 3,14-dihydroxymorphinans[14].

The method appears to be unsuitable for the dealkylation of aromatic tertiary amines as both *N,N*-dimethylaniline and *N,N*-dimethyl-*p*-toluidine failed to give the corresponding monomethyl products in practical yields.

1-(4-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (3a); Typical Procedure:

To a cooled (ice/salt) stirred solution of 1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1a**; 2.71 g, 10 mmol) in dichloromethane (10 ml) is added in small portions over a period of 10 min *m*-chloroperbenzoic acid (2.0 g, 85% purity, 10 mmol). The mixture is stirred for 20 min and then treated with iron (II) chloride (0.7 ml of 1 molar solution in water). Stirring and cooling are continued for 1 h and then stirring continued for 2 h at room temperature. Ethylenediamine (600 mg), sodium hydroxide (10 ml of 2 normal solution), and petroleum ether (20 ml) are added and, after vigorous shaking, the layers are separated. The aqueous layer is extracted with 1:3 ether/petroleum ether (2 × 60 ml), the combined extracts are dried with potassium carbonate, filtered, and concentrated in vacuo to give crude **3a**. The latter is characterized as its cyclobutanecarboxamide by treatment with cyclobutanecarboxylic acid chloride (900 mg, 8 mmol) and triethylamine (1.0 g). The mixture is washed successively with water, dilute hydrochloric acid, and dilute sodium hydroxide. Drying and evaporation of the solvent gives *2-cyclobutanoyl-1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline* as an oil; yield: 2.2 g (65%); b.p. 190–200°C/0.3 torr

$C_{22}H_{29}NO_2$	calc.	C 77.84	H 8.61	N 4.13
(339.5)	found	77.58	8.69	4.38

(−)-14-Hydroxy-3-methoxymorphinan(3d); Typical Procedure:

To a suspension of (−)-*N*-cyclobutylmethyl-14-hydroxy-3-methoxy-morphinan hydrochloride (**1d**; 3.78 g, 10 mmol) in dichloromethane (20 ml) is added 4 normal sodium hydroxide solution (2.5 ml, 10 mmol) and the mixture stirred until all the solid has dissolved. The solution is cooled to 0°C and treated with *m*-chloroperbenzoic acid (2.0 g, 85%, 10 mmol) in several portions, followed by a 1 normal aqueous solution of iron(II) chloride (4 ml). Stirring is continued at −10 to 0°C for 7 h. The mixture is then treated with a solution of 5 molar hydrochloric acid (20 ml) and the dichloromethane removed in vacuo. The aqueous residue is extracted twice with diethyl ether to remove *m*-chlorobenzoic acid, basified with sodium hydroxide, and then extracted twice with dichloromethane. The extract is dried and concentrated in vacuo to give an oil which is dissolved in methanol and treated with L-tartaric acid (1.6 g). The resultant solid product is isolated by suction to give the L-tartarate salt of **3d**; yield: 3.39 g (80%); m.p. 208–211°C (Ref.[17], m.p. 214–217°C).

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[1] Present address: Bristol-Myers Company, Pharmaceutical Research and Development Division, Syracuse, New York 13221–4755, U.S.A.

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Fodor, G., Abidi, S. Carpenter, T.C. *J. Org. Chem.* **1974**, *39*, 1507.
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[5] Olofson, R.A., Tartz, J.T., Senet, J.P., Piteau, M., Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
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[7] Russell, G.A., Mikol, G.J. in: *Mechanisms of Molecular Migrations*, Vol. 1, Thyagarajan, B.S., Ed., Interscience, New York, 1968, pp. 176–194.
Šunjić, V., Kajfež, F., Kolbah, D., Hofman, H., Stromer, M. *Tetrahedron Lett.* **1973**, 3209.
Mangeney, P., Andriamialisoa, R.Z., Langlois, N., Langlois, Y., Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.
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[9] Scherer, C.A., Dorschel, C.A., Cook, J.M., LeWuesne, D.W. *J. Org. Chem.* **1972**, *37*, 1083.
[10] Kametani, T., Ihara, M., Takemura, M., Satoh, Y. *Heterocycles* **1980**, *14*, 817.
[11] Lindsay Smith, J.R., Norman, R.O.C., Rowley, A.G. *J. Chem. Soc. Chem. Commun.* **1970**, 1238.

[12] If the amine is supplied as an inorganic salt it can be used as such. A slurry of the salt in dichloromethane is first treated with an equivalent of 4 normal sodium hydroxide.
[13] Schneider, O., Brossi, A., Vogler, K. *Helv. Chim. Acta* **1954**, *37*, 710.
[14] Monković, I., Bachand, C., Wong, H. *J. Am. Chem. Soc.* **1978**, *100*, 4609.
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[16] Murphy, J.G. Ager, J.H. May, E.L. *J. Org. Chem.* **1960**, *25*, 1386.
[17] Monković, I., Wong, H., Pircio, A.W., Perron, Y.G., Pachter, I.J., Belleau, B. *Can. J. Chem.* **1975**, *53*, 3094.
[18] Lambert, Y., Daris, J.P., Monković, I., Pircio, A.W. *J. Med Chem.* **1978**, *21*, 423.
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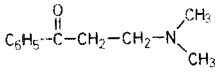
[20] This compound has been identified as a metabolite of **1e**: Cowan D.A., Huizing, G. Beckett, A.H., *Xenobiotica* **1976**, *6*, 605.

Errata and Addenda 1985

K. Matsumoto, A. Sera, T. Uchida, *Synthesis* **1985** (1), 1–26:
The structure of the second product in Table 16 (p. 18) should be:

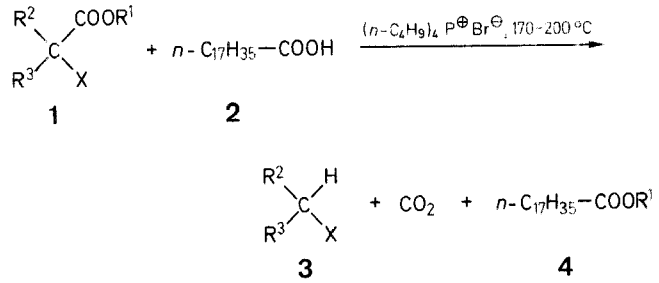


Y. Vo Quang, D. Carniato, L. Vo Quang, F. Le Goffic, *Synthesis* **1985** (1), 62–64:
The substituents R^1 for the compounds **2–4b** and **c** (p. 63) should be $C_6H_5—CH_2—O—CO—$ and $C_2H_5—O—CO—$, respectively.

K. N. Mehrotra, I. S. Singh, J. Roy, *Synthesis* **1985** (1), 81–83:
In the Table (p. 82), the I. R. assignment (C=O) should read (C=C) for all products.

J. M. Aizpurua, C. Palomo, *Synthesis* **1985** (2), 206–207:
The following paragraph should be added:
The procedure described is a specific adaption of Roesky's method [H. W. Roesky, H. H. Gieve, *Z. Naturforsch. [b]* **25**, 773 (1970)].
The authors regret the omission of this acknowledgement in the above communication.

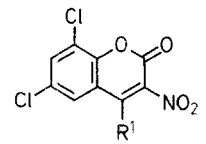
E. V. Dehmlow, E. Kunesch, *Synthesis* **1985** (3), 320–321:
The first formula scheme (p. 320) should be:



X = $COOC_2H_5$, $COOCH_3$, $CO—CH_3$, —CN

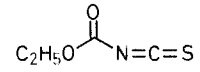
R. J. K. Taylor, *Synthesis* **1985** (4), 364–392:
The heading for the experimental procedure on p. 379 should be:
2-Benzyl-3-*n*-butylcyclopentanone (23)[90]:

A. Caşcaval, *Synthesis* **1985** (4), 428–429:
The structure of product **5** (p. 428) should be:



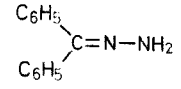
5

Y. Sanemitsu, *Synthesis* **1985** (4), 429–430:
The structure of compound **2** (p. 429) should be:



2

L. Lapatsanis, G. Milias, S. Paraskewas, *Synthesis* **1985** (5), 513–515:
The structure of compound **2** should be:

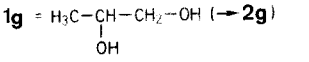


2

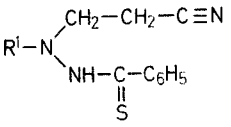
T. Eicher, R. Rohde, *Synthesis* **1985** (6/7), 619–625:
The heading for the last experimental procedure on p. 621 should be:
***endo*/*exo*-6a-Dimethylamino-6-oxo-4,5-diphenyl-2a,6,6a,7-tetrahydro-7*H*-cyclobuta[b]pyrrolizin (*endo*/*exo*-3d):**
The heading for the 3rd experimental procedure on p. 624 (left-hand column) should be:

11a-Dimethylamino-1,2-diphenyl-3-oxo-5,6,11,11a-tetrahydro-3*H*-pyrrolo[2,1-b][3]benzazepin (17):

Xue-Ping Gu, I. Ikeda, M. Okahara, *Synthesis* 1985 (6/7), 649–651:
The structure of product **1g** (p. 650) should be:



I. Yamamoto, K. Fukui, S. Yamamoto, K. Ohta, K. Matsuzaki, *Synthesis* **1985** (6/7), 686–688:
The structure of compounds **3e, f** should be:

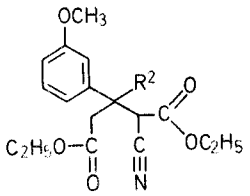


3e,f

I. Monkovic, H. Wong, C. Bachand, *Synthesis* **1985** (8), 770–773:
Reference 9 (p. 772) should be:
[9]Scherer, C. A., Dorschel, C. A., Cook, J. M., Le Quesne, P. W. *J. Org. Chem.* **1972**, *37*, 1083.

A. Cornelis, P. Laszlo, *Synthesis* **1985** (10), 909–918:
Footnotes a and b of Table 10 (p. 916) should be:
[a] 5-Methyl-2-nitro product.
[b] 3-Hydroxy-4-nitro product.

Abstract 7192, *Synthesis* **1985** (11), 1079:
The structure of product **3** should be:



3

D. Moderhack, *Synthesis* **1985** (12), 1083–1096:
The abbreviated name of compound **23** (p. 1087) should read 3-amino-4-imino-2-azetine.

S. M. Fahmy, R. M. Mohareb, *Synthesis* **1985** (12), 1135–1137:
The heading for the last experimental procedure on p. 1136 should be:
3-Amino-N^5-(2-aminophenyl)-2-cyano-2-pentenediamide (15):

F. Fülöp, G. Bernáth, *Synthesis* **1985** (12), 1148–1149:
The heading for the first experimental procedure on p. 1148 should be:
2-Substituted-1,2,3,4,5,6,7,8-octahydroquinazolines (3); General Procedure: