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A General, Selective, High-Yield N-Demethylation Procedure for Tertiary Amines by Solid Reagents in a Convenient Column Chromatography-like Setup

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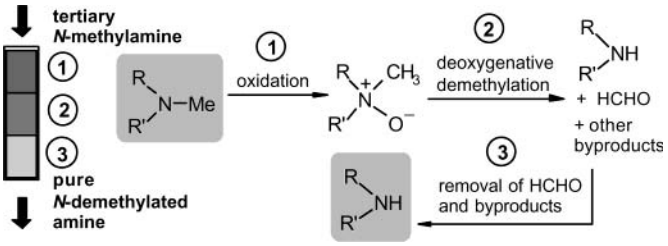
ABSTRACT



A traditional preparative chromatographic column can be used to achieve quantitative N-demethylation of tertiary *N*-methylamines and alkaloids. The filling is the crucial part and is loaded with different solid reagents in three reaction zones. The parent compound is charged on the column, and the neat N-demethylated secondary amine leaves the column some minutes later.

Tertiary *N*-methyl groups represent key elements in many natural products, especially in the realm of alkaloids and related drugs. In drug design, pharmacological developments, and metabolic studies, the removal or replacement of *N*-methyl substituents is a frequently required synthetic step. While nature is able to accomplish this N-demethylation elegantly by means of oxidative (P450) enzymes, producing *N*-desmethyl compounds from the corresponding tertiary *N*-methylamines remains a comparatively intricate task in organic chemistry, especially in the case of complex natural products.

N-Methyl groups exhibit superior stability toward many kinds of reaction conditions, which is an obstacle to cleaving *N*-methyl groups in molecules with other functional groups. Although several procedures are known to effect N-demethylation, they are often incompatible with common requirements for high yields, chemoselectivity, and mild reaction conditions.[1] Especially the standard methods, employing BrCN (*von Braun* reaction)[2] or chloroformates,[3] suffer from these disadvantages. Later approaches, using for instance diethyl azodicarboxylate[4] or *N*-iodosuccinimide,[5] give excellent yields in special cases but have limited general applicability. Also, various photochemical approaches avail-

(1) Marson, C. M.; Hobson, A. D. *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: New York, 1995; Vol. 5, p 302.

(2) (a) von Braun, J. *Chem. Ber.* **1907**, *40*, 3914. (b) von Braun, J. *Chem. Ber.* **1909**, *42*, 2219. (c) von Braun, J. *Chem. Ber.* **1911**, *44*, 1250.

(3) For examples, see: (a) Flynn, E. H.; Murphy, H. W.; McMahon, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 3104. (b) Morimoto, S.; Misawa, Y.; Adachi, T.; Nagate, T.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1990**, 286. (c) Watanabe, Y.; Kashimura, M.; Asaka, T.; Adachi, T.; Morimoto, S. *Heterocycles* **1993**, *36*, 761. (d) Campbell, A. L.; Pilipauskas, D. R.; Knanna, I. K.; Rhodes, R. A. *Tetrahedron Lett.* **1987**, *28*, 2331. (e) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028.

(4) Fang, Q. K.; Senanayake, C. H.; Han, Z.; Morency, C.; Grover, P.; Malone, R. E.; Bulter, H.; Wald, S. A.; Cameron, T. S. *Tetrahedron: Asymmetry* **1999**, *10* (23), 4477.

(5) Stenmark, H. G.; Brazzale, A.; Ma, Z. *J. Org. Chem.* **2000**, *65* (12), 3875.

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able[6] have a satisfying outcome but require rather specialized reagents and are mostly applicable to one special alkaloid only. In general, there is currently no robust, all-purpose N-demethylation procedure.

Here we would like to communicate a general method for the selective N-demethylation of tertiary *N*-methylamines (**1**) in near-quantitative yields, on a scale of up to 10 g. The approach takes the "detour" via the corresponding *N*-oxides (Figure 1), as it was elaborated from previous results on

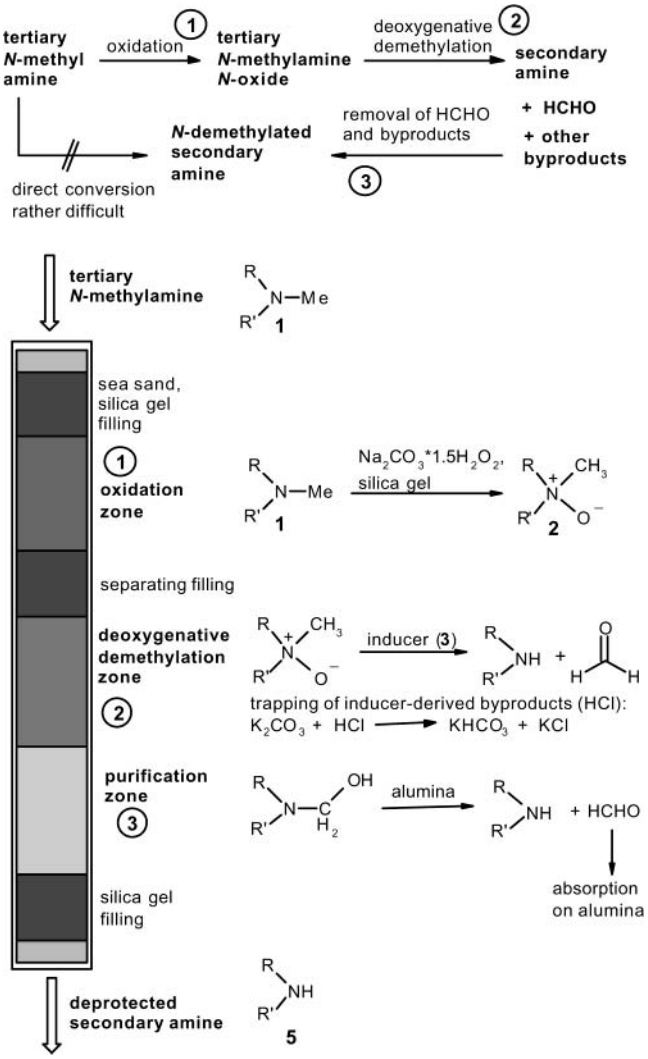

Figure 1. Column setup for the N-demethylation of tertiary *N*-methylamines.

amine *N*-oxides and their different degradation pathways.[7] The main feature is a deceptively simple work routine, requiring only solid chemicals in a chromatography-like setup: a column containing the coreactants as fillings is charged with the tertiary *N*-methylamine (**1**), which passes through the different reaction zones and leaves the column as neat *N*-desmethyl compound (**5**) a few minutes later in more than 90% yield without any need for further purification.

The N-demethylation approach consists of three stages, corresponding to the three "zones" of the demethylation column (see Figure 1): first, the intermediate formation of the tertiary amine *N*-oxide **2**, second, the deoxygenative demethylation into secondary amine **5** and HCHO,[8] and third, the removal of the latter upon its formation.

The oxidation (step 1) was favorably carried out by sodium percarbonate $Na_2CO_3 \cdot 1.5\ H_2O_2$, which converts tertiary amines quantitatively into the corresponding amine *N*-oxides, as previously demonstrated.[9] Primary and secondary amines and hydroxyls remained unchanged. The reagent combined the oxidative power of hydrogen peroxide as the oxidant of choice for amine *N*-oxide generation with the preparative advantages of a solid reagent[10] such as insolubility in all nonaqueous organic solvents and was thus superior to comparable reagents such as urea$-H_2O_2$ adduct or perborates. A 5-fold molar excess of the oxidant and reaction times over 10 min guaranteed quantitative conversion of the tertiary amine.[11]

The following deoxygenative demethylation (step 2) of the *N*-oxide intermediate **2** is the key step in the N-demethylation sequence. The autocatalytic degradation of tertiary *N*-methylamine *N*-oxides into secondary amines and HCHO catalyzed by carbenium-iminium ions[12] (*Mannich* intermediates) was the optimal choice for this reaction, as it proceeded in a quantitative and strictly methyl-selective

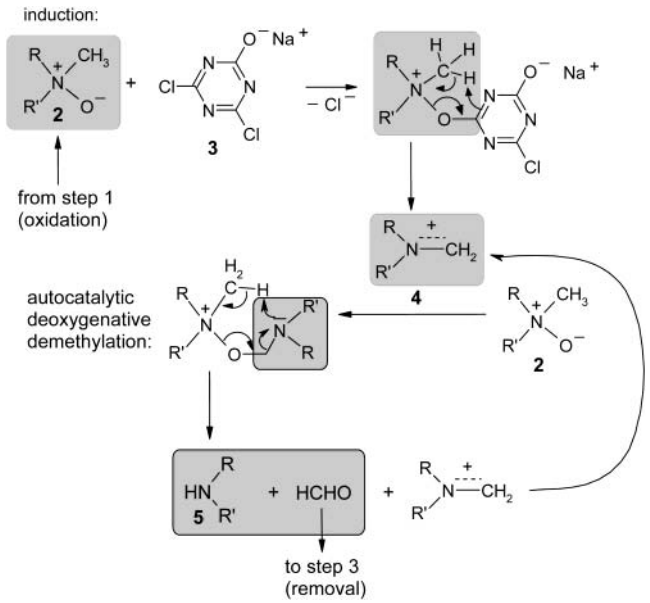

Figure 2. Mechanism of the deoxygenative demethylation reaction (step 2). The fate of the starting amine *N*-oxide through the conversion is shown by gray shading.

(6) (a) Nelson, A.; Chou, S.; Spencer, T. A. *J. Am. Chem. Soc.* **1975**, *97* (3), 648. (b) Baciocchi, E.; Lanzalunga, O.; Lapi, A.; Manduchi, L. *J. Am. Chem. Soc.* **1998**, *120* (23), 5783. (c) Sako, M.; Shimada, K.; Hirota, K.; Maki, Y. *J. Am. Chem. Soc.* **1986**, *108* (19), 6039. (d) Santamaria, J.; Ouchabane, R.; Rigaudy, J. *Tetrahedron Lett.* **1989**, *30*, 2927. (e) For a review, see: Ripper, J. A.; Tiekink, E. R. T.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **2001**, *11* (4), 443.

(7) For a review see: Rosenau, T.; Potthast, A.; Sixta, H.; Kosma, P. *Prog. Polym. Sci.* **2001**, *26* (9), 1763.

Table 1. N-Demethylation of Tertiary *N*-Methylamines According to the Column Approach

starting tertiary *N*-methylamine	N-demethylated product	yield [%]
1-methylmorpholine (**6**)	morpholine	96
dibenzylmethylamine (**7**)	*N*,*N*-dibenzylamine	89
1-methylimidazole (**8**)	imidazole	96
N-ethyl-*N*-methylaniline (**9**)	*N*-ethylaniline	98
1-methylpiperidine (**10**)	piperidine	98
N,*N*-dimethylaniline (**11**)	*N*-methylaniline	92
9-methyl-9*H*-carbazole (**12**)	carbazole	92
2-dimethylaminoethanol (**13**)	2-methylaminoethanol	91
tert-butyldimethylamine (**14**)	*tert*-butylmethylamine	93
ethyl 1-methyl-piperidine-3-carboxylate (**15**)	ethyl piperidine-3-carboxylate (ethyl nipecotate)	94
methyl 1-methyl-1,2,5,6-tetrahydro-pyridine-3-carboxylate (arecoline, **16**)	methyl 1,2,5,6-tetrahydro-pyridine-3-carboxylate	94
(±)-nicotine (**17**)	(±)-nornicotine	95

manner. The organic-insoluble sodium salt of 4,6-dichloro-2-hydroxy-[1,3,5]triazine (**3**) was used to induce the formation of *N*-(methylene)iminium ions (**4**), which then carry the reaction further, see Figure 2. Larger amounts of inducing agent, more than 1.5% relative to the starting amine, caused the reaction to become uncontrollable (which manifested in an esthetically rewarding, fountain-like discharge of the column filling, but was otherwise of little value). The evolving HCl was trapped in situ by pulverized anhydrous potassium carbonate; also here, the trapping agent and the trapping product are insoluble in organic solvents. Cyanuric chloride as the inducer[13] as well as stable *Mannich* intermediates such as *Eschenmoser's* salt proved to be overly reactive (and were moreover soluble) and thus unsuitable. Yield losses, even though in the low percent range, were mainly due to the side reaction between the inducer and already formed **5**.

The purification (step 3) brings the N-demethylation sequence to a close. The HCHO formed from the former *N*-methyl group is removed by absorption on a 1/1 mixture of neutral and basic alumina.[14] While other absorbers such as activated carbon, starch, or cellulose powder also efficiently absorbed the formaldehyde, they failed to cleave off and then bind the part of HCHO that was still bound to the product amine as *N*-hydroxymethyl compound, and they might retain larger amounts of product in addition.

In the demethylation sequence, the presence of water must be avoided. First, water lowers the efficiency of the deoxygenative demethylation step by quenching the catalytically active carbenium-iminium ions into *N*-hydroxymethyl compounds, and second, it changes the mechanism of the interaction between amine *N*-oxide and cyanuric chloride derivatives[13] so that no N-demethylation occurs. Chloroform was the eluant of choice. CH_2Cl_2, Et_2O, and other low-boiling solvents must be avoided because of the exothermicity of steps 1 and 2, which might cause cavity formation and impair the smooth passage through the column. The compatibility of the procedure with different functional groups was preliminarily checked.[15] While double bonds as well as hydroxy, ester, amide, and epoxide groups did not interfere, carboxyl groups and primary as well as secondary amines did. The latter consume the inducer in step 2; the former are retained by the aluminum oxide used in step 3.

The column technique[16] was optimized with regard to a quick (no clogging of the column) and complete conversion (no starting material left) as well as minimum retention of products (no reactions and absorption), employing *N*-methylmorpholine (**6**) and dibenzylmethylamine (**7**). Several other tertiary *N*-methylamines (**8**−**17**) were demethylated according to the present approach, among them some

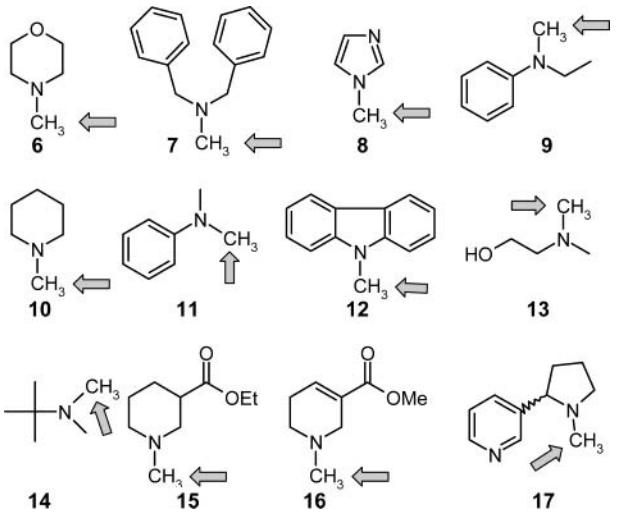

Figure 3. Demethylated tertiary *N*-methylamines. Cleaved CH_3 groups are indicated by an arrow.

(8) Process thus resembles the metabolic N-dealkylation pathway, which mostly starts with α-hydroxylation, the leaving group being cleaved in the aldehyde stage.

(9) Rosenau, T.; Potthast, A.; Kosma, P. *Synlett* **1999**, 1972.

(10) Muzart, J. *Synthesis* **1995**, *11*, 1325.

(11) Reaction time refers to the time of contact between the solute and the respective column filling as the solid coreactant.

(12) Rosenau, T.; Potthast, A.; Kosma, P.; Chen, C. L.; Gratzl, J. S. *J. Org. Chem.* **1999**, *64*, 2166.

(13) Rosenau, T.; Potthast, A.; Kosma, P. *Tetrahedron* **2002**, *58* (49), 9808.

(14) Acidic alumina must be avoided, as it retains amines. See also: Thompson, A. M. *Tellus* **1980**, *32*, 376.

medicinally important alkaloids.[17] Table 1 and the corresponding Figure 3 give illustrative examples. In all cases, the *N*-desmethyl compound was obtained in analytical purity simply by passing through the demethylation column, followed by conversion into the hydrochloride and evaporation of $CHCl_3$ as the eluant. The astonishing selectivity of the dealkylation allowed methyl cleavage in the presence of other alkyl groups, which appeared to be completely inert under the reaction conditions. This behavior can be explained with the transition state geometry of the deoxygenative demethylation step, in which the reaction centers, the C−N of the attacking carbenium-iminium ion **4** and the O−N−C−H structure of the amine *N*-oxide **2**, assemble in a six-membered, chairlike arrangement.[18] Here, a methyl group is sterically much more readily accommodated than any larger substituent.

Weighing the pros and cons of the procedure, the limitation to *N*-methyl groups can be regarded as a drawback but also as a bonus because it means complete methyl selectivity. Moreover, demethylation occurs strictly just once in dimethylamino structures. The limitation to tertiary amines is a clear shortcoming, as is the requirement of an oxidation step, which might interfere with oxidant-sensitive structures, although this was not reflected in yield losses so far. The exclusive use of solid and cheap, mostly inorganic reagents is positive with regard to environmental concerns, as it limits the use of organic solvents and the production of related waste. The broad applicability along with good yields, but most notably the quick and easy protocol, are the main benefits of the method, which is currently being applied to candidates out of the atropine and amaryllidaceae alkaloid group.

Acknowledgment. This work was supported by the Austrian Science Fund (FWF) Grant P14687.

Supporting Information Available: Typical experimental procedure, proof of purity (elemental analyses), and typical NMR spectra of N-demethylated amines. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Functional groups were contained either in the amines to be demethylated or in non-amine test compounds, of which the clear passage through the column without yield loss was taken as indication of minimum interference with the column fillings.

(16) **Preparation of Column.** Four different column fillings (mixtures A−D) were prepared as suspensions of the solids in the eluant $CHCl_3$ (mixture A, silica gel; mixture B, a 1/1 mixture of neutral and basic alumina (Brockmann grade 1); mixture C, a 3/1/1 mixture of silica gel, pulverized anhydrous K_2CO_3 and neutral alumina (Brockmann grade 1); mixture D, a 1/3 mixture of pulverized sodium percarbonate and silica gel. A standard chromatography column (i.d. 2.4 cm) is loaded successively with the fillings; filling heights given in the following refer to the settled solid material and are calculated for 10 mmol of amine to be N-demethylated. The following solids are charged from the bottom: sea sand (∼1 cm), mixture A (∼2 cm), mixture B (10 cm), mixture C containing 0.1 mmol of freshly prepared and dried **3** (4 cm), a mixture of **3** (0.05 mmol) and 2 g of silica gel, mixture A (∼2 cm), mixture D (10 cm), and sea sand (∼3 cm).

(17) **N-Demethylation Procedure.** Tertiary *N*-methylamine (10 mmol) was dissolved in $CHCl_3$ (2 mL) and applied to the column. Chloroform (30 mL) was added on top, and 30 mL of eluant was withdrawn from the bottom; the flow was stopped for 10 min (contact time between amine and mixture D, which can be extended without problems). An eluant reservoir was added, and elution was resumed at 2 mL/min until no more amine left the column (TLC control). The eluate fractions were combined, and the solvents were evaporated in vacuo to give the pure N-demethylated amine. In the case of low-boiling amines, the combined eluate fractions were treated with ethereal HCl prior to solvent evaporation to give the product amines as hydrochlorides (for examples and yields, see Table 1).

(18) This is also supported by DFT computations.