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Novel Palladium and Ruthenium Catalysed Transformation of Tertiary Amines to Secondary Amines and Sulphides with Thiolate Anions

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Summary The reaction of tertiary amines with phenylmethane- and benzene-thiolates in the presence of a palladium or ruthenium catalyst gives secondary amines and the corresponding sulphides selectively.

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DEALKYLATION of tertiary amines is an important transformation particularly for synthesis of biologically active compounds.[1] We report here a novel and convenient method for the transformation of a tertiary amine to a secondary amine and the corresponding sulphide [equation (1)]. This is the first successful capture of the iminium ion intermediate,[2] prepared by the metal catalysed activation of the carbon–hydrogen bond of a tertiary amine, with nucleophiles and provides a novel type of method for the preparation of iminium ions which are highly versatile synthetic intermediates.[3]

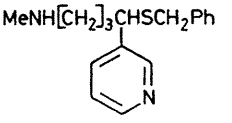
$$R^1R^2R^3N + R^4SNa \xrightarrow[\text{ii, } H_3O^+]{\text{i, Pd}} R^4SR^1 + R^2R^3NH \qquad (1)$$

Simple tertiary amines undergo dealkylation to give secondary amines and benzyl or phenyl sulphides, when treated with phenylmethane- or benzene-thiolates in excess of thiols in the presence of palladium black. Other palladium compounds such as $PdCl_2$ and $Pd(OAc)_2$ gave similar results. Alternatively, soluble ruthenium catalysts such as ruthenium trichloride can be used conveniently, giving similar results. This method is easy to carry out, as shown by the following typical procedure for the preparation of the sulphide (**1**). Thus, a mixture of nicotine (1·23 g), palladium black (0·10 g), and sodium phenylmethanethiolate, prepared from sodium (0·23 g) and phenylmethanethiol (5 ml), was stirred at 200 °C for 48 h in a sealed tube under argon. The mixture was then dissolved in ether and filtered. The usual work-up followed by silica-gel chromatography gave (**1**) in 90% yield. Further results obtained under similar conditions are summarized in the Table. Milder conditions can be utilized. Although the reaction temperature is high, the method is operationally simple, highly selective, and efficient, and hence in many instances offers advantages over previous methods.

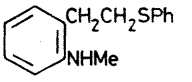
TABLE. Transformation of tertiary amines[a]

Amine	Product[b]	Yield/ %[c]
Bu_3N	$BuSCH_2Ph$	92
Bu_2NMe	$BuSCH_2Ph$	69[d]
N-Methylindoline	(**2**)	(80)
(**3**)	(**4**)	91
(**3**)	(**5**)	88
Nicotine	(**1**)	(90)
(**6**)	(**7**)	(86)
(**8**)	(**9**)	(72)
N-Methylpiperazine[e]	(**10**)	(82)
(**11**)	(**12**)	(62)

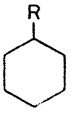
[a] See text for conditions. [b] All products were identified by ^1H n.m.r., i.r., and mass spectroscopy and elemental analyses. [c] G.l.c. yields based upon the starting amine. Yields in parentheses are isolated yields following chromatographic separation. [d] Benzyl methyl sulphide was obtained in 22% yield. [e] The sodium salt of *N*-methylpiperazine was used.



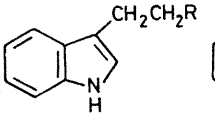
(1)



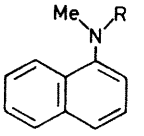
(2)



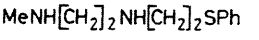
(3) R = NMe_2
(4) R = SCH_2Ph
(5) R = SPh



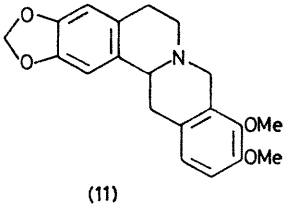
(6) R = NMe_2
(7) R = SPh



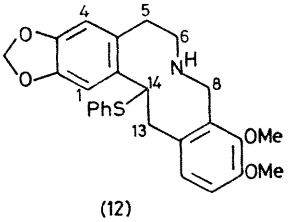
(8) R = Me
(9) R = H



(10)



(11)



(12)

The cleavage of the carbon–nitrogen bond of an unsymmetrical tertiary amine occurs preferentially in the order of tertiary > secondary > primary carbon–nitrogen bond. Consequently, cyclic nitrogen compounds undergo selective ring opening to produce amino-sulphides which are often important intermediates in natural product synthesis. *N*-Methylindoline can be converted into 2-(2-*N*-methylamino)phenyl ethyl sulphide (**2**), the indole structure normally being inert towards cleavage. One alkyl group can be removed from a dialkylarylamine efficiently. Secondary and primary amines do not undergo the transformation,† and this may be of practical use. *N*-Methylpiperazine can be converted into the diamine (**10**) selectively in 82% yield. As a practical synthetic example,[4] we have applied

† The reaction of an amine with compounds containing an N–H bond proceeds *via* a Schiff base intermediate (N. Yoshimura, I. Moritani, T. Shimamura, and S.-I. Murahashi, *J. Amer. Chem. Soc.*, 1973, **95**, 3038).

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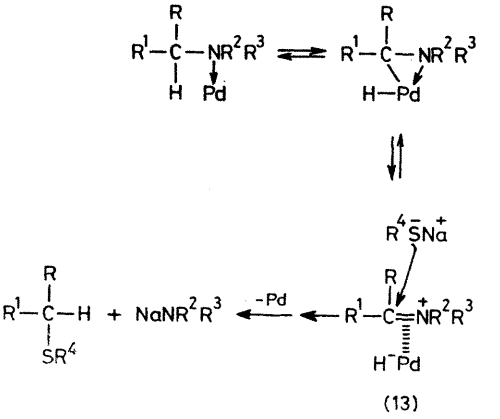
the method to the transformation of canadine (**11**). The reaction of (**11**) with benzenethiolate in the presence of a catalytic amount of anhydrous ruthenium trichloride (150 °C; 10 h) gave the azecine (**12**), m.p. 146—148 °C in 62% yield:‡ ^{1}H n.m.r. ($CDCl_3$) 1·25 (s, 1H, NH), 2·55—3·88 (m, 6H), 3·62 (s, 1H, 8-H), 3·83 (s, 6H, OMe), 4·10 (s,1H, 8-H), 4·37 (s, 1H, 14-H), 5·87 (s, 2H, OCH_2O), 6·56 (s, 1H, 4-H), 6·67 (s, 2H, 1- and 11-H), 6·70 (s, 1H, 12-H), and 7·32 (m, 5H, ArH) (the coupling constant between the C-8 protons is close to 0); *m/e* 449, 448, 372, 340, 109, and 77. In general, the technique is valuable because the incorporation of the PhS group permits a variety of modifications to be made to the products.

While it is not yet possible to provide any detailed mechanistic information, the course of the reaction can be readily accounted for by the mechanism in the Scheme. Recently, we reported the palladium catalysed alkyl-exchange reaction of tertiary amines and suggested the intermediacy of an iminium ion–palladium complex,[2] formed from the insertion of palladium co-ordinated to nitrogen into a carbon–hydrogen bond adjacent to the nitrogen.[2,5] In the present reaction, nucleophilic attack of thiolate anion on the intermediate (**13**) occurs faster than that of the second molecule of the tertiary amine, giving a sulphide and a sodium amide.



(13)

SCHEME

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‡ The hydrolysis product of (**11**), 2,3-dihydroxy-9,10-dimethoxytetrahydroprotoberberine, was also formed.

[1] N. Langlois, F. Gvéritte, Y. Langlois, and P. Potier, *J. Amer. Chem. Soc.*, 1976, **98**, 7017; P. W. Jeffs and J. D. Scharver, *ibid.*, p. 4301; J. P. Kutney, G. K. Figendolf, H. Matse, A. Murai, K. Tanaka, W. L. Sung, K. Wada, and B. R. Worth, *ibid.*, 1978, **100**, 938.
[2] S.-I. Murahashi, T. Hirano, and T. Yano, *J. Amer. Chem. Soc.*, 1978, **100**, 348.
[3] H. Böhme and M. Haake, *Adv. Org. Chem.*, 1976, **9**, 107; N. L. Holy and Y. F. Wang, *J. Amer. Chem. Soc.*, 1977, **99**, 944, and references therein.
[4] T. Kametani, 'The Total Synthesis of Natural Products,' ed. J. ApSimons, Wiley-Interscience, London, vol. **3**, 1977, p. 1.
[5] R. M. Laine, D. W. Thomas, L. W. Cary, and S. E. Buttrill, *J. Amer. Chem. Soc.*, 1978, **100**, 6527.

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