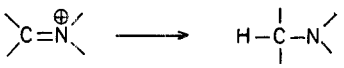
A Mild and Chemoselective Reduction of Cyclic Iminium Salts

Giovanni PALMISANO*, Giordano LESMA, Micaela NALI, Bruno RINDONE, Stefano TOLLARI

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano; Centro di Studio per le Sostanze Organiche Naturali del C.N.R., Via Venezian 21, I-20133 Milano, Italy

N-Substituted cyclic iminium salts are conveniently reduced to the corresponding tertiary amines in good yields by reaction with tributylstannane in methanol at room temperature. A variety of functional groups (such as ketonic groups) present in the molecule are not affected under these conditions.

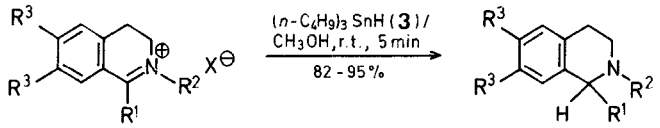
The reduction of iminium salts to the corresponding amines can be achieved by a variety of methods such as, for example, dissolving-metal methods, catalytic hydrogenation, or reduction with metal hydrides[1,2].



Some of the methods utilizing the dissolution of metals in protic solvents require strongly acidic conditions, the second of the above-mentioned methods suffers from the drawback that it cannot be used with unsaturated compounds (e.g., **1b**) and other hydrogenation-sensitive substrates (e.g., **1d, e, g**). The last method is not suitable for carbonyl compounds (e.g. **1f, g, l**).

Tributylstannane[3] **(3)** has proven to be a useful reagent for effecting a variety of preparative transformations[4]. We now report that tributylstannane can be conveniently used for the reduction of cyclic iminium salts **(1)** at room temperature without the usually required presence of azoisobutyronitrile as a radical initiator. Simple stirring of substrates **1** and reagent **3** (2.5 equiv) in a protic solvent affords the tertiary amines **2** as the only isolable product. As shown in Table 1, various types of cyclic tertiary amines **2** can be prepared in uniformly high yields by a virtually instantaneous reaction (< 5 min). The reaction is broadly applicable, tolerating many substituents such as halogen, double bond, and nitro groups. Since reagent **3** has been found to be compatible with the presence of carbonyl groups in the substrate, reduction of the *N*-(4-bromophenacyl)-iminium salt **1g** to the *N*-(4-bromophenacyl)-amine **2g** can now also be conveniently achieved whereas the reduction of **1** with metal hydrides at room temperature (sodium borohydride in 2-propanol or lithium alanate in 1,2-dimethoxyethane) leads to the formation of significant quantities (26–30%) of the corresponding *N*-[2-(4-bromophenyl)-2-hydroxyethyl)-amine (**4**, see Table 2).

The reductions of iminium salt **1j** and of 3-dehydroajmalicine perchlorate **1k** with reagent **3** afford the essentially pure diastereoisomers **2j** and **2k** (ajmalicine), respectively. In these cases, the high stereoselectivity associated with the reduction of the iminium function can be explained by steric hindrance of the β-face of $C{=}N^{\oplus}$, forcing hydride delivery from the axial direction. The same stereochemical result has been observed with mixed metal hydrides. The compatibility of reducing agent **3** with a considerable number of functional groups, combined with its mild nature, may render this procedure a method of choice for the reduction of highly functionalized iminium salts.



1a-i 2a-i

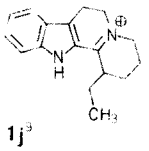
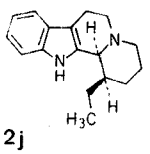
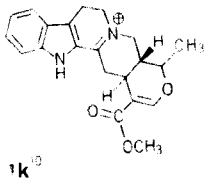
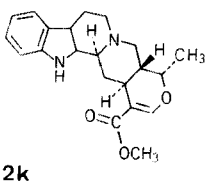
Educt	Product	X	R^1	R^2	R^3
1a[6]	2a · HCl	J	H	CH_3	OCH_3
1b	2b	Br	H	$-CH_2-CH=CH_2$	OCH_3
1c	2c	Br	H	$-CH_2-C_6H_5$	OCH_3
1d[6]	2d	Br	H	$-CH_2-C_6H_4-NO_2$	OCH_3
1e	2e	Br	H	$-CH_2-C_6H_4-CH_2Br$	OCH_3
1f	2f	Br	H	$-CH_2-C(=O)-C_6H_4-OCH_3$	OCH_3
1g	2g	Br	H	$-CH_2-C(=O)-C_6H_4-Br$	OCH_3
1h	2h · HCl	J	$-CH_2-C_6H_5$	CH_3	OCH_3
1i	2i	J	H	CH_3	H
		ClO_4^-	–	–	–
1j[9]	2j				
		ClO_4^-	–	–	–
1k[10]	2k				

Table 1. Cyclic Tertiary Amines (**2**) prepared from Cyclic Iminium Salts (**1**) by Reduction with Tributylstannane (**3**)

Amine 2	Yield [%]	m.p. [°C]	Molecular Formula[a] or m.p. [°C] reported
2a · HCl	82	215–216° (methanol)	216–217°[11]
2b	87	48–50° (hexane/ether)	$C_{14}H_{19}NO_2$ (233.3)
2c	95	87–89° (hexane/ether)	88–90°[7]
2d	86	119–121° (ether)	$C_{18}H_{20}N_2O_4$ (328.4)
2e	92	88–90° (dec) (ether)	$C_{19}H_{22}BrNO_2$ (376.3)
2f	87	114–116° (ether)	$C_{20}H_{23}NO_4$ (341.4)
2g	90	96–98° (hexane/ether)	$C_{19}H_{20}BrNO_3$ (390.3)
2h · HCl	84	173–174° (methanol)	173–174°[12]
2i	92	215–216° (methanol/water)	217–218°[13]
2j	95	116–118° (hexane)	116–119°[14]
2k	90	256–257° (methanol)	254–256°[15]

[a] The microanalyses for the new compounds were in satisfactory agreement with the calculated values: C ±0.21, H ±0.29, N ±0.23.

The reductions were performed with commercially available tributylstannane (**3**) the purity of which was checked by ^{1}H-N.M.R. analysis [δ of Sn—H = 4.87 ppm (sept, $J \approx 2$ Hz)].

Cyclic Iminium Salts 1b, f, g; General Procedure:
A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline[5] (0.478 g, 2.5 mmol) and the alkyl bromide (R^2—Br; 2.7 mmol) in dimethylformamide (5 ml) is heated to boiling on a steam bath for 20 min. The cooled solution is added to ether (100 ml) with efficient stirring to precipitate the yellow iminium salt as a solid in nearly quantitative yield. Purification (which is not necessary for the following reduction) may be achieved by repeated recrystallization from ethanol/ether.

2-Allyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Bromide (**1b**): m.p. 161–163°C.

6,7-Dimethoxy-2-(4-methoxyphenacyl)-3,4-dihydroisoquinolinium Bromide (**1f**): m.p. 186–188°C.

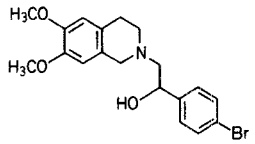
2-(4-Bromophenacyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Bromide (**1g**): m.p. 192–193°C.

Reduction of Iminium Salts 1 to Cyclic Tertiary Amines 2 with Tributylstannane (3); General Procedure:
Dry methanol (50 ml), the iminium salt **1** (1.0 mmol), and tributylstannane (**3**; 728 mg, 2.5 mmol) are placed in a 100 ml round-bottom flask fitted with stirrer and nitrogen inlet. The deep yellow color of the solution fades immediately. The mixture is stirred for 5 min after time T.L.C. analysis (chloroform/methanol 4/1) indicates complete disappearance of **1** and formation of the amine **2**. The solvent is removed on a rotary evaporator and the residue suspended in dichloromethane (50 ml). This suspension is extracted with 0.1 normal hydrocloric acid (2 × 20 ml). The aqueous extracts are combined, saturated with sodium chloride and made basic with conc. ammonia. The product is extracted with dichloromethane (2 × 20 ml) and the extract dried with sodium sulfate. Removal of the solvent by rotary evaporator followed by pumping for 10 min at 0.01 torr gives the crude amine **2** which is purified by crystallization (see Table 1). Alternatively, the crude amine is converted into the hydrochloride by treatment with hydrogen chloride gas in ether, and recrystallization of the hydrochloride.

Table 2. Selected ^{1}H-N.M.R. Data of the New Compounds **1**, **2**, and **4**

Compound	^{1}H-N.M.R. (solvent/TMS_{int})	
	Solvent	δ [ppm]
1b	$CDCl_3$	3.23 (t, 2H, J = 7 Hz, 4,4-H_2); 3.91 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 4.88 (d, 2H, J = 5.5 Hz, CH_2—CH=CH_2); 5.35–6.30 (m, 3H, CH_2—CH=CH_2); 6.83, 7.70 (2s, 1H each); 10.13 (s, 1H, 1-H)
1f	$CDCl_3$	3.51 (t, 2H, J = 7 Hz, 4,4-H_2); 4.05 (s, 3H, OCH_3); 4.10 (s, 3H, OCH_3); 4.20 (s, 3H, OCH_3); 6.18 (s, 2H, N—CH_2); 6.82, 7.45 (2s, 1H each); 9.83 (s, 1H, 1-H)
1g	DMSO-d_6	3.31 (t, 2H, J = 7 Hz, 4,4-H_2); 4.00 (s, 6H, $2OCH_3$); 4.08 (t, 2H, J = 7 Hz, 3,3-H_2); 6.41, 6.85 (2s, 1H each); 6.45–8.10 (AA′XX′ pattern, 2H); 10.00 (s, 1H, 1-H)
2b	$CDCl_3$	3.18 (br. d, 2H, J = 5.5 Hz, CH_2—CH=CH_2); 3.60 (s, 3H, 1,1-H_2); 3.85 (s, 6H, $2OCH_3$); 5.05–5.40 (m, 2H, CH_2—CH=CH_2); 5.7–6.2 (m, 1H, CH_2—CH=CH_2); 6.53 (s, 1H, 8-H); 6.60 (s, 1H, 5-H)
2e	$CDCl_3$	3.70 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 4.80 (s, 2H, CH_2=Br); 6.05 (s, 1H, 8-H); 6.51 (s, 1H, 5-H); 7.30–7.65 (AA′XX′ pattern, 2H)
2f	$CDCl_3$	2.84 (s, 2H); 3.75 (s, 2H, 1,1-H_2); 3.8–3.9 (s, 9H, $3OCH_3$); 6.51 (s, 1H, 8-H); 6.60 (s, 1H, 5-H); 6.85–8.15 (AA′XX′ pattern, 2H)
2g	$CDCl_3$	2.85 (s, 4H); 3.73 (s, 2H, 1,1-H_2); 3.83 (s, 6H, $2OCH_3$); 3.91 (s, 2H); 6.50 (s, 1H, 8-H); 6.60 (s, 1H, 5-H); 7.5–8.1 (AA′XX′ pattern, 2H)
4[a]	$CDCl_3$	3.45–4.15 (AB part of ABX system, 2H, CH_2—CHOH—Ar); 3.93 (s, 6H, $2OCH_3$); 4.86 (dd, 1H, J_1 = 10 Hz, J_2 = 6 Hz, CH_2—CHOH—Ar); 6.60 (s, 1H, 8-H); 6.70 (s, 1H, 5-H); 7.2–7.55 (AA′XX′ pattern, 2H)

[a] **4** =



obtained in 26–30% yield together with **2g** (55–60%) by reduction of **1g** with $NaBH_4$ in 2-propanol or $LiAlH_4$ in 1,2-dimethoxyethane; m.p. 86–88°C (hexane/ethyl acetate).

Received: April 17, 1985

* Address for correspondence.

[1] See, for example: Shamma, M., in: *The Isoquinoline Alkaloids*, Academic Press, New York · London, 1972.

[2] An interesting reductive alkylation of iminium salts was reported by: Shono, T., Hamaguchi, H., Sasaki, M., Fujita, S., Nagami, K. *J. Org. Chem.* **1983**, *48*, 1621.

[3] Kuivila, H.G. *Synthesis* **1970**, 499.

[4] For more recent applications, see:
Keinan, E., Greenspoon, N. *Tetrahedron Lett.* **1982**, *23*, 241.
Keinan, E., Gleize, P.A. *Tetrahedron Lett.* **1982**, *23*, 477.
Four, P., Guibé, F. *Tetrahedron Lett.* **1982**, *23*, 1825.

[5] Haworth, R.D. *J. Chem. Soc.* **1927**, 2281.

[6] Wholey, M., Meadow, M. *J. Chem. Soc.* **1953**, 1067.

[7] Chapman, J.H., Holton, P.G., Ritchie, A.C., Walker, T., Webb, G.B., Whiting, K.D.E. *J. Chem. Soc.* **1962**, 2471.

[8] Shamma, M., Tökc, L. *Tetrahedron* **1975**, *31*, 1991.

[9] Danicli, B., Lesma, G., Palmisano, G. *J. Chem. Soc. Chem. Commun.* **1980**, 860.

[10] Wenkert, E., Roychaudhuri, D.K. *J. Org. Chem.* **1956**, *21*, 1315.

[11] Finkelstein, J., Brossi, A. *J. Heterocyclic Chem.* **1967**, *4*, 315.

[12] Knabe, J., Kubitz, J. *Arch. Pharm. (Weinheim)* **1963**, *296*, 532.

[13] Boekelheide, V., Ainsworth, C. *J. Am. Chem. Soc.* **1950**, *72*, 2132.

[14] Wenkert, E., Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914.

[15] Pakrashi, S.C., Djerassi, C., Wasicky, R. Neuss, N. *J. Am. Chem. Soc.* **1955**, *77*, 6687.