New Chiral Isoquinolinium Salt Derivatives from Chiral Primary Amines *via* Zincke Reaction

Denis Barbier, Christian Marazano,* Bhupesh C. Das,* and Pierre Potier

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex, France

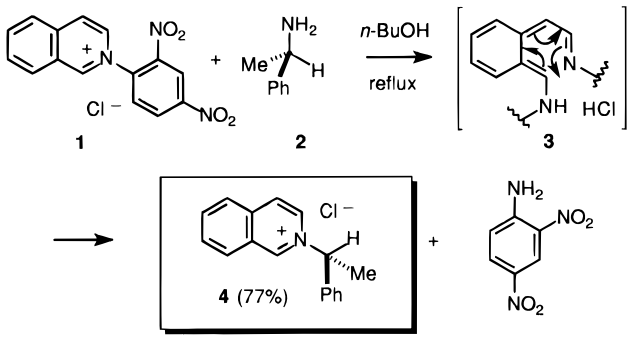
Received August 7, 1996

Recent publications from our laboratory have shown that the Zincke reaction with chiral primary amines provides a very practical entry to new pyridinium salt derivatives of interest in asymmetric synthesis.[1] Selective reduction of these salts to 1,2- or 1,4-dihydropyridines, which could be equilibrated to dihydropyridinium salt equivalents, afforded versatile intermediates for the enantioselective synthesis of alkaloids containing substituted six-membered nitrogen heterocycles.[2] We now describe the extension of this methodology to the syntheses of chiral isoquinolinium salt derivatives of practical interest for the asymmetric synthesis of substituted tetrahydroisoquinolines.

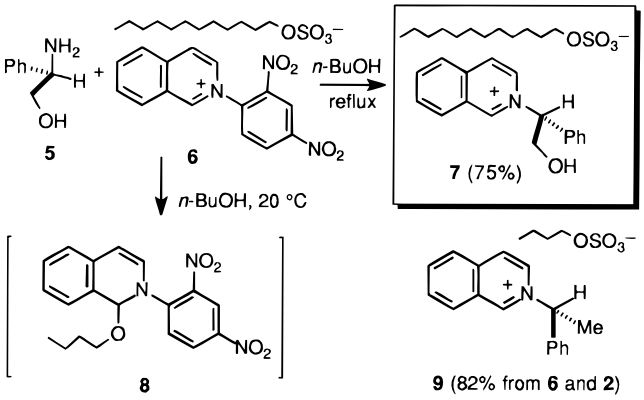
Reaction of salt **1** (Scheme 1), easily obtained from isoquinoline and 1-chloro-2,4-dinitrobenzene, with anilines to give *N*-phenylisoquinolinium salts was reported by Zincke and Weisspfenning.[3] This reaction proceeded in the same way as that for the corresponding pyridinium salts. It was thus not surprising to observe that the treatment of salt **1** with 1.2 equiv of (*R*)-(+)-1-phenylethylamine (**2**) in refluxing 1-butanol, according to the conditions found appropriate in the pyridine series,[1] gave, presumably *via* intermediates such as **3**,[4] the desired chiral isoquinolinium salt **4**, which was recovered in 77% yield after a simple extraction procedure.

By contrast, the Zincke reaction of salt **1** with (*R*)-(−)-phenylglycinol (**5**) (Scheme 2) in refluxing 1-butanol did not proceed at all, the only products obtained, along with the unreacted amine **5**, being isoquinoline and 1-chloro-2,4-dinitrobenzene resulting from decomposition of salt **1**. A simple explanation for this failure was that the chloride anion was nucleophilic enough to compete favorably with the chiral amine. A straightforward alternative was to make use of a less nucleophilic counteranion. We therefore selected a lipophilic dodecyl sulfate group which, in addition to being less nucleophilic, should provide salts better soluble in organic solvents.[2b] Salt **6** was thus easily obtained by treatment of **1** with sodium dodecyl sulfate. As anticipated, this new salt gave a good yield of the desired chiral derivative **7** in refluxing 1-butanol. Formation of a precipitate of adduct **8**, characterized as a crystalline solid, was observed at ambient temperature. Such an adduct was not obtained in the pyridine series. The butyl sufate salt **9** was obtained in place of the expected dodecyl sulfate salt when salt **6** was refluxed with (*R*)-(+)-1-phenylethylamine (**2**) in 1-butanol.

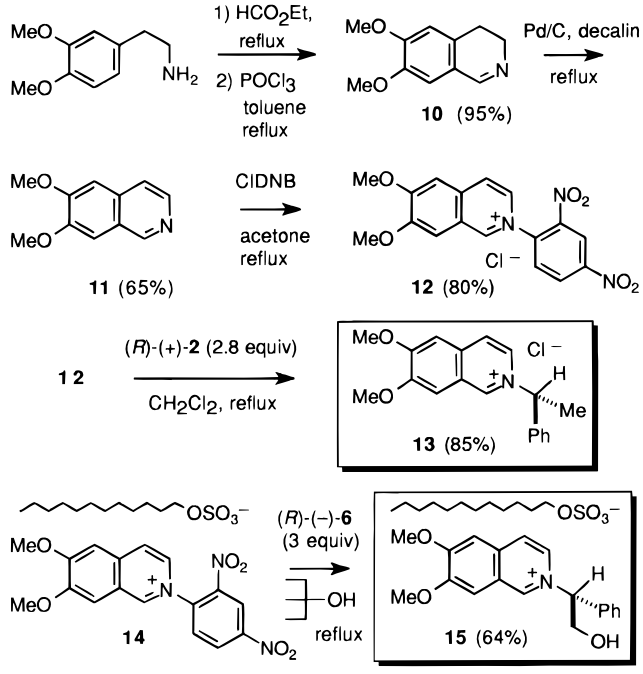
Scheme 1



Scheme 2



Scheme 3



Extension of this approach to methoxy-substituted isoquinoline derivatives was also investigated, and the results are summarized in Scheme 3. The Bischler−Napieralski reaction of (dimethoxyphenyl)ethylamine[5] gave the dihydroisoquinoline derivative **10**, whose aro-

(1) Génisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431.

(2) (a) Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1991**, 625. (b) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052. (c) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Das, B. C. *Tetrahedron Lett.* **1994**, *35*, 707. (d) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39*, 811.

(3) Zincke, T. H.; Weisspfenning, G. *Justus Liebigs Ann. Chem.* **1913**, *396*, 103. For an extension of this reaction to hydrazine derivatives, see: Agai, B.; Lempert, K. *Tetrahedron* **1972**, *28*, 2069.

(4) For a description of the mechanism, see ref 1 and two reviews: (a) Kost, A. N.; Gromov, S. P.; Sagitullin, R. S. *Tetrahedron* **1981**, *37*, 3423. (b) Becher, J. *Synthesis* **1980**, 589.

(5) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc* **1989**, *111*, 4859.

S0022-3263(96)01539-3 CCC: $12.00

matization[6] afforded the required dimethoxyisoquinoline **11**.[7] Condensation of **11** with 1-chloro-2,4-dinitrobenzene met with no difficulty. In contrast to Zincke salt **1**, the reaction of salt **12** with chiral amines to give products resulting from opening of the isoquinolinium ring (see intermediate **3**) failed completely, the primary amine attacking the 2,4-dinitrobenzene ring and thus regenerating dimethoxyisoquinoline **11**. Such failures were already reported in the case of the treatment of salt **12** with other primary amines such as anilines,[8] and no alternative conditions were found. This behavior could obviously be attributed to a decreased electrophilicity of the isoquinolinium ring due to the donor effects of the methoxy groups. We therefore applied conditions previously selected by us to overcome similar drawbacks in the pyridine series.[1,2b] As expected, attack of the isoquinolinium ring with an excess of **2** was thus effected by using dichloromethane as solvent to give the desired open form intermediates (see **3**). The electrocyclization of these intermediates now seemed to be assisted by the donor effect of the methoxy groups: simply refluxing the dichloromethane solution leads to salt **13** in good yield.

Finally, treatment of dodecyl sulfate salt **14** with an excess of **5** in refluxing 3-methyl-3-pentanol gave the desired salt **15**, these last conditions being also identical to those found appropriate in the substituted pyridine series.[1]

Use of these new chiral isoquinolinium salt derivatives for the enantioselective syntheses of 1- and/or 3-substituted tetrahydroisoquinolines will be reported shortly.

Experimental Section

2-(2,4-Dinitrophenyl)isoquinolinium Chloride (1). Finely powdered 1-chloro-2,4-dinitrobenzene (34.5 g, 170.5 mmol) was added to isoquinoline (22 g, 170.5 mmol), and the resulting mixture was heated at 60 °C with vigorous stirring for 2 h [after 0.25 h, acetone (10 mL) was added in order to avoid formation of a glassy solid]. Salt **1** was then precipitated with acetone and filtered. Orange crystals (49.2 g, 148.4 mmol, 87%) were collected from MeOH−EtOAc: mp 199−200 °C; ^{1}H NMR (250 MHz, CD_3OD) δ 8.22 (ddd, J = 1.4, 7, 8.3 Hz, 1 H), 8.37 (d, J = 8.7 Hz, 1 H), 8.44 (ddd, J = 1.2, 7, 7.5 Hz, 1 H), 8.50 (d, J = 7.5 Hz, 1 H), 8.60 (d, J = 8.3 Hz, 1 H), 8.74 (d, J = 6.8 Hz, 1 H), 8.91 (dd, J = 1.5, 6.8 Hz, 1 H), 8.96 (dd, J = 2.5, 8.7 Hz, 1 H), 9.31 (d, J = 2.5 Hz, 1 H), 10.29 (d, J = 1.5 Hz, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 123.3, 127.2, 128.6, 128.9, 131.3, 132.8, 133.2, 133.4, 136.4, 139.9, 140.4, 144.6, 150.8, 152.7; MS (FAB) m/z (relative intensity) 296 (M^+, 100), 204 (23), 130 (5). Anal. Calcd for $C_{15}H_{10}O_4N_3Cl\cdot 0.1H_2O$: C, 54.02; H, 3.08; N, 12.6; O, 19.67; Cl, 10.63. Found: C, 54.02; H, 3.28; N, 12.34; O, 19.77; Cl, 10.91.

(+)-2-[(1*R*)-1-Phenylethyl]isoquinolinium Chloride (4). To a solution of Zincke salt **1** (2.5 g, 7.5 mmol) in *n*-BuOH (50 mL) was added (+)-(1*R*)-1-phenylethylamine (**2,** 1.1 mL, 9.1 mmol), and this mixture was boiled under reflux for 15 h. Removal of solvent under reduced pressure left a gum which was dissolved in water and filtered. The aqueous phase was collected, basified with a few drops of concentrated ammonia, and washed twice with AcOEt in order to remove the remaining 2,4-dinitrophenylamine and the excess of **2**. Evaporation of water gave salt **4** (1.57 g, 5.8 mmol, 77%) as a pale brown gum: $[\alpha]_D$ +46 (*c* 3.3, EtOH); ^{1}H NMR (300 MHz, CD_3OD) δ 2.21 (d, J = 7 Hz, 3 H), 6.30 (q, J = 7 Hz, 1 H), 7.42−7.50 (m, 3 H), 7.55−7.59 (m, 2 H), 8.08 (ddd, J = 1.7, 6.5, 8.3 Hz, 1 H), 8.25 (ddd, J = 1.3, 6.5, 8.3 Hz, 1 H), 8.30 (dd, J = 1.7, 8.3 Hz, 1 H), 8.45 (d, J = 6.9 Hz, 1 H), 8.54 (dd, J = 1.3, 8.3 Hz, 1 H), 8.67 (dd, J = 1.6, 6.9 Hz, 1 H), 10.12 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 20.7, 71.8, 127.8, 128.4, 128.6, 129.1, 130.5, 130.8, 131.9, 132.6, 134.3, 138.5, 138.9, 139.03, 149.7; MS (FAB) m/z (relative intensity) 234 (M^+, 78), 130, 105.

2-(2,4-Dinitrophenyl)isoquinolinium Dodecyl Sulfate (6). A solution of Zincke salt **1** (60.1 g, 181.3 mmol) and sodium dodecyl sulfate (57.5 g, 200 mmol) in CH_2Cl_2 (1 L) was refluxed for 3 h. After filtration over Celite and removal of solvent, orange crystals of salt **6** were obtained from AcOEt in a quantitative yield: mp 75−82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.4 Hz, 3 H), 1.16−1.43 (m, 18 H), 1.38 (m, 2 H), 3.61 (t, J = 6.9 Hz, 2 H), 7.98 (ddd, J = 4, 4, 8 Hz, 1 H), 8.19 (d, J = 8.7 Hz, 1 H), 8.23 (d, J = 4 Hz, 1 H), 8.25 (d, J = 4 Hz, 1 H), 8.45 (d, J = 6.8 Hz, 1 H), 8.59 (dd, J = 2.5, 8.7 Hz, 1 H), 8.61 (d, J = 8 Hz, 1 H), 8.82 (dd, J = 1.5, 6.8 Hz, 1 H), 8.99 (d, J = 2.5 Hz, 1 H), 10.46 (d, J = 1.5 Hz, 1 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 13.8, 22.3−31.6 (10 C), 67.0, 121.9, 125.7, 127.1, 127.3, 129.6, 131.5, 131.8, 131.9, 135.2, 138.1, 138.7, 138.8, 142.8, 148.8, 151.6; MS (FAB) m/z (relative intensity) 296 (M^+, 100), 130 (6). Anal. Calcd for $C_{27}H_{35}O_8N_3S\cdot 0.9H_2O$: C, 56.12; H, 6.42: N, 7.27; O, 24.64; S, 5.55. Found: C, 56.18; H, 6.42; N, 7.06; O, 24.55; S, 5.41.

(−)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]isoquinolinium Dodecyl Sulfate (7). Zincke salt **6** (28.9 g, 51.51 mmol) dissolved in 1-butanol (300 mL) was added dropwise to a solution of (−)-(*R*)-phenylglycinol (**5**, 7.8 g, 64.37 mmol) in 1-butanol (200 mL) with stirring. A precipitate of orange crystals was formed. An analytical sample of these crystals was filtered and identified as 1-(butyloxy)-2-(2,4-dinitrophenyl)-1,2-dihydroisoquinoline (8): mp 124−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 7.3 Hz, 3 H), 1.15−1.31 (m, 2 H), 1.35−1.48 (m, 2 H), 3.08 (ddd, J = 6.3, 6.3, 8.9 Hz, 1 H), 3.25 (ddd, J = 6.3, 6.3, 8.9 Hz, 1 H), 6.05 (dd, J = 1.2, 7.5 Hz, 1 H), 6.12 (d, J = 7.5 Hz, 1 H), 6.27 (d, J = 1.2 Hz, 1 H), 7.22−7.45 (m, 4 H), 8.08 (d, J = 9.2 Hz, 1 H), 8.61 (dd, J = 2.7, 9.2 Hz, 1 H), 8.72 (d, J = 2.7 Hz, 1 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 13.7, 19.4, 31.8, 62.8, 85.9, 108.4, 122.5, 124.1, 125.0, 126.7, 127.0, 127.9, 128.2, 129.5, 130.9, 141.3, 141.8, 144.0; MS (EI) m/z (rel. intensity) 369 ($M^{\bullet+}$, 10), 236 (100), 204 (2). Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38; O, 21.38. Found: C, 61.58; H, 5.21; N, 11.38; O, 21.66. The heterogeneous solution obtained above was then refluxed overnight. After removal of solvent, the residue was chromatographed over silica gel (800 g) using a gradient of CH_2Cl_2−MeOH (100:0 to 85:15) to give salt **7** (20.2 g, 39.22 mmol, 75%) as a pale brown gum: $[\alpha]_D$ −37 (*c* 3.4, EtOH); ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J = 6.6 Hz, 3 H), 1.12−1.43 (m, 18 H), 1.60 (2 H), 4.0 (t, J = 6.6 Hz, 2 H), 4.42 (dd, J = 4.1, 12.5 Hz, 1 H), 4.64 (dd, J = 9.2, 12.5 Hz, 1 H), 6.19 (dd, J = 4.1, 9.2 Hz, 1 H), 7.43−7.50 (m, 3 H), 7.56−7.62 (m, 2 H), 8.03 (ddd, J = 1.7, 6.5, 8.3 Hz, 1 H), 8.20 (ddd, J = 1.1, 6.5, 8.3 Hz, 1 H), 8.26 (dd, J = 1.7, 8.3 Hz, 1 H), 8.44 (d, J = 6.9 Hz, 1 H), 8.54 (dd, J = 1.1, 8.3 Hz, 1 H), 8.66 (dd, J = 1.6, 6.9 Hz, 1 H), 10.09 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 14.4, 23.6−32.9 (10 C), 63.1, 69.0, 77.3, 127.6, 128.3, 128.8, 129.3, 130.5, 131.0, 131.9, 132.4, 134.5, 135.3, 138.4, 139.0; MS (FAB) m/z (relative intensity) 250 (M^+, 100), 130 (88), 121 (19).

2-(2,4-Dinitrophenyl)-6,7-dimethoxyisoquinolinium Chloride (12). Finely powdered 1-chloro-2,4-dinitrobenzene (11.73 g, 57.9 mmol) was added to 6,7-dimethoxyisoquinoline (**11**, 7.3 g, 38.6 mmol) in acetone (200 mL), and the resulting mixture was refluxed for 4 h. Salt **12** precipitated during the reaction. This precipitate was filtered and dissolved in a minimum of hot AcOEt; this, on cooling, gave **12**, which was collected as an orange powder (12.1 g, 30.9 mmol, 80%): mp 162−167 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.10 (s, 3 H), 4.21 (s, 3 H), 7.83 (s, 1 H), 8.32 (d, J = 8.6 Hz, 1 H), 8.41 (d, J = 6.8 Hz, 1 H), 8.63 (dd, J = 1.4, 6.8 Hz, 1 H), 8.90 (dd, J = 2.5, 8.6 Hz, 1 H), 9.25 (d, J = 2.5 Hz, 1 H), 9.76 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 57.4, 58.0, 107.1, 108.8, 123.2, 124.4, 125.5, 131.0, 133.0, 134.7, 138.8, 140.7, 145.1, 147.0, 150.8, 155.4, 161.9; MS (FAB) m/z (relative intensity) 356 (M^+, 100), 190 (46).

(+)-2-[(1*R*)-1-Phenylethyl]-6,7-dimethoxyisoquinolinium Chloride (13). A solution of Zincke salt **12** (2 g, 5.5 mmol) in MeOH (10 mL) was diluted with CH_2Cl_2 (150 mL). **2** (2 mL, 15.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise to this solution with stirring, and the resulting mixture was refluxed overnight. Isoquinolinium salt **13** was isolated as a pale brown

(6) Zhao, B.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 5277.
(7) For an alternative synthesis of isoquinoline **11**, see: Birch, A. J.; Jackson, A. H.; Shannon, V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185.
(8) Kabachnik, M. I., Zitser, A. I. *Zh. Obshch. Khim.* **1937**, *7*, 162; *Chem. Abstr.* **1937**, *31*, 4320.

gum (1.4 g, 4.3 mmol, 85%) using the workup procedure used for the preparation of salt **4**: $[\alpha]_D$ +23 (*c* 2, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.17 (d, J = 7 Hz, 3 H), 4.03 (s, 3 H), 4.06 (s, 3H), 6.25 (q, J = 7 Hz, 1 H), 7.47−7.6 (m, 5 H), 7.61 (s, 1 H), 7.71 (s, 1 H), 8.2 (d, J = 6.9 Hz, 1 H), 8.5 (dd, J = 1.6, 6.9 Hz, 1 H), 9.78 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 20.7, 57.23, 57.7, 70.7, 106.6, 108.4, 125.1, 125.8, 128.4−130.6 (5 C), 132.9, 137.4, 139.4, 144.6, 154.6, 159.8; MS (FAB) *m*/*z* (relative intensity) 294 (M^+, 100), 190 (40), 105 (64).

(−)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxyisoquinolinium Dodecyl Sulfate (15). Dodecyl sulfate salt **14** (4 g, 6.44 mmol), obtained from the corresponding chloride **12** according to the procedure used for the preparation of salt **6**, was dissolved in 3-methyl-3-pentanol (100 mL). A solution of **5** (2.2 g, 16.06 mmol) in 3-methyl-3-pentanol (25 mL) was added dropwise with stirring. After 2 h at ambient temperature, the resulting mixture was refluxed for 1 h. Removal of solvent under vacuum gave a residue, which was chromatographed over silica gel (100 g) using acetone as eluent to give isoquinolinium salt **15** (2.35 g, 4.08 mmol, 64%) as a pale brown gum: $[\alpha]_D$ −18 (*c* 2.6, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.2 Hz, 3 H), 1.21−1.37 (m, 18 H), 1.65 (m, 2 H), 4.06 (s, 6 H), 4.08 (t, J = 6.9 Hz, 2 H), 4.33 (dd, J = 4.1, 12.9 Hz, 1 H), 4.67 (dd, J = 10.5, 12.9 Hz, 1 H), 6.16 (dd, J = 4.1, 10.5 Hz, 1 H), 7.17 (s, 1 H), 7.26−7.41 (m, 5 H), 7.83 (s, 1 H), 7.89 (d, J = 6.9 Hz, 1 H), 8.17 (dd, J = 1.4, 6.9 Hz, 1 H), 9.84 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.1, 22.7−31.9 (10 C), 56.9, 57.1, 63.0, 68.3, 75.2, 105.1, 108.1, 123.7, 124.4, 127.8−129.9 (5 C), 132.2, 134.5, 135.7, 144.5, 153.0, 158.2; MS (FAB) *m*/*z* (relative intensity) 310 (M^+, 68), 190 (100), 121 (23).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**, **4**, **6**−**9**, and **12**−**15** with attribution of signals (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961539B