Oxiranes in the Ritter reaction: synthesis of 6,7-(or 5,8-)dimethoxy-3,4-dihydroisoquinolines by a tandem alkylation–cyclization procedure

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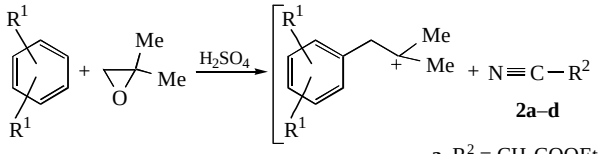
Treatment of 1,2- (or 1,4)-dimethoxybenzene with isobutylene oxide and an appropriate nitrile RCN in concentrated sulfuric acid leads to 1-R-6,7-(or 5,8-)dimethoxy-3,3-dimethyl-3,4-dihydroisoquinolines.

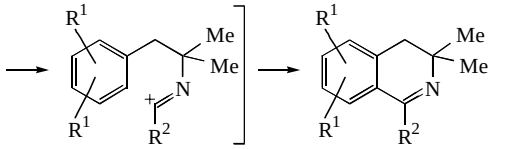
Numerous syntheses of the isoquinoline ring are known to date.[1] Most of them include formation of C_4–C_{4a} or C_1–C_{8a} bonds as a crucial stage. Here we describe a method for the preparation of substituted 3,4-dihydroisoquinolines *via* the convergent formation of these bonds step by step in a one-pot procedure.†



2a–d

1a $2R^1$ = 1,2-$(MeO)_2$
1b $2R^1$ = 1,4-$(MeO)_2$

a R^2 = CH_2COOEt
b R^2 = Me
c R^2 = SMe
d R^2 = Ph



3a–d $2R^1$ = 6,7-$(MeO)_2$
4a–c $2R^1$ = 5,8-$(MeO)_2$

Traditional syntheses of 3,4-dihydroisoquinolines using the Ritter reaction need styrenes[2] or benzylcarbinols[3] as precursors of the carbocation. To the best of our knowledge, until the present time the use of oxiranes in this reaction has not been documented.

We examined an application of substituted epoxide, namely isobutylene oxide, in the acid-catalysed alkylation of activated aromatic compounds, involving generation of the carbonium ion in the first stage of the Ritter reaction, with subsequent electrophilic attack on the appropriate nitrile, giving the immonium salt, which is susceptible to cyclization to 3,3-dimethyl-3,4-dihydroisoquinolines **3a–d**, **4a–c**.

The structure of compounds **3a–d**, **4a–c** was confirmed by elemental analysis, NMR and IR spectroscopy.‡ It should be noted that the ^{1}H NMR spectra of these substances after typical work-up show only one set of signals, *i.e.* the isobutylene oxide ring opens regioselectively under the reaction conditions. The mode of its opening is confirmed unambiguously by an independent synthesis of compounds **3b–d** by the traditional method.[3] Substance **3c** was described earlier.[4]

The low yields of **3b**, **4b** (37% and 25%) are due to the fact that these compounds are obtained after hydrolysis and decarboxylation of **3a**, **4a** in dilute sulfuric acid during the workup, and partial demethylation of **3b**, **4b** takes place.

The reaction described provides a simple and convenient one-pot procedure for preparing 1-substituted 3,3-dimethyl-3,4-dihydroisoquinilines with electron-donating groups. The value of this protocol lies in the ability to obtain analogues of naturally occurring 6,7-dimethoxy-3,4-dihydroisoquinilines, as well as 5,8-dimethoxy substituted ones, which can be readily oxidized to the corresponding quinones, structural moieties of antimicrobial substances.[5]

† A typical experimental procedure was as follows. A mixture of veratrole (or 1,4-dimethoxybenzene, 13.82 g, 0.1 mol), isobutylene oxide (9.94 ml, 0.11 mol) and the appropriate nitrile (0.1 mol) in 120 ml of toluene was added, dropwise with vigorous stirring, to concentrated sulfuric acid (40 ml, 0.75 mol) for 20 min (temperature runs from 20 to 55 °C; for syntheses of **3a** and **4a** the temperature was maintained in the range 20–25 °C). After 1 h of stirring the reaction mixture was poured on to 300 g of crushed ice. The organic layer was separated and washed with 50 ml of water, the combined water layers were washed twice with 40 ml of toluene and made basic with ammonium carbonate up to pH 8, extracted with ether and dried over magnesium sulfate. Products were isolated and purified by vacuum distillation (**3b**,**c**, **4b**), recrystallization (**3a**,**d**, **4c**) or column chromatography on silica gel (**4a**). Compound **3a** was isolated from the residue after ether extraction by treatment with methanol and recrystallization from hexane. Hydrochlorides of **3a**,**d** were obtained by passing dry HCl through ether solutions of **3a**,**d** and recrystallization from ethanol–ether. In the case of compounds **3b**, **4b** the water layer was made basic up to pH ~1 and refluxed for 3 h, cooled, treated with ammonium carbonate (pH ~8) and worked-up as described above.

‡ **3a**: mp 104–105 °C (hexane), yield 80%; ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.21 (s, 6H, 3-Me), 1.24 (t, 3H, Me, *J* 9.0 Hz), 2.69 (s, 2H, 4-CH_2), 3.83 (s, 6H, 6,7-OMe), 4.10 (q, 2H, OCH_2, *J* 10.0 Hz), 4.98 (s, 1H, CH=), 6.55 (s, 1H, 5-H), 7.06 (s, 1H, 8-H). (Compound exists in the form of enamine[3]). IR (Nujol, ν/cm^{-1}): 3260 (N–H), 1725 (C=O), 1645 (C=N), 1600, 1570, 1510, 1405, 1295, 1265 ($\nu_{as\ C–O–C}$), 1235, 1210, 1185, 1150, 1090, 1040 ($\nu_{s\ C–O–C}$), 1005, 950, 870.

3a·HCl: mp 184–186 °C (decomp.). ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.16 (t, 3H, Me), 1.51 (s, 6H, 3-Me), 3.03 (s, 2H, 4-CH_2), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.13 (q, 2H, OCH_2), 4.56 (s, 2H, CH_2), 6.88 (s, 1H, 5-H), 7.09 (s, 1H, 8-H), 14.50 (wide s, 1H, NH) (enamine is protonated by β-C atom).

3b: bp 148–150 °C (12 mmHg), mp 75–76 °C (hexane), yield 37%, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.13 (s, 6H, 3-Me), 2.28 (s, 3H, 1-Me), 2.55 (s, 2H, 4-CH_2), 3.84 (s, 6H, 6,7-OMe), 6.58 (s, 1H, 5-H), 6.93 (s, 1H, 8-H); IR (Nujol, ν/cm^{-1}): 1620 (C=N), 1595, 1570, 1510, 1345, 1290, 1265 ($\nu_{as\ C–O–C}$), 1225, 1205, 1150, 1060 ($\nu_{s\ C–O–C}$), 980, 965, 835.

3c·HCl: mp 199–203 °C (decomp.).

3d: mp 139–141 °C (acetone–ether), yield 55%, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.21 (s, 6H, 3-Me), 2.66 (s, 2H, 4-CH_2), 3.63 (s, 3H, 7-MeO), 3.87 (s, 3H, 6-MeO), 6.60 (s, 2H, 5,8-H), 7.28–7.48 (m, 5H, H arom.); IR (Nujol, ν/cm^{-1}): 1600 (C=N), 1555, 1510, 1270 ($\nu_{as\ C–O–C}$), 1210, 1030 ($\nu_{s\ C–O–C}$).

4a: oil, yield 72%, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.15 (s, 6H, 3-Me), 1.20 (t, 3H, Me), 2.69 (s, 2H, 4-CH_2), 3.67 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.05 (q, 2H, OCH_2), 5.69 (s, 1H, HC=), 6.72 (s, 2H, 6,7-H), 9.21 (s, 1H, NH); IR (neat, ν/cm^{-1}): 3250 (NH), 1730, 1600, 1505, 1305, 1270, 1175, 1090.

4b: oil, bp 147–150 °C (7 mmHg), yield 25%, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.09 (s, 6H, 3-Me), 2.36 (s, 3H, 1-Me), 2.50 (s, 2H, 4-CH_2), 3.68 (s, 6H, 5,8-MeO), 6.68 and 6.72 (2s, 2H, 6,7-H); IR (neat, ν/cm^{-1}): 1610 (C=N), 1590, 1580, 1330, 1270 ($\nu_{as\ C–O–C}$), 1250, 1200, 1150, 1090, 1055 ($\nu_{s\ C–O–C}$), 1035, 970, 910, 800.

4c: mp 82–83 °C (methanol–water), ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.19 (s, 6H, 3-Me), 2.28 (s, 3H, MeS), 2.53 (s, 2H, 4-CH_2), 3.72 (s, 3H, MeO), 3.79 (s, 3H, MeO), 6.75 (d, 2H, 6,7-H); IR (Nujol, ν/cm^{-1}): 1590, 1555, 1325, 1275, 1200, 1080, 1020, 1005, 980.

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Received: Moscow, 30th September 1997
Cambridge, 6th November 1997; Com. 7/07583I