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Benzo[*b*]furan in the Povarov reaction

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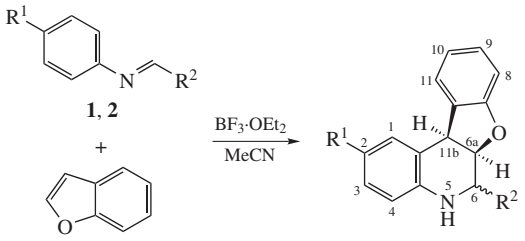
The Povarov-type condensation of ethyl 2-(arylimino)acetates, 1-aryl-2-aryliminoethanones or *N*-benzylideneanilines with benzo[*b*]furan affords 5,6,6a,11b-tetrahydrobenzofuro[2,3-*c*]quinolines and/or related benzofuro[2,3-*c*]quinolines.

Interaction of the Schiff bases with activated olefins (the Povarov reaction[1]) is recognized as a versatile method for the synthesis of 1,2,3,4-tetrahydroquinolines annulated to tetrahydrofuran and tetrahydropyran,[2] pyrrolidine,[3] indole,[4] oxazole and thiazole[5] moieties. In contrast to 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran,[2] only one example is known of the use of benzo[*b*]furan in the Povarov reaction, namely, a three-component condensation with substituted anilines and glyoxylic acid.[6] In the course of our synthetic studies,[7] we have explored condensation of benzo[*b*]furan with ethyl 2-(arylimino)acetates **1**, 1-aryl-2-aryliminoethanones **2** and arylideneanilines **3** (Schemes 1 and 2).



1, **4**: **a** R^1 = Br, R^2 = C(O)OEt
b R^1 = Me, R^2 = C(O)OEt
c $R^1 = R^2$ = C(O)OEt

2, **5**: **a** R^1 = H, R^2 = C(O)C_6H_4OMe-4
b R^1 = F, R^2 = C(O)C_6H_4OMe-4
c R^1 = F, R^2 = C(O)C_6H_4Cl-4

Scheme 1

Initially, we found that the three-component condensation gives low conversion, so we chose the traditional approach involving preliminary synthesis of imines **1** and **2**. Also, it seemed reasonable to use the Schiff bases from ethyl glyoxylates and arylglyoxals, which, according to the literature, are the good candidates for this purpose.[8]

Optimization of a solvent and a catalyst was performed for compound **4a** obtained from ethyl 4-bromophenyliminoacetate.[9] The following solvents were tested: acetonitrile (89% yield), 2,2,2-trifluoroethanol (94% yield), 1,1,1,3,3,3-hexafluoropropan-2-ol. In the last case, aromatization of 1,2,3,4-tetrahydroquinoline core takes place giving rise to the respective benzofuro[2,3-*c*]-quinoline in 55% yield along with 10% of **4a**. The appropriability of 2,2,2-trifluoroethanol as a solvent for the Povarov condensation was mentioned earlier.[2(*g*),7(*b*)] Catalysts [BF_3·OEt_2, $InCl_3$, $Dy(OTf)_3$] were tested in acetonitrile. All the above mentioned catalysts showed high activity (~89–92% yields). So, taking into account the results obtained, we used further MeCN as a solvent and BF_3·OEt_2 as a catalyst (see Scheme 1).

This protocol provides a straightforward route to substituted 5,6,6a,11b-tetrahydrobenzofuro[2,3-*c*]quinolines which are promising subjects for medicinal chemistry.[6] General synthetic approaches to benzofuro[2,3-*c*]quinolines are scarce. In 1990, Yamaguchi had reported two methods for the synthesis of benzofuro[2,3-*c*]quinolines: condensation of 2-amino-2′-hydroxybenzophenone with chloroacetone[10] or photocyclization of *N*-benzyl-*N*-phenyl-2-benzofurancarboxamides.[11]

It is interesting to note that regioselectivity of benzo[*b*]furan in the reaction resembles that of indene:[12] the electrophilic attack of imine is aimed at C(2) atom rather than C(3) (as in 2,3-dihydrofuran).[2,13]

Compounds **4** and **5** were isolated in yields of 58–96%.[†] According to the structure of compound **4a**, its ^{1}H NMR spectrum exhibits signals of $C^{6a}H$ proton at δ 5.62 ppm (dd, *J* 9.6 Hz, *J* 2.4 Hz), C^6H_{ax} at δ 3.98 ppm (d, *J* 2.4 Hz) and HC^{11b} at δ 4.65 ppm (d, *J* 9.6 Hz). For an alternative structure of benzofuro[3,2-*c*]-

[†] All new compounds have correct analytical and spectral data. Some experimental details and selected spectral characteristics [^{1}H (300 MHz), ^{13}C (75 MHz) NMR, GC-MS] are as follows.

General procedure for the preparation of compounds **4–6**. BF_3·OEt_2 (7 μl, 7.9 mg, 0.15 mmol) was added to Shiff base **1–3** (1 mmol) in 10 ml of MeCN with stirring, and after 10 min benzofuran (0.21 ml, 0.23 g, 2 mmol) was added. After 1 h of stirring at 25 °C the mixture was poured into water (50 ml), extracted with ethyl acetate (2×25 ml), washed with $NaHCO_3$ solution (15 ml), brine (20 ml), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–light petroleum, 19:1) and crystallized from ethanol.

*Ethyl (6*R*S*,6a*R*,11b*R*)-2-bromo-5,6,6a,11b-tetrahydrobenzofuro[2,3-*c*]quinoline-6-carboxylate* **4a**. Yield 89%, colourless needles, mp 172.3 °C. ^{1}H NMR, δ: 1.38 (t, 3H, Me, *J* 7.2 Hz), 3.98 (d, 1H, H^6, *J* 2.4 Hz), 4.39 (q, 3H, OCH_2 + NH, *J* 7.2 Hz), 4.65 (d, 1H, H^{11b}, *J* 9.3 Hz), 5.62 (dd, 1H, H^{6a}, ^3J 9.3 Hz, ^3J 2.4 Hz), 6.53 (d, 1H, H^4, *J* 8.4 Hz), 6.78 (m, $2H_{arom}$), 7.06 (d, $1H_{arom}$, *J* 7.5 Hz), 7.11 (dd, 1H, H^3, ^3J 8.4 Hz, ^4J 2.4 Hz), 7.16 (d, $1H_{arom}$, *J* 7.5 Hz), 7.41 (d, 1H, H^1, ^4J 2.4 Hz). ^{13}C NMR, δ: 14.2 (Me), 43.2 (C^{11b}), 58.2 (OCH_2), 62.0 (C^6), 83.4 (C^{6a}), 109.8 (C^2), 111.8 (C^8), 117.7 (C^4), 121.0, 124.7, 126.7, 128.8, 129.1, 130.2, 130.4, 143.1 (C^{4a}), 159.1 (C^{7a}), 168.9 (C=O). GC-MS, *m*/*z*: 373 [$M^{+\bullet}$]. Found (%): C, 57.49; H, 4.45; N, 3.67. Calc. for $C_{18}H_{16}BrNO_3$ (%): C, 57.77; H, 4.31; N, 3.74.

*Ethyl (6*R*S*,6a*R*,11b*R*)-2-methyl-5,6,6a,11b-tetrahydrobenzofuro[2,3-*c*]quinoline-6-carboxylate* **4b**, *ethanol solvate*. Yield 61%, colourless crystals, mp 144.8 °C. ^{1}H NMR, δ (a mixture of two diastereomers at C^6, *R*:*S* ~ 1:1): 1.07 (t, 3H, Me, *J* 7.2 Hz), 1.21 (t, 3H, *J* 7.2 Hz, Me), 1.37 (t, 3H, Me, *J* 7.2 Hz), 2.23 (s, 3H, Ar–*Me*), 2.27 (s, 3H, Ar–*Me*), 3.97 (d, 1H, H^6, *J* 2.1 Hz), 4.09 (q, 3H, OCH_2, *J* 7.2 Hz), 4.16 (q, 3H, OCH_2, *J* 7.2 Hz), 4.67 (d, 1H, H^{11b}, *J* 9.3 Hz), 5.63 (dd, 1H, H^{6a}, *J* 9.3 and 2.1 Hz), 6.59 (d, $1H_{arom}$, *J* 8.7 Hz), 6.73–6.87 (m, $3H_{arom}$), 7.00–7.17 (m, $3H_{arom}$). GC-MS, *m*/*z*: 309 [$M^{+\bullet}$]. Found (%): C, 70.88; H, 6.40; N, 3.79. Calc. for $C_{19}H_{19}NO_3$·C_2H_5OH (%): C, 70.96; H, 7.09; N, 3.94.

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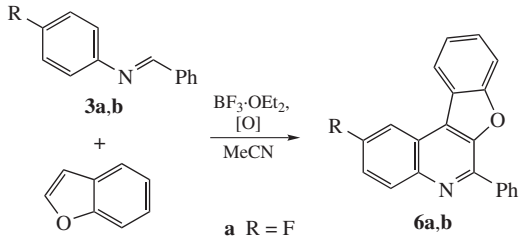

Scheme 2

quinoline, we should have observed a dublet HC^{6a} at downfield aliphatic region δ 5.52–5.54 ppm (J 7 Hz).[14]

It is worth mentioning the high *endo*-selectivity of the condensation. The prevailing *endo*-addition (classification according to the review[1(*b*)]) is widely documented in the literature,[15] it was recently confirmed by the X-ray diffraction[16] as well as justified by theoretical calculations.[17]

To our regret, all our attempts to produce a crystal suitable for X-ray diffraction analysis have failed, therefore, stereochemistry of compounds **4**, **5** was proposed on the basis of published data. Compounds **4a–c**, **5a–c** were characterized as a mixture of *endo*-annulated *R**/*S** diastereomers at C^6 atom.

The condensation of the Schiff bases **3a**,**b** with benzo[*b*]furan required higher temperatures (70–90 °C) due to the lower electrophilicity of their imine entity; moreover, in the course of processing such 1,2,3,4-tetrahydroquinolines underwent aromatization affording the respective benzofuro[2,3-*c*]quinolines **6a**,**b** in moderate yields (58–60%) (see Scheme 2).‡

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Online Supplementary Materials

Supplementary data (synthesis and characteristics of compounds **1–3** and characteristics of compounds **4c** and **5c**) associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.06.010.

6-(4-Methoxybenzoyl)-5,6,6a,11b-tetrahydrobenzofuro[2,3-c]quinoline **5a**. Yield 58%, colourless crystals, mp 177.7 °C. ^{1}H NMR, δ: 3.87 (s, 3 H, OMe), 4.77 (d, 1H, H^{11b}, J 9.0 Hz), 4.86 (d, 1H, H^6, J 2.1 Hz), 5.71 (dd, 1H, H^{6a}, ^3J 9.0 Hz, ^3J 2.1 Hz), 6.63 (d, 1H_{arom}, J 8.1 Hz,), 6.71 (m, 2H_{arom}), 6.84 (m, 1H_{arom}), 6.98 (d, 2 H, $H^{3'}$, $H^{5'}$, ^3J 8.7 Hz), 7.03 (m, 1H_{arom}), 7.12 (d, 1H_{arom}, ^3J 7.8 Hz), 7.32 (d, 1H_{arom}, ^3J 7.8 Hz), 7.98 (d, 2 H, $H^{2'}$, $H^{6'}$, ^3J 8.7 Hz), NH group is not observed in the ^{1}H NMR spectrum due to proton exchange. GC-MS, *m*/*z*: 355 [$M^{+\bullet}$ – 2]. Found (%): C, 77.18; H, 5.32; N, 3.75. Calc. for $C_{23}H_{19}NO_3$ (%): C, 77.29; H, 5.36; N, 3.92.

6-(4-Methoxybenzoyl)-2-fluoro-5,6,6a,11b-tetrahydrobenzofuro[2,3-c]-quinoline **5b**. Yield 75%, colourless crystals, mp 156.0 °C. ^{1}H NMR, δ: 3.88 (s, 3 H, OMe), 4.72 (d, 1H, H^{11b}, J 9.3 Hz), 4.83 (d, 1H, H^6, J 2.1 Hz), 5.67 (dd, 1H, H^{6a}, ^3J 9.3 and 2.1 Hz), 6.65 (m, 2H_{arom}), 6.77 (m, 2H_{arom}), 6.98–7.06 (m, 4H_{arom}), 7.13 (d, 1H_{arom}, J 7.2 Hz), 7.98 (d, 2 H, $H^{2'}$, $H^{6'}$, J 8.7 Hz); NH group is not observed in the ^{1}H NMR spectrum due to proton exchange. GC-MS, *m*/*z*: 373 [$M^{+\bullet}$ – 2]. Found (%): C, 73.42; H, 4.84; N, 3.77. Calc. for $C_{23}H_{18}FNO_3$ (%): C, 73.59; H, 4.83; N, 3.73.

‡ *2-Fluoro-6-phenylbenzofuro[2,3-c]quinoline* **6a**. Yield 60%, colourless crystals, mp 164.7 °C. ^{1}H NMR, δ: 7.45–7.66 (m, 6H_{arom}), 7.78 (d, 1H_{arom}, J 7.8 Hz), 8.09 (dd, 1H_{arom}, J 9.0 and 3.0 Hz), 8.32 (m, 2H_{arom}), 8.51 (m, 2H_{arom}). GC-MS, *m*/*z*: 313 [$M^{+\bullet}$]. Found (%): C, 79.50; H, 3.46; N, 4.26. Calc. for $C_{21}H_{12}FNO$ (%): C, 80.50; H, 3.86; N, 4.47.

2-Bromo-6-phenylbenzofuro[2,3-c]quinoline **6b**. Yield 58%, colourless crystals, mp 178.9 °C. ^{1}H NMR, δ: 7.50–7.66 (m, 5H_{arom}), 7.78 (m, 2H_{arom}), 8.16 (d, 1H_{arom}, ^3J 9.0 Hz), 8.35 (d, 1H_{arom}, ^3J 7.8 Hz), 8.51 (m, 1H_{arom}), 8.61 (d, 1H_{arom}, ^4J 2.1 Hz). ^{13}C NMR, δ: 112.85, 121.27, 122.77, 122.84, 124.10, 124.65, 124.86, 124.49, 128.70, 128.90, 129.23, 130.04, 131.05, 132.18, 135.98, 143.07, 145.60, 148.35, 156.14. GC-MS, *m*/*z*: 373 [$M^{+\bullet}$]. Found (%): C, 67.30; H, 3.14; N, 3.66. Calc. for $C_{21}H_{12}BrNO$ (%): C, 67.40; H, 3.23; N, 3.74.

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