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Mendeleev Commun., 1993, **3(4)**, 146–148
Mendeleev Communications

A Novel Synthesis of Benzofuro[3,2-*c*]pyridine Derivatives

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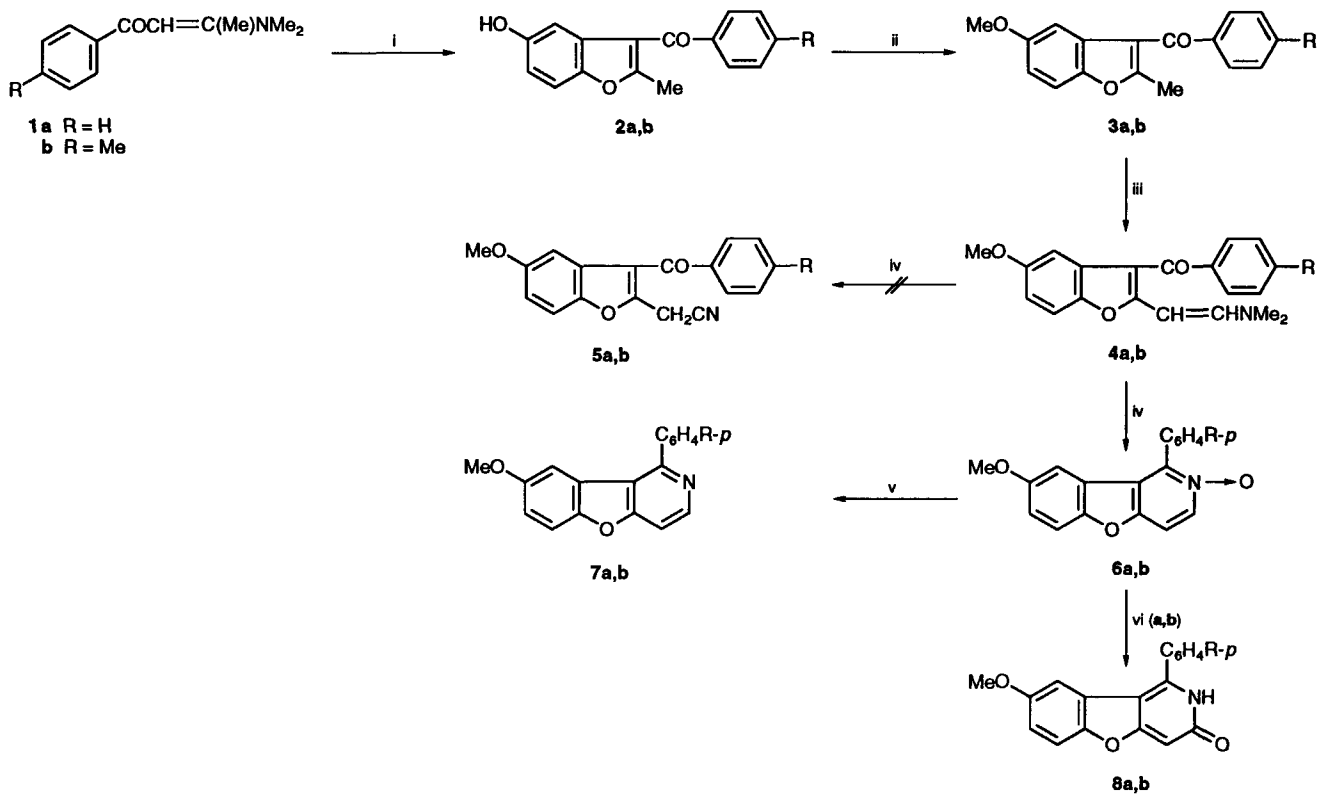
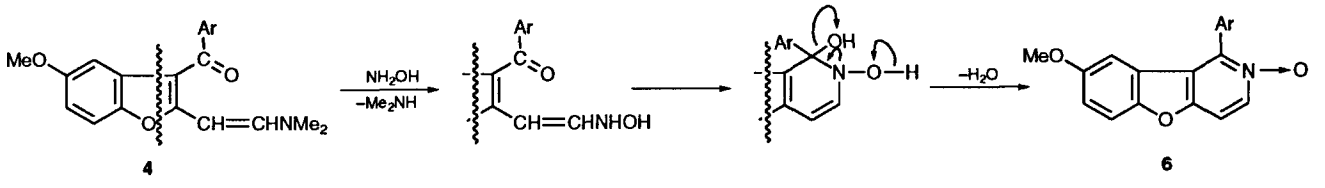
A new synthesis of benzofuro[3,2-*c*]pyridine derivatives **6a,b**, **7a,b** and **8a,b**, based on the reactions of 2(β-dimethylaminovinyl)-3-acyl-5-methoxybenzofurans **4a,b** with hydroxylamine hydrochloride, is described.

It has already been reported that the tertiary enaminoketone β-dimethylamino-β-methylacrylophenone **1a** enters smoothly into the Nenitzescu reaction to yield 2-methyl-3-benzoyl-5-hydroxybenzofuran **2a**, *O*-methylation of which gives the 5-methoxy derivative **3a**. The 2-Me group of this compound is sufficiently mobile that on heating with dimethylformamide diethylacetal it readily yields enamine **4a**.[1] Analogously, in the present work, *p*-methyl derivatives **2b**, yield 36%, m.p. 174–176 °C (AcOH), **3b**, yield 100% (under phase-transfer catalysis), m.p. 71–72 °C (heptane) and **4b**, yield 91%, m.p. 126–128 °C (Pr^iOH) have been synthesised (Scheme 1).

The presence of electron-donating enamine groups at position 2 in the benzofuran ring of **4a,b** reduces the reactivity of the 3-carbonyl substituents, hence the formation of oximes is unlikely. Besides, it is known that the interaction of 3-formyl-5-nitro-2(β-dimethylaminovinyl)indole with hydroxylamine yields 2-cyanomethyl-3-formyl-5-nitroindole, *i.e.* the reaction does not proceed on the aldehyde group.[2] Thus, one could expect that the first stage of interaction between **4a,b** and $NH_2OH \cdot HCl$ would result in a transamination reaction with the formation of *N*-hydroxyenamines. Refluxing in DMFA of these compounds can lead to a second-order Beckmann rearrangement and formation of the corresponding nitriles **5a,b**.[2,3] However, it has been established that the above reaction proceeds in another direction. In the compounds **6a,b** obtained characteristic IR absorption of CN and CO groups at 1600–2500 cm^{-1} is absent. Compound **6a**, m.p. 219–222 °C (benzene) is isolated in 81% yield; the yield of **6b** is 85%, m.p. 192–194 °C (benzene). The mass spectrum of **6a,b** shows molecular ion peaks *m/z* 291 (100%) and 305(100%), respectively. The important diagnostic peculiarity of the mass spectrum of **6a,b** is the presence of intense peaks of ions $[M-O]^+$ and $[M-OH]^+$.[4] The spectra of these compounds are characterized by intense peaks $[M-H]^+$. The proton donors for their formation (*i.e.* $[M-H]^+$, $[M-OH]^+$) are probably the aryl substituents α to the N-atom of the pyridine ring. We note that loss of an oxygen atom can be explained not only by molecular ion fragmentation but also by thermal decomposition of molecules in the ion source. During the observation spectra change with $[M-O]^+$ (*m/z* 275 for **6a** and 289 for **6b**)



Scheme 1 *Reagents and conditions:* i, ref. 1; ii, combination of Me_2SO_4: NaOH: TEBAC: **2a,b** = 3:1.5:0.1:1, CH_2Cl_2, H_2O, 3 h, 20 °C; iii, $Me_2NCH(OEt)_2$, DMFA, reflux for 4 h; iv, NH_2OH·HCl, DMFA, reflux for 1 h,; v, Zn, AcOH, reflux for 1 h; vi, (*a*) Ac_2O reflux for 5 h and (*b*) Pr^iOH + 36% HCl, reflux for 4 h.



Scheme 2

becoming the principal peak. We can conclude from the above that the reaction of **4a,b** with hydroxylamine forms *N*-oxides of benzofuro[3,2-*c*]pyridines **6a,b**[†,‡] (Scheme 1).

We suppose that the formation of *N*-oxides **6a,b** is based on initial transamination with evolution of dimethylamine, followed by attack of the hydroxylamine NH-group fragment on the carbonyl group and further dehydration, Scheme 2.

Additional proof for the *N*-oxide nature of the compounds obtained is the reduction of **6a** to 1-phenyl-8-methoxybenzofuro[3,2-*c*]pyridine **7a**, yield 84%, m.p. 92–93 °C (Pr^iOH).[§] Tricycle **7b** is synthesised analogously and this compound is isolated as the hydrochloride, yield 66%, m.p. 231–233 °C Pr^iOH). Refluxing of *N*-oxides **6a,b** in Ac_2O gives mixtures of tricyclic 2-pyridones **8a,b** and their *O*-acyl derivatives [IR: ν(CO-ester) 1765 cm^{-1}, ν(CO-amide) 1665 cm^{-1}].[¶] These mixtures are hydrolysed to **8a**, yield 66%, m.p. 245–247 °C (DMFA)[‖] or **8b**, yield 50%, m.p. 263–265 °C (DMFA) on heating with hydrochloric acid. The mass spectra of **8a** differ from the spectra of the isomeric *N*-oxide **6a** in that in the former, ion peaks $[M-O]^+$ and $[M-OH]^+$ are absent. Instead, a characteristic peak due to ions $[M-CONH]^+$, *m/z* 248 is present. Spectroscopic data for **8b** are similar.

Thus, a new preparative method for the synthesis of benzofuro[3,2-*c*]pyridine derivatives, oxa analogues of γ-carbolines, has been developed. The heterocyclic system in benzofuro[3,2-*c*]pyridine is of great interest because a number of compounds with similar structure possess *e.g.*, analgesic, sedative and psychotropic activity.[7–9]

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† Spectroscopic data for **6a** ^1H NMR ([$^2H_6$]Me_2SO)δ: 3.57 (s, 3H, OMe), 6.31 (d, J = 2.7 Hz, 1H, 9–CH), 7.18 (qd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H, 7–CH), 7.71 (d, J = 9.1 Hz, 1H, 6–CH), 7.66 (s, 5H, Ph), 7.85 (d, J = 7.2 Hz, 1H, 4–CH) and 8.46 (d, J = 7.2 Hz, 1H, 3–H). Spectroscopic data for **6b** are similar.

‡ All new compounds gave the expected IR, ^1H NMR and mass spectra and satisfactory elemental analysis.

§ Spectroscopic data for **7a** ^1H NMR ([$^2H_6$]Me_2SO) δ: 3.64 (s, 3H, OMe), 7.10 (d, J = 2.6 Hz, 1H, 9–CH), 7.16 (qd, J_1 = 9 Hz, J_2 = 2.6 Hz 1H, 7–CH), 7.67 (d, J = 9 Hz, 1H, 6–CH), 7.59–7.85 (m, 5H, Ph), 7.69 (d, J = 6.7 Hz, 1H, 4–CH) and 8.68 (d, J = 6.7 Hz, 1H, 3–CH).

¶ The formation of 2-acetoxypyridine under the interaction of pyridine *N*-oxide with Ac_2O, see refs. 5 and 6.

‖ Spectroscopic data for **8a** ^1H NMR ([$^2H_6$]Me_2SO)δ: 3.61 (s, 3H, OMe), 6.40 (s, 1H, 4–CH), 6.66 (d, J = 2.7 Hz, 1H, 9–CH), 6.92 (qd, J_1 = 9 Hz, J_2 = 2.7 Hz, 1H, 7–CH), 7.44 (d, J = 9 Hz, 1H, 6–CH), 7.61–7.73 (m, 5H, Ph).

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Received, Moscow 26th March 1993
Cambridge, 11th May 1993; Com. 3/01839C