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Synthesis of benzofuroquinolizine for α-2 adrenoceptor antagonist MK-912: an O-analogue of the Pictet–Spengler reaction

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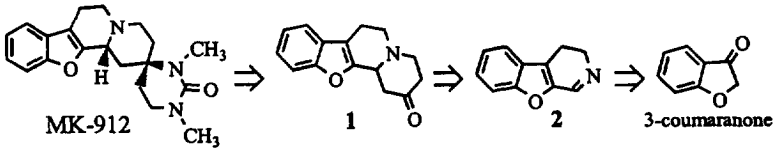
Abstract

Efficient synthesis of benzofuroquinolizine ketone **1** was accomplished in four steps from ethyl 3-benzofuranacetate. The O-analogue of the Pictet–Spengler cyclization was used to form the benzofuroquinolizine ring structure as a key step. © 1999 Elsevier Science Ltd. All rights reserved.

The synthetic modification of naturally occurring bioactive molecules is an important avenue for the discovery of novel medicinal agents. Historically, plant derived alkaloids constitute the most important class of naturally derived medicinal agents, and carbazoles, such as yohimbine, reserpine, corynantheidine, and deplancheine have been the subject of numerous biological and synthetic studies.[1] Remarkably, only very few examples are reported where the isoelectronic substitution of the NH group in these alkaloids with O led to the analogous benzofurans as bioactive molecules.[2] The highly potent and selective α-2 adrenoceptor antagonist MK-912 is a highly successful implementation of this strategy. MK-912 and analogous compounds are retrosynthetically connected to the key benzofuroquinolizine ketone **1**. An elegant five-step synthesis of ketone **1** was reported earlier starting from 3-coumaranone (*Scheme 1*). The key step consisted of a hetero Diels–Alder reaction of imine **2**.[3] Despite its deceptively simple structure, 3-coumaranone is difficult to prepare on a large scale. It is unstable to basic and acidic conditions as well as light, thus severely limiting its use as an attractive starting material.



Scheme 1.

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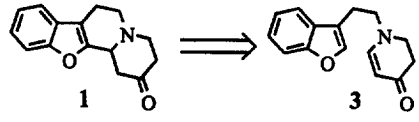
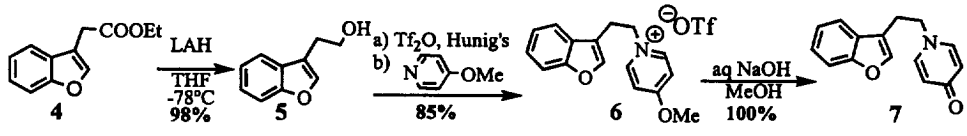
We envisioned an alternative retrosynthetic disconnection in analogy to the Pictet–Spengler cyclizations that dominate carbazole chemistry (Scheme 2). The greatly reduced nucleophilicity of the benzofuran system compared to the indole put an onus on this disconnection. We wish to report the successful realization of this strategy: efficient preparation of **3**, followed by the acid catalyzed O-analogue of the Pictet–Spengler cyclization to produce the key intermediate **1**.



Scheme 2.

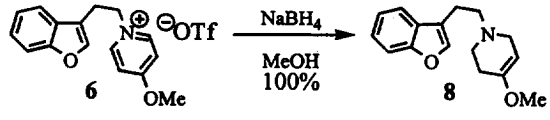
Starting material for our synthesis was ethyl 3-benzofuranacetate (**4**), which was readily prepared following the procedure of Larock.[4] Reduction of the ester to the primary alcohol **5** ($LiAlH_4$, 98% yield) was followed by activation with triflic anhydride and displacement with 4-methoxypyridine (Scheme 3). As expected,[5a] *N*-alkylation took place and pyridinium salt **6** was isolated as a crystalline solid in 85% yield. Salt **6** was readily hydrolyzed by a dilute aqueous sodium hydroxide wash to provide pyridone **7** as a crystalline material in quantitative yield. Thus the complete carbon skeleton was rapidly assembled.



Scheme 3.

Initially we attempted cyclization at the pyridinium oxidation state using either **6** or **7** with various Brönsted and Lewis acids. Either no reaction occurred or decomposition was observed. Thus it appeared necessary to increase the electrophilicity of the iminium coupling partner.

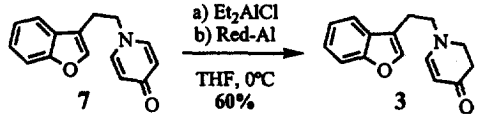
To this end, we decided to remove the aromatic stabilization of **6** and **7** by a partial reduction to produce enaminone **3** (Scheme 2). This partial reduction was expected to be difficult based on literature precedent.[5] We explored the use of several reducing agents on **6** and **7**. Reduction of salt **6** using $NaBH_4$ in methanol cleanly produced the over-reduced product **8** in quantitative yield, with none of the desired partial reduction product **3** detectable (Scheme 4). Use of $LiBH_4$ led to a complex mixture. $LiAlH_4$ experiments on either salt **6** or pyridone **7** gave complex mixtures and produced the desired enaminone **3** in less than 10% yields. In marked contrast to the reactivity of salt **6**, pyridone **7** was inert to $NaBH_4$ reduction.



Scheme 4.

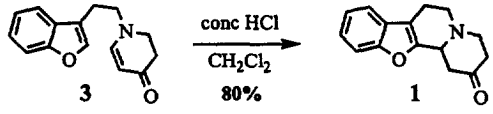
Under optimal conditions, two equivalents of Red-Al reduced **7** to **3** in 50% isolated yield.[5d] Remarkably, not even partial conversion was observed employing only one equivalent of Red-Al: two equivalents were required. This result could be explained by assuming complexation of the first equivalent of Red-Al followed by reduction with the second equivalent. This mechanistic rationale appears to be reasonable. We discovered that we could effect the reduction by pre-complexation of **7** with one equivalent of Et_2AlCl followed by the addition of one equivalent of Red-Al to give **3** in 60% yield (Scheme 5). The course of the reduction was markedly dependent on the Lewis acid used for the pre-complexation. Mono-dentate boron-containing Lewis acids such as $BF_3 \cdot OEt_2$ or 9-BBN-OTf did not allow any reduction to take place

with one equivalent of Red-Al. On the other hand, pre-complexation with $ZnCl_2$ caused over-reduction to give enol ether **8** exclusively. Interestingly, Red-Al reductions of salt **6** were consistently lower yielding.



Scheme 5.

The Pictet–Spengler cyclization of indoles generally calls for dilute acid for the reaction to occur. Alkyl enol ethers have been reported to react with Mannich reagents in a similar fashion,[6] and furans have been shown to react with *N*-acyliminium ions to give cyclized products,[7] but only one example of an O-analogous Pictet–Spengler cyclization of benzofurans has been reported. Unlike the case of indoles, addition of dilute acid to enaminone **3** caused no reaction at all. However, by simply increasing the concentration of the acid, cyclization of enaminone **3** was readily accomplished with excess conc. hydrochloric acid to provide ketone **1** in 80% yield (Scheme 6).



Scheme 6.

In conclusion, we have demonstrated an efficient, chromatography-free, scalable synthesis of the key benzofuroquinolizine ketone **1**.[8] We have explored the partial reduction of *N*-alkylpyridone **7**, and we have shown the viability of the O-analogue of the Pictet–Spengler cyclization reaction.

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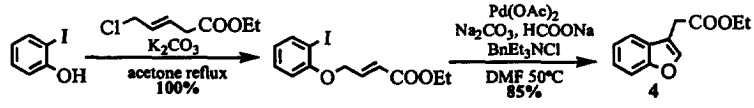

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8. Preparation and selected data for new compounds: **Alcohol 5**. A 1 M soln of $LiAlH_4$ (49 mL) was added to a stirred soln of ester **4** (30 g, 0.15 mol) in THF (300 mL) at –78°C, and stirred for 16 h slowly warming to rt. The reaction was cooled to 0°C and quenched with water and 15% aq. NaOH soln, followed by addition of $MgSO_4$. The salts were removed by filtration and the filtrate was concentrated to give a yellow oil 24 g (99%). ^{1}H NMR: 1.53 (br s, 1H), 2.95 (t, *J*=6.3, 2H), 3.94 (t, *J*=5.6, 2H), 7.23–7.33 (m, 2H), 7.48 (d, *J*=8.0, 2H), 7.52 (s, 1H), 7.57 (d, *J*=7.4, 2H). ^{13}C NMR: 27.0, 61.7, 111.5, 116.7, 119.5, 122.4, 124.3, 127.9, 142.1, 155.3. **Salt 6**. Neat triflic anhydride (10.4 mL, 62 mmol) was added to a soln of alcohol **5** (10 g, 62 mmol) and Hünig's base (10.8 mL, 62 mmol) in 62 mL of acetonitrile at –40°C. The reaction was allowed to age for 10 min. A soln of 4-methoxypyridine (6.73 g, 62 mmol) in 10 mL of acetonitrile was added and stirred at –20°C for 1 h. The reaction mixture was extracted with hexanes, and the acetonitrile layer was concentrated to 1/4 volume and partitioned between water and dichloromethane. The organic layer was dried and concentrated to approximately 1/10 volume. MTBE was added to precipitate the product which was collected by filtration to give tan crystalline solids 22 g (85%). ^{1}H NMR: 3.37 (t, *J*=6.3, 2H), 4.04 (s, 3H), 4.80 (t, *J*=6.4, 2H), 7.19–7.34 (m, 4H), 7.42 (s, 1H), 7.43–7.52 (m, 2H), 8.47 (d, *J*=6.5, 2H). ^{13}C NMR (CD_3OD): 26.0, 58.6, 60.4, 112.6, 114.5, 116.0, 120.2, 124.0, 126.0, 128.3, 144.6, 147.1, 156.9, 173.0. ^{19}F NMR (CD_3OD): –76.2. **Pyridone 7**. An aqueous NaOH soln (20%, 50 mL) was added to a stirred soln of salt **6** (10 g, 25 mmol) in 25 mL of MeOH and stirred for 1 h. The reaction was extracted with dichloromethane, dried, passed through a thin (1/4 inch) pad of silica gel and concentrated to a solid 5.9 g (quant.). ^{1}H NMR: 3.12 (t, *J*=6.8, 2H), 4.07 (t, *J*=6.7, 2H), 6.29 (d, *J*=5.8, 2H), 7.11 (d, *J*=5.8, 2H), 7.25–7.34 (overlapping m, 2H), 7.34 (s, 1H), 7.43 (d, *J*=7.9, 1H), 7.50 (d, *J*=8.0, 1H). ^{13}C NMR: 25.0, 55.6, 111.4, 114.6, 118.0, 118.5, 122.5, 124.4, 126.5, 139.5, 142.2, 154.8, 178.3. **Enaminone 3**. A 1 M soln of Et_2AlCl (3.8 mL) was added to a cold (0°C) stirred soln of pyridone **7** (900 mg, 3.8 mmol) in THF 10 mL. A 65% soln in toluene of Red-Al (1.35 mL) was added and stirred for 2 h. The reaction was quenched with a sat. aq. soln of Rochelle's salt and stirred overnight. The reaction was extracted into dichloromethane and stirred with 0.1 N HCl soln for 4 h, neutralized and the layers separated. The organic layer was dried and filtered through a thin pad of florisil and concentrated to give a yellow oil, 546 mg (60%). ^{1}H NMR: 2.44 (t, *J*=7.9, 2H), 2.99 (t, *J*=6.9, 2H), 3.49 (t, *J*=7.9, 2H), 3.54 (t, *J*=6.9, 2H), 4.87 (d, *J*=7.5, 1H), 6.86 (d, *J*=7.5, 1H), 7.24–7.35 (overlapping m, 2H), 7.46 (s, 1H), 7.48–7.54 (overlapping m, 2H). **Ketone 1**. Conc. HCl (3.5 mL) was added to a stirred soln of enaminone **3** (1 g) in 50 mL of dichloromethane and stirred for 1 h. Another 5 mL HCl was added and reaction was stirred another hour. HPLC indicated completion of reaction. The reaction was poured into a sat. aq. soln of sodium carbonate and extracted five times with dichloromethane, dried, filtered through a thin pad of silica gel and concentrated to give a yellow oil that solidified upon standing, 804 mg (80%). The NMRs matched authentic material.