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A new access to efaroxan and its 5-amino derivatives

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This Letter is dedicated to the memory of Charles Mioskowski who has brought an outstanding contribution in all the fields of the Organic Chemistry, including efaroxan synthesis

Abstract

The formal total synthesis of racemic efaroxan, a 2-disubstituted 2,3-dihydrobenzofuran having interesting therapeutic properties, and the preparation of some 5-amino derivatives were achieved using a convergent approach. The key intermediates of both syntheses were obtained after a [3+2] cycloaddition reaction between two easily accessible partners.

Keywords: 2,3-Dihydrobenzofuran; Quinone imide; Hydrazone; Efaroxan

Efaroxan (**1**), a 2,3-dihydrobenzofuranic derivative bearing an imidazoline ring, displays a range of interesting biological activities. This compound in a racemic form was originally designed as a powerful α_2-adrenoceptor antagonist[1] and further investigations have shown that biological effects were related to the configuration of the asymmetric centre at the 2-position (Fig. 1). The dextrorotatory enantiomer[2] was found to keep the selective α_2-adrenergic antagonist effect[3] and was planned for the treatment of neurodegenerative troubles such as Parkinson's[4] and Alzheimer's[5] diseases.[6] Its optical antipode isomer is described as an imidazoline ligand[7] that induces insulin secretion, mediated by the blocking of ATP-sensitive potassium channels in pancreatic β-cells, with a possible application of treating diabetes.[8]

Regarding to the potential clinical applications of efaroxan and to provide for medicinal chemists versatile synthetic ways of this lead drug, we wish to describe herein a new synthetic approach to racemic efaroxan as well as its 5-amino analogues **2** ($R = NR'_2$ where R′ could be H, alkyl, aryl or sulfonyl groups) (Fig. 1).

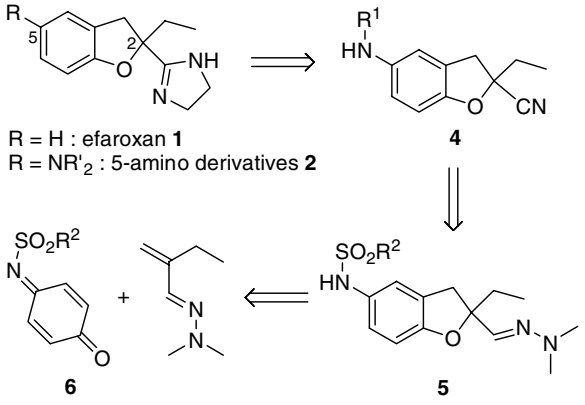

Fig. 1.

Although various 5-substituted efaroxan derivatives, including 5-NH_2,[9] have been described in the literature, we propose a new efficient convergent approach of compounds **2** which could be useful for a fine-tuning of both pharmacological activity and bioavailability of the parent drug efaroxan.

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The direct precursor of the imidazoline-containing compound **1** is 2-ethyl-2,3-dihydrobenzofuran-2-carbonitrile (**3**),[10] as previously reported by many research groups.[1a–c] This nitrile **3** is obtained from the corresponding 2-ethyl-2,3-dihydrobenzofuran-2-carboxylic acid,[11] usually using a three step sequence: conversion of the acid into an acyl chloride or an ester,[12] formation of the amide which is submitted to dehydration under harsh conditions to give the nitrile. In our synthetic approach, compound **3** could be obtained after a deamination reaction of aniline **4** ($R^1 = H$, Fig. 1) and the dimethylhydrazone functionality in 2,3-dihydrobenzofuran **5** could be of prime interest for the preparation of the cyano group via an oxidation step. We have recently described an efficient synthesis of this crucial intermediate **5**, starting from phenylsulfonyl quinone monoimide **6** ($R^2 = Ph$)[13] and the appropriate azadiene, 2-ethyl acrolein *N*,*N*-dimethylhydrazone (Fig. 1).[14]

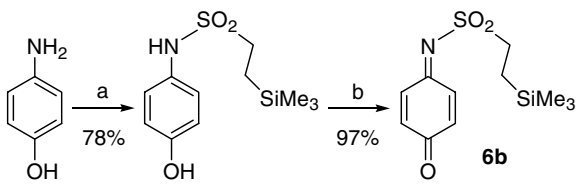
With this efficient methodology in hand, we then decided to apply this convergent approach to the 2,3-dihydrobenzofuran core of efaroxan and its 5-amino derivatives.

Although the phenylsulfonyl amide ($R^2 = Ph$) could be helpful in terms of solid-supported synthesis,[15] the removal of such group appears to be somewhat troublesome since it requires a three step sequence.[16] Indeed, the preparation of efaroxan from intermediate **4** requires the removal of the sulfonamide. A good alternative for the phenylsulfonyl group lies in the use of 2-trimethylsilyl ethylsulfonyl (SES) group which is easily cleaved by fluoride-promoted β-elimination.[17]

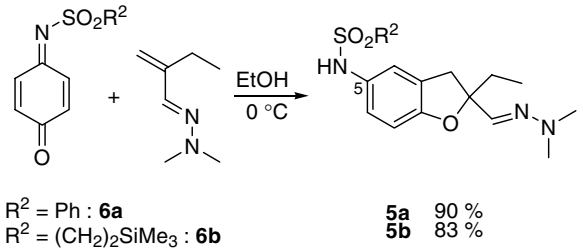
The synthesis of the SES-protected quinone monoimide **6b** was then realized in two steps: first N-sulfonylation with SES chloride[18] in dimethylformamide (DMF) in the presence of pyridine as a base and subsequent oxidation of the sulfonamide with lead tetracetate in acetic acid in an excellent 97% yield (Scheme 1).[19]

This protecting group opens up also a possible application of our methodology for the elaboration of analogues libraries since the water-soluble SES-functionalized polyethylene glycol (PEG) polymer has been developed and applied for the preparation of different compounds.[20]

The reaction between the quinone imide **6b**, having a SES group instead of a phenylsulfonyl one, proceeded well under the developed conditions (slow addition of an alcoholic solution of the quinone imide on the azadiene) as



Scheme 1. Reagents and conditions: (a) $Me_3Si(CH_2)_2SO_2Cl$ 1.0 equiv, pyridine/DMF 1:2, 0 °C to rt, then rt for 2 h; (b) $Pb(OAc)_4$ 1 equiv, glacial AcOH, rt, 1 h.



Scheme 2.

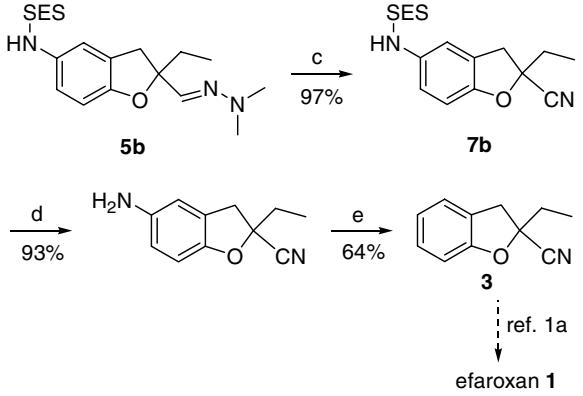
the corresponding 2,3-dihydrobenzofuran **5b** was isolated in a very good 83% yield (Scheme 2).

The hydrazone moiety was converted into a nitrile with the oxidative reagent magnesium bis(monoperoxyphtalate) (MMPP)[21] and the cleavage of the SES group in compound **7b** was carried out using caesium fluoride, in DMF. For this deprotection, the heating at 140 °C was necessary to ensure a fast and complete conversion of the substrate into the corresponding aniline in a very good 93% isolated yield (Scheme 3).[22]

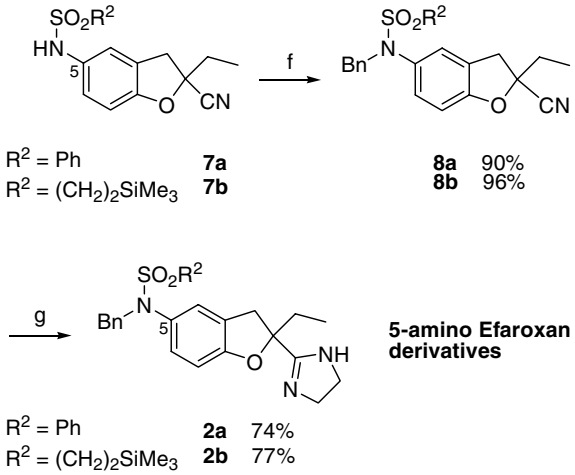
A diazotation reaction of the aromatic free amine followed by an in situ reductive step with sodium bisulfite in ethanol[23] afforded then 2-ethyl-2,3-dihydrobenzofuran-2-carbonitrile **3** in a good global yield (36% yield from *p*-aminophenol).[24] The nitrile is the direct precursor of the imidazoline ring of efaroxan **1**: our strategy allowed us to achieve a new formal total synthesis of this compound (Scheme 3).

The synthesis of the 5-amino derivatives of this lead compound was completed using a similar strategy, starting from intermediates **5a**,**b**.

After oxidation of the dimethylhydrazone functionality with MMPP (MeOH, 0 °C, 30 min) into a cyano group in very good yields (quantitative yield for **7a** where $R^2 = Ph$), the sulfonamides were protected with a benzyl group (Scheme 4). The synthesis of the target compounds was completed by the formation of the imidazoline ring, according to Chapleo's method.[1a] This step was realized



Scheme 3. Reagents and conditions: (c) MMPP 2 equiv, MeOH, 0 °C, 30 min; (d) CsF 4 equiv, DMF, 140 °C, 19 h; (e) $NaNO_2$, AcOH/EtOH, 0 °C and then $NaHSO_3$ solution in water, 0 °C, 2 h.



Scheme 4. Reagents and conditions: (f) NaH 1.1 equiv, DMF, 50 °C, BnBr 1.05 equiv, 1 h 30; (g) (1) 0.5 equiv MeONa, MeOH, 21 h, rt; (2) 1.3 equiv ethylenediamine, then 1.3 equiv HCl (1 M in MeOH), 0 °C to rt, 18 h.

by first, formation of an imidate intermediate by alkaline treatment of the nitrile with sodium methoxide in methanol and then the reaction with a slight excess of ethylene diamine in the presence of hydrogen chloride. Compounds **2** were then obtained as their free base, after an alkaline work-up with sodium bicarbonate, in good isolated yields (Scheme 4).[25]

To conclude with this work, we have described an efficient formal synthesis of racemic efaroxan and a versatile approach to the corresponding 5-amino derivatives. After the present validation of this synthetic pathway, further developments of the described methodology for the preparation of enantioenriched compounds **3** and **2** are actually under investigation and will be reported in due course.

Acknowledgement

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para-aminophenol (820 mg, 3.0 mmol) in 10 mL of glacial acetic acid was added 95% lead tetracetate $Pb(OAc)_4$ (1.40 g, 3.0 mmol) in one portion. The colourless solution faded to orange. The resulting mixture was allowed to stir at room temperature for 1 h, after which ethylene glycol (1 mL) was added. After a 10 min stirring, water (40 mL) and ethyl acetate (50 mL) were added. After decantation, the organic phase was washed with water (2 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate. After filtration, removal of AcOEt in vacuo and drying, the quinone monoimide **6b** was obtained as a yellow powder (786 mg, 97%); mp 65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 0.10$ (9H, s), 1.13–1.19 (2H, m), 3.22–3.28 (2H, m), 6.64 (1H, dd, $J = 10.6$, 2.3 Hz), 6.72 (1H, dd, $J = 10.2$, 2.3 Hz), 7.03 (1H, dd, $J = 10.2$, 2.6 Hz), 8.01 (1H, dd, $J = 10.6$, 2.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = -1.9$, 9.8, 51.5, 130.7, 135.0, 135.7, 140.2, 164.8, 185.9. HRMS (CI): *m*/*z* calcd for $C_{11}H_{18}NO_3SSi$: 272.0777 [MH^+]; found: 272.0778.

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25. Typical experimental procedure for the preparation of 5-sulfonamido efaroxan derivative **2a**: To a solution of the cyano compound **8a** (150 mg, 0.36 mmol) in 2 mL of anhydrous methanol was added sodium methoxide (10 mg, 0.18 mmol). After a 21 h stirring at room temperature, the mixture was cooled down to 0 °C and an ethylene diamine (31 μL, 0.464 mmol) solution in MeOH (0.5 mL) was added dropwise. After a 5 min stirring, a 1 M HCl solution in MeOH (470 μL, 0.466 mmol) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and was stirred for an additional 18 h. After this time, the volatiles were removed under reduced pressure and the residue was taken up into 10 mL of $NaHCO_3$ saturated aqueous solution. Two extractions were realized on the aqueous phase with dichloromethane (2 × 15 mL) and the organic phases were washed with water (10 mL), dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH 1:1) to give compound **2a** as an off-white powder (123 mg, 74%); mp 53–55 °C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): $\delta = 0.79$ (3H, t, $J = 7.4$ Hz), 1.86 (2H, q, $J = 7.4$ Hz), 2.97 (1H, d, $J = 16.2$ Hz), 3.42 (4H, br s), 3.59 (1H, d, $J = 16.2$ Hz), 4.69 (1H, d, $J = 15.1$ Hz), 4.75 (1H, d, $J = 15.1$ Hz), 6.60 (1H, d, $J = 8.7$ Hz), 6.69 (1H, dd, $J = 8.7$, 2.3 Hz), 6.86 (1H, d, $J = 2.3$ Hz), 7.18–7.30 (5H, m), 7.59–7.75 (5H, m). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): $\delta = 7.9$, 31.5, 37.6, 49.5, 54.2, 89.7, 108.8, 125.8, 127.1, 127.4, 127.4, 128.0, 128.2, 128.3, 129.3, 131.3, 133.1, 136.5, 138.1, 157.5, 168.3. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{28}N_3O_3S$: 462.1851 [MH^+]; found: 462.1853.