Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 3021–3022

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A NEW EFFICIENT SYNTHESIS OF EFAROXAN

P. Mayer, P. Brunel, T. Imbert *

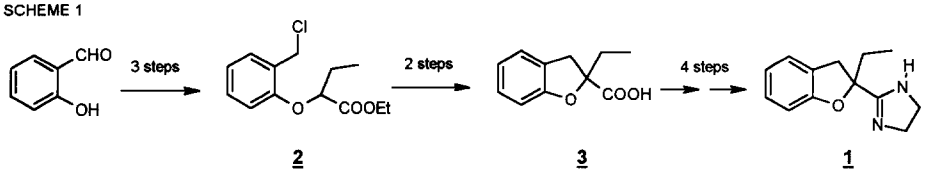
Centre de Recherche Pierre Fabre, Division de Chimie Médicinale, 17, Avenue Jean Moulin, F 81100 Castres, France.

Received 14 June 1999; accepted 14 September 1999

Abstract : The key step of the synthesis of efaroxan was the dihydrobenzofuran ring formation involving an intramolecular cyclization of the tertiary alcohol intermediate with the fluoroaromatic moiety in basic medium. This carbinol was prepared according to two routes, either from reaction of a benzyl Grignard reagent with an α-ketoester, or from a Darzens condensation.

Efaroxan **1**, 2-(2-(2-ethyl-2,3-dihydrobenzofuranyl))-2-imidazoline, has been shown as a potent and selective α_2-adrenoceptor antagonist,[1] and was formerly developed for depression and diabetes. Our interest to evaluate α_2-adrenoceptor antagonists, as a new approach for the treatment of the progression of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, led us to undertake pharmacological investigations with efaroxan. Over the course of our studies we needed an efficient synthesis of efaroxan, in a preparative scale. The early synthesis[1,2] involved, as the key step, an intramolecular cyclization of an oxyacetate grouping, with an *ortho*-benzylchloride **2** (scheme 1).

SCHEME 1



2 **3** **1**

This strategy rather proved to be problematic because of the great number of steps. Our aim was to explore a shorter path featuring another disconnection approach, as shown in scheme 2.

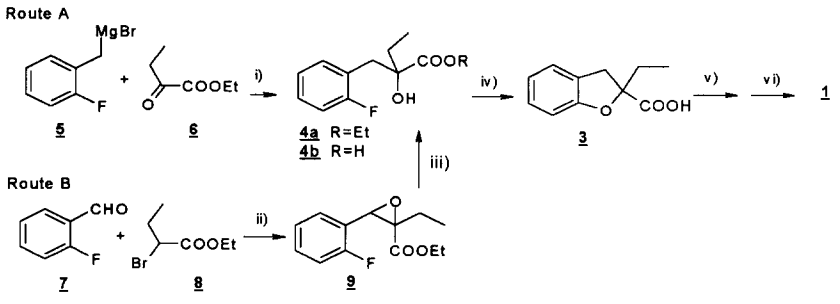
The key intermediate was identified as the tertiary alcohol **4**, which could undergo intramolecular cyclization to dihydrobenzofuran **3**. Such related cyclizations have rarely been described in the literature.[3,4] This intermediate **4** was prepared by a coupling reaction with the Grignard reagent **5** on an α-ketoester (scheme 2, route A). The starting material, ethyl 2-oxobutyrate **6**, was obtained by addition at -78°C of ethylmagnesium bromide to diethyloxalate according to a procedure already described.[5] The reaction of *ortho*-fluorobenzylmagnesium bromide **5**, with ethyl 2-oxobutyrate **6** in THF proceeded smoothly at -78°C, and afforded the crude ester **4a**, which was directly subjected to saponification with sodium hydroxide in aqueous THF. The resulting acid **4b** was obtained in 51% overall yield. However, for development purpose, this strategy suffered two steps at low temperature.

The second method to prepare the carbinol **4** (scheme 2, route B) used a Darzens condensation reaction between 2-fluorobenzaldehyde **7** and ethyl 2-bromobutyrate **8**, in the presence of *t*-BuOK in dioxane at room temperature

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00531-4

for 16 h . The crude epoxyester **9** was obtained as a mixture of diastereoisomers in 62% yield, and was used without further purification in the next step. The ring opening of the epoxide **9**, under an atmosphere of hydrogen in ethanol in the presence of Pd/C, gave the carbinol **4a** in 89% yield.

SCHEME 2



Reaction conditions :
i) **5**, Et_2O, -78°C, **6**, then r.t. 16 h.; 1N NaOH, THF, r.t. 48 h. ii) **7** + **8**, dioxane, 0°C, tBuOK (1 eq.), then r.t. 16 h.
iii) H_2, Pd/C 10%, EtOH, 16 h. iv) **4b**, NaH (2 eq.), toluene- DMF (8-2), 110°C, 16 h. v) $SOCl_2$/EtOH, reflux.
vi) $AlMe_3$, ethylenediamine, toluene, 0°C, then ester addition, reflux, 3 h.

Direct saponification, under the same condition as above, led quantitatively to the acid **4b**. This procedure appeared superior to the previous one, in view of the easy and economic scale-up of the reaction.

The desired cyclization of the obtained carbinol **4b** into the corresponding 2,3-dihydrobenzofuran **3** took place with sodium hydride in DMF at 110°C for 16 h in 72% yield. Best results were obtained when the acid carbinol **4b** was used for cyclization, instead of the ethyl ester **4a**. The remaining steps to yield efaroxan consisted in esterification of the acid **3**, with $SOCl_2$ in ethanol. The ester was directly converted into imidazoline **1** (efaroxan) in one step, with trimethylaluminium and ethylene diamine in refluxing toluene, in 65% yield, according to a process already described.[6] Dexefaroxan is the active enantiomer, and the chiral resolution of enantiomers would be better carried out at the dihydrobenzofuran acid **3b** step,[7] rather than at the imidazoline last step, as already performed.[8] These new synthetic routes outlined above in 5 or 6 steps provide a great improvement relative to the previous method. Another approach of the synthesis of efaroxan is presented in another paper.[9]

References

1. Chapleo, C. B.; Myers, P.L.; Butler, R.C.M.; Davis, J.A.; Doxey, J.C.; Higgins, S.D.; Myers, M.; Roach, A.G.; Smith, C.F.C.; Stillings, M.R.; Welbourn, A.P. *J. Med. Chem.* **1984**, *27*, 570.
2. Edwards, C.R.; Readhead, M.J.; Tweedle, N.J. *J. Heterocyclic Chem.* **1987**, 495.
3. Effland, R.C.; Gardnerand, B.A.; Strupczewski, J. *J. Heterocyclic Chem.* **1981**, 811.
4. Palucki, M.; Wolfe, J.P.; Buchwald, S.L. *J. Amer. Chem. Soc.* **1996**, *118*, 10333-10334.
5. Creary, X. *J. Org. Chem.* **1987**, *52*, 5026.
6. Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem.* **1981**, *46*, 2824-2826.
7. Imbert, T.; Mayer, P. Patent WO 96/35682.
8. Chapleo, C.B.; Doxey, J.C.; Stillings, M.R. Patent WO 92/05171.
9. Couture, K.; Gouverneur, V.; Mioskowski, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3023-3026.