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Incorporation of an indole-containing diarylbutylamine pharmacophore into furo[2,3-*a*]carbazole ring systems

Faye Maertens, Suzanne Toppet, Georges J. Hoornaert and Frans Compernolle*

Laboratorium voor Organische Synthese, K.U.Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

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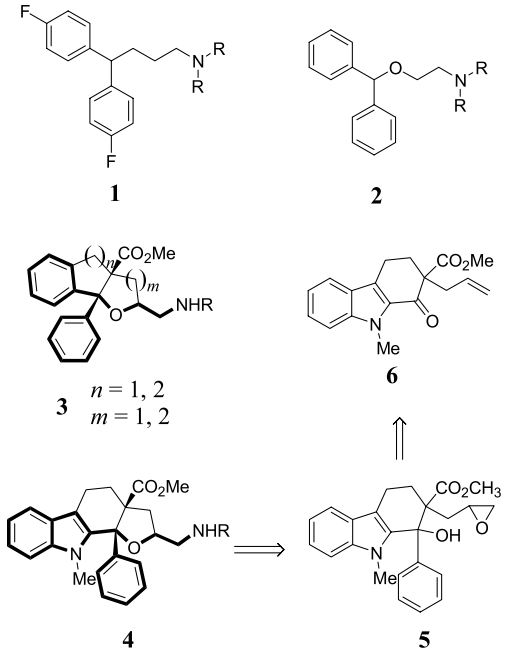
Abstract—Due to concurrent oxidation of the indole moiety in the starting carbazole alkenol, an epoxidation route aiming at incorporation of a conformationally constrained diarylbutylamine failed to give the desired furo[2,3-*a*]carbazole ring system. Instead, an indole epoxide intermediate was generated, which underwent rearrangement involving participation of a vicinal OH group. The required furo[2,3-*a*]-carbazole could, however, be accessed via a Hg^{2+}-induced cyclisation of a carbazole alkynol.

1. Introduction

Recently, we reported the synthesis of various indeno-[1,2-*b*]furan, indeno[1,2-*b*]pyran, naphtho[1,2-*b*]furan and benzo[*h*]chromene ring systems **3** encompassing a conformationally constrained diarylbutylamine pharmacophore.[1] This is a general approach for improving the binding affinity and selectivity of neurotransmitter ligands to receptor molecules. Specifically, these compounds can be viewed as constrained analogues of dopamine receptor ligands **1** and the antihistamine difenhydramine **2**.[2–4]

Since the indole moiety is an essential feature of many bioactive molecules, we conceived target structures of furo[2,3-*a*]carbazole[5] type **4** as constrained analogues of 2-indolylbutylamines. Similar to the strategy used for the synthesis of tricycic compounds **3**, our present approach (Scheme 1) involves regioselective opening of the epoxide ring in precursor **5** by the tertiary alcohol centre. This precursor in its turn may be derived from the 2-alkenyl substituted β-keto-ester **6** via sequential Grignard reaction and epoxidation.



Scheme 1.

2. Results and discussion

Our synthetic approach required the preparation of the carbazole alkenol precursor **12** (Scheme 2). An acid-catalysed ring closure of 3-indolebutyric acid afforded the six-membered ring ketone **8**,[6] which was *N*-methylated to give compound **9**.[7,8] β-Keto ester **10** was prepared by treatment of **9** with potassium hydride and dimethyl carbonate.[9] Subsequent allylation gave the 2-allyl-1-oxo-1*H*-carbazole-2-carboxylate **11**, which was submitted to a Grignard reaction with freshly prepared PhMgBr. Following chromatographic purification alcohol **12** was isolated as the major diastereoisomer with a d.e. of 46%.

Keywords: Heterocyclic compounds; Epoxidation; Indole; Bromocyclisation.
* Corresponding author. Tel.: +32 16 32 74 07; fax: +32 16 32 79 90; e-mail: frans.compernolle@chem.kuleuven.ac.be

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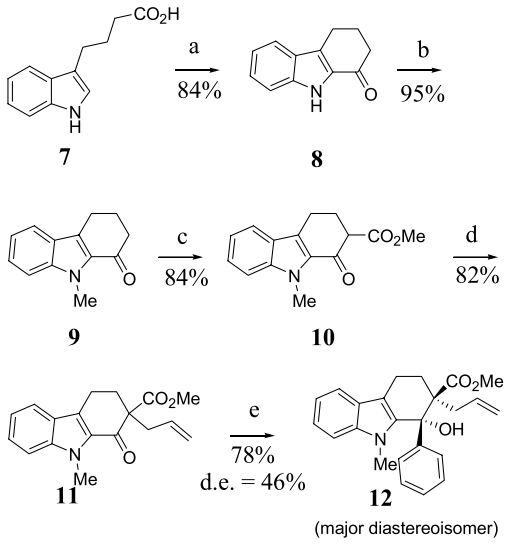


Scheme 2. Reagents and conditions: (a) PPA, toluene, 110 °C; (b) KOH, MeI, acetone; (c) KH, $(CH_3O)_2CO$, reflux; (d) NaH, allyl bromide, DMF; (e) PhMgBr, THF, −78 °C.

A NOESY analysis of **12** reveals a *trans*-diaxial orientation of the phenyl and allyl groups. NOEs are observed between H-2′ of the allyl group and both H-3eq and H-4ax. Proton H-1′b shows a NOE with H-4ax, while H-1′a correlates with the tertiary alcohol proton (see geometrically optimised conformation, Fig. 1). These findings confirm the (Ph, allyl) *trans*-diaxial relation of the major product, in agreement with our previous report regarding the diastereoselectivity of the Grignard reaction in similar systems.[10]

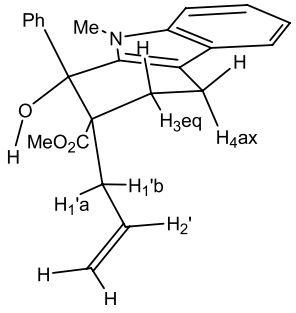
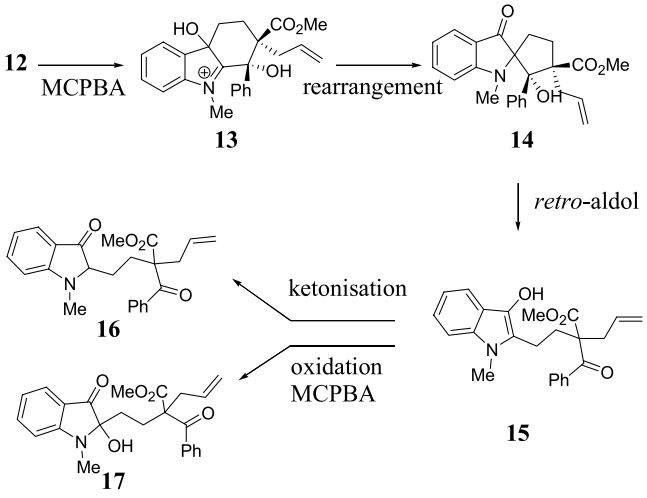


Figure 1. Geometrically optimised conformation of **12**.

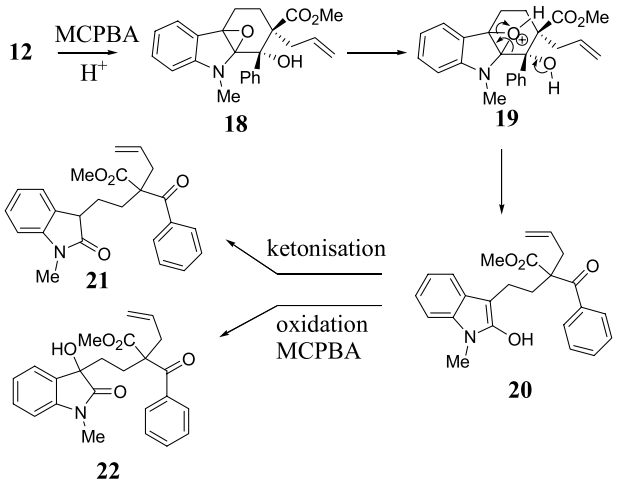
Alkenol **12** was submitted to reaction with *m*-chloroperbenzoic acid (MCPBA) but the two major products isolated from the reaction mixture clearly were not the expected epoxide or ring-closed product. Indeed, tetrahydrocarbazole derivatives have been reported to give 2,2-spiro-annulated 3-indolone products upon oxidation with MCPBA. Apparently, these 3-indolones are generated via a pinacol-type rearrangement, which involves a ring contraction of the 3-hydroxyindolium intermediate.[11]

Initially, we assumed that hydroxylation at the 3-position of the indole moiety of **12** would trigger a similar rearrangement of the cation intermediate **13** to form the spiro product **14** (Scheme 3). For both compounds the presumed spiro structure, however, was refuted based on the observation of three carbonyl signals in each of the ^{13}C NMR spectra. This finding suggested the existence of the ring-opened indolone structures **16** and **17**, which could be formed via an acid-catalysed *retro*-aldol reaction of β-hydroxy ketone **14**. The resulting enol intermediate **15** then would be converted into the corresponding ketone **16** or oxidized to yield the 2-OH product **17**.



Scheme 3. Initially suggested course of MCPBA oxidation.

Surprisingly, the HMBC spectra of the two indolone products revealed a correlation between the *N*-methyl protons ($\delta = 3.17$) and one of the carbonyl groups ($\delta = 176.9$). This finding clearly is not consistent with 3-indolone structures **16** and **17**, but rather with the analogous 2-indolone products **21** and **22**. Actually these 2-indolones also may be generated via initial epoxidation of the indole moiety to form epoxide **18** (Scheme 4).



Scheme 4. Actual course of MCPBA oxidation.

A further literature search indeed revealed that both 2- and 3-indolones can be generated upon epoxidation of 2,3-disubstituted indoles.[12–15] Instead of being converted to the stabilised 3-hydroxyindolium ion **13** (see Scheme 3 before), the protonated epoxide intermediate **19** is subject to an alternative ring cleavage process, which is assisted by the vicinal OH group. The resulting enol intermediate **20** is then