Regioselective and Versatile Synthesis of Indoles via Intramolecular Friedel–Crafts Heteroannulation of Enaminones

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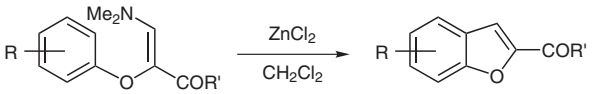
Received 21 December 2005

Abstract: A new approach is described for the synthesis of substituted indoles **5**, through an intramolecular and regioselective Friedel–Crafts cyclization of enaminones **6a–h** catalyzed by Lewis acids. Compounds **6** were prepared from the 2-anilinocarbonyl compounds **7**, by treatment with DMFDMA under thermal or microwave (MW) irradiation conditions. An alternative and shorter one-pot two-step synthesis of indoles **5** was achieved starting from compounds **7** and promoted by MW radiation, including the elusive 2-acetylindoles **5i–m**.

Key words: indoles, enaminones, Friedel–Crafts annulations, Lewis acid catalysis, microwaves

Enaminones have proved to be privileged Michael acceptors in the addition of a large variety of nucleophiles.[1] Among the latter, activated aromatic rings have been efficient in adding enaminones through a Friedel–Crafts reaction.[2] Recently, we reported a novel synthesis of 2-methoxycarbonylbenzofurans **1** by an intramolecular Friedel–Crafts cyclization of methyl 2-aryloxy-3-dimethylaminopropenoates **2**, promoted by Lewis acid catalysis (Scheme 1).[3] The efficiency of this key synthetic step depended on the presence of electron-donating groups in the aromatic ring. Moreover, the conjugate addition in the enaminone analogues 3-aryloxy-4-dimethylamino-3-buten-2-ones **3**, which was much faster than in substrates **2**, led to the regioselective formation of 2-acylbenzofurans **4**, which included some natural products of the genus *Calea*.[4]

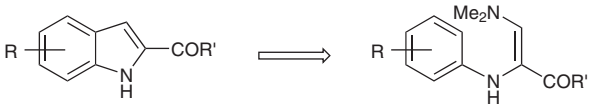


2, R' = OMe
3, R' = Me

1, R' = OMe
4, R' = Me

Scheme 1

Encouraged by success in the synthesis of benzofurans, we investigated the potential of this methodology in the preparation of other heterocycles. Owing to the importance of indoles[5] because of their widespread presence as natural alkaloids[6] as well as pharmacologically active compounds,[7] versatile synthons,[8] and synthetic targets,[9] we now report that this methodology provides a valuable new route for the synthesis of this crucial framework. Therefore, we decided to prepare 2-acyl- and 2-alkoxycarbonyl-indoles **5** by an intramolecular Friedel–Crafts heteroannulation of enaminones **6** (Scheme 2).



5, R' = Me, OMe, OEt

6, R' = Me, OMe, OEt

Scheme 2

Although benzofurans **1** and **4** were prepared efficiently,[3,4] the benzene ring of precursors **2** and **3** needed strong electron-donating groups *R* to achieve the cyclization step. In the case of indoles **5**, it was expected that the amino group attached to the benzene ring in the precursor **6** would be a stronger activating group in the heteroannulation process than the oxygen atom in the benzofuran enaminones **2** and **3**, due to the lower electronegativity and higher polarizability of the nitrogen atom. Hence, we evaluated the electron-demand of the aromatic ring required in this process. Consequently, we prepared the series of dimethylaminopropenoates **6b–h**, whose aromatic rings are substituted either by weak electron-donating groups such as the methyl group (**6b** and **6c**) or the chlorine atom (**6d** and **6e**), or by a stronger one such as the methoxy groups (**6f–h**). The non-activated anilino derivative **6a** was also examined.

Starting from anilines **8a–h**, the preparation of the series of compounds **6a–h** was achieved in a two-step synthetic sequence, via the corresponding α-anilino esters **7a–h** (Scheme 3). Thus, in the first step, the reaction of anilines **8a–e** with methyl bromoacetate (**9**) took place smoothly in the presence of K_2CO_3 in refluxing acetone for 12 hours, to give compounds **7a–e** in high yields (83–86%).[10] Ethyl esters **7f–h** were obtained in similar yields (78–81%) by reacting the respective anilines **8f–h** with ethyl bromoacetate (**10**). This methodology was successfully extended to the preparation of α-anilinoacetones **7i–o**, carrying out the reaction between anilines **8a**,**b**,**d–h** and α-chloroacetone (**11**) to furnish the desired products **7i–o**, respec-

SYNLETT 2006, No. 5, pp 0749–0755
Advanced online publication: 09.03.2006
DOI: 10.1055/s-2006-933135; Art ID: S12505ST