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Zinc mediated straightforward access to diacylpyrroles

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ABSTRACT

In this article, we report the preparation of various 2,4- and 2,5-diacylpyrroles via two zinc-mediated acylation reactions of non-protected pyrroles.

1. Introduction

2-Ketopyrroles and 2,5-ketopyrroles are two substructures underrepresented in the literature while these motives are well represented in biologically relevant molecules (for example, X-14547A [1], and calcimycin [2] in Fig. 1), in polymer chemistry (see in Fig. 1 for representative ligands) [3,4], or in hydroamination reactions [5].

Some procedures have been reported for the monoacylation of pyrroles (including the Vilsmeier–Haack reaction) [6–11]. The diacetylation reaction of pyrroles is less studied and can lead to two regioisomers: the 2,4- and the 2,5-disubstituted pyrroles. Only few syntheses have been reported, even if the corresponding 2,5-diiminopyrrole ligands (prepared by condensation of aromatic amines and mono- or diacylpyrroles) are emerging as suitable ligands [12] in polymerization reactions [4], or in hydroamination reactions catalyzed by organometallic complexes [5]. As an example, Gao et al. reported a sequential acylation reaction of a pyrrole (Scheme 1) [13]. The second acylation was carried out at room temperature for two weeks. The regioselectivity of this sequence was in favour of the 2,4-isomer (ratio: 3/1) and the 2,5-diacylated compound was isolated in a low 16% overall yield. A step wise diacylation of non protected pyrroles was initially reported by Olsson in 1981 [14]. This procedure allowed the synthesis of the sole 2,5-isomer in an overall yield of 34% but required a protection step before the introduction of the second carbonyl function (Scheme 1). To the best of our knowledge, the most efficient and general route to diketopyrroles was described by Fochi et al. [15] 2-Substituted 1,3-benzoxathiolium tetrafluoroborate was used as a masked acylating reagent in this protocol. In the presence of an excess of this derivative, the 2,5-disubstituted pyrroles were isolated regioselectively in high yields (Scheme 1). One of the advantages of this methodology is that identical or different acyl groups could be introduced at the 2- and 5-position. However, all these methodologies suffer from some drawbacks, such as harsh conditions, problem of selectivity, indirect methods of synthesis or long reaction times.

To date, no simple and direct procedure has yet been reported for the synthesis of diketopyrroles. In this work,

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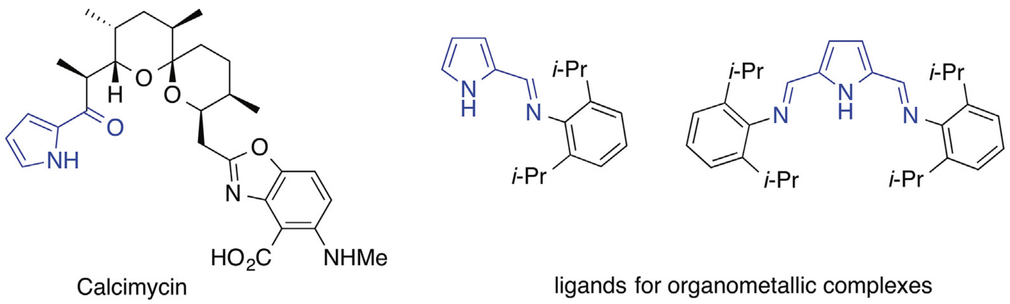
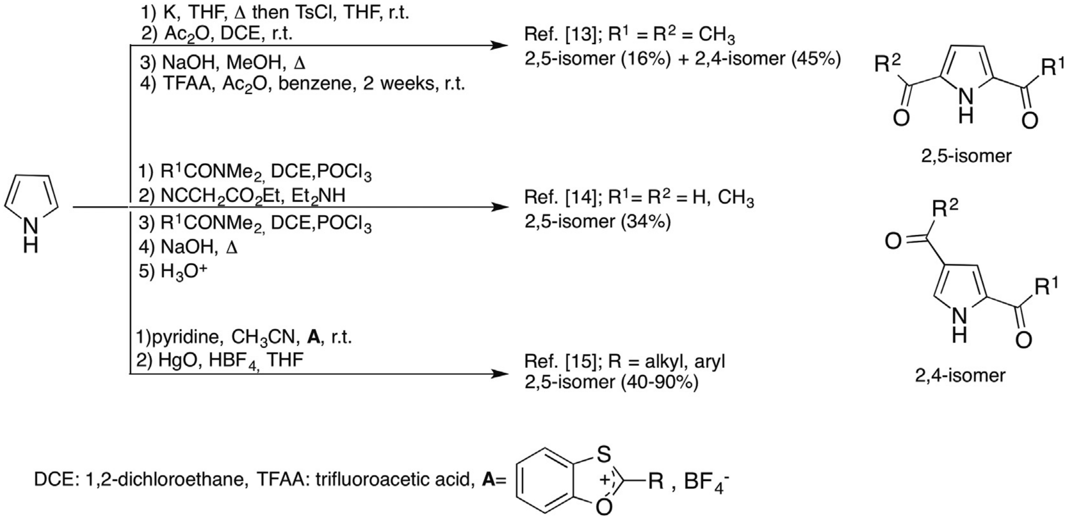


Fig. 1. Natural compounds and ligands for organometallic complexes containing acylpyrrole or diacylpyrrole subunits.



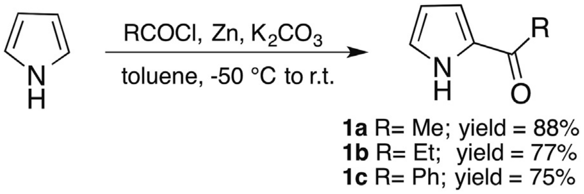
Scheme 1. Reported procedures for the synthesis of diacetyl pyrroles.

we report on a straightforward synthesis of diacetylated pyrroles from non-protected pyrroles and commercially or easily prepared acyl chloride derivatives.

2. Results and discussion

In 2002, Yadav et al. described an efficient method for the regioselective preparation of 2-acylpyrroles from pyrroles and various acyl chlorides in the presence of zinc powder at room temperature in toluene [10]. Due to our interest for the synthesis of functionalized pyrroles, we envisioned to develop a rapid and simple access to disubstituted pyrroles. For this purpose, we synthesized three 2-ketopyrroles (**1a**–**c**) in toluene, from −50 °C to room temperature, in 75–88% yield, according to a modified procedure (Scheme 2). It is worth mentioning that, in our hands, the yields were lower due to the polymerization of pyrroles if no base was added and if the addition of the acyl chloride was carried out at room temperature.

Having the monoacylated pyrroles, we next defined the optimized reaction conditions. The second acylation step was initially carried out with **1a** and acetyl chloride, as acylating reagent, in the presence of different metals (Zn, Fe, Al, Mn, and Mg) at various temperatures and in various solvents (Table 1). An initial attempt at 80 °C in toluene led to a complete decomposition of the starting material (entry 1, Table 1). However, a decrease of the temperature to room temperature overnight led gratifyingly to a mixture of diacetylpyrroles in 75% conversion and a ratio **2a**:**3a** of 1:2.33, without any N-acylation (entry 2, Table 1). The two regioisomers can easily be separated by chromatography on silica gel (see Experimental section). Variation of the solvent was also examined. In polar solvents, such as acetonitrile and THF, no or almost no reactivity was noticed (entries 5–6, Table 1), while in dichloroethane (DCE) complete conversion and moderate regioselectivity in favour of the 2,4-isomer were obtained (ratio **2a**:**3a** of 1:1.5, entry 4, Table 1). Surprisingly, dichloromethane (DCM) led



Scheme 2. Synthesis of ketopyrrole **1a**–**c**.