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A novel one-pot synthesis of 2-benzoylpyrroles from benzaldehydes

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ABSTRACT

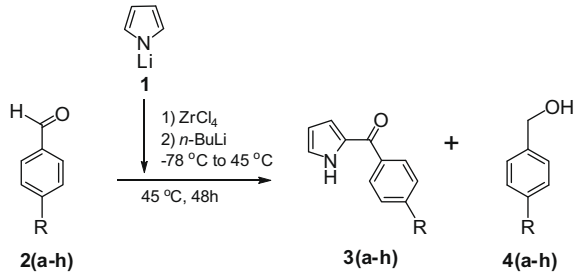
We herein report a novel one-pot reaction for benzoylation of pyrrole. The key step in the reaction is generation of di(1*H*-pyrrol-1-yl)zirconium(IV) chloride complex which reacts with benzaldehydes and methyl benzoates to give 2-benzoylpyrroles as the major product.

Pyrrole[1] is the core unit of many therapeutically active molecules such as tolmetin, atorvastatin, chlorfenapyr, premazepam, pyrvinium, roseophilin, zomepirac and natural products such as bilins, bilanes, phycobilin, porphyrin and chlorophyll.[2] Synthesis of pyrrole derivatives involves two types of strategies: (a) condensation reactions of α-aminocarbonyl compounds and activated ketones (Knorr pyrrole synthesis[3]) or α-halocarbonyl compounds, β-keto esters and ammonia (Hantzsch pyrrole synthesis[4]) or 1,4-dicarbonyl compounds and primary amines (Paal–Knorr synthesis[5]) and (b) functionalization of pyrrole by substitution reactions.[6] The reactions of pyrrole are dominated by electrophilic substitution because of the lone pair of electrons on the nitrogen and consequent stability of the σ-complexes.[7] Such reactions necessitate that a delicate balance[8] be achieved between the exploitation of nucleophilicity for the required electrophilic substitution, and the containment of nucleophilicity either through electronic or steric means to inhibit over-substitution and/or unwanted transformations.

2-Benzoylpyrroles have been mostly synthesized using Friedel–Crafts acylation[9] or Vilsmeier–Haack reaction.[10] Friedel–Crafts acylation has posed serious drawbacks. The activation of carboxylic acid is usually necessary and in most cases it is converted to the reactive acid chloride in a separate step. The water sensitive Lewis acid aluminium chloride usually forms a stable complex with the product making isolation difficult. Also the reagent causes severe problems in effluent management since neutralization of it results in a gelatinous mass adding significant threats to the environment. Further, the Friedel–Crafts reactions are usually carried out in halogenated solvents or volatile hydrocarbon solvents which are not eco-friendly. Vilsmeier–Haack reaction is seriously hampered by the limited substrate availability and substrate specificity. Polymerization of pyrrole and substituted pyrroles forming polypyrroles, often happens in these reactions leading to poor yields.[11] Though it is well known that pyrrole reacts with aldehydes to form porphyrin,[12] in our efforts to obtain functionalized pyrrole, we have observed the formation of 2-benzoylpyrrole from benzaldehyde using a preformed complex of zirconium tetrachloride and pyrrole.

The reactions of pyrrole at position 2 often requires the use of protecting groups at *N1* which needs the additional steps of protection and deprotection.[13] In search of a viable methodology by which pyrrole could be functionalized in a simple and straightforward manner, we found that a complex of pyrrole and zirconocene dichloride reacts with benzaldehyde to afford a mixture of non-isolable compounds. The high rates of these reactions, the uncertainty in the exact nature of the zirconocene species that initiate the coupling and the fact that intermediate species have a transitory disposition which is difficult in identifying make the kinetic and mechanistic investigations of these reactions more difficult.[14] Therefore an alternate strategy was adopted by replacing the cyclopentadienyl group by pyrrole-1-ide and the resulting zirconium complex was treated with *n*-butyllithium followed by the addition of benzaldehyde at 45 °C. Quite interestingly the complex generated in situ reacted with benzaldehyde to give 2-benzoylpyrrole along with benzyl alcohol (Scheme 1). The scope of this method was generalized by employing various substituted benzaldehydes bearing electron-withdrawing groups and electron-donating groups (Table 1, entries 1–8).

For a detailed examination, the reaction between di(1*H*-pyrrol-1-yl)zirconium(IV) chloride and 4-fluorobenzaldehyde (**2d**) was considered. The addition of the aldehyde at different temperatures helped us to draw important conclusions regarding the



Scheme 1. General strategy for synthesis of 2-benzoylpyrroles.

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Table 1
Reactions with benzaldehydes and methyl benzoates

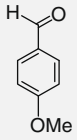
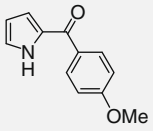
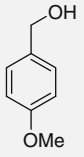
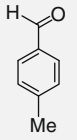
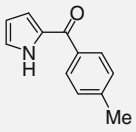
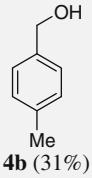
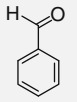
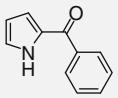
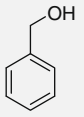
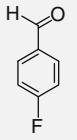
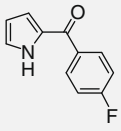
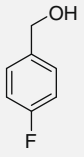
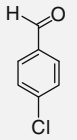
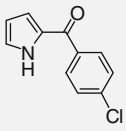
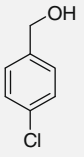
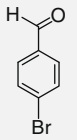
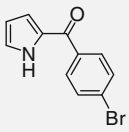
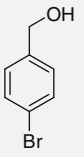
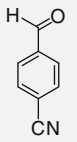
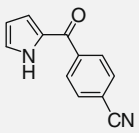
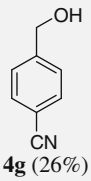
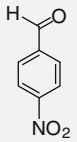
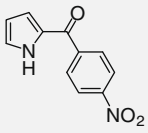
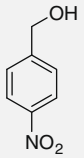
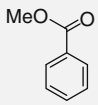
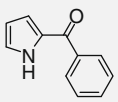
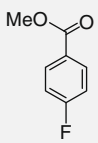
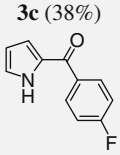
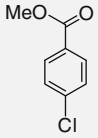
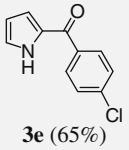
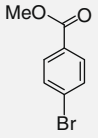
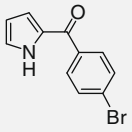
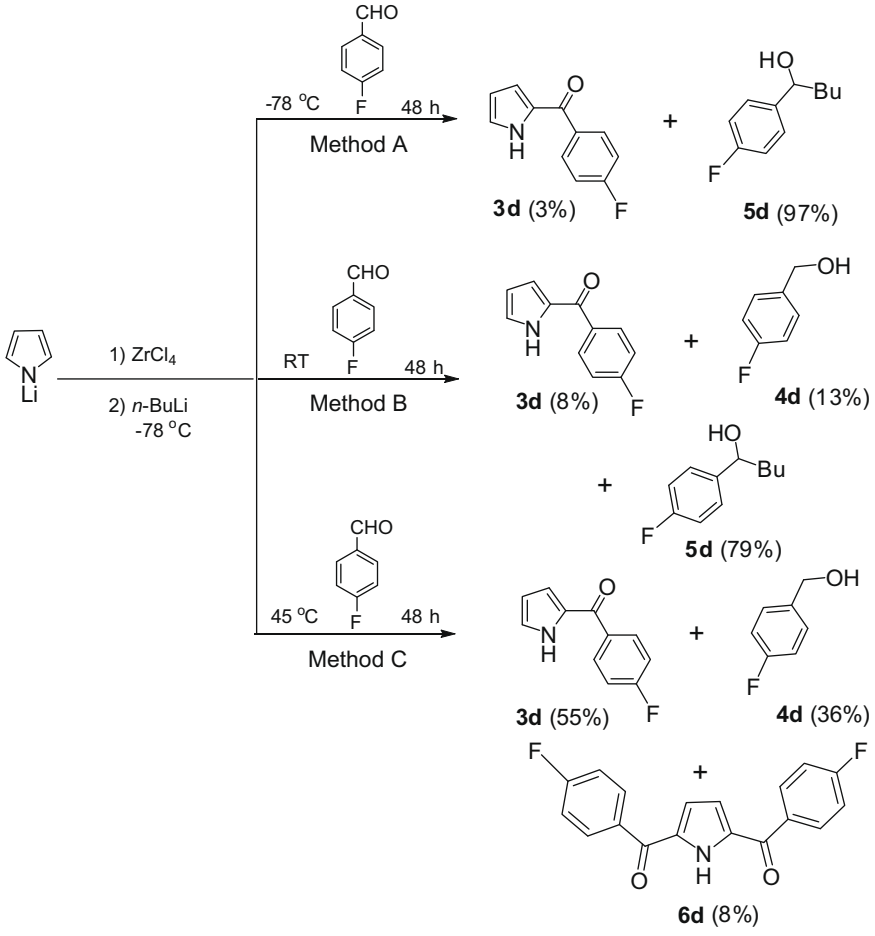
Entry	Starting material	Products (% Yield)	
1		 **3a** (62%)	 **4a** (30%)
2		 **3b** (65%)	 **4b** (31%)
3		 **3c** (45%)	 **4c** (40%)
4		 **3d** (55%)	 **4d** (36%)
5		 **3e** (63%)	 **4e** (28%)
6		 **3f** (67%)	 **4f** (23%)
7		 **3g** (61%)	 **4g** (26%)
8		 **3h** (74%)	 **4h** (21%)
9		 **3c** (38%)	Nil
10		 **3d** (58%)	Nil

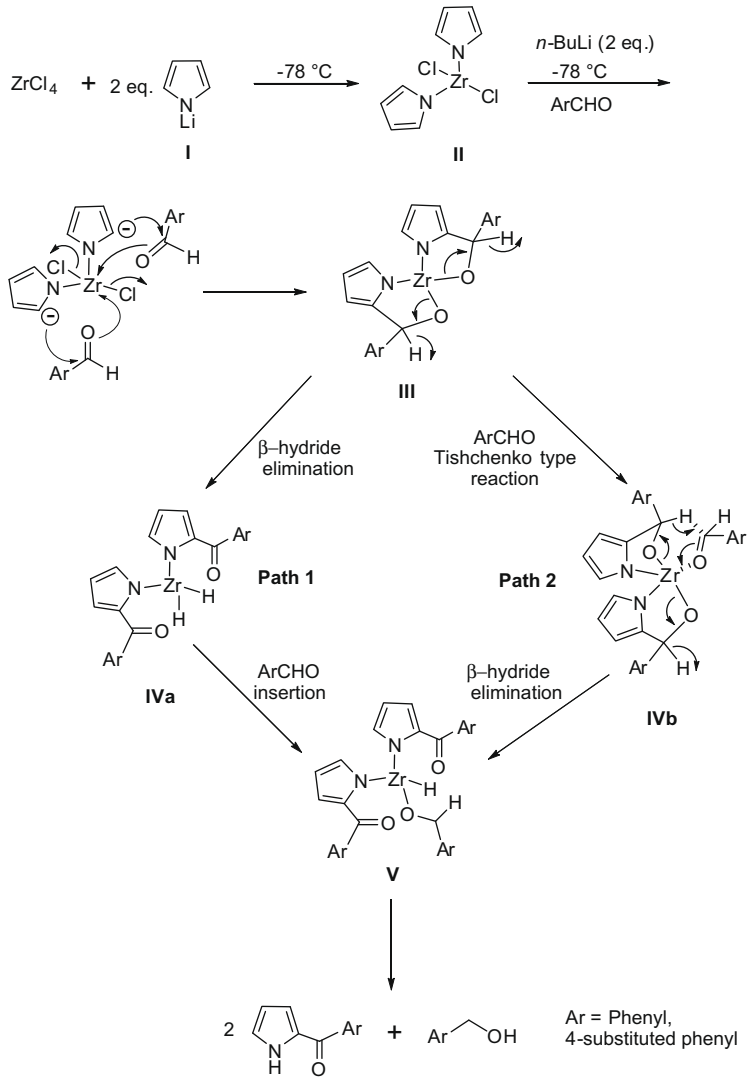
Table 1 (*continued*)

Entry	Starting material	Products (% Yield)	
11		 **3e** (65%)	Nil
12		 **3f** (73%)	Nil

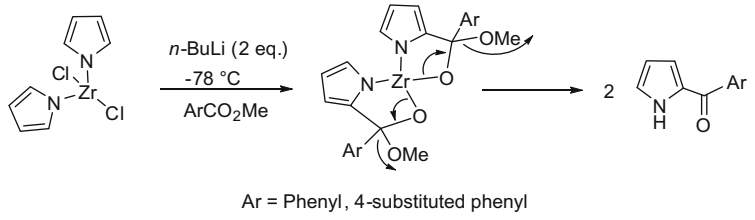
mechanistic aspects and the intermediates involved (Scheme 2). Addition of the aldehyde at −78 °C to the complex generated in situ afforded 1-(4-fluorobenzoyl)pentan-1-ol (**5d**) as the major product along with a small amount of 2-(4-fluorobenzoyl)pyrrole (**3d**), while addition at room temperature witnessed the formation of 4-fluorobenzyl alcohol (**4d**) and 2-(4-fluorobenzoyl)pyrrole (**3d**) along with 1-(4-fluorophenyl)pentan-1-ol (**5d**) as the major product. When addition was carried out at 45 °C, 4-fluorobenzyl alcohol (**4d**) and 2,5-di(4-fluorobenzoyl)pyrrole (**6d**) were formed with 2-(4-fluorobenzoyl)pyrrole (**3d**) as the major product. No improvement in the reaction was observed with further increase in temperature. Based on these observations, we tried to depict a plausible mechanism for the reaction (Scheme 3). Zirconium tetrachloride reacts with 2 equiv of N-lithiated pyrrole to afford di(1*H*-pyrrol-1-yl)zirconium(IV) chloride (**II**), which on reaction with benzaldehyde in the presence of *n*-butyllithium might form the intermediate (**III**) and subsequently endure β-hydride eliminations followed by insertion of benzaldehyde into the hydride complex (**IVa**) or undergo a Tishchenko-type reaction[15] with benzaldehyde to form the intermediate (**IVb**) ensued by a β-hydride elimination to afford bis(2-benzoyl-1*H*-pyrrol-1-yl)(benzyloxy)zirconium(IV) hydride (**V**). Workup of the reaction mixture yields 2-benzoylpyrrole along with benzyl alcohol.



Scheme 2. Temperature-based reactions of 4-fluorobenzaldehyde.



Scheme 3. Plausible mechanism for the formation of 2-benzoylpyrroles.



Scheme 4. Reactions of di(1*H*-pyrrol-1-yl)zirconium(IV) chloride with esters.

To add more authenticity to the proposed intermediate (**III**), the reaction was carried out with different esters (Table 1, entries 9–12) where the possibility of β-hydride elimination is completely ruled out (Scheme 4). Interestingly and in agreement to our notion, the reaction afforded 2-benzoylpyrroles as the only products which justifies the intermediate involved and the formation of primary alcohols occurring with benzaldehydes.

To conclude, a novel one-pot reaction for benzoylation of pyrrole using benzaldehydes and methyl benzoates was developed.[16] This improves upon previous syntheses of 2-benzoylpyrroles, which had taken place in three to four steps affording products with low yields.

Acknowledgement

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16. In a typical experiment, to a solution of pyrrole (100 mg, 1.5 mmol) in dry tetrahydrofuran (5 mL), *n*-butyllithium (2.0 M in cyclohexane, 0.75 mL, 1.5 mmol) was added at −78 °C and stirred for 20 min under nitrogen atmosphere. The solution of lithium pyrrole-1-ide was then added to a solution of zirconium(IV) chloride (174 mg, 0.75 mmol) in dry tetrahydrofuran (5 mL) at −78 °C and was stirred for additional 20 min. To this suspension, *n*-butyllithium (0.75 mL, 1.5 mmol) was added dropwise and stirred for 10 min. The reaction was then allowed to attain the room temperature and further heated at 45 °C for 2 h, followed by the addition of benzaldehyde (0.75 mmol). Stirring was continued for 48 h at 45 °C and the progress of the reaction was monitored by GCMS. Reaction mixture was then cooled to room temperature, quenched with saturated aqueous ammonium chloride solution, filtered over Celite and extracted into ethyl acetate. The organic layer was then washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude mixture. The product was isolated from the crude mixture by column chromatography on silica gel (60–120 mesh) using ethyl acetate–hexane mixture (6:94) as an eluent and characterized by spectral methods; also compared with the reported data[9b,c] available for compounds **3a–f** and **3h**.
4-(1H-Pyrrole-2-carbonyl)benzonitrile (**3g**) Mp = 157–158 °C; IR (KBr) ν_{max} cm^{-1} 3287, 2230, 1618, 1540, 1434, 1396, 1262, 1129, 1050, 896, 857, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (br s, 1H), 7.99–7.96 (m, 2H), 7.85–7.81 (m, 2H), 7.23–7.21 (m, 1H), 6.86–6.84 (m, 1H), 6.39–6.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 142.0, 132.2, 130.5, 129.3, 126.5, 120.2, 118.1, 115.1, 111.6; MS (EI): *m*/*z* = 195.82 [M^+]. Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.54; H, 4.22; N, 14.09.