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Synthesis of 2-Benzoylpyrrole Derivatives via C-H Functionalization Adjacent to Nitrogen of Pyrrole

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KEYWORDS: Synthesis; Benzoylation; Pyrrole; alkali metalation; 2, 6-dimethylaniline

ABSTRACT: A direct transition-metal-free synthesis of 2-benzoylpyrrole derivatives from free (N-H) pyrroles and benzaldehyde has been developed. The benzoylation reaction at the 2 or 5-position of pyrrole proceeded well under the alkali metalation system and with 2, 6-dimethylaniline as the additive in moderate to good yields. This strategy offers a simple, efficient approach to synthesis of the 2-benzoylpyrrole derivatives.

For pyrroles are important units of many biologically active natural products and pharmaceutical compounds, their synthesis and further functionalization are of considerable

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importance [1]. Among many efforts, the benzylation reaction at the 2 or 5-position of pyrroles attracts much attention in organic synthesis due to they are the key drug intermediate and present in core structures in many biologically active derivatives [2]. Generally, the traditional synthetic protocols for 2-benzoylpyrrole derivatives mainly include Friedel-Crafts acylations [3], Vilsmeier-Haack reactions [4] and Grignard reactions [5]. However, the most frequently used Friedel-Crafts acylation requires the use of protecting groups at N1 which needs additional steps of protection and deprotection [6]. Vilsmeier-Haack reaction is seriously hampered by the limited substrate availability and substrate specificity. In a word, the existing methods often involve uncommonly used acylated reagents or unbenign reaction conditions. Therefore, a simple and efficient approach to synthesis of the 2-benzoylpyrrole derivatives is highly desired.

The direct sp^2 C–H bond activation adjacent to nitrogen of pyrrole followed by C–C bond formation is the most efficient and promising construction of 2-benzoylpyrrole derivatives. So far, though there have many cases of C–C bond formation through activation of the C–H bond adjacent to the heteroatom [7], to the best of our knowledge, only two examples reported for benzylation of pyrrole using benzaldehydes by Raines [2b] and Nair' [8] group. In Raines' studies, the benzylation reaction was carried out in 54% yield using equimolar quantities of the sodium derivative of pyrrole and the aromatic aldehyde. No significant change in yield took place when 2 moles of the aromatic aldehyde were added to 1 mole of the sodium derivative of pyrrole. In Nair' paper, one-pot synthesis of 2-benzoylpyrroles from benzaldehydes needs 2 equiv of N-lithiated pyrrole react with Zirconium tetrachloride to afford di(1H-pyrrol-1-yl)zirconium(IV) chloride, then treated with benzaldehyde in the presence of 2 equiv n-butyllithium yield 2-benzoylpyrrole along with benzyl alcohol. Herein, we report a simple and highly efficient reaction to form 2 or 5-substituted benzoylpyrrole derivatives by alkali metallised pyrrole with benzaldehydes using 2, 6-dimethylaniline as an additive. In this reaction,

the C-C bond was formed simultaneously to afford these important heterocyclic compounds in moderate to good yields.

Our initial studies focused on lithium complexes containing bidentate dianionic pyrrolyl ligands and their catalytic activity for amidation of aldehydes with amines [9]. Surprisingly, the yield of acylamide was very low when 2, 6-dimethylaniline was used. After careful separations and recrystallizations, the benzoylpyrrole compound **3** was isolated partially from reaction mixture, and its structure was confirmed by NMR spectra and X-ray crystal analysis (Figure 1).

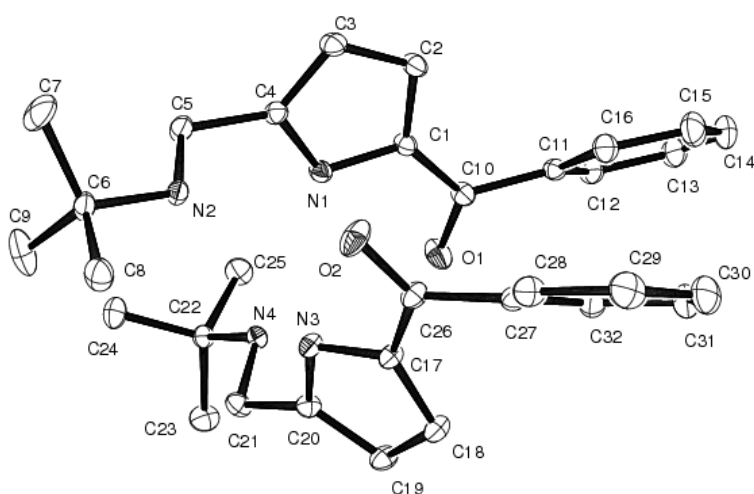
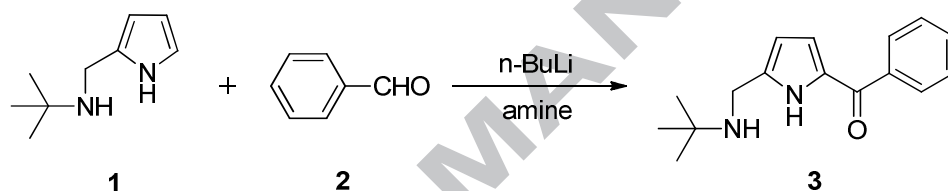


Figure 1. The molecular structure of **3**. Thermal ellipsoids are drawn at the 20% probability level. Hydrogen atoms are omitted for clarity

Thus, we became interested in the 2, 6-dimethylaniline which was used as an additive in the direct acylation reactions of pyrrole with aldehydes. In view of the byproducts, acylamide, alcohol and ester, should be produced in the present of lithium complex in this process. After the 2-(BuNHCH_2) $\text{C}_4\text{H}_3\text{NH}$ was deprotonated with $n\text{-BuLi}$, 1 equiv 2, 6-dimethylaniline and 3 equiv benzaldehyde was added, the reaction went to completion in 5 h with 90.1% isolated yield (Table 1). Decreasing the amount of aldehyde from 3 equivalents to 2 and 1 equivalents led to a drop in yield to 87.4% and 49.3% (Table 1, entries 1-3), respectively, and lowering the amount of 2, 6-

dimethylaniline from 1 equivalent to 0.5 and 0.3 equivalent did prove its effects is minimal (Table 1, entries 2, 4-5). However, the isolated yield was only 57.9% without 2, 6-dimethylaniline (Table 1, entries 6). To further examine the effect of steric and electronic properties of amines on the reaction. Tert-butylamine, diphenylamine and 2, 6-diisopropylaniline were investigated (Table 1, entries 7-9), the results indicated the amines play a important role in this reaction, and the properties of amines affect the reaction. The ortho-position substituted phenylamine were conducive to the benzoylation of pyrroles. Among the different solvents used for optimization (Table 1, entries 4, 10-12), ether yielded best results.

Table 1. Optimization of reaction conditions^a



Entry	benzaldehyde (equiv)	Amine (equiv)	solvent	Yield (%)
1	3	2,6-Dimethylaniline (1)	Et ₂ O	90.1
2	2	2,6-Dimethylaniline (1)	Et ₂ O	87.4
3	1	2,6-Dimethylaniline (1)	Et ₂ O	49.3
4	2	2,6-Dimethylaniline (0.5)	Et ₂ O	87.1
5	2	2,6-Dimethylaniline (0.3)	Et ₂ O	85.9
6	2	2,6-Dimethylaniline (0)	Et ₂ O	57.9
7	2	Tert-butylamine (0.5)	Et ₂ O	68.7
8	2	Diphenylamine (0.5)	Et ₂ O	79.8
9	2	2,6- Diisopropylaniline (0.5)	Et ₂ O	86.7
10	2	2,6-Dimethylaniline (0.5)	Hex	71.3
11	2	2,6-Dimethylaniline (0.5)	Toluene	73.4


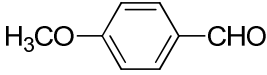
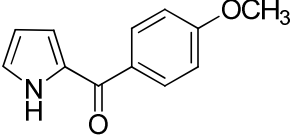

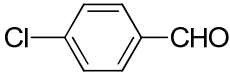
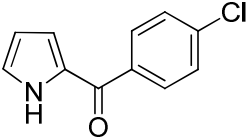

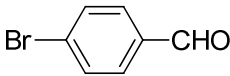
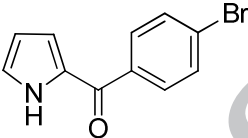

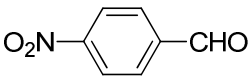
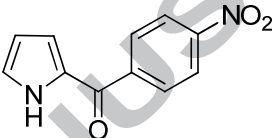

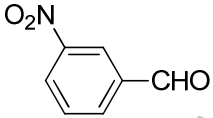
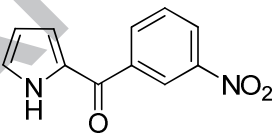
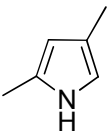
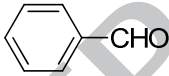
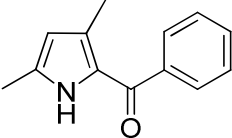
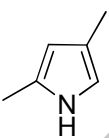
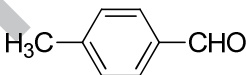
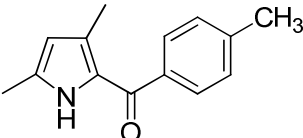
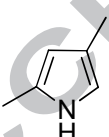
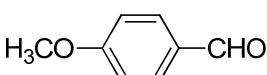
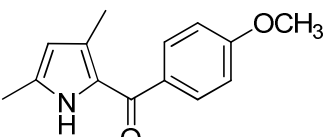
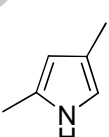
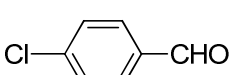
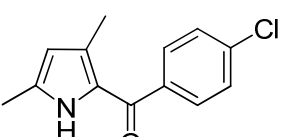
12 2 2,6-Dimethylaniline (0.5) THF 63.6

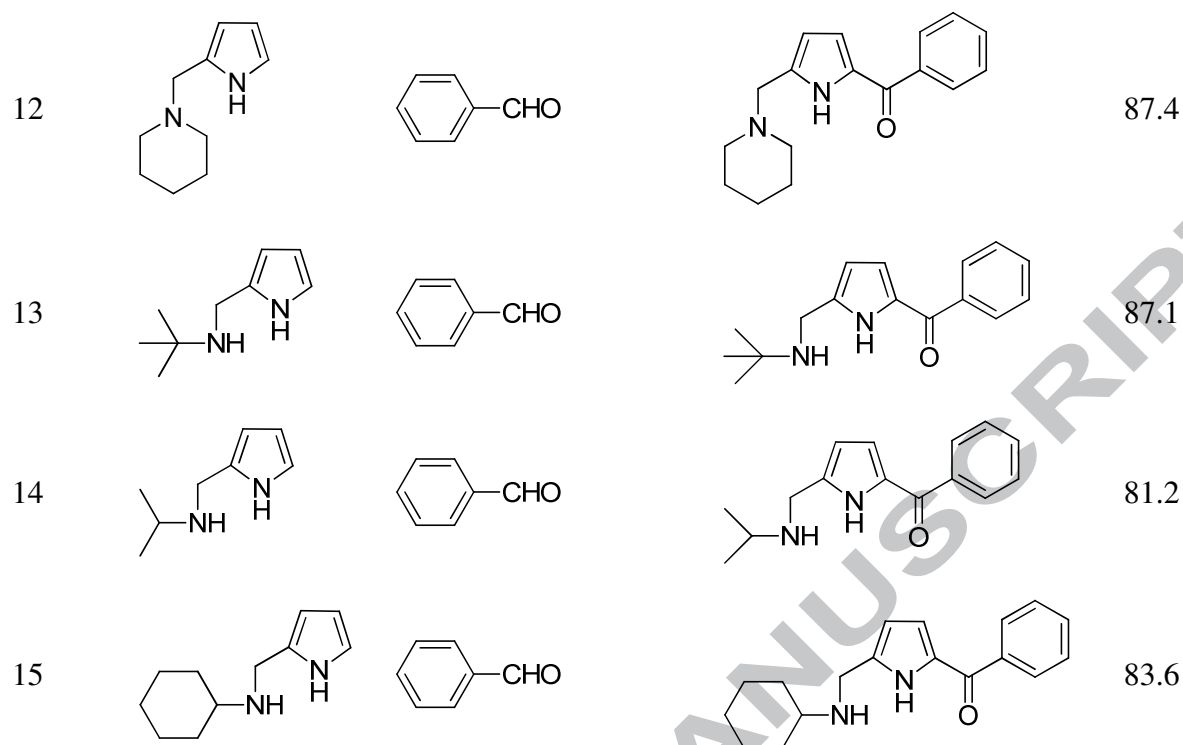
^[a] Reaction conditions: 2-(^tBuNHCH₂)C₄H₃NH (3 mmol), 30 °C. ^[b] Isolated yield.

To further investigate the scope of the application for this benzoylation reaction under the optimized conditions, we paid attention to the representative pyrrole and the other substituted pyrroles. And the results are summarized in Table 2. Firstly, the pyrrole and different substituted benzaldehyde were explored. To our delight, benzaldehydes bearing electron-neutral (4-H, 4-CH₃), electron-rich (4-OCH₃), and halogenated (4-Br) groups all participated in this reaction smoothly to afford the desired products in moderate to excellent yields (61.9-88.6%, entries 1-7). Subsequently, the scope was also extended to some substituted pyrroles. 2, 4-dimethylpyrrole and 2-(piperidylmethyl)pyrrole were applied to this transformation and giving the corresponding products in 80.4 and 89.5% yields (Table 2, entries 8-12), respectively. The other aminomethyl pyrroles also worked well under the optimized reaction conditions and obtained in 81.2-87.1% yields (Table 2, entries 13-15).

Table 2. The benzoylation reaction of pyrroles with aldehyde^a

Entry	Pyrroles	Aldehyde	Products	Yield (%)
1				81.5
2				74.3

3				61.9
4				85.8
5				88.6
6				67.9
7				71.8
8				80.4
9				81.7
10				83.4
11				89.5

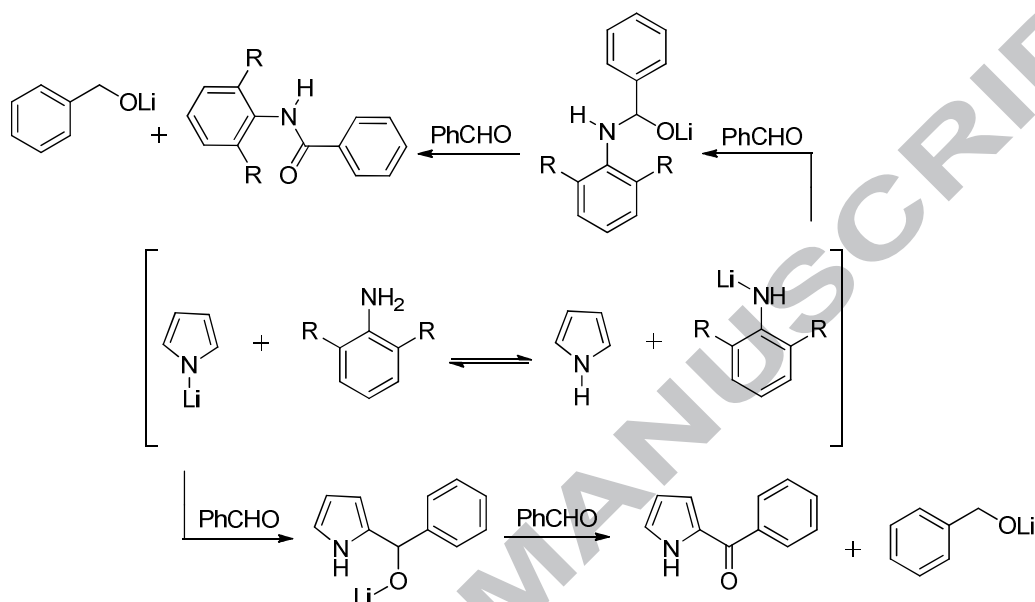


^[a] Reaction conditions: pyrroles (3 mmol), benzaldehyde (6 mmol), 2, 6-Dimethylaniline (1.5 mmol), Et₂O as solvent, 30 °C. ^[b] Isolated yield

Although the mechanistic details and the role of 2, 6-dimethylaniline are not clear at this stage, the above experimental results and related literature suggest that there is an equilibrium between the pyrrole lithium and adding amine (Scheme 1), the steric factors of amine appear to affect the reaction, the products are mainly amides when R is hydrogen, the products are benzoylpyrrole derivatives when the R is methyl groups. In other words, the reaction equilibrium shifts to the left when 2, 6-dimethylaniline was used as adding amine, which can be proved by obtained crystal structure from the concentrated reaction solution of pyrrolyl lithium complex with 2, 6-dimethylaniline in optimized reaction conditions (see supporting information). And the reaction equilibrium shifts to the right when phenylamine was used as adding amine, unfortunately, despite repeated attempts using a variety of different methods, no expected intermediates were isolated, but the reaction process should follow a route similar to that for alkali metal compounds

catalyzed amidation reactions is suggested [9]. Further investigations are needed to elucidate the detailed mechanism.

Scheme 1. Possible mechanism for benzylation of pyrrole derivatives.



CONCLUSIONS

In conclusion, we demonstrated a simple and efficient method for synthesis of 2 or 5-substituted benzoylpyrrole derivatives by alkali metallised pyrrole with benzaldehydes using 2,6-dimethylaniline as additive. This method shows good functional group tolerance and the C-C bond is formed simultaneously to afford these benzoylpyrrole derivatives in moderate to good yields.

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Supplementary data

The general experimental procedure and characterization data of the products are available as supporting information. Supplementary data associated with this article can be found, in the online version or by direct contacting the authors.

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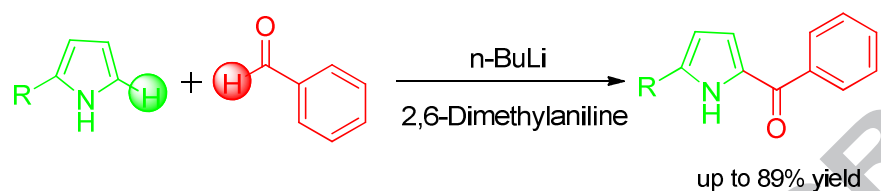
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Graphical abstract

A direct transition-metal-free synthesis of 2-benzoylpyrrole derivatives from free (N-H) pyrroles and benzaldehyde has been developed. This strategy offers a simple, efficient approach to synthesis of the 2-benzoylpyrrole derivatives.

ACCEPTED MANUSCRIPT