Solvent Free Synthesis of N-Substituted Pyrroles Catalyzed by Calcium Nitrate

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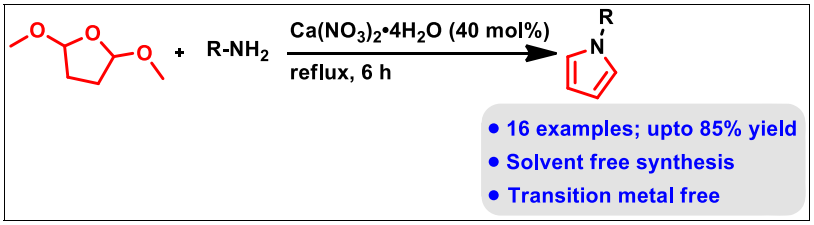

Moderated and mild way for synthesizing N-substituted pyrrole has been demonstrated herein. No solvents need to be used for this reaction, and instead, reactants themselves acted as a reaction medium. In fact, the reaction is carried out using catalytic amount of $Ca(NO_3)_2.4H_2O$. The reaction conditions are selective and mild that helped to tolerate a wide variety of functional groups to give the desired products in good chemical yields.

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INTRODUCTION

N-Substituted pyrroles are emerging class of heterocycles in bioactive molecules. Perhaps, their presence is strongly anticipated in well-known drugs—atorvastatin, isamoltane, aloracetam Figure 1 [1], etc. Apart from those, the ongoing medicinal chemistry research has highlighted several potential hits possessing N-substituted pyrrole. The most traditional and widely used way to prepare pyrrole from synthetic chemists is the Paal–Knorr synthesis [2,3]. Hence, it is not surprising to see extensive research happening on this reaction [4].

Generally, the Paal–Knorr synthesis of pyrrole can be achieved in two different ways where the nature of the product is completely depend on the electrophiles used. For example, one method could lead to di-, tri-, tetra-carbon substituted products, and other could led to only N-substituted product, leaving wide scope for late stage derivatization. However, this method where only N-substituted pyrroles could be obtained is not studied widely due to necessity of special reaction conditions such as transition metals, ultrasounds, and microwave. Removing trace transition metals from biologically active products including heterocycles is a great challenge. Scientists are concerned to use transition metals due to their human toxicity at parts per million (ppm) level and strict recent pharma regulations [5].

Hence, the use of alternative metals such as alkaline earth metals in chemical reactions could be promising due to their low toxicity. We are continuously exploring the ability of $Ca(NO_3)_2•4H_2O$ as a catalyst and/reagent in heterocyclic chemistry [6]. Calcium nitrate being a salt of strong acid and weak base possesses acidic property (pH = 6). We proposed that mild Lewis acidity of calcium nitrate could be useful for Clauson–Kaas reaction [7]. In the event, we tried heating 2,5-dimethoxytetrahydrofuran (DMTHF) with aniline and catalytic amount of $Ca(NO_3)_2•4H_2O$ in water.

RESULTS AND DISCUSSION

It is noteworthy to mention that this preliminary research work resulted in the formation of the desired product although in low yield (Table 1, entry 1).

Further, an optimization study was carried out to find out the best reaction condition (Table 1). Different polar solvents were screened, and DMF was found to be the best of all (entry 4). Surprisingly, without solvent, the reaction was even faster and led to comparatively good yield of the desired product (70%) (entry 7). It should be mentioned that the reaction yield was decreased when catalyst loading was decreased to 20 mol% (entry 7, yield in parentheses). Other metal catalyzed reported reaction is cited in the table showing good chemical yield; however, the reaction conditions were not satisfactory to be used in large scale due to the use of ultrasound (entry 8) [8]. Another reaction using bismuth as a catalyst was also reported for the synthesis of N-substituted pyrrole. However, the reaction scope was not extended by using DMTHF, but instead, 2,5-diketone (Scheme 1; upper equation where $R^2 = R^3 = H$, $R^1 = R^4 = CH_3$, and $R^5 = Ph$) was used

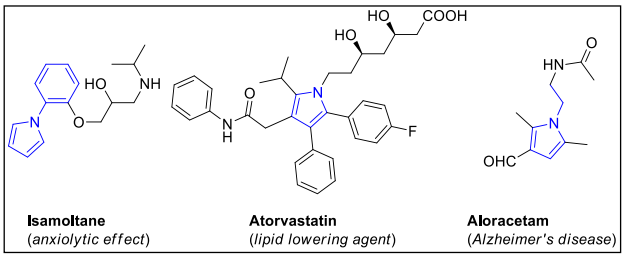


Figure 1. Few important drugs containing N-substituted pyrrole motifs. [Color figure can be viewed at wileyonlinelibrary.com]

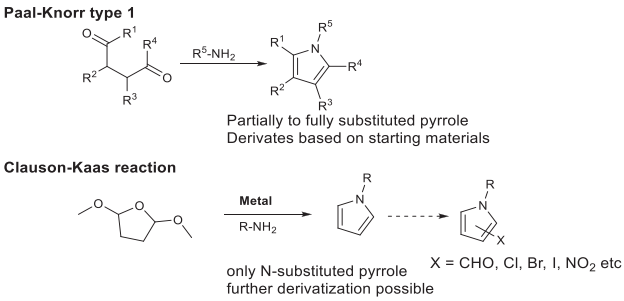
Table 1

Optimization of reaction condition[a].

Entry	Catalysts	Solvent	*t* (h)	Yield[b] (%)
1	$Ca(NO_3)_2{\cdot}4H_2O$	Water	12	40
2	$Ca(NO_3)_2{\cdot}4H_2O$	Acetonitrile	6	50
3	$Ca(NO_3)_2{\cdot}4H_2O$	DMSO	8	20
4	$Ca(NO_3)_2{\cdot}4H_2O$	DMF	8	55
5	$Ca(NO_3)_2{\cdot}4H_2O$	Ethanol	12	40
6	$Ca(NO_3)_2{\cdot}4H_2O$	Water	12	40
7	$Ca(NO_3)_2{\cdot}4H_2O$	Solvent free	4.5	70 (30)[c]
8	$UO_2(NO_3)_2.6H_2O$	Methanol	0.5	90[8]
9	$Bi(NO_3)_2.5H_2O$	CH_2Cl_2	10	96[9]

[a]Reaction conditions: Aniline (2.0 mmol), 2,5-dimethoxytetrahydrofuran (3.0 mmol), refluxed.
[b]Isolated yield.
[c]Reaction was carried out using 20 mol% catalyst for 6 h.

Scheme 1. Paal–Knorr and Clauson–Kaas synthesis of pyrroles using two approaches.

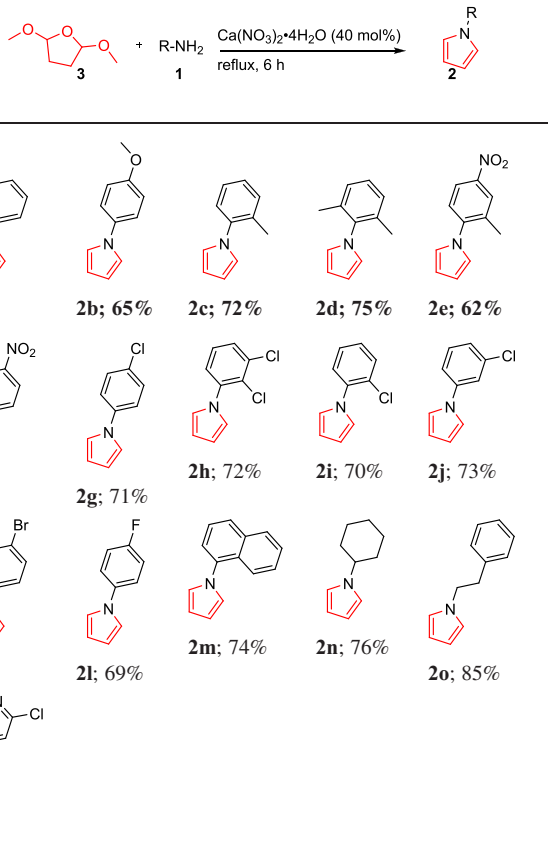


that resulted in the formation of 2,5-disubstituted product (entry 9) [9]. Also, dichloromethane, which is used as a solvent, is a known carcinogen.

Optimized conditions in hand, a variety of aliphatic, aromatic, heteroaromatic amines were used as a nucleophiles, and results are summarized in Table 2 [10]. Electron donating groups on amines helped to give good yields compared with strong electron withdrawing groups (entries **2a**–**2d** vs **2e** and **2f**). Sterically, bulky amines were also found to give satisfactory yield of the desired product (entries **2d**, **2e**, **2h**, **2i**). Halo-substituted aryl

Table 2

Substrate scope for N-substituted pyrroles catalyzed by calcium nitrate.

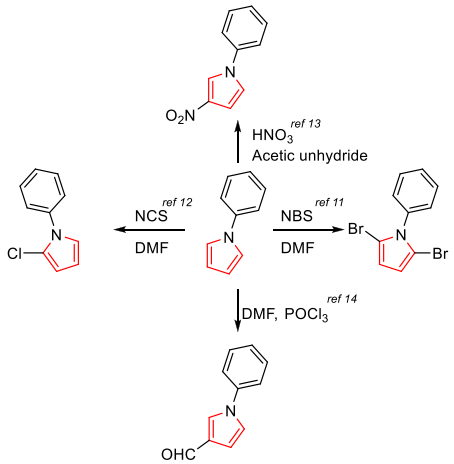


amines showed no difference in normal reactivity (entries **2g**–**2l**). Aliphatic amines were found give better chemical yields compared with aryl amines (entries **2n** and **2o**). Heterocyclic amine such as **1p** gave good yield of the desired product **2p**.

One of the importance of this type of reaction is that the late stage functionalization of the product could be carried out. Scheme 2 represents few important fundamental reactions that could be carried out on pyrrole ring of *N*-phenylpyrrole. Bromination using *N*-bromosuccinimide [11], chlorination using *N*-chlorosuccinimide [12], nitration using nitric acid [13], and formylation using Vilsemier–Hack reaction [14] could be performed.

To investigate the possible reaction pathway, we carried out several control experiments as summarized in Figure 2. Initially, only DMTHF in the absence and presence of calcium nitrate was refluxed, and the nuclear magnetic resonance (NMR) of crude reaction mixture of both conditions was recorded. As shown in the figure, only in the presence of calcium nitrate, succinaldehyde was formed (Fig. 2, reaction 2), while in the absence of catalyst, no succinaldehyde was formed (Fig. 2, reaction 1). To check the role of catalyst in the next step, a separate reaction on

Scheme 2. Literature procedures to derivatize N-substituted pyrroles. [Color figure can be viewed at wileyonlinelibrary.com]



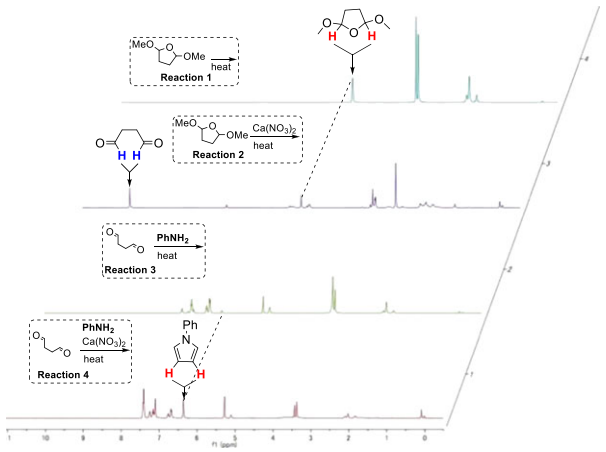
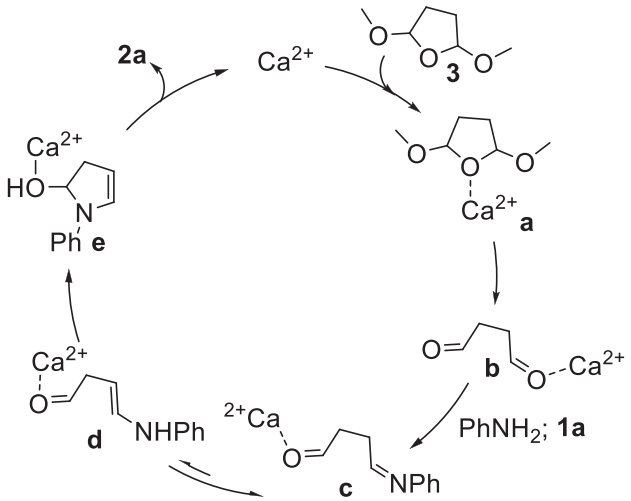


Figure 2. The importance of the catalyst in both reaction steps has been confirmed in this nuclear magnetic resonance study. [Color figure can be viewed at wileyonlinelibrary.com]

succinaldehyde with aniline in the absence and presence of the catalyst was performed. It was interesting to know that only the trace amount of product was formed in the absence of catalyst (Fig. 2, reaction 3). On the other hand, reaction in the presence of catalyst resulted in excellent conversion to *N*-phenylpyrrole (Fig. 2, reaction 4).

Based on these facts, a possible reaction pathway is proposed in Scheme 3. Calcium nitrates activate degradation of DMTHF **a** to succinaldehyde **b**, which then undergoes nucleophilic addition to give corresponding imine **c**. Intramolecular nucleophilic attack by enamine **d** onto carbonyl (which is in small equilibrium with imine **c**) resulted in the formation of cyclic hemiaminal intermediate **e**. Further, dehydration and aromatization resulted in the formation of product **2** along with the regeneration of catalyst. While following

Scheme 3. Plausible reaction pathway for the synthesis of N-substituted pyrroles.



this path, calcium nitrate could transform to calcium oxide or even hydroxide. The actual catalytic active species is difficult to predict here and requires additional studies. However, when either CaO or $Ca(OH)_2$ was used as a catalyst instead of $Ca(NO_3)_2$, no reaction was occurred, hence the possibility of these two species in reaction mechanism could be eliminated.

CONCLUSION

In summary, we have shown that alkaline earth metal-based catalyst could be used for the synthesis of pyrroles in good chemical yields. Reactions were carried out without organic solvents which is an additional advantage for minimizing organic waste. With the help of nuclear magnetic resonance studies, it was clear that $Ca(NO_3)_2$ is necessary for both the steps and hence for the reaction to occur. With this important info in hand, this inexpensive catalyst could open path for interesting chemical reactions in future.

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[10] For Experimental procedure and characterization data of selected compounds, follow; General procedure for the synthesis of N-Substituted Pyrroles: To the reaction mixture of primary amines (2 mmol) and 2, 5-dimethoxy tetrahydrofuran (1.5 equiv.) was added calcium nitrate (40 mol%). The reaction was stirred at reflux (100 ^{o}C). The progress of the reaction was monitored by TLC. After completion of reaction 10 mL ethyl acetate added. The reaction mixture is filtered, and filtrate was evaporated using rota evaporator under vacuum to get crude product. Crude product is purified by column chromatography using silica as stationary phase and hexane: ethyl acetate (10:0 to 8:2) as mobile phase to afford pure product. All products are known compounds and were identified by their melting point, ^{1}H NMR spectra according to the literature. For example, **2a**; White solid, Mp 59–60°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.38 (m, 4H), 7.28–7.25 (m, 1H), 7.13–7.10 (m, 2H), 6.47–6.29 (m, 2H); ^{13}C NMR (75MHz, CDCl3): δ = 140.74, 129.51, 125.59, 120.51, 119.29, 110.35; $C_{10}H_9N$; MS m/z143 (M^+) **2e**; Yellow Solid, Mp 43–46°C, ^{1}H NMR, (400 MHz, $CDCl_3$) δ 8.14 (d, J = 36.8 Hz, 1H), 7.30 (d, J = 47.5 Hz, 2H), 6.83 (d, J = 1.9 Hz, 2H), 6.37 (d, J = 1.9 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.12, 145.70, 134.46, 126.79, 126.58, 122.07, 121.72, 110.24, 77.34, 76.71, 18.63; $C_{11}H_1N_2O_2$, MS m/z 202(M^+).

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SUPPORTING INFORMATION

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