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An approach to the Paal–Knorr pyrroles synthesis catalyzed by $Sc(OTf)_3$ under solvent-free conditions

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Abstract—A facile synthesis of N-substituted pyrroles by the Paal–Knorr condensation has been accomplished using a simple procedure. Among different metal triflates screened, 1 mol % $Sc(OTf)_3$ efficiently promoted the reaction to give excellent yield (89–98%) under mild reaction conditions. Additionally, $Sc(OTf)_3$ could be recovered easily after the reactions and reused without evident loss in activity.

Pyrrole is one of the most important heterocyclic compounds, having become increasingly important in medicinal chemistry and organic synthesis.[1] Consequently, the enormous number of procedures have been developed for the construction of pyrroles. The classic methods for pyrroles synthesis are as follows: (i) the Hantzsch reaction,[2] which provides pyrroles from reaction of α-chloromethyl ketones with β-ketoesters and ammonia; (ii) the Knorr reaction,[3] which assembles pyrroles by the reaction between α-aminoketones derived from α-haloketones and ammonia, and β-ketoesters; (iii) the Paal Knorr reaction,[4] one of the most common approaches in which γ-diketone are converted to pyrroles from the reaction with primary amines (or ammonia) in the presence of various promoting agents;[5] (iv) some other methods were also reported.[6]

However, some of these methods often suffer from certain drawbacks such as hazardous organic solvents, high cost, long reaction time, use of stoichiometric and even excess amounts of acids because they can be trapped by amine in this condensation, and drastic reaction conditions. Therefore, the development of facile and environment friendly methods for the synthesis of pyrroles is necessary part of organic synthesis.

As the increase in environmental consciousness chemical research and industry, the challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents, or even better, do not need solvent at all. Metal triflates are unique Lewis acids that are currently of great research interest.[7] Metal triflates have low toxicity, low cost, high stability, ease to handle and recover from water. In addition, metal triflates are still active in the coexistence of many substrates containing nitrogen, oxygen, phosphorus, and sulfur atoms. Due to these advantages, they were widely used in organic synthesis.[8] Our previous research[9] using metal triflates stimulated us to investigate unceasingly the Paal–Knorr reaction under solvent-free conditions. Although the preparation of N-substituted pyrroles by Paal–Knorr condensation reaction of amines with 1,4-diketones under solvent-free conditions could be achieved using zirconium complex,[5d] we found that metal triflates were also excellent promoters for this reaction. Herein, the presented protocol not only is very simple and high-yielding but also greatly decreases environmental pollution.

At the onset of this work, we have investigated a variety of conditions with the model reaction using metal triflates as catalyst. The results are summarized in Table 1.

Keywords: Scandium triflate; Pyrrole; Paal–Knorr; Solvent-free conditions.

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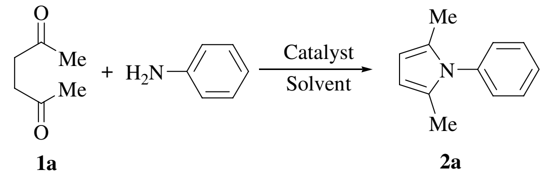
Table 1. Paal–Knorr reaction of acetonylacetone (**1a**) with aniline under different reaction conditions[a]



Entry	Solvent	Catalyst	Loading (mol %)	Yields (%)[b]
1	None	$Cu(OTf)_2$	5	78
2	None	$Mg(OTf)_2$	5	47
3	None	$Bi(OTf)_3$	5	72
4	None	$Yb(OTf)_3$	5	87
5	None	$Ga(OTf)_3$	5	90
6	None	$Y(OTf)_3$	5	89
7	None	$La(OTf)_3$	5	89
8	None	$Sm(OTf)_3$	5	88
9	None	$Eu(OTf)_3$	5	88
10	None	$Sc(OTf)_3$	0.5	80
11	None	$Sc(OTf)_3$[c]	1	93, 92, 89
12	None	$Sc(OTf)_3$	2.5	94
13	None	$Sc(OTf)_3$	5	96
14	None	$Sc(OTf)_3$	10	96
15	H_2O	$Sc(OTf)_3$	5	64
16	CH_2Cl_2	$Sc(OTf)_3$	5	77
17	CH_3NO_2	$Sc(OTf)_3$	5	63
18	None	$CuCl_2$	5	34 (55[d])
19	None	None	—	31

[a] 30 °C for 25 min.
[b] Isolated yield.
[c] Catalyst was reused for three times.
[d] In the presence of 40 mol % $CuCl_2$.

We examined different solvents such as CH_3NO_2, CH_2Cl_2, and H_2O. It shows that dichloromethane is a better solvent (yield 77%) than other solvents tested (such as water (64%), CH_3NO_2 (63%)). The best results were obtained by carrying out the reaction at 30 °C for 25 min in the presence of a catalytic amount of $Sc(OTf)_3$ without any solvent. In contrast, the corresponding product was obtained in only low yield (31%) in the absence of metal triflates (Table 1, entry 19). All metal triflates with the exception of $Mg(OTf)_2$ showed good catalytic effects, but $Sc(OTf)_3$ was particularly effective for this condensation reaction. On the other hand, we also examined the activity of recycled $Sc(OTf)_3$ catalyst as a representative $M(OTf)_n$ (Table 1, entry 11). $Sc(OTf)_3$ could be reused three times without evident loss of activity (with the yield of the corresponding product being 93%, 92%, and 89% yield, respectively). Lewis acid $CuCl_2$ gave lower yield in the presence of 5 mol % (yield 34%) even up to 40 mol % (yield 55%) of catalyst (Table 1, entry 18). In addition, we also studied influence of the amount of $Sc(OTf)_3$ on the reaction yields. We found that the yield was not significantly affected by adding different amount of $Sc(OTf)_3$·1 mol % of $Sc(OTf)_3$ was sufficient, excessive amount of catalyst did not increase the yield remarkably (Table 1, entries, 10–14). In the light of this, subsequent studies were carried out under the following optimized conditions, that is, with 1 mol % $Sc(OTf)_3$ at 30 °C in the absence of solvent.

Due to the good results obtained, we applied the optimal protocol to a variety of amines and the results were summarized in Table 2. In all cases, $Sc(OTf)_3$-catalyzed Paal–Knorr condensation reaction proceeded smoothly and gave the corresponding products in excellent yield.

As shown in Table 2, a series of aromatic amines bearing either electron-donating (Table 2, entries 2, 5–7) or electron-donating (Table 2, entries 3, 4, and 8) groups on aromatic ring was investigated. The substitution group on the phenyl ring did not make any difference in the Paal–Knorr reaction. Moreover, we also examined the Paal–Knorr reaction of aliphatic amines with **1a** (Table 2, entries 9–14, 17). Similarly, the corresponding products were obtained with excellent yield. Under further observation, it is observed that the reaction of chiral amine such as (*R*)-(+)-phenylethanamine with acetonylacetone do not cause any changes to the chirality of the molecule. This phenomenon is also observed with (*S*)-(−)-phenylethanamine when reacted with acetonylacetone.

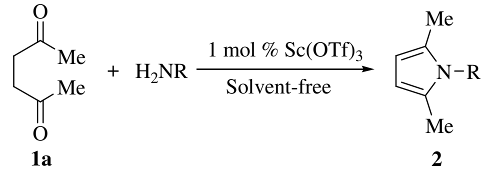
Furthermore, we examined the reactivity of heterocyclic amines with **1a** in the presence of $Sc(OTf)_3$. Thus, with 1 mol % $Sc(OTf)_3$ the Paal–Knorr reaction of heterocyclic amine such as 2-aminopyridine and **1a** without any solvent at 30 °C affords 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (**2s**), in 89% yield (Table 2, entry 19). Similarly, 2-amino-5-methylpyridine also gave 5-methyl-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (**2t**) in 92% yield (Table 2, entry 20). Therefore, heterocyclic amines exhibited analogous behavior to that of aromatic amines and aliphatic amines.

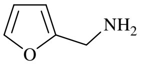
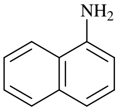
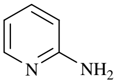
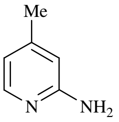
The reaction using $Sc(OTf)_3$ as catalyst has exhibited one additional important feature, that is the ability to tolerate various amines including aliphatic, aromatic, and heterocyclic amines. Interestingly, using the present protocol, the sterically hindered amines such as 2,6-diisopropylaniline, *sec*-butylamine, and 2,6-dimethylaniline[10] smoothly reacted with **1a** in high yield (Table 2, entries 5, 6, and 14). Unfortunately, no reaction of *tert*-butylamine with **1a** was observed under the same conditions. On the other hand, the present protocol that was also applied to less nucleophilic aromatic amine such as 1-aminonaphthalen is superior to the previous methods by montmorillonite KSF,[5e] I_2[5e] and $Bi(NO_3)_3$·$5H_2O$[5k] (Table 2, entry 18). That means better yield was obtained in shorter time.

To extend the scope of triflate-catalyzed method of pyrroles formation, other substituted diketones such as 1, 4-diphenylbutane-1, 4-dione (**1b**) and 1-phenylpentane-1, 4-dione (**1c**) were used. Clean formation of pyrroles (**2u**, **2v**) was observed with **1b**, **1c** under solvent-free conditions. The formation of **2u** from **1b** required longer time (Scheme 1).

Next, we investigated the reaction of diamines with **1a** (Scheme 2). In this reaction, two equivalents of **1a** were required in order to have a complete conversion of diamines. When aliphatic diamines such as ethylenedi-

Table 2. $Sc(OTf)_3$ catalyzed synthesis of pyrroles under solvent-free conditions[a]



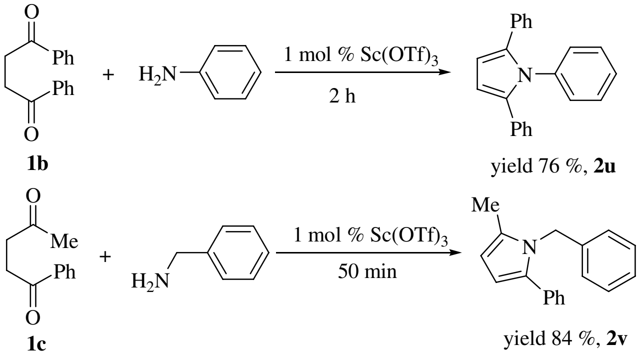
Entry	Amine	Product	Time (min)	Yield (%)[b]
1	$C_6H_5NH_2$	**2a**	25	93
2	p-$(CH_3)C_6H_4NH_2$	**2b**	30	92
3	p-$(Cl)C_6H_4NH_2$	**2c**	30	91
4	p-$(I)C_6H_4NH_2$	**2d**	40	87
5	$2,6$-$(^i\mathrm{Pr})_2C_6H_3NH_2$	**2e**	35	89
6	$2,6$-$(CH_3)_2C_6H_3NH_2$	**2f**	35	90
			2	75 (Ref. 10a)
7	o-$(OH)C_6H_4NH_2$	**2g**	30	91
8	p-$(NO_2)C_6H_4NH_2$	**2h**	30	90
9	$C_6H_5CH_2NH_2$	**2i**	30	94
10	p-$(OCH_3)C_6H_4CH_2NH_2$	**2j**	30	98
11	p-$(F)C_6H_4CH_2NH_2$	**2k**	30	93
12	$C_6H_5CH_2CH_2NH_2$	**2l**	30	95
13	$CH_3CH_2CH_2CH_2NH_2$	**2m**	30	94
14	$CH_3CH_2CH(CH_3)NH_2$	**2n**	40	81
			300	72 (Ref. 5d)
15	R-(+)-$C_6H_5CH(CH_3)NH_2$	**2o**	35	92
16	S-(−)-$C_6H_5CH(CH_3)NH_2$	**2p**	35	91
17		**2q**	30	94
18		**2r**	40	90
			60	85 (Ref. 5e)
			660	83 (Ref. 5e)
			660	83 (Ref. 5k)
19		**2s**	30	89
			60	78 (Ref. 5e)
			1500	70 (Ref. 5e)
			1500	70 (Ref. 5k)
20		**2t**	40	92

[a] Reaction conditions: amine (5 mmol), **1a** (5 mmol), and $Sc(OTf)_3$ (1 mol %), 30 °C.

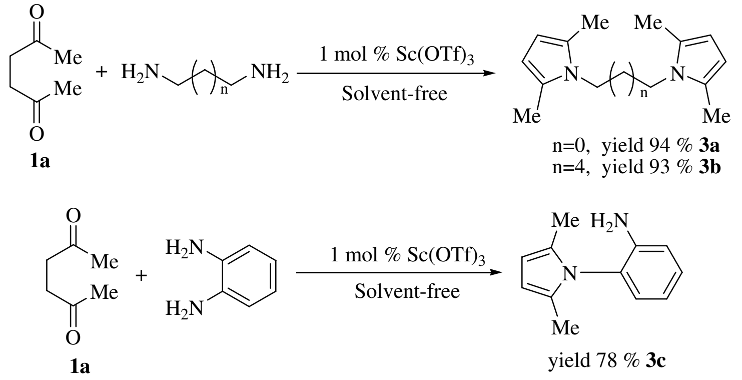
[b] Isolated yield.

amine and hexylenediamine were examined, the corresponding bis-pyrrole products (**3a**,**b**) were obtained in 94% and 93% yields, respectively. However, sterically more hindered aromatic diamine such as 1,2-benzenediamine was examined, the reaction gave the only monopyrrole product (**3c**) in the presence of two equivalents and even three equivalents **1a**.

In summary, a new catalytic protocol to synthesize pyrroles by Paal–Knorr condensation has been developed. Compared to previous reported methodologies, the present protocol features simple work-up, short reaction time, environmentally benign, easy recovery and reuse of metal triflates and mild reaction conditions with



Scheme 1. Paal–Knorr condensation was carried out at 35 °C under solvent-free conditions.



Scheme 2. Paal–Knorr condensation was conducted with diamines at 30 °C under solvent-free conditions.

excellent yield. Currently, studies on the extension of this protocol are ongoing in our laboratory.

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