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$Bi(OTf)_3/[bmim]BF_4$ as novel and reusable catalytic system for the synthesis of furan, pyrrole and thiophene derivatives

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Abstract—$Bi(OTf)_3$ immobilized in 1-butyl-3-methylimidazolium tetrafluoroborate $[bmim]BF_4$ has been utilized for the first time as a novel and reusable catalytic system for the synthesis of heteroaromatics such as furan, pyrrole and thiophene derivatives from 1,4-diketones. This new procedure offers significant improvements in reaction rates and yields. The recovered ionic liquid containing bismuth triflate can be reused for subsequent runs with only a gradual decrease in activity.

Heterocycles such as furan, pyrrole and thiophene are versatile pharmacophores possessing a variety of biological activities.[1] In particular, pyrroles are found in many naturally occurring compounds such as heme, chlorophyll and vitamin B_{12}.[2] Therefore, many synthetic methods for the preparation of pyrrole derivatives have been reported in the literature.[3] Among them, the Paal–Knorr reaction remains one of the most attractive methods for the synthesis of pyrroles.[4] The furan moiety is a core structure of many alkaloids such as kallolides and cembranolides.[5] The thiophene moiety also exists in many biologically active compounds.[6] Thus, syntheses of these heterocycles are of great importance. Generally, furan, pyrrole and thiophene derivatives are prepared from 1,4-dicarbonyl compounds using acid catalysts. Strong acids such as concd H_2SO_4, P_2O_5, *p*-TSA and montmorillonite KSF and basic reagents including TsCl/DBU, alumina, zirconium phosphate/zirconium sulfophenyl phosphate as well as microwave irradiation have been employed for their synthesis.[7,8] However, the synthesis of pyrroles and furans remains a challenge for synthetic chemists because of their sensitivity to acids. Furthermore, many of the current methods demand aqueous work-up for catalyst separation. Moreover, no attempt has been made to recycle the catalyst. Recently, ionic liquids have emerged as environmentally benign alternatives for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[9] They are used as green solvents as well as catalysts for effecting various transformations.[10] Lanthanide triflates are unique Lewis acids that are currently of great interest.[11] Their high catalytic activity, low toxicity, moisture and air tolerance, and their recyclability, make the use of lanthanide triflates attractive alternatives to conventional Lewis acids.[12] However, lanthanide triflates are rather expensive and their use in large-scale synthesis is limited, therefore, cheaper and more efficient catalysts are desirable. Bismuth triflate has evolved as a remarkable Lewis acid catalyst for effecting various organic transformations.[13] Compared to lanthanide triflates, bismuth triflate is cheap and is easy to prepare even on a multi-gram scale, from commercially available bismuth oxide and triflic acid.[14] To the best of our knowledge, this is the first report on the use of bismuth triflate as a catalyst for the synthesis of oxygen-, nitrogen- and sulfur-containing heterocycles.

In this article, we report a mild and efficient method for the synthesis of furan, pyrrole and thiophene derivatives from 1,4-diketones using 5 mol % $Bi(OTf)_3$ immobilized in air and moisture stable $[bmim]BF_4$. Accordingly, treatment of 1-phenyl-3-(2-thienyl)-1,4-octanedione with 5 mol % of $Bi(OTf)_3$ in $[bmim]BF_4$ at 90 °C afforded 2-butyl-5-phenyl-3-(2-thienyl)furan **2a** in 85% yield (Scheme 1).

In a similar manner, various substituted 1,4-diketones underwent smooth cyclization to give the corresponding

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Keywords: Ionic liquids (ILs); Bismuth catalysis; 1,4-Diketones; Heteroaromatics.

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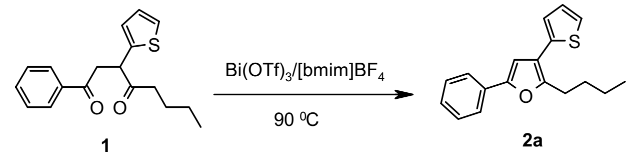


Scheme 1.

trisubstituted furan derivatives (Table 1, entries a–c). In the absence of bismuth(III) triflate, no cyclization was observed in the ionic liquid alone. The starting 1,4-diketones were prepared according to procedures reported in literature.[15] Furthermore, treatment of 1,4-diketones with aryl amines under similar conditions resulted in the formation of the corresponding pyrrole derivatives (Scheme 2).

A variety of 1,4-diketones reacted smoothly with various aryl amines under identical conditions to give the respective tetrasubstituted pyrroles in good yields (Table 1, entries d–h). In addition, 1,4-diketones reacted effi-

Table 1. Bi(OTf)$_3$/[bmim]BF$_4$-catalyzed synthesis of pyrrole, furan and thiophene derivatives

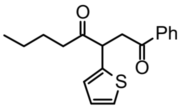
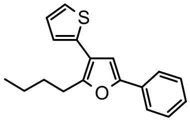
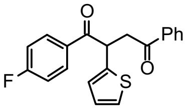
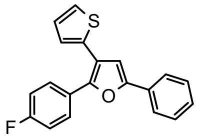
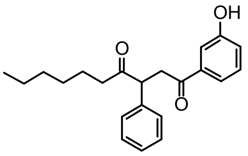
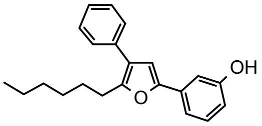
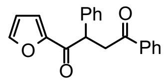
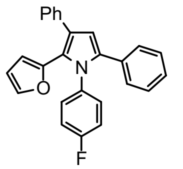
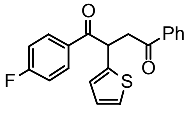
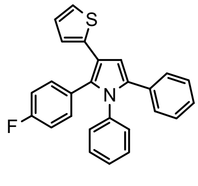
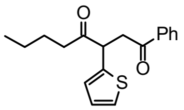
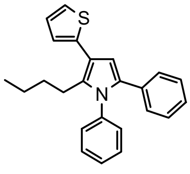
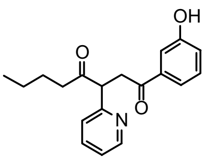
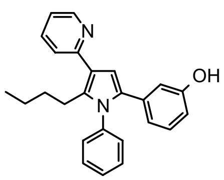
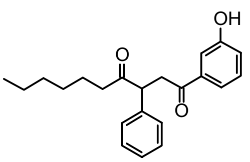
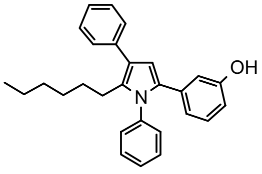
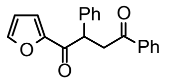
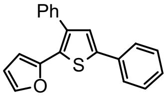
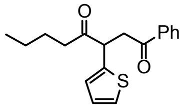
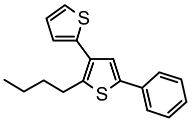
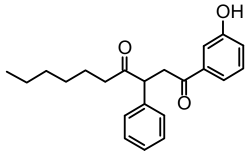
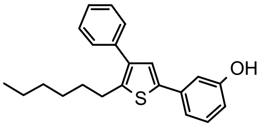
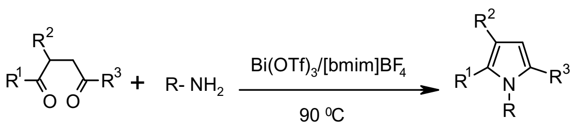
Entry	1,4-Diketone	Product[a]	Time (h)	Yield (%)[b]
a			4.0	85
b			4.5	80
c			4.0	82
d			4.5	88
e			4.0	90
f			4.5	83
g			4.0	85
h			5.0	82

Table 1 (*continued*)

Entry	1,4-Diketone	Product[a]	Time (h)	Yield (%)[b]
i			4.5	87
j			5.0	80
k			4.5	86

[a] All products were characterized by ^{1}H NMR, IR and mass spectrometry.

[b] Yield refers to the isolated pure products after column chromatography.



1 **3**

Scheme 2.

ciently with Lawesson's reagent under similar reaction conditions to give trisubstituted thiophene derivatives (Table 1, entries i–k, Scheme 3).

1,4-Diketones have been used as the common precursor for the synthesis of furan, pyrrole and thiophenes. This method is clean and free from side-products.[16] The reactions were complete within 4–5.0 h and the products were easily isolated by simple extraction with diethyl ether. The remaining ionic liquid containing the catalyst was recovered and recycled in subsequent reactions with only a gradual decrease in activity being observed. For instance, 1-(2-furyl)-2,4-diphenyl-1,4-butanedione and Lawesson's reagent afforded 87%, 85%, 81% and 76% yields over four cycles. The reactions proceeded smoothly not only in ionic liquids but also in refluxing toluene in the presence of 5 mol% of $Bi(OTf)_3$. The use of 5 mol% of bismuth triflate/[bmim]BF_4 was found to be the ideal catalytic system for these condensations. Moreover, the recovery and reuse of bismuth triflate is especially easy in ionic liquids compared to toluene. Among the various metal triflates tested, $Bi(OTf)_3$ was found to be the most effective catalyst in terms of conversion and reaction rates.

In summary, we describe a novel and efficient method for the synthesis of furan, pyrrole and thiophene derivatives from 1,4-dicarbonyl compounds using $Bi(OTf)_3$/[bmim]BF_4 as a novel and recyclable catalytic system.

Acknowledgements

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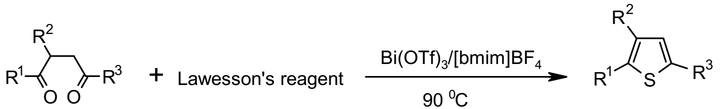

1 **4**

Scheme 3.

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16. *General procedure for the synthesis of substituted furans* (Table 1, entries a–c): A mixture of the 1,4-diketone (1 mmol) and Bi(OTf)_3 (5 mol %) in $[\text{bmim}]\text{BF}_4$ (3 mL) was heated at 90 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with diethyl ether (6 × 10 mL). The combined organic layers were dried, then concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 3%) to afford the pure furan derivative. Spectroscopic data for selected **2b**: *2-(4-fluorophenyl)-5-phenyl-3-(2-thienyl)furan*, liquid, IR (KBr): $\nu_{\max}$: 2925, 1674, 1596, 1498, 1413, 1225, 1153, 1022, 840, 770, 695, 594 cm^{-1}. ^{1}H NMR (200 MHz, CDCl_3): δ 7.80–7.60 (m, 4H), 7.40–7.28 (m, 5H), 7.15–7.0 (m, 3H), 6.78 (s, 1H). FAB Mass: 320 (M$^+$, 55), 123 (25), 105 (30), 95 (35), 81 (45), 69 (80), 55 (100). HRMS calcd for $C_{20}H_{14}FOS$: 321.0749. Found: 321.0706 (M+1). *General procedure for the synthesis of substituted pyrroles* (Table 1, entries d–h): A mixture of 1,4-diketone (1 mmol), aryl amine (1.5 mmol) and Bi(OTf)_3 (5 mol %) in $[\text{bmim}]\text{BF}_4$ (3 mL) was heated at 90 °C for the appropriate time (Table). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with diethyl ether (6 × 10 mL). The combined organic layers were dried, then concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 3%) to afford the pure pyrrole derivative. *2-Butyl-1,5-diphenyl-3-(2-thienyl)-1-pyrrole* (**3f**): Liquid, IR (KBr): $\nu_{\max}$: 2925, 1598, 1496, 1372, 757, 694 cm^{-1}. ^{1}H NMR (200 MHz, CDCl_3): δ 7.40–6.98 (m, 13H), 6.50 (s, 1H), 2.78 (t, $J = 6.9$ Hz, 2H), 2.15–2.05 (m, 4H), 0.98 (t, $J = 6.9$ Hz, 3H). FAB Mass: m/z: 357 (M$^+$, 75), 314 (90), 302 (10), 289 (5), 278 (5), 267 (5), 254 (5), 254 (5), 241 (5), 230 (5), 197 (10), 180 (55), 165 (25), 154 (55), 136 (55), 121 (10), 115 (10), 105 (55), 91 (50), 77 (100), 65 (30), 55 (100). HRMS calcd for $C_{24}H_{24}NS$: 358.1629. Found: 358.1661 (M+1). *General procedure for the synthesis of substituted thiophenes* (Table 1, entries i–k): A mixture of 1,4-diketone (1 mmol), Lawesson's reagent (1.5 mmol) and Bi(OTf)_3 (5 mol %) in $[\text{bmim}]\text{BF}_4$ (3 mL) was heated at 90 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with diethyl ether (5 × 10 mL). The combined organic layers were dried, then concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 3%) to afford the pure thiophene derivative. *2-Butyl-5-phenyl-3-(2-thienyl)thiophene* (**4j**): Liquid, IR (KBr): $\nu_{\max}$: 3069, 2956, 1705, 1653, 1564, 1456, 1378, 1213, 1053, 934, 811, 761, 693, 482 cm^{-1}. ^{1}H NMR (200 MHz, CDCl_3): δ 7.65–6.70 (m, 2H), 7.40–7.15 (m, 4H), 7.10–7.04 (m, 2H), 6.80 (s, 1H), 2.80 (t, $J = 7.1$ Hz, 2H), 2.15–2.05 (m, 4H), 0.98 (t, $J = 7.1$ Hz, 3H). EIMS: m/z: 298 M$^+$, 282 (70), 239 (100), 105 (40), 77 (30). HRMS calcd for $C_{18}H_{18}S_2$: 298.0849. Found: 298.0806.