

Zinc tetrafluoroborate-catalysed synthesis of highly substituted pyrroles by a solvent-free reaction

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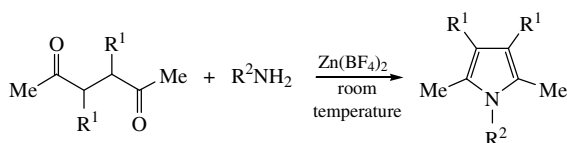
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A simple and highly efficient synthesis of penta- and tri-substituted pyrroles has been developed using the Paal–Knorr reaction catalysed by aqueous zinc tetrafluoroborate at room temperature under solvent-free conditions.

Pyrroles are important heterocyclic constituents of natural products,¹ bioactive molecules² and electrically conducting materials.³ Hence, substantial efforts have been made to develop efficient methods for the synthesis of these compounds.⁴ The Paal–Knorr reaction, in which 1,4-dicarbonyl compounds are converted into pyrroles *via* acid-mediated cyclization with primary amines, remains most common and attractive. Procedures using catalysts such as potassium exchanged layered zirconium phosphate (1–24 h, room temperature),^{4(a)} montmorillonite–KSF (10–25 h, room temperature),^{4(b)} ionic liquid (0.5–6 h, room temperature),^{4(c)} Bi(OTf)₃/[bmIm]BF₄ (4–5 h, 90 °C),^{4(d)} microwave (3 min)^{4(e),4(f),4(o)} and Bi(NO₃)₃ (10–25 h, room temperature)^{4(g)} have been employed for the Paal–Knorr synthesis of pyrroles. There are also other approaches to the synthesis of these compounds.^{4(h)–(n)} However, these procedures provide primarily tri-substituted pyrroles and access to tetra- and penta-substituted ones is very limited.^{4(f),4(k)} Many of these procedures require long reaction times and expensive catalysts.

We report here a very simple and efficient methodology for the synthesis of penta- and tri-substituted pyrroles by the Paal–Knorr reaction catalysed by aqueous zinc tetrafluoroborate⁵ without any organic solvent (Scheme 1).



Scheme 1

1,4-Diketones were condensed with aliphatic and aromatic amines by this reaction to produce substituted pyrroles.[†] The results are summarised in Table 1. Functional groups such as OMe, CO₂H, OH, Cl and SH on the amines remained intact under the reaction conditions. On the other hand, both electron-

withdrawing and electron-donating substituents on the 1,4-diketones are well acceptable in this procedure.

In general, the reactions are very clean, fast and high yielding. This procedure gives an easy access to penta-substituted pyrroles,

[†] *General procedure for the synthesis of pyrroles.* A mixture of a primary amine (1.2 mmol) and 1,4-diketone (1 mmol) was stirred at room temperature in the presence of a catalytic amount (0.01 ml, 2 mol%) of an aqueous solution (40%) of zinc tetrafluoroborate for a few minutes as required to complete the reaction (TLC). The reaction mixture was then extracted with diethyl ether (3×10 ml), and the extract was washed successively with aqueous HCl (1.3 N) and water. It was then dried (Na₂SO₄) and evaporated to leave the crude product, which was purified by column chromatography on silica gel (hexane–ethyl acetate, 95:5) to provide the pure product (61–90%). The new compounds (Table 1, entries 2, 3, 5–11) are properly characterised by their spectroscopic data (IR, ¹H and ¹³C NMR) and elemental analyses.

Entry 2: white solid, mp 48 °C. IR (ν /cm⁻¹): 1429, 1544, 1693. ¹H NMR (300 MHz, CDCl₃) δ : 0.88 (t, 3H, *J* 5.1 Hz), 1.13–1.19 (m, 2H), 1.24 (t, 6H, *J* 7.1 Hz), 1.42–1.50 (m, 2H), 2.19 (s, 6H), 3.67 (t, 2H, *J* 7.8 Hz), 4.15 (q, 4H, *J* 7.1 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : 10.5 (2C), 13.4, 13.9 (2C), 22.0, 32.1, 43.2, 59.6 (2C), 115.6 (2C), 132.5 (2C), 165.5 (2C). Found (%): C, 65.35; H, 8.77; N, 4.56. Calc. for C₁₆H₂₅NO₄ (%): C, 65.06; H, 8.53; N, 4.74.

Entry 3: white solid, mp 53 °C. IR (ν /cm⁻¹): 1544, 1683, 1703. ¹H NMR (300 MHz, CDCl₃) δ : 0.89 (t, 3H, *J* 6.3 Hz), 1.21–1.31 (m, 6H), 1.38 (t, 6H, *J* 7.2 Hz), 1.54–1.61 (m, 2H), 2.36 (s, 6H), 3.73 (t, 2H, *J* 7.8 Hz), 4.25 (q, 4H, *J* 7.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : 10.6 (2C), 13.7, 14.0 (2C), 22.3, 26.2, 30.1, 31.1, 43.6, 59.8 (2C), 112.0 (2C), 132.5 (2C), 165.6 (2C). Found (%): C, 66.57; H, 8.91; N, 4.15. Calc. for C₁₈H₂₉NO₄ (%): C, 66.84; H, 9.04; N, 4.33.

Entry 5: reddish gummy oil. IR (ν /cm⁻¹): 1382, 1610, 1701. ¹H NMR (300 MHz, CDCl₃) δ : 1.23 (t, 6H, *J* 7.0 Hz), 2.03 (s, 6H), 3.76 (s, 3H), 4.18 (q, 4H, *J* 7.0 Hz), 6.89 (d, 2H, *J* 7.0 Hz), 6.97 (d, 2H, *J* 7.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : 11.5 (2C), 14.1 (2C), 55.3, 59.9 (2C), 112.1 (2C), 114.5 (2C), 128.9 (2C), 129.2, 134.3 (2C), 159.6, 165.5 (2C). Found (%): C, 66.08; H, 6.66; N, 3.99. Calc. for C₁₉H₂₃NO₅ (%): C, 66.07; H, 6.71; N, 4.06.

Table 1 Synthesis of pyrroles catalysed by Zn(BF₄)₂.

Entry	R ¹	R ²	t/min	Yield (%) ^a	Ref.
1	CO ₂ Et	PhCH ₂	20	89	6
2	CO ₂ Et	<i>n</i> -Butyl	5	95	
3	CO ₂ Et	<i>n</i> -Hexyl	25	90	
4	CO ₂ Et	Ph	30	90	7
5	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	20	92	
6	CO ₂ Et	<i>p</i> -HO ₂ CC ₆ H ₄	60	90	
7	CO ₂ Et	<i>o</i> -HSC ₆ H ₄	15	70	
8	CO ₂ Et	<i>o</i> -MeC ₆ H ₄	25	61	
9	CO ₂ Et	<i>p</i> -BrC ₆ H ₄	30	92	
10	CO ₂ Et	NHPh	30	93	
11	CO ₂ Et	H ₂ NCH ₂ CH ₂	30	88	
12	H	PhCH ₂	5	95	4(b)
13	H	Cyclohexyl	15	85	4(c)
14	H	<i>n</i> -Hexyl	5	95	8
15	H	Ph	10	90	4(b)
16	H	<i>p</i> -HO ₂ CC ₆ H ₄	10	96	9
17	H	<i>m</i> -ClC ₆ H ₄	30	87	4(e)
18	H	<i>o</i> -HOC ₆ H ₄	10	92	4(a)
19	H	<i>o</i> -HSC ₆ H ₄	5	93	10
20	H	<i>o</i> -MeOC ₆ H ₄	8	96	11
21	H	α -Naphthyl	15	93	4(b)
22	H	H ₂ NCH ₂ CH ₂	10	92	4(b)

^aThe yields refer to those of the pure isolated products characterised by spectroscopic (IR, ¹H and ¹³C MNR) data.

which are not addressed adequately in the well-known procedures.⁴ This also provides scope to put a substituent of choice in the pyrrole ring by proper choice of the same in 1,4-diketone and amine.

Entry 6: white solid; mp 185 °C. IR (ν /cm⁻¹): 1537, 1608, 1697, 2925, 2979. ¹H NMR (300 MHz, CDCl₃) δ : 1.36 (t, 6H, *J* 7.0 Hz), 2.15 (s, 6H), 4.31 (q, 4H, *J* 7.0 Hz), 7.36 (d, 2H, *J* 8.4 Hz), 8.33 (d, 2H, *J* 8.4 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : 11.6 (2C), 14.1 (2C), 60.2 (2C), 113.0 (2C), 128.2 (2C), 130.0, 131.4 (2C), 133.6 (2C), 141.2, 165.3 (2C), 170.2. Found (%): C, 63.32; H, 5.77; N, 3.73. Calc. for C₁₉H₂₁NO₆ (%): C, 63.50; H, 5.89; N, 3.90.

Entry 7: yellow gummy oil. IR (ν /cm⁻¹): 1541, 1701, 2981. ¹H NMR (300 MHz, CDCl₃) δ : 1.30 (t, 6H, *J* 7.2 Hz), 2.09 (s, 6H), 3.02 (s, 1H), 4.28 (q, 4H, *J* 7.2 Hz), 7.08–7.11 (m, 1H), 7.22–7.44 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ : 11.2 (2C), 14.2 (2C), 60.1 (2C), 113.2 (2C), 126.4, 129.3, 129.5, 129.9, 133.2, 133.6 (2C), 133.7, 165.4 (2C). Found (%): C, 62.34; H, 5.92; N, 3.88. Calc. for C₁₈H₂₁NO₄S (%): C, 62.23; H, 6.09; N, 4.03.

Entry 8: yellow gummy oil. IR (ν /cm⁻¹): 1496, 1542, 1701. ¹H NMR (300 MHz, CDCl₃) δ : 1.30 (t, 6H, *J* 7.2 Hz), 1.93 (s, 3H), 2.04 (s, 6H), 4.29 (q, 4H, *J* 7.2 Hz), 7.06–7.09 (m, 1H), 7.29–7.37 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ : 11.2 (2C), 14.1 (2C), 17.0, 59.9 (2C), 112.4 (2C), 127.0, 128.2, 129.3, 131.0, 133.6, 135.6 (2C), 136.2, 165.4 (2C). Found (%): C, 68.89; H, 6.86; N, 4.07. Calc. for C₁₉H₂₃NO₄ (%): C, 69.28; H, 7.04; N, 4.25.

Entry 9: yellow solid; mp 86–88 °C. IR (ν /cm⁻¹): 1542, 1695, 1720. ¹H NMR (300 MHz, CDCl₃) δ : 1.33 (t, 6H, *J* 7.0 Hz), 2.13 (s, 6H), 4.30 (q, 4H, *J* 7.0 Hz), 7.06 (d, 2H, *J* 8.4 Hz), 7.66 (d, 2H, *J* 8.4 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : 11.6 (2C), 14.2 (2C), 60.1 (2C), 112.9 (2C), 123.1, 129.6 (2C), 132.8 (2C), 133.7 (2C), 135.7, 165.3 (2C). Found (%): C, 54.55; H, 4.99; N, 3.23. Calc. for C₁₈H₂₀NO₄Br (%): C, 54.85; H, 5.11; N, 3.55.

Entry 10: yellow solid, mp 84–86 °C. IR (ν /cm⁻¹): 1602, 1701, 3269. ¹H NMR (300 MHz, CDCl₃) δ : 1.90 (t, 6H, *J* 7.1 Hz), 2.73 (s, 6H), 4.84 (q, 4H, *J* 7.1 Hz), 7.03–7.05 (m, 2H), 7.40–7.45 (m, 1H), 7.72–7.77 (m, 2H), 8.04 (br. s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ : 9.8 (2C), 14.1 (2C), 60.2 (2C), 110.0 (2C), 118.8 (2C), 120.6, 129.3 (2C), 134.8 (2C), 146.1, 165.5 (2C). Found (%): C, 65.23; H, 6.51; N, 8.27. Calc. for C₁₈H₂₂N₂O₄ (%): C, 65.44; H, 6.71; N, 8.48.

Entry 11: white solid [a bis(pyrrole)], mp 196–198 °C. IR (ν /cm⁻¹): 1475, 1542, 1693. ¹H NMR (300 MHz, CDCl₃) δ : 1.30 (t, 12H, *J* 7.0 Hz), 2.22 (s, 12H), 3.97 (s, 4H), 4.23 (q, 8H, *J* 7.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ : 10.4 (4C), 14.2 (4C), 43.0 (2C), 60.1 (4C), 113.3 (4C), 132.4 (4C), 165.2 (4C). Found (%): C, 61.82; H, 7.15; N, 5.48. Calc. for C₂₆H₃₆N₂O₈ (%): C, 61.89; H, 7.19; N, 5.55.

In conclusion, the present procedure using an inexpensive catalyst like zinc tetrafluoroborate provides a very simple one-pot synthesis of pyrroles. The significant advantages offered by this procedure are: (a) easy access to highly functionalised units; (b) faster reaction (5–60 min) compared to other methods; (c) mild conditions (room temperature); (d) organic solvent-free reaction and (e) cost effectiveness.

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