A facile method for the synthesis of 2-(3-aryl-2-cyanopropenoyl)-1-methylpyrrole catalysed by KF/Al_2O_3 with microwave irradiation

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Knoevenagel reaction of 2-cyanoacetylpyrrole with aromatic aldehydes afforded 2-(3-aryl-2-cyanopropenoyl)-1-methylpyrrole in 81–94% yields in ethanol catalysed by KF/Al_2O_3 under microwave irradiation. This method has the advantages of simplicity, good yields and low costs.

Keywords: 2-(3-aryl-2-cyanopropenoyl)-1-methylpyrrole derivatives, 2-cyanoacetylpyrrole, aromatic aldehydes, microwave irradiation, KF/Al_2O_3

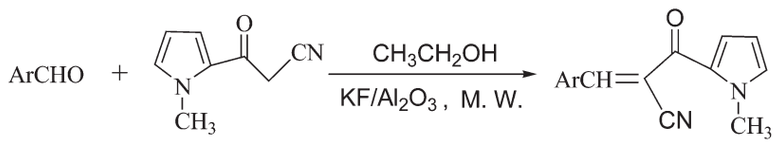
The Knoevenagel condensation as carbon–carbon bond forming reaction is one of the well-known reactions in organic chemistry owing to synthesis of important compounds for coumarin derivatives,[1] perfumes,[2] pharmaceuticals,[3] fine chemicals[4] and polymers.[5] It is the condensation of aldehydes with active methylene group compounds in organic solvents in the presence of basic sites[6–9] such as primary, secondary or tertiary amine and ammonium salts, amino acids, dimethylaminopyridine and potassium fluoride mixture. Lewis acid,[10] zeolites[11] and other heterogeneous catalysts[12] have also been employed to catalyse the reaction. Also this reaction has been carried in aqueous medium using catalysts like diammonium hydrogen phosphate and 12-tungstophosphoric acid.

Recently, the use of solid supported reagents in organic synthesis has received considerable attention due to their friendly nature and unique properties, such as enhanced reactivity, selectivity, mild conditions, avoidance of cumbersome aqueous work-up and decreased solvent handling issues, *etc.* KF/Al_2O_3 is a widely used solid supported reagent for catalysis of a variety of reactions. Due to its strongly basic nature it has been used as a replacement for organic bases in a number of organic reactions.[13–16]

In this report, we describe a simple and economical reaction of aromatic aldeheydes **1** with 2-cyanoacetylpyrrole[17] 2 catalysed by KF (40% by weight)/Al_2O_3 in dry ethanol under microwave irradiation. (Scheme 1 and Table 1).

It should be noted that in the absence of catalyst lower yields of product were observed even with prolonged reaction time. For example, entry 2 without catalyst after 30 minutes only 46% yield of product was obtained in ethanol under microwave irradiation, whereas 93% yield was obtained with catalyst for 10 minutes. The reaction worked better in ethanol than in methanol, which may be due to its higher boiling temperature than that of methanol. In addition, we applied the synthesis of **3b** in ethanol under classical heating conditions. After refluxing for 1 h, the desired product **3b** was obtained in 66% yield. However, under microwave irradiation condition, the yield of **3b** was up to 93% (Table 1, entry 2). Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction times and improving the reaction yields.

In this study, the structures of the compounds **3a**–**m** were fully supported by IR, ^1H NMR and elementary analysis as demonstrated for compound **3a** as follows: the IR spectral



1a - 1m **2** **3a - 3m**

Scheme 1

Table 1 Synthesis of compounds **3a–m** catalysed by KF/Al_2O_3 under microwave irradiation

Entry	Ar	Product[a]	Time/min	Yield/%[b]	M. p. /°C
1	C_6H_5	**3a**	10	91	71 °C
2	4-$CH_3C_6H_4$	**3b**	10	93	81–82 °C
3	2,4-$(CH_3)_2C_6H_3$	**3c**	10	92	113 °C
4	3,4-$(CH_3)_2C_6H_3$	**3d**	10	94	84–85 °C
5	4-$N(CH_3)_2C_6H_4$	**3e**	10	90	192–193 °C
6	2-$CH_3OC_6H_4$	**3f**	10	92	135 °C
7	3,4-(CH=CH-CH=CH)C_6H_3	**3g**	10	90	132–133 °C
8	4-$PhCH_2C_6H_4$	**3h**	12	88	80–81 °C
9	2,4-$Cl_2C_6H_3$	**3i**	12	83	137–138 °C
10	3-$NO_2C_6H_4$	**3j**	12	82	147–148 °C
11	4-$NO_2C_6H_4$	**3k**	12	81	170–171 °C
12		**3l**	10	90	103–104 °C
13		**3m**	10	94	241–242 °C

[a] The products were characterised by ^1H NMR, IR and elementary analysis.
[b] Isolated yield.

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analysis of **3a** showed two peaks at 1633 cm^{-1} which correspond to the carbonlys. The peak at 2210 cm^{-1} correspond to the CN. In the ^1H NMR spectrum of **3a**, the $–NCH_3$ protons of the pyrrole exhibited a singlet at δ 3.98.

In conclusion, we have demonstrated the efficiency for the synthesis of 2-(3-aryl-2-cyanopropenoyl)-1-methylpyrrole derivatives involving Knoevenagel condensation of 2-cyanoacetylpyrrole with aromatic aldehydes in ethanol catalysed by KF/Al_2O_3 under microwave irradiation. High efficiency and short reaction time were the advantages of this protocol.

Experimental

Melting points were recorded on an electrothermal digital melting point apparatus and uncorrected. ^1H NMR spectra were determined on a Varian VXP-500s spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. IR Spectra was obtained on a Nicolet FT-IR 6700 spectrophotometer using KBr pellets. Elementary analyses were performed by a Carlo-Erba EA1110 CNNO-S analyser. Microwave reactions were carried out in a Xianghu XH-100B microwave oven.

The mixture of **1** (1 mmol), **2** (0.15 g, 1 mmol), KF/Al_2O_3 (0.02 g) and anhydrous C_2H_5OH (10 mL) were irradiated for the appropriate number of minutes at 80 °C. After complete conversion as indicated by TLC, the solvent was then removed under reduced pressure and extracted with dichloromethane, washed with cool water (3×10 mL) and the organic layer dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica gel (200–300 mesh) using a mixture of petroleum ether and dichloromethane as eluent to afford the pure product **3a–m**.

3a: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.09 (s, 1H), 8.00–7.98 (m, 2H), 7.54–7.49 (m, 3H), 7.37 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 6.97 (d, 1H, *J* = 1.5 Hz), 6.23 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 3.98 (s, 3H). IR (KBr) ν 3112, 2210, 1633, 1578, 1561, 1458, 1446, 1401, 1370 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.31; H, 5.08; N, 11.94%.

3b: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.90 (d, 2H, *J* = 8.5 Hz), 7.36 (dd, 1H, *J* = 1.5 Hz and *J* = 4.5 Hz), 7.31 (d, 2H, *J* = 8.5 Hz), 6.95 (t, 1H, *J* = 2.0 Hz), 6.20 (dd, 1H, *J* = 2.0 Hz and *J* = 4.5 Hz), 3.98 (s, 3H), 2.44 (s, 3H). IR (KBr) ν 3110, 2207, 1638, 1578, 1560, 1456, 1406, 1372 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.86; H, 5.70; N, 11.13%.

3c: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.36 (s, 1H), 8.20 (d, 1H, *J* = 8.0 Hz), 7.36 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 7.15 (d, 1H, *J* = 8.0 Hz), 7.15 (s, 1H), 6.96 (t, 1H, *J* = 1.5 Hz), 6.22 (dd, 1H, *J* = 2.5 Hz and *J* = 4.5 Hz), 3.99 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H). IR (KBr) ν 3111, 2208, 1628, 1582, 1558, 1458, 1371 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.26; H, 6.15; N, 10.52%.

3d: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.04 (s, 1H), 7.79 (d, 1H, *J* = 8.0 Hz), 7.76 (s, 1H), 7.35 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 7.26 (d, 1H, *J* = 7.5 Hz), 6.95 (t, 1H, *J* = 1.5 Hz), 6.21 (dd, 1H, *J* = 2.5 Hz and *J* = 4.5 Hz), 3.97 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H). IR (KBr) ν 3108, 2210, 1632, 1585, 1561, 1460, 1410, 1364 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.20; H, 6.14; N, 10.51%.

3e: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.99 (dd, 2H, *J* = 1.5 Hz and *J* = 7.5 Hz), 7.37 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 6.89 (t, 1H, *J* = 1.5 Hz), 6.71 (d, 2H, *J* = 7.5 Hz), 6.19 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 3.96 (s, 3H), 3.11 (s, 6H). IR (KBr) ν 3104, 2918, 2201, 1633, 1610, 1557, 1523, 1458, 1371 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.19; H, 6.17; N, 15.08%.

3f: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.56 (s, 1H), 8.30 (dd, 1H, *J* = 1.5 Hz and *J* = 8.0 Hz), 7.52–7.48 (m, 1H), 7.31 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 7.08 (t, 1H, *J* = 7.5 Hz), 6.97–6.95 (m, 2H), 6.21 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 3.98 (s, 3H), 3.89 (s, 3H). IR (KBr) ν 3115, 2917, 2223, 1624, 1602, 1587, 1485, 1470, 1412, 1329 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.21; H, 5.37; N, 10.48%.

3g: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40 (s, 1H), 8.25 (s, 1H), 8.20 (dd, 1H, *J* = 1.5 Hz and *J* = 8.5 Hz), 7.96–7.93 (m, 2H), 7.89 (d, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 7.41 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 6.98 (t, 1H, *J* = 1.5 Hz), 6.24 (dd, 1H, *J* = 2.5 Hz and *J* = 4.5 Hz), 4.00 (s, 3H). IR (KBr) ν 3109, 2973, 2209, 1640, 1545, 1459, 1408, 1377 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.79; H, 4.87; N, 9.69%.

3h: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.97 (d, 4H, *J* = 2.0 Hz), 7.68–7.65 (m, 2H), 7.54–7.50 (m, 4H), 6.96 (dd, 1H, *J* = 1.5 Hz and *J* = 4.5 Hz), 6.92 (t, 1H, *J* = 1.5 Hz), 6.19 (dd, 1H, *J* = 2.5 Hz and *J* = 4.5 Hz), 3.95 (s, 3H), 3.87 (s, 2H). IR (KBr) ν 3112, 2215, 1633, 1580, 1559, 1458, 1373 cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.87; H, 5.65; N, 8.66%.

3i: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.36 (s, 1H), 8.20 (d, 1H, *J* = 8.5 Hz), 7.53 (d, 1H, *J* = 2.0 Hz), 7.41 (d, 1H, *J* = 8.5 Hz), 7.34 (dd, 1H, *J* = 1.5 Hz and *J* = 4.5 Hz), 7.00 (t, 1H, *J* = 2.0 Hz), 6.24 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 3.99 (s, 3H). IR (KBr) ν 3110, 2216, 1630, 1600, 1556, 1458, 1342 cm^{-1}. Anal. Calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.10; H, 3.32; N, 9.25%.

3j: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.70 (s, 1H), 8.41 (d, 1H, *J* = 8.0 Hz), 8.39–8.37 (m, 1H), 8.11 (s, 1H), 7.73 (t, 1H, *J* = 8.0 Hz), 7.40 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 7.01 (t, 1H, *J* = 1.5 Hz), 6.26 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 4.00 (s, 3H). IR (KBr) ν 3109, 2215, 1635, 1599, 1515, 1456, 1338 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.11; H, 3.86; N, 14.98%.

3k: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.36–8.34 (m, 2H), 8.14–8.10 (m, 3H), 7.40 (dd, 1H, *J* = 1.5 Hz and *J* = 4.5 Hz), 7.02 (t, 1H, *J* = 1.5 Hz), 6.26 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 4.00 (s, 3H). IR (KBr) ν 3111, 2218, 1633, 1600, 1516, 1458, 1343 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.11; H, 3.95; N, 14.87%.

3l: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.00 (s, 1H), 7.73 (d, 1H, *J* = 1.5 Hz), 7.45 (dd, 1H, *J* = 1.0 Hz and *J* = 4.5 Hz), 7.42 (d, 1H, *J* = 3.5 Hz), 6.94 (s, 1H), 6.65 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 6.21–6.22 (m, 1H), 3.96 (s, 3H). IR (KBr) ν 3108, 2919, 2207, 1643, 1601, 1533, 1460, 1379 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.11; H, 4.45; N, 12.32%.

3m: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.02 (s, 1H), 8.72 (s, 1H), 8.68 (s, 1H), 7.84 (d, 1H, *J* = 7.0 Hz), 7.49 (dd, 1H, *J* = 1.5 Hz and *J* = 7.5 Hz), 7.45 (dd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz), 7.36–7.30 (m, 2H), 6.93 (t, 1H, *J* = 1.5 Hz), 6.23 (dd, 1H, *J* = 2.5 Hz and *J* = 4.0 Hz), 4.00 (s, 3H). IR (KBr) ν 3281, 2212, 1613, 1588, 1560, 1504, 1459, 1412, 1330 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.13; H, 4.85; N, 15.35%.

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