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Microwave-assisted facile synthesis of trisubstituted pyrrole derivatives

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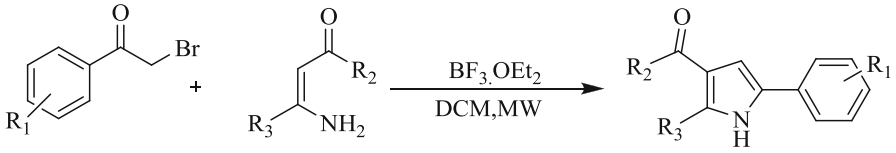
Abstract We report efficient synthesis of pyrrole derivatives by use of microwave irradiation. Quantitative yields were obtained in short reaction times. Low yields of product were obtained from alicyclic amino unsaturated ketone derivatives; higher yields were obtained from aliphatic amino unsaturated ketone derivatives.

Graphical Abstract



Keywords Pyrroles · Microwave irradiation · Time saved · Ring effect

Introduction

In recent times, synthetic methods have been developed to save time and achieve quantitative yields. Microwave irradiation has increased in importance because of its several advantages, including experimental simplicity, reduced reaction time, lower energy requirement, improved substrate reactivity, and product formation

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efficiency, because energizing the reactions leads to almost quantitative yields. Theoretical calculations have also suggested that reactions with high activation energies can be performed under microwave irradiation without use of harsh reaction conditions. Nowadays, numerous important heterocycles have been synthesized by use of microwave irradiation [1–6]. Among five-membered heterocycles, the pyrrole core is a ubiquitous structural unit of many natural compounds, including hemoglobin, chlorophyll, vitamin B12, L-tryptophan [7, 8], alkaloids [9, 10], and numerous essential drugs [11, 12] and synthetic pharmacologically valuable substances with antibacterial [13–15], antifungal [16, 17], antioxidant [18], antitumor, and anti-HIV activity [19], As a result, development of new methods for synthesis of these molecules has been an objective of organic synthesis for several years [20–25]. *N*-Heterocyclic compounds are obtained by use of several traditional routes, including the Knorr reaction [26], Paal–Knorr cyclization [27] and Hantzsch synthesis [28]. Recently, other elegant approaches for construction of pyrrole derivatives have been reported, for example dehydrogenative cyclization reactions [29], oxidative coupling of enamides and alkynes [30], multicomponent reactions [31, 32], tandem rearrangement of a-diazo oxime ethers [33], oxidative cyclization of *N*-allylimines and sulfonyl migrations [34], and domino aminocyclization/1,3-sulfonyl migrations [35]. Chiba et al. developed a method for synthesis of polysubstituted *N–H* pyrroles from vinyl azides and 1,3-dicarbonyl compounds [36]. There are, moreover, many reported methods for synthesis of substituted pyrroles by use of phenacyl bromide, unsaturated amines, and diketones [37–39]. Many of these methods suffer from such disadvantages as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, long reaction times, and use of expensive and moisture-sensitive catalysts. Hence, there is a need for time saving and efficient methods for synthesis of pyrrole derivatives by use of microwave irradiation. In this paper we report efficient method for synthesis of a variety of polysubstituted pyrroles under very mild reaction conditions.

Experimental

General considerations

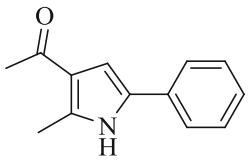
^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 75 MHz, respectively. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard ($\delta = 0$). Results are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constant in Hz. For ^{13}C NMR, $CDCl_3$ ($\delta = 77.27$) was used as internal standard and spectra were obtained with complete proton decoupling. Low-resolution MS and HRMS data were obtained by use of electrospray ionization. Melting point data were measured with micro melting point apparatus and were uncorrected. Reactions were conducted in a Catalyst-4R microwave oven (a research model made in India).

General procedure for synthesis of substituted pyrrole derivatives (**3a**–**l**)

A substituted amino unsaturated ketone (**2**, 1 mmol) and boron trifluoride diethyletherate (10 mol%) in dichloromethane (5 ml) were added to a solution of substituted phenacyl bromide (**1**, 1 mmol) and the mixture was irradiated with microwaves for 10–16 min at 130 °C (250 W). After completion of the reaction, as indicated by TLC analysis, the reaction mixture was poured on to crushed ice, neutralized with sodium bicarbonate, extracted with ethyl acetate, and the extract was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography with hexane–EtOAc (7:3) as eluent to afford the pyrrole derivatives **3**.

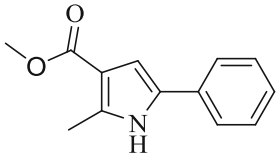
1-(2-Methyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone (**3a**)

White solid, m.p. 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (brs, 1 H), 7.42 (d, $J = 6.9$ Hz, 2 H), 7.36–7.32 (m, 2 H), 7.22–7.18 (m, 1 H), 6.71(s, 1 H), 2.61 (s, 3 H) 2.43 (s, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 135.9, 131.7, 128.9, 126.7, 123.7, 107.5, 28.5, 14.1 ppm; IR (KBr): ν 3260, 2921, 2855,1601, 1438, 1253, 1170, 899, 754 cm^{-1}; MS (ESI): *m/z* ($[M + Na]^+$): 222; HRMS (ESI): *m/z* calcd for ($C_{13}H_{13}NO + Na^+$): 222.089; found: 222.0875.



Methyl 2-methyl-5-phenyl-1*H*-pyrrol-3-carboxylate (**3b**)

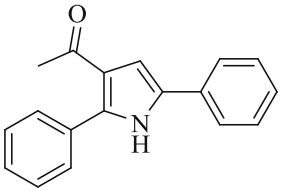
White solid, m.p. 90–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (brs, 1 H), 7.50–7.33 (m, 4 H), 7.25–7.20 (m, 1 H), 6.83 (d, $J = 3.0$ Hz, 1 H), 3.83 (s, 3 H), 2.60 (s, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.35, 166.0, 129.95, 129.0, 128.8, 128.6, 126.5, 123.6, 112.9, 107.2, 50.8, 22.6 ppm; IR (KBr): ν 3328, 2925, 2854, 1709, 1679, 1453, 1236, 1100, 760 cm^{-1}; MS (ESI): *m/z* ($[M + H]^+$): 216; HRMS (ESI): *m/z* calcd for ($C_{13}H_{13}O_2N + H^+$): 216.101; found: 216.1026.



1-(2,5-Diphenyl-1*H*-pyrrol-3-yl)ethanone (**3c**)

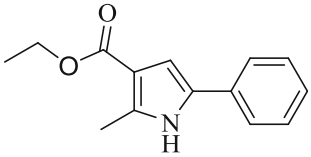
Yellow solid, m.p. 159–160 °C; ^{1}H NMR (500 MHz, CDCl3): δ 8.59 (brs, 1 H), 7.88–7.82 (m, 2 H), 7.57–7.42 (m, 5 H) 7.41–7.34 (m, 2 H), 6.68 (s, $J = 2.2$ Hz,

1H), 2.65 (s, 3 H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 192.4, 140.9, 137.5, 133.0, 131.7, 131.2, 129.7, 129.1, 129.1, 128.9, 128.9, 128.7, 126.7, 109.1, 13.9 ppm; IR (KBr): ν 3261, 3058, 2922, 1598, 1557, 1440, 1254, 1172, 901, 756, 695 cm^{-1}; MS (ESI): *m/z* ([M + H]$^+$): 262; HRMS (ESI): m/z calcd for ($C_{18}H_{15}ON + H^+$): 262.122; found: 262.1238.



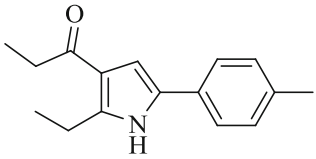
Ethyl 2-methyl-5-phenyl-1*H*-pyrrol-3-carboxylate (**3d**)

White solid, m.p. 94–96 °C; ^{1}H NMR (500 MHz, CDCl3): δ 8.63 (brs, 1 H), 7.51–7.43(m, 2 H), 7.39–7.32 (m, 2 H) 7.27–7.17 (m, 1 H), 6.84 (d, J = 3.0 Hz, 2 H), 4.29 (q, J = 7.2 Hz, 2 H), 2.58 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 165.7, 136.3, 134.1, 131.8, 130.0, 128.9, 128.8, 128.5, 126.3, 123.6, 107.2, 59.5, 14.5, 13.3 ppm; IR (KBr): ν 3314, 2980, 2927, 1672, 1609, 1479, 1448, 1236, 1099, 780 cm^{-1}; MS (ESI): *m/z* ([M + H]$^+$): 230; HRMS (ESI): *m/z* calcd for ($C_{14}H_{15}O_2N + H^+$): 230.117; found: 230.1180.



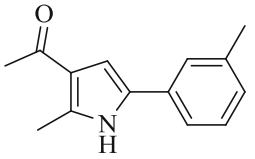
1-(2-Ethyl-5-*p*-tolyl-1*H*-pyrrol-3-yl)propan-1-one (**3e**)

White solid, m.p.162-164 °C; ^{1}H NMR (500 MHz, CDCl3): δ 8.44 (brs, 1 H), 7.36 (d, J = 7.9 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 2 H), 6.74 (d, J = 2.6 Hz, 1 H), 3.06 (q, J = 7.5 Hz, 2 H), 2.83(q, J = 7.3 Hz, 2 H), 2.36 (s, 3 H), 1.29(t, J = 7.5 Hz, 3 H), 1.19 (t, J = 7.3 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, CDCl3):δ 197.9, 141.4, 136.7, 129.9, 129.6, 129.0, 120.7, 123.7, 106.4, 21.2, 21.1, 13.1, 8.4 ppm; IR (KBr): ν 3274, 2974, 2926, 1629, 1460, 1211, 1012, 918, 801 cm^{-1}; MS (ESI): *m/z* ([M + H]$^+$): 242; HRMS (ESI): *m/z* calcd for ($C_{16}H_{19}ON + H^+$): 242.153; found: 242.1463.



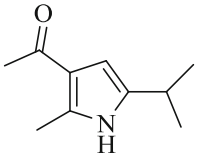
1-(2-Methyl-5-*m*-tolyl-1*H*-pyrrol-3-yl)ethanone (**3f**)

Yellow solid, m.p. 160–162 °C; ^{1}H NMR (500 MHz, CDCl3): δ 8.58 (brs, 1 H), 7.33–7.25 (m, 4 H),7.07 (s, 1 H), 6.75(s, 1 H), 2.64 (s, 3 H) 2.45 (s, 3 H) 2.40 (s, 3 H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 195.2, 138.7, 135.9, 131.8, 131.7, 129.9, 128.9, 127.5, 124.3, 107.3, 28.4, 21.5, 13.8 ppm; IR (KBr): ν 3289, 2920, 2854, 1635, 1573, 1437, 1239,1170, 942, 776 cm^{-1}; MS (ESI): *m*/*z* ([M + H]$^{+}$): 214; HRMS (ESI): *m*/*z* calcd for ($C_{14}H_{15}NO$ + H^{+}): 214.123; found; 214.1246.



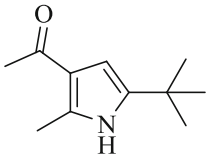
1-(5-Isopropyl-2-methyl-1*H*-pyrrol-3-yl)ethanone (**3g**)

White solid, m.p. 116–118 °C; ^{1}H NMR (500 MHz, CDCl3): δ 7.95 (brs, 1 H), 6.09 (s, 1 H), 2.86–2.79 (m, 1 H) 2.50 (s, 3 H), 2.34 (s, 3 H), 1.25 (d, J = 7.0, 6 H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 195.1, 136.7, 136.3, 133.7, 104.9, 28.3, 26.7, 22.3, 13.9 ppm; IR (KBr): ν 3228, 2963, 2925, 1618, 1463, 1262, 1024, 957, 824 cm^{-1}; MS (ESI): *m*/*z* ([M + H]$^{+}$): 166; HRMS (ESI): *m*/*z* calcd for ($C_{10}H_{15}NO$ + Na^{+}): 188.105; found: 188.1068.



1-(5-*Tert*-butyl-2-methyl-1*H*-pyrrol-3-yl)ethanone (**3h**)

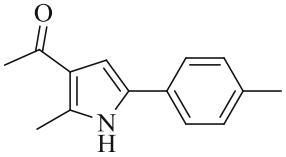
Yellow solid, m.p. 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (brs, 1 H), 6.19(s, 1 H), 2.52 (s, 3 H), 2.39 (s, 3 H), 1.55 (s, 9 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 139.9, 139.8, 134.1, 104.4, 31.2, 30.2, 29.7, 28.4, 26.8, 13.8 ppm; IR (KBr): ν 3248, 2960, 1620, 1525, 1455, 1243, 1018, 821, 775 cm^{-1}; MS (ESI): *m*/*z* ([M + H]$^{+}$): 180; HRMS (ESI): *m*/*z* calcd for ($C_{11}H_{17}ON$ + H^{+}): 180.138; found: 180.1360.



1-(2-Methyl-5-*p*-tolyl-1*H*-pyrrol-3-yl)ethanone (**3i**)

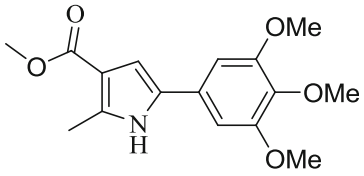
Yellow solid, m.p. 168–170 °C; ^{1}H NMR (500 MHz, CDCl3): δ 8.66 (brs, 1 H), 7.35–7.30 (m, 2 H), 7.16–7.13 (s, 2 H), 6.65 (s, 1 H), 2.60 (s, 3 H) 2.42 (s, 3 H) 2.36

(s, 3 H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 195.3, 136.4, 135.7, 130.0, 129.5, 128.9, 123.6, 106.7, 28.4, 21.0, 14.0 ppm; IR (KBr): ν 3261, 2916, 1637, 1582, 1445, 1236, 1167, 942, 795 cm^{-1}; MS (ESI): *m/z* ([M + H]$^+$): 214; HRMS (ESI): *m/z* calcd for ($C_{14}H_{15}NO$ + H^+): 214.125; found: 214.1236.



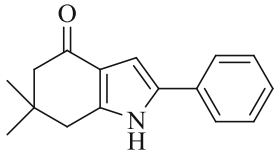
Methyl 2-methyl-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrol-3-carboxylate (**3j**)

White solid, m.p. 192–194 °C; ^{1}H NMR (500 MHz, CDCl3): δ 9.09 (brs, 1 H), 7.16 (s, 2 H), 6.66 (d, J = 1.0 Hz, 1 H), 3.95–3.82 (m, 12 H), 2.61 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 174.2, 153.4, 153.1, 136.8, 136.2, 130.1, 127.8, 127.3, 112.6, 106.9, 105.2, 101.2, 60.8, 56.2, 56.0, 13.1 ppm; IR (KBr); ν 3326, 2925, 2850, 1743, 1707, 1679, 1450, 1276, 1234, 1160, 1133, 760, 695 cm^{-1}; MS (ESI): *m/z* ([M + H]$^+$): 306; HRMS (ESI): *m/z* calcd for ($C_{16}H_{19}O_5N$ + H^+): 306.136; found: 306.1330.



6,6-Dimethyl-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (**3k**)

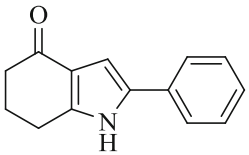
White solid, m.p. 226–228 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (brs, 1 H), 7.50–7.45 (m, 2 H), 7.36 (t, J = 7.5 Hz, 2 H), 7.27–7.20 (m, 1 H), 6.80 (d, J = 3.0 Hz, 1 H), 2.73 (s, 3 H), 2.38 (s, 3 H), 1.14 (s, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 143.7, 133.1, 131.6, 128.8, 126.8, 124.0, 120.4, 102.1, 51.9, 36.8, 35.7, 28.5 ppm; IR (KBr): ν 3259, 2954, 1626, 1489, 1224, 1162, 1060, 760, 686 cm^{-1}; MS (ESI): *m/z* ([M + H]$^+$): 240; HRMS (ESI): *m/z* calcd for ($C_{16}H_{17}ON$ + H^+): 240.131; found: 240.1382.



2-Phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (**3l**)

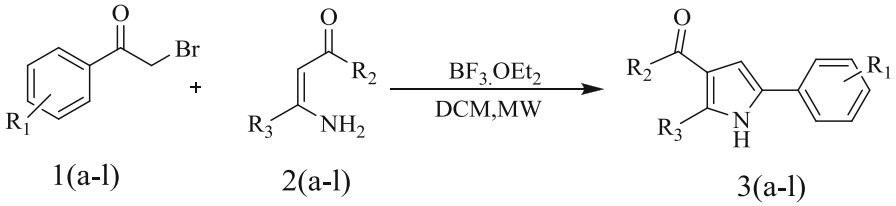
White solid, m.p. 226–228 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (brs, 1 H), 7.55–7.50 (m, 2 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.27–7.25 (m, 1 H), 6.85 (d,

$J = 3.0$ Hz, 1 H), 2.78 (s, 2 H), 2.50 (s, 2 H), 2.28 (s, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7., 144.7, 132.9, 131.6, 128.9, 126.9, 124.0, 121.7, 102.3, 37.7, 23.8, 22.8 ppm; IR (KBr): ν 3260, 2955, 1636, 1459, 1234, 1182, 1060, 760, 686 cm^{-1}; MS (ESI): *m/z* ($[M + H]^+$): 240; HRMS (ESI): *m/z* calcd for ($C_{14}H_{13}ON + H^+$): 212.126; found: 212.1285.



Results and discussion

In this paper we report a facile synthetic condensation reaction using microwave irradiation as another development in organic chemical synthesis. The process is adaptable for assembly of compound libraries, which have recently attracted much attention in pharmaceutical research. Equimolar amounts of starting compounds **1** and **2** were placed in an open Pyrex vessel and irradiated in a microwave oven, in the presence of boron trifluoride diethyl etherate (10 mol%) in dichloromethane (5 ml), for 10–16 min (Scheme 1). Workup gave products **3a–l** in 68–93 % yield (Table 1). All product yields were between 80 and 93 % except for compounds **3k** (68 %) and **3l** (70 %), possibly because alicyclic amino unsaturated keto derivatives gave low product yields whereas aliphatic amino unsaturated keto derivatives furnished higher yields. Another reason for low yields of **3k** and **3l** could be that the unsaturated keto functional group is within the six membered ring and would lead to the ring effect and low reactivity of the alicyclic amino unsaturated ketone; the other compounds had ring-free unsaturated keto functional groups which may have enhanced their activity. It should be noted that the desired product **3c** was obtained in high yield (93 %, entry **3**), when the reaction was conducted between phenacyl bromide (**1c**) and the benzene ring-substituted unsaturated ketone (**2c**) under microwave irradiation in dichloromethane. The reaction time was 10 min. Compounds **3a** and **3b** were obtained in excellent yield, 90 and 92 %. The other compounds were obtained in 80–90 % yield. To study the effect of solvent and the catalyst, we treated phenacyl bromide (**1**) with substituted amino unsaturated ketone (**2**) and a variety of acid catalysts (Table 2) in different



Scheme 1 Synthesis of trisubstituted pyrrole derivatives

Table 1 Reaction times, and yields of products **3(a–l)**

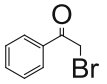
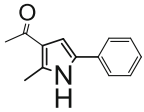
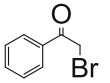
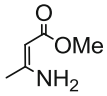
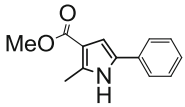
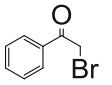
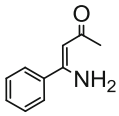
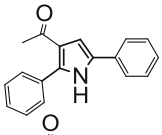
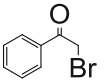
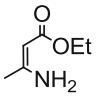
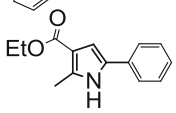
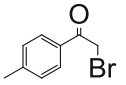
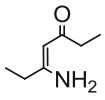
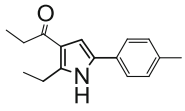
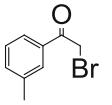
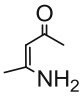
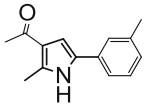
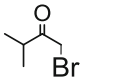
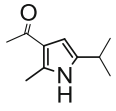
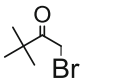
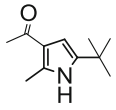
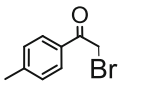
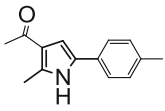
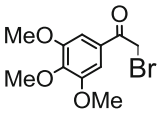
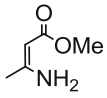
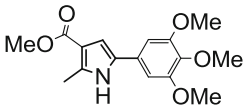
Entry	Compounds 1(a-l)	Compounds 2 (a-l)	Product 3 (a-l)	Time(min.)	Yield (%)
a				15	90
b				10	92
c				12	93
d				15	85
e				11	80
f				13	87
g				15	84
h				16	86
i				15	89
j				14	91

Table 1 continued

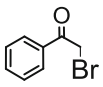
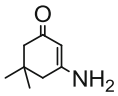
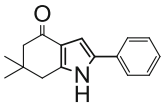
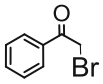
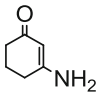
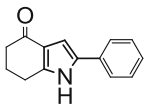
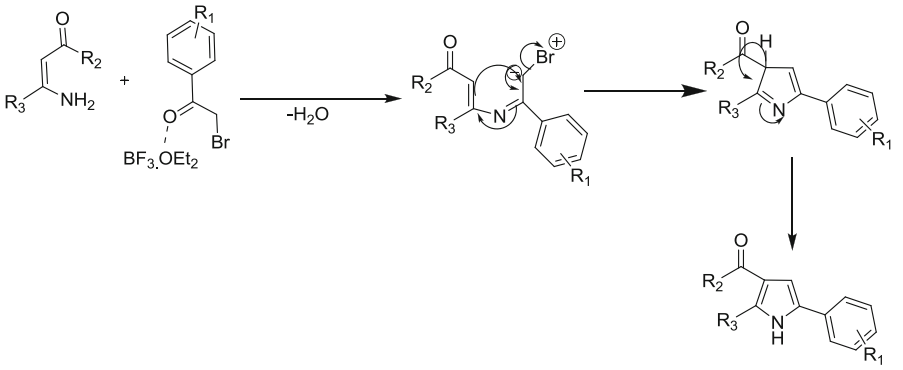
Entry	Compounds 1(a-l)	Compounds 2 (a-l)	Product 3 (a-l)	Time(min.)	Yield (%)
k				11	68
l				13	70

Table 2 Results from use of different catalysts and solvents

Entry	Acid catalyst	Solvent	Time in MW (min)	Yields			
				3a	**3b**	**3k**	**3l**
1	$FeCl_3$	CH_2Cl_2	15	54	57	45	41
2	$Cu(oTf)_2$	Toluene	12	51	49	32	26
3	$Cu(oTf)_2$	THF	10	62	68	54	49
4	$InCl_3$	$ClCH_2CH_2Cl$	18	35	41	<20	<20

solvents under microwave irradiation. As shown in Table 2, use of Cu-$(OTf)_2$ as catalyst and tetrahydrofuran as solvent gave the best results in terms of reaction time and yields of compounds **3a** and **3b** (entry 3, Table 2). Interestingly, the same catalyst in toluene as solvent gave only ~50 % yields. Products **3a** and **3b** were obtained in better yield by use of $FeCl_3$ in dichloromethane. Dichloroethane was ineffective in this reaction. Use of $InCl_3$ as catalyst resulted in poor yields of all the compounds (Table 2). Compounds **3k** and **3l** were obtained in low yields with all these catalysts and solvents, as discussed above. The quantitative yields obtained in short times were indicative of spectacular acceleration of these reactions as a consequence of microwave-assisted three-dimensional heating of the reaction mixture, which cannot be achieved by classical heating. Improved yields and clean reaction pathways are additional advantages of microwave-assisted preparation of organic compounds. Indeed, reactions that do not occur if conventional heating is used can be effectively performed by use of microwaves. The proposed pathway for formation of substituted pyrroles is depicted in Scheme 2. The Lewis acid activates the carbonyl group of the phenacyl compound which acts as an electrophile and reacts with the amino group of the enamine, leading to the pyrrole.



Scheme 2 Mechanism of formation of the pyrrole ring

Conclusion

Trisubstituted pyrrole derivatives have been synthesized with short reaction times and in quantitative yields by use of microwave irradiation. The presence of alicyclic amino unsaturated keto derivatives resulted in low yields of product whereas aliphatic amino unsaturated keto derivatives furnished higher yields.

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