Efficient one-pot synthesis of substituted pyridines through multicomponent reaction†

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A facile and convenient synthesis of substituted pyridines has been developed *via* a one-pot multicomponent reaction of easily available 1,3-dicarbonyl compounds, aromatic aldehydes, malononitrile and alcohol in the presence of NaOH under mild conditions. A series of functionalized pyridines were thus obtained by this multicomponent reaction, in which four new bonds were formed in a highly chemo- and regioselective manner, and alcohol played dual roles as both reactant and reaction medium. Particularly valuable features of this protocol including mild conditions, simple execution, broad substrate scope, and good yields of products make it an efficient and promising synthetic strategy to build pyridine skeleton.

Introduction

The pyridine substructure is one of the most prevalent heterocycles found in numerous natural and synthetic products along with useful bio-, physio- and pharmacological activities.[1] The synthesis of the pyridine derivatives can principally be realized either by modification of the pre-constructed pyridine nucleus or through the construction of the pyridine ring from appropriately substituted open chain precursor, which have been extensively reviewed.[2] Nevertheless, simple and efficient synthetic protocols for the construction of more elaborate and usefully functionalized pyridines are still desirable.

Multicomponent reactions (MCRs) have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry.[3] The MCRs strategy offers significant advantages over conventional multistep synthesis due to its flexible, convergent, and atom economic nature.[4] In a true sense, MCRs represent environmentally friendly processes by reducing the number of steps, energy consumption, and waste production.[5] These features make MCRs well-suited for the easy construction of diversified arrays of, *e.g.*, valuable heterocyclic scaffolds. Actually, MCRs have been demonstrated as a straightforward approach to the synthesis of pyridines, which often involves classical carbonyl condensation chemistry.[6] Besides aldehydes, 1,3-dicarbonyl compounds and/or their analogous nitrile derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a variety of synthetic transformations.[7] Recently, Evdokimov *et al.* developed a one-pot synthesis of 3,5-dicarbonitrile-pyridines by a MCR of an aldehyde, malononitrile, and a thiol in the presence of a base catalyst such as piperidine, DABCO or triethylamine.[8] Ranu *et al.* modified this method by employing a basic ionic liquid as both catalyst and reaction medium and hence improved the yields of the products.[9] Chen *et al.* reported the synthesis of 3,5-dicarbonitrile-pyridines *via* a MCR under basic conditions, also they applied the use of microwave irradiation to the MCR preparation.[10] Sridhar *et al.* investigated MCRs of aldehydes, malononitrile and thiophenol using a variety of Lewis acids such as $ZnCl_2$, $AlCl_3$ and $FeCl_3$ as catalysts, and achieved one-pot synthesis of 3,5-dicarbonitrile-pyridines.[11] Similarly, Thirmurugan *et al.* synthesized 3,5-dicarbonitrile-pyridines *via* a MCR mediated by $InCl_3$.[12] Additionally, one-pot synthesis of cyanopyridines through a four-component reaction using organic acid, such as *p*-toluenesulfonic acid, as a catalyst was reported by Shaabani *et al.*[13]

During the course of our studies on the synthetic utility of 1,3-dicarbonyl compounds, we found that the easily available and structurally flexible β-oxo amide derivatives showed fascinating structural features as versatile organic intermediates, and successfully developed a range of synthetic approaches to construct aromatic and heterocyclic ring skeletons.[14] In MCRs of carbonyl compounds, we achieved efficient one-pot synthesis of highly substituted thiophenes by using the sequential addition of reactants,[15] and one-pot synthesis of polysubstituted benzenes *via* sequential Michael addition, Knoevenagel condensation and nucleophilic cyclization reactions of readily available chalcones with malononitrile and nitroethane in guanidinium ionic liquids.[16]

In connection with these studies and the aim to establish novel synthetic approaches for heterocyles, we explored the reactions of β-oxo amides, aromatic aldehydes, malononitrile in the presence of a base. By this research, we developed efficient one-pot synthesis of substituted pyridines *via* four-component reaction. Herein, we wish to report our experimental results and the mechanism involved.

Results and discussion

In an initial attempt, the reaction of 3-oxo-*N*-phenylbutanamide **1a**, benzaldehyde **2a** (1.0 equiv.) and malononitrile **3** (1.0 equiv.) was performed in ethanol in the presence of NaOH (2.0 equiv.) at room temperature. As monitored by TLC, the reaction could

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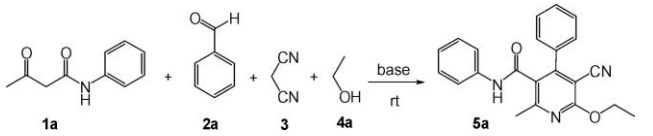
Table 1 Optimization of reaction conditions of the multicomponent reactions of **1a**, **2a**, **3** and **4a**



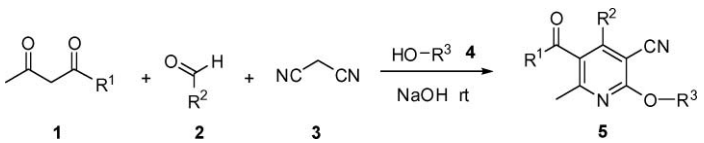
Entry[a]	Base	Amount (equiv.)	Solvent	Time/h	Yield[b](%)
1	NaOH	2.0	EtOH	8.0	56
2	NaOH	3.0	EtOH	3.0	82
3	NaOH	4.0	EtOH	3.0	83
4	K_2CO_3	3.0	EtOH	8.0	24
5	NaOH	3.0	DMF	8.0	0
6	NaOH	3.0	CH_2Cl_2	8.0	0

[a] In the cases of entries 5 and 6, EtOH was added as a reactant (1.1 equiv.). [b] Isolated yields.

proceed, and a new product was formed though some of the starting materials were still not consumed after 8.0 h. The reaction was quenched by addition of diluted aqueous HCl. After work-up and purification by column chromatography of the resulting mixture, a white solid product was obtained, which was characterized as 5-cyano-6-ethoxy-2-methyl-*N*, 4-diphenylnicotinamide (56% yield), a substituted cyanopyridine **5a**, on the basis of its spectra and analytical data (Table 1, entry 1). Obviously, the result indicated that ethanol took part in the reaction as a reactant. The optimization of the reaction conditions, including the nature of base, amount of base and reaction medium was then investigated. It was observed that when the amount of NaOH was increased to 3.0 equivalents, the reaction rate was speeded up for the shorter reaction time and high conversion (Table 1, entry 2), but further increase of the amount of NaOH had nearly no significant effect on the reaction (Table 1, entry 3). When K_2CO_3 was used as a base, the reaction proceeded sluggishly to afford **5a** in very low yield even after prolonged reaction time (Table 1, entry 4). Subjecting **1a**, **2a** (1.0 equiv.), **3** (1.0 equiv.) and ethanol **4a** (1.1 equiv.) in DMF or CH_2Cl_2 at room temperature, however, no desired product **5a** was obtained (Table 1, entries 5, 6).

Next, we intended to determine the scope and limitations of the multicomponent reaction with respect to the substrates bearing varied substituted groups, *e.g.* R^1, R^2 and R^3. Thus, a series of reactions of malononitrile, aromatic aldehydes, 1,3-dicarbonyl compounds and alcohol were carried out under the reaction conditions as described in Table 1, entry 2. As shown in Table 2, all the reactions of aromatic aldehydes **2a–e** bearing electron-donating groups (R^2 = 4-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$), and electron-withdrawing groups (R^2 = 4-ClC_6H_4, 4-$NO_2C_6H_4$) with 3-oxo-*N*-phenylbutan-amide **1a** and malononitrile **3** in ethanol in the presence of NaOH proceeded smoothly to afford the corresponding substituted pyridines **5a–e** in good yields (entries 1–5). The multicomponent reactions proved to be suitable for β-oxo amides **1b–g** bearing either an electron-donating or an electron-withdrawing group in *para* or *ortho* position with benzaldehyde

Table 2 Multicomponent reaction for the synthesis of substituted pyridines **5**



	Substrates						Products	Time	Yield[a]
Entry	**1**	R^1	**2**	R^2	**4**	R^3	**5**	(h)	(%)
1	**1a**	C_6H_5NH	**2a**	C_6H_5	**4a**	C_2H_5	**5a**	3.0	82
2	**1a**	C_6H_5NH	**2b**	4-$CH_3C_6H_4$	**4a**	C_2H_5	**5b**	4.0	85
3	**1a**	C_6H_5NH	**2c**	2-$CH_3OC_6H_4$	**4a**	C_2H_5	**5c**	3.5	85
4	**1a**	C_6H_5NH	**2d**	4-ClC_6H_4	**4a**	C_2H_5	**5d**	3.5	79
5	**1a**	C_6H_5NH	**2e**	4-$NO_2C_6H_4$	**4a**	C_2H_5	**5e**	5.5	71
6	**1b**	4-$CH_3C_6H_4NH$	**2a**	C_6H_5	**4a**	C_2H_5	**5f**	3.5	79
7	**1c**	2-$CH_3C_6H_4NH$	**2a**	C_6H_5	**4a**	C_2H_5	**5g**	3.5	73
8	**1d**	4-$CH_3OC_6H_4NH$	**2a**	C_6H_5	**4a**	C_2H_5	**5h**	4.0	81
9	**1e**	2-$CH_3OC_6H_4NH$	**2a**	C_6H_5	**4a**	C_2H_5	**5i**	3.0	85
10	**1f**	4-ClC_6H_4NH	**2a**	C_6H_5	**4a**	C_2H_5	**5j**	3.5	77
11	**1g**	2-ClC_6H_4NH	**2a**	C_6H_5	**4a**	C_2H_5	**5k**	4.0	86
12	**1h**	OC_2H_5	**2a**	C_6H_5	**4a**	C_2H_5	**5l**	2.5	89
13	**1i**	CH_3	**2a**	C_6H_5	**4a**	C_2H_5	**5m**	4.0	0
14	**1a**	C_6H_5NH	**2a**	C_6H_5	**4b**	CH_3	**5n**	4.0	87
15	**1b**	4-$CH_3C_6H_4NH$	**2a**	C_6H_5	**4b**	CH_3	**5o**	4.5	83
16	**1c**	2-$CH_3C_6H_4NH$	**2a**	C_6H_5	**4b**	CH_3	**5p**	4.5	76
17	**1d**	4-$CH_3OC_6H_4NH$	**2a**	C_6H_5	**4b**	CH_3	**5q**	5.0	84
18	**1e**	2-$CH_3OC_6H_4NH$	**2a**	C_6H_5	**4b**	CH_3	**5r**	4.0	73
19	**1f**	4-ClC_6H_4NH	**2a**	C_6H_5	**4b**	CH_3	**5s**	4.5	87
20	**1g**	2-ClC_6H_4NH	**2a**	C_6H_5	**4b**	CH_3	**5t**	4.5	79
21	**1h**	OC_2H_5	**2a**	C_6H_5	**4b**	CH_3	**5u**	2.0	88
22	**1a**	C_6H_5NH	**2a**	C_6H_5	**4c**	n-C_4H_9	**5v**	4.0	73
23	**1a**	C_6H_5NH	**2a**	C_6H_5	**4d**	$CH(CH_3)_2$	**5w**	5.0	0

[a] Isolated yield.

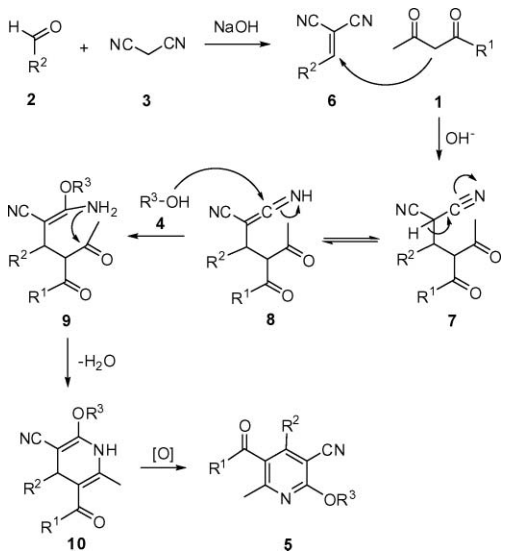
2a and malononitrile **3** in ethanol in the presence of NaOH (Table 2, entries 6–11). The validity of this pyridine synthesis was further evaluated by subjecting β-oxo ester **1h** to the identical conditions (Table 2, entry 12). However, the synthesis of pyridine of type **5** from acetyl acetone **1i** was unsuccessful (Table 2, entry 13). To expand the scope of the above cyclization, a series of reactions was performed on substrates **1–3** in other alcohols. Thus, the corresponding substituted pyridines **5n–u** were synthesized in moderate to good yields when β-oxo amides **1a–g** or β-oxo ester **1h** were reacted with benzaldehyde **2a** and malononitrile **3** in methanol in the presence of NaOH (Table 2, entries 14–21). It was also observed that the reaction of 3-oxo-*N*-phenyl butanamide **1a**, benzaldehyde **2a** and malononitrile **3** in *n*-butanol could proceed to afford substituted pyridine **5v** in 73% yield (Table 2 entry 22). Unfortunately, in the case of sterically hindered isopropanol, the desired pyridine **5w** was not obtained (Table 2 entry 23). Nevertheless, all the obtained results demonstrated the efficiency and synthetic value of the one-pot multicomponent reaction for the synthesis of substituted pyridines of type **5**, in which four new bonds were formed in highly chemo- and regioselective manner. It should be noted that the richness of the functionality of substituted pyridines **5**, for example acyl and cyano groups, may render them versatile as synthons in further synthetic transformations.[17]

To gain much more clear insight into the mechanism for the pyridine synthesis, some supporting experiments were conducted. No reaction was observed when **1a** was treated with **2a** or malononitrile **3** in ethanol in the presence of NaOH at room temperature. The results indicated the synthesis of pyridine of type **5** should be initiated from the Knoevenagel reaction of **2a** and malononitrile **3**, which prompted us to perform a stepwise reaction. Thus, the reaction of **2a** and malononitrile **3** was carried out in *N*,*N*-dimethylformamide, to circumvent the influence of ethanol, in the presence of weak base triethylamine at room temperature, which furnished the Knoevenagel adduct **6a** in 91% yield. By treatment of adduct **6a** with **1a** in ethanol in presence of NaOH at room temperature for 2.0 h, a product was obtained, which was characterized as pyridine **5a** (84% yield).

On the basis of the above results together with reported literatures,[8,10,18] a plausible mechanism for the formation of substituted pyridines **5** is depicted in Scheme 1. In the presence of NaOH, Knoevenagel condensation between aldehyde **2** and malononitrile **3** occurs to generate an adduct **6**. Subsequent Michael addition of 1,3-dicarbonyl compounds **1** to **6** leads to the fomation of intermediate **7**. The attack of alcohol **4** to intermediate **8**, tautomer of **7**, forms intermediate **9**, which undergoes intramolecular cyclization to afford Hantzsch dihydropyridine derivative **10** with an elimination of water.[19] Finally, aromatization of **10** *via* an oxidation process gives rise to substituted pyridine of type **5**.[10–12,20]

Conclusion

In summary, we have developed a novel, convenient, and efficient one-pot four-component synthesis of substituted pyridines of potential synthetic and pharmacological interest, and a plausible mechanism for the reaction was proposed. The use of easily available starting materials, mild reaction conditions, high chemo- and regioselectivity, and good yields of products are the main advantages of this method. High efficiency and simple execution make this new strategy attractive for academic research and



Scheme 1 Plausible mechanism for the synthesis of substituted pyridines **5**.

potential applications. The scope and synthetic applications of the methodology are currently under investigation in our laboratory.

Experimental

General remarks

All chemicals used were reagent grade and were used as received without further purification. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 MHz and 75 MHz, respectively, using TMS as internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400–4000 cm^{-1}.

General experimental procedure

Typical procedure for the synthesis of substituted pyridines 5 (5a as an example). To a solution of 3-oxo-*N*-phenylbutanamide **1a** (354 mg, 2.0 mmol), benzaldehyde **2a** (0.20 mL, 2.0 mmol), and malononitrile **3** (132 mg, 2.0 mmol) in ethanol (20 mL) was added NaOH (240 mg, 6.0 mmol) in one portion at room temperature. The reaction mixture was stirred at room temperature for 3.0 h. After the starting material was consumed (monitored by TLC), and then the reaction mixture was poured into saturated aqueous NaCl (20 mL). The mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by evaporation. The crude product was purified by flash chromatography (silica gel, petroleum ether: diethyl ether = 10: 1) to give product **5a** (585 mg, 82%) as a white solid.

Physical data of compounds isolated. **5a**: White solid: mp 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.48 (t, J = 6.6 Hz, 3H), 2.67 (s, 3H), 4.58 (q, J = 7.2 Hz, 2H), 6.79 (s, 1H), 7.08–7.10 (m, 3H), 7.21–7.27 (m, 2H), 7.46–7.48 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.4, 23.4, 63.7, 90.4, 114.7, 120.4, 125.2, 125.7, 128.2, 128.9, 129.0, 130.0, 134.2, 136.7, 153.6, 159.7, 164.9. IR (KBr, cm^{-1}) 747, 1161, 1327, 1442, 1550, 1645, 2228, 2986. anal.

calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76; found: C, 73.79; H, 5.41; N, 11.66.

5b: White solid: mp 219–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.47 (t, J = 6.8 Hz, 3H), 2.35 (s, 3H), 2.65 (s, 3H), 4.55–4.60 (q, J = 6.8 Hz, 2H), 6.76 (s, 1H), 7.08–7.13 (m, 3H), 7.23–7.25 (m, 4H), 7.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4, 23.1, 23.4, 63.7, 93.6, 114.8, 120.4, 125.1, 125.7, 128.2, 128.9, 129.8, 131.3, 136.9, 140.2, 153.8, 159.7, 163.8, 165.1. anal. calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31; found: C, 74.45; H, 5.61; N, 11.25.

5c: White solid: mp 226–228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.47 (t, J = 6.8 Hz, 3H), 2.35 (s, 3H), 2.65 (s, 3H), 4.55–4.60 (q, J = 6.8 Hz, 2H), 6.76 (s, 1H), 7.08–7.13 (m, 3H), 7.23–7.25 (m, 4H), 7.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4, 23.4, 56.0, 63.6, 95.0, 111.6, 114.4, 120.0, 121.6, 123.7, 124.8, 126.3, 128.9, 129.7, 131.5, 137.1, 151.3, 155.4, 159.7, 163.3, 164.7. anal. calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85; found: C, 71.48; H, 5.40; N, 10.79.

5d: White solid: mp 198–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (t, J = 7.2 Hz, 3H), 2.66 (s, 3H), 4.58 (q, J = 7.2 Hz, 2H), 7.16 (t, J = 8.1 Hz, 2H), 7.28–7.31 (m, 4H), 7.45 (m, 3H). ^{13}C NMR (75 MHz, DMSO) δ = 14.3, 22.8, 63.4, 93.0, 114.4, 119.6, 124.1, 128.4, 128.5, 128.8, 130.2, 131.0, 132.2, 134.6, 138.2, 152.6, 158.0, 162.6, 164.0. IR (KBr, cm^{-1}) 748, 1093, 1183, 1325, 1445, 1549, 1639, 2227, 2989. anal. calcd for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72; found: C, 67.47; H, 4.66; N, 10.75.

5e: Yellow solid: mp 236–237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.48 (t, J = 7.2 Hz, 3H), 2.67 (s, 3H), 4.58–4.63 (m, 2H), 6.96 (s, 1H), 7.13–7.16 (m, 1H), 7.19–7.21 (m, 2H), 7.27–7.29 (m, 2H), 7.69 (d, J = 8.8 Hz, 2H), 8.32 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.3, 23.3, 64.1, 93.4, 114.0, 120.0,124.0, 125.5, 129.1, 129.6, 129.8, 136.6, 140.4, 148.5, 151.4, 159.7, 163.6, 164.2. anal. calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45; found: C, 66.63; H, 4.81; N, 13.62.

5f: White solid: mp 256–258 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (t, J = 8.5 Hz, 3H), 1.75 (s, 3H), 2.62 (s, 3H), 4.55 (q, J = 7.2 Hz, 2H), 7.04–7.15 (m, 5H), 7.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.4, 17.2, 23.2, 63.7, 93.5, 114.6, 123.8, 126.1, 126.5, 128.5, 128.9, 130.0, 130.5, 134.3, 134.4, 153.4, 159.3, 163.6, 165.3. IR (KBr, cm^{-1}) 700, 1023, 1165, 1319, 1584, 1625, 1654, 2230, 2985, 3463. anal. calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31; found: C, 74.33; H, 5.74; N, 11.25.

5g: White solid: mp 182–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (t, J = 7.2 Hz, 3H), 1.79 (s, 3H), 2.67 (s, 3H), 4.58 (q, J = 5.7 Hz, 2H), 6.75–6.78 (d, J = 8.7 Hz, 1H), 7.07–7.12 (m, 3H), 7.23 (s, 1H), 7.48 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.3, 17.1, 23.1, 63.6, 114.5, 123.6, 126.0, 126.4, 128.4, 128.8, 129.9, 130.4, 134.2, 134.3, 153.3, 159.3, 163.5, 165.1. anal. calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31; found: C, 74.45; H, 5.63; N, 11.25.

5h: White solid: mp 192–193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (t, J = 7.5 Hz, 3H), 2.66 (s, 3H), 3.75 (s, 3H), 4.58 (q, J = 7.5 Hz, 2H), 6.66 (s, 1H), 6.76 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 8.1 Hz, 2H), 7.47 (m, 4H). ^{13}C NMR (75 MHz, DMSO) δ = 14.3, 22.9, 55.1, 63.3, 93.0, 113.9, 114.6, 121.3, 127.1, 128.3, 129.5, 131.2, 134.4, 153.8, 155.8, 157.9, 162.6, 163.7. anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25; found: C, 74.67; H, 5.77; N, 7.31.

5i: White solid: mp 180–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.48 (t, J = 6.3 Hz, 3H), 2.66 (s, 3H), 3.67 (s, 3H), 4.58 (q, J = 6.6 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.03–7.06 (m, 1H), 7.39–7.46 (m, 6H), 8.17 (d, J = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ = 14.3, 22.9, 55.7, 63.2, 92.8, 111.5, 114.7, 120.0, 123.7, 125.8, 126.0, 127.3, 128.2, 128.5, 129.4, 134.5, 151.2, 153.8, 157.8, 162.5, 164.5. IR (KBr, cm^{-1}) 751, 1028, 1160, 1325, 1462, 1542, 1649, 2226, 2980. anal. calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85; found: C, 71.75; H, 5.37; N, 10.81.

5j: White solid: mp 256–257 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (t, J = 6.9 Hz, 3H), 2.62 (s, 3H), 4.56 (q, J = 8.2 Hz, 2H), 7.01–7.04 (d, J = 7.5 Hz, 3H), 7.17 (d, J = 8.1 Hz, 2H), 7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.3, 23.3, 63.8, 93.4, 114.5, 121.5, 125.4, 128.1, 128.9, 129.0, 130.2, 134.1, 135.3, 153.6, 159.8, 163.7, 164.9. anal. calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17; found: C, 70.88; H, 4.87; N, 7.21.

5k: White solid: mp 179–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.48 (t, J = 7.2 Hz, 3H), 2.67 (s, 3H), 4.59 (q, J = 6.6 Hz, 2H), 7.00–7.05 (m, 1H), 7.20–7.29 (m, 3H), 7.42–7.47 (m, 5H), 8.10 (t, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ = 14.3, 23.0, 63.3, 92.9, 114.6, 126.7, 126.9, 127.4, 127.9, 128.4, 128.5, 129.6, 133.8, 134.4, 154.0, 157.8, 162.7, 164.8. anal. calcd for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72; found: C, 67.67; H, 4.61; N, 10.81.

5l: White solid: mp 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, J = 6.6 Hz, 3H), 1.45 (t, J = 7.2 Hz, 3H), 2.57 (s, 3H), 3.67 (q, J = 7.2 Hz, 2H), 4.56 (q, J = 6.6 Hz, 2H), 7.35 (m, 2H), 7.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.4, 14.3, 23.3, 61.4, 63.6, 94.0, 114.4, 128.0, 128.5, 129.4, 135.1, 155.0, 159.1, 163.5, 167.1. IR (KBr, cm^{-1}) 704, 1019, 1152, 1274, 1561, 1721, 2226, 2979, 3020. anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; found: C, 69.73; H, 5.82; N, 9.00.

5n: White solid: mp 238–239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.68 (s, 3H), 4.13 (s, 3H), 6.84–6.87 (d, J = 10.5 Hz, 1H), 7.09–7.11 (m, 3H), 7.22–7.24 (m, 2H), 7.46–7.47 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 23.3, 54.8, 114.6, 120.4, 125.1, 128.2, 128.8, 129.0, 130.0, 134.0, 136.7, 153.6, 159.7, 163.8, 164.8, 173.2. IR (KBr, cm^{-1}) 744, 1154, 1320, 1377, 1442, 1560, 1647, 2223, 2950, 3441. anal. calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24; found: C, 73.57; H, 5.00; N, 12.31.

5o: White solid: mp 270–271 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.27 (s, 3H), 2.66 (s, 3H), 4.11 (s, 3H), 6.86 (s, 1H), 6.95 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 7.45–7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.8, 23.3, 54.8, 114.6, 120.6, 126.0, 128.2, 128.9, 129.3, 130.0, 134.0, 134.9, 153.6, 159.7, 163.8, 164.7. IR (KBr, cm^{-1}) 699, 820, 1326, 1513, 1560, 1659, 2227, 3040. anal. calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76; found: C, 73.87; H, 5.43; N, 11.79.

5p: White solid: mp 186–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.79 (s, 3H), 2.71 (s, 3H), 4.13 (s, 3H), 6.67 (s, 1H), 7.08–7.13 (m, 3H), 7.29 (m, 1H), 7.49 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.2, 23.2, 54.8, 93.3, 114.6, 124.0, 126.2, 126.4, 128.5, 128.9, 130.0, 130.5, 130.9, 134.2, 134.4, 153.5, 159.3, 163.7, 165.2. anal. calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76; found: C, 73.82; H, 5.43; N, 11.87.

5q: White solid: mp 235–236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.68 (s, 3H), 3.76 (s, 3H), 4.12 (s, 3H), 6.68 (s, 1H), 6.76 (d, J = 9.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 7.48 (m, 5H). ^{13}C NMR (75 MHz, DMSO) δ = 22.8, 54.8, 55.1, 92.9, 113.8, 114.6, 121.3, 127.3, 128.3, 128.6, 129.5, 130.3, 131.2, 134.3, 153.8, 155.8, 157.9, 162.9, 163.7. anal. calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25; found: C, 70.71; H, 5.11; N, 11.23.

5r: White solid: mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.68$ (s, 3H), 3.67 (s, 3H), 4.12 (s, 3H), 6.76 (d, $J = 7.2$ Hz, 1H), 6.91–6.94 (m, 1H), 7.00–7.02 (m, 1H), 7.39–7.47 (m, 6H), 8.17 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO) $\delta = 22.8$, 54.7, 55.6, 92.8, 111.5, 114.7, 120.0, 123.6, 125.8, 126.0, 127.5, 128.2, 128.5, 129.4, 134.5, 151.2, 153.8, 157.8, 162.8, 164.4. IR (KBr, cm^{-1}) 768, 1255, 1460, 1530, 1560, 1664, 2227, 2975, 3334. anal. calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25; found: C, 70.89; H, 5.17; N, 11.21.

5s: White solid: mp 243–245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.68$ (s, 3H), 4.13 (s, 3H), 6.73 (s, 1H), 7.03 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 7.47 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 22.8$, 54.9, 93.1, 114.5, 121.1, 127.0, 127.8, 128.3, 128.4, 128.7, 129.6, 134.2, 137.1, 153.9, 157.9, 163.0, 164.3. anal. calcd for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12; found: C, 66.87; H, 4.21; N, 11.17.

5t: White solid: mp 189–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.69$ (s, 3H), 4.14 (s, 3H), 7.03–7.06 (m, 1H), 7.25 (m, 3H), 7.42–7.48 (m, 5H), 8.11 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO) $\delta = 22.9$, 54.8, 93.0, 114.6, 126.88, 126.9, 127.3, 127.9, 128.4, 128.6, 129.6, 133.8, 134.3, 153.9, 157.8, 163.0, 164.8. anal. calcd for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12; found: C, 66.87; H, 4.22; N, 11.17.

5u: White solid: mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.88$ (t, $J = 7.2$ Hz, 3H), 2.59 (s, 3H), 3.98 (q, $J = 7.2$ Hz, 2H), 4.10 (s, 3H), 7.36 (m, 2H), 7.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 13.3$, 23.2, 54.7, 61.4, 93.9, 114.2, 123.1, 127.9, 128.4, 128.5, 129.4, 134.9, 154.9, 159.1, 163.7, 166.9. IR (KBr, cm^{-1}) 757, 1001, 1153, 1274, 1558, 1732, 2228, 2954, 2990. anal. calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45; found: C, 68.84; H, 5.47; N, 9.41.

5v: White solid: mp 174–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.00$ (t, $J = 7.6$ Hz, 3H), 1.50–1.54 (m, 2H), 1.80–1.85 (m, 2H), 2.66 (s, 3H), 4.52 (t, $J = 6.4$ Hz, 2H), 6.78 (s, 1H), 7.07–7.10 (m, 3H), 7.21–7.25 (m, 2H), 7.44–7.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 13.8$, 19.1, 23.4, 30.8, 67.6, 93.6, 114.5, 120.5, 125.2, 125.7, 128.2, 128.2, 128.9, 129.3, 130.0, 134.3, 136.7, 153.6, 159.8, 163.9, 164.9. anal. calcd for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90; found: C, 74.86; H, 5.97; N, 10.79.

References

1 (*a*) G. Jones, In *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, A. McKillop, ed. Pergamon: Oxford, 1996; Vol. 5, p 167; (*b*) X. Ma and D. R. Gang, *Nat. Prod. Rep.*, 2004, **21**, 752–772; (*c*) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043–6061; (*d*) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627–646; (*e*) F. F. Wagner and D. L. Comins, *Tetrahedron*, 2007, **63**, 8065–8082; (*f*) S. Sun, Y. Liu, Q. Liu, Y. Zhao and D. Dong, *Synlett*, 2004, 1731–1734; (*g*) S. J. Teague, *J. Org. Chem.*, 2008, **73**, 9765–9766; (*h*) A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko and S. A. Essawy, *Synthesis*, 1999, 2114–2118; (*i*) M. Movassaghi and M. D. Hill, *J. Am. Chem. Soc.*, 2006, **128**, 4592–4593; (*j*) J. Hu, Q. Zhang, H. Yuan and Q. Liu, *J. Org. Chem.*, 2008, **73**, 2442–2445; (*k*) R. León, J. Marco-Contelles, A. G. García and M. Villarroya, *Bioorg. Med. Chem.*, 2005, **13**, 1167–1175.

2 (*a*) *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds, Pergamon Press: Oxford, 1996; Vol. 5; (*b*) J. A. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787–3802; (*c*) A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2125–2126; (*d*) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043–6061; (*e*) F. Mongin and G. Queguiner, *Tetrahedron*, 2001, **57**, 4059–4090; (*f*) M. C. Bagley, C. Glover and E. A. Merritt, *Synlett*, 2007, 2459–2482.

3 (*a*) S. Tu, B. Jiang, Y. Zhang, R. Jia, J. Zhang, C. Yao and S. Feng, *Org. Biomol. Chem.*, 2007, **5**, 355–359; (*b*) D. Tejedor and F. Garcia-Tellado, *Chem. Soc. Rev.*, 2007, **36**, 484–491; (*c*) D. J. Ramon and Y. Miguel, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602–1634; (*d*) *Multicomponent Reactions*: J. Zhu, H. Bienayme, Wiley-VCH: Weinheim, Germany 2005; (*e*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17–89.

4 J. P. Wan, S. F. Gan, G. L. Sun and Y. J. Pan, *J. Org. Chem.*, 2009, **74**, 2862–2865.

5 (*a*) P. A. Wender, S. T. Handy and D. L. Wright, *Chem. Ind.*, 1997, 765–769; (*b*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281.

6 (*a*) M. Movassaghi, M. D. Hill and O. K. Ahmad, *J. Am. Chem. Soc.*, 2007, **129**, 10096–10097; (*b*) S. Cui, X. Lin and Y. Wang, *J. Org. Chem.*, 2005, **70**, 2866–2869; (*c*) C. Allais, T. Constantieux and J. Rodriguez, *Chem.–Eur. J.*, 2009, **15**, 12945–12948.

7 (*a*) C. Simon, T. Constantieux and J. Rodriguez, *Eur. J. Org. Chem.*, 2004, 4957–4980; (*b*) S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto and V. Zanirato, *Chem. Rev.*, 1995, **95**, 1065–1114; (*c*) P. Langer, *Chem.–Eur. J.*, 2001, **7**, 3858–3866; (*d*) P. Langer, *Synthesis*, 2002, 441–459; (*e*) V. Nair, N. Vidya, A. T. Biju, A. Deepthi, K. G. Abhilash and E. Suresh, *Tetrahedron*, 2006, **62**, 10136–10140.

8 (*a*) N. M. Evdokimov, I. V. Magedov, A. S. Kireev and A. Kornienko, *Org. Lett.*, 2006, **8**, 899–902; (*b*) N. M. Evdokimov, A. S. Kireev, A. A. Yakovenko, M. Y. Antipin, I. V. Magedov and A. Kornienko, *J. Org. Chem.*, 2007, **72**, 3443–3453.

9 B. C. Ranu, R. Jana and S. Sowmiah, *J. Org. Chem.*, 2007, **72**, 3152–3154.

10 (*a*) T. R. K. Reddy, R. Mutter, W. Heal, K. Guo, V. Gillet, S. Pratt and B. Chen, *J. Med. Chem.*, 2006, **49**, 607–615; (*b*) K. Guo, M. J. Thompson, T. R. K. Reddy, R. Mutter and B. Chen, *Tetrahedron*, 2007, **63**, 5300–5311; (*c*) V. Mathew, J. Keshavayya, V. P. Vaidya and D. Giles, *Eur. J. Med. Chem.*, 2007, **42**, 823–824.

11 M. Sridhar, B. C. Ramanaiah, C. Narsaiha, B. Mahesh, M. Kumarswamy, K. K. R. Mallu, V. M. Ankathi and P. S. Rao, *Tetrahedron Lett.*, 2009, **50**, 3897–3900.

12 P. Thirmurugan and P. T. Perumal, *Tetrahedron*, 2009, **65**, 7620–7629.

13 A. Shaabani, M. Seyyedhamzeh, A. Maleki, M. Behnam and F. Rezazadeh, *Tetrahedron Lett.*, 2009, **50**, 2911–2913.

14 For formal [5+1] annulations, see: (*a*) X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhao and B. Li, *J. Am. Chem. Soc.*, 2005, **127**, 4578–4579; (*b*) D. Dong, X. Bi, Q. Liu and F. Cong, *Chem. Commun.*, 2005, 3580–3582. For Vilsmeier reactions, see: (*c*) W. Pan, D. Dong, K. Wang, J. Zhang, R. Wu, D. Xiang and Q. Liu, *Org. Lett.*, 2007, **9**, 2421–2423; (*d*) D. Xiang, Y. Yang, R. Zhang, Y. Liang, W. Pan, J. Huang and D. Dong, *J. Org. Chem.*, 2007, **72**, 8593–8596; (*e*) D. Xiang, K. Wang, Y. Liang, G. Zhou and D. Dong, *Org. Lett.*, 2008, **10**, 345–348; (*f*) R. Zhang, Y. Liang, G. Zhou, K. Wang and D. Dong, *J. Org. Chem.*, 2008, **73**, 8089–8092; (*g*) K. Wang, D. Xiang, J. Liu, W. Pan and D. Dong, *Org. Lett.*, 2008, **10**, 1691–1694; (*h*) Y. Yang, D. Xiang, X. Zhao, Y. Liang, J. Huang and D. Dong, *Tetrahedron*, 2008, **64**, 4959–4966. For PIFA-mediated oxidative cyclization, see: (*i*) J. Huang, Y. Lu, B. Qiu, Y. Liang, N. Li and D. Dong, *Synthesis*, 2007, 2791–2796; (*j*) J. Huang, Y. Liang, W. Pan, Y. Yang and D. Dong, *Org. Lett.*, 2007, **9**, 5345–5348; (*k*) K. Wang, X. Fu, J. Liu, Y. Liang and D. Dong, *Org. Lett.*, 2009, **11**, 1015–1018.

15 (*a*) Y. Wang, D. Dong, Y. Yang, J. Huang, Y. Ouyang and Q. Liu, *Tetrahedron*, 2007, **63**, 2724–2728; (*b*) Y. Wang, J. Huang, Y. Chai, Q. Liu, Y. Liang and D. Dong, *J. Comb. Chem.*, 2008, **10**, 511–516.

16 X. Xin, Y. Wang, W. Xu, Y. Lin, H. Duan and D. Dong, *Green Chem.*, 2010, **12**, 893–898.

17 (*a*) J. A. Varela, L. Castedo and C. Saá, *J. Org. Chem.*, 2003, **68**, 8595–8598; (*b*) A. H. H. Elghandour, M. K. A. Ibrahim and S. M. M. Elshikh, *Tetrahedron*, 1992, **48**, 9295–9304; (*c*) W. Liu, H. Jiang, S. Zhu and W. Wang, *Tetrahedron*, 2009, **65**, 7985–7988; (*d*) C. V. Asokan, E. R. Anabha, A. D. Thomas, A. M. Jose, K. C. Lethesh, M. Prasanth and K. U. Krishanraj, *Tetrahedron Lett.*, 2007, **48**, 5641–5643.

18 X. Xin, X. Guo, H. Duan, Y. Lin and H. Sun, *Catal. Commun.*, 2007, **8**, 115–117.

19 (*a*) E. M. Bottorff, R. G. Jones, E. C. Kornfeld and M. J. Mann, *J. Am. Chem. Soc.*, 1951, **73**, 4380–4383; (*b*) G. E. H. Elgemeie, H. A. Elfahham and H. A. Nabey, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4431–4433; (*c*) S. Kobayashi, R. Akiyama and M. Moriwaki, *Tetrahedron Lett.*, 1997, **38**, 4819–4822; (*d*) M. Hagimori, N. Mizuyama, Y. Hisadome, J. Nagaoka, K. Uedab and Y. Tominagab, *Tetrahedron*, 2007, **63**, 2511–2518.

20 K. Guo, M. J. Thompson and B. Chen, *J. Org. Chem.*, 2009, **74**, 6999–7006.

