Microwave-assisted synthesis of tetrazolyl pyrazole amides

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A rapid and efficient microwave-assisted synthesis N-(1H-tetrazol-5-yl) derivatives of 3-methyl-1-phenyl-1*H*-pyrazole-5-carboxamide is described. These tetrazole pyrazole amides have interesting bacteriocidal, pesticidal, herbicidal and antimicrobial activities. They were identified by IR and ^{1}H NMR elemental analyses. The target compounds were obtained in a shorter reaction time compared to conventional heating methods.

Keywords: tetrazole, pyrazole, microwave-assisted synthesis

Recently, there has been considerable study of N-heterocyclic compounds in the context of their bacteriocidal and other biological activities.[1–3] Among various N-heterocyclic scaffolds, tetrazole and pyrazole rings have attracted attention for their promising bioactive potency. The tetrazole ring is of importance as a pharmacophore due to its well known biological activities including bacteriocidal, pesticidal, herbicidal and other activities.[4–7] Studies of the synthesis and activity of tetrazole derivatives have attracted interest in recent years. Compounds containing the pyrazole nucleus have pronounced biological properties such as antipyretic, analgesic, insecticidal, herbicidal and antimicrobial activities.[8–12]

Compared with the traditional heating reactions, the microwave (MW) reaction technique has rapid, convenient, environmental and economic advantages.[13–15] MW irradiation is currently used to carry out a wide range of reactions.[16–18]

According to the principles of hybridisation, a series of novel derivatives with tetrazole and pyrazole rings were designed and synthesised under microwave irradiation.

Results and discussion

Substituted 3-methyl-1-phenyl-N-(1*H*-tetrazol-5-yl)-1*H*-pyrazole-5- carboxamide (**6a–f**) were prepared by the reaction of various 3-methyl-1-phenyl-1*H*-pyrazole-5-carbonyl chlorides (**4a–f**) and 1*H*-tetrazol-5-amine (**5**) under microwave irradiation as shown in Scheme 1. The compound **5** was prepared by the reaction of dicyandiamide with sodium azide. The reactive acid chlorides **4a–f** were synthesised from the corresponding pyrazole-5-carboxylic acids (**3a–f**) with oxalyl chloride. The acids **3a–f** were obtained by hydrolysing 3-methyl-1-substituted phenyl-1*H*-pyrazole-5-carboxylic ester (**2a–f**) which were synthesised by the condensation of ethyl acetopyruvate (**1**) with substituted phenyl hydrazines. Compound **1** was prepared by the reaction of diethyl oxalate with acetone in presence of sodium ethylate.

Preliminary experiments to define the reaction time and irradiation power were performed using **4a** (10 mmol) and **5** (10 mmol) as a model system to synthesise compound **6a** (Table 1). Various reaction times and irradiation power were tested (Table 1, entries 1–7). The optimum yield of **6a** (85%) was obtained by carrying out the reaction under MW irradiation (400 W) for 20 min at 110 °C. The reaction was also carried out with conventional heating (Table 1, entry 8), which required more heating time (5 h) but gave a lesser yield (62%). The preparative reactions were carried out under these optimal microwave conditions to give **6a–f** in yields of 78–90%.

In conclusion, we have developed a fast, convenient, and efficient preparation of 3-methyl-1-substituted phenyl-N-(1*H*-tetrazol-5-yl)-1*H*-pyrazole-5- carboxamides under MW irradiation. The simplification of the reaction procedure with very short reaction time and a high yield made this procedure a useful and attractive alternative to the currently available methods.

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Experimental

Melting points were recorded on an X-4 binocular microscope melting point apparatus. ^{1}H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm are reported with TMS as the internal standard. IR spectra in KBr were recorded by a Perkin-Elmer PE-683 infrared spectrometer. Elemental analyses were performed on an Elementer Vario EL III elementary analysis instrument. MW experiments were carried out on a WF-4000M microwave fast reaction system (Shanghai Qiyao Analysis Instrument Co., Shanghai, China).

Preparation of **2a–f***; general procedure*

A mixture of 10 mmol of ethyl acetopyruvate (1) and 5 mL of ethanol was added dropwise with stirring, at 0 °C, to a suspension consisting of 10 mmol of the substituted phenylhydrazine and 15 mL of ethanol, over a period of one hour, and then the catalytic amount of acetic acid was added. After stirring had been continued for a further 4 hours at room temperature, the reaction mixture was evaporated under reduced pressure, then the compounds **2a–f** were obtained which were used immediately.

Ethyl 1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**2c**): Yield 83%; m.p. 211–212 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 1.15(t, 3H, CH_2CH_3), 2.25(s, 3H, CH_3), 3.37(s, 3H, OCH_3), 4.15(m, 2H, $–CH_2–$), 6.84(s, 1H, pyrazole C–H), 6.98–7.32(m, 4H, ArH); IR (KBr) υ: 3135, 2840, 1731, 1518, 1370, 1251cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.36; H, 6.46; N, 10.33%.

Preparation of **3a–f***; general procedure*

A mixture of **2a–f** (10 mmol), and NaOH (5 g) in water was stirred and the temperature raised to reflux. After stirring had been continued for a further 2 hours, the pH of the reaction solution was adjusted to the range of 2–3 with concentrated hydrochloric acid. The crude product was precipitated, filtered, washed with water, dried and recrystallised from ethanol to afford compounds **3a–f**.

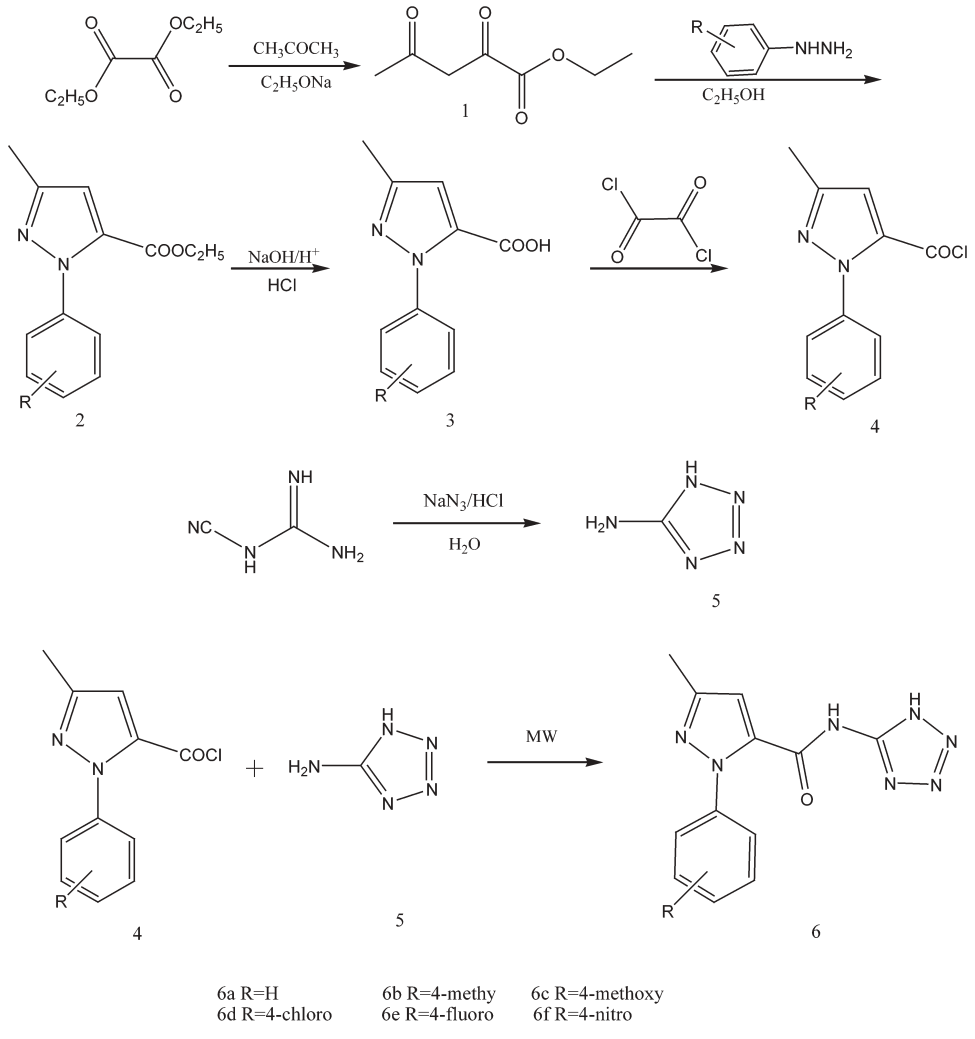
1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**3c**): Yield 89%; m.p. 234–235 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.22(s, 3H, CH_3), 3.79(s, 3H, OCH_3), 6.84(s, 1H, pyrazole C–H), 6.98–7.32(m, 4H, ArH), 13.03(s, 1H, COOH); IR (KBr) υ: 3141, 2837, 1701, 1517, 1338cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.23; H, 5.12; N, 12.33%.

Preparation of **4a–f***; general procedure*

Oxalyl chloride (20 mmol) was added dropwise with stirring, at room temperature, to a suspension consisting of 10 mmol of **3a–f** and 20 mL of dry toluene. After the reaction was completed, the reaction mixture was distilled under reduced pressure to remove the solvent and residual oxalyl chloride to afford compound **4a–f** which were used immediately.

Preparation of **5***; general procedure*

A suspension of dicyandiamide(10 mmol) and sodium azide (15 mmol) in 15 mL water was stirred and allowed to rise in temperature at 65 °C on the water-bath. After stirring had been continued for a



Scheme 1 The synthetic route of compounds **6a–f**.

Table 1 Synthesis of compound **6a**

Entry	Mode of activation	Time	Power/temp.	Yield %
1	MW	5 min	400 W	30
2	MW	10min	400 W	48
3	MW	15 min	400 W	69
4	MW	20 min	400 W	85
5	MW	30 min	400 W	87
6	MW	20 min	300 W	65
7	MW	20 min	500 W	88
8	CH	5h	110 °C	62

MW, microware irradiation; CH, conventional heating.

further 1 hour, concentrated hydrochloric acid (20 mmol) was added. After complete addition of the acid the mixture was kept at 65–70 °C on the water-bath for 6 hours during which the product began to crystallise. The semi-solid mass was allowed to stand overnight and was chilled thoroughly before the product was filtered off and washed with ice water. The compound **5** was recrystallised from boiling water. The yield was 73%, M.p. 206–207 °C.[19]

Preparation of **6a–f***; general procedure*

A mixture of compounds **4a–f** (10 mmol) and **5** (10 mmol) in absolute toluene was stirred and irradiated in WF-4000M microwave fast reaction system under 300W for minutes at 110 °C. After cooling and filtering, crude compounds were recrystallised from EtOH to obtain **6a–f**.

*3-Methyl-1-phenyl-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide (***6a**): Yield 85%; m.p. 223–225 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.27(s, 3H, CH_3), 6.83(s, 1H, pyrazole C–H), 7.38–7.41(m, 5H, ArH), 9.39–9.41(t, 1H, –NH–CO–), 14.26(s, 1H, tetrazole N–H); IR(KBr) υ: 3131, 2976, 1701, 1658, 1314cm^{-1}. Anal. Calcd for $C_{12}H_{11}N_7O$: C, 53.53; H, 4.12; N, 36.41. Found: C, 54.06; H, 4.06; N, 37.03%.

3-Methyl-N-(1H-tetrazol-5-yl)-1-p-tolyl-1H-pyrazole-5-carboxamide **6b**: Yield 83%; m.p. 246–247 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.24(s, 3H, CH_3), 2.27(s, 3H, CH_3), 6.83(s, 1H, pyrazole C–H), 7.19–7.36(m, 4H, ArH), 9.41(d, 1H, –NH–CO–), 14.19(s, 1H, tetrazole N–H); IR(KBr)υ: 3140, 2972, 1699, 1606, 1377cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_7O$: C, 55.12; H, 4.63; N, 34.61. Found: C, 55.62; H, 4.71; N, 34.41%.

1-(4-Methoxyphenyl)-3-methyl-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide **(6c):** Yield 82%; m.p. 229–231 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.24(s, 3H, CH_3), 3.80(s, 3H, OCH_3), 6.83(s, 1H, pyrazole C–H), 7.10–7.35(m, 4H, ArH), 9.41(d, 1H, –NH–CO–), 14.26(s, 1H, tetrazole N–H); IR(KBr) υ: 3134, 2964, 1691, 1602, 1312cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_7O_2$: C, 52.17; H, 4.38; N, 32.76. Found: C, 52.30; H, 4.13; N, 32.20%.

*1-(4-Chlorophenyl)-3-methyl-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide (***6d):** Yield 78%; m.p. 264–265 °C; ^{1}H NMR (DMSO-d6, 300 MHz) δ: 2.26(s, 3H, CH_3), 6.86(s, 1H, pyrazole C–H), 7.32–7.62(m, 4H, ArH), 9.42(d, 1H, –NH–CO–), 14.29(s, 1H, tetrazole N–H); IR(KBr) υ: 3135, 2965, 1691, 1520, 1312cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClN_7O$: C, 47.46; H, 3.32; N, 32.28. Found: C, 46.67; H, 3.72; N, 32.69%.

1-(4-Fluorophenyl)-3-methyl-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide (**6e**): Yield 90%; m.p. 249–250 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.20(s, 3H, CH_3), 6.83(s, 1H, pyrazole C–H), 7.28–7.98(m, 4H, ArH), 9.50(d, 1H, –NH–CO–), 14.29(s, 1H, tetrazole N–H); IR(KBr) υ: 3184, 2972, 1699, 1607, 1378cm^{-1}. Anal. Calcd for

$C_{12}H_{10}FN_7O$: C, 50.17; H, 3.51; N, 34.13. Found: C, 50.08; H, 3.28; N, 34.30.

3-Methyl-1-(4-nitrophenyl)-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide (**6f**): Yield 85%; m.p. 296–297 °C; ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.27(s, 3H, CH_3), 6.86(s, 1H, pyrazole C–H), 8.14–8.62(m, 4H, ArH), 9.42(d, 1H, –NH–CO–), 14.31(s, 1H, tetrazole N–H); IR(KBr) υ: 3178, 2972, 1699, 1697, 1378cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_8O_3$: C, 45.86; H, 3.21; N, 35.66. Found: C, 45.17; H, 3.42; N, 35.63.

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