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Microwave-assisted synthesis of 1,2,4-triazole-3-carboxamides from esters and amines under neutral conditions

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Abstract A series of 1,2,4-triazole-3-carboxamides have been prepared from 1,2,4-triazole-3-carboxylates under mild conditions. Efficient synthesis of amides directly from esters and amines is achieved under mild, neutral conditions with liberation of alcohol as by-product. Both primary and secondary aliphatic and aromatic amines can be utilized. This unprecedented, general, environmentally benign reaction proceeds in toluene under microwave conditions. The newly synthesized compounds were characterized by spectral and elemental analyses.

Keywords 1,2,4-Triazoles · Hydrazones · Trimethyl aluminium · Microwave assistance

Introduction

1,2,4-Triazole and its derivatives constitute an important class of organic compounds with diverse agricultural [1], industrial [2] and biological activities [3], including anti-microbial [4, 5], anti-proliferative [6], sedative [7], anti-convulsant [8] and anti-inflammatory actions [9]. Pyridine as a heterocyclic nucleus played a vital role in the development of different medicinal agents and in the field of agrochemicals. This nucleus is present in many products such as drugs, vitamins, food, flavourings, plant dyes, adhesives and herbicides. As part of our program aimed at developing new biologically active compounds, in this work we report the synthesis of some pyridin-3-yl-1,2,4-triazole-3-carboxamides. This report describes a convenient alternative synthesis for triazole carboxamides with improved yields.

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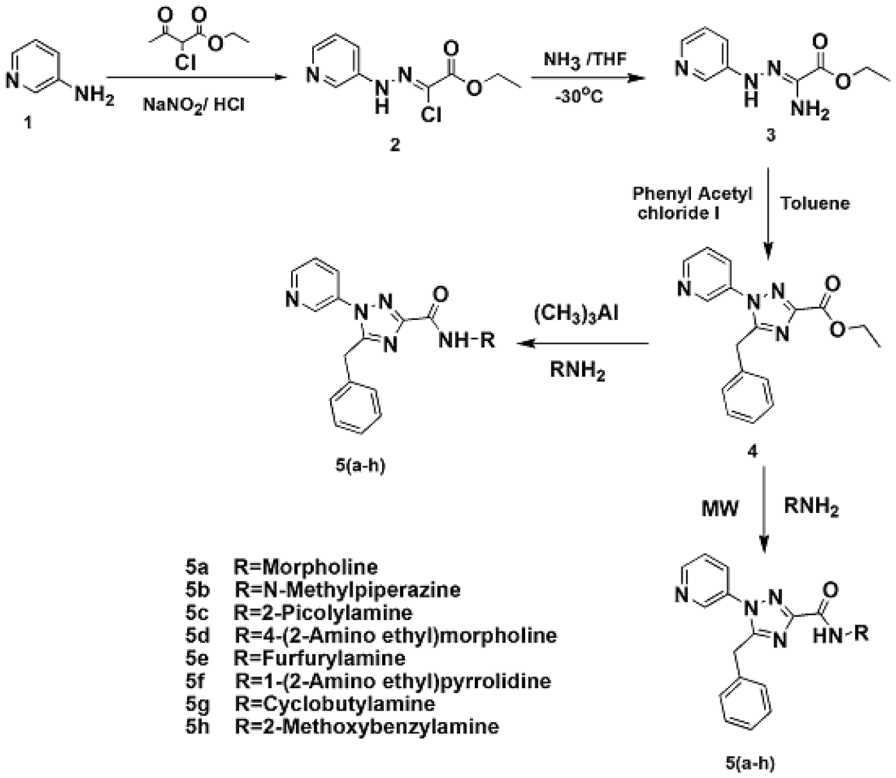
In the past few years, use of microwave energy to heat and drive chemical reactions has become increasingly popular in the medicinal chemistry community. This non-classical heating method has matured from a laboratory curiosity to an established technique that is heavily used in academia and industry. One of the many advantages of using rapid "microwave flash heating" for chemical synthesis is the dramatic reduction in reaction times—from days and hours to minutes and seconds. It was found that the reaction rate was accelerated by about 50 times under isothermal microwave condition compared with conventional isothermal condition, which induces translational and vibrational energy levels and reaction acceleration. The effect of a microwave field on dielectric materials is to induce rapid rotation of the polarized dipoles in the molecules. This generates heat due to friction, simultaneously increasing the probability of contact between the molecules, thus enhancing the reaction rate and reducing the activation energy. As discussed herein, there are good reasons why many pharmaceutical companies are incorporating microwave chemistry into their drug discovery efforts.

Chemistry

1,2,4-Triazole-3-carboxamides used to be synthesized from 4-arylazo-2-aryl-2-oxazolin-5-ones reacting with the appropriate amine. Dyck et al. [10] and Lange et al. [11] prepared 1,2,4-triazole-3-carboxylates and converted these esters to the corresponding amides by saponification, to give carboxylic acid, followed by amidation. The 1,2,4-triazole-3-carboxamides **5a**–**h** described herein were prepared using a different synthetic pathway as outlined in Scheme 1. Diazotization of commercially available 3-aminopyridine in presence of hydrochloric acid gave the diazonium salt, which was directly coupled with ethyl 2-chloroacetoacetate to afford the oxobutanoate **2** [12]. Subsequent treatment with ammonia led to the amine **3**. Cyclization of **3** with phenylacetyl chloride was achieved by refluxing with toluene. Preparation of the final 1,2,4-triazole-3-carboxamides **5a**–**h** was achieved by adopting a simple one-pot procedure.

In fact, the commonest procedure to prepare carboxamides of heterocycles involves three classical steps: hydrolysis of the ester to acid, followed by acid chloride formation, and finally reaction with the appropriate amine to give the corresponding carboxamide. Conversion of ethyl esters to carboxamides under mild reaction conditions via organoaluminium reagents has been described by Benderly and Stavchansky [13]. Applying this procedure to our 1,2,4-triazole series, the 1,2,4-triazole-3-carboxamides **5a**–**h** were obtained in good yield in a one-step synthesis by treatment of the triazole carboxylate **4** with 2 equiv. of an aluminium complex which was previously prepared in situ by reacting trimethylaluminium with the corresponding amine. However, trimethylaluminium catches fire spontaneously on exposure to air and releases flammable gases in contact with water during work-up. To avoid these practical difficulties, we introduced an atom-economical, environmentally benign direct synthesis of amides from esters and amines under microwave conditions without any catalyst or metal complex [14–16].



Scheme 1 (a) (i) $NaNO_2$, aq. HCl, 0 °C; (ii) ethyl 2-chloroacetoacetate, NaOAc, EtOH, H_2O, 0 °C; (b) NH_3 gas, THF; (c) phenylacetyl chloride, toluene, reflux; (d) [i] corresponding amines for **5a–h**, $Al(Me)_3$, N_2 atm, toluene, 100 °C; [ii] corresponding amines, toluene, MW, 130 °C

Table 1 Conventional heating versus microwave irradiation for amidation reaction

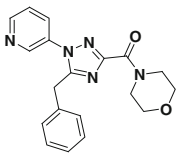
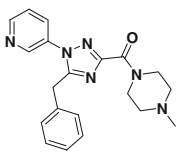
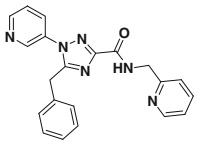
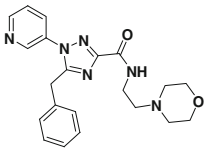
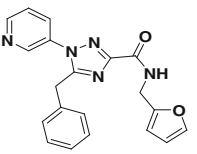
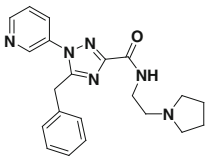
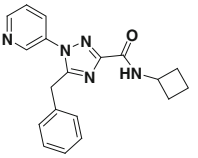
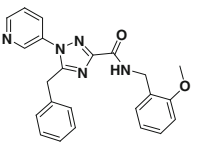
Compound	Product	Conventional method			Microwave irradiation		
		Time (h)	Temp. (°C)	Yield (%)	Time (min)	Temp. (°C)	Yield (%)
5a		12	100	62	30	130	80
5b		14	100	76	30	130	85

Table 1 continued

Compound	Product	Conventional method			Microwave irradiation		
		Time (h)	Temp. (°C)	Yield (%)	Time (min)	Temp. (°C)	Yield (%)
5c		14	100	75	30	130	90
5d		14	100	65	30	130	84
5e		16	100	60	30	130	76
5f		18	100	50	30	130	65
5g		16	100	80	30	130	88
5h		12	100	82	30	130	90

Experimental

All reagents were purchased from Aldrich and used as received. Dry tetrahydrofuran (THF), ethanol and toluene were supplied by Spectrochem. All chemistry was performed under nitrogen atmosphere using standard techniques. Microwave reactions were carried out with a single-mode-cavity Discover microwave

apparatus. Microwave experiments were performed in a 10-ml sealed tube. All nuclear magnetic resonance (NMR) spectra were measured using a Bruker AMX 400 instrument with 5-mm PABBO BB-1H tubes. ^{1}H and ^{13}C NMR spectra were measured for approximately 0.03 M solutions in d_6-dimethyl sulphoxide (DMSO) at 400 MHz with tetramethylsilane (TMS) as internal reference. Infrared (IR) spectra were measured on potassium bromide pellets using a PerkinElmer 1600 series Fourier-transform infrared (FTIR) spectrometer. Liquid chromatography–mass spectrometry (LC-MS) was carried out using an Agilent 1200 series LC and Micromass zQ spectrometer. Column chromatography was performed using silica gel (230–400 mesh). Combustion analysis was performed on a Costech Elemental Combustion System CHN elemental analyzer.

General procedure for preparation of intermediates

*Ethyl 2-chloro-2-[2-(3-pyridyl)hydrazono]acetate (**2**)*

3-Aminopyridine (25 g, 0.265 mol) was dissolved in 250 ml of 6 N HCl (250 ml) solution to give a clear solution and cooled to 0 °C. Sodium nitrite (18.2 g, 0.265 mol) in water (50 ml) was added dropwise to the reaction mass and stirred for 30 min at the same temperature. Later, ethyl 2-chloroacetoacetate (43 g, 0.265 mol) in ethanol (100 ml) was added dropwise for 1 h at 0 °C. After 30 min, sodium acetate (65 g, 0.795 mol) in water (200 ml) was added dropwise to the reaction mixture and stirred for 12 h. The precipitated solid was filtered, washed with water, and dried under vacuum to afford pale-yellow crystals of **2** (4 g, 75 %). M.p. = 124–127 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.72 (d, 1H), 8.63 (s, 1H), 7.63 (d, 1H), 7.26 (d, 2H), 4.54 (q, 2H), 1.46 (t, 3H); ^{13}C NMR (400 MHz, DMSO) δ 160.3, 156.7, 150.89, 146.2, 134.5, 133.3, 62.2, 32.6, 14.3; LC-MS 229.04 (M+1); Anal. calcd. for $C_9H_{10}ClN_3O_2$; C: 47.48, H: 4.43, N: 18.46. Found: C: 47.28, H: 4.63, N: 18.30.

*Ethyl 2-amino-2-[2-(3-pyridyl)hydrazono]acetate (**3**)*

Ammonia gas was bubbled through a solution of **2** (10 g, 0.044 mol) at −30 °C for 30 min and stirred at room temperature (RT) for 2 h. Thin-layer chromatography (TLC) indicated all **2** had been converted to amine **3**. The solvent and excess of ammonia were removed under vacuum; the residue was dissolved in 50 ml of dry chloroform and filtered to remove NH_4Cl. The filtrate was evaporated and triturated with diethyl ether (25 ml) to afford pale-brown solid of **3** (6.5 g, 70 %). M.p. = 85–88 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.71 (m, 1H), 8.59 (s, 1H), 7.61 (d, 1H), 7.38 (d, 1H), 4.65 (br, 2H), 4.32 (q, 2H), 1.34 (t, 3H); ^{13}C NMR (400 MHz, DMSO) δ 159.3, 154.5, 140.2, 134.4, 125.4, 123.0, 116.2, 62.5, 14.1; MS 209.2 (M+1); Anal. $C_9H_{12}N_4O_2$. C: 51.92, H: 5.81, N: 26.91. Found: C: 47.98, H: 5.83, N: 26.90.

*Ethyl 5-benzyl-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxylate (**4**)*

Phenylacetyl chloride (4.4 g, 0.0288 mol) was added dropwise to a stirred solution of **3** (5 g, 0.024 mol) in toluene (25 ml) at 0 °C. The reaction mass was warmed to RT

and heated to reflux for 12 h. After completion of the reaction, the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (120 ml) and washed successively with 1 N HCl, 10 % $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (hexane/EtOAc 6:4) to give the desired product **4** as a brown gummy solid (0.31 g, 36 %). M.p. = 160–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, 1H), 8.59 (S, 1H), 7.61 (d, 1H), 7.38 (dd, 2H), 7.26 (d, 2H), 7.04 (d, 2H), 4.52 (dd, 2H), 4.24 (S, 2H), 1.46 (t, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 150.89, 146.24, 133.5, 129.38, 128.34, 127.45, 123.8, 62.23, 32.63, 14.31; LC-MS: 315.4 (M+1). Anal.calcd. for $C_{17}H_{16}N_4O_2$ C: 66.22, H: 5.23, N: 18.17, O: 10.38. Found: C: 66.20, H: 5.26, N: 18.20.

*General procedure for synthesis of 1,2,4-triazole-3-carboxamides **5a–h***

Conventional method: To a solution of the corresponding amine (1.1 eq.) in dry toluene (5 ml) was added a solution of $Al(Me)_3$ in toluene (2 M, 2.0 eq.) under N_2 atmosphere. The reaction mixture was stirred at RT for 1 h. A solution of **4** (1 eq.) in dry toluene (6 ml) was then added dropwise. The mixture was heated to 90 °C during the respective time, then carefully poured onto 1 N HCl (30 ml). The biphasic solution was heated to 40 °C for 30 min and cooled to RT. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography.

Microwave irradiation: To a solution of the corresponding amine (1.1 eq.) in dry toluene (5 ml) was added **4**(1 eq.), followed by heating to 130 °C under microwave conditions for 30 min. The solvent was removed under vacuum, and the crude purified by column chromatography.

*[5-Benzyl-1-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl](morpholino)methanone (**5a**)*

Conventional method: Compound **5a** was prepared from **4** (250 mg, 0.8 mmol), morpholine (83 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 12 h; purified by flash chromatography [pet.ether/EtOAc (4:6)]; yield: 175 mg (62 %) as brown solid.

Microwave irradiation: Compound **5a** was prepared from **4** (250 mg, 0.8 mmol) and morpholine (83 mg, 0.9 mmol), 30 min; purified by flash column chromatography [pet. ether/EtOAc (4:6)]; yield: 226 mg (80 %) as brown solid. M.p. = 195–198 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.72 (d, 1H), 8.63 (s, 1H), 7.63 (d, 1H), 7.40 (m, 1H), 7.26 (m, 3H), 7.09 (d, 2H), 4.20 (s, 2H), 3.96 (t, 2H), 3.85 (m, 2H), 3.80 (m, 2H), 3.74 (m, 2H); ^{13}C NMR (400 MHz, DMSO) δ 150.6, 146.0, 132.7, 128.9, 128.4, 127.4, 123.8, 67.0, 66.8, 47.5, 42.9, 32.5. LC-MS: 350.3 (M+1). Anal. calcd. for $C_{19}H_{19}N_5O_2$; C: 65.32, H: 5.48, N: 20.04. Found: C: 65.30, H: 5.50, N: 20.07.

*[5-Benzyl-1-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl](4-methylpiperazin-1-yl)methanone (**5b**)*

Conventional method: Compound **5b** was prepared from **4** (250 mg, 0.8 mmol), *N*-methylpiperazine (90 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction

time: 14 h; purified by flash column chromatography [pet. ether/EtOAc (4:6)]; yield: 214 mg (76 %) as off-white solid.

Microwave irradiation: Compound **5b** was prepared from **4** (250 mg, 0.8 mmol) and *N*-methylpiperazine (90 mg, 0.9 mmol), 30 min; purified by flash column chromatography [pet. ether/EtOAc (4:6)]; yield: 249 mg (85 %) as off-white solid. M.p. = 115–118 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.71 (d, 1H), 8.63 (s, 1H), 7.65 (d, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.26 (d, 2H), 7.01 (d, 2H), 4.22 (S, 2H), 3.92 (t, 4H) 2.48 (t, 4H), 2.33 (s, 3H); ^{13}C NMR (400 MHz, DMSO) δ 160.0, 157.5, 155.2, 150.5, 146.0, 134.8, 133.6, 132.7, 130.0, 128.9, 128.3, 127.4, 123.8, 55.3, 54.6, 46.9, 45.9, 42.4, 32.5. LC-MS (ESI) *m/z*: 363.1(M+1). Anal. calcd. for $C_{20}H_{22}N_6O$; C: 66.28; H: 6.12; N: 23.19. Found: C: 66.30, H: 6.15, N: 23.20.

*5-Benzyl-N-(pyridin-2-yl)methyl)-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide (**5c**)*

Conventional method: Compound **5c** was prepared from **4** (250 mg, 0.8 mmol), 2-picolylamine (97 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 14 h; purified by flash chromatography; yield: 226 mg (75 %), 270 mg (90 %) as brown solid.

Microwave irradiation: Compound **5c** was prepared from **4** (250 mg, 0.8 mmol) and 2-picolylamine (97 mg, 0.9 mmol), 30 min; column purification [pet. ether/EtOAc(5:5)]; yield: 270 mg (90 %) as brown solid. M.p. = 145–148 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.71 (d, 1H), 8.63 (s, 1H), 8.59 (d, 1H), 8.24 (br, 1H), 7.67 (m, 2H), 7.39 (m, 2H), 7.21–7.31 (m, 4H), 7.1 (d, 2H), 4.82 (d, 2H), 4.22 (S, 2H); ^{13}C NMR (400 MHz, DMSO) δ 150.6, 149.1, 146.0, 136.5,132.8, 128.9, 128.3, 127.4, 123.8, 122.5, 122.3, 44.4, 32.6. LC-MS (ESI) *m/z*: 371.4 (M+1). Anal. calcd. for $C_{21}H_{18}N_6O$; C: 68.09; H: 4.90; N: 22.69. Found: C: 68.01; H: 4.30; N: 22.30.

*5-Benzyl-N-(morpholinoethyl)-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide (**5d**)*

Conventional method: Compound **5d** was prepared from **4** (250 mg, 0.8 mmol), 2-aminoethyl morpholine (117 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 14 h; purified by flash chromatography [pet. ether/EtOAc (5:5)]; yield: 206 mg (65 %) as off-white solid.

Microwave irradiation: Compound **5d** was prepared from **4** (250 mg, 0.8 mmol) and 2-aminoethyl morpholine (117 mg, 0.9 mmol), 30 min; purified by flash chromatography [pet. ether/EtOAc (1:1)]; yield: 267 mg (84 %) as brown solid. M.p = 115–118 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.71 (d, J=5 Hz, 1H), 8.63 (m, 2H), 7.68 (d, J=8 Hz, 1H), 7.60 (br,1H), 7.41 (m, 1H), 7.21-7.31 (m, 3H), 7.1 (d, J=5.6 Hz, 2H), 4.22 (s, 2H), 3.72 (m, 4H), 3.62 (m, 2H), 2.63 (m, 2H), 2.53 (m, 4H); ^{13}C NMR (400 MHz, DMSO) δ 158.9, 155.9, 150.6, 146.0, 134.7, 133.6, 132.8, 129.5, 128.9, 128.3, 66.9, 56.9, 53.3, 35.8, 32.6. LCMS : 393.2 (M+1). Anal. Calcd for $C_{21}H_{24}N_6O_2$; C: 64.27; H: 6.16; N: 21.41. Found: C: 64.01; H: 6.30; N: 21.30.

*5-Benzyl-N-[(furan-2-yl)methyl]-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide (**5e**)*

Conventional method: Compound **5e** was prepared from **4** (250 mg, 0.8 mmol), furfurylamine (87 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 16 h; purified by flash chromatography [pet. ether/EtOAc (5:5)]; yield: 174 mg (60 %): 152 mg as brown viscous liquid.

Microwave irradiation: Compound **5e** was prepared from **4** (250 mg, 0.8 mmol) and furfurylamine (87 mg, 0.9 mmol), 30 min; purified by flash chromatography [pet. ether/EtOAc (1:1)]; yield: 221 mg (76 %) as viscous brown liquid. ^{1}H NMR (400 MHz, DMSO) δ 8.71 (d, 1H), 8.63 (s, 1H), 7.68 (d, 1H), 7.42 (br, 1H), 7.38 (m, 2H), 7.31 (m, 3H), 7.09 (d, 2H), 6.33 (d, 2H), 4.68 (s, 2H), 4.19 (s, 2H); ^{13}C NMR (400 MHz, DMSO) δ 150.7, 146.0, 142.4, 132.8, 129.0, 128.3, 127.4, 123.8, 110.5, 107.9, 36.3, 32.5. LC-MS (ESI) *m/z*: 360.3(M+1). Anal. calcd. for $C_{20}H_{17}N_5O_2$; C: 66.84; H: 4.77; N: 19.49; Found: C: 66.44, H: 4.97, N: 19.69.

*5-Benzyl-1-(pyridin-3-yl)-N-[2-(pyrrolidin-1-yl)ethyl]-1H-1,2,4-triazole-3-carboxamide (**5f**)*

Conventional method: Compound **5f** was prepared from **4** (250 mg, 0.8 mmol), 1-(2-aminoethyl)pyrrolidine (102 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 18 h; purified by flash chromatography [pet. ether/EtOAc (5:5)]; yield: 198 mg (65 %): 152 mg as dark-brown semi-solid.

Microwave irradiation: Compound **5f** was prepared from **4** (250 mg, 0.8 mmol) and 1-(2-aminoethyl)pyrrolidine (102 mg, 0.9 mmol), 30 min; column purification [pet. ether/EtOAc(1:1)]; yield: 198 mg (65 %) as dark-brown semi-solid. M.p. = 142–145 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.70 (d, 1H), 8.62 (s, 1H), 7.68 (d, 1H), 7.59 (br, 1H), 7.38 (m, 1H), 7.21–7.29 (m, 3H), 7.09 (d, 2H), 4.21 (s, 2H), 3.62 (t, 2H), 2.75 (t, 2H), 2.61 (t, 4H), 1.81 (t, 4H). ^{13}C NMR (400 MHz, DMSO) δ 158.9, 157.1, 155.9, 150.6, 146.0, 134.7, 133.7, 132.8, 128.9, 128.3, 127.4, 54.7, 54.0, 38.2, 32.5, 23.5. LC-MS (ESI) *m/z*: 377.4 (M+1). Anal. calcd. for $C_{21}H_{24}N_6O$; C: 67.00; H: 6.43; N: 22.32. Found: C: 66.91; H: 6.30; N: 22.3.

*5-Benzyl-N-cyclobutyl-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide (**5g**)*

Conventional method: Compound **5g** was prepared from **4** (250 mg, 0.8 mmol), cyclobutylamine (64 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 16 h; purified by flash column chromatography. [pet. ether/EtOAc (5:5)]; yield: 217 mg (80 %) as pale-yellow solid.

Microwave irradiation: Compound **5g** was prepared from **4** (250 mg, 0.8 mmol) and cyclobutylamine (64 mg, 0.8 mmol), 30 min; purified by flash column chromatography [pet. ether/EtOAc (1:1)]; yield: 237 mg (88 %) as pale-yellow solid. M.p. = 172–175 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.71 (d, 1H), 8.61 (s, 1H), 7.65 (d, 1H), 7.39 (m, 1H), 7.21–7.31 (m, 4H), 7.09 (d, 2H), 4.65 (m, 1H), 4.21 (s, 2H), 2.48 (m, 2H), 2.05 (m, 2H), 1.79 (m, 2H); ^{13}C NMR (400 MHz, DMSO) δ158.9, 157.1, 155.9, 150.6, 146.0, 134.7, 133.7, 132.8, 128.9, 128.3, 127.4, 54.7,

54.0, 38.2, 32.5, 23.5. LC-MS (ESI) *m/z*: 377.4 (M+1). Anal. calcd. for $C_{19}H_{19}N_5O$: C: 68.45; H: 5.74; N: 21.01. Found: C: 68.51; H: 5.65; N: 21.10.

*N-(2-Methoxybenzyl)-5-benzyl-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide (**5h**)*

Conventional method: Compound **5h** was prepared from **4** (250 mg, 0.8 mmol), 2-methoxybenzylamine (123 mg, 0.9 mmol) and $Al(Me)_3$ (3.2 ml, 1.6 mmol); reaction time: 12 h; purified by flash column chromatography [pet. ether/EtOAc (5:5)]; yield: 265 mg (82 %) as off-white solid.

Microwave irradiation: Compound **5h** was prepared from **4** (250 mg, 0.8 mmol) and 2-methoxybenzylamine (123 mg, 0.9 mmol), 30 min; purified by column chromatography [pet. ether/EtOAc (1:1)]; yield: 291 mg (90 %) as off-white solid. M.p. = 115–118 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.71 (d, 1H), 8.63 (s,1H), 7.65 (m, 2H), 7.39 (m, 2H), 7.31 (m, 2H), 7.09 (d, 2H), 6.91 (m, 2H), 4.70 (d, 2H), 4.19 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (400 MHz, DMSO) δ 150.6, 132.8, 129.9, 129.0, 128.9, 128.3, 127.4, 123.8, 120.7, 110.3, 55.3, 39.1, 32.5. LC-MS (ESI) *m/z*: 400.1 (M+1). Anal. calcd. for $C_{23}H_{21}N_5O_2$: C: 69.16; H: 5.30; N: 17.53. Found: C: 69.11; H: 5.38; N: 17.50.

Conclusions

We have developed a simple and efficient method with excellent yields for synthesis of 1,2,4-triazole-3-carboxamides via one-pot synthesis, without using any other catalysts, in toluene. In this work, eight new compounds were successfully synthesized using both our reported method and the conventional method. The advantages of the present procedure are experimental simplicity, easy work-up procedure, mild reaction conditions and no requirement to use other catalysts. The yield of the present procedure is comparatively greater than for the conventional method (Table 1), not only that the unreacted starting materials were isolated from the present work.

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