J. Indian Chem. Soc.,
Vol. 96, March 2019, pp. 401-405

Conventional vs microwave assisted synthesis of different substituted heterocyclic amides

Pardeep Kaur[a], Sunita Sharma[b]*, Jyoti Gaba[a] and Rashmi[a]

[a]Department of Chemistry, [b]Department of Plant Breeding and Genetics,
Punjab Agricultural University, Ludhiana-141 004, Punjab, India

E-mail: pardip2493@gmail.com, sunita_sharma@pau.edu, jyotgcw@gmail.com, rashmibakshi280@gmail.com

Manuscript received online 05 September 2018, revised 20 February 2019, accepted 26 February 2019

Amides have great importance in the field of synthetic organic chemistry because of their presence in many biologically active molecules. Condensation of different carboxylic acids with different amines is one of the most convenient method for amide synthesis. Different substituted amides (**1**-**10**) were synthesized by reacting different substituted acids with different substituted amines in the presence of catalytic amount of triethylamine in dichloromethane/ethanol. Synthesis of amides has been done using both conventional as well as microwave method. The yield of amides synthesized by microwave method was more as compared to conventional method and also took lesser time for the completion of reaction. The increase in yield of synthesized products fluctuated between 8–36%. Purity of the synthesized compounds was checked by thin layer chromatography technique. Physical data (yield, melting point, state and color) of the synthesized products was determined.

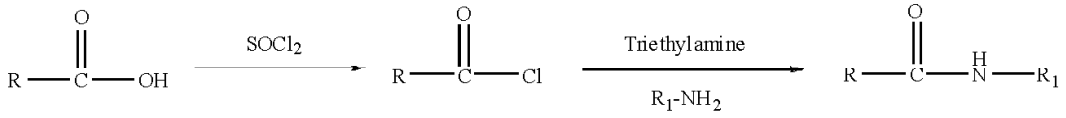
Keywords: Amides, 4-aminophenazone, 2-aminopyridine, microwave irradiation method.

Introduction

Heterocyclic chemistry has constituted largest areas of research in the field of synthetic organic chemistry. Heterocyclic compounds contain electron-rich nitrogen or oxygen atom along with carbon atom in a ring and plays an important role in wide range of biological activities. These have been frequently found as a key structural unit in many synthetic pharmaceuticals and agrochemicals. Among the nitrogen-containing heterocyclic compounds, amides are the most important due to their vast applications in synthesis and medicinal chemistry[1]. Amide functionality is one of the most essential chemical building blocks found in nature. It is found in naturally-occurring products such as peptides and proteins[2]. They exhibit a wide range of pharmacological activities such as anti-inflammatory[3], antibacterial[4], antiparasitic[5], anticancer[6], antiviral and anti-hypoglycaemic effects[7]. There are a multitude of well-known methods for efficient synthesis of amides. Carboxylic acids, esters, aldehydes, alcohols, nitriles and oximes can be used as a starting material for the synthesis of different substituted amides[8]. Carboxylic acids and amines in the presence of base can react together to form salts and further strong heating of these salts can lead to amide formation[1]. Requiring high temperature, tedious procedure and harsh reaction conditions, have limited these methods. Reaction of activated carboxylic acids with amines proved to be the most efficient method for the synthesis of amides[9]. For this purpose, different carboxamides were prepared by the reaction of carboxylic acid derivatives with aromatic and aliphatic amines using $SOCl_2$[10], $POCl_3$[11], PCl_5 or SO_2Cl_2[12]. Due to the vast applications of amides, finding new, efficient and practical methods for their synthesis are desirable. Within the last decade, the application of microwave technology in organic chemistry has been explored extensively. Amides can be synthesized by direct amidation of amine-carboxylic acid mixtures by microwave irradiation. Now a days, the use of microwave irradiation has simplified and improved the classic organic reactions and has become a very popular method because it may enhance the regio- and stereo-selectivity of reactions and lead to a remarkable decrease in reaction time, increased yields, easier work up matching with green chemistry protocols. Keeping in view the above utility of amides and replacement of cumbersome procedures with eco-friendly and less time consuming methods of synthesis, the present study was carried out in comparative mode.

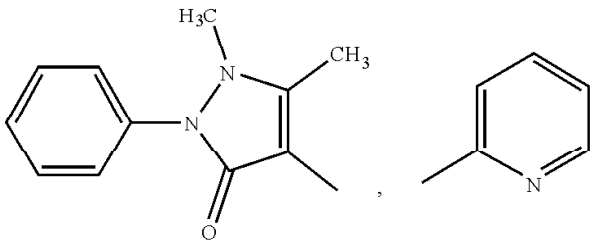
Results and discussion

Different heterocyclic amides (**1**-**10**) were synthesized according to the Schemes 1 and 2. For this purpose different



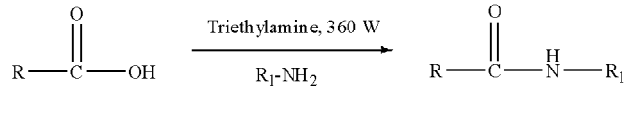
R = $-CH_2OC_6H_5$, $-CH_2C_6H_4Cl$, $-CCl_3$, $-CH_2Cl$ and $-CH_3$

R_1 =

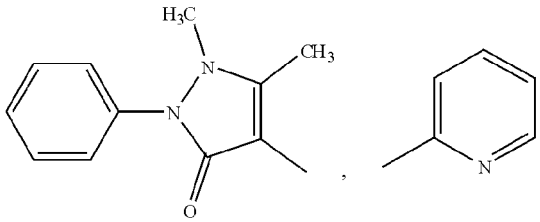


1 R = $-CH_2OC_6H_5$, R_1 = $-C_{12}H_{14}N_2O$
2 R = $-CH_2OC_6H_5$, R_1 = $-C_6H_7N$
3 R = $-CH_2C_6H_4Cl$, R_1 = $-C_{12}H_{14}N_2O$
4 R = $-CH_2C_6H_4Cl$, R_1 = $-C_6H_7N$
5 R = $-CCl_3$, R_1 = $-C_{12}H_{14}N_2O$
6 R = $-CCl_3$, R_1 = $-C_6H_7N$
7 R = $-CH_2Cl$, R_1 = $-C_{12}H_{14}N_2O$
8 R = $-CH_2Cl$, R_1 = $-C_6H_7N$
9 R = $-CH_3$, R_1 = $-C_{12}H_{14}N_2O$
10 R = $-CH_3$, R_1 = $-C_6H_7N$

Scheme 1. Synthesis of different substituted amides by conventional method.



R_1 =



1 R = $-CH_2OC_6H_5$, R_1 = $-C_{12}H_{14}N_2O$
2 R = $-CH_2OC_6H_5$, R_1 = $-C_6H_7N$
3 R = $-CH_2C_6H_4Cl$, R_1 = $-C_{12}H_{14}N_2O$
4 R = $-CH_2C_6H_4Cl$, R_1 = $-C_6H_7N$
5 R = $-CCl_3$, R_1 = $-C_{12}H_{14}N_2O$
6 R = $-CCl_3$, R_1 = $-C_6H_7N$
7 R = $-CH_2Cl$, R_1 = $-C_{12}H_{14}N_2O$
8 R = $-CH_2Cl$, R_1 = $-C_6H_7N$
9 R = $-CH_3$, R_1 = $-C_{12}H_{14}N_2O$
10 R = $-CH_3$, R_1 = $-C_6H_7N$

Scheme 2. Synthesis of different substituted amides by microwave irradiation method.

substituted acids namely phenoxyacetic acid, chlorophenylacetic acid, chloroacetic acid, trichloroacetic acid and propanoic acid were reacted with different substituted heterocyclic amines i.e. 4-aminophenazone and 2-aminopyridine. These were synthesized by both conventional and microwave irradiation method. In microwave irradiation method, amides were synthesized by direct condensation of different acids with different amines in the presence of catalytic amount of triethylamine whereas in case of conventional method the acids were firstly converted into their active form i.e. acid chlorides using thionyl chloride and then reacted with different substituted amines viz. 4-aminophenazone and 2-aminopyridine. Characterization of synthesized compounds was done by IR and ^{1}H NMR spectroscopic techniques. Table 1 shows the physical parameters, comparison of yield and time for synthesized compounds. The yield of different amides (**1**-**10**) ranged from 50–72% with conventional method while it was 75–87% with microwave irradiation method. Therefore, microwave assisted method gave more yield as compared to conventional method. The highest increase in yield was 36% in case of compound **2** having pyridine moiety with no substitution on phenyl ring of the acid. Compound **8** was synthesized in highest yield i.e. 72% with conventional

Table 1. Physical parameters of different substituted heterocyclic amides

Compd.	Molecular formula	Molecular Weight (g)	Time taken in MW method[a] (min)	Yield (%)		R_f value
				Conventional method	MW method	
1	$C_{19}H_{19}N_3O_3$	337	9	67	80	0.63
2	$C_{13}H_{12}N_2O_2$	228	34	50	86	0.61
3	$C_{19}H_{18}N_3O_2Cl$	355	39	71	87	0.65
4	$C_{13}H_{11}N_2OCl$	246	42	55	83	0.60
5	$C_{13}H_{14}N_3O_2Cl$	279	30	55	85	0.62
6	$C_7H_7N_2OCl$	170	10	45	75	0.68
7	$C_{13}H_{12}N_3O_2Cl_3$	348	16	59	82	0.65
8	$C_7H_5N_2OCl_3$	244	18	72	80	0.60
9	$C_{14}H_{17}N_3O_2$	259	36	62	80	0.63
10	$C_8H_{10}N_2O$	150	33	65	83	0.65
Range	–	–	9–42	50–72	75–87	–

[a]The time taken for the synthesis of amides by conventional method was 13 h.

method whereas it was highest for compound **3** i.e. 87% with microwave irradiation method. Time taken to complete the reaction was 13 h with conventional method whereas it ranged from 9–42 min with microwave irradiation method. Minimum time was taken by compound **1** to complete the reaction (9 min). Synthesis of organic compounds via conventional method took longer reaction time. So microwave assisted synthesis could be preferred over conventional as it is eco-friendly, solvent free, less tedious procedure, cost effective, better atom economy, cleaner and resulted in enhanced rate of reaction and increased yields. Color, state and melting point of all the different substituted heterocyclic amides by both methods were same. Sharma *et al.* (2015) has also reported the similar comparsion of yield and time for the synthesis of amides.

IR data:

IR spectra of different substituted heterocyclic amides showed a broad band due to N-H stretching in the range of 3188–3424 cm^{-1} and a sharp bands at 1638–1695 cm^{-1} and 1408–1470 cm^{-1} due to C=O and C=N stretching respectively. These prominent bands in IR confirmed the formation of amide linkage.

^{1}H NMR data:

Due to -NH proton of secondary amide, a broad singlet was observed near δ value 8.31–9.26 ppm hence confirmed the formation of -CONH- linkage. In case of amides, -NH proton of amide linkage was most deshielded and therefore observed at higher δ value. The broad singlet due to -NH of proton of amide was not observed when ^{1}H NMR was taken in D_2O. Absence of this broad singlet also confirmed the formation of amide bond.

Conclusion

Different substituted heterocyclic amides (**1**-**10**) were synthesized by reacting different substituted carboxylic acids with different substituted amines in the presence of catalytic amount of triethylamine in dichloromethane/ethanol. These were synthesized by both conventional as well as microwave irradiation method. The reaction that takes hours or days by conventional method gets completed in minutes in microwave irradiation method. Therefore, microwave assisted synthesis of amides was preferred over conventional method for synthesis of amides. Also, microwave irradiation method gave more yield[13].

Experimental

General:

The melting points of different substituted heterocyclic amides were determined in open capillaries and are uncorrected. The purity of compounds was checked by Thin Layer Chromatography and the visualization was done in iodine chamber. Fourier transform infrared spectra and nuclear magnetic resonance spectra were got scanned from Sophisticated Analytical Instrumentation Facility (SAIF), Central Instrument Laboratory (CIL), Panjab University, Chandigarh.

FT-IR spectra recorded on Perkin-Elmer FT-IR spectrophotometer with λ_{max} in cm^{-1}. ^1H NMR spectra were recorded on Bruker Avance II 400 MHz spectrophotometer using TMS as internal standard. The chemical shifts were expressed in δ (ppm) values and the abbreviations used for ^1H NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. C H N analysis of different substituted heterocyclic amides was recorded on Vario E L III Elementor CHNS analyser.

General scheme for synthesis of amides using conventional method (***1***-***10***):

To a cold solution of different substituted acid (0.01 mol) in dry dichloromethane (50 mL), thionyl chloride (0.01 mol) was added slowly at 0°C, then the solution was stirred for 30 min at room temperature and refluxed at 40°C for 1 h. The solution was then allowed to cool at room temperature and the resulting solution was stirred in ice-cold water and different substituted amines (0.01 mol) were added dropwise. Triethylamine (0.01 mol) was added dropwise from the dropping funnel over 15 min after the addition of amine. The reaction mixture was brought to ambient temperature and stirred further for 2 h. The resulting solution was partitioned between dichloromethane and 2.7 *N* HCl (50 mL) and the two layers were separated. The aqueous layer was again extracted with dichloromethane (50 mL). Excess of dichloromethane was removed by distillation and saturated solution of aqueous sodium bicarbonate was added. The resulting mixture was transferred to a 500 mL separatory funnel. The two layers were separated and the aqueous layer was again extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate (anhydrous) and concentrated on rotary vacuum evaporator. The solid product was recrystallized from ethanol. The purity of the synthesized amides was checked by Thin Layer Chromatography.

General scheme for synthesis of amides using microwave irradiation method (***1***-***10***):

A mixture of different substituted acids (0.01 mol) and different amines (0.01 mol) in ethanol was taken in a beaker. Five drops of triethylamine were added to it. The mixture was irradiated in microwave oven at 360 W. The progress of reaction was monitored by thin layer chromatography at an interval of one minute. After the completion of reaction, the resulting solid was filtered off and the product was recrystallized from ethanol.

Characterization data:

These compounds were characterized by IR and ^1H NMR spectroscopic technique and spectral data was reported by Kaur *et al.* (2017)[14].

*N-(2,3-Dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-4-yl)-2-phenoxyacetamide (**1**):* Brown crystals; yield 67% (conventional); 80% (microwave); m.p. 102–104°C; IR (KBr, cm^{-1}): 3424 (N-H str.), 1647 (C=O str.), 1429 (C-N str.); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.31 (s, 1H, N**H**), 6.94–7.47 (m, 10H, Ar-**H**), 4.62 (s, 2H, C$\mathbf{H}_2$), 3.08 (s, 3H, C$\mathbf{H}_3$), 2.25 (s, 3H, C$\mathbf{H}_3$). Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.61; H, 5.65; N, 12.47. Found: C, 67.64; H, 5.68; N, 12.46%.

2-Phenoxy-N-(pyridin-2-yl)acetamide (**2**): White crystals; yield 50% (conventional); 86% (microwave); m.p. 60–62°C; IR (KBr, cm^{-1}): 3397 (N-H str.), 1695 (C=O str.), 1432 (C-N str.); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.41 (s, 1H, N**H**), 6.90–8.25 (m, 9H, Ar-**H**), 4.56 (s, 2H, C$\mathbf{H}_2$). Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.32; N, 12.28. Found: C, 68.41; H, 5.30; N, 12.27%.

*2-(4-Chlorophenyl)-N-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-4-yl)acetamide (**3**):* Brown crystals, yield 71% (conventional); 87% (microwave); m.p. 170–172°C; IR (KBr, cm^{-1}): 3242 (N-H str.), 1651 (C=O str.), 1411 (C-N str.); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.08 (s, 1H, N**H**), 7.20–7.44 (m, 10H, Ar-**H**), 3.54 (s, 2H, C$\mathbf{H}_2$), 3.06 (s, 3H, C$\mathbf{H}_3$), 2.14 (s, 3H, C$\mathbf{H}_3$). Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.10; H, 5.13; N, 11.80. Found: C, 64.13; H, 5.10; N, 11.82%.

2-(4-Chlorophenyl)-N-(pyridin-2-yl)acetamide (**4**): Brown crystals; yield 55% (conventional); 83% (microwave); m.p. 150–152°C; IR (KBr, cm^{-1}): 3247 (N-H str.), 1645 (C=O str.), 1408 (C-N str.); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.11 (s, 1H, N**H**), 7.20–7.32 (m, 8H, Ar-**H**), 3.63 (s, 2H, C$\mathbf{H}_2$). Anal. Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.30; H, 4.50; N, 11.38. Found: C, 63.29; H, 4.49; N, 11.36%.

*2-Chloro-N-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-4-yl)acetamide (**5**):* White crystals; yield 55% (conventional); 85% (microwave); m.p. 154–156°C; IR (KBr, cm^{-1}): 3391 (N-H str.), 1650 (C=O str.), 1470 (C-N str.); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.41 (s, 1H, N**H**), 7.20–7.49 (m, 5H, Ar-**H**), 4.12 (s, 2H, C$\mathbf{H}_2$), 3.11 (s, 3H, C$\mathbf{H}_3$), 2.25 (s, 3H, C$\mathbf{H}_3$). Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.81; H, 5.06; N, 15.03. Found: C, 55.83; H, 5.04; N, 15.02%.

*2-Chloro-N-(pyridin-2-yl)acetamide (**6**):* Light pink crys-

tals; yield 45% (conventional); 75% (microwave); m.p. 172–174°C; IR (KBr, cm^{-1}): 3389 (N-H str.), 1653 (C=O str.), 1468 (C-N str.); ^{1}H NMR (D_2O, 400 MHz, δ ppm): 6.79–7.77 (m, 4H, Ar-**H**), 4.66 (s, 2H, C**H**$_2$). Anal. Calcd. for $C_7H_7ClN_2O$: C, 49.30; H, 4.12; N, 16.43. Found: C, 49.28; H, 4.14; N, 16.42%.

*2,2,2-Trichloro-N-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-yl)acetamide (**7**):* Orange crystals, yield 59% (conventional); 82% (microwave), m.p. 78–80°C; IR (KBr, cm^{-1}): 3188 (N-H str.), 1638 (C=O str.), 1436 (C-N str.); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.49 (s, 1H, N**H**), 7.28–7.49 (m, 10H, Ar-**H**), 3.29 (s, 3H, C**H**$_3$), 2.53 (s, 3H, C**H**$_3$). Anal. Calcd. for $C_{13}H_{12}Cl_3N_3O_2$: C, 44.78; H, 3.49; N, 12.03. Found : C, 44.79; H, 3.47; N, 12.05%.

*2,2,2-Trichloro-N-(pyridin-2-yl)acetamide (**8**):* White crystals; yield 72% (conventional); 80% (microwave); m.p. 30–32°C; IR (KBr, cm^{-1}): 3200 (N-H str.), 1640 (C=O str.), 1440 (C-N str.); ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.80 (s, 1H, N**H**), 7.30–7.58 (m, 8H, Ar-**H**). Anal. Calcd. for $C_7H_5Cl_3N_2O$: C, 34.40; H, 4.10; N, 11.47. Found: C, 34.38; H, 4.12; N, 11.46%.

*N-(2,3-Dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-4-yl)propionamide (**9**):* White crystals; yield 62% (conventional); 80% (microwave); m.p. 174–176°C; IR (KBr, cm^{-1}): 3398 (N-H str.), 1642 (C=O str.), 1426 (C-N str.); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.53 (s, 1H, N**H**), 7.24–7.47 (m, 5H, Ar-**H**), 3.07 (s, 3H, C**H**$_3$), 2.28–2.34 (q, *J* 7.60, 2H, C**H**$_2$), 2.22 (s, 3H, C**H**$_3$), 1.12–1.16 (t, *J* 7.56, 3H, C**H**$_3$). Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.87; H, 6.60; N, 16.22. Found: C, 64.85; H, 6.61; N, 16.20%.

*N-(pyridin-2-yl)propionamide (**10**):* White colored semi solid product; yield 65% (conventional); 83% (microwave); IR (KBr, cm^{-1}): 3188 (N-H str.), 1638 (C=O str.), 1429 (C-N str.); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.26 (s, 1H, N**H**), 6.52–7.89 (m, 8H, Ar-**H**), 2.33–2.38 (q, *J* 7.56, 2H, C**H**$_2$), 1.14–1.18 (t, *J* 8.00, 3H, C**H**$_3$). Anal. Calcd. for $C_8H_{10}N_2O$: C, 64.03; H, 6.70; N, 18.63. Found: C, 63.99; H, 6.71; N, 18.65%.

Acknowledgement

The authors are thankful to Punjab University, Chandigarh for providing IR and ^{1}H NMR spectral data of synthesized compounds.

References

1. Valeur and M. Bradley, *J. Indian Chem. Soc.,* 2009, **87**, 606.
2. V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471.
3. P. M. Chandrika, T. Yakaiah, A. R. R. Rao, N. C. N. Reddy, V. Sridhar and J. V. Rao, *Eur. J. Med. Chem.,* 2007, **43**, 846.
4. D. Kohli, S. R. Hashim, S. Vishal, M. Sharma and A. K. Singh, *Int. J. Pharm. Pharm. Sci.,* 2009, **1**, 163.
5. S. K. Tipparaju, S. P. Muench, E. J. Mui, S. N. Ruzheinikov, J. Z. Lu, S. L. Hutson, M. J. Kirisits, S. T. Prigge, C. W. Roberts, F. L. Henriquez, A. P. Kozikowski, D. W. Rice and R. L. McLeod, *J. Med. Chem.,* 2010, **53**, 6287.
6. A. Sun, A. Prussia, W. Zhan, E. E. Murray, J. Doyle, L. T. Cheng, J. J. Yoon, E. V. Radchenko, V. A. Palyulin, R. W. Compans, D. C. Liotta, R. K. Plemper and J. P. Snyder, *J. Med. Chem.,* 2006, **49**, 5080.
7. A. P. G. Nikalje, D. Deshpande and H. D. Une, *Eur. J. Exp. Biol.,* 2012, **2**, 343.
8. C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405.
9. L. J. Gooben, D. M. Ohlmann and P. P. Lange *Synthesis*, 2009, **24**, 160.
10. A. S. Kooner, S. Sharma and P. Sharma, *J. Indian Chem. Soc.*, 2014, **91**, 293.
11. S. Sharma, J. Kaur, T. Bansal and J. Gaba, *Asian J. Res. Chem.,* 2013, **6**, 1110.
12. V. Ulgar, I. Maya, J. Fuentes and J. G. Fernandez-Bolanos, *Tetrahedron,* 2002, **58**, 7967.
13. S. Sharma, T. Bansal and J. Gaba, *Indian J. Ecol.*, 2015, **42**, 335.
14. P. Kaur, S. Sharma, S. Joshi and N. Aggarwal, *Indian J. Heterocycl. Chem*., 2017, **27**, 129.