Asian Journal of Chemistry; Vol. 23, No. 8 (2011), 3683-3685

ASIAN JOURNAL OF CHEMISTRY

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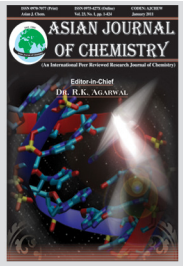

Microwave Synthesis of New Pyrazolo[3,4-d]pyrimidin-4-ones in Solvent-Free Condition

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(*Received*: 13 December 2010; *Accepted*: 27 April 2011) AJC-9877

An efficient method for the synthesis of new pyrazolo[3,4-*d*]pyrimidin-4-ones through heterocyclization reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides with aroyl halides under microwave irradiation in solvent-free condition is described. In comparison with classical conditions the reactions are faster and the yields are higher under microwave irradiation.

Key Words: Pyrazolo[3,4-*d*]pyrimidin-4-ones, Microwave irradiation, Aroyl halides, Solvent-free condition.

INTRODUCTION

Thieno[2,3-d]pyrimidines are a class of fused heterocycles exhibit a number of biological activities. Antimicrobial[1-3], fungicidal[4,5], herbicidal[6-8] and vasodilatory[9], activities have been reported for some of the derivatives. Also, a number of these compounds are known to inhibit enzymes such as Bruton's tyrosine kinase[10], phosphodiesterase[11], adenosine deaminase[12] and plasmodium falciparum PfPK7 protein kinase[13].

The routes to thieno[2,3-d]pyrimidines mainly involve cyclocondensation of suitably functionalized pyrimidines or pyrazoles with different electrophiles and nucleophiles such as isocyanates[14], methylhydrazine in combination with aldehydes[15], thiophosgene in combination with amines[16] and allylamine, ammonium and ethylenediamine[17]. In spite of much work on the synthesis of these compounds, a closer look at the literature disclosed that cyclocondensation of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides (**1a** and **1b**) with aroyl halides (**2a-e**) for the synthesis of 1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones (**3a-f**) using microwave irradiation has not been reported.

In recent years microwave assisted reactions are of great interest because of simplicity in operation and enhanced reaction rates. Thus, microwave irradiation which has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds under solvent free conditions is used to enhance the rates of classical organic reactions[18-23].

In pursuing these studies and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities[24-34] and in continuation of our previous works using of microwave irradiation in organic reactions[35-37], in this paper we wish to report a convenient synthesis of new 1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones **3a-f** in synthetically useful yields by reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides (**1a** and **1b**) with aroyl halides (**2a-e**) under conventional heating and microwave irradiation in solvent-free conditions (**Scheme-I**).

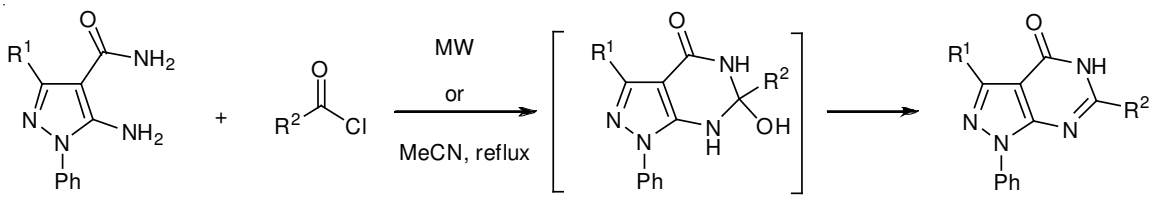
EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument.

General procedure for the synthesis of 1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-ones (3a-f)

Method A: A mixture of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides (**1a** or **1b**) (2 mmol) and aroyl halides (**2a-e**) (2.5 mmol) was subjected to microwave irradiation at 1000W for the indicated time (Table-1). After the completion of the reaction, the crude product was washed with hot *n*-hexane and recrystallized from ethanol to give compounds **3a-f** in 87-94 % yields (Table-1).

Method B: A mixture of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides (**1a** or **1b**) (2 mmol) and aroyl halides (**2a-e**) (2.2 mmol) in acetonitrile (10 mL) was heated under reflux for 300-480 min. After the completion of the reaction, the solvent was evaporated *in vacuo*. The crude product was collected, washed with hot *n*-hexane and recrystallized from ethanol to give compounds **3a-f** in 73-86 % yields (Table-1).



1a: R^1 = H
1b: R^1 = Me
2a: R^2 = Me
2b: R^2 = 4-BrC_6H_4
2c: R^2 = 3-ClC_6H_4
2d: R^2 = 4-ClC_6H_4
2e: R^2 = 3-$O_2NC_6H_4$

3a: R^1 = H, R^2 = 4-ClC_6H_4
3b: R^1 = Me, R^2 = Me
3c: R^1 = Me, R^2 = 4-BrC_6H_4
3d: R^1 = Me, R^2 = 3-ClC_6H_4
3e: R^1 = Me, R^2 = 4-ClC_6H_4
3f: R^1 = Me, R^2 = 3-$O_2NC_6H_4$

Scheme-I: Synthesis of 1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-ones

TABLE-1
COMPARISON OF TIME AND YIELDS ON THE FORMATION OF COMPOUNDS **3a-f** USING MICROWAVE IRRADIATION AND CONVENTIONAL HEATING

Entry	R^1	R^2	Products	Conventional heating		Microwave irradiation		m.p. (ºC)	t_c/t_{mw}
				Time (min) t_c	Yield (%)[a]	Time (min) t_{mw}	Yield (%)[a]		
1	H	4-ClC_6H_4	**3a**	420	74	6	93	176-178	70.0
2	Me	Me	**3b**	300	73	4	87	296-298	75.0
3	Me	4-BrC_6H_4	**3c**	360	79	4	91	201-203	90.0
4	Me	3-ClC_6H_4	**3d**	480	77	6	88	178-180	80.0
5	Me	4-ClC_6H_4	**3e**	360	85	4	94	179-181	90.0
6	Me	3-$O_2NC_6H_4$	**3f**	360	86	6	93	183-185	90.0

[a]Isolated yields.

Spectral data of compounds 3a-f

6-(4-Chlorophenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (3a): FTIR (KBr, ν_{max}, cm^{-1}): 3197 (NH), 1684 (C=O). ^1H NMR ($CDCl_3$): δ 6.90-7.50 (m, 9H, arom-H), 7.67 (s, 1H, CH), 11.74 (s. br., 1H, NH). MS: m/z 322 (M^+), 324 (M^+ + 2).

3,6-Dimethyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (3b): FTIR (KBr, ν_{max}, cm^{-1}): 3224 (NH), 1689 (C=O). ^1H NMR (DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.25-8.10 (m, 5H, arom-H), 12.20 (s. br., 1H, NH). MS: m/z 240 (M^+).

6-(4-Bromophenyl)-3-methyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (3c): FTIR (KBr, ν_{max}, cm^{-1}): 3158 (NH), 1691 (C=O). ^1H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3), 7.35-8.05 (m, 9H, arom-H), 11.48 (s. br., 1H, NH). MS: m/z 380 (M^+), 382 (M^+ + 2).

6-(3-Chlorophenyl)-3-methyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (3d): FTIR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1690 (C=O). ^1H NMR ($CDCl_3$) δ: 2.40 (s, 3H, CH_3), 7.20-7.80 (m, 9H, arom-H), 8.50 (s. br., 1H, NH). MS: m/z 336 (M^+), 338 (M^+ + 2).

6-(4-Chlorophenyl)-3-methyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (3e): FTIR (KBr, ν_{max}, cm^{-1}): 3145 (NH), 1680 (C=O). ^1H NMR ($CDCl_3$) δ: 2.51 (s, 3H, CH_3), 7.35-8.10 (m, 9H, arom-H), 10.73 (s. br., 1H, NH). MS: m/z 336 (M^+), 338 (M^+ + 2).

3-Methyl-6-(3-nitrophenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (3f): FT IR (KBr, ν_{max}, cm^{-1}): 3191 (NH), 1684 (C=O). ^1H NMR ($CDCl_3$) δ: 2.55 (s, 3H, CH_3), 7.40-8.95 (m, 9H, arom-H), 11.85 (s. br., 1H, NH). MS: m/z 347 (M^+).

RESULTS AND DISCUSSION

The starting materials 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides (**1a** and **1b**) were prepared according to the literature method[38]. Firstly, treatment of these compounds with aroyl halides (**2a-e**) using microwave irradiation in solvent-free conditions were explored. Thus, the reactants were mixed together and then irradiated at 1000W for the indicated time, using a domestic microwave oven Model LG MS-543XD, to give 1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-ones (**3a-f**) in high yields. The formation of the products **3a-f** was assumed to proceed *via* intermediates I. However, under these conditions, attempts to isolate the intermediates I failed when we carefully monitored the reactions.

The structure of the products **3a-f** were established from their spectral data. For example, the IR spectrum of **3b** did not exhibit the stretching vibration bands at 3185, 3302, 3357 and 3414 cm^{-1} due to precursor **1b** but showed a sharp band at 3224 cm^{-1} for NH vibration. The ^1H NMR spectrum in DMSO-d_6 showed the disappearance of two broad 2H signals belonging to NH_2 moieties of compound **1b** and the appearance of a

singlet broad 1H (NH) signal at δ 12.20 ppm which was removed on deuteration along with a multiplet at 7.25-8.10 ppm due to 5 aromatic protons as well as two singlets at 2.36 and 2.47 ppm for methyl groups. Also, the molecular ion of compound **3b** was observed at m/z 240 (M^+), corresponding to the molecular formula $C_{13}H_{12}N_4O$.

For comparison, a classical method for the preparation of compounds **3a-f** was also investigated by refluxing **1a** or **1b** with **2a-e** in acetonitrile for the indicated time (Table-1). It is obvious that the classical approach for the synthesis of compounds **3a-f** is a tedious method affording a relatively lower yield with much longer reaction time.

Conclusion

A microwave promoted synthesis of 1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones in solvent-free conditions is reported. A classical method for the preparation of these compounds was also investigated. In comparison, the reactions carried out with the assistance of microwave technique are faster and the yields are higher than conventional method.

ACKNOWLEDGEMENTS

The authors are thankful to Islamic Azad University, Mashhad Branch for financial support.

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