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A rapid synthesis of isoxazolo[5,4-d]pyrimidin-4(5H)-ones under microwave irradiation with solid acid catalysis in solvent-free conditions

A. Davoodnia *, M. Roshani, S.H. Malaeke, M. Bakavoli

Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad Branch, Mashhad 91735-413, Iran

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Abstract

A rapid and efficient method for the synthesis of isoxazolo[5,4-d]pyrimidin-4(5H)-ones has been developed through cyclocondensation of 5-aminoisoxazole-4-carboxamides with orthoesters under conventional heating and solvent-free microwave irradiation with solid acid catalysis. In comparison, the reactions are faster and the yields are higher under microwave irradiation.

Keywords: Isoxazolo[5,4-d]pyrimidin-4(5H)-ones; Orthoesters; Microwave irradiation; Conventional heating

The isoxazolo[5,4-d]pyrimidines have received considerable attention due to their pharmacological applications as antibacterial, antifungal, antimicrobial, antiinflammatory and anticancer agents [1–7]. Also, some isoxazolo[5,4-d]pyrimidines are active as enzyme and growth factor TGF inhibitors [8,9]. The synthesis of this heterocyclic ring system from cyclocondensation of suitably functionalized isoxazoles with different electrophiles has already been reported [10–14]. A literature survey disclosed that microwave promoted solvent-free cyclization of 5-aminoisoxazole-4-carboxamides with orthoesters in the presence of solid acidic catalyst has not been reported.

The application of microwave irradiation to organic synthesis for conducting reactions at accelerated rates is an emerging technique. In fact, in recent years, the use of microwaves has become popular among chemists both as a means to improve classical organic reactions and promote new reactions [15–19]. Furthermore, the use of solid acidic catalyst such as acidic silica gel has attracted considerable attention in different area of organic synthesis which can largely simplify the synthetic step and operation under environmentally benign conditions [20,21].

Prompted by these findings and due to our interest in utilisation of microwave irradiation for the synthesis of heterocyclic compounds [22–25], in this paper we wish to report a rapid and efficient approach for the synthesis of isoxazolo[5,4-d]pyrimidin-4(5H)-ones **3a–d** through cyclocondensation of 5-aminoisoxazole-4-carboxamides **1a–b** and orthoesters **2a–b** under conventional heating and microwave irradiation on the surface of silica gel impregnated with sulfuric acid (Scheme 1).

* Corresponding author.
E-mail address: adavoodnia@yahoo.com (A. Davoodnia).

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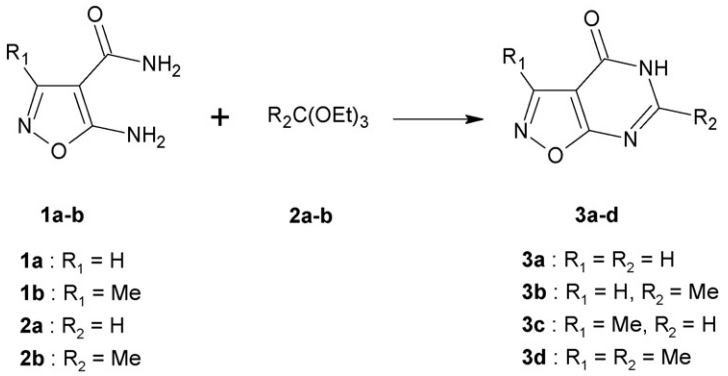

Scheme 1.

The starting material **1a–b** were prepared according to the literature method [10]. Firstly, treatment of these compounds with orthoesters **2a–b** using microwave irradiation in presence and absence of acidic silica gel under solvent-free conditions were explored. Thus, the reactants were mixed together and then irradiated at 700 W for the indicated time, using a domestic microwave oven Model LG MS-543XD to give isoxazolo[5,4-d]pyrimidin-4(5H)-ones **3a–d**. The structure of new products (**3a** and **b**) were established from their spectral and microanalytical data and for known compounds (**3c** and **d**) by comparison with authentic samples. For example, the ^{1}H NMR spectrum of **3a** did not show the two NH_2 signals at δ 7.13 and 7.52 ppm and a sharp 1H signal at δ 8.54 belonging to the isoxazole ring of the precursor **1a**, but instead showed a broad 1H signal at δ 7.05 ppm for NH group and two singlet at δ 8.79 and 9.20 ppm for the aromatic rings indicating the formation of the bicyclic compound **3a**. The IR spectrum showed a band at 3170 cm^{-1} for NH absorption and a band at 1695 cm^{-1} for C=O group. The MS of **3a** showed a molecular ion peak at *m/z* 137 (M^+) corresponding to the molecular formula $C_5H_3N_3O_2$. Also this compound gave satisfactory microanalytical data (Section 1).

For comparison, a classical method for the preparation of the isoxazolo[5,4-d]pyrimidin-4(5H)-ones **3a–d** was also investigated by refluxing compounds **1a–b** with **2a–b** in presence and absence of acidic silica gel in ethanol for the indicated time (Table 1). It was very obvious that the classical approach for the synthesis of isoxazolo[5,4-d]pyrimidin-4(5H)-ones is a tedious method affording a relatively lower yield of **3a–d** with much longer reaction time. Furthermore, it can be concluded that the reactions in the presence of acidic silica gel are faster and the yields are higher than its absence.

In conclusion we have reported a microwave assisted synthesis of isoxazolo[5,4-d]pyrimidin-4(5H)-ones using acidic silica gel as an inexpensive catalyst. The notable features of this procedure are mild and solvent-free reaction conditions, improved yields and enhanced reaction rates.

Table 1
Comparison of time and yields on the formation of compounds **3a–d** using microwave and conventional heating

Entry	Conventional heating				Microwave irradiation				mp (°C)	T_{c2}/T_{mw2}
	Without catalyst		Using acidic silica gel		Without catalyst		Using acidic silica gel			
	Time (min) T_{c1}	Yield (%)	Time (min) T_{c2}	Yield (%)	Time (min) T_{mw1}	Yield (%)	Time (min) T_{mw2}	Yield (%)		
3a	300	57	120	66	7	67	4	71	231–233	30
3b	360	56	170	63	9	64	6	66	208–211	28
3c	330	61	130	63	8	72	5	82	219–221 [Lit. [12] 217–219]	26
3d	380	55	180	67	10	61	6	70	266–268 [Lit. [12] 268–269]	30