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Microwave-Assisted Synthesis of 2-amino-4-substituted Phenyl-thiazole

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The reaction time needed to synthesize substituted 2-amino-4-phenyl-thiazole was substantially reduced from hours to minutes by means of microwave irradiation. Microwave assisted techniques have many advantages, *i.e.*, very rapid reactions, low energy consumption and safe operation, high yield and less time.

Key Words: 2-Amino-4-substituted phenyl-thiazole, Microwave irradiation.

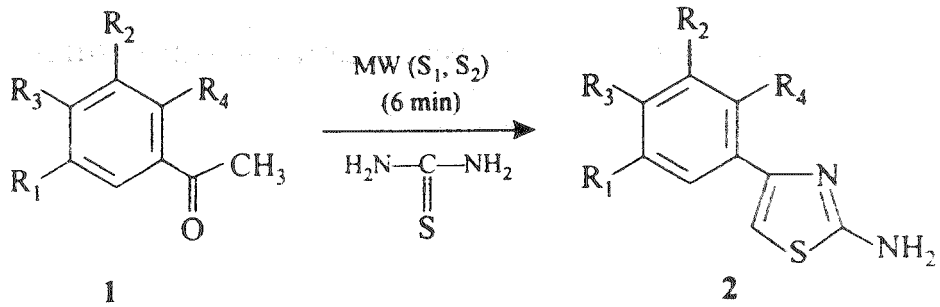
INTRODUCTION

The chemistry of 2-amino-thiazoles has been reviewed[1] and the importance of such heterocycles and derivatives in medicinal chemistry is recognized[2]. In view of the wide range of biological activity present in substituted amino thiazoles[1, 2], many workers[3–5, 14] have synthesized 2-amino-4-aryl-thiazole. A general conventional method for the synthesis of 2-amino-4-aryl-thiazoles is the condensation of various substituted ketones[5] with thiourea in I_2/Br_2-ethanol as solvent under reflux for 12–14 h.

In recent years, microwave irradiation using commercial domestic ovens has been rapidly increased for optimization and acceleration of organic synthesis under solvent free conditions[6–11]. Such a synthesis of heterocycles[12] has been reported for a variety of reactions and more recently for synthesis of polymers[13], because of advantages such as reduction in reaction time, improved energy utilization, potential for lower processing temperature and improved product uniformity.

Here, we report herein the synthesis of several 2-amino-4-aryl-thiazoles in minimum solvent and minimum time under microwave irradiation. (**Scheme-1**, Table-1).

In conventional method, for the synthesis of several 2-amino-4-aryl-thiazoles, the molar ratio of ketone and thiourea (1 : 10) was taken in I_2/ethanol and refluxed for 12 h for effective condensation. In contrast, under microwave irradiation, the reactions are completed within 6–8 min in equimolar proportion and almost in all the cases afford the product in high yields. The products were characterized on the basis of their m.p., m.m.p.,TLC, IR and ^{1}H NMR.



1 2

Scheme-1

EXPERIMENTAL

All the synthesized compounds were purified by recrystallization by using ethanol. The melting points were recorded on melting point apparatus in open capillaries and are uncorrected. All melting points were compared with the authentic samples3 and are found to be the same. The purity of compounds was checked by TLC. All reactions were carried out in a commercially available IFB domestic microwave oven having a maximum power output of 110 W operating at 2450 Hz. IR spectra were obtained on a Perkin-Elmer 1800 spectrophotometer using KBr discs. 1H NMR spectra were recorded using AC Bruker 300 F.

General Procedure

Synthesis of 2-amino-4-(2-hydroxy-5-methyl phenyl) thiazole (2a)

Method A (Conventional)[3]: 2-Hydroxy-5-methyl acetophenone (**1a**) (0.01 mol, 1.5 g) and thiourea (0.1 mol, 7.6 g) were dissolved in 25 mL of rectified spirit. To this 0.01 mol I_2/Br_2 was added. The contents were refluxed on a water bath for 12 h. The reaction mixture was diluted and excess of alcohol was distilled off. The solution was filtered. On addtion of NH_4OH to the filtrate, thiazole (**2a**) was obtained. It was filtered, washed and dried followed by recrystallization from ethanol. Yield 58%, m.p. 160°C.

Method B (Microwave Irradiation): 2-Hydroxy-5-methyl acetophenone (1a) (0.01 mol, 1.5 g) and thiourea (0.01 mol, 0.76 g) were dissolved in 10 mL of rectified spirit. To this 0.01 mol I2/Br2 was added. The contents were thoroughly mixed. The reaction mixture was subjected to microwave irradiation in a commercially available IFB domestic microwave oven having a maximum power output of 110 W operating at 2450 Hz intermittently at 30 s intervals for 6–8 min. On completion of reaction, as monitored by TLC, the product was diluted with water. The reaction mixture was boiled and filtered. On addition of NH4OH (to maintain pH 10)l4 to the filtrate, thiazole (2a) was obtained. It was filtered, washed and dried followed by recrystallization from ethanol. The purity of the compounds was checked with TLC (m.p., m.m.p., Rf and yields compared with authentic sample). Yield 90%, m.p. 160°C.

2a: IR λ_{max} (KBr, cm–1): 3455 ν(OH), 3338ν (NH2), 1525 ν(C—N), 1251 ν(C—N), 1390 ν(C—S—C). 1H NMR: δ 2.3 (s, 3H, Ar-CH3), 6.8 (s, 1H, —CH), 6.9–7.1 (m, 3H, Ar-H), 7.8 (s, 2H, NH2), OH peak off the scale.

All other thiazoles were prepared by similar method; bromine gives better and cleaner yield than iodine (Table-1).

TABLE-1
PHYSICAL DATA AND COMPARISON OF REACTION TIME AND YIELDS OF COMPOUNDS (2a–p)

S.N.	Comp.	R_1	R_2	R_3	R_4	m.p. (°C)	Method A		Method B	
							S_1 Y/t %/hr	S_2 Y/t %/min	S_1 Y/t %/min	S_2 Y/t %/min
1.	a	CH_3	H	H	OH	160	58/12	40/30	90/6	90/6
2.	b	CH_3	Br	H	OH	205	60/12	55/30	90/6	92/6
3.	c	CH_3	NO_2	H	OH	170	50/12	46/30	85/6	90/6
4.	d	CH_3	I	H	OH	199	50/12	43/30	90/6	90/6
5.	e	H	H	CH_3	OH	178	65/12	60/30	92/6	92/6
6.	f	H	H	OH	CH_3	200	60/12	57/30	80/6	87/6
7.	g	Cl	H	H	OH	200	50/12	45/30	87/6	90/6
8.	h	Cl	Br	H	OH	180	45/12	40/30	87/6	90/6
9.	i	Cl	NO_2	H	OH	185	49/12	43/30	90/6	85/6
10.	j	Cl	I	H	OH	310d	55/12	—	80/6	85/6
11.	k	H	Cl	H	OH	165	45/12	40/30	80/6	87/6
12.	l	Cl	H	OH	H	204	49/12	45/30	70/6	75/6
13.	m	H	H	OH	H	195–200	45/12	42/30	75/6	65/6
14.	n	H	H	H	OH	135	48/12	44/30	70/6	70/6
15.	o	H	H	H	H	130	50/12	—	75/6	78/6
16.	p	H	H	OH	OH	210	52/12	—	80/6	75/6

Y = yield; t = time in minutes; S_1 = ethanol; S_2 = DMSO; d = decomp.

Conclusion

We have described a novel and highly efficient rapid microwave induced modification of the synthesis of 2-amino-4-substituted phenyl-thiazole. MORE chemistry reactions are highly accelerated, they are cleaner than conventional reactions and lead to higher atom economy (less chemical waste) and follow the environmental-friendly protocol to include a reaction set-up not requiring specialized equipment, high product yields, short reaction times and elimination of the usage of excess of solvents in some reactions.

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