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An efficient one pot route to 3,5-disubstituted 1,2,4-triazoles

Shahnaz Rostamizadeh*, Masoumeh Nojavan

Department of Chemistry, K.N.Toosi University of Technology, P.O.Box 15875-4416, Tehran, (IRAN)

E-mail: rostamizadeh@hotmail.com

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ABSTRACT

3,5-disubstituted 1,2,4-triazoles (**3a-e**) have been prepared in a few minutes from the reaction of acid hydrazides, (**1**) S-methyl isothiobenzamide hydroiodide, (**2**) in the presence of aqueous sodium hydroxide in DMF under microwave irradiation. © 2008 Trade Science Inc. -INDIA

KEYWORDS

Acid hydrazide;
Isothiocyanate;
Isothiobenzamide
hydroiodide;
Microwave irradiation;
Triazole.

INTRODUCTION

During recent years there has been increased attention towards different classes of 1,2,4,-triazole derivatives. Compounds with 1,2,4-triazole moieties in their structure are known to display a wide range of potent biological properties such as hypoglycemic^[1], antifungal^[2,3] antibacterial^[4], anticonvulsant^[5], antituberculosis^[7], and anti-inflammatory activity^[7,8].

In addition, in recent years increased interest has arisen in using microwave methodology for organic synthesis owing to several advantages such as enhanced reaction rates and higher yields of pure products under milder conditions^[9].

EXPERIMENTAL

All products are known compounds and were characterized by comparison of their spectral and physical data with those of known samples.

Melting points were taken on an Electrothermal 9100 melting point apparatus.

IR spectra were taken with a Shimadzu IR-408

spectrometer (KBr).

The ¹HNMR spectra were determined in methanol-d₄ and DMSO-d₆ solution on a Bruker DRX-500 Avance (500MHz). Microwave irradiation was carried out in a modified Moulinex microwave oven, AET 5. Merck Silica gel 60GF254 was used for analytical and preparative TLC.

General procedure for one pot synthesis of 3,5-disubstituted 1,2,4-triazoles

Acid hydrazide (1mmol), S-methyl isothiobenzamide hydroiodide (1mmol) was dissolved in DMF (5ml) and placed in a Teflon vessel (especially prepared for microwave reactions in solvent). To the mixture, sodium hydroxide 2N (1ml) was added and subjected to microwave irradiation at appropriate power (700W) and time (TABLE 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitated solids were dissolved in ethyl acetate (30ml). Water (30ml) and three drops of HCl was added to this mixture and introduced into a dropping funnel. The organic layer was then separated and dried over magnesium sulfate. The solvent was removed in vacuo

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and the precipitated solids were further purified by recrystallization from EtOH-H₂O.

General procedure for synthesis of 3,5-diphenyl-1,2,4-triazole in two steps

Benzhydrazide (1mmol), S-methyl isothioamide hydroiodide (1mmol) were dissolved in DMF (5ml) and placed in a Teflon vessel and subjected to microwave irradiation at 900W. The progress of the reaction was monitored by TLC. After completion of the reaction (7min.) crystals of the intermediate (**3a**) were formed and identified as N₃-benzoyl benzamidrazone hydroiodide. In the next step, 0.39mmol of **3a** was dissolved in DMF (5ml) and 2N NaOH (2ml) was added and placed in a Teflon vessel. The mixture was then subjected to microwave irradiation at (700W). The progress of the reaction was monitored by TLC. After completion of the reaction (6min.), the precipitated solids were dissolved in ethyl acetate (30ml). Water (30ml) and three drops of HCl was added and introduced into a dropping funnel. The organic layer was washed with water, and dried over magnesium sulfate. The solvent was removed *in vacuo*, the precipitated solids were filtered off and further purified by recrystallization from EtOH-H₂O.

RESULTS AND DISCUSSION

A number of approaches towards the synthesis of 3,5-disubstituted 1,2,4-triazoles have been developed, one of which is formation of these compounds from hydrazine and its derivatives^[10-12]. They have also been prepared from the reaction of acid hydrazides with amidines^[13], ammonium thiocyanate^[14], and nitriles^[15,16]. Formation of these compounds from amidrazones^[17] oxadiazoles^[18], and aminoguanidine^[1], were also reported in the literature.

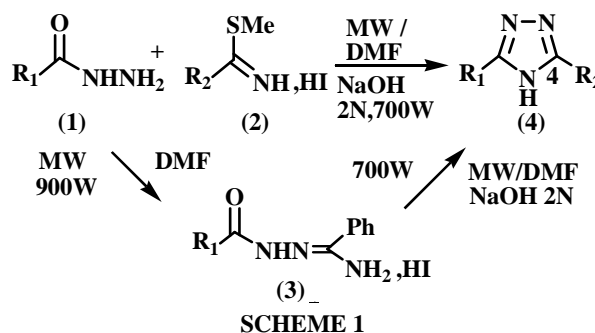
Another synthetic route to these compounds was reported using soluble polymer support-poly (ethylene glycol)^[19].

Due to these findings and as part of our research program, we are interested in finding a new methodology to 3,5-disubstituted 1,2,4-triazoles.

In this research, 3,5-disubstituted 1,2,4-triazoles have been prepared in one step from the reaction of acid hydrazides (**1**) and S-methyl isothioamide hydroiodides (**2**) in the presence of aqueous sodium hydroxide in DMF under microwave irradiation. 3,5-

TABLE 1: Condensation of acid hydrazides (1) and S-methyl isothioamide hydroiodide(2)

Product	R ₁	R ₂
4a	C ₆ H ₅	C ₆ H ₅
4b	4-Cl-C ₆ H ₄	C ₆ H ₅
4c	4-NO ₂ -C ₆ H ₄	C ₆ H ₅
4d	4-Br-C ₆ H ₄	C ₆ H ₅
4e	2-thienyl	C ₆ H ₅
4f	2-furyl	C ₆ H ₅



diphenyl 1,2,4-triazole (**4a**), was also prepared in two steps (SCHEME 1, TABLE 1).

As part of our ongoing research program on developing efficient and new methodologies for the synthesis of important heterocyclic compounds^[20], we wish to report an easy and one pot procedure for the synthesis of 1,2,4-triazoles.

In the present work, first, the synthesis of 3,5-diphenyl 1,2,4-triazole (**4a**) was investigated through a two-step pathway (SCHEME 1). In the first step, the reaction of benzoic acid hydrazide (**1a**) with S-methyl isothioamide hydroiodide (**2a**), was performed in different solvents (DMSO, DMF, EtOH etc) under microwave irradiation and the best result was obtained by using DMF. When we used DMF, after (7) minutes the intermediate (**3a**) was obtained and identified as N₃-benzoyl benzamidrazone hydroiodide. In the second step we tried to cyclize the intermediate (**3a**) with different bases (triethylamine, different concentration of NaOH, pyridine, piperidine) and again various solvents in which the best result was obtained in 2N NaOH / DMF. In this step, 3,5-diphenyl 1,2,4-triazole (**4a**) was formed within 6 minutes. It should be mentioned that neither of triethylamine, pyridine or piperidine were able to convert the intermediate (**3a**) to the triazole (**4a**). Based on the above observation, we decided to investigate the one-pot synthesis of 3,5-diphenyl 1,2,4-triazole (**4a**) without isolating the intermediate (**3a**). Therefore, the reaction of benzoic acid hydrazide (**1a**)

TABLE 2: Yield and physical characteristics of 3,5-disubstituted 1,2,4-triazoles (4a-f)

Products	Yield (%)	Time (min)	Power (W)	M.p °C	Lit.M.p °C	Ref.
4a	98	3	700	189-191	188-190	14,20
4b	90	5	700	213-215	212-214	20
4c	90	3	700	235-237	234-236	20
4d	90	3	700	258-260	262-264	21
4e	97	5	700	214	212-214	14
4f	82	4	700	192-194	190-193	14

and S-methyl isothiobenzamide hydroiodide (**2a**) was performed in the presence of 2N NaOH in DMF at 700W. The only product which formed after (**3**) minutes was identified as 3,5-diphenyl-1,2,4-triazole in 98% yield. In a similar manner, compounds (**4b-c**) were also prepared under this condition and the results are summarized in TABLE 2.

The required acid hydrazides were purchased directly or prepared by treatment of the corresponding carboxylic acid esters and hydrazine hydrates following the reported procedure^[22]. S-methyl isothiobenzamide hydroiodide was prepared according to literature method^[23].

High yield, short reaction time, formation of only one product and easy work-up are advantages of this procedure compared to our previous work and other methods in the literature.

CONCLUSIONS

In conclusion, the synthesis of a series of 3,5-diphenyl-1,2,4-triazoles was achieved as a one pot procedure without isolating the intermediate N₃-benzoyl benzamidrazone hydroiodides (**3a**) from the reaction of acid hydrazides, and S-methyl isothiobenzamide hydroiodide, in the presence of aqueous sodium hydroxide in DMF under microwave irradiation.

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