AN EFFICIENT SYNTHESIS OF 4 –ARYL-*4H* –[1,2,4]TRIAZOLES UNDER MICROWAVE IRRADIATION IN DRY MEDIA

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Abstract
A microwave-enhanced synthesis of 4–aryl-*4H* –[1,2,4]triazole under solvent free conditions is described. The yields and especially the reaction time are noticeably improved in comparison with conventional heating.

Keywords: 4 –Aryl-*4H* –[1,2,4]triazole; microwave irradiation

Introduction

N-aryl-1,2,4-triazole derivatives are important compounds, particularly in pharmaceutical research (1-3). A number of them have received considerable attention because molecules with these structural features have been found to display a wide range of potent biological activities, such as cardiotonic (4,5), antidiuretic (6) .

On the other hand, the *N*-aryl-1,2,4-triazole framework has been found to be a useful building-block to construct new fused heterocyclic compounds (7,8). In this field, we recently reported a convenient synthesis of new triazoloisoindole derivatives starting from 1,2,4-triazole moiety (9).

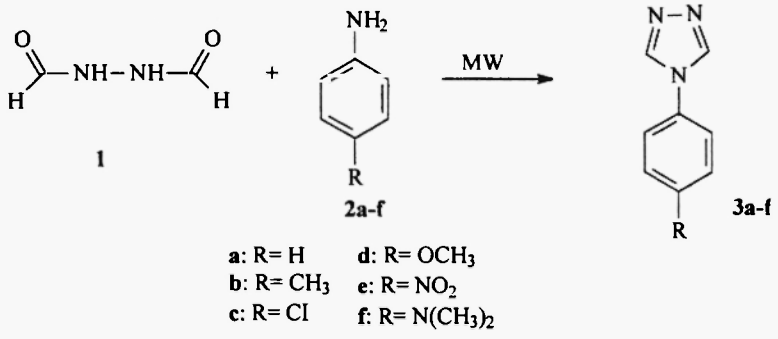
The literature offers several methods for the synthesis of these compounds. Among them, the most straightforward route involves the direct formation of the triazole ring: (i) reaction of *N*-arylformamide at high temperature with acetic acid hydrazide (10), (ii) condensation of substituted anilines with formidazine derivatives in toluene in acid condition (11), (iii) reaction of *N,N'*-bis phenylformamidine with the formic acid hydrazide (12) and (iv) treatment of the diformylhydrazide with susbtituted anilines in the presence of ammonium sulfate (13).

However, these reactions have some drawbacks, since they require either a solvent, an additive compound and harsh reaction conditions (high temperatures, long reaction times) which cause the decomposition of the reagents or/and of the final products.

Results and Discussion

Microwave radiation is becoming an increasingly useful activation technique in synthetic organic chemistry (14-17). Due to the efficiency of microwave heating, this synthetic technique decreases the

reaction time, enhances the reaction rates, and generally gives higher yields as compared with conventional heating. In continuation of our work on microwave assisted organic reactions (18-20), herein, we now describe a microwave accelerated synthesis of substituted *4*-aryl-4H-[1,2,4]triazoles by reacting, in solvent free conditions and in the absence of any additive compound, substituted anilines with diformylhydrazide (Scheme. 1).



a: R= H **d**: R= OCH_3
b: R= CH_3 **e**: R= NO_2
c: R= Cl **f**: R= $N(CH_3)_2$

Scheme. 1: Solvent free synthesis of 4-aryl-*4H*-[1,2,4]triazoles **3a-f**

Conventional heating and microwave irradiation are compared. All reactions take place with the convenient and commercially available Prolabo Synthewave 402 (open oven, monomode system, 300 W) apparatus. In a first step, in order to establish the most efficient operating process, the reaction was carried out with aniline under conventional heating (pre-heated oil bath) and microwave irradiation using the same starting material. In a typical run, a mixture of aniline **2a** (4mL, 0.04 mol) and diformylhydrazide **1** (3.86g, 0.04 mol) is stirred and heated (oil bath or microwave oven) at 180°C. After cooling, the crude product is poured in chloroform and the unreacted diformylhydrazide is eliminated by filtration. Then, the organic layer is dried over Na_2SO_4 and concentrated under reduced pressure . The crude product is precipitated with diethyl ether. Finally, the solid is collected by filtration and washed with diethyl ether to furnish the pure compound **3a**.

Different experiments with variable reaction time were performed (Fig.1), the most satisfactory result was obtained after 20 minutes of irradiation. It is noteworthy that under classical heating a longer time (180 min) was required to achieve comparable yield. In an attempt to optimise the reaction temperature, we have also carried out the reaction at lower reaction temperature (100°C, 125°C, 150°C). Nevertheless, in all cases, the yields decreased dramatically.

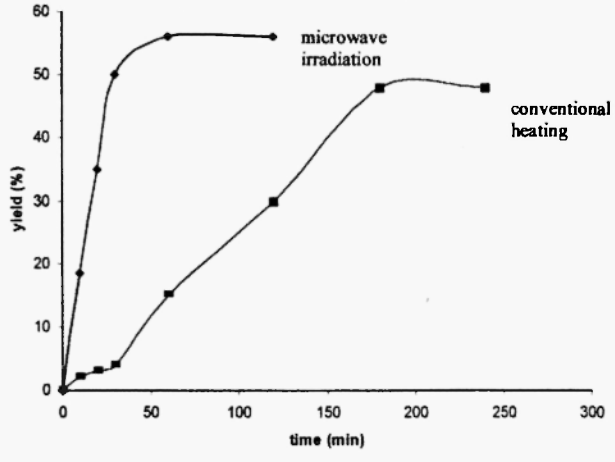


Fig. 1. Yield versus time for the 4–phenyl-*4H*–[1,2,4]triazole **3a** at 180°C.

These conditions (20 minutes at 180°C) were then applied to various aniline derivatives **2b-f**. All compounds were characterised by ^{1}H NMR, mass spectrometry and by their melting point.

As regards to the results depicted in Table 1, all compounds were isolated advantageously within a few minutes and in better yields under microwave irradiation than under conventional heating.

Table. I :Synthesis of 4-aryl-*4H*-[1,2,4]triazoles **3a-f**.

Product	Conventionnal Heating[a]	Microwave Irradiation[b]	m.p (°C)	
	Yields (%)	Yields (%)		Lit[13]
3a	48	56	120	119
3b	53	67	111	112
3c	65	85	118c	118
3d	63	79	181[c]	182-184
3e	70	81	319[c]	320
3f	78	95	168	166-169

[a] reaction performed at 180°C for 180 min in an oil bath
[b] reaction performed at 180°C for 20 min in a microwave oven
[c] melting point obtained after recristallization from acetic acid

Conclusion

We have presented an alternative and efficient multi-gram synthesis of 4-aryl-*4H*-[1,2,4]triazoles under microwave activation. A particularly attractive feature of this simple and practical method is that in all cases, the reaction was considerably shorter and provided higher yields.

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