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A FACILE SYNTHESIS OF SUBSTITUTED BENZODIAZEPINES USING SOLID SUPPORT

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An easy and convenient synthetic procedure for the preparation of benzodiazepines by coupling microwaves with the solvent technique have been elaborated.

Keywords: benzodiazepines, *o*-phenylenediamine, microwave irradiation, solid support.

1,5-Benzodiazepines and their derivatives have been investigated extensively by organic chemists due to their medicinal properties [1] such as analgesic and anti-inflammatory activities [2]. The seven-membered rings are generally synthesized *via* the [4+3] condensation reaction, most commonly by condensing 1,2-diamines with carbonyl compounds. This procedure involves the use of carcinogenic solvents like xylene [3], which often afforded imidazole [4] as a by-product or as a major component along with benzodiazepines.

The use of microwave irradiation (MWI) is well known for the synthesis of a variety of compounds [5, 6] where the chemical reactions are accelerated because of selective absorption of microwaves by polar molecules. The coupling of MWI together with solid-supported reagents under solvent-free conditions [7-9] provides unique chemical processes with special attributes such as enhanced reaction rate, higher yield, greater selectivity, and ease of manipulation [10]. The limitations of microwave-assisted reactions in solution, namely the development of high pressure and the need for specialized vessels, are circumvented *via* this solid state strategy which enables organic reactions to occur rapidly in open vessels at atmospheric pressure [11].

In view of the reported limitations [12, 13] in the synthesis of 1,5-benzodiazepine and our continued interest in the development of environmentally benign protocols [14-16], we describe herein a microwave-assisted solid state approach for the rapid synthesis of 3H-1,5-benzodiazepines and 3H-1,5-benzodiazepin-2-ones (Scheme 1).

o-Phenylenediamine (**1**) and ethyl acetoacetate (**2**) were condensed according to the literature [3, 4] to yield 4-methyl-3H-1,5-benzodiazepin-2-one (**3**) in 3-6 h of conventional heating (method A) or 10 min of MWI in solution (method B). The same reaction when carried out using neutral alumina as solid support was completed within 40-60 s of MWI (method C) with yield improved from about 60 to 90%. Moreover, the desired product was obtained exclusively, which was characterized by literature mp and spectral data.

The encouraging result in the synthesis of benzodiazepinone prompted us to attempt a similar modification (method C) in the condensation reaction of diamine **1** with other conjugated carbonyl compounds. The reaction of diamine **1** with α,β-unsaturated ketones **4a**,**b** over acidic alumina as energy-transfer medium under MWI afforded 3H-1,5-benzodiazepines **5** in 90-94% yield. IR bands in the region of 3430-3440 (N–H), 1628-1630 (C=N) and 1300-1450 cm^{-1} (C–N) and ^1H NMR signals at δ 4.0-4.5 (2H, s, CH_2) and 5.0-6.0 ppm (1H, s, CH) confirm the formation of the required products.

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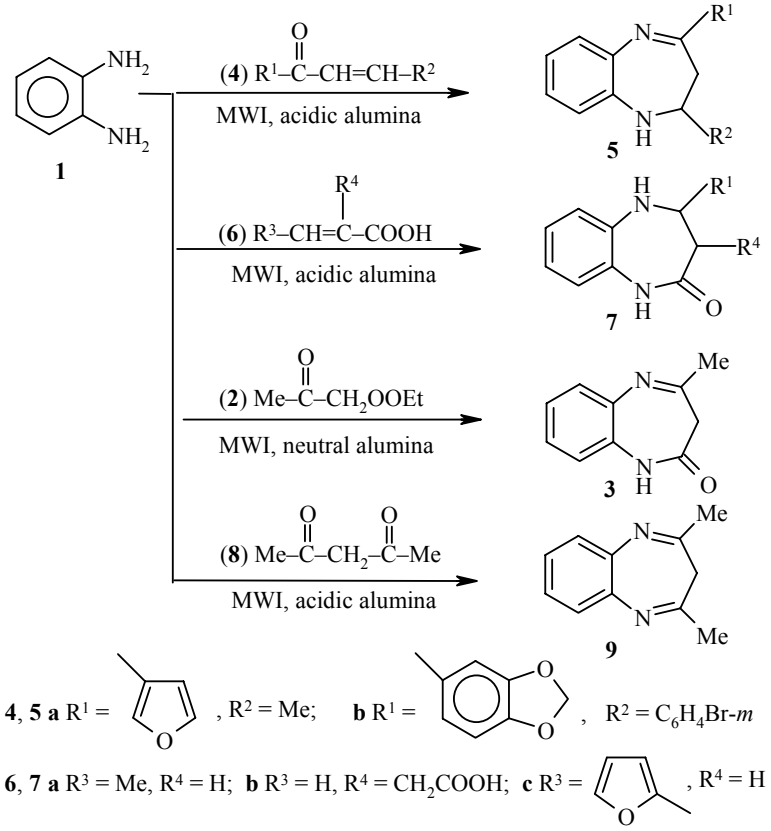
Scheme 1



Condensation with α,β-unsaturated acids **6a-c** over acidic alumina afforded 3,4-dihydro-1,5-benzodiazepin-2-ones **7** within seconds of irradiation. The products were characterized by the appearance of bands in the IR spectra at 3500-3200 (NH) and 1700-1670 cm^{-1} (C=O) and signals in the ^1H NMR spectra at δ 2.6-4.6 ppm (1H, s, CH).

Similarly using acidic alumina the condensation of acetylacetone (**8**) with *o*-phenylenediamine **1** yielded 2,4-dimethyl-3H-1,5-benzodiazepine (**9**), which was confirmed by literature mp and spectral data.

All the above reactions were also pursued under MWI in solution (me-thod B) as well as the conventional method (method A) for a comparative study. Solid-supported reactions gave improved yield and were completed within seconds of MWI in comparison to hours and minutes in conventional and microwave-assisted syntheses in solution, respectively.

In conclusion, we have developed an easy and convenient synthetic procedure for the preparation of benzodiazepines by coupling microwaves with the solvent-free technique. Through modernization and simplification of the classical procedure, and avoidance of volatile and toxic solvents and external bases, we have discovered an efficient protocol for organic chemists.

EXPERIMENTAL

Melting points were determined by an Electrothermal melting point apparatus and are un-corrected. IR spectra (in KBr) were recorded on a 1710 Perkin–Elmer FT infrared spectro-photometer. ^1H NMR spectra were recorded on a FT NMR Hitachi R-600 (60 MHz) spectrometer in $CDCl_3$ + DMSO-d_6 taking TMS as reference. Elemental analysis were performed on a Heraeus CHN-Rapid Analyser. For MWI a Kenstar microwave oven,

TABLE 1. Characteristics of compounds synthesized

Compound	mp, °C	Lit. mp, °C [Ref.]	Emprical formula	Found, % / Calculated, %			Yield, % (method, reaction period)		
				C	H	N	A (h)	B (min)	C (s)
3	121	121 [14]	$C_{10}H_9N_2O$	—	—	—	58 (2)	73 (10)	95 (50)
5a	245	—	$C_{14}H_{13}N_2O$	74.67 / 74.66	5.79 / 5.77	12.43 / 12.44	57 (5)	78 (6)	93 (50)
5b	246	—	$C_{22}H_{17}BrN_2O_2$	62.71 / 62.72	4.02 / 4.03	6.64 / 6.65	68 (5)	74 (7)	90 (40)
7a	184	185 [18]	$C_{10}H_{12}N_2O$	—	—	—	47 (4)	65 (8)	92 (40)
7b	255	—	$C_{11}H_{11}N_2O_3$	60.26 / 60.27	5.03 / 5.02	12.79 / 12.78	48 (6)	72 (5)	93 (60)
7c	185	—	$C_{13}H_{12}N_2O_2$	68.43 / 68.42	5.28 / 5.26	12.29 / 12.28	59 (4)	75 (9)	94 (60)
9	201	202 [17]	$C_{11}H_{12}N_2$	—	—	—	67 (3)	79 (5)	97 (40)

Model OM9925E (2450 MHz, 800 W), was used. The purity of the compounds was checked on silica gel coated Al plates (Merck).

Preparation of Benzodiazepine Derivatives (Table 1). A. Solutions of compounds **2**/**4a**,**b**/**6a-c**/**8** (0.01 mol) and *o*-phenylenediamine **1** (0.01 mol) in xylene (10 ml)/glacial acetic acid + ethanol (1:2)/hydrochloric acid (5.5 N)/glacial acetic acid + ethanol (1:2), respectively, were refluxed under constant stirring for 4-6 h. The progress of the reaction was monitored on TLC. The reaction mixtures were cooled and the products that separated were filtered off, dried and recrystallized from ethanol.

B. Diamine **1** (0.01 mol) was added to solutions of compounds **2**/**4a**,**b**/**6a-c**/**8** (0.01 mol) in xylene (5-10 ml) taken in an Erlenmeyer flask, and the contents were subjected to MW1 for an appropriate time and worked up as described in method A.

C. Alumina was added to a solution of diamine **1** and compound **2**/**4a,b**/**6a-c**/**8** in ethanol. The reaction mixture was dried and placed in the alumina bath inside the microwave oven at 560 W for 40-60 s. The progress of reaction was monitored by TLC at intervals of 10 s. On completion of the reaction, the reaction mixture was cooled to room temperature, the product was extracted with ethanol (3 × 10 ml), and the solvent was removed under reduced pressure to yield the corresponding title compounds.

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