

An expeditious synthesis of 3,4-dihydrobenzo[2,3-*d*]pyrimidines using inorganic solid supports

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(Received 4 September 2003)

Abstract: A series of novel 5-substituted-8-cyano-4,6,7-triphenyl-3,4-dihydrobenzo[2,3-*d*]pyrimidines were synthesized by the condensation of 6-substituted-2-amino-1-benzoyl-3-cyano-5-hydroxy-4,5-diphenyl-1,3-cyclohexadiene and formamide, using inorganic solid supports under microwaves. Some of the compounds were found to be effective against some fungal and bacterial strains.

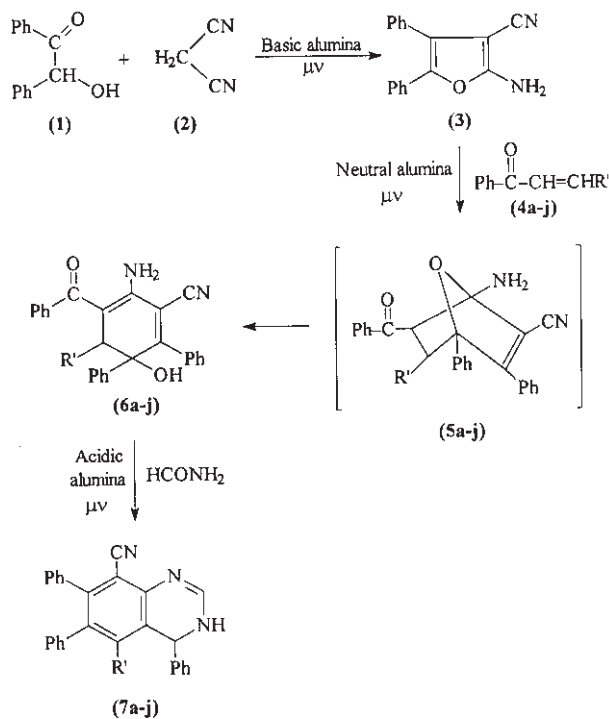
Keywords: benzopyrimidines, inorganic solid supports, microwave, environmentally benign synthesis, antimicrobial.

INTRODUCTION

Benzopyrimidines have found application in a wide range of medicinal chemistry because of their diverse biological activities, such as antibacterial,^{1,2} anticonvulsant,³ antiinflammatory,^{4–6} antitumor^{7–9} and antifungal¹⁰ activities. These chemotherapeutic applications of benzopyrimidine derivatives prompted us to synthesize some new highly substituted 3,4-dihydrobenzo[2,3-*d*]pyrimidines (**7a–j**) by adopting a new route under solid supported microwave irradiations.

Several methods have been reported^{11–14} for the synthesis of benzopyrimidine derivatives. However, these methods suffer from drawbacks, such as longer reaction time, complicated workup, use of expensive and hazardous chemicals with low yield. The title compounds were synthesized in this study using commonly available reagents under dry media microwave irradiation to overcome the mentioned drawbacks. Microwave assisted organic synthesis proceeds with facile reactions to provide high yield within a very short reaction time period.¹⁵ This methodology also avoids the use of excess solvents and harmful acids or bases, which are generally used for the catalysis of the reactions.^{16–19} Solution phase microwave organic reactions have some limitations, such as the possibility of super heating of the solvents which may result in series explosions.^{20,21} Microwave activated dry

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|---|--|
| a. C ₆ H ₅ | f. 4-HOC ₆ H ₄ |
| b. 4-CH ₃ C ₆ H ₄ | g. 4-O ₂ NC ₆ H ₄ |
| c. 4-CH ₃ OC ₆ H ₄ | h. 2-furyl |
| d. 4-ClC ₆ H ₄ | i. 2-thienyl |
| e. 4-BrC ₆ H ₄ | j. 2-pyridinyl |

Scheme 1.

media synthesis on solid inorganic supports is the most efficient and ecofriendly technology.^{22,23} Reactions can be carried out easily at ambient pressure in open vessels by using domestic microwave ovens.²⁴ Moreover, the use of solid acid and base catalysts reduces the amount of toxic wastes and by-product formation.²⁵

Pharmaceutical interest in benzopyrimidines prompted us to synthesize a series of new 3,4-dihydrobenzo[2,3-*d*]pyrimidines (**7a-j**) in dry media under microwave irradiations by the cyclization of 1,3-cyclohexadiene derivatives (**6a-j**) with formamide under acidic conditions (Scheme 1).

EXPERIMENTAL

The microwave reactions were carried out in a Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W) and the IR spectra were recorded on a Perkin Elmer FTIR-1710 spectrophotometer using KBr pellets. The ¹H-NMR spectra were recorded on a FT NMR Hitachi R-600 (60 MHz) instrument. Elemental analyses were performed using a Heraeus CHN-Rapid Analyser. The temperature of the reaction mixture was measured using an AZ, Mini Gun Type, Non-contact IR thermometer, Model

No. 8868. The melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Chemical shifts, δ , for $^1\text{H-NMR}$, are given in ppm, relative to the internal reference, tetramethylsilane (TMS) and the IR frequencies, ν , in cm^{-1} . The purity of the compounds were checked on aluminium plates coated with silica gel (Merck).

Synthesis of 2-amino-3-cyano-4,5-diphenylfuran (3)

This compound was synthesized using microwave technology based on a literature method.^{26,27}

Synthesis of α , β -unsaturated ketones or chalcones (4a-j)

These compounds were synthesized by a modified literature method.²⁸

General procedure for the synthesis of 6-substituted-2-amino-1-benzoyl-3-cyano-5-hydroxy-4,5-diphenyl-1,3-cyclohexadiene (6a-j)

Equimolar amounts (0.01 mol) of 2-amino-3-cyano-4,5-diphenyl furan (**3**) and α,β -unsaturated ketone or chalcone (**4a-j**) were dissolved in 10 ml of EtOH. The solution was then adsorbed on 20 g of neutral alumina or montmorillonite K10 clay or silica gel in a small beaker. The reaction mixture was dried in air and the beaker was put in an alumina bath inside the microwave oven and irradiated for 5–6 min. The progress of the reaction was monitored by TLC at intervals of 30 s. The product (**6a-j**) was extracted into EtOH and obtained in the solid state after removal of the solvent by distillation under reduced pressure.

*General procedure for the synthesis of 5-substituted-8-cyano-4,6,7-triphenyl-3,4-dihydrobenzo[2,3-*d*]pyrimidines (7a-j)*

Conventional reactions (Method A). 0.01 mol of 1,3-cyclohexadiene derivative (**6a-j**) was dissolved in 10 ml of formamide and 2 ml of formic acid was also added to the solution, which was then refluxed under stirring for 6–7 h. After the completion of the reaction, as indicated by TLC examination, the hot solution was poured onto crushed ice followed by basification with ammonia. The product (**7a-j**) precipitated out during stirring for 10 min. The product was filtered and washed with cold water followed by recrystallization from MeOH.

Microwave reactions (Method B). 0.01 mol of 1,3-cyclohexadiene derivative (**6a-j**) was dissolved in 10 ml of formamide and the solution was adsorbed on 20 g of acidic alumina or montmorillonite K10 clay or silica gel in a small beaker. The reaction mixture was dried in air and the beaker was put in an alumina bath inside the microwave oven and irradiated for 4–5 min. The progress of the reaction was monitored every 30 s. The product (**7a-j**) was extracted with EtOH (4 \times 10 ml) and obtained in the solid state after removal of solvent by distillation under reduced pressure. The product was recrystallized from MeOH.

TABLE I. Comparison of reaction time and yield of compounds (**7a-j**)*

Compd. No	M.p./ $^{\circ}\text{C}$	Reaction time		Yield/%	
		Method A/h	Method B/min	Method A	Method B
7a	157	7.0	5.0	53	75
7b	162	6.5	4.5	54	78
7c	170	6.5	4.0	57	81
7d	185	6.0	4.0	65	87
7e	179	6.5	4.5	60	82
7f	182	7.0	5.0	52	73
7g	175	6.5	4.5	63	85

TABLE I. Continued

Compd. No	M.p./°C	Reaction time		Yield/%	
		Method A/h	Method B/min	Method A	Method B
7h	193	6.0	4.0	56	79
7i	186	6.0	4.0	58	81
7j	180	7.0	4.5	56	76

*All the compounds showed satisfactory elemental analysis within the variation ± 0.04 %.

TABLE II. Spectral data of the compounds (**7a–j**)

Compd. No.	IR, ν/cm^{-1} , KBr pellets	$^1\text{H-NMR}$, δ/ppm , CDCl_3
7a	1600 (C=N)	4.6 (s, 1H, C-4)
	3350 (N-H)	7.1–7.2 (m, 20H, Ar-H & 1H at C-2)
	2240 (C \equiv N)	11.5 (brs, 1H, NH)
7b	1605 (C=N)	2.3 (s, 3H, CH ₃)
	3352 (N-H)	4.6 (s, 1H, C-4)
	2243 (C \equiv N)	7.1–7.3 (m, 19H, Ar-H & 1H at C-2) 11.5 (brs, 1H, NH)
7c	1602 (C=N)	4.0 (s, 3H, OCH ₃)
	3350 (N-H)	4.7 (s, 1H, C-4)
	2240 (C \equiv N)	7.0–7.4 (m, 19H, Ar-H & 1H at C-2) 11.4 (brs, 1H, NH)
7d	1600 (C=N)	4.7 (s, 1H, C-4)
	3348 (N-H)	7.1–7.4 (m, 19H, Ar-H & 1H at C-2)
	2242 (C \equiv N)	11.5 (brs, 1H, NH)
7e	1608 (C=N)	4.6 (s, 1H, C-4)
	3355 (N-H)	7.0–7.3 (m, 19H, Ar-H & 1H at C-2)
	2247 (C \equiv N)	11.5 (brs, 1H, NH)
7f	1610 (C=N)	4.2 (brs, 1H, OH)
	3360 (N-H)	4.7 (s, 1H, C-4)
	2250 (C \equiv N)	7.1–7.3 (m, 19H, Ar-H & 1H at C-2) 11.4 (brs, 1H, NH)
7g	1602 (C=N)	4.7 (s, 1H, C-4)
	3345 (N-H)	7.2–7.8 (m, 19H, Ar-H & 1H at C-2)
	2247 (C \equiv N)	11.5 (brs, 1H, NH)

TABLE II. Continued

Compd. No.	IR, ν/cm^{-1} , KBr pellets	$^1\text{H-NMR}$, δ/ppm , CDCl_3
7h	1612 (C=N)	4.6 (<i>s</i> , 1H, C-4)
	3356 (N-H)	6.4–7.5 (<i>m</i> , 18H, Ar-H & 1H at C-2)
	2254 (C≡N)	11.5 (<i>brs</i> , 1H, NH)
7i	1615 (C=N)	4.6 (<i>s</i> , 1H, C-4)
	3360 (N-H)	7.1–7.4 (<i>m</i> , 18H, Ar-H & 1H at C-2)
	2255 (C≡N)	11.4 (<i>brs</i> , 1H, NH)
7j	1605 (C=N)	4.7 (<i>s</i> , 1H, C-4)
	3357 (N-H)	6.9–8.2 (<i>m</i> , 20H, Ar-H & 1H at C-2)
	2252 (C≡N)	11.5 (<i>brs</i> , 1H, NH)

TABLE III. *In vitro* antibacterial and antifungal activities of compounds (**7a–j**)

Compound	Bacterial strains				Fungal strains		
	<i>E. coli</i>	<i>Rhizobium japonicum</i>	<i>Enterobacter aerogenes</i>	<i>Burkholderia cepacia</i>	<i>Bacillus mojavensis</i>	<i>Aspergillus niger</i>	<i>Aspergillus flavus</i>
7a	–	+	+	+++	–	++	+++
7b	–	+	–	+	++	++	++
7c	–	–	+	+++	+	++	+++
7d	–	+	–	++	++	++	++
7e	–	–	–	–	–	–	–
7f	–	–	–	–	–	–	+
7g	–	+	+	++	+	+	++
7h	–	–	–	+	–	+	+
7i	–	+	–	–	+	+	+
7j	–	–	–	–	–	–	–
Oxytetracycline*/Salicylic acid**	+++++	++++	++++	+++++	+++++	++++	+++++

*Reference drug in antibacterial screening: – : No measurable activity; + : 2–7 mm; ++ : 8–12 mm; +++ : 13–17 mm; ++++ : 18–22 mm; +++++ : 23–26 mm.

**Reference drug in antifungal screening: – : No measurable activity; + : 3–8 mm; ++ : 9–13 mm; +++ : 14–18 mm; ++++ : 19–23; +++++ : 24–28 mm.

RESULTS AND DISCUSSION

Synthesis

Benzoin (**1**) and malononitrile (**2**) were condensed on a solid support, either basic alumina or montmorillonite K10 clay or silica gel, under microwave irradiation to afford 2-amino-3-cyano-4,5-diphenylfuran (**3**) in good yield. This is a mod-

ification of a literature method. Precursor (**3**) was treated with an α,β -unsaturated ketone (**4a–j**) under microwave irradiations to afford a 1,3-cyclohexadiene derivative (**6a–j**) via an intermediate (**5a–j**) after a short reaction time in high yield. The 1,3-cyclohexadiene derivatives were then cyclised with formamide on an acidic alumina solid support under microwave irradiation to obtain 3,4-dihydrobenzo[2,3-*d*]pyrimidine derivatives (**7a–j**) (Scheme 1). The use of acetic acid, hydrochloric acid, and formic acid employed in the literature method for the conversion of (**6a–j**) into (**7a–j**) is avoided in the presented procedure. Only 4–5 min were required for completion of the reaction in 87 % yield by the present method as compared to 6–7 h reaction time with 65 % yield by the literature method (Table I). These observations demonstrate that our method is an expeditious, facile and environmentally benign one for organic synthesis.

The structures of synthesized 3,4-dihydrobenzo[2,3-*d*]pyrimidines (**7a–j**) were evidenced from spectral and analytical data. IR absorption band at 1600–1615 cm^{-1} confirmed the (C=N) cyclic linkage in the pyrimidine ring and the band at 2240–2255 cm^{-1} indicated the presence of a cyano group (C \equiv N) in the compounds. Moreover, the appearance of an IR absorption band at 3345–3360 cm^{-1} confirmed the presence of a secondary amino group (N–H) in the synthesized 3,4-dihydrobenzo[2,3-*d*]pyrimidines (**7a–j**). The singlet at δ 4.6–4.7 in the $^1\text{H-NMR}$ spectra was due to the proton at C-4 and the broad singlet at δ 11.4–11.5 was due to the NH proton in the compounds. All the aromatic protons, including that of furyl, thienyl, pyridinyl substituents, in the synthesized compounds appear at δ 6.4–8.2 ppm in the $^1\text{H-NMR}$ spectra (Table II).

Antifungal and antibacterial activities

3,4-Dihydrobenzo[2,3-*d*]pyrimidines (**7a–j**) were tested for their *in vitro* antifungal activities against *Aspergillus niger* and *Aspergillus flavus* by the paper disc diffusion method²⁹ and for their *in vitro* antibacterial activities against *E. coli*, *Rhizobium japonicum*, *Enterobacter aerogenes*, *Burkholderia cepacia* and *Bacillus mojavensis* by the cup diffusion method.³⁰ Salicylic acid and oxytetracycline were used as reference drugs in the antifungal and antibacterial screenings, respectively. The to be tested compounds were dissolved in DMF at a concentration of 50 $\mu\text{g/ml}$. The inhibition zone was measured in millimeters. Among the 3,4-dihydrobenzo[2,3-*d*]pyrimidines synthesized, **7a–d** were found to be moderately active against the mentioned bacteria and fungi (Table III).

Acknowledgement: One of the authors, A. D. Mishra, is thankful to the University Grants Commission of the Government of Nepal for financial support.

ИЗВОД

БРЗА СИНТЕЗА 3,4-ДИГИДРОБЕНЗО[2,3-*d*] ПИРИМИДИНА УЗ ПОМОЋ НЕОРГАНСКЕ ЧВРСТЕ ПОДЛОГЕ

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Синтетизован је низ нових 5-супституисани-8-циано-4,6,7-трифенил-3,4-дигидробензо[2,3-*d*]пириимидине кондензацијом 6-супституисаних-2-амино-1-бензоил-3-циано-5-хидрокси-4,5-дифенил-1,3-циклохексадиена и формамида коришћењем неорганске чврсте подлоге и микроталаса. Нађено је да су нека од једињења активна у односу на неке гљиве и бактерије.

(Примљено 4. септембра 2003)

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