A Novel Route to New Bis(benzopyrano) Fused Dihydropyridines Using Dry Media

Mazaahir Kidwai,* Shweta Rastogi, and Richa Mohan

Department of Chemistry, University of Delhi, Delhi-110007, India
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A new and efficient synthesis of the novel bioactive bis(benzopyrano) fused dihydropyridines is described. The conventionally developed route is a two step multicomponent condensation reaction. This is latter modified by a one pot microwave (MW) assisted reaction using inorganic solid support *via* the arylidene derivative intermediate. With this environmentally benign approach, the reaction time is brought down from hours to minutes along with a yield enhancement. Furthermore, the role of different solid supports is studied and it is concluded that the acidic alumina is the best solid support for the present investigation.

Key Words : Benzopyran, Pyridine, Solid support, Microwave irradiation, Ecofriendly

Introduction

The fused pyridines represent the heterocyclic system of remarkable pharmacological efficiency as PAF-acether antagonists,[1] calcium antagonists[2] and antihypertensives.[3] The dihydropyridine (DHP) ring system is of considerable interest because of its presence in the coenzyme, diphosphopyridine nucleotide (DPNH).[4] 4-Hydroxy-3-(3-oxo-2-*p*-menthylmethyl) coumarin is an important anticoagulant.[5] Several substituted coumarin-7-yloxyalkanoic acids and esters have been reported to possess antiatherosclerotic,[6] coronary vasodilatory[7] and antiovulatory[8] activities. As coumarin themselves have been ascribed as pharmacologically important, their fusion to form a polycyclic fused pyridine ring may result in compounds with enhanced biological activity. The use of 4-hydroxy-2H-1-benzopyran-2-one (4-hydroxy coumarin) as an addendum in Michael addition reactions[9,10] prompted us to undertake the title investigation. Many methods for the synthesis of fused pyridines have been reported.[11-13] However, all these methods fail to provide bis(benzopyrano) fused dihydropyridines.

We herein report a method that allows the rapid synthesis of polycyclic DHPs that does not rely on the conventional procedure. Instead, our procedure involves a microwave (MW)-promoted, solvent-free new variation of the pyridine synthesis. The application of microwave irradiation (MWI) in organic synthesis[14] has been the focus of considerable attention in recent years and is becoming an increasingly popular technology. Chemical technology necessitates much more efficient use of energy and resources in order to minimise the undesirable environmental impact.[15] With the development of MW assisted dry media solid supported reactions,[16] significant advancement can be made in the area of green chemistry.[17] Coupling of solvent free conditions with MW[18] offers the advantages of reaction rate enhancement, high yield, minimum yield losses, optimum utilisation of energy, minimum solvent requirement and cleaner products. These solid supports which are usually of mineral origin act as both catalysts[19] as well as energy transfer media. Such dry media reactions are specially appealing as they provide an opportunity to work with open vessels. Thus avoiding the risk of high pressure development with the possibility of upscaling the reactions to industrial scale.[20]

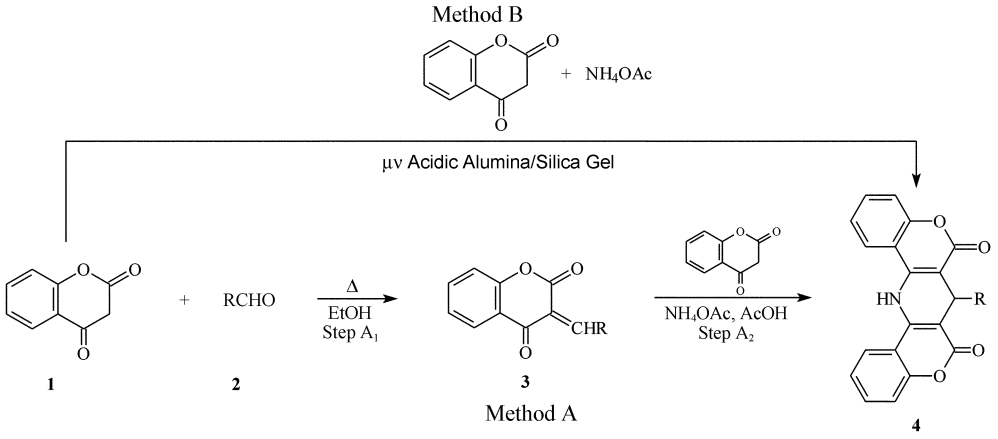
In view of the medicinal importance of polycyclic 1,4-DHP and in continuation of our ongoing program towards ecofriendly synthesis, it was thought worthwhile to synthesise novel bis(benzopyrano) fused 1,4-DHP derivatives under microwaves using dry media technique.

Results and Discussion

One mole of 4-hydroxy-2H-1-benzopyran-2-one **1** was condensed with one mole of aldehyde **2** under conventional heating for 3-4 h afforded the arylidene derivative **3** (Step A_1). The latter was further condensed with another mole of 4-hydroxy-2H-1-benzopyran-2-one in the presence of ammonium acetate and acetic acid (Step A_2) to furnish 8-aryl-bis(2-oxo-1-benzopyrano)[3,4-b:4',3'-e]-1,8-dihydropyridine **4** (Method A) (Scheme 1). This provided only low to moderate yield of the desired target molecule **4** in particular when substituted aromatic or heteroaromatic aldehydes **2** are employed. Since the reaction involved 2 moles of 4-hydroxy-2H-1-benzopyran-2-one **1**, an attempt was made to carry out one pot conventional synthesis of **4** starting from 2 moles of 4-hydroxy-2H-1-benzopyran-2-one **1**, one mole of aldehyde **2** and 3 g of ammonium acetate in acetic acid. Unfortunately, the reaction did not go to completion even after 36 h of refluxing.

In order to be able to carry out such multicomponent condensation reaction in a rapid and more efficient way-eliminating the usage of solvent and reflux condition, we investigated the influence of MWI on different solid supports, acidic alumina, neutral alumina and silica gel for the synthesis of the required pyridine derivatives **4**. The mixture of reactants, 4-hydroxy-2H-1-benzopyran-2-one **1**, aromatic or heteroaromatic aldehyde **2** and ammonium

*Corresponding Author. Fax: +91-11-27666235; e-mail: mkidwai@mantraonline.com



where, R = Phenyl, 2-Chloroquinolinyl, 5-Piperonyl, 3-Indolyl, 2-Hydroxynaphthyl, 2-Furyl

Scheme 1

acetate as the cyclisation agent (Method B) (Scheme 1) was adsorbed over the appropriate solid support and irradiated under microwaves. With acidic[21] alumina and silica[22] gel the desired product **4** was obtained in one pot. The arylidene derivative **3** obtained upon further irradiation afforded the 1,4-DHP derivative **4** in 60-85% yields within 20 m instead of 9-20 h as required in conventional procedure (Method A). Further, it was observed that acidic alumina was a better solid support than silica gel. Acidic alumina gave 75-85% yields in 10-15 m but silica gel afforded 60-75% yields in 15-25 m (Table 1). The reaction with neutral alumina did not go to completion even after 30 m of irradiation. The structures of **4** were confirmed on the basis of spectroscopic data (Table 2). In the IR spectrum, appearance of band at 1720-1740 cm^{-1} for δ lactone, 1650-1680 cm^{-1} for C=C and 3330-3350 cm^{-1} for NH showed the presence of such functional group. In the ^{1}H NMR, the appearance of the signal at 5.8 δ due to methine proton and 9.6-10 δ due to NH confirmed the formation of products **4**.

As the most important synthesis of pyridines is the Hantzsch synthesis[23] which involves the condensation of 2 moles of ethyl acetoacetate with 1 mole of aldehyde ammonia either in acetic acid or refluxing in alcohol for a longer time. A number of modified methods[25] under improved conditions, reported for the Hantzsch synthesis have been found unsuccessful from an environmental point of view.[24] The MW expedited novel synthesis of coumarin fused pyridine ring described herein is based on the finding that 4-hydroxy-2H-1-benzopyran-2-one **1** exists in tautomeric form with corresponding 2-hydroxy-4-pyrone[24] and is an active methylene reagent. The plausible mechanism of the desired synthesis involves the condensation of an aldehyde with 2 moles of 4-hydroxy-2H-1-benzopyran-2-one in presence of ammonium acetate and acetic acid. Ammonium acetate seems to react with 4-hydroxy-2H-1-benzopyran-2-one to yield β-aminobenzopyran-2-one while the aldehyde molecule undergoes an acid catalysed condensation with the second molecule of 4-hydroxy-2H-1-benzopyran-2-one to give the arylidene derivative. Addition of β-aminobenzopyran-2-one across the double bond of arylidene takes place in a Michael type reaction and subsequently cyclization *via* dehydration yields 1,4-dihydropyridine derivative **4**.

Experimental Section

Melting points were taken in Thomas Hoover melting point apparatus and were uncorrected. IR (KBr) spectra (ν_{max} in cm^{-1}) were obtained on Perkin-Elmer FTIR 1710 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on FT NMR Hitachi R-600 spectrometer operating at 60 MHz using TMS as an internal standard (chemical shifts in δ ppm). Elemental analyses were performed on Haraeus CHN Rapid Analyser. A Kenstar (Model No. OM9925E) household microwave oven (2450 MHz, 800 Watts) was used for all experiments. The purity of the compounds was checked on silica gel coated aluminium plates (Merck).

Table 1. Comparison of reaction time and yield of compounds **4**

Compd. No.	R	M.Pt. (°C)	Method A Time (hr)/Yield (%)	Method B	
				Acidic Alumina Time (min)/ Yield (%)	SilicaGel Time (min)/ Yield (%)
4a	Phenyl	182-184	9/62	10/87	16/76
4b	2-Chloro-quinolinyl	188-190	20/56	14/75	25/65
4c	5-Piperonyl	106-108	12/60	12/78	20/60
4d	3-Indolyl	224-226	14/50	15/75	22/63
4e	2-Hydroxy-naphthyl	274-276	8/65	8/85	13/75
4f	2-Furyl	202-204	15/60	12/80	18/70

Table 2. Spectroscopic Data of Compounds* **4**

Compd. No.	IR (KBr) (ν/cm^{-1})			^{1}H NMR/δ ($CDCl_3$, DMSO-d_6, 60 MHz, δ ppm)
	NH	C = C	δ Lactone	
4a[a]	3335	1660	1730	5.8 (s, 1H, H-8), 7.2-8.0 (m, 13H, Ar-H), 9.6 (brs, 1H, NH)
4b[b]	3342	1675	1740	6.0 (s, 1H, H-8), 7.2-8.3 (m, 13H, Ar-H and quinolinyl), 9.8 (brs, 1H, NH)
4c[c]	3345	1665	1738	5.8-6.0 (2s, 3H, CH_2 and H-8), 7.0-8.0 (m, 11H, Ar-H and piperonyl), 9.8 (brs, 1H, NH)
4d[d]	3340	1670	1735	5.9 (s, 1H, H-8), 6.6-8.2 (m, 14H, Ar-H and indolyl), 9.9 (brs, 1H, NH)
4e[e]	3330	1650	1728	5.8 (s, 1H, H-8), 6.7-8.2 (m, 14H, Ar-H), 5.5 (s, 1H, OH), 9.6 (brs, 1H, NH)
4f[f]	3350	1680	1740	6.0 (s, 1H, H-8), 6.6-8.0 (m, 11H, Ar-H and furyl), 10.0 (brs, 1H, NH)

*Analysis for. [a]Found: C, 76.32; H, 3.85; N, 3.55. Calcd. for $C_{25}H_{15}NO_4$: C, 76.33; H, 3.84; N, 3.56. [b]Found: C, 70.21; H, 3.13; N, 5.84. Calcd. for $C_{28}H_{15}ClN_2O_4$: C, 70.22; H, 3.16; N, 5.85. [c]Found: C, 71.39; H, 3.44; N, 3.21. Calcd. for $C_{26}H_{15}NO_6$: C, 71.40; H, 3.46; N, 3.20. [d]Found: C, 74.93; H, 3.75; N, 6.47. Calcd. for $C_{27}H_{16}N_2O_4$: C, 74.92; H, 3.74; N, 6.48. [e]Found: C, 75.82; H, 3.72; N, 3.04. Calcd. for $C_{29}H_{17}NO_5$: C, 75.81; H, 3.73; N, 3.05. [f]Found: C, 72.05; H, 3.43; N, 3.66. Calcd. for $C_{23}H_{13}NO_5$: C, 72.06; H, 3.42; N, 3.65.

General procedure for the synthesis of 8-aryl-bis(2-oxo-1-benzopyrano)[3,4-b:4',3'-e]-1,8-dihydropyridine 4.

Method A: Two pot conventional solution phase.

Step A_1: A mixture of 4-hydroxy-2H-1-benzopyran-2-one (**1**, 0.01 mole), aldehyde (**2**, 0.01 mole) in ethanol (25 mL) was refluxed for 3-4 h. The progress of the reaction was monitored through TLC examination. Upon completion of reaction, the reaction mixture was cooled, concentrated and filtered. The arylidene derivative **3** was used as such for further reaction without purification.

Step A_2: To the arylidene derivative (**3**, 0.01 mole), 4-hydroxy-2H-1-benzopyran-2-one **1**, 0.01 mole) and ammonium acetate (3 g) in acetic acid was refluxed for 15-20 h The progress of the reaction was monitored through TLC examination. Upon completion of the reaction as followed by TLC, the reaction mixture was cooled, worked up with water and recrystallised from chloroform and methanol mixture.

Method B: One pot solid support microwave.

To a solution of 4-hydroxy-2H-1-benzopyran-2-one (**1**, 0.02 mole), aldehyde (**2**, 0.01 mole) and ammonium acetate (3 g) in ethanol (10 mL), added acidic alumina/silica gel (15 g) with constant stirring. The mixture was air dried at room temperature, placed in an alumina bath and subjected to microwave irradiation. Upon completion of reaction as followed by TLC examination at an interval of 30 s. The reaction mixture was cooled to room temperature and product was extracted from ethanol (3 × 10 mL). Evaporation of the solvent under reduced pressure afforded the desired product **4** which was recrystallised from chloroform and methanol mixture.

Conclusion

In conclusion, we have described the pyridine ring formation starting from benzopyran moiety. A novel, facile and highly efficient MW assisted one pot modification of the conventionally developed two pot multicomponent condensation reaction is introduced that allows the rapid assembly of structurally diverse DHPs. The advantages of this ecofriendly and safe protocol include a simple reaction set up, good product yield, short reaction time and above all, solvent elimination. Large collections of DHPs can thus be prepared applying the MW expedited high throughput dry media technique.

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