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Sodium bromide catalysed one-pot synthesis of tetrahydrobenzo[*b*]pyrans via a three-component cyclocondensation under microwave irradiation and solvent free conditions

Ipsita Devi and Pulak J. Bhuyan*

Medicinal Chemistry Division, Regional Research Laboratory, Jorhat 785006, Assam, India

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Abstract—Sodium bromide catalysed three-component cyclocondensation of aryl aldehydes, alkyl nitriles and dimedone proceeds under microwave irradiation in solvent free conditions to give highly functionalised tetrahydrobenzo[*b*]pyrans in excellent yields.

Development of new solid phase (solvent free) reactions and transferring solution phase reactions to solid phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimisation of drug candidates.[1] One-pot multicomponent reactions (MCRs) by virtue of their convergence, productivity, facile execution and generally high yield of products have attracted considerable attention from the point of view of ideal synthesis.[2] The first MCR was initiated by Strecker in 1850 for the synthesis of amino acids.[3] However, in the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs.[4] The potential application of microwave technology in organic synthesis, particularly in solid phase organic reactions is increasing rapidly because of reaction simplicity, less pollution and minimum reaction times providing rapid access to large libraries of diverse small molecules.[5]

4*H*-Benzo[*b*]pyrans are an important class of compounds which have received considerable attention in recent years due to their wide range of biological activities.[6] Compounds with these ring systems have diverse pharmacological activities such as anti-coagulant, anticancer, spasmolytic, diuretic, anti-ancaphylactia, etc.[7]

4*H*-Pyrans also constitute the structural unit of a series of natural products.[8] A number of 2-amino-4*H*-pyrans are useful as photoactive materials.[9] In the conventional reported synthesis of 4*H*-benzo[*b*]pyrans, the use of organic solvents like DMF/acetic acid make the work-up procedure complicated and leads to poor yields of the products besides polluting the environment.[10] Thus new routes for the synthesis of these molecules have attracted considerable attention in the search for methods for rapid entry to these heterocycles. Recently, Kaupp et al. reported a novel method for the synthesis benzo[*b*]pyrans utilising the reactants in solid or molten state.[11] This reaction has its own merit and some limitations: the two-step reaction was performed at very high temperature and required a longer period of time. Moreover the reaction was applied for the synthesis of only a few compounds. As part of our continued interest[12] in the development of highly expedient methods for the synthesis of heterocyclic compounds of biological importance, we report here a very simple and highly efficient method for the synthesis of 4*H*-benzo[*b*]pyrans via a three-component cyclocondensation reaction under microwave irradiation using simple and inexpensive sodium bromide as catalyst in solvent free conditions (Scheme 1).

In a typical experimental procedure,[13] equimolar amounts of benzaldehyde **1a**, alkyl nitrile **2a** and

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* Corresponding author. Tel.: +91 376 2370121; fax: +91 376 2370011; e-mail: pulak_jyoti@yahoo.com

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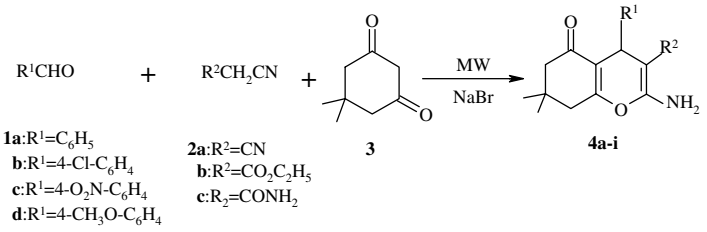
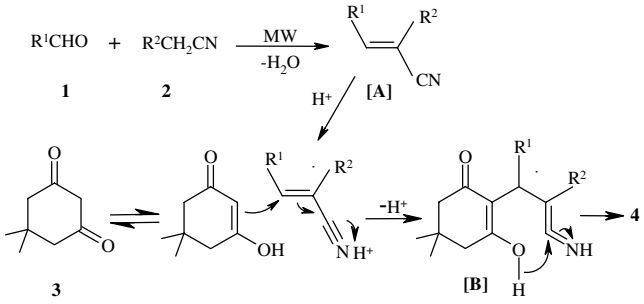


Scheme 1.

dimedone (5,5-dimethyl-1,3-cyclohexanedione) **3**, were mixed thoroughly with a catalytic amount of sodium bromide. The reaction mixture was irradiated with microwaves (Synthwave 402 Monomode Reactor from Prolabo) at 60% power and at 70 °C for 10 min to afford the 4*H*-benzo[*b*]pyran **4a** in excellent yield. The structure of the compound was confirmed from spectroscopic data and found to be comparable in all respect with an authentic sample.[14] With suitable conditions established for the microwave-assisted reaction, a number of 4*H*-benzo[*b*]pyrans **4b–i** were synthesised by utilising various aromatic aldehydes **1a–d** and alkyl nitriles **2a–c**, with dimedone **3** and the structures of the products were confirmed from spectroscopic data. Although, the reaction is applicable to various alkyl nitriles, the activity of cyanoacetamide is poor in comparison to malononitrile and ethyl cyanoacetate. Our observations are recorded in Table 1.

A mechanism for the reaction is outlined in Scheme 2. The reaction occurs via initial formation of the cyano olefin [**A**] from the condensation of aryl aldehyde **1** and alkyl nitrile **2**, which reacts with **3** to give the intermediate [**B**] which subsequently cyclises to afford the desired compound **4**. The water molecule eliminated in the first step plays a key role in the cyclisation process as no reaction occurs in its absence. This was evident from the fact that when the cyano olefin, prepared by conventional Knoevenagel condensation, was reacted directly with compound **3** under microwave irradiation at 70–90 °C, in the presence of NaBr as catalyst, the starting materials were found to remain intact. On the other hand, when the same reaction was performed with the addition of two drops of water to the reaction mixture, the reaction occurred smoothly and gave the desired cycloadduct. In another experiment, we performed the three-component reaction by adding a few drops of



Scheme 2.

water and eliminating the catalyst and isolated the cyano olefin intermediate and unreacted **3**. Thus it was concluded that initial protonation of the nitrile group in the presence of NaBr took place and initiated the cycloaddition process. Moreover, the ionic catalyst is not involved in formation of the cyano olefin but must help its conversion to the cycloadduct.

In conclusion we have demonstrated a novel, sodium bromide catalysed, one-pot, three-component reaction under microwave irradiation in solvent free conditions that offers a simple and efficient route for the synthesis of 4*H*-benzo[*b*]pyrans of biological importance in good to excellent yields.

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Table 1. Sodium bromide catalysed three-component reactions under microwave irradiation (MW) and solvent free conditions

Product	R^1	R^2	MW			Yield (%)	Mp (°C)	
			Power (%)	Temp (°C)	Time (min)		Found	Reported
4a	C_6H_5	CN	60	70	10	95	231–233	233–234[14]
4b	4-Cl–C_6H_4	CN	60	70	10	90	215–217	218[10a]
4c	4-O_2N–C_6H_4	CN	60	70	10	90	177–178	177–178[11]
4d	4-CH_3O–C_6H_4	CN	70	80	15	85	199–201	198–200[10b]
4e	C_6H_5	CO_2–C_2H_5	60	70	10	85	190–192	Not rep.
4f	4-Cl–C_6H_4	CO_2–C_2H_5	60	80	10	80	256–259	Not rep.
4g	4-CH_3O–C_6H_4	CO_2–C_2H_5	70	85	15	87	182–184	Not rep.
4h	C_6H_5	$CONH_2$	70	85	15	63	216–218	Not rep.
4i	4-Cl–C_6H_4	$CONH_2$	70	85	15	60	189–191	Not rep.

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13. In a simple experimental procedure equimolar amounts of **1a** (212 mg, 2 mmol), **2a** (132 mg, 2 mmol) and **3** (280 mg, 2 mmol) were mixed thoroughly with a catalytic amount of sodium bromide (42 mg, 0.4 mmol) and allowed to react under microwave irradiation at 60% power and 70 °C for 10 min. The microwave's automatic mode stirrer helps in mixing and uniform heating of the reactants. The reaction vessel was allowed to cool to room temperature and the solid compound obtained was washed with water and finally recrystallised from ethanol to afford **4a** (558 mg, in 95% yield). The structures of the products was fully characterised by spectroscopic methods. Compound **4a**: mp 231–233 °C. ^{1}H NMR (300 MHz): δ 1.03 (s, 3H), 1.10 (s, 3H), 2.15 (1H, d, J = 16 Hz), 2.25 (1H, d, J = 16 Hz), 2.48 (br s, 2H), 4.32 (s, 1H), 5.85 (s, 2H), 7.10–7.30 (m, 5H). ^{13}C NMR (75 MHz): δ 26.3, 27.6, 31.2 (C-7), 35.0 (C-4), 39.8 (C-8), 49.9 (C-6), 60.3 (C-3), 113.0 (C-4a), 118.4 (CN), 126.1, 126.6 (2C), 127.5 (2C), 143.2, 157.7 (C-2), 161.3 (C-8a), 195.1 (C=O). IR (KBr) ν_{max} 3392, 3289, 2930, 2200, 1688, 1600 cm^{-1}. Similarly the compounds **4b**–**i** were synthesised and characterised (Table 1). The spectroscopic data of some selected compounds are given below.
Compound **4e**: mp 190–192 °C. ^{1}H NMR (300 MHz): δ 1.01 (s, 3H), 1.09 (s, 3H), 1.25 (t, 3H, J = 7.3 Hz), 2.16 (1H, d, J = 16 Hz), 2.25 (1H, d, J = 16 Hz), 2.46 (br s, 2H), 4.20 (q, 2H, J = 7.3 Hz), 4.30 (s, 1H), 5.89 (s, 2H), 7.12–7.30 (m, 5H). ^{13}C NMR (75 MHz): δ 19.1, 26.5, 28.1, 31.1 (C-7), 35.2 (C-4), 39.9 (C-8), 50.1 (C-6), 60.4 (C-3), 71.1, 113.3 (C-4a), 126.0, 126.5 (2C), 127.6 (2C), 144.1, 156.9 (C-2), 161.0 (C-8a), 172.3, 195.1 (C=O). IR (KBr) ν_{max} 3416, 2959, 2928, 1745, 1594, 1360 cm^{-1}.
Compound **4h**: mp 216–218 °C. ^{1}H NMR (300 MHz): δ 1.04 (s, 3H), 1.12 (s, 3H), 2.16 (1H, d, J = 16 Hz), 2.28 (1H, d, J = 16 Hz), 2.52 (br s, 2H), 4.38 (s, 1H), 5.88 (s, 2H), 7.10–7.30 (m, 5H). ^{13}C NMR (75 MHz): δ 26.7, 27.9, 31.2 (C-7), 35.4 (C-4), 40.4 (C-8), 49.9 (C-6), 61.0 (C-3), 113.7 (C-4a), 126.0, 126.7 (2C), 128.1 (2C), 143.7, 157.7 (C-2), 162.1 (C-8a), 171.3, 195.5 (C=O). IR (KBr) ν_{max} 3399, 3184, 2955, 1687, 1595 cm^{-1}.
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