Short communication

Tetrabutylammonium Bromide in Water as a Green Media for the Synthesis of Pyrano[2,3-*d*]pyrimidinone and Tetrahydrobenzo[*b*]pyran Derivatives

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Abstract

Tetrabutylammonium bromide (TBAB) was used as a green catalyst for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone derivatives in water as a solvent. Use of nontoxic reaction components, short reaction times, easy work-up and high yields are some important advantages of this method.

Keywords: Tetrabutylammonium bromide, multicomponent reaction, catalyst, Knoevenagl reaction.

1. Introduction

Recently, the development of environmentally benign and clean synthetic procedures has become the goal of organic synthesis. Water plays an essential role in life processes and also as a medium for organic reactions.[1,2] The use of water as a reaction medium exhibits a remarkable benefit because of its highly polarity and therefore immiscibility with the most organic compounds. Reactions in aqueous media are environmentally safe, have less carcinogenic effects with a simple work up and are especially important in industry. Thus, there is a need for developing multicomponent reactions (MCR's) in water, without the use of any harmful organic solvents and catalysts.

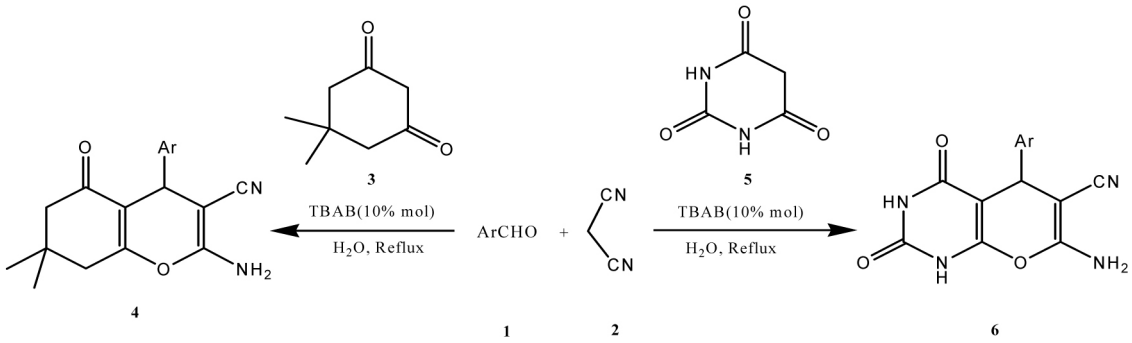
Tetrahydrobenzo[*b*]pyrans are an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals. These compounds are widely used as anti-coagulant, diuretic, spasmolytic, anticancer and anti-anaphylactic agents.[3–5] Numerous methods have been reported for the synthesis of *4H*-benzo[*b*]pyrans.[3,6–14] However, some of these methods have drawbacks such as long reaction times, use of expensive reagents, low yields, harsh reaction conditions, effluent pollution and tedious work-up procedures. On the other hand, due to the diverse biological properties of pyranopyrimidinone derivatives, there is a widespread interest in their synthesis. Compounds with an uracil moiety, have shown antitumor, antibacterial, anti hypertensive, hepatoprotective, vasodilator, antiallergic, antifungal, antimalarial and herbicidal activities.[15–20] There are several methods for the synthesis of pyranopyrimidinones under traditional thermal condition or microwave irradiation.[21–25] Each of these methods has its own advantages with some limitations such as extreme experimental conditions, long reaction times, low yields, and effluent pollution.

In addition to its use as an ionic liquid, tetrabutylammonium bromide (TBAB) has been used as an efficient catalyst in various organic transformations.[26–31] TBAB is an inexpensive, readily available and has inherent properties like environmental compatibility, greater selectivity, operational simplicity, non-corrosive nature and ease of reusability.

As a part of our work on one-pot multicomponent reactions (MCRs) for the synthesis of various heterocyclic compounds,[32,33] we report here a highly efficient procedure for the preparation of 4*H*-benzo[*b*]pyrans and pyrano[2,3-*d*]pyrimidinones via a domino Knoevenagel-cyclocondensation reaction using TBAB as a catalyst in water.

2. Results and Discussion

In a typical experimental procedure, a mixture of aromatic aldehyde **1**, malononitrile **2**, dimedone **3** or barbituric acid **5** in water under reflux condition, was stirred in the presence of a catalytic amount of TBAB (10 mol%) to afford the 4*H*-benzo[*b*]pyrans (**4a**-**n**) and pyrano[2,3-*d*]pyrimidinones (**6a**-**h**) in high yields (Scheme 1).



Scheme 1: TBAB in water efficiently catalyzed the synthesis of pyrano[2,3-*d*]pyrimidinones and 4*H*-benzo[*b*]pyrans.

In the absence of TBAB, the reaction was not preceded and only a poor yield of products was obtained after 10 h.

The structure of products was confirmed by physical and spectroscopic (IR, ^{1}H NMR) data, and by elemental analysis. The work-up of the reaction is accomplished by simple filtration of the product after cooling of the reaction mixture, followed by recrystalization. Tables 1 and 2 show the results obtained in the reaction of a series of aldehydes with malononitrile and dimedone or barbituric acid. Reactions are very clean and yield 4*H*-benzo[*b*]pyrans (**4a**-**n**) or pyrano[2,3-*d*]pyrimidinones (**6a**-**h**) as a sole products within short reaction times in good to high yields.

In Scheme 2 we have proposed a possible mechanism for this reaction. In the first step of the reaction, the olefin **8** is produced by a Knoevenagel condensation between aryl aldehyde **1** and malononitrile **3,** promoted by TBAB. Barbituric acid in the presence of TBAB could be converted to its corresponding tetrabutylammonium barbiturate **9** that could easily react with olefin **8** to give intermediate **10** which converts to product **6** after proton transfer and tautomerization. The formation of intermediate **8** was confirmed by the separate condensation of benzaldehyde and malonitrile in the presence of TBAB.

3. Experimental

3. 1. General

Melting points were determined using an electro thermal digital apparatus and are uncorrected. IR spectra were recorded on a Galaxy series FT-IR 5000 spectrometer and NMR spectra were recorded on a

Table 1: TBAB catalyzed synthesis of 4*H*-benzo[*b*]pyrans in water.

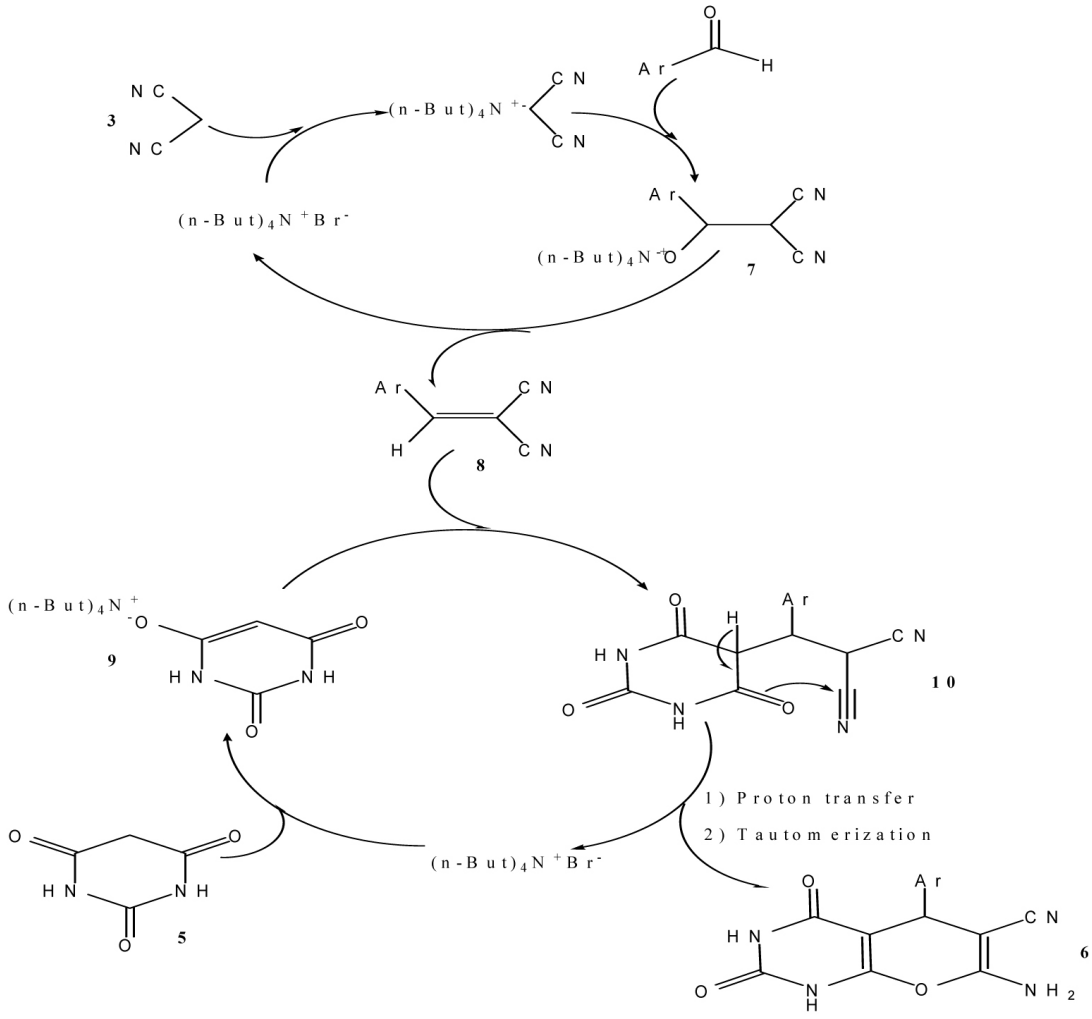
Product	Ar	Time (min)	Yield (%)[a]	m.p. (°C) Found	m.p. (°C) Reported [Lit.]
4a	C_6H_5	40	90	227–229	228–230 [6]
4b	4-Br-C_6H_4	30	95	205–207	203–205 [7]
4c	3-Cl-C_6H_4	45	89	229–231	224–225 [9]
4d	4-Cl-C_6H_4	35	94	212–214	209–211 [6]
4e	2,3-Cl_2-C_6H_3	40	90	249–252	252–254 [13b]
4f	2,4-Cl_2-C_6H_3	30	92	182–183	180–182 [13b]
4g	4-OH-C_6H_4	35	90	205–207	206–208 [13a]
4h	3-OH-C_6H_4	35	91	229–231	236–238 [13a]
4i	3-NO_2-C_6H_4	40	90	210–212	212–214 [9]
4j	4-NO_2-C_6H_4	45	93	178–180	177–178 [9]
4k	2-NO_2-C_6H_4	45	91	227–230	224–226 [9]
4l	4-CH_3-C_6H_4	30	94	212–215	223–225 [13a]
4m	4-$N(Me)_2$-C_6H_4	35	92	223–225	230 [12]
4n	4-OCH_3-C_6H_4	40	95	201–203	203 [12]

[a] Yields refer to isolated products.

Table 2: TBAB catalyzed synthesis of pyrano[2,3-*d*]pyrimidinones in water.

Product	Ar	Time (min)	Yield (%)[a]	m.p. (°C) Found	Reported [Lit.]
6a	4-Br-C_6H_4	25	85	229–230	230–231 [24]
6b	3-Cl-C_6H_4	30	80	242–244	240–241 [24]
6c	2,3-Cl_2-C_6H_3	35	88	243–245	240–242 [24]
6d	2,4-Cl_2-C_6H_3	30	90	239–241	241–242 [24]
6e	3-OH-C_6H_4	30	87	160–162	158–160 [24]
6f	3-NO_2-C_6H_4	35	81	271–272	268–270 [24]
6g	4-NO_2-C_6H_4	35	80	239–241	239–240 [24]
6h	4-CN-C_6H_4	30	88	252–253	254–256 [24]

[a] Yields refer to isolated products.



Scheme 2: The proposed mechanism for one-pot synthesis of pyrano[2,3-*d*]pyrimidinones catalyzed by TBAB in water as a solvent medium.

Bruker 300 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III). The progress of the reaction was followed by TLC using n-hexane/ethyl acetate (3:1 v/v) as an eluent.

3. 2. General Procedure for Synthesis of Tetrahydrobenzo[*b*]pyrans and Pyrano[2,3-*d*]pyrimidinones:

A mixture of an aromatic aldehyde (**1**, 1mmol), malononitrile (**2**,1 mmol), dimedone (**3**, 1mmol) or barbituric

acid (**5**,1 mmol) and TBAB (10% mol) in H_2O (10 ml) was stirred under reflux condition for a suitable time (see Table 1). After completion of the reaction as indicated by TLC, water was added and the mixture cooled in a refrigerator. The solid product was filtered and washed with cold water (2 × 10 ml). The pure product was obtained by recrystallization from ethanol:water (4:1).

3. 3. Selected Data for Products (4a-n), (6a-h) and Intermediate 8

Intermediate 8: IR (KBr) ν: 3032, 2224, 1591, 1568, 1450, 1217, 678 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.13 (2H, t, H–Ar), 7.22 (1H, t, H–Ar), 7.37 (1H, s, H-Vinyl), 7.50 (2H, d, H-Ar) ppm. Anal. Calcd for $C_{10}H_6N_2$: C, 77.91; H, 3.92; N, 18.17. Found C, 78.05; H, 3.98; N, 18.04.

4a: IR (KBr) ν: 3393, 3317, 3185, 2958, 2196, 1687, 1652, 1367 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 0.94 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.08 (1H, d, J = 16.0 Hz, H-6), 2.23 (1H, d, J = 16.0 Hz, H-6´), 2.50 (2H, m, CH_2), 4.11 (1H, s, H-4), 7.06 (2H, br s, NH_2), 7.19 (3H, m, H–Ar), 7.33 (2H, m, H–Ar) ppm. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found C, 73.97; H, 6.79; N, 9.42.

4b: IR (KBr) ν: 3398, 3319, 3211, 2966, 2191, 1683, 1656, 1369 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 0.97 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.12 (1H, d, J = 16.0 Hz, H-6), 2.28 (1H, d, J = 16.0 Hz, H-6´), 2.54 (2H, m, CH_2), 4.21 (1H, s, H-4), 7.13 (2H, br s, NH_2), 7.15 (2H, d, J = 8.5 Hz, H–Ar), 7.50 (2H, d, J = 8.5 Hz, H–Ar) ppm. Anal. Calcd for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51. Found C, 58.17; H, 4.71; N, 7.43.

4f: IR (KBr) ν: 3533, 3364, 3153, 2966, 2193, 1685, 1658, 1367 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 1.00 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.11 (1H, d, J = 16.0 Hz, H-6), 2.27 (1H, d, J = 16.0 Hz, H-6´), 2.47–2.61 (2H, m, CH_2), 4.70 (1H, s, H-4), 7.15 (2H, br s, NH_2), 7.25 (1H, d, J = 8.4 Hz, H–Ar), 7.39 (1H, d, J = 8.4 Hz, H–Ar), 7.56 (1H, s, H–Ar) ppm. Anal. Calcd for $C_{18}H_{16}Cl_2N_2O_2$: C, 59.52; H, 4.44; N, 7.71. Found C, 59.91; H, 4.63; N, 7.63.

4j: IR (KBr) ν: 3394, 3323, 3213, 2970, 2193, 1683, 1655, 1523, 1365 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 0.99 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.14 (1H, d, J = 16.0 Hz, H-6), 2.30 (1H, d, J = 16.0 Hz, H-6´), 2.53–2.57 (2H, m, CH_2), 4.39 (1H, s, H-4), 7.24 (2H, br s, NH_2), 7.48 (2H, d, J = 8.4 Hz, H–Ar), 8.21 (2H, d, J = 8.4 Hz, H–Ar) ppm. Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found C, 63.99; H, 5.17; N, 12.25.

4m: IR (KBr) ν: 3381, 3321, 3209, 2962, 2191, 1682, 1656, 1367 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 0.97 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.10 (1H, d, J = 16.0 Hz, H-6), 2.27 (1H, d, J = 16.0 Hz, H-6´), 2.47–2.55 (2H, m, CH_2), 2.87 (6H, s, -$N(Me)_2$), 4.06 (1H, s, H-4), 6.66 (2H, d, J = 8.7 Hz, H–Ar), 6.95 (2H, br s, NH_2), 6.97 (2H, d, J = 8.7 Hz, H–Ar) ppm. Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.49; H, 6.71; N, 12.33.

6a: IR (KBr) ν: 3391, 3302, 3188, 3072, 2197, 1718, 1674, 1408, 1280 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 4.26 (1H, s, H-5), 7.20 (2H, br s, NH_2), 7.22 (2H, d, J = 8.2 Hz, H–Ar), 6.51 (2H, d, J = 8.2 Hz, H–Ar) 11.12 (1H, br s, NH), 12.14 (1H, br s, NH) ppm. Anal. Calcd for $C_{14}H_9BrN_4O_3$: C, 46.56; H, 2.51; N, 15.51. Found C, 47.11; H, 2.63; N, 15.39.

6d: IR (KBr) ν: 3389, 3305, 3184, 3078, 2193, 1718, 1676, 1410, 1282 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6) δ: 4.75 (1H, s, H-5), 7.25 (2H, br s, NH_2), 7.38 (2H, s, H–Ar), 7.57 (1H, s, H–Ar), 11.13 (1H, br s, NH), 12.17 (1H, br s, NH) ppm. Anal. Calcd for $C_{14}H_8Cl_2N_4O_3$: C, 47.89; H, 2.30; N, 15.96. Found C, 47.72; H, 2.41; N, 15.85.

4. Conclusions

We have developed an efficient and ecologically safe method for the synthesis of 4*H*-benzo[*b*]pyrans and pyrano[2,3-*d*]pyrimidinone derivatives using a green procedure. This methodology has some advantages such as operational simplicity, neutral conditions, high yields, use of TBAB as a green, nontoxic and efficient catalyst, and easy work-up.

5. Acknowledgment

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6. References

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Povzetek

V prispevku je opisana uporaba tetrabutilamonijevega bromida (TBAB) kot okolju prijaznega katalizatorja za sintezo derivatov tetrahidrobenzo[*b*]pirana in pirano[2,3-*d*]pirimidinona v vodi kot topilu. Pomembne prednosti te reakcije so kratki reakcijski časi, enostavna izolacija produkta, visoki izkoristki in uporaba nestrupenih reaktantov.