Tetrahedron Letters 50 (2009) 4125–4127

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Tetrabutylammonium bromide (TBAB): a neutral and efficient catalyst for the synthesis of biscoumarin and 3,4-dihydropyrano[*c*]chromene derivatives in water and solvent-free conditions

Jitender M. Khurana *, Sanjay Kumar

*Department of Chemistry, University of Delhi, Delhi 110 007, India*

ARTICLE INFO

*Article history:*
Received 1 March 2009
Revised 25 April 2009
Accepted 28 April 2009
Available online 3 May 2009

ABSTRACT

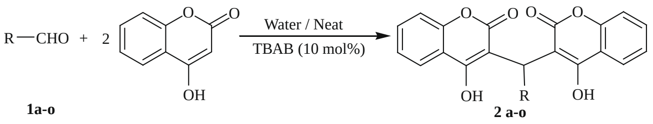
A simple, efficient and ecofriendly procedure has been developed using tetrabutylammonium bromide as catalyst for the synthesis of biscoumarin and dihydropyrano[*c*]chromene derivatives in water and solvent-free neat conditions. The present methodology offers several advantages such as excellent yields, short reaction time and environmentally benign milder reaction conditions.

## Introduction

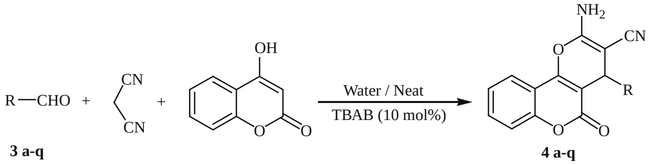
Multicomponent reactions (MCRs) have attracted the attention of synthetic organic chemists for building highly functionalized organic molecules and pharmacologically important heterocyclic compounds.[1] Application of environmentally benign water- and solvent-free solid state organic reactions represents powerful green procedure.[2] Recently tetrabutylammonium bromide (TBAB) has emerged as mild, water-tolerant, inexpensive and environmentally compatible homogenous catalyst in various organic transformations.[3–7] Biscoumarins and dihydropyrano[*c*]chromenes are of considerable interest due to their widespread biological properties.[8–10] A number of methods have been reported for the synthesis of biscoumarins.[11–13] However, comparatively fewer methods have been described for the synthesis of 3,4-dihydropyrano[*c*]chromenes.[14,15] Most of these procedures require refluxing for hours in organic solvents, use of expensive catalysts and tedious work-up. In view of the above-mentioned observations, we decided to investigate the application of TBAB as a catalyst for synthesis of biscoumarins and 3,4-dihydropyrano[*c*]chromenes in water and under solvent-free neat conditions (Schemes 1 and 2).

## Results and discussion

We report herein a green approach for the synthesis of some novel biscoumarins and dihydropyrano[*c*]chromenes catalyzed by TBAB in water and solvent-free neat conditions. In order to optimize the reaction conditions and to evaluate catalytic activity of TBAB, reactions of 4-chlorobenzaldehyde and 4-hydroxycoumarin were carried out in water under reflux in presence of catalysts,



**Scheme 1.**



**Scheme 2.**

for example, $HBF_4$, pTSA, sulfamic acid, $NH_4Cl$, LiBr, TBAB and TBAF to afford 3,3′-(4-chlorophenylmethylene)-bis-(4-hydroxycoumarin) **2b**. The results with different catalysts are given in Table 1.

The best results were obtained with the condensation of one mole of 4-chlorobenzaldehyde with 2 mol of 4-hydroxycoumarin using 10 mol % of TBAB as catalyst in water under reflux. Ninety-five percent of 3,3′-(4-chlorophenylmethylene)-bis-(4-hydroxycoumarin) **2b** was obtained by simple recrystallization from ethanol. Reaction with 5 mol % of catalyst required longer reaction time while reaction with 1 mol % of catalyst was incomplete even after 5 h and only 65% of the product was obtained. TBAF was found to be equally effective as catalyst while the reactions with other catalysts such as $HBF_4$, pTSA, sulfamic acid, $NH_4Cl$ and LiBr were sluggish.

We have also investigated the synthesis of our target compounds under solvent-free neat conditions since a number of reactions have been reported to proceed efficiently and with higher

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* Corresponding author. Tel.: +91 11 27667725; fax: +91 11 27667624.
*E-mail address:* jmkhurana1@yahoo.co.in (J.M. Khurana).

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doi:10.1016/j.tetlet.2009.04.125

**Table 1**
Evaluation of catalytic activity of different catalysts for the condensation of 4-chlorobenzaldehyde and 4-hydroxycoumarin in water

| S.No. | Catalyst | Mol (%) | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $HBF_4$ | 10 | 10 h | 55 |
| 2 | pTSA | 10 | 10 h | 48 |
| 3 | Sulfamic acid | 10 | 10 h | 45 |
| 4 | $NH_4Cl$ | 10 | 10 h | 40 |
| 5 | LiBr | 10 | 3 h | 71 |
| 6 | TBAB | 10 | 25 min | 95 |
| 7 | TBAB | 5 | 2 h | 87 |
| 8 | TBAB | 1 | 5 h | 65 |
| 9 | TBAB | 0 | 10 h | 40 |
| 10 | TBAF | 10 | 30 min | 88 |

selectivity under such conditions.[16] Therefore, 4-chlorobenzaldelyde, 4-hydroxycoumarin and TBAB were mixed thoroughly in a round-bottomed flask and the mixture was heated in an oil bath maintained at 120 °C. Interestingly, the reaction was complete in 20 min and 87% of pure **2b** was obtained.

Subsequently, the condensation of a series of aromatic, heteroaromatic and aliphatic aldehydes with 4-hydroxycoumarin was carried out using TBAB as catalyst under both the conditions outlined above. All aldehydes reacted almost equally well to afford biscoumarins (**2a**–**o**) in excellent yields. A comparison of aqua-mediated synthesis with those performed under neat conditions is drawn in Table 2. It can be inferred from Table 2 that high yields of biscoumarins were obtained by both methods, though, the reaction times were slightly shortened in neat conditions, and the yields were also slightly lower.

Encouraged by these results, we tried to extend the scope of the present protocol for condensation of aldehydes, 4-hydroxycoumarin and malononitrile to afford 2-amino-4-alkyl/aryl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile derivatives. The desired 2-amino-4-chlorophenyl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile **4b** was obtained in 93% yield by condensation of a one mole of 4-chlorobenzaldehyde with 1 mole of 4-hydroxycoumarin and 1.5 mol of malononitrile in presence of 10 mol % of TBAB as catalyst in water under reflux after 45 min. The condensation under solvent-free conditions yielded 88% of pure **4b** in 40 min. Thereafter, a series of differently substituted 3,4-dihydropyrano[*c*]chromene derivatives were prepared successfully from different aliphatic, heteroaromatic and aromatic aldehydes bearing electron-withdrawing and electron-donating groups, 4-hydroxycoumarin and malononitrile in water and under solvent-free neat conditions. These results are listed in Table 3.

**Table 2**
Synthesis of biscoumarins by condensation of aldehydes and 4-hydroxycoumarin using TBAB (10 mol %) as catalyst[17]

| Entry | R | Product | Method A | | Method B | |
|---|---|---|---|---|---|---|
| | | | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 1 | $C_6H_5$ | **2a** | 25 | 92 | 20 | 85 |
| 2 | $4\text{-}ClC_6H_4$ | **2b** | 30 | 95 | 20 | 87 |
| 3 | $4\text{-}BrC_6H_4$ | **2c** | 30 | 88 | 20 | 87 |
| 4 | $3\text{-}ClC_6H_4$ | **2d** | 30 | 87 | 20 | 85 |
| 5 | $4\text{-}NO_2C_6H_4$ | **2e** | 25 | 91 | 20 | 91 |
| 6 | $4\text{-}CH_3C_6H_4$ | **2f** | 30 | 92 | 20 | 88 |
| 7 | $4\text{-}CH_3OC_6H_4$ | **2g** | 30 | 84 | 20 | 78 |
| 8 | $-CH{=}CH-C_6H_5$ | **2h** | 35 | 82 | 20 | 81 |
| 9 | $3,4\text{-}(CH_3O)_2C_6H_3$ | **2i** | 40 | 87 | 20 | 77 |
| 10 | $3,4,5(CH_3O)_3C_6H_2$ | **2j** | 40 | 84 | 20 | 75 |
| 11 | $4\text{-}(CH_3)_2CHC_6H_4$ | **2k** | 30 | 91 | 20 | 85 |
| 12 | Piperonyl | **2l** | 30 | 88 | 20 | 85 |
| 13 | 2-Furanyl | **2m** | 35 | 88 | 20 | 77 |
| 14 | 2-Pyridyl | **2n** | 35 | 90 | 20 | 78 |
| 15 | $CH(CH_3)_2$ | **2o** | 35 | 82 | — | — |

Method A: Reaction carried out in water.
Method B: Reaction carried out under solvent-free conditions.

**Table 3**
Synthesis of 3,4-dihydropyrano[*c*]chromenes by condensation of aldehydes, 4-hydroxycoumarin and malononitrile using TBAB (10 mol %) as catalyst[17]

| Entry | R | Product | Method A | | Method B | |
|---|---|---|---|---|---|---|
| | | | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 1 | $C_6H_5$ | **4a** | 45 | 91 | 40 | 88 |
| 2 | $4\text{-}ClC_6H_4$ | **4b** | 45 | 93 | 40 | 85 |
| 3 | $4\text{-}BrC_6H_4$ | **4c** | 50 | 91 | 40 | 85 |
| 4 | $3\text{-}ClC_6H_4$ | **4d** | 50 | 89 | 40 | 78 |
| 5 | $4\text{-}NO_2C_6H_4$ | **4e** | 45 | 86 | 40 | 89 |
| 6 | $4\text{-}CH_3C_6H_4$ | **4f** | 50 | 88 | 40 | 82 |
| 7 | $2,4\text{-}Cl_2C_6H_3$ | **4g** | 50 | 87 | 40 | 87 |
| 8 | $4\text{-}FC_6H_4$ | **4h** | 60 | 84 | 40 | 81 |
| 9 | $4\text{-}(CH_3)_2NC_6H_4$ | **4i** | 50 | 88 | 40 | 78 |
| 10 | $4\text{-}HOC_6H_4$ | **4j** | 60 | 85 | 40 | 82 |
| 11 | $4\text{-}CH_3OC_6H_4$ | **4k** | 60 | 85 | 40 | 78 |
| 12 | $-CH{=}CH-C_6H_5$ | **4l** | 45 | 87 | 40 | 75 |
| 13 | $4\text{-}(CH_3)_2CHC_6H_4$ | **4m** | 45 | 91 | 40 | 81 |
| 14 | 1-Naphthyl | **4n** | 45 | 87 | 40 | 78 |

Method A: Reaction carried out in water.
Method B: Reaction carried out under solvent-free conditions.

The results clearly indicate that reactions can tolerate a wide range of differently substituted aldehydes. The three-component reactions proceeded smoothly and were complete within 1 h. Excellent yields of products were obtained by both methods. However, in case of aliphatic aldehydes, reactions were not performed under solvent-free conditions because of low boiling point of the aldehydes.

In conclusion, we have reported an easy, efficient and green protocol for the synthesis of biscoumarins and 3,4-dihydropyrano[*c*]chromenes in water and solvent-free neat conditions. The method offers marked improvement with its operational simplicity, low reaction time and high yields of pure products without use of any organic solvent.

## Acknowledgment

S.K. thanks C.S.I.R., New Delhi, India for grant of Junior and Senior research fellowships.

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17. *General procedure for the synthesis of 3,3'-arylmethylenebis-(4-hydroxycoumarin) and 2-amino-4-aryl/alkyl-5-oxo-4H, 5H-pyrano[3,2-c]chromene-3-carbonitrile*: *Method A*: In a typical reaction for the preparation of biscoumarins, a mixture of 4-hydroxycoumarin (5 mmol), aldehyde (2.5 mmol), TBAB (10 mol %) and 20 mL of water was stirred magnetically at 100 °C for appropriate time as mentioned in Table 2. After completion of the reaction as monitored by TLC, reaction mixture was cooled to room temperature. Water was decanted and hot ethanol (15 mL) was added. The solid product obtained was filtered using pump and dried. The crude product was recrystallized from ethanol to yield pure product. For the preparation of pyrano[*c*]chromene derivatives, the reaction of 4-hydroxycoumarin (5 mmol), aldehyde (2.5 mmol), malononitrile (7.5 mmol) and TBAB (10 mol %) was carried out as described above for reaction times given in Table 3.
    *Method B*: In another procedure, the components as mentioned above were mixed thoroughly and heated in an oil bath maintained at 120 °C for appropriate time. The reaction mixture was then cooled to room temperature. Hot ethanol was added to the solid mass thus obtained and the reaction was worked up as described in Method A.