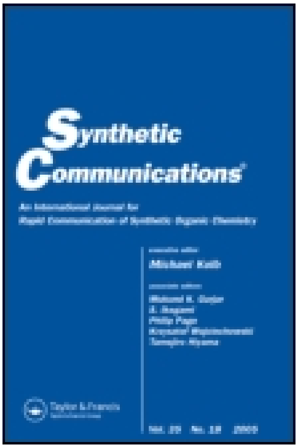


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Clean, One-Pot Synthesis of 4H-Pyran Derivatives Catalyzed by Hexadecyltrimethyl Ammonium Bromide in Aqueous Media

Tong-Shou Jin [a], Li-Bin Liu [a], Ying Zhao [a] & Tong-Shuang Li [a]

[a] Department of Chemistry, College of Chemistry and Environmental Science, Hebei University, Baoding, China

To cite this article: Tong-Shou Jin, Li-Bin Liu, Ying Zhao & Tong-Shuang Li (2005) Clean, One-Pot Synthesis of 4H-Pyran Derivatives Catalyzed by Hexadecyltrimethyl Ammonium Bromide in Aqueous Media, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:14, 1859-1863, DOI: 10.1081/SCC-200064898

To link to this article: http://dx.doi.org/10.1081/SCC-200064898

Synthetic Communications®, 35: 1859–1863, 2005
Copyright © Taylor & Francis, Inc.
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200064898

Clean, One-Pot Synthesis of 4*H*-Pyran Derivatives Catalyzed by Hexadecyltrimethyl Ammonium Bromide in Aqueous Media

Tong-Shou Jin, Li-Bin Liu, Ying Zhao, and Tong-Shuang Li
Department of Chemistry, College of Chemistry and Environmental
Science, Hebei University, Baoding, China

Abstract: An efficient and convenient synthetic route to 4*H*-pyran derivatives in water in the presence of hexadecyltrimethyl ammonium bromide (HTMAB) as catalyst is described. This method provides several advantages such as environment friendliness, high yields, and a simple workup procedure. In addition, water was chosen as a green solvent.

Keywords: Bisarylidenecyclohexanone, green synthesis, 4*H*-pyran derivatives, HTMAB

INTRODUCTION

With the increasing environmental concerns and the regulatory constraints faced by the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research.[1] Therefore, more and more chemists are devoted to the researching "green synthesis," which means the reagent, solvent, and catalyst are environmentally friendly in the organic chemical reactions. Recently, organic reactions in water without use of harmful organic solvents have attracted much attention, because water is

Received in Japan January 11, 2005

Address correspondence to Tong-Shou Jin, Department of Chemistry, College of Chemistry and Environmental Science, Hebei University, No. 88 Hezuo Road, Baoding 071002, Hebei Province, China. E-mail: orgsyn@mail.hbu.edu.cn

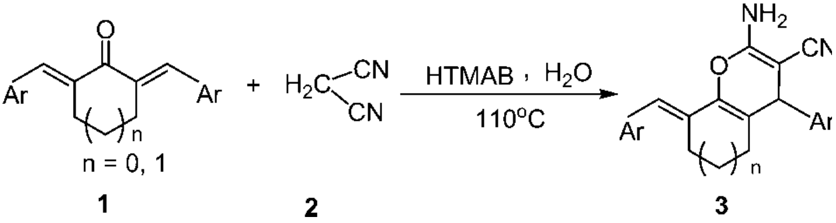
a cheap, safe, and environmentally benign solvent.[2] In the course of our investigations to develop new synthetic methods in water, we examined the synthesis of 4*H*-pyran derivatives in water, as a green solvent.

Pyran derivatives occupy an important place in the realm of natural and synthetic organic chemistry because of their biological and pharmacological properties as antisterility and anticancer agents.[3] In addition, polyfunctionalized 4*H*-pyrans are a common structural unit in a number of natural products.[4] Moreover, 2-amino-3-cyano-4*H*-pyrans possess photochemical activity.[5] These findings stimulated our interest in the synthesis of heterocyclic derivatives of these ring systems.

As a good phase-transfer catalyst, hexadecyltrimethyl ammonium bromide (HTMAB) has been used in a number of organic reactions. However, the use of HTMAB as a catalyst in the synthesis of 4*H*-pyran derivatives has not been reported. In this article, we report a general and highly efficient route for the synthesis of 4*H*-pyran derivatives using an inexpensive and commercially available HTMAB as catalyst. This a novel, one-pot combination using water as a green solvent not only preserves the simplicity but also consistently gives the corresponding products in good to excellent yields (Scheme 1).

In a typical experimental procedure, a solution of bisarylidenecyclohexanone **1** and malononitrile **2** in water was heated in the presence of a catalytic amount of HTMAB, and the corresponding 4*H*-pyran derivatives **3** were obtained in good to excellent yields. The results are summarized in Table 1.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. To test the catalysts, the reaction of bisbenzalidenecyclohexanone and malononitrile in water was selected as a model reaction. Among the catalysts tested, HTMAB was found to be the most efficient catalyst. The catalysts we tested, DBSA (dodecylbenesulfonic acid), TBAB (tetrabutylammonium bromide) and TEBA (tetraethylammonium bromide), did not give products. HTMAB formed a white turbid reaction mixture, whereas TBAB and TEBA formed two immiscible layers. This indicates that the long alkyl chain of HTMAB is necessary for the formation of the colloidal dispersion that is assumed to lead to efficient catalysis. We



Scheme 1.

Table 1. Synthesis of 4*H*-pyran derivatives catalyzed by HTMAB in aqueous media

Entry	Ar	*n*	Product	Yield[a] (%)	Mp (°C)	
					Found	Reported
1	C_6H_5 **1a**	1	**3a**	93	230–231	228–230[6]
2	2-ClC_6H_4 **1b**	1	**3b**	80	237–238	237–238[7]
3	3-ClC_6H_4 **1c**	1	**3c**	77	201–202	—
4	4-ClC_6H_4 **1d**	1	**3d**	87	215–216	217–219[6]
5	4-$CH_3C_6H_4$ **1e**	1	**3e**	82	161–162	162–163[7]
6	4-$NO_2C_6H_4$ **1f**	1	**3f**	76	216–218	—
7	C_6H_5 **1g**	0	**3g**	78	227–228	228–230[7]
8	2-ClC_6H_4 **1h**	0	**3h**	85	213–214	214–215[7]

[a] Isolated yield.

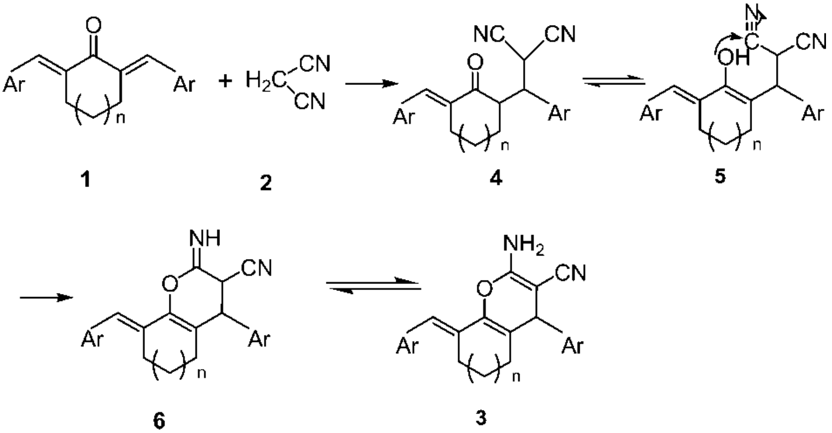
examined several experiments and found that the amount of the catalyst also had a crucial effect on these conversions. For example, bisbenzalidenecyclohexanone reacted with malononitrile in the presence of 1 mol% HTMAB to give the product **3a** in quantitative yield (66%) in refluxing water after 8 h of reaction time. Increasing the catalyst to 5 and 10 mol% results to increase the reaction yields 84% and 93% respectively. Use of merely 10 mol% HTMAB in refluxing water is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. Therefore, 10 mol% HTMAB was chosen as a quantitative catalyst for the reactions.

The catalyst could be reused five times for the synthesis of **3a** without significant loss of activity. The results are summarized in Table 2. In addition, it must be pointed out that all of these reactions were carried out in water.

The formation of the compounds **3** was assumed to proceed via formation of a Michecal adduct intermediate followed by cyclization according to Scheme 2. A bisarylidenecyclohexanone **1** was firstly condensed with malononitrile **2** to afford the intermediate **4**; this step can be regarded as a Michael addition. Then, the intermediate **5** cyclized by nucleophilic attack of the OH

Table 2. Reuse of the catalyst for the synthesis of **3a** catalyzed by HTMAB

Entry	Yield (%)
1	93.0
2	92.7
3	92.0
4	91.7
5	90.9



Scheme 2.

group on the cyano (CN) moiety and gave the intermediate **6**. Finally, the expected products **3** were afforded (**5** → **6** → **3**). In this process, HTMAB could promote these reactions as an emulsifier.

In conclusion, we have described a general and highly efficient procedure for the preparation of 4*H*-pyran derivatives by catalyzed HTMAB, in water cooler than 110°C. In addition, it is possible to apply the tenets of green chemistry to the generation of interesting products using aqueous media methods that are less expensive and less toxic than those with organic solvents. Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reactions, and minimal environmental effects, which makes it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

The new compounds prepared were characterized by ^{1}H NMR, IR, and elemental analysis and are described in the experimental section. IR spectra were recorded on a Bio-rad FIS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on an AVAVCE-400 spectrometer using TMS as internal standard and $CDCl_3$ as solvent.

General Procedure for 2-Amino-3-cyano-4*H*-pyran Derivatives

A mixture of the bisarylidenecyclohexanone **1** (1 mmol), malononitrile **2** (1 mmol), and HTMAB (10 mol%) in water (20 mL) was stirred at 110°C for 8 h. Then, the mixture was cooled to room temperature, the solid was filtered off, and it was washed with H_2O (40 mL). The crude products were purified by recrystallization with ethanol (95%). Data of some compounds are shown:

3c. ^{1}H NMR (CD_3Cl) δ (ppm) 1.58–1.70 (m, 2H, CH_2), 1.94–2.07 (m, 2H, CH_2), 2.55–2.74 (m, 2H, CH_2), 3.98 (s, 1H, CH), 4.58 (s, 2H, NH_2), 6.83 (s, 1H, CH═), 7.15–7.33 (m, 8H, $2 \times C_6H_4$); IR (KBr), ν(cm^{-1}) 3461, 3323, 2924, 2846, 2194, 1671, 1637, 1595, 1415, 1129. Anal. calcd. for $C_{23}H_{18}Cl_2N_2O$: C, 67.48; H, 4.40; N, 6.84. Found: C, 67.35; H, 4.46; N, 6.92.

3f. ^{1}H NMR (CD_3Cl) δ (ppm) 1.58–1.71 (m, 2H, CH_2), 1.96–2.09 (m, 2H, CH_2), 2.63–2.74 (m, 2H, CH_2), 4.17 (s, 1H, CH), 4.67 (s, 2H, NH_2), 6.96 (s, 1H, CH═), 7.46–8.25 (m, 8H, $2 \times C_6H_4$); IR (KBr), ν(cm^{-1}) 3484, 3373, 2931, 2188, 1667, 1632, 1590, 1514, 1411, 1261, 1131. Anal. calcd. for $C_{23}H_{18}N_4O_5$: C, 64.19; H, 4.19; N, 13.02. Found: C, 64.08; H, 4.11; N, 13.15.

ACKNOWLEDGMENT

This project was supported by the National Natural Science Foundation of China, Educational Ministry of China, Educational Department of Hebei Province, and Science and Technology Commission of Hebei Province.

REFERENCES

1. Anastas, P.; Williamson, T. *Green Chemistry, Frontiers in Benign Chemical Synthesis and Procedures*; Oxford Science Publications: Oxford, 1998.
2. (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, 1998; (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (c) Cornils, B.; Herrmann, W. A. *Aqueous-phase Organometallic Chemistry—Concepts and Applications*; Wiley-VCH: Weinheim, 1998.
3. (a) Morianka, Y.; Takahashi, K. *J. Jpn. Kokai.* **1977**, *17*, 498; (b) Montandon, J. B.; Zijlstra, F. J.; Wilson, J. H. P. *J. Int. Tissue. Reac.* **1989**, *11*, 107; (c) Brooks, G. T. *J. Pestic. Sci.* **1998**, *22*, 41; (d) Hyana, T.; Saimoto, H. Japanese patent 1987, 621 812 768.
4. Martin, N.; Martin, G.; Secoane, A. C.; Marco, J. L.; Albert, A.; Cano, F. H. *Liebigs Ann. Chem.* **1993**, 801.
5. Ocallaghan, C. N.; Mcmurry, T. B. H. *J. Chem. Res. Synop.* **1999**, 457.
6. Zhou, J. F. *Synth. Commun.* **2003**, *33*, 99.
7. Wang, X. S.; Shi, D. Q.; Tu, S. J. *Chin. J. Chem.* **2004**, 122.