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Uncatalyzed Reactions in Aqueous Media: Three-Component, One-Pot, Clean Synthesis of Tetrahydrobenzo[*b*]pyran Derivatives

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The synthesis of various tetrahydrobenzo[*b*]pyran derivatives has been carried out by means of an uncatalyzed, three-component, one-pot, clean condensation of aromatic aldehydes, reactive methylene compounds, and dimedone in aqueous medium. Simple workup, and mild and neutral conditions that give quantitative yields of products in pure form, are the attractive features of this method.

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With increasing environmental concerns and the regulatory constraints faced in the chemical and pharmaceutical industries, the development of environmentally benign organic reactions has become crucial and demanding research.[1] Therefore, more and more chemists' synthetic endeavours are devoted toward 'green chemistry', which means the reagents, solvents, and catalysts are environmentally friendly. Recently, Wender defined the ideal synthesis as one in which the target components are produced in one step in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally acceptable process.[2] One-pot multi-component condensations represent a possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building up complex molecules with maximum simplicity and brevity.[3] The art of performing efficient chemical transformations by coupling three or more components in a single operation with or without catalyst and avoiding the stoichiometric use of toxic reagents, large amounts of organic solvents, and expensive purification techniques represents a fundamental target of modern organic synthesis.[4]

In recent years in organic synthesis, increasing attention has been focussed on reactions in aqueous media.[5] When a solvent must be used, water is the most acceptable in terms of cost and environmental impact. However, despite its large liquid range and extremely high specific heat capacity, it is frequently overlooked as a solvent for organic reactions. Most catalysts and reagents are deactivated or decompose in water and, in general, organic compounds are insoluble in water. Therefore, carrying out organic reactions in water poses important challenges in the area of reaction design. The use of water as a solvent in organic synthesis is often surprisingly effective even for reactions that are traditionally carried out under anhydrous conditions, despite the fact that the reaction involves a dehydration step.

Tetrahydrobenzo[*b*]pyran and its derivatives have attracted considerable attention from organic and medicinal chemists because of their useful biological and pharmacological properties, such as anti-coagulant, spasmolytic, diuretic, anti-cancer, and anti-anaphylactin characteristics.[6–10] Some 2-amino-4*H*-pyrans can be useful as photoactive materials,[11] whereas polysubstituted 4*H*-pyran constitutes a structural unit of a series of natural products.[12,13] Most of the reported conventional methods of syntheses for 4*H*-benzo[*b*]pyran involves use of organic solvents, such as acetic acid or dimethylformamide.[14,15] Some recent reports also describe the synthesis of tetrahydrobenzo[*b*]pyrans.[16] While each of the above methods has its own merit, these syntheses are plagued by the limitations of poor yields, difficult workup, and effluent pollution. 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, tetrahydrobenzo[*b*]pyrans have been synthesized using catalysts such as KF–alumina[15] or KF–basic alumina under ultrasonic irradiation,[17] hexadecyltrimethyl ammonium bromide,[18] sodium bromide under microwave irradiation,[19] (*S*)-proline,[20] or using the reactants in solid or molten state[22] and microwave irradiation.[22] However, these methods have one or more limitations such as: (1) multi-step reactions;[15,21,22] (2) the reactions were performed at very high temperature and required longer times;[21] (3) catalyst loading is high;[15,17–20] (4) the reaction only applies to the synthesis of a limited number of compounds.[21] Consequently, there is scope for further renovation of the method, which avoids both an organic solvent and the need for a catalyst, and involves simple workup and furnishes greater yields.

We report here for the first time a general, practical, and highly efficient route for the synthesis of tetrahydrobenzo[*b*]pyran without catalyst in tap water that involves

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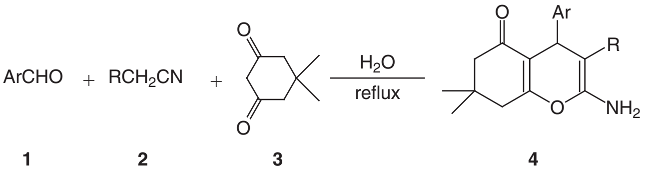
a three-component, one-pot, clean procedure. The title compounds are obtained in almost pure form and in high yield (Scheme 1).

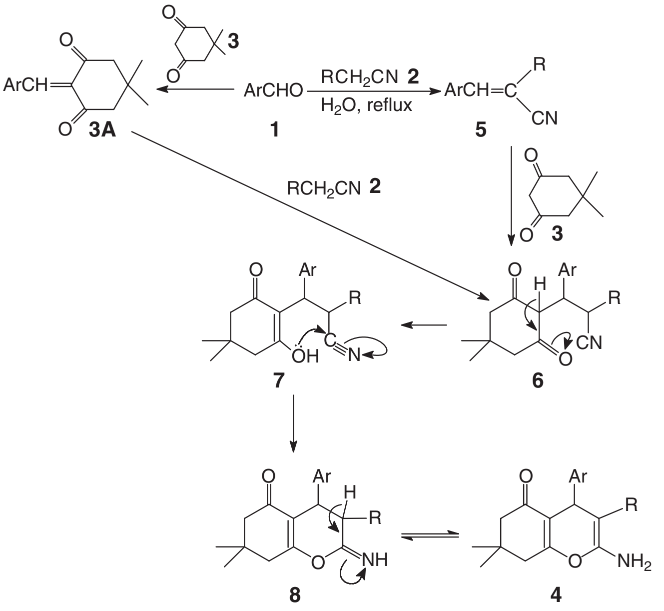
Carbonyl compounds undergo a Knoevenagel condensation with active methylene compounds in the presence of acids or bases in organic solvents. Recently, however, the Knoevenagel condensation has been performed in water without a catalyst.[23] These results encouraged us to carry out a one-pot sequential Knoevenagel condensation and Michael addition without a catalyst in water. The results presented in Table 1 indicate that electronic effects and the nature of substituents on the aromatic ring did not show a strong effect in terms of yield and reaction time. The three-component cyclocondensation reaction proceeded smoothly in water under reflux conditions to furnish excellent yields of products. It is important to note that the procedure is eco-friendly and involves water as a green solvent; it does not require catalyst or tedious workup, and the products do not require purification. Pure products are obtained by simple filtration.

In the proposed mechanism (Scheme 2), an aromatic aldehyde **1** was first condensed with the reactive methylene compound **2** to afford α-substituted cinnamonitrile derivative **5**, which underwent Michael addition with dimedone **3** under reflux conditions in tap water without catalyst. It is believed that this is the first example of a Michael addition without catalyst in tap water. The active methylene moiety in **3** reacts with the electrophilic C=C double bond to give intermediate **6**. Alternatively, aldehyde **1** reacted with dimedone **3** first, followed by Michael addition of the methylene compound **2** with olefin **3A** to result in the formation of intermediate **6**. The intermediate **6** was then cyclized by nucleophilic attack of OH on the cyano group and yielded the intermediate **7**. Finally the expected products **4** were formed by tautomerization of **8**.



Ar = Aryl; R = CN, CO_2Et, $CONH_2$

Scheme 1.



Scheme 2. Proposed mechanism.

Table 1. Three-component, one-pot, clean synthesis of tetrahydrobenzo[*b*]pyran derivatives without catalyst

Products were characterized using IR, ^{1}H NMR, mass spectroscopy, and elemental analysis.

Derivative	Ar	R	Time [h]	Yield^A [%]	mp [°C]
4a	C_6H_5	CN	3.5	99	228–290[18]
4b	4-BrC_6H_4	CN	2.0	99	203–204[20]
4c	4-ClC_6H_4	CN	1.5	98	208–209[18]
4d	4-CNC_6H_4	CN	2.0	95	208–210[20]
4e	2,4-$Cl_2C_6H_3$	CN	1.5	99	192–194[18]
4f	2-$NO_2C_6H_4$	CN	1.5	98	222–223[18]
4g	4-$NO_2C_6H_4$	CN	1.5	99	177–178[18]
4h	4-MeC_6H_4	CN	3.0	92	215–216[18]
4i	4-$N(Me)_2C_6H_4$	CN	3.0	96	220–222[18]
4j	3,4-$OCH_2OC_6H_3$	CN	3.0	81	211–212[18]
4k	3-$NO_2C_6H_4$	CO_2Et	3.0	98	182–183[20]
4l	4-$NO_2C_6H_4$	CO_2Et	2.5	99	184–185[20]
4m	4-ClC_6H_4	CO_2Et	3.0	99	153–154[20]
4n	2,4-$Cl_2C_6H_4$	CO_2Et	2.5	99	172–173[20]
4o	4-MeC_6H_4	CO_2Et	3.0	92	156–157[20]
4p	C_6H_5	CO_2Et	3.5	94	155–156[20]
4q	3,4-$OCH_2OC_6H_3$	CO_2Et	3.0	84	156–157[18]
4r	C_6H_5	CO_2Me	3.0	95	146–147[15]
4s	4-MeC_6H_4	CO_2Me	3.0	93	172–173[15]
4t	3-$NO_2C_6H_4$	CO_2Me	2.5	98	190–191[20]
4u	4-ClC_6H_4	CO_2Me	2.5	99	166–167[20]
4v	C_6H_5	$CONH_2$	4.0	99	216–217[19]
4w	4-ClC_6H_4	$CONH_2$	4.0	99	189–190[19]

^{A}Yield of pure isolated products.

In conclusion, we have developed a green procedure for the synthesis of biologically interesting products, benzopyran derivatives **8**, without a catalyst in tap water under reflux conditions. The products are obtained in almost pure form by simple filtration or, if necessary, the products were purified by crystallization in ethanol.

Experimental

Typical Procedure

A mixture of 4-chlorobenzaldehyde **1c** (1 mmol), dimedone **3** (1 mmol), and malononitrile **2** (2 mmol) in tap water (10 mL) was refluxed for 1.5 h. After completion of the reaction (TLC), the mixture was cooled in ice and filtered to give almost pure product in 98% yield.

Compound **4c**. $\nu_{\max}$ (KBr) 3300, 3200, 3040, 2990, 2970, 2240, 1650, 1610, 1490, 850 cm^{-1}. δ_H (CDCl$_3$) 1.01 (s, 3H, CH$_3$), 1.09 (s, 3H, CH$_3$), 2.22 (s, 2H, CH$_2$), 2.59 (s, 2H, CH$_2$), 3.07 (br s, 2H, NH$_2$), 4.30 (s, 1H, CH), 7.30 (m, 4H, ArH). (Found: C 65.7, H 5.3, N 8.4, Cl 10.6%; $C_{18}H_{17}N_2O_2Cl$ (328.11) requires C 65.9, H 5.2, N 8.5, Cl 10.7%.)

Accessory Publication

Spectroscopic data for **4a**–**w** are available from the author or, until April 2012, the *Australian Journal of Chemistry*.

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