

A Green Synthesis of Tetrahydrobenzo[*b*]pyran Derivatives through Three-Component Condensation Using *N*-Methylimidazole as Organocatalyst

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Summary. An efficient and convenient approach to the synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives using *N*-methylimidazole as the organocatalyst (20 mol%) is described. This method has several advantages, such as mild conditions, high yields, and simple work-up procedure.

Keywords. Tetrahydrobenzo[*b*]pyran; *N*-Methylimidazole; Organocatalyst.

Introduction

In recent years, 4*H*-benzo[*b*]pyrans and their derivatives become of considerable interest due to their wide range of biological properties [1], such as anticoagulant, spasmolytic, diuretic, anticancer, and antianaphylactin characteristics. A number of 2-amino-4*H*-pyrans are useful as photoactive materials [2]. Furthermore, 4*H*-benzo[*b*]pyrans constitute the structural unit of a series of natural products [3].

The conventional methods for syntheses of 4*H*-benzo[*b*]pyrans use organic solvents, such as acetic acid or *DMF* [4]. Recently, there have been many methods reported for the preparation of 4*H*-benzo[*b*]pyrans through two-component or three-component condensations including the use of microwave irradiation [5], ultrasonic irradiation [6], or use of (diethylamino)propylated silica [7], hexadecyltrimethylammonium bromide (*HTMAB*) [8], triethylbenzylammonium chloride (*TEBA*) [9], (*S*)-proline [10], and rare earth perfluorooctanoate [*RE(PFO)*₃] [11] as catalysts. Each of the above protocols has

its own merit, with at least one of the drawbacks of low yields, long reaction times, harsh reaction conditions, and tedious work-up procedures.

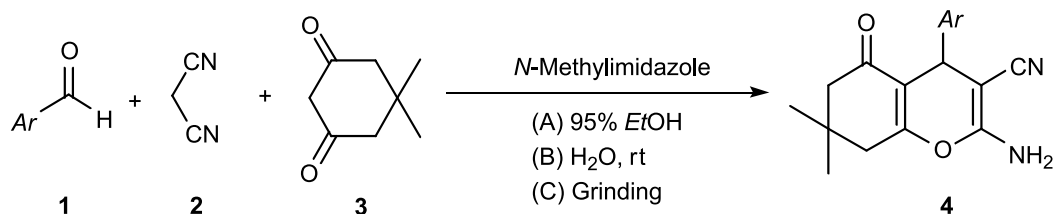
In the past few years organocatalysts have emerged as a powerful approach for the preparation of important building blocks or compounds. Organocatalysts are small organic molecules, like cinchona alkaloids or L-proline. Their derivatives are readily commercially available catalysts and they have been used in various transformations with excellent yields [12].

N-Methylimidazole has been used rather seldom in organic reactions as an organocatalyst [13]. The use of *N*-methylimidazole as a catalyst in the synthesis of the 4*H*-benzo[*b*]pyran derivatives has not yet been reported. As part of our work on one-pot multicomponent reactions catalyzed by organocatalysts for the synthesis of various heterocyclic compounds of biological importance we wish to report a general and highly efficient procedure for the preparation of this kind of compounds. It is achieved *via* a one-pot three-component tandem *Knoevenagel*-cyclocondensation reaction using the inexpensive and commercially available *N*-methylimidazole as organocatalyst.

Results and Discussion

When 4-chlorobenzaldehyde, malononitrile, and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) were treated with a single drop of *N*-methylimidazole under three different sets of reaction conditions, namely (i) using traditional ethanol as solvent (Method A); (ii) using water as reaction medium (Method

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Scheme 1

Table 1. Synthesis of tetrahydrobenzo[*b*]pyrans catalyzed by *N*-methylimidazole

Entry	Ar	Product	Time/min			Yield ^a /%			Mp/°C	
			EtOH	H ₂ O	Grind	EtOH	H ₂ O	Grind	Found	Ref.
1	4-Cl-C ₆ H ₄	4a	60	90	4	95	90	93	209–210	209–211 [10]
2	2-Cl-C ₆ H ₄	4b	60	780	38	93	95	89	215–216	217–218 [8]
3	2,4-2Cl-C ₆ H ₃	4c	60	– ^b	35	98	– ^b	93	116–117	115–117 [11]
4	4-NO ₂ -C ₆ H ₄	4d	10	150	10	92	94	92	177–179	177–178 [8]
5	C ₆ H ₅	4e	60	90	2	91	90	91	224–225	226–228 [11]
6	4-Me-C ₆ H ₄	4f	90	420	45	87	87	90	214–215	214–216 [8]
7	4-HO-C ₆ H ₄	4g	150	180	53	87	97	94	217–218	214–215 [8]
8	4-MeO-C ₆ H ₄	4h	256	720	36	83	92	87	199–200	199–201 [8]
9	3-MeO-4-HO-C ₆ H ₃	4i	420	540	55	94	95	96	227–228	228–230 [5]
10	furyl	4j	120	90	3	95	91	87	216–217	218–220 [4b]

^a Yields refer to those of pure isolated products characterized by spectroscopic data

^b Mixtures including the desired product and an intermediate

B); and (iii) dry grinding in a mortar with pestle (Method C) at room temperature, the three-component cyclocondensation reaction proceeded smoothly to give the desired products derivatives 2-amino-3-cyano-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran in high to excellent yields (Scheme 1). To explore the scope of this reaction, we extended the reaction to various aromatic aldehydes carrying either electron withdrawing or electron releasing substituents. Both gave the desired products. The results are shown Table 1.

As can be seen from Table 1, electronic effects and the nature of substituents on the aromatic ring showed strongly obvious effects in terms of reaction time under the three reaction conditions mentioned above. When aromatic aldehydes containing electron-donating groups (such as hydroxy, alkoxy, or methyl group) were employed (Table 1, entries 6–9), a longer reaction time was required than those encountered with electron-withdrawing groups (such as nitro or halide) on aromatic rings (Table 1, entries 1–4). It is note worthy, that the reaction proceeded without the protection of acidic hydroxy substituents (Table 1, entries 7 and 9). It should also be mentioned that mixtures including the desired product

and an intermediate were observed with water as the reaction medium compared with the other two methods in the case that a chloride substituent occupied *o*- and *p*-positions of the aromatic ring (Table 1, entry 3).

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Taking the 4-chlorobenzaldehyde reaction with malononitrile and dimedone as a reference, the reaction could not be carried out in the absence of the catalyst at room temperature.

Among the above methods, the solvent-free approach (Method C) provided the best results. Although the reaction carried out in water (Method B) showed similar results as in ethanol (Method A), Method A apparently facilitates higher reaction rates than Method B due to the homogeneous reaction.

In conclusion, we developed a facile and effective procedure for the synthesis of 2-amino-4-aryl-3-cyano-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-ones from aromatic aldehydes, malononitrile, and dimedone in the presence of the organocatalyst *N*-methylimidazole. Compared to the existing method, it has the advantages of excellent yields, inexpensive operation, and environmental friendliness.

Experimental

Melting points were measured on an Electrothermal X₆ microscopy digital melting point apparatus. IR spectra were recorded on a Bruker Equinox-55 spectrometer using KBr pellets. ¹H NMR spectra were recorded in DMSO-d₆ on a Bruker AVANCE 300 (300 MHz) instrument with TMS at δ = 0.00 ppm as an internal standard. Benzaldehyde and furyl aldehyde were purified by distillation. All other chemicals were of commercial grade without further purification.

General Experimental Procedure: Methods A and B

A solution of an aromatic aldehyde **1** (3 mmol), 198 mg malononitrile (**2**, 3 mmol), 420 mg dimedone (**3**, 3 mmol) and *N*-methylimidazole (one drop, ca. 20 mol%) in 10 cm³ 95% EtOH (Method A) or in 10 cm³ H₂O (Method B) was vigorously stirred at room temperature for the specific time indicated in Table 1. The end of the reaction was monitored by TLC. Then, the mixture was poured into water (Method A) or was cooled in a refrigerator overnight (Method B) to precipitate the solid. The crude product obtained was filtered off by suction and washed with 3 × 10 cm³ H₂O. The pure product was obtained by recrystallization from ethanol.

General Experimental Procedure: Method C

A mixture of as given above for Methods A and B was ground for the appropriate time using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidified within 4–30 min. The solid was washed with cold water and recrystallized from ethanol.

All of the products are known and the data were found to be identical with those reported in literature.

Acknowledgements

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