



Basic Catalyzed Rapid Three-Component Synthesis of tetrahydrobenzo[b]pyran at Ambient Temperature

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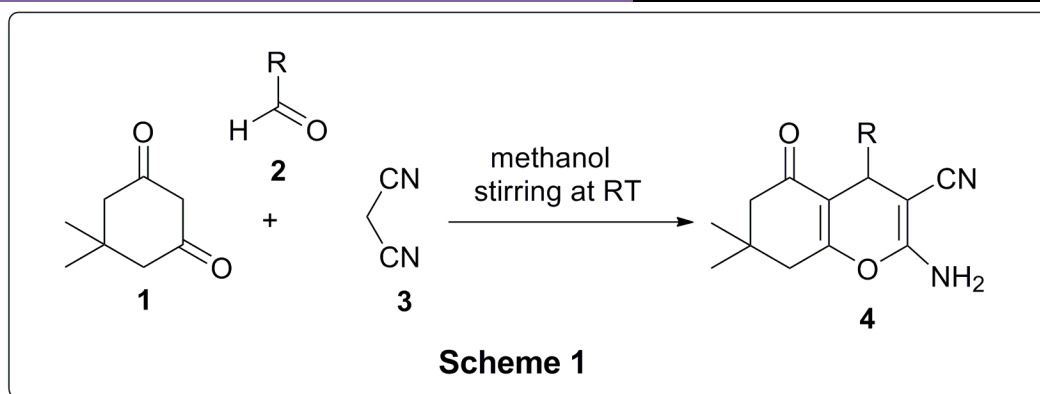
Abstract:

An efficient and convenient approach for the synthesis of tetrahydrobenzo[b]pyran derivatives under mild condition using the piperidine as an efficient base catalyst is described. A wide range of aromatic aldehydes easily undergo condensation with malononitrile and 5,5-dimethylcyclohexane-1,3-dione (dimedone) to afford the desired products in excellent yields. Taking into account the environmental and economical considerations, the present protocol has the merits of environmentally benign procedure such as shorter reaction time, low cost, recycling of the catalyst and simple workup.

Keywords: *Green procedure, Multicomponent reaction, One pot synthesis, Tetrahydrobenzo[b]pyran*

1. Introduction

Tetrahydrobenzo[b]pyrans have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals because of their wide range of biological activities. These compounds show anticoagulant, anticancer, spasmolytic, diuretic and anti-ancaphylactia activity (1). Tetrahydrobenzo[b]pyrans are the structural unit of a number of natural products and are used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring (2). Recently, many synthetic methods used for the synthesis of tetrahydrobenzo[b]pyrans were reported in acetic acid (3) or dimethylformamide (4). Some improved methods are also reported for the synthesis of tetrahydrobenzo[b]pyran derivatives using hexadecyltrimethyl ammonium bromide (5), sodium bromide (6), phase transfer catalyst (7), rare earth perfluorooctanoate (8), KF-Alumina (9), sodium selenate (10), proline (11), 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate (TMGT) as an ionic liquid (12), 4-amino-1-(2,3-dihydroxypropyl)pyridinium hydroxide [ADPPY][OH] (13), N-Methylimidazole (14), diammonium hydrogen phosphate (DAHP) (15), or by electrochemical reactions (16) as catalysts, as well as with the assistance of microwave (17) and ultrasound irradiation (18). Most of the reported methods have employed strong acidic or basic conditions, high temperature and required long reaction times, or use of expensive catalysts. The search for the new readily available and green catalysts that lead to tetrahydrobenzo[b]pyrans via an efficient and convenient procedure is still being actively pursued these years. As a part of this program, we recently introduced an apparently safe and simple synthesis of tetrahydrobenzo[b]pyran derivatives by multi-component condensation



2. Results and Discussion

Chen et al. (21) and Liu et al. (22) have respectively reported synthesis of tetrahydrobenzo[b]pyran using N,N-Dimethylamino-functionalized basic ionic liquid and acyclic acidic ionic liquid as catalysts under conventional conditions at 60°C and 90°C for 30-80 min. and 1-1.5 hrs. Gong et al. (23) also reported synthesis of polyfunctionalized pyrans catalyzed by [bmim]OH in aqueous media. Herein we report synthesis of tetrahydrobenzo[b]pyran at ambient temperature within 1-8 min using piperidine in methanol as co-solvent.

Initially, the reaction of vanillin, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and malononitrile was selected as a model reaction to optimize the reaction conditions in the presence of different amounts of piperidine (0–20 mol%) in different solvents at room temperature for a certain period of time as required for completion of reaction (by TLC). The best result was achieved by carrying out the reaction with 1:1:1.2 molar ratio of vanillin: dimedone: malononitrile at 25°C in presence of piperidine (20 mole %) in methanol as co-solvent.

A brief screening of solvents showed that water, THF, methylene dichloride, acetonitrile and toluene were less effective than methanol. Upon examining the influence of the amount of ionic liquid on the reaction, it was found that without IL the reaction did not proceed.

Optimization of reaction conditions for the synthesis of tetrahydrobenzo[b]pyran in different solvent

Entry	Ionic Liquid	Co-Solvent ^a	Mol%	Time (min.)	Yield(%) ^b
1	piperidine	Water	20	25 ^c	77
2	piperidine	THF	20	30	75
3	piperidine	Methylene dichloride	20	15	70
4	piperidine	Acetonitrile	20	13	79
5	piperidine	Toluene	20	45	68
6	piperidine	Methanol	20	5	89
7	piperidine	Methanol	15	8	82
8	piperidine	Methanol	10	15	77
9	piperidine	Methanol	5	20	74
10	piperidine	Methanol	0	120	-
11	piperidine	Methanol	30	5	88
12	NaOH	Methanol	20	8	75

20 mol% of catalyst was sufficient to promote the reaction efficiently. The yield is found to decrease significantly below 20 mol% of catalyst even after prolonging the duration. When the amount of catalyst was increased over 20 mol% equivalent, no significant improvement was observed in reaction yield as well as in duration of the reaction. Under this optimized conditions, a variety of aromatic

aldehydes undergo condensation with active methylene compound (malononitrile) and dimedone to provide the corresponding tetrahydrobenzo[b]pyrans derivatives. All the reactions were observed to

Synthesis of tetrahydrobenzo[b]pyran derivatives

Entry	R	Time (min.)	Yield ^b (%)	M.P.(°C) (observed)	M.P. (°C) (reported)
4a	C ₆ H ₅	2	94	230-232	228-230 (11)
4b	4-NO ₂ C ₆ H ₄	3	91	180-181	179-180(11)
4c	4-OH-3-OMe-C ₆ H ₃	5	89	231-233	229-231(24)
4d	4-OCH ₃ C ₆ H ₄	2.5	94	200-201	199-201(25)
4e	2-furyl	2	90	226-228	225-226(26)
4f	4-Cl C ₆ H ₄	5	91	209-210	209-211(11)
4g	3- NO ₂ C ₆ H ₄	5	88	210-212	212-214(11)
4h	2- NO ₂ C ₆ H ₄	2	92	228-230	222-223(11)
4i	2-Cl C ₆ H ₄	1.5	90	216-218	215-216(14)
4j	4-F C ₆ H ₄	1	93	188-189	191-193(25)
4k	3,4,5-(OCH ₃) ₃ C ₆ H ₂	8	87	175-177	-
4l	4-(CH ₃) ₂ NC ₆ H ₄	7	86	210-212	212-213(11)

be very fast (1-10 min) and good yielding (85-95%) compared to other existing procedures. The electronic nature of the substituents on the aromatic ring did not show a strong effect in terms of yields under these reaction conditions. Both aromatic aldehydes containing electron-withdrawing groups (such as nitro, halo) or electron-donating groups (such as alkoxy group) gave good to excellent yields of the corresponding tetrahydrobenzo[b]pyran

No side reactions were observed in any of the reactions.

The IR spectrum of all compounds revealed the presence of cyano and amino groups due to the appearance of absorption bands at around 2188 and 3326 & 3398 cm⁻¹ respectively. The ¹³C NMR spectra of these compounds exhibited signals in the carbonyl, cyano, aromatic and aliphatic regions. For all the compounds, the spectra showed five quaternary carbon signals, one tertiary carbon signal and two secondary carbon signals. In ¹³C NMR spectra, two signals for C-2 and C-8a (Fig.1) are observed at higher δ values than expected for typical olefinic carbons. In contrast, carbons C-3 and C-4a appeared at unusually lower δ values. These findings could be accounted for the strong push-pull effect of the groups linked to the olefinic double bond. The carbonyl carbon in these systems resonates in the narrow range 195–197 ppm. The cyano carbon appears at 119–121 ppm. The signal at around δ 59.00 ppm is assigned to carbon attached with carbonitrile while signals around δ 127.03-145.21 ppm are attributed to all the aromatic carbons of the compounds. ¹H NMR spectrum indicated the presence of one singlet in the range δ 4.032-4.389 ppm of -CH proton. Moreover, singlet in the range δ 6.949-7.263 ppm and multiplets in the range δ 6.522-7.346 ppm have appeared for amine and aromatic protons respectively.

The mechanism of this reaction has not been unequivocally established, but a plausible explanation is using malononitrile as a substrate based on the previous literature (27). According to the plausible mechanisms, in first step an aldehyde is condensed with malononitrile to afford the α -cyanocinnamitrile derivative. During such reaction, formation of many side products such as enaminoitrile, higher adducts and malononitrile self addition products have been noticed in earlier publications (28). Increase in yield of the product may be due to higher basicity in this reaction which may have suppressed the formation of these side products.

4. Experimental

4.1 General

All Chemicals used were of commercial grade, and they were used without any further purification. Melting points were measured in open capillaries and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F₂₅₄ (Merck). IR spectra were recorded on a FTIR Perkin Elmer Spectrum 100 spectrometer, elemental analysis on Perkin Elmer PE 2400 elemental analyzer and ¹H and ¹³C NMR spectra were recorded on Bruker Avance 400 MHz instrument with TMS as an internal standard.

Representative procedure for the synthesis of Tetrahydrobenzo[b]pyran derivative

The ionic liquid, 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate [DBU][Ac](20 mole%) was added to a mixture of dimedone1 (1 mmol), aldehyde2 (1 mmol), malononitrile3 (1.2 mmol) in methanol (5 ml). The resulting mixture was stirred for the required time as shown in Table 2. The solid product obtained after the completion of the reaction was filtered through small Buchner funnel under vacuum, washed with ethanol-water (1:2) to leave the crude product which was purified by crystallization in ethanol.

Spectral data for selected compounds

2-Amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4a):

IR (KBr) ν : 3398,3326, 3210, 2956, 2188, 1678, 1598, 1367, 1215,1031 cm^{-1} ; ¹H NMR (d₆-DMSO, 400 MHz) δ : 0.967(s, 3H, CH₃), 1.050 (s, 3H, CH₃), 2.095-2.284 (q, 2H, CH₂), 2.526 (s,2H, CH₂), 4.189 (s, 1H, CH), 6.998 (s, 2H, NH₂)7.146–7.314 (m, 5H, Ar) ppm; ¹³C NMR (d₆-DMSO,100 MHz), δ : 27.29, 28.87, 32.27,36.07, 50.47, 58.84,113.25, 120.17, 127.03, 127.62, 128.79, 145.21, 158.98, 162.94, 196.08 ppm.

2-Amino-3-cyano-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8 tetrahydrobenzo[b]pyran (4c)

IR (KBr) ν : 3440, 3310, 3272, 2186, 1680 cm^{-1} ; ¹H NMR (d₆-DMSO 400 MHz) δ : 0.981 (s, 3H, CH₃), 1.046 (s, 3H, CH₃), 2.097-2.0284(dd, 2H, CH₂), 2.514-2.561 (dd, 2H, CH₂), 3.723 (s, 3H, OCH₃), 4.091 (s, 1H, CH), 6.905 (s, 2H, NH₂), 6.522–6.697 (m, 3H, Ar-H), 8.8 (br s, 1H, OH) ppm. ¹³C NMR (d₆-DMSO, 100 MHz), δ : 27.11, 28.99, 32.21, 35.46, 50.53, 56.08, 59.26, 111.96, 113.53, 115.82, 119.87, 120.32, 136.29, 145.74, 147.72, 158.85, 162.61, 196.13 ppm.

Conclusion

We have demonstrated an efficient protocol for multicomponent synthesis of tetrahydrobenzo[b]pyran derivatives at ambient temperature. In addition, the procedure offers several advantages including high yields, operational simplicity, environment friendly and cleaner reaction, which is a practical alternative to the existing procedures to satisfy the need of academy as well as industry.

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