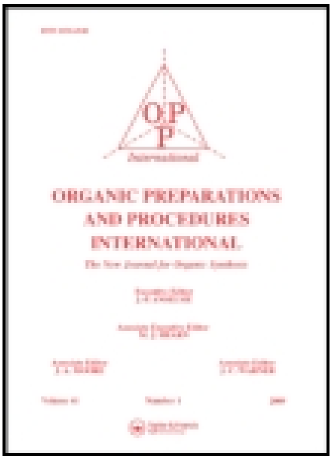

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

One-Pot Synthesis of Tetrahydrobenzo[b]pyran Derivatives Catalyzed by Amines in Aqueous Media

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Published online: 14 Apr 2009.

To cite this article: Li-Qin Yu, Fei Liu & Qi-Dong You (2009) One-Pot Synthesis of Tetrahydrobenzo[b]pyran Derivatives Catalyzed by Amines in Aqueous Media, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 41:1, 77-82, DOI: 10.1080/00304940802711275

To link to this article: http://dx.doi.org/10.1080/00304940802711275

Organic Preparations and Procedures International, 41:77–82, 2009

ISSN: 0030-4948 print
DOI: 10.1080/00304940802711275

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One-Pot Synthesis of Tetrahydrobenzo[*b*]pyran Derivatives Catalyzed by Amines in Aqueous Media

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One important symbol of green chemistry is to diminish of the use of organic solvents because of the economical and environmental concerns associated with them. Water is a green and cheap solvent. In 1980, Breslow discovered that Diels-Alder reactions could be performed in water with a huge acceleration.[1–3] This discovery led to considerable interest of synthetic organic chemists in the study of using water as reaction solvent.[4–7] To date, a great number of organic reactions have been carried out in water successfully.[8–10]

The tetrahydropyran ring system is present in numerous biologically active natural products as well as many synthetic compounds.[11] Tetrahydrobenzo[*b*]pyrans and their derivatives have a broad spectrum of biological and pharmacological activity, such as anti-cancer, anti-coagulant, diuretic, spasmolytic, and anti-anaphylactic activity.[12–14] Additionally, tetrahydrobenzo[*b*]pyran derivatives have recently been used as cognitive enhancers for the treatment of neurodegenerative disease.[15]

Conventionally, synthesis of tetrahydrobenzo[*b*]pyrans has been performed in DMF or acetic acid catalyzed by pyridine or ammonium acetate.[7–17] In recent years, microwave and ultrasound irradiation have been applied to the synthesis of tetrahydrobenzo[*b*]pyrans.[18–20] However, organic solvents were also necessary. Moreover, each of the above methods had at least one drawback such as poor yields, difficult workup, long reaction time or hash reaction conditions. It was also reported that this reaction could be catalyzed by hexadecyltrimethylammonium bromide, 4-dodecylbenzenesulfonic acid, or triethylbenzylammoniumchloride in water.[21–23] However, these aqueous reactions needed a relatively long reaction time and were performed at reflux temperature. More recently, Fotouhi *et al*. described the mild synthesis of tetrahydrobenzo[*b*]pyran derivatives *via* electroreduction of malononitrile at a platinum electrode.[24] Lalaie *et al*. reported that (*S*)-proline could be used as a mild, efficient, and neutral catalyst in this reaction.[25] In our experiments, we found that other amino acids and amines were also efficient in this reaction (*Scheme 1*). In addition, these other amines were much more efficient than (*S*)-proline or other amino acids, and we report our results here.

Received August 29, 2008; in final form November 4, 2008
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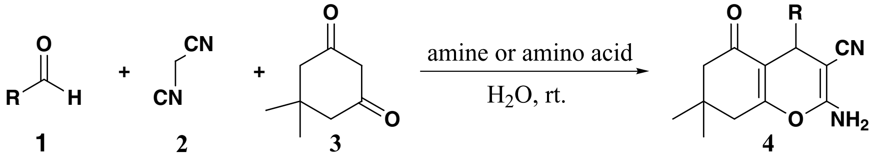
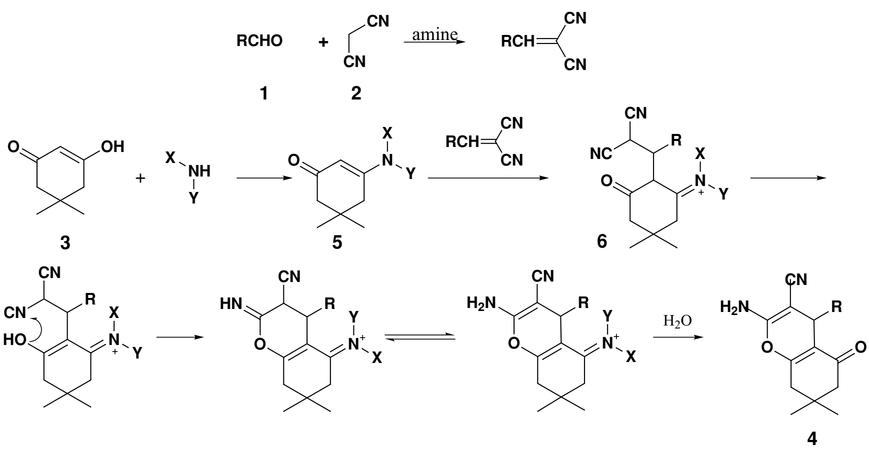


Scheme 1

In our initial research, aromatic aldehyde was selected as the representative aldehyde to examine the catalytic activity of different amines. In a typical general experimental procedure, a solution of aromatic aldehyde (10 mmol), malononitrile (11 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (10 mmol) in water (40 mL) was stirred at room temperature in the presence of a primary or secondary amine (10 mol%). Then the mixture was cooled in an ice bath and filtered. The residue was washed with ice cold EtOH or recrystallized from 95% EtOH to yield the final product. As a result, we can see from Table 1 that all amines examined were very effective and all the reactions were completed within 15 min with excellent yields. Additionally, the work-up is quite simple. (*S*)-Proline and other two amino acids were also used in this study as the catalysts and it was found that the amines were relatively more efficient than the amino acids. Tertiary amines proved inactive in this reaction. When triethylamine (TEA) or N, N-diisoproylethylamine (DIPEA) were investigated as catalysts in this reaction, no product was formed.

Encouraged by these results, we extended this study using various aromatic aldehydes in the presence of a catalytic amount of amine. Considering the reaction time and the yield, ethanolamine was selected as the optimum catalyst used in the following study. The results are summarized in Table 2. The reaction appears quite general and the electronic characteristic of the aldehydes had little influence on the reaction yields. Furfural and propanal gave somewhat lower yield and required comparatively longer reaction time.

We propose a possible mechanism to account for the reaction (*Scheme 2*). Firstly, the aldehyde is condensed with malononitrile to form α-cyanocinnamonitrile *via* a Knoevenagel reaction. As is known, an amine or amino acid is an effective catalyst for



Scheme 2

Table 1
Examples of Amines or Amino Acids Catalyzed Synthesis of 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile

Entry	Catalyst	Time (min)	Yield (%)
1	$NH_2CH_2CH_2OH$	15	97
2	$(CH_3)_2NCH_2CH_2CH_2NH_2$	15	93
3	$(CH_3)_3CNH_2$	15	93
4	piperidine	15	91
5	morpholine	15	87
6	$(C_2H_5)_3N$	60	—
7	$((CH_3)_2CH)_2NC_2H_5$	60	—
8	NH_2CH_2COOH	60	82
9	$NH_2CH_2CH_2COOH$	60	87

the Knoevenagel reaction.[21-23] The amine or amino acid is also effective in the Michael reaction of 5,5-dimethyl-1,3-cyclohexanedione with the α-cyanocinnamonitrile for the formation of intermediates **5** and **6**. Finally, after an intramolecular cyclization, the expected product **4** is obtained.

In summary, an efficient and environmentally friendly method for the synthesis of tetrahydrobenzo[*b*]pyran derivatives in high yield has been developed. There are several key advantages in this methodology such as the use of an environmentally friendly solvent, high yields, short reaction time, and simple work-up.

Table 2
Ethanolamine-catalyzed Synthesis of 4H-Benzo[*b*]pyran Derivatives

Entry	R	Product	Yield (%)	Time (min)	Mp (°C) Found	Mp (°C) Lit.[21]
1	C_6H_5	**4a**	97	15	229–231	229–231
2	$3\text{-}HOC_6H_4$	**4b**	94	15	236–238	—
3	$4\text{-}HOC_6H_4$	**4c**	89	15	213–215	214–215
4	$3\text{-}NO_2C_6H_4$	**4d**	92	15	209–210	208–211
5	$3\text{-}CH_3C_6H_4$	**4e**	92	15	206–208	—
6	$3\text{-}ClC_6H_4$	**4f**	95	15	224–226	224–225
7	$4\text{-}CH_3OC_6H_4$	**4g**	90	15	197–199	199–201
8	$2,5\text{-}CH_3OC_6H_3$	**4h**	94	15	178–180	—
9	$2\text{-}CH_3OC_6H_4$	**4i**	92	15	204–205	—
10	2-Furyl	**4j**	76	30	217–219	—
11	CH_3CH_2	**4k**	70	60	180–182	—

Experimental Section

The ^{1}H NMR spectra were recorded on a Bruker AV 300 spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ units. The EI-MS were obtained on Shimadzu GCMS-QP2010. Melting points (uncorrected) were obtained on a Thomas Hoover apparatus.

General Procedure for Synthesis of 4H-Benzo[b]pyran Derivatives

A mixture of aromatic aldehyde (**1**) (10 mmol), malononitrile (**2**) (11 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**3**) (10 mmol), and an amine or an amino acid (10 mol%) in water (40 mL) was stirred at room temperature for 15–60 min. Then the mixture was cooled in an ice bath and the solid residue was collected and washed with ice-cold EtOH or recrystallized from 95% EtOH. The structures of **4a-4i** were confirmed by spectroscopic data.

2-Amino - 3 - cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]-pyran (4a) obtained from benzaldehyde (1.06 g, 10.0 mmol) (**1a**), malononitrile (0.73 g, 11.0 mmol) (**2**), 5,5-dimethyl-1,3-cyclohexane- dione (1.40 g, 10.0 mmol) (**3**) and ethanolamine (0.06 g, 1.0 mmol) in water (40 mL) according to the general procedure to yield the product (2.85 g, 97%) as a white solid, mp 229–231°C, *lit.*[21] 229–231°C. ^{1}H NMR: δ 0.96 (s, 3H), 1.04 (s, 3H), 2.10 (d, 1H), 2.25 (d, 1H), 2.50 (s, 2H), 4.17 (s, 1H), 6.99 (s, 2H), 7.13–7.31 (m, 5H). IR (KBr) νmax: 3359, 2959, 2199, 1670, 1370, 1214 cm^{-1}. EI-MS (*m/z*): 294 ($M+$).

2-Amino - 3 -cyano - 4-(3-hydroxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahy-drobenzo[*b*]pyran (4b). The general procedure was used to give **4b** (93%) as a white solid, mp 236–238°C. ^{1}H NMR: δ 0.97 (s, 3H), 1.04 (s, 3H), 2.10 (d, 1H), 2.26 (d, 1H), 2.57 (s, 2H), 4.06 (s, 1H), 6.54 (s, 2H), 6.97–7.08 (m, 4H), 9.31 (s, 1H). IR (KBr) νmax: 3310, 2964, 2191, 1652, 1359, 1211 cm^{-1}. EI-MS (*m/z*): 310 ($M+$).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.85; H, 5.67; N, 9.22.

2-Amino - 3 - cyano -4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahy-drobenzo[*b*]pyran (4c). The general procedure was used to give **4c** (89%) as a white solid, mp 213–215°C, *lit.*[21] 214–215°C. ^{1}H NMR: δ 0.94 (s, 3H), 1.03 (s, 3H), 2.10 (d, 1H), 2.23 (d, 1H), 2.48 (s, 2H), 4.04 (s, 1H), 6.63 (s, 1H), 6.89–6.92 (m, 4H), 9.25 (s, 1H). IR (KBr) νmax: 3350, 2957, 2176, 1658, 1399, 1218 cm^{-1}. EI-MS (*m/z*): 310 ($M+$).

2-Amino - 3 - cyano -4-(3-nitrophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydro-benzo[*b*]pyran (4d). The general procedure was used to give **4d** (92%) as a light yellow solid, mp 209–210°C, *lit.*[21] 208–211°C. ^{1}H NMR: δ 0.96 (s, 3H), 1.05 (s, 3H), 2.11 (d, 1H), 2.27 (d, 1H), 2.55 (s, 2H), 4.42 (s, 1H), 7.17 (s, 2H), 7.59–8.09 (m, 4H). IR (KBr) νmax: 3426, 2955, 2185, 1676, 1530, 1210 cm^{-1}. EI-MS (*m/z*): 339 ($M+$).

2-Amino-3 - cyano-4-m-tolyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]-pyran (4e). The general procedure was used to give **4e** (92%) as a white solid, mp 206–208°C. ^{1}H NMR: δ 0.95 (s, 3H), 1.03 (s, 3H), 2.08 (d, 1H), 2.22 (d, 1H), 2.25 (s, 3H), 2.49 (s, 2H), 4.11 (s, 1H), 6.92 (s, 2H), 6.96–7.17 (m, 4H). IR (KBr) νmax: 3350, 2964, 2190, 1655, 1371, 1214 cm^{-1}. EI-MS (*m/z*): 308 ($M+$).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.21; H, 6.42; N, 9.18.

2-Amino-3-cyano-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (4f). The general procedure was used to give **4f** (95%) as a white solid, mp 224–226°C, *lit.*[21] 224–225°C. ^{1}H NMR: δ 0.96 (s, 3H), 1.04 (s, 3H), 2.12 (d, 1H), 2.26 (d, 1H), 2.50 (s, 2H), 4.21 (s, 1H), 7.12 (s, 2H), 7.16–7.34 (m, 4H). IR (KBr) νmax: 3325, 2958, 2167, 1656, 1379, 1220 cm^{-1}. EI-MS (*m/z*): 328 (*M*+).

2-Amino-3-cyano - 4 - (4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (4g). The general procedure was used to give **4g** (90%) as a white solid, mp 197–199°C, *lit.*[21] 199–201°C. ^{1}H NMR: δ 0.95 (s, 3H), 1.03 (s, 3H), 2.08 (d, 1H), 2.22 (d, 1H), 2.25 (s, 3H), 2.49 (s, 2H), 3.34 (s, 3H), 4.11 (s, 1H), 6.85 (s, 2H), 6.82–7.06 (m, 4H). IR (KBr) νmax: 3356, 2969, 2157, 1658, 1382, 1217 cm^{-1}. EI-MS (*m/z*): 324 (*M*+).

2-Amino-3-cyano-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (4h). The general procedure was used to give **4h** (94%) as a white solid, mp 178–180°C. ^{1}H NMR: δ 0.97 (s, 3H), 1.04 (s, 3H), 2.23 (d, 1H), 2.25 (d, 1H), 2.48 (s, 2H), 3.68 (d, 6H), 4.44 (s, 1H), 6.51 (s, 2H), 6.70–6.87 (m, 4H). IR (KBr) νmax: 3375, 2962, 2179, 1642, 1358, 1225 cm^{-1}. EI-MS (*m/z*): 354 (*M*+).

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.89; H, 6.02; N, 7.83.

2-Amino - 3 - cyano-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (4i). The general procedure was used to give **4i** (92%) as a white solid, mp 204–205°C. ^{1}H NMR: δ 0.96 (s, 3H), 1.04 (s, 3H), 2.05 (d, 1H), 2.25 (d, 1H), 2.49 (s, 2H), 3.75 (s, 3H), 4.47 (s, 1H), 6.82 (s, 2H), 6.87–7.18 (m, 4H). IR (KBr) νmax: 3396, 2964, 2188, 1655, 1371, 1251 cm^{-1}. EI-MS (*m/z*): 324 (*M*+).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.29; H, 6.02; N, 8.89.

2-Amino-3-cyano-4-(furan-2-yl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo-[*b*]pyran (4j). The general procedure was used to give **4j** (76%) as a white solid, mp 217–219°C. ^{1}H NMR: δ 0.99 (s, 3H), 1.05 (s, 3H), 2.17 (m, 2H), 2.48 (m, 2H), 4.33 (s, 1H), 6.05 (s, 1H), 6.32 (s, 1H),7.07 (s, 2H), 7.48 (s, 1H),. IR (KBr) νmax: 3355, 2941, 2202, 1680, 1363, 1223 cm^{-1}. EI-MS (*m/z*): 284 (*M*+).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.88; H, 5.56; N, 9.63.

2-Amino - 3 - cyano - 4 - ethyl -7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]-pyran (4k). The general procedure was used to give **4k** (70%) as a white solid, mp 180–182°C. ^{1}H NMR: δ 0.79 (t, 3H), 1.10 (d, 6H), 1.45 (m, 1H), 1.60 (m, 1H), 2.30 (m, 2H), 2.45 (m, 2H), 3.24 (s, 1H), 6.96 (s, 2H), IR (KBr) νmax: 3368, 2961, 2188, 1682, 1382, 1216 cm^{-1}. EI-MS (*m/z*): 246 (*M*+).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.54; H, 7.27; N, 11.18.

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