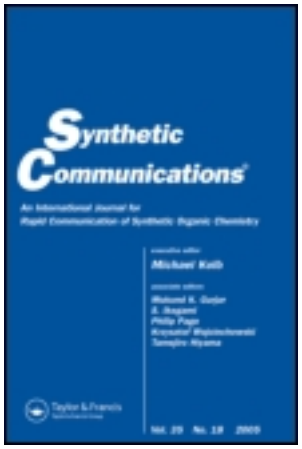

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Lithium Bromide as a Mild, Efficient, and Recyclable Catalyst for the One-Pot Synthesis of Tetrahydro-4H-Chromene Derivatives in Aqueous Media

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LITHIUM BROMIDE AS A MILD, EFFICIENT, AND RECYCLABLE CATALYST FOR THE ONE-POT SYNTHESIS OF TETRAHYDRO-4*H*-CHROMENE DERIVATIVES IN AQUEOUS MEDIA

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A simple, efficient, one-pot method has been developed for the synthesis of tetrahydro-4H-chromene derivatives by concurrent reaction of aryl aldehydes, active methylene compounds, and 1,3-cyclohexanedins using a catalytic amount of lithium bromide in aqueous media. The present approach offers several advantages such as shorter reaction times, good yields, low cost, recycling of the catalyst, and simple workup.

Keywords: Aqueous media; 4*H*-chromene; lithium bromide; multicomponent reaction; one-pot synthesis

INTRODUCTION

The development of new methodologies for the synthesis of 4*H*-chromenes is a subject of continuous interest to synthetic/medicinal chemists because their derivatives have versatile biological and medicinal properties[1–3] and are widely present in various biologically active natural products.[4] Some 4*H*-chromene derivatives bearing a nitrile functionality, especially 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles, are synthetic precursors in medical synthesis[5] and display potent in vitro antileishmanial activity.[6]

The widespread interest in the 4*H*-chromene-containing structures has led to extensive studies of their synthesis. The known procedures for the synthesis of 4*H*-chromene derivatives employ a three-component reaction of aryl aldehydes, active methylene compounds, and 1,3-cyclohexanedins under various reaction conditions. The conventional reported methods for synthesis of 4*H*-chromenes involve use of organic solvents such as dimethylsulfoxide[7] and dimethylformamide.[8] Several improved procedures have been reported using a variety of catalysts such as tetra-methyl ammonium hydroxide (TMAH),[9] tetrabutylammonium fluoride (TBAF),[4] triethylbenzylammonium chloride (TEBA),[10] sodium selenate,[11] rare-earth perfluorooctanoate [RE(PFO)$_3$],[12]

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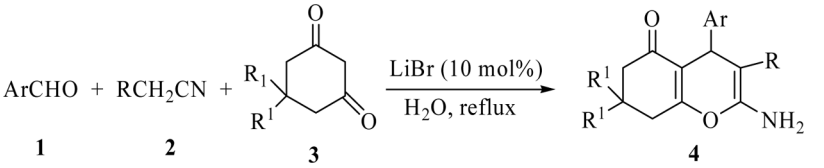

Scheme 1. Synthesis of tetrahydro-4H-chromene derivatives catalyzed by lithium bromide.

D,L-proline,[13] (*S*)-proline,[14] hexadecyltrimethyl ammonium bromide (HTMAB),[15] 4-dodecylbenzenesulfonic acid (DBSA),[16] and $(NH_4)_2HPO_4$.[17] Occasionally, these reactions can be performed under microwave[18–20] and ultrasound irradiations[21] or using an electrocatalytic system.[22,23] None of these methods completely meet the requirements, and they all suffer from severe disadvantages, such as long reaction times, poor yields, use of harmful volatile organic solvents, and nonreusability of catalysts. Thus, there is a need to develop an efficient and environmentally benign method to construct these high-value heterocyclic compounds.

The use of lithium bromide as a mild catalyst to promote various organic transformations is well documented in the literature.[24–32] In particular, lithium bromide has been found to efficiently catalyze Cannizzaro, Tishchenko, and Meerwein–Ponndorf–Verley reactions[33] as well as the three-component coupling of aldehydes, amines, and trimethylsilyl for the synthesis of α-amino nitriles.[34] However, there are no examples of the use of lithium bromide as catalyst for the synthesis of 4*H*-chromene derivatives in water. In continuation of our ongoing research program on the development of new regents/methods,[35] herein we report a facile, extremely rapid, and high-yielding procedure for the synthesis of tetrahydro-4*H*-chromene derivatives by a one-pot, three-component reaction of aryl aldehydes, active methylene compounds, and 1,3-cyclohexanedins using a catalytic amount of lithium bromide in aqueous media (Scheme 1).

RESULTS AND DISCUSSION

The reaction was carried out by adding lithium bromide (10 mol%) to a mixture of benzaldehyde, malononitrile, and dimedone in water. After the mixture was stirred under reflux conditions for 15 min, thin-layer chromatographic (TLC) analysis showed that the starting reactants were consumed, and the corresponding tetrahydro-4*H*-chromene (**4a**) was formed. Using simple workup, the expected product was isolated in 95% yield. In the absence of a catalyst, the reaction was rather sluggish and resulted in poor yield (57%) along with benzylidenemalononitrile (18%), even after a long reaction time (30 min) under the same conditions,[4] thus confirming the effectiveness of LiBr as a catalyst for this reaction. The effect of various lithium salts such as LiCl, $LiClO_4$, and $LiBF_4$ for this transformation were screened. Of these lithium salts, LiBr was found to be superior in terms of yields (Table 1).

To realize the generality and versatility of the catalyst, a variety of electronically divergent aromatic aldehydes, dimedone, and malononitrile were examined, and the results are summarized in Table 2. In general, the aromatic aldehydes carrying either

Table 1. Effect of different lithium salts for the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4a**)

Entry	Catalyst	Time (min)	Yield (%)[a]
1	—	30	57
2	LiCl	15	88
3	$LiClO_4$	15	69
4	$LiBF_4$	15	75
5	LiBr	15	95

[a]Isolated yield.

an electron-withdrawing group or electron-donating group reacted successfully and gave the products in good to excellent yields in less than 15 min. It is indeed gratifying to note that substituents in the aromatic ring of aldehydes did not show any effect on rate of the reaction and yield of the products. The heteroaryl aldehydes, such as 2-furaldehyde, 2-thiophenealdehyde, and 3-pyridinylaldehyde (entries **j–l**) reacted very smoothly to obtain the corresponding derivatives in good yields. These compounds have been reported to exhibit molluscicidal activity.[36] To further expand

Table 2. Lithium bromide–catalyzed preparation of tetrahydro-4*H*-chromene derivatives in aqueous media

					Mp (°C)	
Entry	Aldehydes	R	R^1	Yield (%)[a]	Found	Reported
a	PhCHO	CN	Me	95	230–232	228–230[14]
b	4-MeC_6H_4CHO	CN	Me	93	224–225	223–225[14]
c	4-$MeOC_6H_4CHO$	CN	Me	92	202–203	201–202[4]
d	2,3,4-$(MeO)_3C_6H_2CHO$	CN	Me	89	209–210	
e	4-OHC_6H_4CHO	CN	Me	90	220–222	224–226[4]
f	4-ClC_6H_4CHO	CN	Me	95	214–215	215–216[4]
g	3-NO_2-4-OHC_6H_3CHO	CN	Me	93	226–227	
h	4-BrC_6H_4CHO	CN	Me	94	202–203	203–205[4]
i	4-$NO_2C_6H_4CHO$	CN	Me	91	180–181	179–180[14]
j	2-Furaldehyde	CN	Me	88	225–226	226–228[4]
k	2-Thiophenealdehyde	CN	Me	85	216–218	214–215[36]
l	3-Pyridinylaldehyde	CN	Me	89	225–226	
m	PhCHO	CN	H	93	241–242	239–241[23]
n	4-MeC_6H_4CHO	CN	H	92	224–226	223–225[23]
o	4-$MeOC_6H_4CHO$	CN	H	91	196–198	195–197[23]
p	4-ClC_6H_4CHO	CN	H	93	228–229	226–229[10]
q	2,4-$Cl_2C_6H_3CHO$	CN	H	95	221–222	225–227[10]
r	3-$NO_2C_6H_4CHO$	CN	H	92	198–199	198–200[10]
s	4-$NO_2C_6H_4CHO$	CN	H	92	235–236	234–236[22]
t	2-Furaldehyde	CN	H	86	234–235	232–233[36]
u	2-Thiophenealdehyde	CN	H	85	205–206	204–205[36]
v	PhCHO	CO_2Et	Me	95	157–158	155–157[14]
w	4-MeC_6H_4CHO	CO_2Et	Me	93	157–158	156–158[14]
x	4-ClC_6H_4CHO	CO_2Et	Me	92	154–155	153–155[14]

[a]Isolated yield.

Table 3. Comparative synthesis of compound **4a** using the reported methods versus the present method

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	TBAF	H_2O/reflux	30	97	4
2	TEBA	H_2O/90°C	240	95	10
3	Na_2SeO_4	H_2O-EtOH/reflux	60	97	11
4	$RE(PFO)_3$	EtOH/90°C	300	90	12
5	HTMAB	H_2O/85–90°C	180	91	15
6	DBSA	H_2O/reflux	120	91	16
7	$(NH_4)_2HPO_4$	H_2O/rt	120	97	17
8	LiBr	H_2O/reflux	15	95	This work

the scope of the present method, the replacement of 5,5-dimethyl-1,3-cyclohexanedione with 1,3-cyclohexanedione was examined. To our delight, under the same conditions, the reactions proceeded steadily to provide the targeted tetrahydro-4*H*-chromens in good yields. Similar results were found for these three-component condensation reactions with ethyl caynoacetate (Table 1, entries **v–x**). In all cases, the reaction was remarkably clean, and no chromatographic separation was performed because no impurities were observed.

The feasibility of reusing and recycling the catalyst was examined using sequential reactions of benzaldehyde, malononitrile, and dimedone. In a typical reaction, the catalyst was recovered by simple filtration from the reaction mixture, and the filtrates containing the catalyst were reused for five cycles. The reactions proceeded smoothly with yields of 90–95%. The result indicated that the catalyst could be reused several times without significant loss of its activity.

In comparison with other catalysts such as TBAF, TEBA, Na_2SeO_4, $RE(PFO)_3$, HTMAB, and DBSA, which were recently reported in the formation of tetrahydro-4*H*-chromenes, lithium bromide (employed here) shows equal or more efficient catalytic activity in terms of reaction times and yields of the obtained products (Table 3).

In summary, we have developed a general and highly efficient method for the synthesis of tetrahydro-4*H*-chromene derivatives via lithium bromide–catalyzed, one-pot, three-component reaction of aryl aldehydes, active methylene compounds, and 1,3-cyclohexanedins in aqueous medium. The attractive features of this process are mild reaction conditions, reusability of catalyst, short reaction times, easy isolation of products, operational simplicity, and excellent yields, which make it a valid contribution to the existing processes in the field of chromene derivative synthesis.

EXPERIMENTAL

Melting points were recorded on an X-4 apparatus and are uncorrected. Infrared(IR) spectra were obtained using Shimadzu FTIR-8900 spectrometer using KBr optics. ^{1}H NMR spectra were recorded with a Varain Mercury Plus 400 spectrometer using tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were performed on a ThermoFinnigan LCQ Advantage instrument with an electrospray ionization (ESI) source (4.5 keV). Elemental analyses were performed on Vario EL III CHNOS elemental analyzer.

General Procedure for the Preparation of Tetrahydro-4*H*-chromene Derivatives

Lithium bromide (0.2 mmol) was added to a mixture of aldehyde (2 mmol), active methylene (2 mmol), cyclic 1,3-dicarbonyl compound (2 mmol), and water (5 mL), and the mixture was stirred under reflux condition for 15 min. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature, and the generated solid was filtered off and recrystallized from 95% ethanol to give pure products **4**.

Spectral Data for Selected Compounds

2-Amino-7,7-dimethyl-5-oxo-4-(2,3,4-trimethoxyphenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d). Mp 209–210°C; IR (KBr): 3413, 3301, 3174, 2954, 2185, 1658, 1637, 1600, 1494, 1460, 1400, 1369, 1280, 1089, 1001, 790 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.06 (s, 3H), 1.11 (s, 3H), 2.21 (AB q, $J = 16.4$ Hz, 2H), 2.44 (s, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 4.53 (s, 2H), 4.60 (s, 1H), 6.58 (d, $J = 8.4$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H) ppm; MS (ESI) m/z: 385 $(M+1)^+$. Anal. calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.42; H, 6.15; N, 7.50.

2-Amino-4-(4-hydroxy-3-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4g). Mp 226–227°C; IR (KBr): 3400, 3330, 3193, 2960, 2200, 1685, 1664, 1608, 1533, 1400, 1373, 1247, 1211, 1161, 1035, 854 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (s, 3H), 1.02 (s, 3H), 2.17 (AB q, $J = 16.0$ Hz, 2H), 2.49 (s, 2H), 4.22 (s, 1H), 7.07 (d, $J = 8.8$ Hz, 1H), 7.08 (s, 2H), 7.35 (dd, $J = 2.4$, 8.8 Hz, 1H), 7.61 (d, $J = 2.4$ Hz, 1H), 10.86 (br s, 1H) ppm; MS (ESI) m/z: 356 $(M+1)^+$. Anal. calcd. for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 61.02; H, 4.68; N, 12.02.

2-Amino-7,7-dimethyl-5-oxo-4-thiophen-2-yl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4k). Mp 216–218°C; IR (KBr): 3384, 3132, 2964, 2198, 1676, 1662, 1637, 1400, 1384, 1215, 1110, 1004, 854 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.97 (s, 3H), 1.04 (s, 3H), 2.27 (AB q, $J = 16.0$ Hz, 2H), 2.49 (AB q, $J = 17.6$ Hz, 2H), 4.53 (s, 1H), 6.85 (d, $J = 3.2$ Hz, 1H), 6.90 (dd, $J = 3.2$, 5.2 Hz, 1H), 7.11 (s, 2H), 7.31 (d, $J = 5.2$ Hz, 1H) ppm; MS (ESI) m/z: 301 $(M+1)^+$; Anal. calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.12; H, 5.26; N, 9.55.

2-Amino-7,7-dimethyl-5-oxo-4-pyridin-3-yl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4l). Mp 225–226°C; IR (KBr): 3411, 3365, 3118, 2970, 2192, 1678, 1664, 1612, 1589, 1431, 1400, 1367, 1215, 1132, 1004, 839 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (s, 3H), 1.03 (s, 3H), 2.17 (AB q, $J = 16.0$ Hz, 2H), 2.48–2.49 (m, 2H), 4.23 (s, 1H), 7.10 (s, 2H), 7.31 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.52 (dd, $J = 2.0$, 7.6 Hz, 1H), 8.38 (dd, $J = 2.0$, 4.8 Hz, 1H) ppm; MS (ESI) m/z: 296 $(M+1)^+$. Anal. calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.98; H, 5.65; N, 14.40.

2-Amino-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4q). Mp 221–222°C; IR (KBr): 3365, 3319, 3159, 2189, 1683, 1647, 1616, 1469, 1400, 1369, 1384, 1213, 1172, 1002, 862 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.84–1.86 (m, 2H), 2.07–2.16 (m, 2H), 2.61–2.66 (m, 2H), 4.67 (s, 1H), 7.06 (s, 2H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.32 (dd, $J = 2.4$, 8.4 Hz, 1H), 7.50 (d, $J = 2.4$ Hz, 1H) ppm; MS (ESI) m/z: 335 $(M + 1)^+$. Anal. calcd. for $C_{16}H_{12}C_{l2}N_2O_2$: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.18; H, 3.47; N, 8.58.

2-Amino-4-furan-2-yl-5-oxo-5,6,7,8-tetrahydro-4h-chromene-3-carbonitrile (4t). Mp 234–235°C; IR (KBr): 3400, 3327, 3213, 2974, 2187, 1678, 1652, 1602, 1400, 1384, 1361, 1211, 1011, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.96–2.01 (m, 2H), 2.23 (t, $J = 6.0$ Hz, 2H), 2.59 (t, $J = 6.0$ Hz, 2H), 4.23 (s, 1H), 6.06 (d, $J = 2.4$ Hz, 1H), 6.22 (t, $J = 2.4$ Hz, 1H), 7.08 (s, 2H), 7.48 (d, $J = 2.4$ Hz, 1H) ppm; MS (ESI) m/z: 257 $(M + 1)^+$. Anal. calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.48; H, 4.56; N, 11.05.

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