# LiBr-Mediated, solvent free von Pechmann reaction: facile and efficient method for the synthesis of 2*H*-chromen-2-ones

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**Abstract**
4-Substituted 2*H*-chromen-2-ones were synthesized in high yields employing lithium bromide via von Pechmann condensation of phenols and β-keto esters under solvent free condition.

**Keywords:** 4-Substituted 2*H*-chromen-2-ones, von Pechmann condensation, solvent-free reaction, phenols, β-keto esters

## Introduction

2*H*-Chromen-2-ones (coumarins) continue to be investigated because of their importance to medicinal chemists due to a variety of biological activity. Associated with the coumarin scaffold are antibacterial,[1a] antiviral,[1b] anticancer[2b,c] activity as well as inhibition of platelet aggregation[2a] and inhibition of steroid 5a-reductase.[3] Coumarins are used in drug and pesticidal preparations,[4] they have also found applications as photosensitizers,[5] fluorescent and laser dyes.[6]

Because of the significance of these molecules the search for efficient syntheses is of considerable interest. Usual methods of their preparation are von Pechmann,[7] Knoevenagel,[8] Perkin,[9] Reformatsky,[10] and Wittig reactions.[11] The von Pechmann reaction is simple and straight forward employing β-keto esters and substituted phenols together with an acid catalyst.

In the past, strong acids like $H_2SO_4$,[7a,b] TFA, $P_2O_5$, $AlCl_3$, $ZnI_2$, $TiCl_4$, $Bi(NO_3)_3{\cdot}5H_2O$,[12–13] ionic liquids,[14] sulfated zircona,[15] indium halides,[16a] and palladium[16b] have been used. Some of the catalyst used so far are harsh or hazardous, or have to be used in considerable excess;[7, 12c] some are not very efficient in terms of time (up to several days[7a,b]), yield[7c] (even when the catalyst is used in excess.[7a,b,12a,14b]), or lead to the formation of side products[17] (Table 1). These shortcomings certainly demand the search for a safe, more convenient and efficient method.

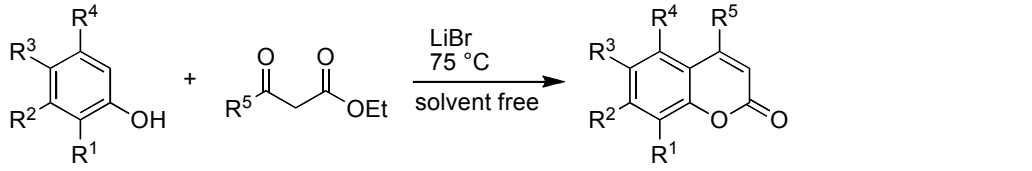
## Result and Discussion

We and others[18] have used LiBr as a mild Lewis acid[19] in many chemical transformations like Friedel-Crafts reaction, preparation of acylals, opening of epoxides, Knoevenagel condensation, Ehrlich-Sachs reaction, Biginelli condensation, and recently in the synthesis of dibenzo-[*b*]xanthenes and tetrahydrobenzo[*a,j*]pyrans.[18g] In most of these reported reactions, LiBr is reported to be a near neutral Lewis acid catalyst.[19] In continuation of our studies we employed LiBr in the synthesis of coumarins via von Pechmann reaction under solvent free condition (Scheme 1).

**Table 1.** Activity of catalysts in the synthesis of 7-hydroxy-4-methyl-2*H*-chromen-2-one **3a**

| Entry | Catalyst | Amount of catalyst used | Reaction time | Yield (%) | Reference |
|---|---|---|---|---|---|
| 1 | TFA | excess | 20 h | 91 | [12a] |
| 2 | Amberlite IR 120 | 25% w/w of total reactants | 40 min | 79 | [7c] |
| 3 | Sulfated zircona | 0.01 eq | 24 h | 91 | [15a] |
| 4 | Sulfated $Ce_xZr_{1-x}O_2$ | 0.1 eq | 143 min | 87 | [15b] |
| 5 | [bmim]$PF_6$ | excess | 45 min | 91 | [14b] |
| 6 | LiBr | 0.1 eq | 15 min | 92 | this report |

Phenols **1** and β-keto esters **2** reacted in the presence of LiBr without solvent at 75 °C within 15–40 min to furnish 2*H*-chromen-2-ones **3** (Table 2; **3ga**, **3ha** at 125 °C and 90 min). Microwave irradiation gave comparable yields at reduced reaction times of 2–5 min. All the products **3** were characterized by spectroscopic analyses (IR, $^1$H NMR) and – with the exception of the novel products **3da**, **3ea**, and **3ia** – by comparison with reported data.




**Scheme 1**

The catalyst efficacy is fairly general; an increased reaction time resulted in no significant improvement. It is worth mentioning that the present procedure showed no evidence for the formation of side products of the chromanone type.[17] This procedure worked also at multi-gram levels (up to 0.1 mol). Various phenols **1** and three β-keto esters **2** (ethyl acetoacetate, ethyl 4-chloroacetoacetate, ethyl benzoylacetate) were successfully employed. Phenols **1** with an electron-donating group $R^2$ in *meta* position (position 3) generally gave high yields in shorter

reaction times (Table 2): enhancement of electron density at position 6 facilitates the electrophilic substitution. Phenol (**1g**) gave a lower yield of **3ga** and required a higher temperature as well as a longer reaction time because of the lack of an electron-donating group.

In conclusion, this solvent-free procedure using a safe catalyst under mild reaction conditions provides an efficient, economical, and environmentally benign method for the synthesis of 2*H*-chromen-2-ones **3**.

**Table 2**. LiBr-Mediated (10 mol%) preparation of 4-substituted 2*H*-chromen-2-ones **3** (at 75 °C)

| **1** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | **2** | $R^5$ | Reaction time [min] | **3** | Yield (%)[a] | mp [°C] (lit. mp)[ref] |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | H | OH | H | H | **2a** | Me | 15 | **3aa** | 92 | 185–186 (185–186)[13a] |
| **1a** | H | OH | H | H | **2b** | $CH_2Cl$ | 18 | **3ab** | 90 | 179–181 (180–182)[20a] |
| **1a** | H | OH | H | H | **2c** | Ph | 30 | **3ac** | 86 | 253–255 (256.5–257)[12a] |
| **1b** | H | OH | H | OH | **2a** | Me | 15 | **3ba** | 91 | 286–287 (283–285)[13c] |
| **1b** | H | OH | H | OH | **2c** | Ph | 15 | **3bc** | 83 | 244–246 (246–247)[12a] |
| **1c** | H | MeO | H | H | **2a** | Me | 20 | **3ca** | 89 | 160–161 (161–163)[15c] |
| **1d** | H | H | MeO | H | **2a** | Me | 25 | **3da** | 84 | 164–166 |
| **1e** | H | EtO | H | H | **2a** | Me | 20 | **3ea** | 86 | 115–116 |
| **1f** | H | Me | H | H | **2a** | Me | 40 | **3fa** | 74 | 133–134 (131–132)[13c] |
| **1g** | H | H | H | H | **2a** | Me | 90[b] | **3ga** | 54 | 80–81 (83–84)[13c] |
| **1h** | –(CH)$_4$– | | H | H | **2a** | Me | 90[b] | **3ha** | 66 | 154–156 (154–156)[13c] |
| **1i** | OH | OH | H | H | **2a** | Me | 20 | **3ia** | 82 | 240–242 |
| **1i** | OH | OH | H | H | **2b** | $CH_2Cl$ | 25 | **3ib** | 81 | 196–198 (198–199)[20b] |
| **1i** | OH | OH | H | H | **2c** | Ph | 25 | **3ic** | 78 | 196–198 (195–197)[12a] |

[a] Isolated pure product.

[b] Reaction temperature was 125 °C; 20 mol% LiBr was used.

## Experimental Section

**General Procedures.** Melting points were determined in open capillaries, those of the known products **3** were compared with reported data. IR spectra were obtained with a Perkin-Elmer 237B infrared spectrometer (KBr discs). NMR spectra were recorded on a Varian Gemini 300 spectrometer with tetramethylsilane (TMS) as internal standard. Commercial grade LiBr was used as procured from Aldrich; all other chemicals were purified by distillation or crystallization prior to use.

**7-Hydroxy-4-methyl-2*H*-chromen-2-one (3aa). Typical procedure.** A mixture of resorcinol **1a** (1.1 g, 10 mmol) and ethyl acetoacetate **2a** (1.3 g, 10 mmol) was heated at 75 °C in the presence of LiBr (86 mg, 10 mol%) for 15 min. The reaction was monitored by TLC for the disappearance of reactants, $R_f$ = 0.729 (**1a**) and $R_f$ = 0.505 (**2a**). The reaction mixture was cooled to room temperature, poured onto crushed ice (20 mL), and stirred for 5 min. The solid precipitate was filtered off and recrystallized from ethanol to afford colorless crystals **3aa** (1.62 g, 92%); mp 185–186 °C (lit.[13a] mp 185–186 °C).

**6-Methoxy-4-methyl-2*H*-chromen-2-one (3da).** Colorless crystals, $R_f$ = 0.33 (hexane/ethyl acetate, 70:30), mp 164–166 °C. IR (KBr): 2935, 1683, 1626, 1485, 1238, 1187, 804 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.41 (3H, s), 3.89 (3H, s), 6.36 (1H, s), 7.15 (1H, d, *J* = 9.1 Hz), 7.26 (1H, s), 7.35 (1H, d, *J* = 9.1 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 18.4, 56.1, 108.3, 115.3, 117.4, 119.7, 120.2, 146.9, 153.2, 155.4, 160.1. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.43; H, 5.30. Found: C, 69.45; H 5.27.

**7-Ethoxy-4-methyl-2*H*-chromen-2-one (3ea).** Colorless crystals, $R_f$ = 0.32 (hexane/ethyl acetate, 70:30), mp 115–116 °C. IR (KBr): 2942, 1681, 1618, 1497, 1239, 1168, 817 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, t, *J* = 6.4 Hz), 2.31 (3H, s), 4.12 (2H, q, *J* = 6.4 Hz), 6.38 (1H, s), 6.96 (1H, s), 7.16 (1H, d, *J* = 9.4 Hz), 7.62 (1H, d, *J* = 9.1 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 15.7, 18.6, 66.1, 108.7, 110.1, 118.2, 119.7, 126.2, 146.2, 153.7, 156.8, 162.3. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.52; H, 5.86.

**7,8-Dihydroxy-4-methyl-2*H*-chromen-2-one (3ia).** Colorless crystals, $R_f$ = 0.25 (hexane/ethyl acetate, 70:30), mp 240–242 °C. IR (KBr): 3417, 3223, 1676, 1620, 1585, 1443, 1156, 811 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.37 (3H, s), 6.12 (1H, s), 6.86 (1H, d, *J* = 8.6 Hz), 7.11 (1H, d, *J* = 8.6 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 18.4, 109.8, 112.1, 112.7, 116.1, 131.8, 143.5, 149.6, 154.1, 160.3. Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.54; H, 4.15.

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