

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

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Abstract

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

Introduction

2H-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 5 α -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 H₂SO₄,^{7a,b} TFA, P₂O₅, AlCl₃, ZnI₂, TiCl₄, Bi(NO₃)₃·5H₂O,¹²⁻¹³ ionic liquids,¹⁴ sulfated zirconia,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 products¹⁷ (Table 1). These shortcomings certainly demand the search for a safe, more convenient and efficient method.

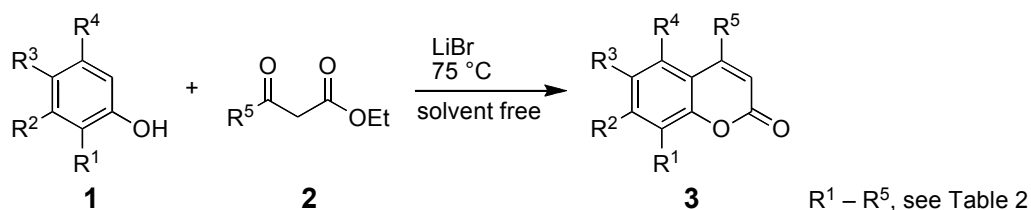
Result and Discussion

We and others¹⁸ have used LiBr as a mild Lewis acid¹⁹ 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 _x Zr _{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, ¹H 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 R² 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 ₂ Cl	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	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 ₂ Cl	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-2H-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-2H-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 $\text{C}_{11}\text{H}_{10}\text{O}_3$: C, 69.43; H, 5.30. Found: C, 69.45; H 5.27.

7-Ethoxy-4-methyl-2H-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 $\text{C}_{12}\text{H}_{12}\text{O}_3$: C, 70.57; H, 5.92. Found: C, 70.52; H, 5.86.

7,8-Dihydroxy-4-methyl-2H-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 $\text{C}_{10}\text{H}_8\text{O}_4$: C, 62.50; H, 4.20. Found: C, 62.54; H, 4.15.

References

1. (a) Maxwell, A. *Mol. Microbiol.* **1993**, *9*, 681. (b) Zembower, D. E.; Liao, S.; Flavin, M. T.; Xu, Z.-Q.; Stup, T. L.; Buckheit, R. W., Jr.; Khilevich, A.; Mar, A. A.; Sheinkman, A. K. *J. Med. Chem.* **1997**, *40*, 1005.

2. (a) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707. (b) Wang, C.-J.; Hsieh, Y.-J.; Chu, C.-Y.; Lin, Y.-L.; Tseng, T.-H. *Cancer Lett.* **2002**, *183*, 163. (c) Dexeus, F. H.; Logothetis, C. J.; Sella, A.; Fitz, K.; Amato, R.; Reuben, J. M.; Dozier, N. *J. Clin. Oncol.* **1990**, *8*, 325.
3. Fan, G. J.; Mar, W.; Park, M. K.; Choi, E. W.; Kim, K.; Kim, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2361.
4. Meuly, W. C. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Edn.; John Wiley and sons: New York, 1979; p. 196.
5. Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Pyran and their Benzo derivatives, Synthesis, Pergamon Press, 1996. vol. 5, p. 301.
6. Green, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Pyran and their Benzo derivatives, Synthesis, Pergamon Press, 1996. vol. 5, p. 469.
7. (a) von Pechmann, H.; Duisberg, C. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2119. (b) von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 929. (c) John, E. V. O.; Israelstam, S. S. *J. Org. Chem.* **1961**, *26*, 240. (d) Rao, Y. V. S.; Kulkarni, S. J.; Subramanyam, M.; Rao, A. V. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1456.
8. (a) Jones, G. *Org. React.* **1967**, *15*, 204. (b) Adams, R.; Bockstahler, T. E. *J. Am. Chem. Soc.* **1952**, *74*, 5346. (c) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257. (d) Kadin, S. B. *J. Org. Chem.* **1966**, *31*, 620.
9. Johnson, J. R. *Org. React.* **1942**, *1*, 210.
10. Shriner, R. L. *Org. React.* **1942**, *1*, 1.
11. (a) Yavari, I.; Hekmat-Shoar, R.; Zonouki, A. *Tetrahedron Lett.* **1998**, *39*, 2391. (b) Abdou, W. M.; Ganoub, N. A. F.; Abdel-Rahman, N. M. *Phosphorus Sulfur Relat. Elem.* **1991**, *61*, 91.
12. (a) Woods, L. L.; Sapp, J. *J. Org. Chem.* **1962**, *27*, 3703. (b) Simonis, H.; Remmert, P. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 2229. (c) Robertson, A. Sandrock, W. F.; Hendry, C. B. *J. Chem. Soc.* **1931**, 2426.
13. (a) Shah, R. C.; Sethna, S. M.; Banerjee, B. C.; Chakravarti, D. *J. Ind. Chem. Soc.* **1937**, *14*, 717. (b) Chavan, S. P.; Shivasankar, K.; Sivappa, R.; Kale, R. *Tetrahedron Lett.* **2002**, *43*, 8583. (c) Valizadeh, H.; Shockravi, A. *Tetrahedron Lett.* **2005**, *46*, 3501. (d) Alexander, V. M.; Bhat, R. P.; Samant, S. D. *Tetrahedron Lett.* **2005**, *46*, 6957.
14. (a) Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2001**, *42*, 9285. (b) Potdar, M. K.; Rasalkar, M. S.; Mohile, S. S.; Salunkhe, M. M. *J. Mol. Catal. A: Chemical* **2005**, *235*, 249.
15. (a) Rodríguez-Domínguez, J. C.; Kirsch, G. *Tetrahedron Lett.* **2006**, *47*, 3279. (b) Reddy, B. M.; Patil, M. K.; Lakshmanan, P. P. *J. Mol. Catal. A: Chemical* **2006**, *256*, 290. (c) Selvakumar, S.; Chidambaram, M.; Singh, A. P. *Catal. Commun.* **2007**, *8*, 777.

16. (a) Bose, D. S.; Rudradas, A. P.; Babu, M. H. *Tetrahedron Lett.* **2002**, *43*, 9195. (b) For palladium see Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643.
17. Livant, P.; Xu, W. *J. Org. Chem.* **1998**, *63*, 636, and references cited therein.
18. (a) Ono, F.; Negoro, R.; Sato, T. *Synlett* **2001**, 1581. (b) Pushin, A. N.; Tkachenko, S. E.; Martynov, I. V. *Dokl. Akad. Nauk USSR* **1988**, *299*, 154. *Chem. Abstr.* **1989**, *110*, 115052a. (c) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102. (d) Prajapati, D.; Lekhok, K. R.; Sandhu, J. S.; Ghosh, A. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 959. (e) Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *Synth. Commun.* **2001**, 1427. (f) Baruah, P. P.; Gadhwal, S.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **2002**, 1038. (g) Saini, A.; Kumar, S.; Sandhu, J. S. *Synlett* **2006**, 1928.
19. (a) Firouzabadi, H.; Karimi, B.; Eslami, S. *Tetrahedron Lett.* **1999**, *40*, 4055. (b) Firouzabadi, H.; Iranpoor, N.; Karimi, M. *Synthesis* **1999**, 58.
20. (a) Zagotto, G.; Gia, O.; Bacchichetti, F.; Uriarte, E.; Palumbo, M. *Photochem. Photobiol.* **1993**, *58*, 486. (b) Khaikin, M. S.; Petrova, N. L.; Kukhtin, V. A. *Zh. Obshch. Khim.* **1963**, *33*, 3941. *Chem. Abstr.* **1964**, *60*, 9235.