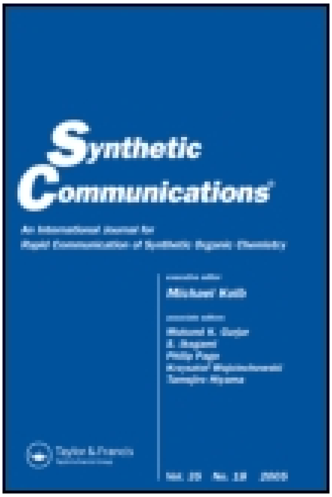


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Gallium Triiodide-Catalyzed Organic Reaction: A Convenient Procedure for the Synthesis of Coumarins

Peipei Sun [a] & Zhixin Hu [a]

[a] College of Chemistry and Environmental Science , Nanjing Normal University , Nanjing, China

To cite this article: Peipei Sun & Zhixin Hu (2005) Gallium Triiodide-Catalyzed Organic Reaction: A Convenient Procedure for the Synthesis of Coumarins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:14, 1875-1880, DOI: 10.1081/SCC-200064906

To link to this article: http://dx.doi.org/10.1081/SCC-200064906

Synthetic Communications®, 35: 1875–1880, 2005
Copyright © Taylor & Francis, Inc.
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200064906

Gallium Triiodide–Catalyzed Organic Reaction: A Convenient Procedure for the Synthesis of Coumarins

Peipei Sun and Zhixin Hu
College of Chemistry and Environmental Science, Nanjing Normal
University, Nanjing, China

Abstract: Gallium triiodide, which was generated in situ by the reaction of gallium metal and iodine, was used as an efficient catalyst in the Pechmann condensation of phenols with ethyl acetoacetate, leading to the formation of coumarins. The reaction proceeded in dichloromethane at room temperature with good to excellent yields.

Keywords: Coumarins, ethyl acetoacetate, gallium triiodide, Pechmann reaction, phenols

INTRODUCTION

Coumarins are a very important group of organic compounds not only in organic synthesis but also in biology and food, as well as in materials science. For example, they can be used as additives to food and cosmetics[1] or fluorescent materials in optical devices, that is, in organic light-emitting diodes[2] and molecular photonic devices.[3] Therefore, the synthesis of coumarins and their derivatives has attracted considerable attention from chemists. Among numerous methods, the Pechmann reaction is an important approach. 4-Substituted coumarins can be synthesized simply by the condensation of substituted phenols with β-ketoesters in an acidic medium.[4] Traditional Pechmann reaction was catalyzed by acidic reagents

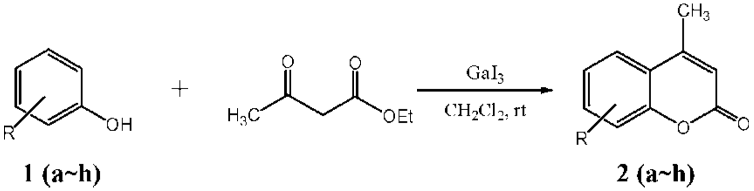
Received in Japan January 11, 2005

Address correspondence to Peipei Sun, College of Chemistry and Environmental Science, Nanjing Normal University, Nanjing 210097, China. E-mail: sunpeipei@njnu.edu.cn

such as H_2SO_4, HCl, CF_3COOH, and so forth.[5] It might also be catalyzed by some solid acids.[6] In these methods, long reaction times or high reaction temperatures, (above 150°C), were needed, which depended on their reactivity. In some cases, undesired side products such as chromones were also generated in addition to coumarins. Moreover, the disposal of excess acid waste might lead to environmental pollution. In recent years, Lewis acids such as $InCl_3$, $AlCl_3$-nBPC, $Yb(OTf)_3$, $ZrCl_4$, and $Sm(NO_3)_3$ as well as acidic ionic liquid were employed to catalyze Pechmann reactions.[7] However, some of these Lewis acids are moisture sensitive and require special care in handling and storage, and some of these methods still need a high reaction temperature or a long reaction time. Furthermore, metal triflates are highly expensive.

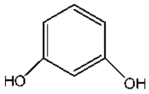
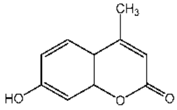
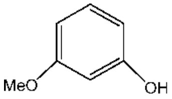
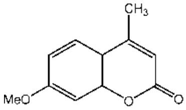
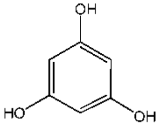
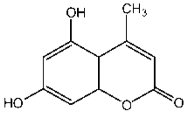
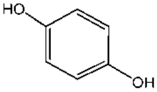
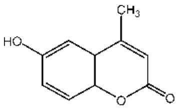
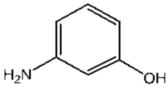
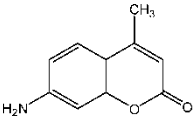
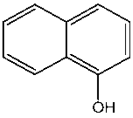
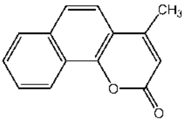
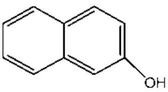
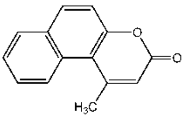
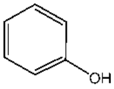
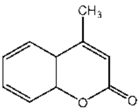
In the course of our recent work on Lewis acid–catalyzed organic reactions, we have found that gallium triiodide has emerged as a powerful Lewis acid catalyst in some reactions such as the Sakurai reaction, the tetrahydropyranylation of alcohols and phenols, and the coupling reaction of carbonyl compounds, amines, and diethyl phosphite.[8] Another evident advantage of this reagent is that it can be prepared in situ by a simple inorganic reaction of gallium with iodine, which can bring some advantages for its application. We suppose that it will have a great potential to be used in organic synthesis. Here, we report the use of gallium triiodide in a convenient synthesis of coumarins by the Pechmann reaction.

4-Methylcoumarins were synthesized by the reaction of phenols and ethyl acetoacetate under the catalysis of gallium triiodide (Scheme 1) in dichloromethane. The results are summarized in Table 1. The Lewis acid catalyst, gallium triiodide, was generated easily in situ by the reaction of gallium metal and iodine, and a small excess of either Ga or I_2 did not make any difference to the normal course of reaction. It showed that GaI_3 exhibited a powerful catalytic activity in an amount as low as 10 mol%, which was enough to complete the reaction at room temperature within a few hours for most of the substrates we used, and a larger amount of catalyst or higher reaction temperature (under reflux) could not enhance the rates or increase the yields evidently. Dichloromethane was found to be the effective solvent for this conversion. The catalyst could dissolve in it to form a homogeneous solution, and thus the strong electrostatic activation to the substrates made the reaction take



Scheme 1.

Table 1. GaI_3-catalyzed Pechmann reaction

Entry	Substrate	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	0.7	96
2	 **1b**	 **2b**	1	90
3	 **1c**	 **2c**	1	94
4	 **1d**	 **2d**	1.5	86
5	 **1e**	 **2e**	1.2	85
6	 **1f**	 **2f**	2	83
7	 **1g**	 **2g**	2.5	80
8	 **1h**	 **2h**	10	65[b]

[a] Isolated yields. The products were characterized by ^{1}HNMR and IR spectra analysis and comparison of their mp with the reports.

[b] Under reflux.

place smoothly. Commercial dichloromethane could be used directly and further purification was not needed. The method was adaptive to the substrates with electron-donating groups, and the reaction gave good to excellent yields in a short time. With unsubstituted phenol, it proceeded slower and moderate yields were given even under reflux for as long as 10 h (Entry 8). To the substrates with electron-withdrawing groups such as *p*-chlorophenol, the reaction was very sluggish and only a trace product was generated after it reacted for 24 h.

In summary, we have developed a new and efficient procedure for a Pechmann reaction catalyzed by GaI_3. The method offers several advantages such as mild reaction conditions, short reaction times, high yields, and a simple experimental operation, leading to a useful and attractive process for the preparation of coumarins. It is also revealed that GaI_3 is an effective and useful Lewis acid catalyst. Its further application in organic synthesis is currently being explored in our laboratory.

EXPERIMENTAL

General Procedure for the Synthesis of Coumarins

Gallium metal (0.1 mmol) and iodine (0.15 mmol) were added to 2 mL of dichloromethane. The mixture was stirred and refluxed under nitrogen atmosphere until the reaction was complete (the reactants disappeared; it needed about 0.5 h), then cooled to room temperature. To this solution was added phenol (1.0 mmol) and ethyl acetoacetate (1.0 mmol). The resulting mixture was stirred at room temperature for an appropriate time (see Table 1, monitored by TLC) and quenched with water. The mixture was then extracted with CH_2Cl_2 or ethyl acetate and purified by column chromatography on silica gel with hexane/ethyl acetate (2:1) as eluent to yield the product.

2a[7b]: mp: 185–187°C (lit.[7b] 182–184°C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, $J = 8.7$ Hz, 1H), 6.93 (s, 1H), 6.85 (d, $J = 8.7$ Hz, 1H), 6.17 (s, 1H), 2.43 (s, 3H); IR (KBr): 3445, 3034, 1686, 1587, 1260, 1075 cm^{-1}.

2b[9]: mp: 160–162°C (lit.[9] 158–159°C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, $J = 8.7$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 6.85 (s, 1H), 6.16 (s, 1H), 3.85 (s, 3H), 2.42 (s, 3H); IR (KBr): 3052, 1690, 1568, 1215, 1088 cm^{-1}.

2c[7b]: mp: 282–284°C (lit.[7b] 284–285°C); ^1H NMR (300 MHz, DMSO-d_6): δ 6.26 (s, 1H), 6.17 (s, 1H), 5.85 (s, 1H), 2.50 (s, 3H); IR (KBr): 3385, 3024, 1703, 1587, 1232, 1064 cm^{-1}.

2d[5d]: mp: 240–242°C (lit.[5d] 241–242°C); ^1H NMR (300 MHz, DMSO-d_6): δ 7.05 (s, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.33 (s, 1H), 2.42 (s, 3H); IR (KBr): 3412, 3010, 1693, 1565, 1225, 1055 cm^{-1}.

2e[10]: mp: 220–222°C (lit.[10] 220–224°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40 (d, $J = 8.7$ Hz, 1H), 6.55 (d, $J = 8.7$ Hz, 1H), 6.40 (s, 1H), 5.90 (s, 1H), 2.30 (s, 3H); IR (KBr): 3468, 3312, 3012, 1688, 1570, 1238, 1052 cm^{-1}.

2f[5d]: mp: 153–154°C (lit.[5d] 155°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, $J = 9.0$ Hz, 1H), 7.89 (d, $J = 9.0$ Hz, 1H), 7.48–7.70 (m, 4H), 6.41 (s, 1H), 2.56 (s, 3H); IR (KBr): 3010, 1708, 1575, 1238, 1046 cm^{-1}.

2g[11]: mp: 177–179°C (lit.[11] 180.5–181); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, $J = 8.7$ Hz, 1H), 8.00 (d, $J = 9.0$ Hz, 1H), 7.94 (d, $J = 8.7$ Hz, 1H), 7.55–7.68 (m, 2H), 7.51 (d, $J = 9.0$ Hz, 1H), 6.42 (s, 1H), 2.97 (s, 3H); IR (KBr): 3024, 1702, 1568, 1242, 1038 cm^{-1}.

2h[9]: mp: 79–80°C (lit.[9] 82°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, $J = 6.0$ Hz, 1H), 7.15–7.42 (m, 3H), 6.32 (s, 1H), 2.42 (s, 3H); IR (KBr): 3020, 1705, 1543, 1238, 1064 cm^{-1}.

ACKNOWLEDGMENT

Financial support of this research from the Natural Science Foundation of the Education Department of Jiangsu Province is gratefully acknowledged (Project 03KJD150109).

REFERENCES

1. Kennedy, R. O.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*; Wiley and Sons: Chichester, 1997.
2. Mitsuya, M.; Suzuki, T.; Koyama, T. Bright red organic light-emitting diodes doped with a fluorescent dye. *Appl. Phys. Lett.* **2000**, *77*, 3272.
3. Adronov, A.; Gilat, S. L.; Frechet, J. M. J.; Ohta, K.; Neuwahl, F. V. R.; Fleming, G. R. Light harvesting and energy transfer in laser-dye-labeled poly(aryl ether) dendrimers. *J. Am. Chem. Soc.* **2000**, *122*, 1175.
4. (a) Pechmann, H. V.; Duisberg, C. Ueber die Verbindungen der Phenole mit Acetessigäther. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2119; (b) Sethna, S.; Phadke, R. The Pechmann reactions. *Org. React. (N.Y.)* **1953**, *7*, 1.
5. (a) Robertson, A.; Sandrock, W. F.; Henry, C. B. Hydroxy-carbonyl compounds. Part V. The preparation of coumarins and 1:4-pyrones from phenol, p-cresol, quinol and α-naphthol. *J. Chem. Soc.* **1931**, 2426; (b) Appel, H. An improved method for the synthesis of coumarins by v. *Pechmann's method. J. Chem. Soc.* **1935**, 1031; (c) Woods, L. L.; Sapp, J. A new one-step synthesis of substituted coumarins. *J. Org. Chem.* **1962**, *27*, 3703; (d) Singh, V.; Singh, J.; Kaur, K. P.; Kad, G. L. Acceleration of the Pechmann reaction by microwave irradiation: Application to the preparation of coumarins. *J. Chem. Res., Synop.* **1997**, 58.
6. (a) Hoefnagel, A. J.; Gennewagh, E. A.; Downing, R. S.; Bekkum, H. V. Synthesis of 7-hydroxycoumarins catalysed by solid acid catalysts. *J. Chem. Soc., Chem. Commun.* **1995**, 225; (b) de la Hoz, A.; Moreno, A.; Vazquez, E. Use of microwave irradiation and solid acid catalysts in an enhanced and environmentally

friendly synthesis of coumarin derivatives. *Synlett* **1999**, 608; (c) Romanelli, G. P.; Bennardi, D.; Ruiz, D. M.; Baronetti, G.; Thomas, H. J.; Autino, J. C. A solvent-free synthesis of coumarins using a Wells–Dawson heteropolyacid as catalyst. *Tetrahedron Lett.* **2004**, *45*, 8935; (d) Singh, P. R.; Singh, D. U.; Samant, S. D. Sulfamic acid—an efficient and cost-effective solid acid catalyst for the Pechmann reaction. *Synlett* **2004**, 1909.

7. (a) Bose, D. S.; Rudradas, A. P.; Babu, M. H. The indium(III) chloride-catalyzed von Pechmann reaction: A simple and effective procedure for the synthesis of 4-substituted coumarins. *Tetrahedron Lett.* **2002**, *43*, 9195; (b) Khandekar, A. C.; Khadilkar, B. M. Pechmann reaction in chloroaluminate ionic liquid. *Synlett* **2002**, 152; (c) Wang, L. M.; Xia, J. J.; Tian, H.; Qian, C. T.; Ma, Y. Synthesis of coumarin by $Yb(OTf)_3$-catalyzed Pechmann reaction under the solvent-free conditions. *Indian J. Chem. B* **2003**, *42*, 2097; (d) Smitha, G.; Reddy, C. S. $ZrCl_4$-catalyzed Pechmann reaction: Synthesis of coumarins under solvent-free conditions. *Synth. Commun.* **2004**, *34*, 3997; (e) Gangadasu, B.; Narender, P.; Raju, B. C.; Rao, V. J. $ZrCl_4$-catalyzed solvent-free synthesis of coumarins. *J. Chem. Res.* **2004**, 480; (f) Bahekar, S. S.; Shinde, D. B. Samarium(III)-catalyzed one-pot construction of coumarins. *Tetrahedron Lett.* **2004**, *45*, 7999; (g) Singh, V.; Kaur, S.; Sapehiyia, V.; Singh, J.; Kad, G. L. Microwave-accelerated preparation of [bmim][HSO_4] ionic liquid. An acid catalyst for improved synthesis of coumarins. *Catal. Commun.* **2005**, *6*, 57.
8. (a) Sun, P. P.; Xian, Y. F.; Xiao, Y. P. GaI_3-catalyzed nucleophilic addition of allyltrimethylsilane to aldehydes. *J. Chem. Res.* **2004**, 216; (b) Sun, P. P.; Hu, Z. X. GaI_3-catalyzed tetrahydropyranylation of alcohols and phenols. *Chin. J. Chem.* **2004**, *22*, 1341; (c) Sun, P. P.; Hu, Z. X.; Huang, Z. H. Gallium Triiodide–catalyzed organic reaction: A convenient synthesis of α–amino phosphonates. *Synth. Commun.* **2004**, *34*, 4293.
9. Mali, R. S.; Yadav, V. J. Convenient synthesis of naturally occurring coumarins, (2-oxo-2H-benzopyrans) and 4-methylcoumarins (4-methyl-2-oxo-2H-benzopyrans). *Synthesis* **1977**, 464.
10. Atkins, R. L.; Bliss, D. E. Substituted coumarins and azacoumarins. Synthesis and fluorescent properties. *J. Org. Chem.* **1978**, *43*, 1975.
11. Nagasawa, K.; Kanbara, H.; Matsushita, K.; Ito, K. A novel and efficient synthesis of 5-substituted and 5,6-disubstituted 4-methylcoumarins using organocerium(III) reagents. *Tetrahedron Lett.* **1985**, *26*, 6477.