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Short communication

Gallium(III) iodide-promoted stereoselective aldol coupling of α,β-acetylenic ketones☆

J.S. Yadav *, B.V.S. Reddy, Manoj K. Gupta, Sushil K. Pandey

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

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Abstract

A simple and highly stereoselective method has been developed for the synthesis of (*Z*)-β-iodo Baylis–Hillman adducts utilizing gallium(III) iodide as a novel reagent. This new procedure offers significant advantages such as high conversions, short reaction times and enhanced *Z*-selectivity together with mild reaction conditions.

Keywords: Gallium compounds; Multi-component reaction; β-Iodo Baylis–Hillman adducts

The coupling of activated vinyl compounds with aldehydes in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), known as Baylis–Hillman reaction, is widely used to construct α-hydroxy alkyl or aryl vinyl systems [1]. In particular, β-halovinyl ketones are versatile building blocks in organic synthesis especially in the preparation of heterocyclic and organometallic compounds [2]. The β-iodovinyl ketones are initially prepared by coupling of aldehydes with α,β-acetylenic ketones using $TiCl_4$/$(n\text{-}Bu)_4NI$ reagent system [3]. Subsequently, various reagents such as $TiCl_4$, $TiBr_4$, Et_2AlI, TMSI, $CeCl_3{\cdot}7H_2O$/NaI and MgI_2 have been used as halogen sources as well as promoters [4,5]. Among these reagents, $TiCl_4$, $TiBr_4$, and $TiCl_4$/$(n\text{-}Bu)_4NI$ are known to generate the E-isomer as the major product at 0 °C, whereas Et_2AlI, TMSI, $CeCl_3{\cdot}7H_2O$/NaI and MgI_2 produced the *Z*-isomer under similar conditions [4,5]. However, the use of corrosive and hazardous reagents is undesirable in view of today's environmental consciousness. Recently, there have been considerable interest in gallium mediated transformations [6]. Due to their unique Lewis acid activity, gallium halides have been widely used for a variety of organic transformations [7]. In particular, gallium(III) compounds are being considered as effective Lewis acids to activate alkynes under extremely mild conditions [8]. However, there have been no reports on the use of gallium(III) iodide for the synthesis of β-iodovinyl ketones.

In this article, we wish to report a simple, convenient and efficient protocol for the synthesis of β-iodovinyl Baylis–Hillman adducts from aldehydes and α,β-acetylenic ketones using gallium(III) iodide as novel reagent. Accordingly, treatment of benzaldehyde **1** with 3-butyn-2-one **2** in the presence of 35 mol% of GaI_3 afforded 3-hydroxy(phenyl)methyl-4-iodo-(*Z*)-3-buten-2-one **3a** in 81% yield (Scheme 1).

In a similar fashion, various aromatic aldehydes such as *p*-nitro-, *p*-fluoro-, *p*-chloro-, *p*-cyano-, *p*-methyl- and *m*-bromobenzaldehyde reacted smoothly with 3-butyn-2-one to afford the corresponding β-iodovinyl ketones (entries b–g, Table 1). Acid sensitive substrates like cinnamaldehyde and hydrocinnamaldehyde (entries h and i, Table 1) underwent smooth coupling with 3-butyn-2-one to give the respective adduct. Other substrate such as thiophene-2-carboxaldehyde also gave the desired product in good yield (entry j, Table 1). Encouraged by these results, we turned our attention towards various substituted ynones. Surprisingly, low conversions were obtained when methyl group of 3-butyn-2-one was replaced by *n*-pentyl group. For example, treatment of benzaldehyde with 1-octyn-3-one gave the corresponding β-iodovinyl ketone in 45% yield having *Z*-selectivity (entries k, Table 1 and Scheme 2).

In case of 3-phenyl-1-propyn-3-one, the reaction took place rapidly at room temperature, but no desired product was obtained

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* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 7160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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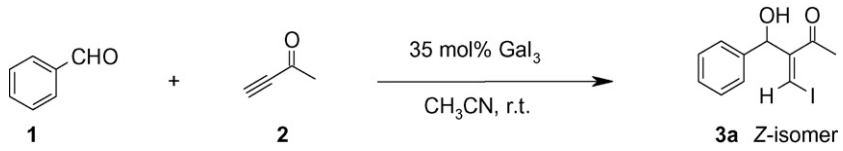
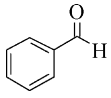
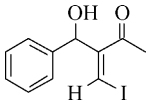
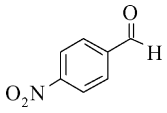
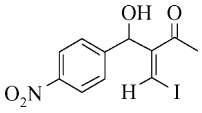
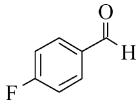
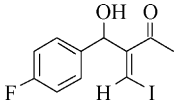
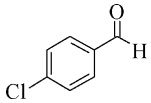
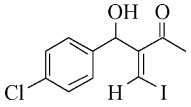
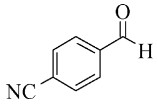
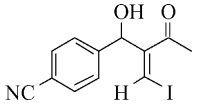
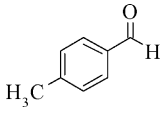
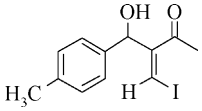
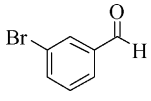
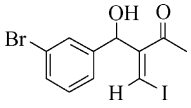
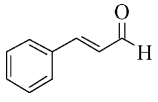
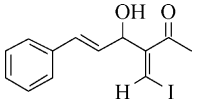
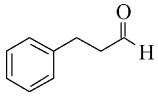
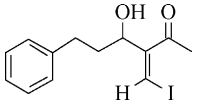
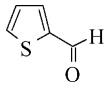
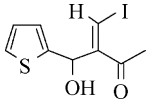
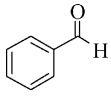
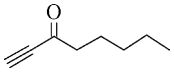
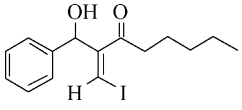
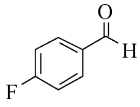
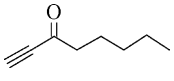
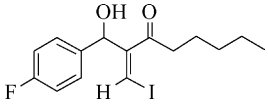
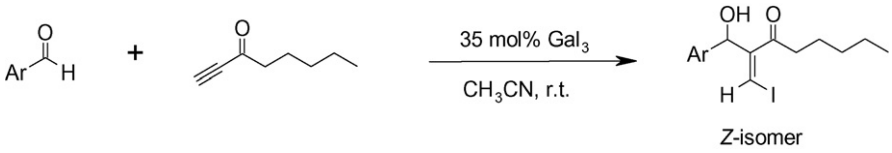


Scheme 1.

Table 1
GaI_3-promoted synthesis of β-iodo Baylis–Hillman adducts

Entry	Aldehyde **1**	Ynones **2**	Product[a] **3**	Time (h)	Yield (%)[b]
a				4.0	81
b				3.5	88
c				3.0	80
d				3.5	79
e				4.0	77
f				5.0	82
g				4.5	75
h				4.0	83
i				5.0	62
j				3.0	68
k				7.5	45
l				7.0	48

[a] All products were characterized by ^1H NMR, IR spectra and mass spectrometry.
[b] Yield refers to the isolated pure products after column chromatography.



Scheme 2.

under the reaction conditions. In this experiment, iodide addition product was obtained instead of desired aldol product. This may be due to intrinsically lower reactivity of aldehydes in comparison to 3-phenyl-1-propyn-3-one. The aldehyde was remain unaffected in the reaction mixture, which was recovered while work-up. Finally, we have attempted the coupling of benzaldehyde with internal alkyne such as 1-phenyl-1-hexyne. No reaction was observed under similar reaction conditions. The reaction was successful only with alkyl substituted terminal ynones. In most of the cases, the reactions were found to be highly stereoselective affording exclusively *Z*-isomers in high yields. The *Z*-stereochemistry of the products were determined on the basis of the chemical shift values of vinyl and allylic protons in the ^{1}H NMR spectrum of the products and also by comparison with reported data [3,4]. It is note worthy that 3-butyn-2-one gave higher yields compared to 1-octyn-3-one. The efficacy of various metal iodides such as GaI_3, InI_3, AlI_3, MgI_2, and ZnI_2 were studied for this transformation. Among these reagents, GaI_3 was found to be more effective in terms of conversion and reaction rates. Best results were obtained with 35 mol% of GaI_3. Similar results were also obtained when reactions were carried out using 10 mol% of GaI_3 and 1 equiv. of NaI. However, the reactions did not take place in the absence of gallium(III) iodide even under refluxing conditions. Among various solvents such as dichloromethane, tetrahydrofuran and toluene tested, acetonitrile appeared to give the best results. The scope and generality of this process was illustrated with respect to various aldehydes and the results are presented in the table [9].

In summary, we have described a simple, convenient and efficient protocol for the synthesis of β-iodovinyl ketones from aldehydes and 3-butyn-2-one/1-octyn-3-one utilizing GaI_3 as novel reagent. GaI_3 is a solid and stable to air or moisture and ease to handle even in multi-gram scale and is found to activate alkynes very effectively under mild conditions. This method offers several advantages such as high conversions, mild reaction conditions, high *Z*-selectivity, experimental simplicity, high promoting activity of GaI_3 which makes it a useful and attractive strategy for the preparation of β-iodovinyl ketones.

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References

[1] (a) A.D. Baylis, M.E.D. Hillman, German Patent 2,155,113 (1972);
(b) S.E. Drewes, G.H.P. Roos, Tetrahedron 44 (1988) 4653;
(c) For review see:
D. Basavaiah, A. Jaganmohan Rao, T Satyanarayana, Chem. Rev. 103 (2003) 811, and references cited therein.

[2] (a) A.E. Pohland, W.R. Benson, Chem. Rev. 66 (1966) 161;
(b) A. Mitra, The Synthesis of Prostaglandins, Wiley–Interscience, New York, 1977;
(c) J.S. Bindra, R. Bindra, Prostaglandins Synthesis, Academic Press, New York, 1977;
(d) E.J. Corey, B.J.J. Beames, Am. Chem. Soc. 94 (1972) 7210.

[3] (a) M. Taniguchi, S. Kobayashi, M. Nakagawa, T. Hino, Y. Kishi, Tetrahedron Lett. 27 (1986) 4763;
(b) M. Taniguchi, T. Hino, Y. Kishi, Tetrahedron Lett. 27 (1986) 4767.

[4] (a) H.X. Wei, S.H. Kim, T.D. Caputo, D.W. Purkiss, G. Li, Tetrahedron 56 (2000) 2397;
(b) H.X. Wei, J.J. Gao, G. Li, Tetrahedron Lett. 42 (2000) 9119;
(c) G. Li, H.X. Wei, J.J. Gao, J. Johnson, Synth. Commun. 32 (2002) 1765.

[5] (a) H.X. Wei, J.J. Gao, G. Li, P.W. Pare, Tetrahedron Lett. 43 (2002) 5677;
(b) H.X. Wei, J. Hu, D.W. Purkiss, P.W. Pare, Tetrahedron Lett. 44 (2003) 949;
(c) J.S. Yadav, B.V.S. Reddy, M.K. Gupta, B. Eeswaraiah, Synthesis (2005) 57.

[6] J.-I. Matsuo, S. Kobayashi, CHEMTRACTS 13 (2000) 431.

[7] (a) N. Chatani, H.T. Kotsuma, S. Murai, J. Am. Chem. Soc. 124 (2002) 10294;
(b) H. Inoue, N. Chatani, S.J. Murai, Org. Chem. 67 (2002) 1414;
(c) M. Yamaguchi, T. Tsukagoshi, M. Arisawa, J. Am. Chem. Soc. 121 (1999) 4074;
(d) N. Asao, T. Asano, T. Ohishi, Y. Yamamoto, J. Am. Chem. Soc. 122 (2000) 4817.

[8] (a) J.S. Yadav, B.V.S. Reddy, B. Eeswaraiah, M.K. Gupta, S.K. Biswas, Tetrahedron Lett. 46 (2005) 1161;
(b) J.S. Yadav, B.V.S. Reddy, B. Padmavani, M.K. Gupta, Tetrahedron Lett. 45 (2004) 7577;
(c) G.S. Viswanathan, M. Wang, C.-J. Li, Angew. Chem. Int. Ed. 41 (2002) 2138;
(d) G.S. Viswanathan, C.-J. Li, Synlett (2002) 1553;
(e) G.S. Viswanathan, C.-J. Li, Tetrahedron Lett. 43 (2002) 1613.

[9] Typical procedure: A mixture of aldehyde (1 mmol), 1-butyn-3-one or 1-octyn-3-one (1.5 mmol), GaI_3 (0.35 mmol) in acetonitrile (10 mL) was stirred at room temperature for the appropriate time (see table). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2× 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure (*Z*)-β-iodovinyl ketones. Spectroscopic data for selected products: (**3a**) 3-hydroxy(phenyl)methyl-4-iodo-(*Z*)-3-buten-2-one [4b]: IR (KBr): υ_{max} 3470, 3063, 2924, 2855, 1668, 1573, 1491, 1450, 1415, 1362, 1298, 1207, 1033, 964, 854, 761, 700, 561 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H), 6.70 (s, 1H), 5.51 (d, *J* = 5.1 Hz, 1H), 2.40 (s, 1H), 2.30 (s, 3H). EIMS: *m/z* (%) 302 (M^+, 8), 175 (70), 131 (30), 105 (50), 77 (65), 43 (100); (**3f**) 3-hydroxy(4-methylphenyl)methyl-4-iodo-(*Z*)-3-buten-2-one [4b]: IR (KBr): υ_{max} 3427, 2923, 1695, 1353, 1219, 1074, 794, 772 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25–7.10 (m, 4H), 6.60 (s, 1H), 5.40 (s, 1H), 2.50 (s, 1H), 2.35 (s, 3H), 2.25 (s, 3H). EIMS: *m/z* (%) 316 (M^+, 8), 189 (80) 171 (10), 149 (10), 119 (50), 91 (48), 43 (100); (**3j**) 3-hydroxy-2-(thiophenyl)methyl-4-iodo-(*Z*)-3-buten-2-one: IR (KBr): υ_{max} 3416, 2928, 2856, 1697, 1459, 1363, 1216,

1162, 1084, 1038, 761, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 1H), 6.98–6.95 (m, 2H), 6.90 (d, $J = 1.5$ Hz, 1H), 5.70 (d, $J = 5.0$ Hz, 1H), 2.88 (d, $J = 5.0$ Hz, 1H), 2.40 (s, 3H). EIMS: *m/z* (%) 308 (M^+, 5), 181 (50), 121 (10), 97 (55), 85 (45), 43 (100); (**3k**) 2-hydroxy(phenyl)methyl-1-iodo-(*Z*)-1-octen-3-one: IR (KBr): υ_{max} 3455, 3022, 2925, 1946, 1699, 1571, 1473, 1423, 1355, 1284, 1177, 1072, 869, 767, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H), 6.58 (s, 1H), 5.41 (s, 1H), 3.02 (s, 1H), 2.50 (m, 2H), 1.48–1.14 (m, 6H), 0.81 (t, $J = 7.2$ Hz, 3H). EIMS: *m/z* (%) 358 (M^+, 10), 289 (8), 231 (30), 181 (10), 159 (18). 131 (150), 105 (40), 77 (75), 55 (65), 43 (100).