Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 122–126

Iodine-catalyzed allylation of 1,3-dicarbonyl compounds with allylic alcohols at room temperature

Weidong Rao, Adeline Hui Ling Tay,† Pei Jing Goh,† Jessica Mun Ling Choy,† Justin Kaijie Ke and Philip Wai Hong Chan*

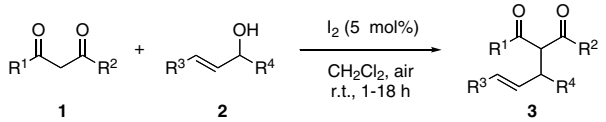
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Received 6 August 2007; revised 22 October 2007; accepted 1 November 2007
Available online 6 November 2007

Abstract—A highly efficient iodine-catalyzed allylation of 1,3-dicarbonyl compounds with a wide variety of allylic alcohols has been developed. The reaction is operationally straightforward and proceeds under very mild conditions at room temperature in good to excellent yields (up to 99%) and regioselectivity.

Carbon–carbon bond formation is a fundamental operation in organic synthesis. An important type of such reactions involves allylation of 1,3-dicarbonyl compounds.[1] Among the myriad of works dedicated to this reaction, those on developing new methods that make use of inexpensive and readily available electrophiles, mild reaction conditions, simple manipulation, atom-economy, and environmentally friendly catalysts have become very topical.[2–13] Indeed, a recent example is the establishment of new synthetic strategies that employ allylic alcohols as the allylating reagent in the presence of Pd, Co, and Cu salts and furnish H_2O as the only side product.[4] Recently, Lewis and Brønsted acids such as $BF_3{\cdot}OEt_2$,[5] $InCl_3$,[6] $FeCl_3$,[7] LnOTf (Ln = La, Yb, Sc, Hf),[8] $Bi(OTf)_3$,[9] *p*-toluenesulfonic acid,[10] and H-Montmorillonite[11] have also been reported to catalyze these reactions efficiently. Despite these advances, it remains a challenge to develop a metal catalyst-free and operationally simple version of this useful carbon–carbon bond forming reaction that can be accomplished under mild conditions. In this context, we envisioned molecular iodine would hold promise as a catalyst for allylation of 1,3-dicarbonyl compounds with allylic alcohols. An inexpensive, commercially available reagent that has a high tolerance to air and moisture, molecular iodine has recently been shown to be versatile in mediating a wide variety of organic transformations in excellent yields and with high selectivity.[12,13] To our knowledge, while the iodine-catalyzed allylation of indoles with allylic acetates has been reported by Chen and co-workers,[13] there are no examples of the iodine-catalyzed allylation of 1,3-dicarbonyl compounds with allylic alcohols. As part of an ongoing program in our group on organic transformations mediated by iodine-based reagents,[14] we report herein the allylation of a wide variety of 1,3-dicarbonyl compounds with allylic alcohols catalyzed by molecular iodine that proceeded in good to excellent yields (up to 99%) and regioselectivity, at room temperature, and without the need for inert and moisture-free reaction conditions (Scheme 1).

Initially, we found that treating a solution of pentane-2,4-dione **1a** (1 equiv) and (*E*)-1,3-di-*p*-tolylprop-2-en-1-ol **2a** (1.2 equiv) in CH_2Cl_2 contained in an open round bottom flask with 5 mol % of iodine as catalyst at room temperature for 2.5 h gave 3-((*E*)-1,3-di-*p*-tolyl-allyl)pentane-2,4-dione **3a** in 88% yield (Table 1, entry



1 **2** **3**

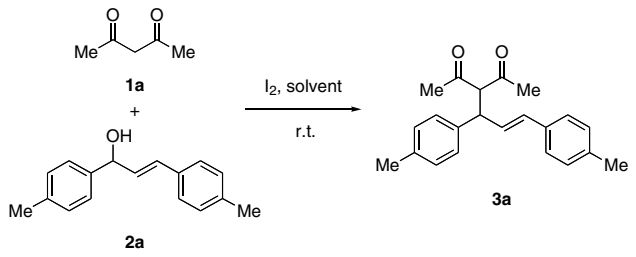
R^1-R^4 = alkyl, aryl

Scheme 1.

* Corresponding author. Tel.: +65 6316 8760; fax: +65 6791 1961; e-mail: waihong@ntu.edu.sg
† Equal contributions to this work.

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.005

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst loading (mol %)	Solvent	Yield[b] (%)
1	5	CH_2Cl_2	88
2	1	CH_2Cl_2	67
3	0.5	CH_2Cl_2	63
4	—[c]	CH_2Cl_2	—[d]
5	5	MeCN	70
6	5	PhMe	20
7	5	C_6H_6	45
8	5	THF	37
9[e]	5	H_2O	52

[a] All reactions were performed at room temperature for 2.5 h with an I_2:**1a**:**2a** ratio = 1:20:24 in solvent.
[b] Isolated yield.
[c] Reaction conducted in the absence of iodine catalyst.
[d] No reaction after 5 h based on TLC analysis.
[e] Reaction carried out with 1 equiv of Bu_4NBr for 15 h.

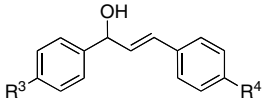
1).[15] The retention of trans-stereochemistry in the allylated product was confirmed by ^1H NMR analysis and X-ray crystal structure determination of a closely related product (see later). Under similar conditions, slightly lower product yields of 63–70% were obtained on decreasing the catalyst loading from 5 to 1, and 0.5 mol %, or with MeCN instead of CH_2Cl_2 as the solvent (entries 2, 3 and 5). In contrast, the analogous reactions conducted in other solvents were less effective and lower product yields of 20–52% were obtained for reactions in C_6H_6, PhMe, THF, or H_2O as the solvent (entries 6–9). As anticipated, no reaction was observed in the absence of the iodine catalyst and both starting materials were recovered in quantitative yields (entry 4).

To define the scope of the iodine-catalyzed reactions, we applied this process to a series of substituted 1,3-dicarbonyl compounds **1a**–**e** and allylic alcohols **2a**–**j**.[16] As shown in Table 2, allylation of a variety of substituted 1,3-dicarbonyl compounds with allylic alcohols bearing electron-withdrawing and electron-donating groups proceeded in good to excellent yields comparable to those obtained in the analogous metal-catalyzed reactions.[4–11] Notably, this included the allylation of less acidic β-ketoesters **1c** and **1d** with **2a**, which gave the adducts **3f** and **3g** in good yields (entries 5 and 6). The present procedure was also shown to work well for the allylation of cyclic 1,3-diketone **1e** with **2a**, giving **3h** in good yield as its enol ether (entry 7). Similarly, the 1,5-diene alcohols **2e** and **2f** were found to be good allylating reagents, affording excellent product yields (entries 8–10). In instances where it was envisaged that reactions with

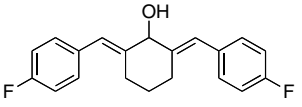
Table 2. Iodine-catalyzed allylation of 1,3-dicarbonyl compounds **1a**–**e** with allylic alcohols **2a**–**j**[a]

1b, $R^1 = R^2 = Ph$
1c, $R^1 = Ph$, $R^2 = OEt$
1d, $R^1 = Me$, $R^2 = OEt$

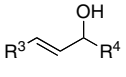
1e



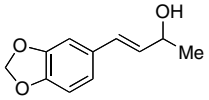
2b, $R^3 = R^4 = H$
2c, $R^3 = R^4 = Br$
2d, $R^3 = Cl$, $R^4 = Me$



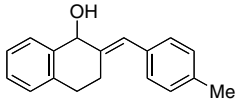
2e



2f, $R^3 = Ph$, $R^4 = CH{=}CHPh$
2g, $R^3 = Ph$, $R^4 = CH_2CH_2Ph$
2h, $R^3 = Ph$, $R^4 = Me$



2i

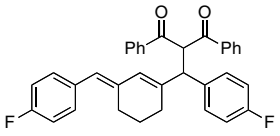
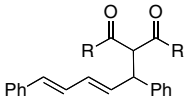
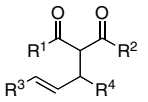
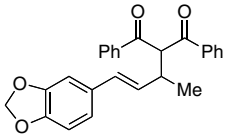
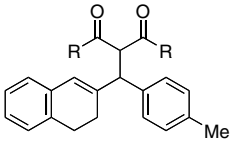


2j

Entry	Substrates	Time (h)	Product	Yield (%)[b]
1	**1a** + **2b**	2.5	**3b**, $R^1 = R^2 = Me$, $R^3 = R^4 = H$	99
2	**1a** + **2c**	2.5	**3c**, $R^1 = R^2 = Me$, $R^3 = R^4 = Br$	68
3	**1a** + **2d**	2	**3d′**, $R^1 = R^2 = R^4 = Me$, $R^3 = Cl$ **3d″**, $R^1 = R^2 = R^3 = Me$, $R^4 = Cl$	91[c]
4	**1b** + **2a**	1.5	**3e**, $R^1 = R^2 = Ph$, $R^3 = R^4 = Me$	90
5	**1c** + **2a**	18	**3f**, $R^1 = Ph$, $R^2 = OEt$, $R^3 = R^4 = Me$	76[d]
6	**1d** + **2a**	15	**3g**, $R^1 = R^3 = R^4 = Me$, $R^2 = OEt$	65[d]
7	**1e** + **2a**	2	**3h**	80

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrates	Time (h)	Product		Yield (%)[b]
8	**1b** + **2e**	3.5		**3i**	85
9	**1a** + **2f**	2.5		**3j**, R = Me	99
10	**1b** + **2f**	1.5		**3k**, R = Ph	80
11	**1b** + **2g**	15		**3l**, $R^1 = R^2 = R^3 = Ph$, $R^4 = CH_2Bn$	73
12	**1a** + **2h**	15		**3m′**, $R^1 = R^2 = R^3 = Me$, $R^4 = Ph$ **3m″**, $R^1 = R^2 = R^4 = Me$, $R^3 = Ph$	89[e]
13	**1b** + **2i**	2		**3n**	56
14	**1a** + **2j**	17		**3o**, R = Me	51
15	**1b** + **2j**	2		**3p**, R = Ph	54

[a] All reactions were performed at room temperature with I_2:**1**:**2** ratio = 1:20:24 in a solution of CH_2Cl_2.
[b] Isolated yield.
[c] Isolated as an inseparable mixture of regioisomers in a ratio = 3:1.
[d] Isolated as an inseparable mixture of diastereomers in a ratio = 1:1.
[e] Isolated as an inseparable mixture of regioisomers in a ratio = 7:1.

allylic alcohols containing two different substituents such as an aryl and alkyl group as in **2f**–**j** would lead to a mixture of regioisomeric products, the exclusive formation of only one product indicates that the present procedure is regioselective (entries 11 and 13–15). This was further confirmed by X-ray structure analysis of **3n**, as shown in Figure 1.[17] The allylations of **1a** with either **2d** or **2h** were the only examples where the products **3d** and **3m** were furnished as a mixture of inseparable regioisomers in ratios of 3:1 and 7:1, respectively (entries 3 and 12). Moreover, in all the above reactions, a side product that we initially presumed to be due to dimerization of **2** was found to form competitively, but disappears on consumption of the starting materials (TLC analysis); this suggested that the dimer itself also readily underwent reaction in the presence of **1**. Indeed, this was confirmed by isolating dimer **4a**[18] as the sole product as a mixture of diastereomers in 97% yield from the reaction of **2a** with 5 mol % of iodine under the

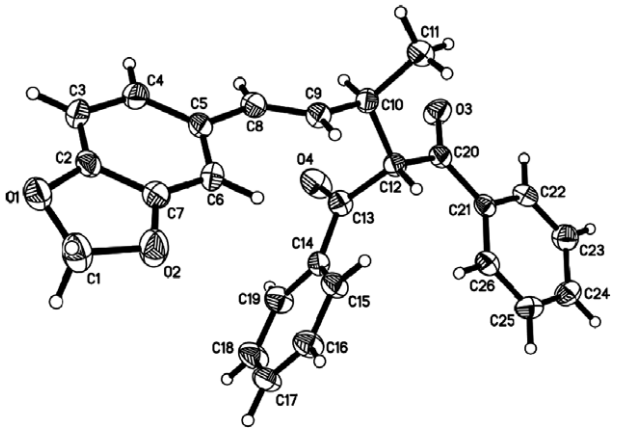
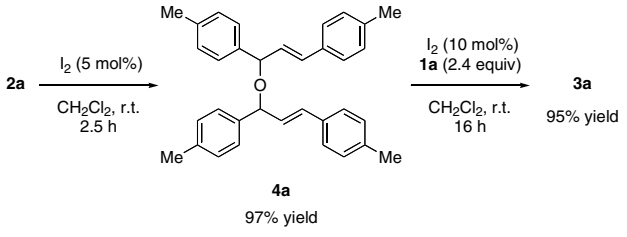


Figure 1. ORTEP drawing of **3n** with thermal ellipsoids at 50% probability levels.[17]



Scheme 2.

conditions described in Scheme 2. Dimer **4a** could be converted to **3a** in 95% yield on treatment with 2.4 equiv of **1a** and 10 mol % of iodine catalyst in CH_2Cl_2 for 16 h at room temperature.

Although the above experimental results do not provide a clear perspective on the mechanism of the present procedure, we tentatively propose that the reaction proceeds via formation of an allylic carbocation species from reaction of the allylic alcohol **2** with HI generated in situ. The regioselectivities obtained in these reactions could be due to subsequent attack at the sterically less hindered carbon of this presumed allylic carbocation intermediate by **1** or another molecule of **2** to produce the reactive dimer **4**, which, as mentioned earlier, reacts further in the presence of **1** to give the allylated product **3**. The role of iodine in facilitating the in situ generation of HI is supported by the fact that **3b** was obtained in a comparable yield of 93% for the analogous reaction of **1a** with **2b** under the same conditions to those described in Table 2, entry 1 but with NaI (5 mol %) and trifluoroacetic acid (5 mol %) in place of iodine as catalyst.

In summary, we have demonstrated a practical and operationally simplistic method for the allylation of 1,3-dicarbonyl compounds under atmospheric conditions at room temperature that proceeded in good to excellent yields. The present protocol is applicable to a variety of 1,3-dicarbonyl compounds and allylic alcohols containing electron-withdrawing and electron-donating, and sterically demanding substrate combinations. Efforts are currently underway to examine the scope and mechanism of this reaction and will be reported in due course as part of a full paper.

Acknowledgement

This work was supported by a College of Science Start-Up Grant from Nanyang Technological University.

References and notes

1. (a) Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1999; (b)*Palladium Reagents and Catalysts*; Tsuji, J., Ed.; Wiley: Chichester, 1995; (c) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 3.3; (d) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140; (e) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.
2. (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695; (b) Trost, B. M. *Science* **1991**, *254*, 1471.
3. (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *91*, 395.
4. (a) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595; (b) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085; (c) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241; (d) Kimura, M.; Mukai, R.; Tanigawa, N.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2003**, *59*, 7767; (e) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968; (f) Mukhopadhyay, M.; Iqbal, J. *Tetrahedron Lett.* **1995**, *36*, 6761; (g) Baruah, J. B.; Samuelson, A. G. *J. Organomet. Chem.* **1989**, *361*, C57.
5. Bisaro, F.; Pretat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823.
6. Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793.
7. (a) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065; (b) Salehi, P.; lranpoor, N.; Behbahani, F. K. *Tetrahedron* **1998**, *54*, 943.
8. (a) Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161; (b) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron Lett.* **2007**, *48*, 3969.
9. Reping, M.; Nahtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825.
10. Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841.
11. Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605.
12. For a recent review, see (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159; For selected examples, see: (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Krishna, A. D. *Tetrahedron Lett.* **2007**, *48*, 5243; (c) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283; (d) Lin, C.; Fang, H.; Tu, Z.; Liu, J.; Yao, C. *J. Org. Chem.* **2006**, *71*, 6588; (e) Gao, S.; Tzeng, T.; Sastry, M. N. V.; Chu, C.; Liu, J.; Lin, C.; Yao, C. *Tetrahedron Lett.* **2006**, *47*, 1889; (f) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *Synlett* **2003**, 2377; (g) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Reddy, S. G. *Synlett* **2003**, 247; (h) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Rao, K. V. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 1401; (i) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653; (j) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Sabitha, G.; Reddy, S. G. *Synthesis* **2000**, 1532.
13. Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 3963.
14. Rao, W.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 3789.
15. *Typical experimental procedure*: To a CH_2Cl_2 (2 mL) solution of **1** (0.3 mmol, 1 equiv) and **2** (0.36 mmol, 1.2 equiv) contained in a round bottom flask open to air at room temperature was added molecular iodine (15 μmol, 5 mol %). The reaction was stirred until completion (TLC analysis). The reaction mixture was quenched with aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated, and purified by flash silica gel column chromatography (*n*-hexane/EtOAc as eluent) to give **3**.
16. *Representative data for* **3c**: white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.11–7.14 (m, 4H), 6.33 (d, 1H, $J = 15.8$ Hz), 6.12 (ddd, 1H, $J = 15.7$, 6.2, 1.3 Hz), 4.13–4.47 (m, 2H), 2.23 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.3, 202.1, 138.9, 135.2, 132.2, 131.0, 129.7, 129.4, 127.9, 121.7, 121.3, 74.3, 48.3, 30.0, 29.7; IR (film, cm^{-1}) 1728, 1697, 1487, 1356, 1072; Anal. Calcd for $C_{20}H_{18}Br_2O_2$: C, 53.36; H, 4.03. Found: C, 53.27; H, 4.29. *Compound* **3k**: white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, 2H, $J = 7.4$ Hz), 7.80 (d, 2H, $J = 7.5$ Hz), 7.08–7.56 (m, 16H), 6.54 (dd, 1H, $J = 15.6$, 10.3 Hz), 6.34 (d, 1H, $J = 15.6$ Hz), 6.14 (dd, 1H, $J = 15.0$, 10.4 Hz), 5.90–5.98 (m, 2H), 4.75 (t, 1H, $J = 9.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.3, 193.8, 140.8, 137.2, 136.9, 133.9, 133.5, 133.3, 132.6, 132.2, 128.9, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 127.4, 126.9, 126.3, 62.8, 50.0; IR (film, cm^{-1}) 1695, 1663, 1447, 1261, 989, 691; Anal. Calcd for $C_{32}H_{26}O_2$: C, 86.85; H, 5.92. Found: C, 86.51; H, 6.52.

17. CCDC 655561 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
18. *Dimer* **4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07–7.32 (m, 16H), 6.53 (dd, 2H, $J = 15.9$, 6.7 Hz), 6.28 (m, 2H), 5.03 (dd, 2H, $J = 10.2$, 7.1 Hz), 2.35 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 137.5, 137.3, 134.0, 131.3, 131.1, 129.8, 129.5, 129.2, 127.1, 126.7, 79.0, 78.9, 21.3; IR (film, cm^{-1}) 3051, 1608, 1512, 1265, 968, 739; MS(EI): m/z 221 $[M–C_{17}H_{17}O]^{+}$.