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Facile synthesis of α-iodo carbonyl compounds and α-iodo dimethyl ketals using molecular iodine and trimethylorthoformate

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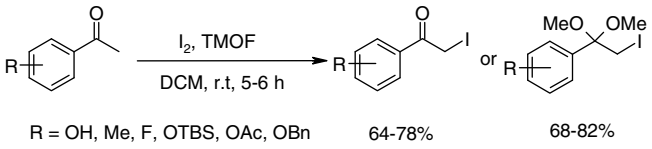
Abstract

A novel and direct method for the synthesis of α-iodo ketones and α-iodo dimethyl ketals from acetophenones using iodine and trimethylorthoformate under neutral conditions is described herein.

The synthesis of α-halogenated ketones particularly α-iodo ketones and their applications as reaction intermediates have attracted considerable attention in various organic transformations.[1] Several methods are available for the synthesis of α-iodo ketones which are either obtained directly by treating ketones with different combinations of reagents such as iodine–cerium(IV) ammonium nitrate—in alcohol or acetic acid,[2] iodine–mercury(II) chloride,[3] iodine–selenium dioxide,[4] NIS–*p*-toluenesulfonic acid,[5] [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB) with MgI_2,[6] Selectfluor F-TEDA-BF_4–I_2,[7] I_2–bis(*tetra-n*-butylammonium)peroxydisulfate,[8] I_2/urea–H_2O_2,[9] I_2–1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate),[10] polymer supported pyridinium dichloroiodate,[11] molecular iodine in DME at 90 °C[12] or indirectly by treating enol silyl ethers or enol acetates with iodinating agents such as iodine copper(II)nitrate or iodine–silver acetate.[13] However, all these reactions employ either harsh acidic conditions, toxic metal salts or elevated temperatures, and thus a simple procedure for α-iodination is welcome to overcome the disadvantages of existing procedures. Herein, we report a novel and direct method for the synthesis of α-iodo ketones or α-iodo dimethyl ketals using iodine[14] and trimethylorthoformate under mild conditions (Scheme 1).



Scheme 1.

In continuation of our studies towards the total synthesis of biologically active natural products,[15] we were interested in the total synthesis of colombiasin A. Towards the synthesis, we wanted to homologate compound **1** to compound **2** (Scheme 2). By applying the known protocol[15a] for this conversion in the presence of trimethyl orthoformate with iodine under the specified conditions, we obtained a mixture of α-iodinated dimethyl ketal **3** and α-iodinated ketone **4** rather than the expected homologated compound **2**.[16b] We believe this reaction to be substrate specific as the reaction worked well with substrate **5** under the reported conditions.[16a]

This result prompted us to further investigate this reaction. Thus, acetophenone was examined at room temperature using iodine and trimethylorthoformate. To our delight, a mixture of α-iodinated acetophenone and keto protected α-iodinated compound was the only products observed. These results led us to optimize this transformation for the preparation of α-iodo acetophenones and α-iodo ketals.

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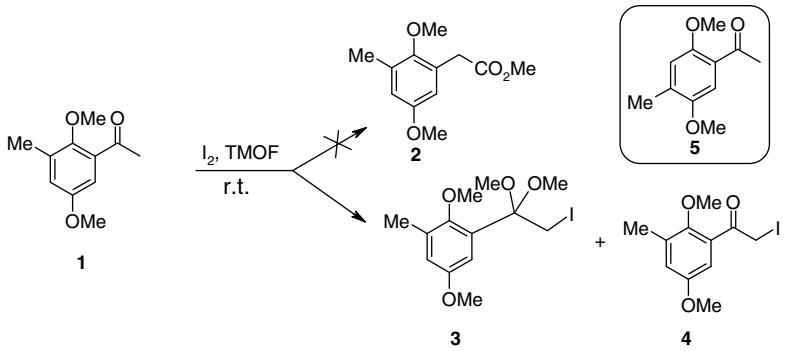
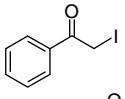
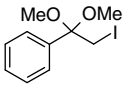
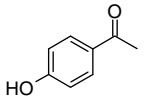
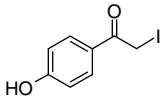
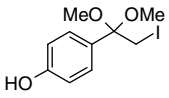
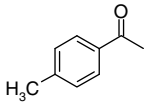
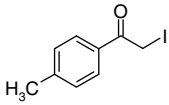
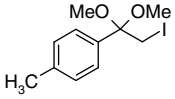
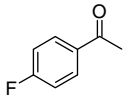
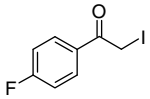
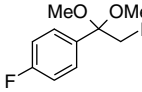
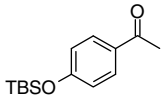
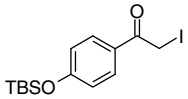
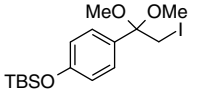
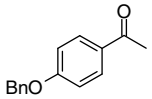
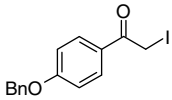
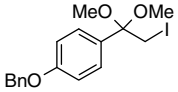
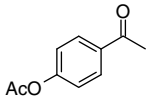
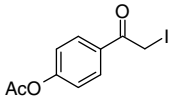
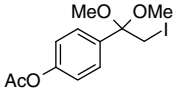
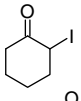
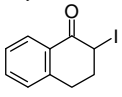
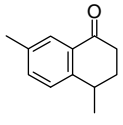
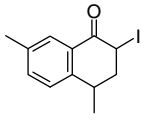


Scheme 2.

Accordingly, several substituted acetophenones were treated with iodine and trimethylorthoformate and the results are shown in Table 1. The advantage of this reaction is that the present protocol tolerated common protecting groups such as *tert*-butyldimethylsilyl, benzyl and acetate.

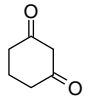
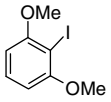
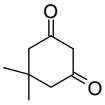
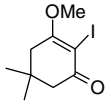
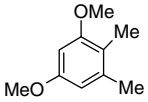
The product selectivity for simple acetophenones with respect to the protected or unprotected α-iodo compounds could be modified by a slight variation in the workup procedures. Upon completion of the reaction, if the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$

Table 1
Preparation of α-iodo acetophenones and α-iodo ketals

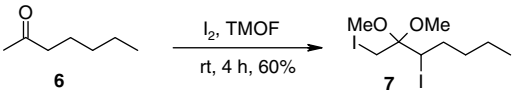
Sl. no.	Ketone **a**	α-Iodo ketone[a] **b**	Time (h)	Yield[b] (%)	α-Iodo ketal[a] **c**	Time (h)	Yield[b] (%)
1			5	72		5	73
2			5	76		5	78
3			5	64		5	68
4			4	76		4	79
5			5	74		5	74
6			5	78		5	82
7			5	74		5	77
8			6	73	—		
9			5	75	—		
10			5	73	—		

(*continued on next page*)

Table 1 (*continued*)

Sl. no.	Ketone **a**	α-Iodo ketone[a] **b**	Time (h)	Yield[b] (%)	α-Iodo ketal[a] **c**	Time (h)	Yield[b] (%)
11			5	70	—		
12			6	75		6	70

[a] The products were characterized by IR, ^{1}H NMR and mass spectroscopy.
[b] Isolated yields after column chromatography.



Scheme 3.

solution and extracted with dichloromethane, the α-iodinated dimethoxy ketal was the main product. However, when the reaction mixture was stirred with water before washing with aq saturated $Na_2S_2O_3$ solution, the α-iodinated ketone was the major product.[17] It is noteworthy to mention that ring directed iodination or α,α-diiodination was never observed during this process. When cyclohexanone and its derivatives were reacted, compounds **8a**, **9a** and **10a** gave only the corresponding α-iodo keto products **8b**, **9b** and **10b**, no α-iodo dimethyl ketals were observed. When 1,3-cyclohexadiones **11a** and substituted 1,3-cyclohexadiones **12a** were subjected to the present conditions, the corresponding iodo substituted compounds **11b**, **12b** and the aromatized product **12c**[18] were obtained. All the products were characterized and analyzed by studying their spectral properties.[19] However, when 2-heptanone **6** was subjected to the present protocol, α,α′-diiodo dimethoxy ketal **7** was obtained as the only product (Scheme 3).

Mechanistically, we believe that initially an enol ether is formed followed by the iodination to give the α-iodo dimethoxy ketal (Scheme 4), which on hydrolysis with water in the presence of HI affords the α-iodo ketone.

In conclusion, an efficient simple protocol for the conversion of acetophenones to α-iodoacetophenones and α-iododimethoxy ketals has been described. This strategy may find applications in the total synthesis of several bioactive natural products involving either the α-iodo keto product or the α-iodo dimethyl ketal substrate.

Acknowledgement

G.K. and M.S.R. thank the CSIR, New Delhi, for financial assistance.

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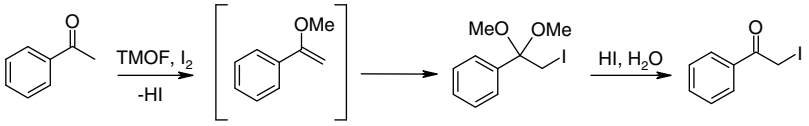
14. For our few earlier contributions with iodine see: (a) Yadav, J. S.; Satyanarayana, M.; Raghavendra, S.; Balanarsaiah, E. *Tetrahedron Lett.* **2005**, *46*, 8745–8748; (b) Yadav, J. S.; Balanarsaiah, E.; Raghavendra, S.; Satyanarayana, M. *Tetrahedron Lett.* **2006**, *47*, 4921–4924; (c) Yadav, J. S.; Reddy, B. V. S.; Narayana Kumar, G. G. K. S.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205–2208; (d) Srihari, P.; Sridhar, P.; Bhunia, D. C.; Reddy, J. S. S.; Mandal, S. S.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8120–8124.



Scheme 4.

15. For our recent publications on natural products see: (a) Yadav, J. S.; Basak, A. K.; Srihari, P. *Tetrahedron Lett.* **2007**, *48*, 2841–2843; (b) Yadav, J. S.; Chetia, L. *Org. Lett.* **2007**, *9*, 4587–4589; (c) Yadav, J. S.; Pratap, T. V.; Rajender, V. *J. Org. Chem.* **2007**, *72*, 5882–5885.
16. (a) Srikrishna, A.; Lakshmi, B. V. *Tetrahedron Lett.* **2005**, *46*, 7029–7031; Even substrate **5** gave iodinated products at room temperature, which on prolonged heating yielded the homologated product. However, compound **2** was obtained at a later stage following the procedure reported in (b) Maruyama, K.; Kozuka, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3586–3589.
17. We assume that the acid HI generated by the addition of water is responsible for the cleavage of dimethoxy ketal to ketone.
18. Similar aromatic compounds were prepared using TFAA and sulfuric acid from dimedones, see: Nelson, P. H.; Nelson, J. T. *Synthesis* **1992**, 1287–1291.
19. General experimental procedure: α-*Iodo dimethyl ketals*: A mixture of keto compound (1.0 mmol) and iodine (2.0 mmol) in trimethylorthoformate (5 mL) was stirred at room temperature for the appropriate amount of time. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane (10 mL) and the organic layer was washed with saturated aq $Na_2S_2O_3$ (2×10 mL) and brine (1×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (1:9) as eluent to afford the pure α-iodo dimethoxy ketal. α-*Iodo ketones*: A mixture of keto compound (1.0 mmol) and iodine (2.0 mmol) in trimethylorthoformate (5 mL) was stirred at room temperature for the appropriate amount of time. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (10 mL) and stirred for an additional 15 min. Then the reaction mixture was extracted with dichloromethane (10 mL), washed with saturated aq $Na_2S_2O_3$ (2×10 mL) and brine (1×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (1:9) as eluent to afford the pure α-iodo ketone. Spectroscopic analysis for **3**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.05 (d, $J = 1.3$ Hz, 1H), 6.70 (d, $J = 1.3$ Hz, 1H), 3.98 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.25 (s, 6H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.82, 149.92, 132.67, 117.41, 113.7, 101.47, 60.74, 55.68, 49.48, 16.97, 7.81. ESIMS: *m*/*z* 389 (M^++Na). HRMS calcd for $C_{13}H_{19}O_4NaI$, 389.0225; found 389.0220. Compound **4**: ^{1}+H NMR ($CDCl_3$, 300 MHz): δ 6.92 (d, $J = 1.3$ Hz, 1H), 6.85 (d, $J = 1.3$ Hz, 1H), 4.49 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.82, 155.73, 151.65, 133.51, 130.28, 122.47, 111.93, 62.52, 55.85, 16.44, 7.86. ESIMS: *m*/*z* 342.9 (M^++Na). HRMS calcd for $C_{11}H_{13}O_3NaI$, 342.9807; found 342.9820.