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Metal catalyst-free direct α-iodination of ketones with molecular iodine

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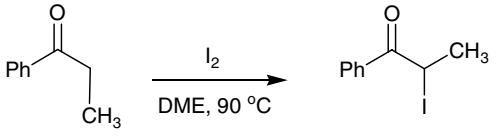
Abstract—Ketones are directly converted to the corresponding α-iodoketones in good yields with molecular iodine under metal catalyst-free conditions. A significant difference in the reactivities was observed for aliphatic and aromatic ketones; whereas aliphatic ketones reacted smoothly at room temperature giving a mixture of 1-iodo, 3-iodo and 1,3-diiodoketones with predominant formation of the 3-iodo product, the α-iodination of aromatic ketones proceeded conveniently under heating to give good yields of α-iodo products.

α-Iodoketones are important building blocks in organic synthesis.[1] Various electrophilic iodonium sources are usually employed for α-iodination of carbonyl compounds.[2,3] The use of molecular iodine as an iodinating agent has been demonstrated only in a few methods for the synthesis of α-iodoketones. These methods, however, employ selenium dioxide,[4a] mercury(II) chloride[4b] or ceric(IV) ammonium nitrate,[4c] etc., in stoichiometric or sub-stoichiometric amounts and entail the use of acetic acid in some cases as a reaction medium. Clearly, harsh acidic conditions and the use of toxic metal salts are serious drawbacks associated with these methods.[4]

In recent years, molecular iodine catalyzed or mediated reactions have grown in importance in organic synthesis.[5] The mild Lewis acidic nature of iodine has been exploited in several of these reactions. We envisaged that molecular iodine could play a dual role as a catalyst that initially promotes enolization and as a reagent that subsequently reacts with the enol to afford α-iodoketones. One advantage of such a method would also be that the equimolar amount of HI that is generated in situ during the reaction may also participate in the enolization of the ketone such that the overall reaction is further expedited. Thus, such a protocol for α-iodination was anticipated, in addition to experimentally being simple, to obviate the use of external metal catalysts, preformed enolates, harsh acidic/basic conditions, etc. Herein, we report the first direct and metal catalyst-free α-iodination of ketones with molecular iodine in a neutral medium.

In our initial experiments, we examined the reactivity of propiophenone (1 equiv) at room temperature as a representative case with molecular iodine (2 equiv) in DME as solvent. The GC analysis of the crude reaction

Table 1. Reaction of propiophenone with molecular iodine at 90 °C



Entry	Solvent	I_2 (equiv)	Time (h)	GC conv. (%)
1.1	DME	2	3	59
1.2	THF	2	3	54
1.3	CH_3CN	2	3	13
1.4	DCE	2	3	<1
1.5	Toluene	2	3	<1
1.6	NMP	2	3	5
1.7	DME	2	6	76
1.8	DME	2	12	76
1.9	DME	2	16	86
1.10	DME	3	3	88
1.11	DME	3	6	96
1.12	DME	4	3	96

Keywords: α-Iodination; Molecular iodine; Ketones; Iodoketones; Metal catalyst-free conditions.
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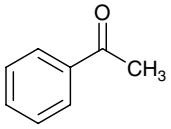
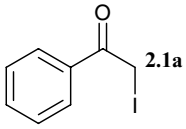
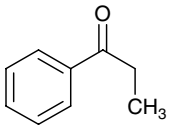
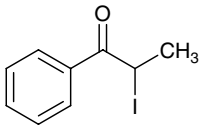
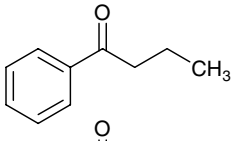
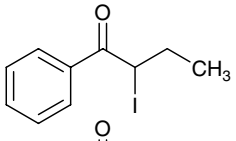
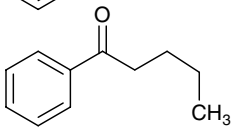
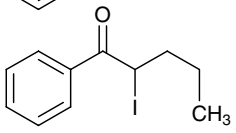
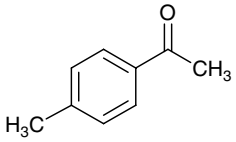
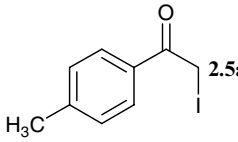
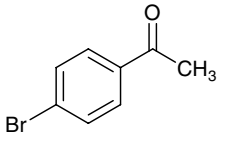
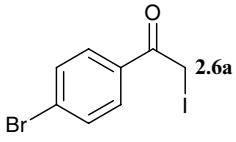
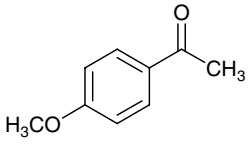
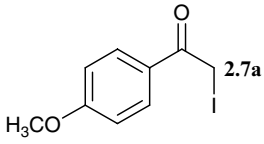
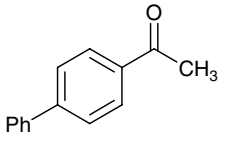
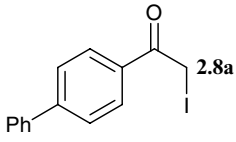
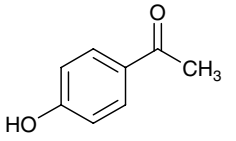
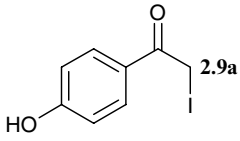
mixture after 12 h did not reveal the formation of α-iodopropiophenone.

Remarkably, heating the reaction mixture at 90 °C for 3 h led to 59% conversion of the ketone. Encouraged by this result, we screened the reaction of propiophenone under various conditions and the results are summarized in Table 1. As can be seen, the reaction was found to be considerably faster in solvents such as DME and THF (entries 1.1 and 1.2) as compared to those in CH_3CN, DCE, toluene and NMP (entries 1.3–1.6) under identical experimental conditions. However, some products that appeared to be derived from the solvent were observed when the reaction was conducted in THF.

Hence, we focused on DME as an appropriate solvent, and the α-iodination of propiophenone was further investigated varying the molar equivalents of iodine and reaction time (entries 1.7–1.12). Thus, it emerged that high conversion of propiophenone to the corresponding α-iodoketone occurred with 2 M equiv of I_2, albeit in a long reaction time (16 h). However, excellent conversion of the ketone occurred in 3 h when 4 M equiv of I_2 were employed. With the objective of achieving high conversions in short reaction times, we further

Table 2. α-Iodination of aromatic ketones at 90 °C[9]

Entry	Ketone	Iodoketone	Yield[a,b] (%)
2.1		 **2.1a**	74
2.2		 **2.2a**	90
2.3		 **2.3a**	86
2.4		 **2.4a**	87
2.5		 **2.5a**	81
2.6		 **2.6a**	77
2.7		 **2.7a**	62
2.8		 **2.8a**	74
2.9		 **2.9a**	64

[a] Isolated yields.
[b] All products were identified by IR, ^1H NMR and ^{13}C NMR analysis.

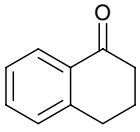
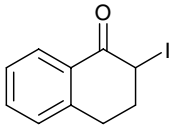
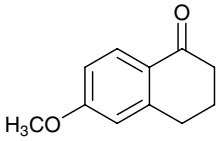
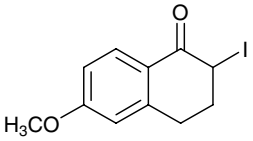
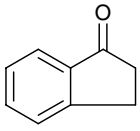
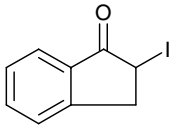
explored the direct α-iodination of various ketones with 4 equiv of molecular I_2.

The results of the α-iodination of various alkyl aryl ketones are given in Table 2. The α-iodination of a variety of ketones with different aryl and alkyl groups proceeded efficiently to afford the corresponding α-iodoketones in 62–90% isolated yields. The reactivity profile of the substituted acetophenones is noteworthy. For example, acetophenone with various substituents on the phenyl ring yielded the corresponding α-iodoketones with only a marginal variation in isolated yields, which suggests that any change in electronic factor of the phenyl ring has only a minor effect on the reaction outcome (entries 2.5–2.9). Cyclic ketones, likewise underwent smooth α-iodination (Table 3). For example, 1-tetralone (entry 3.1), 6-methoxy-1-tetralone (entry 3.2) and 1-indanone (entry 3.3) all gave the corresponding α-iodo products in 94% (**3.1a**), 81% (**3.2a**) and 77% (**3.3a**) yields, respectively. The simplicity of the present method is underscored by the fact that 2-iodotetralones and 2-iodoindanone are prepared directly and readily, while their literature-methods were not straightforward.[2a,6]

At this stage, it was of interest to investigate the reactivity of alkyl ketones with molecular iodine under metal catalyst-free conditions. Remarkably, α-iodination of alkyl ketones proceeded smoothly at room temperature leading to a mixture of α-iodoketones, with the 3-iodo isomer as the major product. For example, the reaction of 2-nonanone with molecular iodine (4 equiv) at room temperature for 12 h produced a 66% yield of 3-iodo-2-nonanone and 1-iodo-2-nonanone (89:11 by ^{1}H NMR)[4a] as a mixture along with a very minor <1% of the 1,3-diiodo product (entry 4.1). Further studies carried out with other alkyl ketones under various conditions are summarized in Table 4.

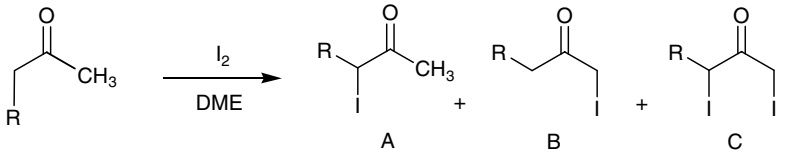
Evidently, an increase in time and molar equivalents of iodine affected the overall yields of 3-iodo, 2-iodo and

Table 3. Reaction of cyclic ketones at 90 °C[9]

Entry	Ketone	Iodoketone		Yield[a,b] (%)
3.1			**3.1a**	94
3.2			**3.2a**	81
3.3			**3.3a**	77

[a] Isolated yields.
[b] All products were identified by IR, ^{1}H NMR and ^{13}C NMR analysis.

Table 4. α-Iodination of alkyl ketones[9]



Entry	Ketone	I_2 (equiv)	Temp (°C)	Time (h)	Conv. (%) (GC)	(A + B + C) yield[a,b] (%)	A:B:C (GC)	A:B:C (^{1}H NMR)
4.1	2-Nonanone	4	rt	12	91	66	93:5:2	89:11:0
4.2	2-Nonanone	2	rt	24	74	59	90:7:3	84:12:4
4.3	2-Nonanone	3	rt	24	—	82	88:3:9	85:3:12
4.4	2-Octanone	2	rt	24	66	30	97:1:2	95:2:3
4.5	2-Octanone	3	rt	24	98	69	84:6:10	81:7:12
4.6	2-Octanone	4	rt	12	86	48	—	82:4:14
4.7	Benzyl acetone	2	rt	24	52	37	—	90:3:7
4.8	Benzyl acetone	3	rt	24	70	49	82:13:5	84:2:14
4.9	Benzyl acetone	4	90	12	100	81 (A + B = 35; C = 46)	89:11 (A:B)	88:12 (A:B)

[a] Isolated yields.
[b] All products were identified by IR, ^{1}H NMR and ^{13}C NMR analysis.

1,3-diiodo product formation in all the cases studied. The product ratio of 3-iodo, 1-iodo and 1,3-diiodo calculated from ^{1}H NMR was almost in agreement with that observed in GC analysis. In the case of benzyl acetone (entries 4.7–4.9), α-iodination was found to be more efficient under heating conditions giving an 81% combined yield (entry 4.9) and this also resulted in an increase in the formation of 1,3-diiodo product. However, the reactivity pattern observed for α-iodination of unsymmetrical ketones was found to be similar to that reported for the corresponding α-bromination reactions.[7] The selective iodination of alkyl ketones observed here appears to be primarily guided by the thermodynamic stability of the enol, which is evident from the formation of 3-iodoketone as the major product, while the 1-iodo isomer is the minor product. The longer reaction times and excess iodine did help the formation of the 1,3-diiodo product, but in low yields. The poor yield of isolated products in some cases was due to the sensitive nature of the products, despite the good conversion (GC analysis) under the present conditions.

As mentioned at the outset, we believe that the direct α-iodination is triggered by molecular iodine, which functions as a Lewis acid in promoting the initial enolization of the ketone. The formation of HI during the course of the reaction leads presumably to autocatalysis.[8] Indeed, the reaction of propiophenone in the presence of 1 equiv of pyridine and I_2 (4 equiv) in DME at 90 °C did not produce α-iodopropiophenone. This also proves the autocatalytic role of in situ generated HI in accelerating the reaction. Insofar as the solvent is concerned, the role of DME in polarizing molecular iodine by way of chelation cannot be ruled out.

In summary, we have developed a new metal catalyst-free direct α-iodination procedure for ketones using molecular iodine. The advantages of the present method include

- in situ generation of the enol from the ketone;
- iodination by molecular iodine;
- neutral reaction medium;
- avoidance of metal catalysts;
- short reaction times.

We are currently exploring further transformations mediated by iodine.

Acknowledgements

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References and notes

1. Selected examples: (a) Kim, S.; Lim, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5378; (b) Kondo, J.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 825; (c) Dobbeleer, C. D.; Ates, A.; Vanherk, J.-C.; Marko, I. E. *Tetrahedron Lett.* **2005**, *46*, 3889; (d) Chai, W.; Takeda, A.; Hara, M.; Ji, S.-J.; Horiuchi, C. A. *Tetrahedron* **2005**, *61*, 2453; (e) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4555; (f) Kim, S.; Lim, C.-J.; Song, C.; Chung, W.-J. *J. Am. Chem. Soc.* **2002**, *124*, 14306; (g) Shimizu, M.; Kobayashi, F.; Hayakawa, R. *Tetrahedron* **2001**, *57*, 9591; (h) Ranu, B. C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* **1998**, *39*, 9557.
2. (a) Sket, B.; Zupet, P.; Zupan, M.; Dolenc, D. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3406; (b) Sha, C. K.; Young, J. J.; Jean, T. S. *J. Org. Chem.* **1987**, *52*, 3919; (c) Vankar, Y. D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233; (d) Rubottom, G. M.; Mott, R. C. *J. Org. Chem.* **1979**, *44*, 1731; (e) Cambie, R. C.; Hayward, R. C.; Jurlina, J. L.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 126; (f) Djerassi, C.; Lenk, C. T. *J. Am. Chem. Soc.* **1953**, *75*, 3493.
3. Selected examples: (a) Barluenga, J.; Marco-Arias, M.; Gonzalez-Bobes, F.; Ballesteros, A.; Gonzalez, J. M. *Chem. Commun.* **2004**, 2616; (b) Lee, J. C.; Park, J. Y.; Yoon, S. Y.; Bae, Y. H.; Lee, S. J. *Tetrahedron Lett.* **2004**, *45*, 191; (c) Lee, J. C.; Bae, Y. H. *Synlett* **2003**, 507; (d) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2002**, 488; (e) Jereb, M.; Stavber, S.; Zupan, M. *Synthesis* **2003**, 853; (f) Olah, G. A.; Wang, Q.; Sandford, G.; Surya Prakash, G. K. *J. Org. Chem.* **1993**, *58*, 3194; (g) Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1731.
4. (a) Bekaert, A.; Barberan, O.; Gervais, M.; Brion, J.-D. *Tetrahedron Lett.* **2000**, *41*, 2903; (b) Barluenga, J.; Martinez-Gallo, J. M.; Najera, C.; Yus, M. *Synthesis* **1986**, 678; (c) Horiuchi, C. A.; Kiji, S. *Chem. Lett.* **1988**, 31.
5. Selected examples: (a) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett.* **2006**, *8*, 2491; (b) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Synlett* **2002**, 319; (c) Karimi, B.; Golshani, B. *Synthesis* **2002**, 784; (d) Banik, B. K.; Chapa, M.; Marquez, J.; Cardona, M. *Tetrahedron Lett.* **2005**, *46*, 2341; (e) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243; (f) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C. F. *Tetrahedron Lett.* **2005**, *46*, 5771; (g) Lee, B. S.; Mahajan, S.; Janda, K. D. *Synlett* **2005**, 1325; (h) Zacuto, M. J.; Cai, D. *Tetrahedron Lett.* **2005**, *46*, 447; (i) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 7187; (j) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485; (k) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett.* **2005**, *46*, 2479.
6. (a) Darko, D. *Synlett* **2000**, 544; (b) Cort, A. D. *J. Org. Chem.* **1991**, *56*, 6708; (c) Motohashi, S.; Satomi, M.; Fujimoto, Y.; Tatsuno, T. *Synthesis* **1982**, 1021.
7. Choi, H. Y.; Chi, D. Y. *Org. Lett.* **2003**, *5*, 411.
8. Pinkus, A. G.; Gopalan, R. *J. Am. Chem. Soc.* **1984**, *106*, 2630.
9. *General procedure for the synthesis of α-iodoketones* (**2.1a**–**2.9a** and **3.1a**–**3.3a**): Ketone (1 mmol) along with iodine (4 mmol) in DME (5 mL) was heated in a Schlenk tube at an oil bath temperature of 90 °C for 3 h. Then the contents were cooled and extracted with ethyl acetate (2 × 25 mL). The combined extract was washed with sodium thiosulfate to remove unreacted iodine. Subsequently, the extract was washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography and the corresponding α-iodo product was isolated. The products were identified by IR, ^{1}H NMR and ^{13}C NMR analysis. In the case of alkyl ketones (Table 3), the same general procedure was followed except that the reaction was stirred at room temperature for the specified time given in Table 3.