Solid-phase organic synthesis of α-iodo ketones using recyclable resin-bound selenium bromide

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A novel facile method for the traceless solid-phase synthesis of α-iodo ketones using a recyclable resin-bound selenium bromide reagent is reported. Various ketones and β-dicarbonyl compounds can be converted to the corresponding α-iodo-substituted compounds in excellent yields and purities with simple workup procedure and mild conditions.

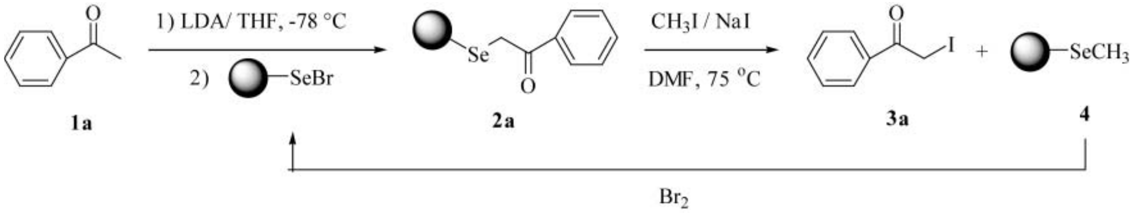
Keywords: α-iodo ketone, solid-phase synthesis, resin-bound selenium bromide

α-Iodo ketones are important building blocks in organic synthesis and their high reactivity makes them available to react with a large number of nucleophiles to provide a variety of useful compounds.[1] Moreover, some α-iodo ketones possess biological activity and their properties have attracted considerable attention in the medicinal field.[2] Generally, α-iodo ketones are prepared from olefins,[3] ketone derivatives [4] (enol silyl ethers and acetates), or by halogen interchange of bromo compounds with sodium iodide.[5] Alternatively, the iodonium-donating systems such as $KI/KIO_3/H_2SO_4$[6] and $NaI/H_2O_2/H_2SO_4$[7] were used for α-iodination of ketones. Additionally, molecular iodide[8] or with oxidising agents such as $I_2/HgCl_2$,[9] $I_2/SeO_2/AcOH$,[10] I_2/N–F reagent,[11] I_2/oxone,[12] I_2/CuO,[13] I_2/MnO_2,[14] $I_2/O_2/NaNO_2$[15] and I_2/*m*-iodobenzoic acid[16] were used to access these compounds. Ionic liquids,[17] microwave irradiation[18] and hypervalent iodine reagents[19] have also been utilised for similar transformations. Alhough several reported methods provide good yields, many of these approaches suffer from limitations such as cumbersome workup procedures, acidic reaction conditions (formation of the acid *in situ*), the use of expensive, or inconvenient and environmentally harmful reagents, and the generation of hazardous waste. Therefore, the development of an efficient, economic and environmentally friendly method is still desirable. Recently, the polymeric selenium reagents[20] have been now developed for solid-phase organic synthesis (SPOS) with a combined advantage of decreased volatility and simplification of the product work-up. As part of an ongoing research programme focused on the use of resin-bound selenium reagents in SPOS,[21] we report here the simple preparation of α-iodo ketones based on resin-bound selenium bromide. To our knowledge, this is a previously unreported method for the α-iodination of ketones. The method is illustrated using acetophenone in the Scheme 1.

In our initial experiments, acetophenone **(1a)** was selected as a representative case to investigate this method. As shown in Scheme 1, treatment of a THF-swollen suspension of cross-linked (1%) polystyrene-bound selenium bromide[20] with the lithium enolate of **1a** for a short time (30min) afforded a pale yellow resin-bound 1-phenyl-2-selenoethanone **(2a)** in near-quantitative yield, monitored by FT-IR showing a strong carbonyl absorption at 1712 cm^{-1}. Then, following the published method for traceless cleavage of a selenium resin,[21] and under further optimised conditions, the target compound 1-phenyl-2-iodoethanone **(3a)** was obtained in 98% yield and with excellent purity (98%) by treatment of **3a** with CH_3I–NaI in DMF at 75 °C overnight. To assess the generality of the method and to evaluate the electronic influence of the aromatic ring substituents, the transformations of various other ketones **(1b–e)** into the corresponding α-iodo ketones **(3b–e)** were further explored (Table 1). As seen from Table 1, propiophenone **(1b)** and acetophenone derivatives **(1c–e)** bearing electron-donating or electron-withdrawing groups on the phenyl ring were all readily transformed into the corresponding 1-arylsubstituted 2-iodoethanones **(3b–e)** in excellent yields, which suggests that any change in an electronic factor of the phenyl ring has little effect on the reaction outcome (entries 3–5). On the other hand, cyclic ketones, likewise underwent smooth α-iodination. For example, cyclohexanone (entry 6), and cyclopentanone (entry 7) all gave the corresponding α-iodo products in 92% (**3f**) and 93% (**3g**) yields with good purities (>95%), respectively. Furthermore, examination of 1,3-diketones **(1h–i)** showed them also to give the corresponding α-iodoketones with good purities but in slightly lower yields (entries 8 and 9). However, in the case of unsymmetrical aliphatic ketones, for example, 2-butanone, two regioisomers of 1-iodo-2-butanone and 3-iodo-2-butanone (55:45 by ^{1}H NMR) as a mixture were obtained in 74% yield.

It should be noted that, after completing the cleavage reaction of the selenium resin, the recovered methyl selenide resin **(4)** is easily converted to selenium bromide resin, which can be reused for further production of α-iodo ketones. For example, after the third regeneration and use, the purity of 1-phenyl-2-iodoethanone (**3a**) (entry 1) remained almost the same as when the first prepared selenium bromide resin was used but with a slight decrease in yield.

In summary, we have developed a new and efficient protocol for the traceless solid-phase synthesis of α-iodo ketones with excellent yields and easy workup procedure employing a selenium-based traceless linker strategy. Moreover, the polymeric selenium bromide reagent can be regenerated and reused as an environmentally friendly benign reagent.



Scheme 1

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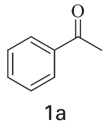
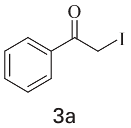
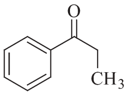
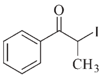
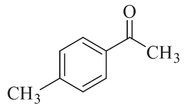
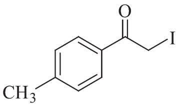
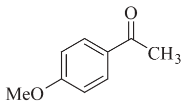
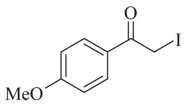
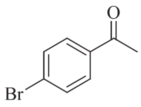
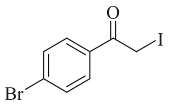
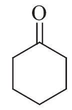
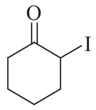
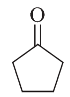
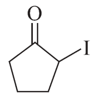
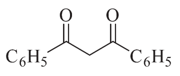
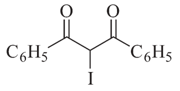
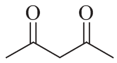
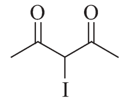
Table 1 The yields and purities of α-iodo ketones **(3a–i)**

Entry	Ketone **(1)**	Product **(3)**	Yield/%[a]	Purity/%[b]
1	 1a	 3a	98 97[c] 95[d] 94[e]	98 97[c] 96[d] 96[e]
2	 1b	 3b	97	96
3	 1c	 3c	97	98
4	 1d	 3d	96	97
5	 1e	 3e	94	95
6	 1f	 3f	92	96
7	 1g	 3g	93	96
8	 1h	 3h	90	94
9	 1i	 3i	85	95

[a] Isolated yields based on polymer-supported selenium bromide (1.20 mmol Br/g).

[b] Determined by HPLC of the crude cleavage product.

[c] With the first regenerated selenium bromide resin.

[d] With the second regenerated selenium bromide resin.

[e] With the third regenerated selenium bromide resin.

Experimental

Melting points were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal reference. FTIR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. HPLC analysis was carried out on Agilent 1100 automated system having a PDA detector (λ_{max} = 254 nm) using a gradient run of 0–100% MeCN in H_2O (1 mL min^{-1}) on a RP-18e column (150 × 4.6 mm). Polystyrene (H 1000, 100–200 mesh, cross-linked with 1% divinylbenzene) for preparation of selenium bromide resin (elemental analysis Br, 1.20 mmol g^{-1})[20] was purchased from Nankai University, the other starting materials were purchased from commercial sources and used without further purification; some of the starting materials were prepared using standard literature procedures. THF was distilled from sodium-benzophenone immediately prior to use.

Preparation of α-iodo ketones **3a**–**i**; *general procedure*

To a stirring solution of LDA (1.40 mmol) in THF (5 mL) under nitrogen at –78 °C was added dropwise a solution of the carbonyl compound **(1)** (1.40 mmol) in THF (5 mL) over 5 min. After stirring for an additional 10 min, polystyrene-supported selenium bromide (1.0 g) was added rapidly. The mixture was warmed to room temperature over a 15 min period and stirred for 15 min. After being acidified with glacial acetic acid, the α-seleno ketone resin **(2)** was collected by filtration and washed successively with H_2O, THF and CH_2Cl_2 (2 × 10 mL of each). Then NaI (1.0 g) and CH_3I (1.0 mL) under nitrogen was added to a suspension of the swollen resin **2** in anhydrous DMF (10 mL). The mixture was stirred at 75 °C overnight and then cooled to room temperature. The mixture was filtered and the residual resin **4** was washed with CH_2Cl_2 (10 × 3 mL). The filtrate was washed successively with saturated $NaHCO_3$ (30 mL), saturated $Na_2S_2O_3$ (30 mL) and H_2O (10 ×3 mL), dried over anhydrous $MgSO_4$ and concentrated to afford crude products **3a**–**i** with 94–98% purity determined by HPLC, which were further purified by passing the crude product through a silica gel chromatographic column (hexane–EtOAc, 10:1) to afford the pure products for their structure analyses if necessary. All of the products were satisfactorily characterised by ^{1}H NMR, ^{13}C NMR and IR, and are identified with the previously reported data in the literature.

1-Phenyl-2-iodoethanone (**3a**): Colourless oil (lit.[12] oil); ^{1}H NMR: δ = 7.98 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.2 Hz, 2H), 4.36 (s, 2H); ^{13}C NMR: δ = 191.0, 137.6, 135.8, 133.8, 130.4, 33.5; IR (film): ν = 1697 cm^{-1}.

1-Phenyl-2-iodopropanone (**3b**): Colourless oil (lit.[7] oil); ^{1}H NMR: δ = 8.97–8.95 (m, 2H), 7.58–7.54 (m, 3H), 4.40–4.37 (m, 1H), 1.90 (d, J = 7.6 Hz, 3H); ^{13}C NMR: δ = 191.2, 137.5, 135.8, 133.3, 130.1, 31.3, 18.6; IR (film): ν = 1702 cm^{-1}.

1-(4-Methylphenyl)-2-iodoethanone (**3c**): Colourless oil (lit.[7] oil); ^{1}H NMR: δ = 7.90 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 4.33 (s, 2H), 2.44 (s, 3H); ^{13}C NMR: δ = 191.5, 140.7, 129.6, 127.2, 124.4, 63.0, 21.5; IR (film): ν = 1695 cm^{-1}.

1-(4-Methoxyphenyl)-2-iodoethanone (**3d**): White solid, m.p. 60–61 °C (lit.[15] m.p. 58–59.5 °C); ^{1}H NMR: δ = 7.95 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.32 (s, 2H), 3.85 (s, 3H); ^{13}C NMR: δ = 191.6, 163.5, 131.3, 126.0, 114.5, 63.7, 55.2; IR (KBr): ν = 1667 cm^{-1}.

1-(4-Bromophenyl)-2-iodoethanone (**3e**): Colourless oil (lit.[7] oil); ^{1}H NMR: δ = 8.12 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 4.37 (s, 2H); ^{13}C NMR: δ = 192.1, 138.2, 134.5, 132.6, 128.2, 33.8; IR (film): ν = 1680 cm^{-1}.

2-Iodocyclohexanone (**3f**): Colourless oil (lit.[3] oil); ^{1}H NMR: δ = 4.22 (t, J = 6.4 Hz, 1H), 2.37 (t, J = 6.4 Hz, 2H), 1.70–1.64 (m, 2H), 1.61–1.55 (m, 2H), 1.45–1.40 (m, 2H); ^{13}C NMR: δ = 198.2, 42.3, 32.1, 29.4, 26.5, 25.1; IR (film): ν = 1710 cm^{-1}.

2-Iodocyclopentanone (**3g**): Colourless oil (lit.[12] oil); ^{1}H NMR: δ = 4.10 (t, J = 6.0 Hz, 1H), 2.45 (t, J = 6.0 Hz, 2H), 1.78–1.66 (m, 2H), 1.52–1.48 (m, 2H); ^{13}C NMR: δ = 201.6, 41.5, 31.8, 26.0, 16.5; IR (film): ν = 1718 cm^{-1}.

2-Iodo-1,3-diphenylpropane-1,3-dione (**3h**): White solid, m.p. 105–106°C (lit.[12] m.p. 104 °C); ^{1}H NMR: δ = 8.05 (d, 4H, J = 8.0 Hz), 7.58 (t, J = 7.2 Hz, 2H), 7.46 (t, J = 8.0 Hz, 4H), 6.95 (s, 1H); ^{13}C NMR: δ = 190.2, 134.2, 133.3, 129.5, 129.2, 34.1; IR (KBr): ν = 1695, 1665 cm^{-1}.

3-Iodopentane-2,4-dione (**3i**): Colourless oil (lit.[12] oil); ^{1}H NMR: δ = 5.02 (s, 1H), 2.50 (s, 6H); ^{13}C NMR: δ = 203.2, 199.5, 33.8, 27.2, 23.5; IR (film): ν = 3433, 1733 cm^{-1}.

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References

1 A.W. Erian, S.M. Sherif and H.M. Gaber, *Molecules*, 2003, **8**, 793.
2 R.H. Seevers and R.E. Counsell, *Chem. Rev.*, 1982, **82**, 575.
3 G. Cardillo and M. Shimisu, *J. Org. Chem.*, 1977, **42**, 4268.
4 G.M. Rubottom and R.C. Mott, *J. Org. Chem.*, 1979, **44**, 1731.
5 Y.D. Vankar and G. Kumaravel, *Tetrahedron Lett.*, 1984, **25**, 233.
6 T. Okamoto, T. Kakinami, T. Nishimura, I. Hermawan and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*,1992, **65**, 1731.
7 J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros and J.M. González, *Chem. Commun.*, 2004, 2616.
8 M.L.N. Rao and D.N. Jadhav, *Tetrahedron Lett.*, 2006, **47**, 6883.
9 J. Barluenga, J.M. Martinez-Gallo, C. Najera and M. Yus, *Synthesis*, 1986, 678.
10 A. Bekaert, O. Barberan, M. Gervais and J.-D. Brion, *Tetrahedron Lett.*, 2000, **41**, 2903.
11 S. Stavber, M. Jereb and M. Zupan, *Chem. Commun.*, 2002, 488.
12 P. Goswami, S. Ali, Md. M. Khan and A.T. Khan, *Arkivoc*, 2007, 82.
13 G.D. Yin, M. Gao, N.F. She, S.L. Hu, A.X. Wu and Y.J. Pan, *Synthesis*, 2007, 3113.
14 G. Le Bras, O. Provot, A. Bekaert, J.-F. Peyrat, M. Alami and J.-D. Brion, *Synthesis*, 2006, 1537.
15 G. Stavber, J. Iskra, M. Zupan and S. Stavber, *Green. Chem.*, 2009, **11**, 1262.
16 M.S. Yusubov, R.Y. Yusubova, T.V. Funk, K.-W. Chi, A. Kirschning and V.V. Zhdankin, *Synthesis*, 2010, 3681.
17 H.M. Meshram, P.N. Reddy, P. Vishnu, K. Sadashiv and J.S. Yadav, *Tetrahedron Lett.*, 2006, **47**, 991.
18 J.C. Lee, J.Y. Park, S.Y. Yoon, Y.H. Bae and S.J. Lee, *Tetrahedron Lett.*, 2004, **45**, 191.
19 J.N. Moorthy, K. Senapati and N. Singhal, *Tetrahedron Lett.*, 2009, **50**, 2493.
20 K.C. Nicolaou, J. Pastor, S. Barluenga and N. Winssinger, *Chem. Commun.*, 1998, 1947.
21 S.R. Sheng, Q. Xin, X.L. Liu, W.K. Sun, R. Guo and X. Huang, *Synthesis*, 2006, 2293.