A Simple and Efficient Method for Transesterification of β-Ketoesters Catalysed by Iodine

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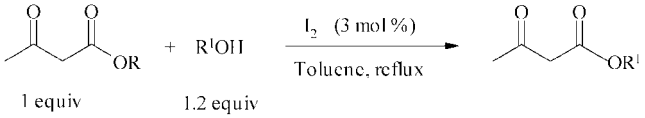
Received 3 July 2003; revised 11 September 2003

Abstract: A facile transesterification of β-ketoesters using catalytic iodine is described.

Key words: transesterification, β-ketoesters, iodine, alcohols

The transesterification of β-ketoesters has been found to be a very useful tool in organic synthesis having wide applications in academic as well as industrial research. A number of methods have been reported to effect transesterification of β-ketoesters. Although uncatalysed transesterification of β-ketoesters is reported in the literature[1–3] they require the use of either an excess of ketoester or longer reaction times and employ high boiling alcohols or utilise unconventional energy sources thus limiting their usage. Similarly uncatalysed transesterification of *tert*-butyl acetoacetate is also reported in the literature.[4] However, this method is confined to *tert*-butyl acetoacetate which itself is not readily available thus limiting its usage. Transesterification of β-ketoesters has been reported using reagents like DMAP,[5] DBU,[6] titanium tetraalkooxide,[7] tetrabutyl distannoxanes,[8,9] *p*-TSA.[10] However, most of these reagents are toxic, expensive or difficult to prepare. We have already described the utility of heterogeneous catalysts like S–SnO_2[11] and Amberlyst-15[12] as efficient catalysts for transesterification of β-ketoesters. Several other catalysts have also been shown to be effective for transesterification of β-ketoesters.[13,14] In recent years reagents like indium triiodide,[15] iodotrimethylsilane/I_2[16] have been used for transesterification. A recent report on the use of iodine[17] for transesterification of esters shows that iodine acts as an efficient catalyst to effect the transesterification. It has limitations, as benzyl alcohol fails to undergo transesterification with normal esters. Additionally the iodine-catalysed protocol involves the use of excess alcohol to push the equilibrium driven reaction in the desired direction and requires longer reaction times. Recently we have demonstrated that zinc can be activated by iodine[18] and this reagent was shown to effect transesterification with normal alcohols as well as phenols to furnish coumarins. In this communication we wish to report that even iodine acts as an efficient catalyst to effect transesterification (Scheme 1). The results of this protocol are summarised in Table 1.



Scheme 1

The noteworthy feature of our protocol is that β-ketoesters like ethyl acetoacetate and ethyl cyclopentanone-2-carboxylate underwent transesterification with benzyl alcohol to furnish the transesterified products in good yields (83% and 88% respectively). In most of the cases only 1.2 equivalents of alcohols were required for efficient conversions. However, in the case of volatile alcohols like 2-propanol, 1-propanol and propargyl alcohol, 2 equivalents of alcohol are required to obtain good yields of the corresponding ester. The other important feature of this protocol is that transesterification of β-ketoesters by various alcohols like benzyl, allylic, propargyl alcohols has been effectively catalysed by iodine giving products with moderate to high yields in comparatively reduced reaction times. Although several aliphatic esters underwent smooth transesterification, phenols did not undergo transesterification with either methyl acetoacetate or ethyl acetoacetate to furnish the coumarins in the presence of iodine as the catalyst. This result may be contrasted with the reactions mediated by zinc and iodine, which furnished the coumarins. This clearly indicates that most likely a complex of zinc and iodine is responsible for the transesterification.

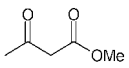
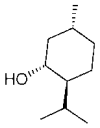
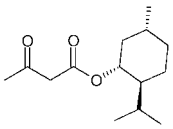
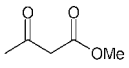
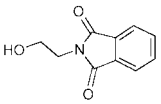
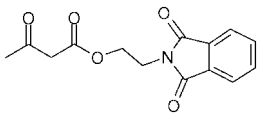
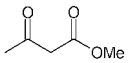
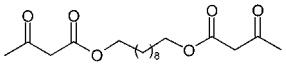
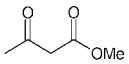
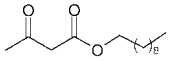
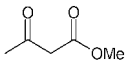
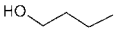
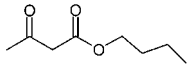
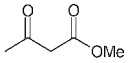
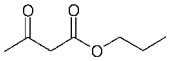
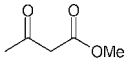
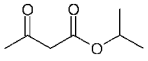
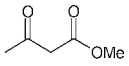
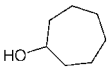
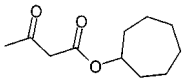
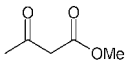
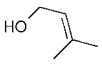
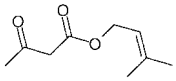
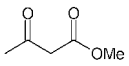
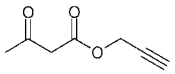
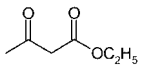
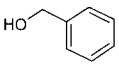
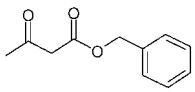
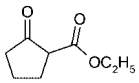
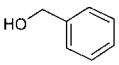
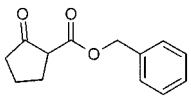
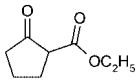
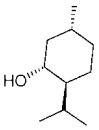
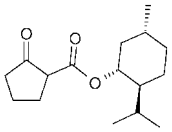
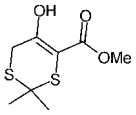
In conclusion, the present protocol describes a simple and efficient method for the transesterification of β-ketoesters by different alcohols catalysed by iodine. The ready availability of iodine along with its efficiency, simplicity and superiority over the existing methods should make this protocol an attractive addition to the arsenal of synthetic chemists.

Transesterification; Typical Procedure

Methyl acetoacetate (1.004 g, 8.655 mmol, 1 equiv), menthol (1.620 g, 10.386 mmol, 1.2 equiv), iodine (66 mg, 0.26 mmol, 3 mol%) and toluene (10 mL) were placed in a 50 mL round bottom flask fitted with a condenser. The reaction mixture was heated to 115–120 °C (oil bath temperature) for 4 h. The reaction was monitored by TLC and after completion the reaction mixture was cooled, washed with sodium thiosulfate solution and subsequently with water and brine. The organic layer was separated, dried over sodium sulfate, filtered

SYNTHESIS 2003, No. 17, pp 2695–2698
Advanced online publication: 14.10.2003
DOI: 10.1055/s-2003-42433; Art ID: Z09503SS

Table 1 Iodine-Catalysed Transesterification of β-Ketoesters[a,e]

Entry	β-Ketoester	Alcohol[b]	Product	Time (h)	Isolated Yields (%)
1				4	96
2				6.5	87
3				7	79[c]
4				5	86
5				5	81
6				7	65[d]
7				7	63[d]
8				5	89
9				4	74
10				6.5	80[d]
11				5	83
12				5	88
13				4.5	92
14				4	96

[a] 3 mol% of iodine used.
[b] 1.2 Equivalents of alcohol used.
[c] 0.5 Equivalents of alcohol used.
[d] 2 Equivalents of alcohol used.
[e] All the compounds were characterised by physical and spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, MS etc.) and by comparison with authentic samples.

and the solvent was removed under vacuum. The residue was purified by column chromatography to give the transesterified product.

Menthyl 3-Oxobutanoate[12]
Yield: 96%; $[\alpha]_D^{25}$ –72.00 (*c* = 10.24, benzene) {lit.[2] $[\alpha]_D^{20}$ –69.3, (*c* = 10, benzene)}.

^{1}H NMR($CDCl_3$, 200MHz): δ = 4.75 (dt, *J* = 4.4, 10.7 Hz, 1 H), 3.45 (s, 2 H), 2.25 (s, 3 H), 1.9–2.1 (m, 2H), 1.65–1.75 (m, 2 H), 1.4–1.5 (m, 2 H), 0.9–1.2 (m, 9 H), 0.85 (d, *J* = 6 Hz, 3 H).

***N*-(2-Pthalimido)ethyl 3-Oxobutanoate[12]**
Yield: 87%; mp 87–88 °C (lit.[12] mp 88–89 °C).

IR ($CHCl_3$): 3022, 1775, 1746, 1717, 1616, 1469, 1429, 1395, 1035, 759 cm^{-1}.

^{1}H NMR($CDCl_3$, 200MHz): δ = 7.85 (dd, *J* = 2.9, 8.3 Hz, 2 H), 7.75 (dd, *J* = 2.9, 8.3 Hz, 2 H), 4.38 (t, *J* = 4.9 Hz, 2 H), 3.97 (t, *J* = 4.9 Hz, 2 H), 3.42 (s, 2 H), 2.25 (s, 3 H).

ESI-MS (CH_3CN–H_2O–CH_3COONH_4): *m*/*z* = 293.02 (M + NH_4^+), 276.02 (M + 1).

Decane-1,10-diyl Bis(3-oxobutanoate)[13e]
Yield: 79%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.09 (t, *J* = 6.4 Hz, 4 H), 3.40 (s, 4 H), 2.24 (s, 6 H), 1.50–1.65 (m, 4 H), 1.10–1.40 (m, 12 H).

Decyl 3-Oxobutanoate[12]
Yield: 86%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.06 (t, *J* = 6.4 Hz, 2 H), 3.37(s, 2 H), 2.21 (s, 3 H), 1.51–1.61 (m, 2 H), 1.14–1.40 (m, 14 H), 0.82 (t, *J* = 6.4 Hz, 3 H).

Butyl 3-Oxobutanoate[12]
Yield: 81%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.11 (t, *J* = 6.8 Hz, 2 H), 3.42 (s, 2 H), 2.24 (s, 3 H), 1.60 (quintet, *J* = 6.8 Hz, 2 H), 1.35 (tq, *J* = 6.8, 7.3 Hz, 2 H), 0.91 (t, *J* = 6.8 Hz, 3 H).

Propyl 3-Oxobutanoate[14]
Yield: 65%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.06 (t, *J* = 6.8 Hz, 2 H), 3.42 (s, 2 H), 2.24 (s, 3 H), 1.65 (tq, *J* = 6.8, 7.3 Hz, 2 H), 0.93 (t, *J* = 6.8 Hz, 3 H).

Isopropyl 3-Oxobutanoate[14]
Yield: 63%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.99 (m, 1 H), 3.33 (s, 2 H), 2.19 (s, 3 H), 1.20 (d, *J* = 6.4 Hz, 6 H).

Cycloheptyl 3-Oxobutanoate[12]
Yield: 89%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.97 (m, 1 H), 3.39 (s, 2 H), 2.25 (s, 3 H), 1.86–1.98 (m, 2 H), 1.42–1.73 (m, 10 H).

Prenyl 3-Oxobutanoate[4]
Yield: 74%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 5.29 (t, *J* = 7.3Hz, 1 H), 4.57 (d, *J* = 7.3 Hz, 2 H), 3.38 (s, 2 H), 2.21 (s, 3 H), 1.72 (s, 3 H), 1.67 (s, 3 H).

Propargyl 3-Oxobutanoate[14]
Yield: 80%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.70 (d, *J* = 2.4 Hz, 2 H), 3.46 (s, 2 H), 2.48 (t, *J* = 2.4 Hz, 1 H), 2.24 (s, 3 H).

Benzyl 3-Oxobutanoate[12]
Yield: 83%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.36 (s, 5 H), 5.18 (s, 2 H), 3.50 (s, 2 H), 2.25 (s, 3 H).

Benzyl 2-Oxocyclopentanecarboxylate[13f]
Yield: 88%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.32 (s, 5 H), 5.14 (s, 2 H), 3.16 (t, *J* = 8.8Hz, 1 H), 2.25–2.33 (m, 4 H), 2.15 (m, 1 H), 1.87 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50MHz): δ = 211.3 (s), 168.9 (s), 135.5 (s), 128.3 (d), 128.0 (d), 127.8 (d), 66.7 (t), 54.4 (d), 37.7 (t), 27.2 (t).

(–)-Menthyl 2-Oxacyclopentanecarboxylate[13f]
Yield: 92%.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 4.75 (m, 1 H), 3.11 (m, 1 H), 2.14–2.43 (m, 4 H), 1.75–2.14 (m, 4 H), 1.55–1.75 (m, 2 H), 1.23–1.55 (m, 3 H), 0.65–1.05 (m, 11 H).

^{13}C NMR ($CDCl_3$, 50MHz, mixture of two diasterisomers, partly doubled signals): δ = 211.1 (s), 168.5 (s), 74.6 (d), 54.6 (d), 54.3 (d), 46.6 (d), 40.4 (t), 37.4 (t), 33.9 (t), 31.0 (d), 27.7 (t), 26.9 (t), 25.8 (t), 25.3 (t), 23.1 (t), 22.8 (t), 21.7 (q), 20.7 (q), 15.9 (q), 15.6 (q).

Menthyl 5-Hydroxy-2,2-dimethyl-4*H*-1,3-dithiine-6-carboxylate
Yield: 96%; $[\alpha]_D^{25}$ –76.30 (*c* = 2.2, benzene).

IR ($CHCl_3$): 2958, 2925, 2871, 1717, 1632, 1587, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 12.81 (s, 1 H), 4.78 (dt, *J* = 3.9, 10.4 Hz, 1 H), 3.45 (d, *J* = 8.6 Hz, 2 H), 1.79–2.08 (m, 2 H), 1.70 (s, 3 H), 1.66 (s, 3 H), 1.47–1.60 (m, 2H), 1.07–1.27 (m, 2 H), 0.89–0.95 (m, 9 H), 0.76 (d, *J* = 7.4, 3 H).

^{13}C NMR ($CDCl_3$, 50MHz): δ = 174.3 (s), 170.0 (s), 95.8 (s), 75.30 (d), 55.9 (s), 46.4 (d), 40.4 (t), 33.9 (t), 32.1 (q), 31.8 (t), 31.1 (d), 26.0 (d), 23.2 (t), 21.7 (q), 20.4 (q), 16.1 (q).

ESI-MS (CH_3CN–H_2O–CH_3COONH_4): *m*/*z* = 362.05 (M + NH_4^+), 345.05 (M + 1).

Methyl 5-Hydroxy-2,2-dimethyl-4*H*-1,3-dithiine-6-carboxylate[19]
Mp 49 °C (pale yellow solid).

IR ($CHCl_3$): 3194, 3168, 3099, 2959, 2907, 2850, 1653, 1571, 1434, 1311, 1203, 1141, 1062, 775 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200MHz): δ = 12.60 (s, 1 H), 3.84 (s, 3 H), 3.46 (s, 2 H), 1.70 (s, 6 H).

^{13}C NMR ($CDCl_3$, 50MHz): δ = 31.9 (q), 32.0 (t), 52.0 (q), 55.8 (s), 95.8 (s), 171.0 (s), 174.4 (s).

MS: *m*/*z* = 220 (34), 188 (20), 170 (18), 160 (28), 146 (21), 127 (60), 114 (82), 103 (21), 86 (100), 74 (90), 69 (15), 59 (43).

Acknowledgement

The authors RRK, KS thank CSIR New Delhi (India) for the award of fellowships. Funding under the YSA (SPC) scheme from CSIR, India is gratefully acknowledged.

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