Synthetic Communications®, 38: 338–345, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701767049

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One-Pot Synthesis of α-Formyloxy Ketones from Enolizable Ketones

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Abstract: One-pot synthesis of α-formyloxy tones as well as α-acetoxy ketones from enolizable ketones and [hydroxy(tosyloxy) iodo] benzene (HTIB)/polymer supported [hydroxy(tosyloxy) iodo] benzene (PSHTIB) in N,N−dimethylformamide (DMF)/ N, N−dimethylacetamide (DMA) in high yields is described.

Keywords: α-acetoxy ketones, α-formyloxy ketones, [hydroxyl(tosyloxy)iodo]benzene, polymer-supported [hydroxyl(tosyloxy)iodo]benzene

The α-formyloxy ketones are useful intermediates for synthesizing (oxodioxolenyl) methylcarbamate as novel nonchiral bioreversible prodrug moieties for chiral amino functional drugs.[1,2] α-Formyloxy/acetoxy indane-1,3-dione derivatives are effective as allergy inhibitors.[3,4] The formate and acetate groups also serve as good protective groups for the hydroxyl function in α-hydroxy ketones,[5] the moiety that is present in many biologically active natural products.[6] The α-acetoxy ketones find applications for biotransformation to optically active 1,2-diols, which are important intermediates in organic synthesis and for staining biologically active compounds.[7] There are various protocols for synthesizing α-acetoxy ketones.[8−12]

Received in India July 12, 2007
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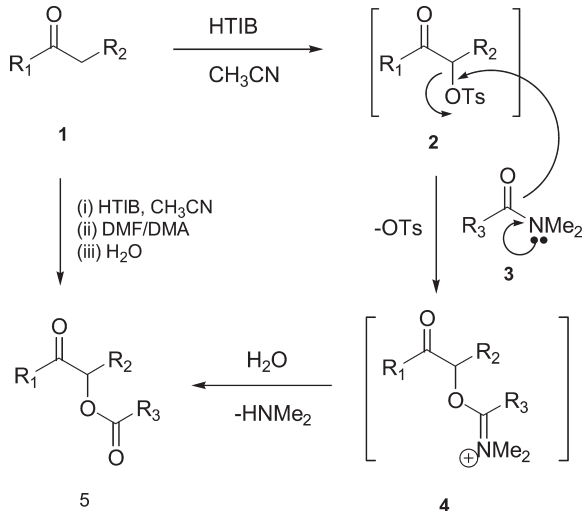

Scheme 1. R_1 = aryl, 2-thienyl, naphthyl; R_2 = H, Me, cycloakyl; and R_3 = H, Me.

Table 1. Physical data of α-formyloxy and α-acetoxy ketones (**5**)[a]

		α-Formyloxy ketone		α-Acetoxy ketone	
Entry	Reactants	Yield (%)	Mp (°C) (lit. mp)	Yield (%)	Mp (°C) (lit. mp)
1	$C_6H_5COCH_3$	75	50 (50–52)[12]	78	45
2	4-$CH_3C_6H_4COCH_3$	70	Liquid[12]	76	Liquid[9]
3	4-$CH_3OC_6H_4COCH_3$	75	65–67	74	69 (84.5)[10]
4	2-$CH_3OC_6H_4COCH_3$	65	48	72	55
5	4-$ClC_6H_6COCH_3$	78	82 (82–85)[12]	80	62 (70.3)[10]
6	4-$BrC_6H_4COCH_3$	80	90	85	70[10]
7	4-$FC_6H_4COCH_3$	75	69	80	42[10]
8	$C_6H_5COCH_2CH_3$	85	Liquid	68	Liquid[10]
9	1-Indanone	66–67		70	Liquid
10	2-Acetylthiophene	70	62	70	
11	1-Acetylnaphthalene	78	Liquid	80	Liquid

[a]The elemental analysis of unknown compounds was found be satisfactory (0.4%), and in IR, the carbonyl band appeared at 1732 ± .8, 1701 ± .8 cm^{-1} in all compounds besides other bands.

Table 2. Spectroscopic data of α-formyloxy ketones (**5**)

Entry	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
1	5.44 (s, 2H, CH_2), 7.47–7.51 (m, 2H, H_3 and H_5), 7.59–7.64 (m, 1H, H_4), 7.90–7.93 (m, 2H, H_2 and H_6), 8.25 (s, 1H, OCHO)	65.3 (CH_2), 127.7 (C-3 and C-5), 128.9 (C-2 and C-6), 133.8 (C-1), 134.0 (C-4), 160.0 (OC═O), 191.1 (C═O)
2	2.34 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 7.21 (d, $J = 8$ Hz, 2H, H_3 and H_5), 7.74 (d, $J = 8$ Hz, 2H, H_2 and H_6), 8.17 (s, 1H, OCHO)	21.8 (CH_3), 65.3 (CH_2), 127.9 (C-2 and C-6), 129.6 (C-3 and C-5), 131.4 (C-1), 145.1 (C-4), 160.1 (OC═O), 190.7 (C═O)
3	3.87 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.96 (dd, $J = 6.9$, 2.0 Hz, 2H, H_3 and H_5), 7.89 (dd, $J = 6.9$, 2.0 Hz, 2H, H_2 and H_6), 8.25 (s, 1H, OCHO)	55.5 (OCH_3), 65.0 (CH_2), 114.1 (C-3 and C-5), 126.8 (C-1), 130.1 (C-2 and C-6), 160.1 (OC═O), 164.1(C-4), 189.5 (C═O)
4	3.96 (s, 3H, OCH_3), 5.34 (s, 2H, CH_2), 7.00 (d, $J = 8.4$ Hz, 1H, H_3), 7.05 (t, $J = 7.4$ Hz, 1H, H_4), 7.54 (1 H, dt, $J = 7.8$, 1.6 Hz, H_5), 7.97 (1 H, dd, $J = 7.6$, 1.6 Hz, H_6), 8.24 (1 H, s, OCHO).	55.7 (OCH_3), 69.4 (CH_2), 111.5 (C-3), 121.1 (C-5), 124.0 (C-1), 131.2 (C-6), 135.2 (C-4), 159.6 (C-2), 160.4 (OC═O), 191.9(C═O)
5	5.32 (s, 2H, CH_2), 7.37–7.41 (m, 2H, H_3 and H_5), 7.76–7.80 (m, 2H, H_2 and H_6), 8.16 (s, 1H, OCHO)	65.4 (CH_2), 128.8 (C-3 and C-5), 130.0 (C-2 and C-6), 135.5 (C-1), 138.2 (C-4), 160.0 (OC═O), 190.3 (C═O)
6	5.40 (s, 2H, CH_2), 7.63–7.66 (m, 2H, H_3 and H_5), 7.77–7.80 (m, 2H, H_2 and H_6), 8.25 (s, 1H, OCHO)	65.1 (CH_2), 129.3 (C-2 and C-6), 129.4 (C-4), 132.3 (C-3 and C-5), 132.6 (C-1), 160.0 (OC═O), 190.3 (C═O)
7	5.41 (2 H, s, CH_2), 7.15–7.21 (m, 2H, H_3 and H_5), 7.93–7.98 (m, 2H, H_2 and H_6), 8.25 (s, 1H, OCHO)	65.1 (CH_2), 116.2 (d, $J_{CF} = 22$ Hz, C-3 and C-5), 130.4 (d, $J_{CF} = 2.8$ Hz, C-1), 130.5 (d, $J_{CF} = 9.00$ Hz, C-2 and C-6), 160.0 (OC═O), 166.0 (d, $J_{CF} = 255.0$ Hz, C-4), 189.6 (C═O)
8	1.57 (d, $J = 7.04$ Hz, 3H, CH_3), 6.12 (q, $J = 7.04$,1H, CH), 7.47–7.52 (m, 2H, H_3 and H_5), 7.59–7.63 (m, 1H, H_4), 7.92–7.96 (m, 2H, H_2 and H_6), 8.13 (s, 1H, OCHO)	17.2 (CH_3), 69.3 (CH), 128.5 (C-3 and C-5), 128.8 (C-2 and C-6), 133.8 (C-4), 134.0 (C-1), 160.1 (OC═O), 195.8 (C═O).

(*continued*)

Table 2. Continued

Entry	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
9	3.10 (dd, $J = 17.0$, 4.8 Hz, 1H), 3.70 (dd, $J = 17.0$, 8.0 Hz, 1H), 5.54–5.57 (m, 1H), 7.42–7.48 (m, 2H), 7.65–7.69 (m, 1H), 7.81 (d, $J = 7.76$ Hz, 1H), 8.23 (s, 1H, OCHO)	33.2 (C-3), 73.5 (C-2), 124.6 (C-6), 126.7 (C-4), 128.3 (C-7), 134.2 (C-7a), 136.1 (C-5), 150.2 (C-3a), 160.2 (OC═O), 199.8 (C═O)
10	5.33 (s, 2H, CH_2), 7.18 (dd, $J = 4.84$, 3.96 Hz, 1H, H_4), 7.40 (dd, $J = 4.9$, 0.8 Hz, 1H, H_5), 7.77 (dd, $J = 3.8$, 0.8 Hz, 1H, H_3) 7.73–7.77 (m, 2H), 8.24 (s, 1H, OCHO)	65.0 (CH_2), 128.4 (C-4), 132.1 (C-3), 134.7 (C-5), 140.0 (C-2), 160.0 (OC═O), 184.3 (C═O)
11	5.39 (s, 2H, CH_2), 7.47–7.62 (m, 3H, H_3, H_6 and H_7), 7.81–7.87 (m, 2H, H_2 and H_5), 8.01 (d, $J = 8.2$ Hz, 1H, H_4), 8.26 (s, 1H, OCHO), 8.63 (d, $J = 8.0$ Hz, 1H, H_8)	66.7 (CH_2), 124.2 (C-3), 125.4 (C-8), 126.8 (C-6), 127.6 (C-7), 128.5 (C-5), 128.7 (C-2), 130.2 (C-8a), 131.9 (C-4a), 133.8 (C-4), 133.9 (C-1), 160.1 (OC═O), 194.8 (C═O)

However, there exist only two reports (i.e., aniodic oxidation of enol carbonate[13] and a thallium(III)triflate[14]) for furnishing α-formyloxy ketones. Keeping in view the importance of α-formyloxy and α-acetoxy ketones, we report herein a smooth conversion of enolizable ketones to α-formyloxy and α-acetoxy ketones using {hydoxy(tosyloxy) iodo}benzene (HTIB) as well as polymer-supported [hydoxy(tosyloxy)iodo]benzene (PSHTIB) in DMF and DMA solvent with high yields.

The enolizable ketones (**I**) are first converted to corresponding α-tosyloxy ketones (**2**) using HTIB or PSHTIB.[15] The reaction of **2** with **3** (R═H, DMF and R═CH_3, DMA) as solvent generated iminium salt intermediate (**4**), which on subsequent treatment with water cleanly afforded α-formyloxy ketones and α-acetoxy ketones (**5**), respectively, within 15–45 min. (Scheme 1). The products were purified by percolation through a column of silica gel using hexane–ethyl acetate as eluent. The structure of the products was established through their physical and spectroscopic (FTIR and NMR) data. The physical data are presented in Table 1. The spectroscopic data of α-formyloxy ketones and α-acetoxy ketones are presented in Tables 2 and 3, respectively.

Further, we also examined the reaction of **1** with diacetoxyiodobenzene in the presence of trifluoromethane sulphonic acid which resulted in the desired product (**5**), but the HTIB-mediated reaction was much cleaner. The reaction was extended to a variety of substrate to afford **5** for generalization. The

Table 3. Spectroscopic data of α-acetoxy ketones (**5**)

Entry	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
1	2.22 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 7.46–7.51 (m, 2H, H_3 and H_5), 7.58–7.63 (m, 1H, H_4), 7.90–7.93 (m, 2H, H_2 and H_6)	20.6 (CH_3), 66.0 (CH_2), 127.8 (C-3 and C-5), 128.9 (C-2 and C-6), 133.9 (C-4), 134.2 (C-1), 170.5 (OC═O), 192.2 (C═O)
2	2.22 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 7.26–7.28 (m, 2H, H_3 and H_5), 7.80–7.82 (m, 2H, H_2 and H_6)	20.6 (CH_3), 21.7 (CH_3), 66.0 (CH_2), 127.9 (C-2 and C-6), 129.5 (C-3 and C-5), 131.8 (C-1), 144.9 (C-4), 170.5 (OC═O), 191.7(C═O)
3	2.22 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2), 6.95 (dd, $J = 6.96$, 2.00 Hz, 2H, H_3 and H_5), 7.90 (dd, $J = 6.96$, 2.00 Hz, 2H, H_2 and H_6)	20.6 (CH_3), 55.5 (OCH_3), 65.8 (CH_2), 114.1 (C-3 and C-5), 127.3 (C-1), 130.1 (C-2 and C-6), 164.1 (C-4), 170.5 (OC═O), 190.6(C═O)
4	2.19 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.96–7.05 (m, 2H, H_3 and H_5), 7.48–7.54 (m, 1H, H_4), 7.91 (dd, $J = 7.8$, 1.8 Hz, 1H, H_6)	20.6 (CH_3), 56.0 (OCH_3), 65.9 (CH_2), 114.0 (C-3), 120.7 (C-5), 123.0 (C-1), 129.6 (C-6), 133.9 (C-4), 162 (C-2), 170.5 (OC═O), 191.2 (C═O)
5	2.22 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 7.45–7.48 (m, 2H, H_3 and H_5), 7.83–7.87 (m, 2H, H_2 and H_6)	20.5 (CH_3), 65.9 (CH_2), 129.2 (C-3 and C-5), 129.3 (C-2 and C-6), 132.6 (C-1), 140.4 (C-4), 170.4 (OC═O), 191.1 (C═O)
6	2.22 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.63 (d, 2H, $J = 8.6$ Hz, H_3 and H_5), 7.78 (d, 2H, $J = 8.6$ Hz, H_2 and H_6)	20.6 (CH_3), 65.8 (CH_2), 129.2 (C-4), 129.3 (C-3 and C-5), 132.3 (C-3 and C-5), 132.9 (C-1) 170.4 (OC═O), 191.3 (C═O)
7	2.22 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.14–7.19 (m, 2H, H_3 and H_5), 7.93–7.97 (m, 2H)	20.6 (CH_3), 65.8 (CH_2), 116.2 (d, $J = 32$ Hz, C-3 and C-5), 130.6 (d, $J = 10.00$ Hz, C-2 and C-6), 130.7 (d, $J = 3.00$ Hz, C-1), 166.0 (d, $J = 255.0$ Hz, C-4), 170.4 (OC═O), 190.7 (C═O)
8	1.52 (d, $J = 7.0$ Hz, 3H, CH_3), 2.13 (s, 3H, CH_3), 5.96 (q, 1H, CH), 7.45–7.48 (m, 2H, H_3 and H_5), 7.55–7.60 (m, 1H, H_4), 7.91–7.95 (m, 2H, H_2 and H_6)	17.0 (CH_3), 20.6 (CH_3), 71.3 (CH), 128.3 (C-3 and C-5), 128.7 (C-2 and C-6), 133.5 (C-4), 134.2 (C-1), 170.3 (OC═O), 196.8 (C═O)

(*continued*)

Table 3. Continued

Entry	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
9	2.19 (s, 3H, CH_3), 3.04 (dd, $J = 16.92$, 4.88 Hz, 1H, H_3), 3.66 (dd, $J = 16.92$, 8.00 Hz, 1H, $H_{3'}$), 5.42 (dd, $J = 8.0$, 4.8 Hz, 1H, H_2), 7.40–7.66 (m, 4H, H_4, H_5, H_6 and H_7)	20.6 (CH_3), 33.4 (C-3), 74.0 (C-2), 124.5 (C-6), 126.6 (C-4), 128.1 (C-7), 134.4 (C-7a), 135.9 (C-5), 150.4 (C-3a), 170.5 (OC═O), 200.7 (C═O)
10	2.22 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 7.16 (dd, $J = 4.96$, 3.8 Hz, 1H, H_4), 7.71 (dd, $J = 4.9$, 0.8 Hz, 1H, H_5), 7.75 (dd, $J = 3.8$, 1.0 Hz, 1H, H_3)	20.5 (CH_3), 65.7 (CH_2), 128.3 (C-4), 132.0 (C-3), 134.3 (C-5), 140.3 (C-2), 170.3 (OC═O), 185.4 (C═O)
11	2.23 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.46–7.62 (m, 3H, H_3, H_6 and H_7), 7.82–7.87 (m, 2H, H_2 and H_5), 8.01 (d, $J = 8.2$ Hz, 1H, H_4), 8.62 (d, $J = 8.4$ Hz, 1H, H_8)	20.6 (CH_3), 67.5 (CH_2), 124.2 (C-3), 125.5 (C-8), 126.8 (C-6), 127.5 (C-7), 128.4 (C-5), 128.5 (C-2), 130.2 (C-8a), 132.3 (C-4a), 133.5 (C-4), 133.9 (C-1), 170.6 (OC═O), 196.1 (C═O)

synthetically useful α-formyloxy and α-acetoxy ketone (**5**) may be deprotected to get α-hydroxy ketone, the moiety that is present in many naturally occurring products and drugs. The α-formyloxy and α-acetoxy ketones (**5**) were also obtained in one pot starting from enolizable ketone (**1**) to first generate the α-tosyloxy ketones *in situ*, followed by subsequent removal of acetonitrile, reflux in DMF/DMA, and addition of water.

In conclusion, this simple, efficient, and economic transformation is superior to the previously described method for the synthesis of α-formyloxy ketones utilizing the reaction of ketones with toxic thallium(III)acetate and costly trifluoromethanesulphonic acid.[14] Further, PSHTIB utilized in these reactions can be regenerated by treatment of the recovered iodopolystyrene with peracetic acid followed by p-toluenesulphonic acid.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. FTIR spectra were obtained in KBr on Perkin-Elmer Spectrum RX1 instruments and are reported in centimeters^{-1}. ^{1}H and ^{13}C NMR spectra were determined on Bruker Avance II 400-MHz and 100-MHz NMR spectrometers, respectively, in $CDCl_3$ and are expressed as parts per million (ppm) with

respect to TMS. Elemental analysis was carried out on a Perkin-Elmer 2400 instrument.

Synthesis of α-Formyloxy and α-Acetoxy Ketones (5): General Procedure

HTIB (2.2 mmol, 758 mg) was added to a solution of enolizable ketone (**1**, 2 mmol) in acetonitrile (20 ml). The reaction mixture was refluxed for 2–3 h. After the completion of the reaction, most of the acetonitrile was removed under vaccum, and 10 ml of dry DMF/DMA was added. The solution was further refluxed for 30–45/15–25 min, respectively. The reaction mixture was cooled, and 2–3 ml of water was added. It was stirred for 15 min, extracted with dichloromethane thrice, and washed with saturated aq. sodium bicarbonate and water. The combined extract was dried over anhydrous sodium sulphate, and the excess of dichloromethane was distilled off. The residue was chromatographed over silica gel (60–120 mesh) using hexane–ethyl acetate (95:5) as eluant to afford **5**.

Alternatively, **5** can also be prepared utilizing polymer-supported [hydoxy(tosyloxy) iodo]benzene (PSHTIB) instead of HTIB. The only difference was that the reaction mixture containing **1** and PSHTIB was refluxed and filtered to remove iodopolystyrene followed by removal of acetonitrile.

ACKNOWLEDGMENT

The authors are thankful to Council of Scientific and Industrial Research (CSIR) and University Grants Commission (UGC), New Delhi, for financial support.

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