

Oxidative rearrangement of alkyl aryl/heteroaryl ketones by 1,2-aryl/heteroaryl shift using iodic acid

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Dedicated to Professor William F. Bailey on the occasion of his 65th birthday

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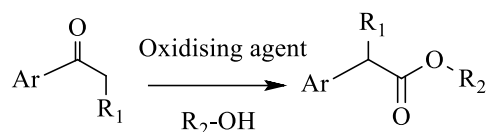
Abstract

A method for synthesis of α -aryl/heteroaryl alkanolic acids involving oxidative rearrangement of alkyl aryl/heteroaryl ketones by 1,2-aryl/heteroaryl shift using iodic acid is described.

Keywords: Oxidative rearrangement, alkyl aryl/heteroaryl ketone, 1,2-aryl shift, iodic acid, hypervalent iodine

Introduction

Improvements in reaction methodologies are yielding useful and simplified new variants.¹ Replacement of hazardous and expensive reagents by safer, cheaper and off-the-shelf reagents is an attractive option towards improved methodologies. α -Aryl/heteroaryl alkanolic acid derivatives have commercial importance as NSAIDs, such as naproxen, ibuprofen, flurbiprofen, diclofenac and indomethacin. Many of them are known for their analgesic, and antipyretic properties too.² There are quite a large number of methods available for their synthesis,³ which include arylation of esters using transition metal catalysed reactions,⁴ carbonylation/carboxylation reactions that includes aryl halides, α -aryl alcohols as counterpart of α -aryl/heteroaryl alkanolic acids.^{3b,5} Another useful and widely followed approach is oxidative rearrangement of alkyl aryl/heteroaryl ketones as shown in Scheme 1.



Scheme 1. Oxidative rearrangement of alkyl aryl/heteroaryl ketones.

This approach is attractive because parent ketones are readily accessible through Friedel-Crafts reactions. Another procedure to synthesise α -aryl/heteroaryl alkanolic acid derivatives is alkylation of corresponding acetic acids; however, selectivity in getting mono substituted product is a major concern.

Early methods reported for this oxidative rearrangement were based on use of lead(IV) acetate,⁶ silver nitrate⁷ and thallium nitrate.^{7,8} Toxicity factor of these metal reagents⁹ lead to the development of other methods, which include iodine, iodine monochloride and iodine trichloride mediated transformations.¹⁰

Hypervalent iodine reagents have also made their entry into this transformation because of their popularity as mild oxidising agents and similar reactivity pattern as of lead and thallium.¹¹ Hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) and iodosobenzene,¹² diacetoxyiodobenzene (DIB),¹³ 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiazole 3,3-dioxide (HMBI),¹⁴ have been used effectively to perform the transformation. Scope still exists to improve the methodology using other hypervalent iodine reagents especially those which are safer and readily available off-the-shelf, such as iodic acid. Our group is actively working on hypervalent iodine mediated oxidative transformations¹⁵ and recently on iodic acid.¹⁶ In this paper we report successful application of iodic acid for oxidative rearrangement.

Results and Discussion

An initial experiment was performed on acetophenone **1a** with 1.1 equiv of HIO₃ in the presence of methanol: trimethylorthoformate (TMOF) (9:1) and a catalytic amount of conc. H₂SO₄, at 65 °C. The rearranged product, methyl phenylacetate **2a**, was found in 92 % yield within 2h. Reaction conditions were studied and the results are given in Table 1.

When the reaction was carried out in absence of sulfuric acid as catalyst at room temperature as well as at 65 °C reaction did not occur (Table 1, entries 1&2). Reaction in the presence of the acid catalyst at room temperature was very slow, and rearranged product **2a** was obtained in 40% in 6 h. When the reaction temperature was raised to 65 °C, reaction was accelerated and **2a** was found in 92% yield in 2 h (Table 1, entry 4). To understand the role of TMOF a reaction was performed in its absence. The reaction was slow and required 6 h to give comparable yield indicating that presence of TMOF is required for faster reaction.

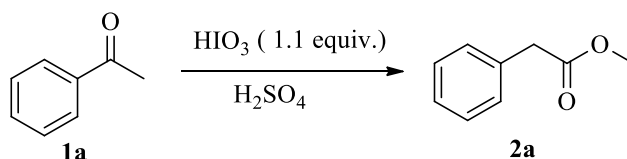
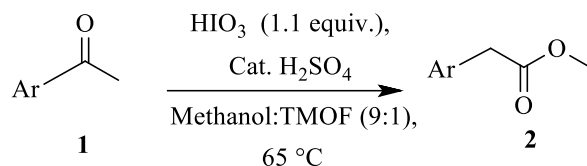


Table 1. Study of reaction conditions^{a,b}

Entry	H ₂ SO ₄ mol %	Methanol :TMOF	Temp/ Time	Yield %
1	-	9:1	rt/ 6 h	Nil
2	-	9:1	65 °C/ 6 h	Nil
3	20	9:1	rt / 6 h	40
4	20	9:1	65 °C/ 2 h	92
5	10	9:1	65 °C/ 2 h	76
6	5	9:1	65 °C/ 2 h	65
7	20	10:0	65 °C/ 6 h	90

^aProducts were characterized by ¹H NMR and IR analysis data, yields presented are after column chromatography. ^bIn some runs even after prolonged heating conversion was incomplete and ≤ 5% of unreacted starting material was recovered.

With these encouraging results in hand we went to check the generality and usefulness of the reaction, by performing the reaction on various substrates including aryl/heteroaryl methyl ketones and other alkyl aryl ketones and the results are summarised in Table 2 and Table 3, respectively.

Table 2. Products of oxidative rearrangement of aryl/heteroaryl methyl ketone derivatives^a

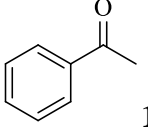
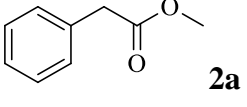
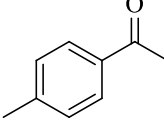
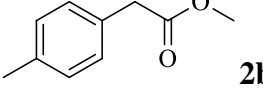
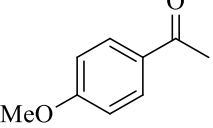
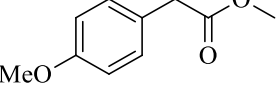
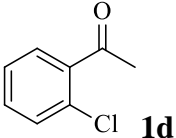
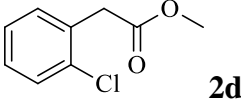
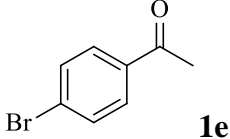
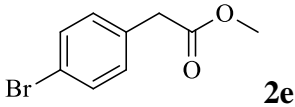
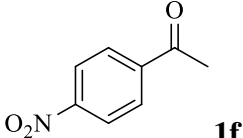
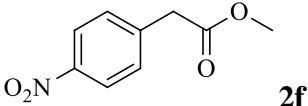
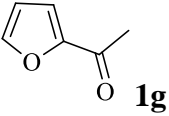
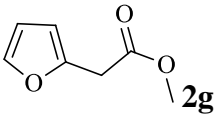
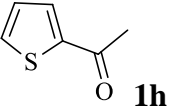
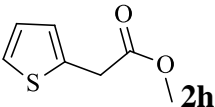
Entry	Substrate	Product	Time/ Yield (%)
1	 1a	 2a	2 h / 92
2	 1b	 2b	2 h / 90
3	 1c	 2c	2 h / 93

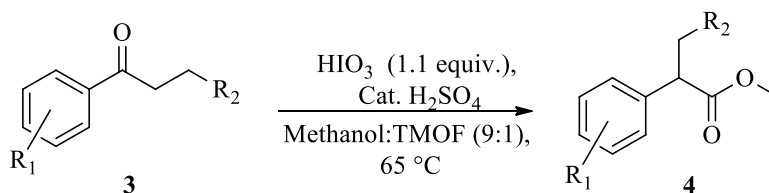
Table 2. Continued

Entry	Substrate	Product	Time/ Yield (%)
4	 1d	 2d	4 h / 83 ^b
5	 1e	 2e	4 h / 79 ^b
6	 1f	 2f	5 h / 65 ^b
7	 1g	 2g	3 h / 85
8	 1h	 2h	3 h / 86

^aProducts were characterized by ¹H NMR and IR analysis data, yields presented are after column chromatography. ^b α -methoxylated products were formed ($\leq 5\%$) however these did not pose any problem during isolation.

Oxidative rearrangement of acetophenones **1b-c** with electron-donating groups happened smoothly and methyl phenylacetates **2b-c** were obtained in good yields (Table 2, entries 2 & 3). Whereas with halogen and electron-withdrawing substituents yields of products **2** were comparatively low (Table 2, entries 4-6). Acetylfuran **1g** and acetylthiophene **1h** reacted equally well and gave the corresponding alkanolic acids **2g** and **2h**, respectively, in good yields (Table 2, entries 7 & 8).

Other alkyl aryl ketones such as propiophenones **3a-c**, butyrophenone **3d**, valerophenone **3e** and 3-benzoylpropanoic acid **3f** were subjected to the transformation. All these substrates underwent the transformation readily and gave good yields of the corresponding rearranged products (Table 3, entries 1-5). In the case of 3-benzoylpropanoic acid under the reaction condition diesterified product **4f** was isolated (Table 3, entry 6).

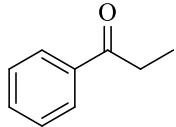
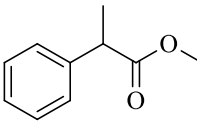
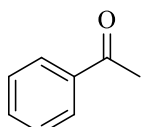
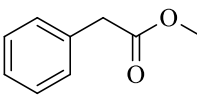
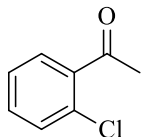
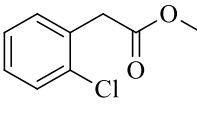
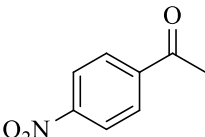
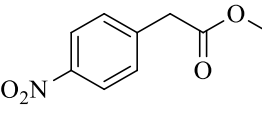
Table 3. Oxidative rearrangement of higher alkyl aryl ketones^a

Entry	Substrate	Product	Time/ Yield (%)
1			2 h / 80
2			2 h / 80
3			2.5 h / 85
4			2 h / 89
5			2 h / 88
6			3 h / 82

^aProducts were characterized by ¹H NMR and IR analysis data, yields presented are after column chromatography

Comparative results of our method with iodine-mediated methods from the literature, with some examples, are given in Table 4. Our method is superior with respect to yield and stoichiometry (Table 4, entry 1), or no requirement of co-oxidant AgNO₃ (Table 4, entries 2-4).

Table 4. Comparison of our method with iodine mediated methods

Entry	Substrate	Reaction conditions	Product	Yield (Yield by our method)(%)	Reference
1	 3a	I ₂ (2 equiv.) 23 °C, 24 h, TMOF	 4a	66 (80)	10a
2	 1a	I ₂ (1.2 equiv.), AgNO ₃ (2 equiv.), methanol/TMOF, Reflux	 2a	90 (92)	7
3	 1d	As above	 2d	23(83)	7
4	 1f	As above	 2f	Nil (65)	7

Conclusions

Iodic acid, a readily available, safer and off-the-self reagent, was found to be suitable for synthesis of α -aryl/heteroaryl alkanolic acids starting from alkyl aryl/heteroaryl ketones through oxidative rearrangement by 1,2-aryl/heteroaryl shift and is superior to iodine-mediated methods.

Experimental Section

General. ¹H NMR spectra were recorded on JEOL MY-60 operating at 60 MHz, chemical shifts are expressed in parts per million downfield from TMS in δ units. IR spectra were recorded on

FTIR RX1 Perkin-Elmer instrument. Melting points were determined with Veego melting point apparatus having stirred paraffin bath. Silica gel, mesh size 60-120 was used for column chromatography and Merck Silica gel 60 F₂₅₄ Plates used for Thin Layer Chromatography (TLC). Commercially available starting materials were used without further purification.

Representative procedure for oxidative rearrangement of acetophenone

To a stirred solution of 20 ml of methanol: TMOF (9:1), was added 0.6 gm (5 mmol) of acetophenone and 0.96 gm (5.5 mmol) of iodic acid. Stirring continued for five min. To this catalytic amount (0.05 mL) of H₂SO₄ was added and heated to 65 °C and monitored by TLC. After two hour, the reaction mixture was concentrated under reduced pressure to one half of the volume and diluted by adding water (20 mL). Reaction mass was neutralised with 10% NaHCO₃ solution and extracted with chloroform (2×20 mL). Organic layer was washed with 10% sodium bisulfite solution (2×10 mL) and dried over anhydrous sodium sulfate and concentrated to get crude product. Pure product was isolated after column chromatography (eluent ethyl acetate: hexane from petroleum ether 5:95).

Spectral data of selected compounds

Methyl phenylacetate (2a). Colourless liquid, (lit.¹³ liquid). R_f, 0.5595 (Ethyl acetate: hexane from petroleum ether 5:95). IR (neat): 1738 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 7.257 (5H, s), 3.69 (3H, s), 3.61(2H, s).

Methyl (4-methylphenyl)acetate (2b). Colourless liquid, (lit.¹³ liquid). R_f, 0.5580 (Ethyl acetate: hexane from petroleum ether 5:95). IR (neat): 1738 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 7.08 (4H, s), 3.66 (3H, s), 3.55(2H, s), 2.26(3H, s).

Methyl (4-methoxyphenyl)acetate (2c). Colourless liquid, (lit.¹³ liquid). R_f, 0.4558 (Ethyl acetate: hexane from petroleum ether 5:95). IR (neat): 1738 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 7.82-7.97 (2H, d, *J* 9 Hz), 6.80-6.95(2H, d, *J* 9 Hz), 3.86 (3H, s), 3.64(3H, s), 3.42(3H, s).

Methyl (2-chlorophenyl)acetate (2d). Yellow liquid, (lit.⁷ liquid). R_f, 0.5000 (Ethyl acetate : hexane from petroleum ether 5:95). IR (neat): 1739 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 7.05-7.46(4H, m), 3.8(2H, s), 3.68(3H, s).

Methyl (4-bromophenyl)acetate (2e). Pale yellow liquid, (lit.⁷ liquid). R_f, 0.4411 (Ethyl acetate : hexane from petroleum ether 5:95). IR (neat): 1739 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 7.22-7.61(4H, m), 3.63(3H, s), 3.55(2H, s).

Methyl (4-nitrophenyl)acetate (2f). White solid, mp 53-54 °C (lit.¹⁷ 54 °C). R_f, 0.4852 (Ethyl acetate: hexane from petroleum ether 5:95). IR (KBr): 1738, 1540, 1350 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 8.11-8.26 (2H, d, *J* 9 Hz), 7.55-7.70 (2H, d, *J* 9 Hz), 3.72 (2H, s), 3.68 (3H, s).

Methyl thiopene-2-ylacetate (2h). Yellow liquid, (lit.¹⁷ liquid). R_f, 0.5882 (Ethyl acetate : hexane from petroleum ether 5:95). IR (neat): 1738 cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 6.8-7.1(3H, m), 3.74 (2H, s), 3.68 (3H, s).

Methyl 2-phenylpropanoate (4a). Pale yellow liquid, (lit.¹³ liquid). R_f , 0.5208 (Ethyl acetate : hexane from petroleum ether 5:95). IR (neat): 1730 cm^{-1} . $^1\text{H NMR}$ (60 MHz, CDCl_3): δ 7.23 (5H, m), 3.72 (1H, q, J 6.6 Hz), 3.68 (3H, s), 2.07 (2H, d, J 6.6 Hz).

Methyl 2-(4-methylphenyl)propanoate (4b). Pale yellow liquid, (lit.¹³ liquid). R_f , 0.5310 (Ethyl acetate: hexane from petroleum ether 5:95). IR (neat): 1730, 1521, 1382 cm^{-1} . $^1\text{H NMR}$ (60 MHz, CDCl_3): δ 7.1 (4H, s), 3.79 (1H, q, J 7 Hz), 3.66 (3H, s), 2.26 (3H, s), 1.46-1.57 (3H, d, J 7 Hz)

Methyl 2-(4-isobutylphenyl)propanoate (4c). Pale yellow liquid, (lit.¹³ liquid). R_f , 0.5416 (Ethyl acetate: hexane from petroleum ether 5:95). IR (neat): 1730 cm^{-1} . $^1\text{H NMR}$ (60 MHz, CDCl_3): δ 6.91-7.21(4H, m), 3.87-4.22 (1H, q, J 7.2 Hz), 3.58 (3H, s), 2.37-2.48 (2H, d, J 6.6 Hz), 1.9 (1H, m), 1.22-1.49 (2H, t, J 7.2 Hz), 0.85-0.97 (6H, d, J 7.2 Hz).

Methyl 2-phenylbutanoate (4d). Pale yellow liquid, (lit.¹⁴ liquid). R_f , 0.5625 (Ethyl acetate: hexane from petroleum ether 5:95). IR (neat): 1730 cm^{-1} . $^1\text{H NMR}$ (60 MHz, CDCl_3): δ 7.22 (5H, s), 3.61(3H, s), 3.23-3.46 (1H, t, J 6.6 Hz), 1.73-2.26 (2H, m), 0.77-1.00 (3H, t, J 6.6 Hz).

Dimethyl 2-phenylsuccinate (4f). White solid, mp 56-57 $^\circ\text{C}$ (lit.¹⁷ 57.5-58.5 $^\circ\text{C}$). R_f , 0.5000 (Ethyl acetate: hexane from petroleum ether 5:95). IR (KBr): 1730 cm^{-1} . $^1\text{H NMR}$ (60 MHz, CDCl_3): δ 7.4 (5H, s), 4.04 (1H, dd, J 6 Hz), 3.6 (6H, s), 2.81-3.4 (2H, m).

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