Hydrogen Peroxide or Peracetic Acid Mediated Self-Titrating α-Halogenation of 1,3-Dicarbonyl Compounds

Ramulu Akula, Marc J. Galligan, Hasim Ibrahim*

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland
Fax +353(1)7161178; E-mail: hasim.ibrahim@ucd.ie
Received 18 August 2010; revised 29 October 2010

Abstract: Efficient oxidative α-halogenation of 1,3-dicarbonyl compounds has been achieved by employing a system comprising of sub-stoichiometric amounts of TiX_4 (X = Cl, Br) in conjunction with environmentally benign hydrogen peroxide (H_2O_2) or peracetic acid ($MeCO_3H$) as the oxidants. The end point of the reaction is accompanied by a sharp colour change.

Key words: halogenation, peroxides, titanium, halides, electrophilic

Electrophilic α-halogenation of 1,3-dicarbonyl compounds is usually performed by treating them with an electrophilic halogenating agent, most commonly *N*-halosuccinimide, in the presence of a base, catalyst or an activating additive.[1,2] Although very useful for small-scale applications, these procedures become less attractive on a large scale, especially when considering the waste byproducts derived from the electrophilic halogenating agent.

A conceptually different approach is the use of a halide source in combination with an oxidant to affect the in situ generation of a halonium ion (X^+) equivalent. Examples for such protocols include the $AlCl_3/Pb(OAc)_4$ and $ZnBr_2/Pb(OAc)_4$ tandems,[3] a biphasic α-bromination utilizing a $V_2O_5/H_2O_2/NH_4Br$ combination[4] and a microwave-induced α-halogenation employing Koser's reagent in conjunction with magnesium halides via the preformed α-tosyloxy compounds.[5] Drawbacks of these procedures are that in many cases the oxidants or additives are toxic, used in excess or generate waste byproducts which renders these protocols uneconomical.

Inspired by enzymatic oxidative halogenation,[6] the use of 'green' oxidants such as hydrogen peroxide has been increasing.[7] This is particularly the case in the oxidative halogenation of aromatic compounds.[7,8] However, the use of atom-economical procedures employing green oxidants in the halogenation of enolisable substrates and especially 1,3-dicarbonyls is still rare. Examples include a hydrogen peroxide mediated α-bromination with potassium bromide[9] or hydrogen bromide[10] as the halide source under strong acidic conditions, and hydrogen peroxide enhanced α-iodination with iodine in water.[11] Furthermore, in a recent study on the α-hydroxylation of β-keto esters catalysed by iron(III) chloride hexahydrate with hydrogen peroxide as the oxidant, it was observed that increasing the iron(III) chloride hexahydrate loading led to competitive α-chlorination.[12]

We reported recently on an efficient α-halogenation of 1,3-dicarbonyls using a system comprising of 0.25–0.3 equivalents of TiX_4 and (diacetoxyiodo)benzene (DIB) as a mild oxidant.[13] A drawback of this procedure is that iodobenzene is formed as a stoichiometric byproduct, which led us to investigate the possibility of employing alternative oxidants such as hydrogen peroxide or peracetic acid. This enabled us to uncover an exceedingly simple and atom-economic α-halogenation where the conversion to the product can be monitored visually.

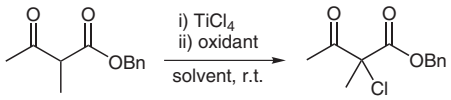
Reacting one equivalent of titanium(IV) chloride with an acetonitrile solution of our test substrate, benzyl 2-methyl-3-oxobutanoate, instantly gave a dark-red Ti(enolato) complex. Upon the complete addition of 1.1 equivalents of 30% aqueous hydrogen peroxide to this solution, an immediate colour change to yellow was observed (Table 1, entry 1). TLC analysis showed that the starting material had been consumed and subsequent crude ^1H NMR analysis confirmed complete conversion into the chlorinated product, which was isolated in 94% yield after short-pad column chromatography. No change in yield was observed when carrying out the reaction under nitrogen and in dry solvent; all subsequent reactions were conducted in untreated solvents and in air (Table 1).

A screen of solvents showed that coordinating solvents such as tetrahydrofuran and diethyl ether were suitable solvents for this reaction (entries 2 and 3), whereas toluene, dichloromethane, and cyclohexane (entries 4–6) were not as effective. An experiment with the neat reactants and hydrogen peroxide gave a poor conversion of 32% after 30 minutes. Reactions with hydrogen peroxide were biphasic in acetonitrile, consequently we decided to examine peracetic acid as an alternative to hydrogen peroxide. Conducting the reaction with peracetic acid gave comparable results to those obtained with hydrogen peroxide, moreover, the reaction mixture remained homogenous which simplified workup. We were pleased to find that lowering the $TiCl_4$/substrate ratio to 0.5 (Table 1, entry 8) and even further to 0.25 when using peracetic acid or hydrogen peroxide (entries 9 and 10) as the oxidant gave

SYNTHESIS 2011, No. 2, pp 0347–0351
Advanced online publication: 15.12.2010
DOI: 10.1055/s-0030-1258367; Art ID: T16410SS

complete conversion, which indicated that the reaction proceeded with 100% halogen incorporation.

Table 1 Reaction Parameter Optimisation Using Hydrogen Peroxide or Peracetic Acid as the Oxidants[a]



Entry	Solvent	$TiCl_4$ (equiv)	Oxidant (1.1 equiv)	Time	Conv.[b] (%)	Yield[c] (%)
1	MeCN	1.0	H_2O_2	<5 s	98	94
2	THF	1.0	H_2O_2	<5 s	98	92
3	Et_2O	1.0	H_2O_2	<5 s	98	82
4	toluene	1.0	H_2O_2	20 min	92	–[d]
5	CH_2Cl_2	1.0	H_2O_2	20 min	56	–[d]
6	C_6H_{12}	1.0	H_2O_2	15 min	63	–[d]
7	MeCN	1.0	$MeCO_3H$	<5 s	98	92
8	MeCN	0.5	$MeCO_3H$	<5 s	98	93
9	MeCN	0.25	$MeCO_3H$	<5 s	98	94
10	MeCN	0.25	H_2O_2	<5 s	98	97

[a] All reactions were performed using: substrate (1.0 mmol), specified solvent (2 mL, 0.5 M).
[b] Determined by ^1H NMR of the crude product.
[c] Yield of isolated product after short-pad column chromatography.
[d] Not determined.

With the optimized conditions from entries 9 and 10 in hand, the chlorination of a series of substrates was first attempted with hydrogen peroxide, which included three β-keto esters (Table 2, entries 1, 4 and 6) two 1,3-diketones (entries 8 and 9), two β-keto amides (entries 10 and 11), and a β-keto phosphonate (entry 12).

Table 2 α-Chlorination of 1,3-Dicarbonyl Compounds Using Hydrogen Peroxide or Peracetic Acid as the Oxidant[a]

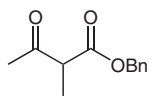
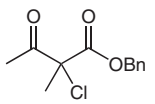
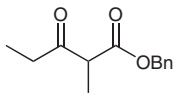
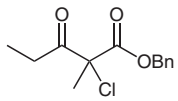
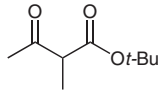
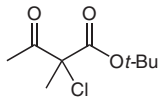
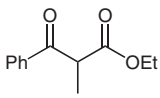
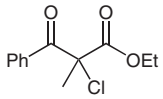
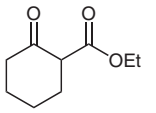
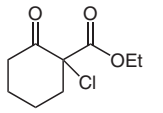
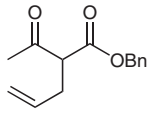
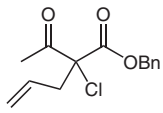
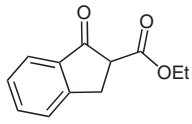
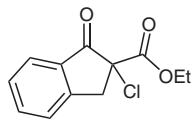
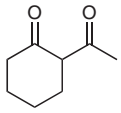
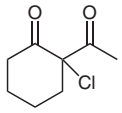
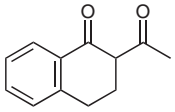
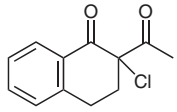
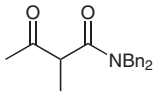
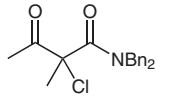
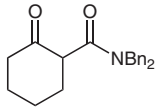
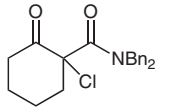
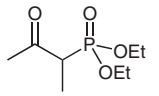
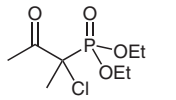
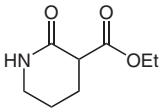
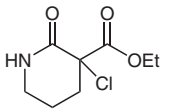
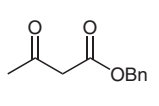
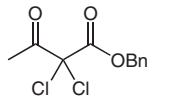
Entry	Substrate	Product	Yield[b] (%)	
			Using H_2O_2	Using $MeCO_3H$
1			96	95
2			–	89
3			–	74

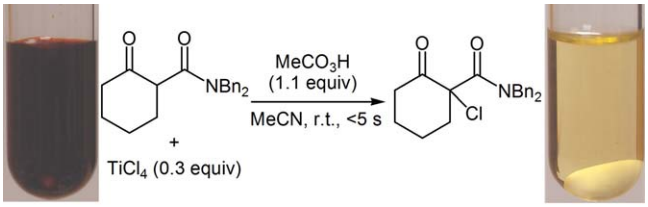
Table 2 α-Chlorination of 1,3-Dicarbonyl Compounds Using Hydrogen Peroxide or Peracetic Acid as the Oxidant[a] (continued)

Entry	Substrate	Product	Yield[b] (%)	
			Using H_2O_2	Using $MeCO_3H$
4			93	94
5			–	85
6			77[c]	60[d]
7			–	93
8			86	92
9			93	93
10			98	97
11			93	94
12			92	95
13			–	93
14[e]			–	90

[a] All reactions were performed using: substrate (1.0 mmol), $TiCl_4$ (0.3 mmol), oxidant (1.1 mmol), MeCN (2 mL, 0.5 M).
[b] Yield of isolated product after short-pad column chromatography.
[c] Reaction was performed with $TiCl_4$ (0.6 mmol) and H_2O_2 (1.1 mmol).
[d] Reaction was performed with $TiCl_4$ (1.0 mmol) and $MeCO_3H$ (1.1 mmol).
[e] Reaction was performed with $TiCl_4$ (0.6 mmol) and $MeCO_3H$ (2.2 mmol).

Conversion to the products was complete upon the addition of hydrogen peroxide, as indicated by an immediate colour change from dark red to yellow and the ^{1}H NMR spectrum of the crude material. The reaction mixture of the allyl-substituted β-keto ester (entry 6), however, remained dark red. All corresponding chlorinated products were obtained in high yields.

The reaction of 1,3-dicarbonyl compounds was next examined with peracetic acid. Again, all reactions were complete after the addition of the oxidant as indicated by a sharp colour change from dark red to yellow. The colour change of the peracetic acid reaction of Table 2, entry 11 is shown in Scheme 1.



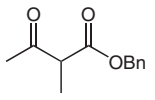
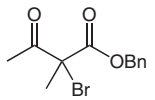
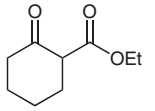
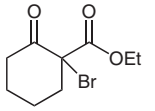
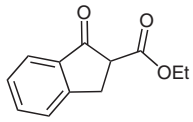
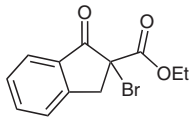
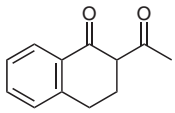
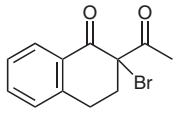
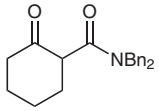
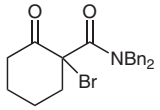
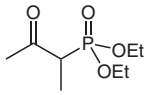
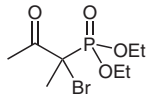
Scheme 1 Self-titrating chlorination mediated by peracetic acid

In general, reactions with peracetic acid gave consistently cleaner crude products than reactions with hydrogen peroxide as judged by ^{1}H NMR. Most substrates gave sufficiently pure crude products after aqueous workup; however, short-pad column chromatography was routinely performed to remove residual traces of titanium dioxide.

In the case of the allyl-substituted β-keto ester (Table 2, entry 6), no colour change was observed and higher amounts of titanium(IV) oxide were required to obtain a moderate yield of the product. The reaction was lower yielding, presumably due to the competing interaction of the oxidant or the in situ generated halogenating agent with the allyl group. In all other cases studied reactions were selective and no benzylic or aromatic halogenation was observed. A non-α-substituted β-keto ester (Table 2, entry 14) was efficiently dichlorinated using 0.6 mmol of titanium(IV) chloride and 2.2 mmol of peracetic acid and the product was obtained in 90% yield. Attempted monochlorination using 0.3 mmol of titanium(IV) chloride gave a 3:1 mixture of the mono- to the dichlorinated products. This ratio could be improved to 5:1 upon conducting the reaction at –30 °C as determined by ^{1}H NMR of the crude product.

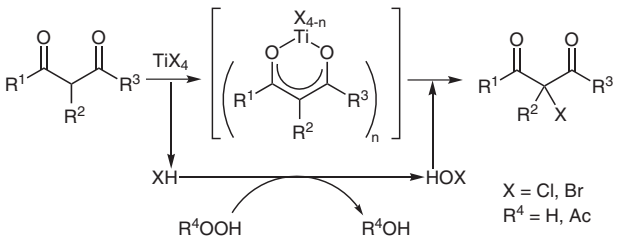
Likewise, brominations were carried out with 0.3 equivalents of titanium(IV) bromide using 1.1 equivalents of peracetic acid. All α-brominated products were obtained in high yields (Table 3). The reaction of ethyl 2-oxocyclohexanecarboxylate (Table 3, entry 2) was run on a 17.6 mmol scale (3.0 g) with 0.27 equivalents of titanium(IV) bromide in order to demonstrate that these reactions can be scaled up without problems; the corresponding α-brominated compound was isolated in 92% yield.

Table 3 α-Bromination of 1,3-Dicarbonyl Compounds Using Peracetic Acid as the Oxidant[a]

Entry	Substrate	Product	Yield[b] (%)
1			90
2[c]			92
3			95
4			85
5			96
6			95

[a] All reactions were performed using: substrate (1.0 mmol), $TiBr_4$ (0.3 mmol), $MeCO_3H$ (1.1 mmol), MeCN (2 mL, 0.5 M).
[b] Yield of isolated product after short-pad column chromatography.
[c] Reaction was performed with substrate (17.6 mmol), $TiBr_4$ (4.76 mmol), $MeCO_3H$ (19.4 mmol).

With regard to the mechanism operating in the presented oxidative halogenation, we propose that the addition of TiX_4 to an acetonitrile solution of the substrate results in the formation of a dark red dihalobis(enolato)titanium complex.[14] This complex is likely present in a mixture of several equilibrating Ti(enolato) complexes, the constitution of which is not clear at present. The subsequent addition of hydrogen peroxide or peracetic acid oxidizes the liberated HX to HOX which acts as the halogenating agent (Scheme 2).[15]



Scheme 2 Mechanistic rationale for the hydrogen peroxide or peracetic acid mediated α-halogenation using TiX_4 as the halide source

In summary, we have developed a cost-effective, scalable, and environmentally benign hydrogen peroxide or peracetic acid mediated α-halogenation of a series of 1,3-dicarbonyls, including substrates with low enol content such as

β-keto amides.[16] The reaction is rapid, gives high yields of the halogenated products, and proceeds with 100% halogen atom economy. Titanium dioxide is the only waste byproduct formed; moreover, the reaction is self-titrating and can be monitored visually. The presented oxidative halogenation leading to α-halo-1,3-dicarbonyls offers an attractive alternative to existing electrophilic procedures for this class of compounds. The utilization of this method for the α-halogenation of other enolisable substrate classes is currently underway in our laboratory and will be reported in due course.

All reagents were obtained from commercial suppliers and used without further purification. HPLC grade MeCN and ~39% $MeCO_3H$ soln in AcOH were purchased from Sigma-Aldrich and used as received. 30% H_2O_2 soln in H_2O was purchased from Fluka and used as received. β-Keto esters (Table 2, entries 1,[17] 2,[1f] 3,[16] 4,[17] 6,[18] 7[19]), β-keto amides (Table 2, entries 10, 11),[20] and diethyl 3-oxobutan-2-ylphosphonate[21] were prepared according to literature procedures. TLC was performed on Merck Aluminium sheets (silica gel 60 F_{254}). Detection was by UV and/or by colouration with ceric ammonium molybdate (CAM) or vanillin. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). NMR spectra were recorded on Varian Inova 300 MHz, Varian 400 MHz FT spectrometers at r.t. with $CDCl_3$ as the internal standard; the reference values used for $CDCl_3$ were δ = 7.26 and 77.0 for ^1H and ^{13}C NMR spectra, respectively. HRMS were measured on a Waters/Micromass GCT and Waters 2996 Photodiode Array Detector instruments. IR spectra were recorded on a Varian 3100 FT-IR spectrophotometer at r.t.

Oxidative Halogenation of 1,3-Dicarbonyl Compounds; General Procedure[22]

TiX_4 was added via a syringe ($TiCl_4$, 56.9 mg, 33 μL, 0.3 mmol) or as a solid in one portion ($TiBr_4$, 111 mg, 0.3 mmol) to a stirred soln/suspension of the substrate (1 mmol) in MeCN (2 mL), which resulted in an immediate colour change to dark red. $MeCO_3H$ (~39% soln in AcOH, 215 mg, 1.1 mmol) or H_2O_2 (30% soln in H_2O, 125 mg, 1.1 mmol) was added dropwise to the above soln at r.t. Once the addition was complete, a colour change to pale yellow was observed, which indicated the completion of the reaction. The mixture was diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by short-pad flash column chromatography.

Ethyl 2-Chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (Table 2, Entry 7)

Short-pad flash column chromatography: silica gel (pentane–Et_2O, 85:15); colourless oil; yield: 222 mg (93%).

IR (neat): 3077, 2985, 1756, 1732, 1605, 1428, 1274, 1248, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 3.55 (d, *J* = 17.8 Hz, 1 H, ArC*H*H), 4.09 (d, *J* = 17.8 Hz, 1 H, ArCH*H*), 4.21–4.32 (m, 2 H, OCH_2CH_3), 7.45–7.49 (m, 2 H, ArH), 7.65–7.75 (m, 1 H, ArH), 7.85 (d, *J* = 7.7 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 43.4, 63.4, 67.9, 125.9, 126.3, 128.5, 132.5, 136.4, 150.5, 167.1, 195.1.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}O_3Cl$: 239.0475; found: 239.0473.

Ethyl 2-Bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (Table 3, Entry 3)

Short-pad flash column chromatography (silica gel, pentane–Et_2O, 85:15); pale-yellow oil; yield: 269 mg (95%).

IR (neat): 3076, 2983, 1748, 1723, 1604, 1466, 1274, 1242, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 3.68 (d, *J* = 18.1 Hz, 1 H, ArC*H*H), 4.21 (d, *J* = 18.1 Hz, 1 H, ArCH*H*), 4.25–4.23 (m, 2 H, OCH_2CH_3), 7.42–7.51 (m, 2 H, ArH), 7.67–7.71 (m, 1 H, ArH), 7.83–7.91 (m, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 43.8, 58.4, 63.5, 125.9, 126.3, 128.5, 132.2, 136.2, 150.1, 167.0, 195.1.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}O_3Br$: 282.9970; found: 282.9979.

Benzyl 2,2-Dichloro-3-oxobutanoate (Table 2, Entry 14)[22]

$TiCl_4$ (0.066 mL, 0.6 mmol) was added via a syringe to a stirred soln of benzyl 3-oxobutanoate (192 mg, 1 mmol) in MeCN (2 mL), which resulted in an immediate colour change to dark red. $MeCO_3H$ (~39% soln in AcOH, 429 mg, 2.2 mmol) was added dropwise to the above soln at r.t. Once the addition was complete, an immediate colour change to pale yellow was observed. Work-up was as stated in the general procedure. The crude product was purified by short-pad flash column chromatography (silica gel, pentane–Et_2O 90:10) to give the title compound (235 mg, 90%) as a colourless oil.

Acknowledgment

This work was supported by Science Foundation Ireland (07/RFP/CHEF394) and UCD's School of Chemistry and Chemical Biology.

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