Oxidative Chlorination of Activated Methylene Compounds with Sodium Chloride

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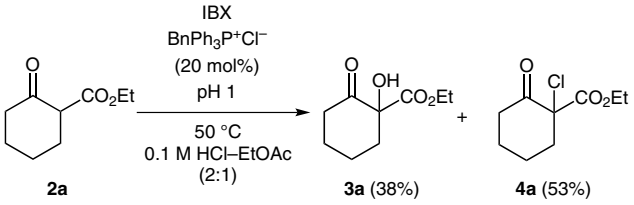
Abstract: An operationally simple protocol for the direct chlorination of 1,3-dicarbonyls (and related compounds such as α-cyano ketones) is described. The procedure relies on mild conditions using IBX–SO_3K as the stoichiometric oxidizing agent and the ubiquitous sodium chloride. The presence of a phase-transfer catalyst is supportive to obtain good yields in a THF–water mixture.

Key words: hypervalent iodine, oxidations, chlorides, carbonyls, nitriles

Enolizable 1,3-dicarbonyl compounds are ideal substrates for the electrophilic functionalization.[1] For example, the introduction of a halogen substituent at the activated α-position is easily achieved when using an electrophilic halogenating agent. In particular, the use of *N*-halosuccinimides (NXS), alone or in combination with additives, has developed as a standard strategy for the halogenation of 1,3-dicarbonyls.[2–4] Only recently, several methods were reported that produce the electrophilic halogens through in situ oxidation of halide equivalents by strong oxidants.[5,6] The arguably most effective method of this type appears to be the one reported by Maulide and co-workers in 2012 that employs a combination of commercially available sulfoxides and trimethylsilyl triflate to accomplish the formal oxidation of alkali halides and subsequent dicarbonyl halogenation.[7a] Also of relevance, Zhou and co-workers recently reported a convenient method that allows the direct chlorination of ketones by use of ammonium chloride and oxone.[7b]

Our recent works focused on the oxidative functionalization of enolizable carbonyls with hypervalent iodine compounds, specifically with iodoxybenzoic acid (IBX).[8,9] In the course of these studies, we found that, when using IBX–SO_3K (**1**) as a mild oxidant and sodium azide in aqueous DMSO, the pretty chemoselective azidation of 1,3-dicarbonyls is possible.[10,11] Given that this azidation apparently involves nothing more than combining a water-soluble IBX derivative and a sodium salt with a nucleophilic anion, we challenged whether this oxidant and simple alkali halides could actually be used to install halogens onto the 1,3-dicarbonyl skeleton. While hypervalent iodine compounds such as Koser's reagent[6b] or (diacetoxyiodo)benzene[6a,d,f] were previously used for the umpolung of halide reactivity in conjunction with, for example, $TiCl_4$ as chloride source, we now report a protocol for the chlorination of 1,3-dicarbonyls that relies on the mild oxidation power of IBX–SO_3K and the ubiquitous sodium chloride. The reaction conditions show great functional group tolerance, in particular in comparison with the previously described methods[5,6,7b] that make use of significantly harsher oxidants. Of primary importance, our combination of reagents is also capable of chlorinating α-cyano and α-nitro carbonyl substrates.

When testing the pH dependence of the IBX-mediated oxygen transfer on 1,3-dicarbonyls,[9] we set up an experiment in which β-keto ester **2a** was treated with IBX at pH 1 in a 2:1 mixture of aqueous HCl and EtOAc (Scheme 1). It was found that, in the presence of benzyltriphenylphosphonium chloride at 50 °C, the expected tertiary alcohol **3a** was formed alongside with the chlorinated product **4a**. Our following optimization studies towards the formation of tertiary chloride **4a** then revealed that IBX–SO_3K is likewise suited for the oxidation. Since IBX–SO_3K exhibits, in comparison to the IBX parent, enhanced functional group orthogonality,[9,12] it became the chosen oxidant for the further investigations summarized in Table 1. Good results with regard to the formation of chloride **4a** were obtained at 50 °C; higher and lower temperatures led to significantly reduced yield. The solvent screening indicated that EtOAc and THF are the best choices. Although both solvents showed a similar performance, we preferred the use of THF due to the fact that a homogeneous solution was formed with the chloride-containing aqueous phase. While the chloride source had little influence, the addition of a phase-transfer catalyst[13] such as benzyltriphenylammonium or methyltrioctylammonium chloride (20 mol%) was of great importance to obtain substantial conversion of the starting 1,3-dicarbonyl. Further screening experiments with respect to chloride concentrations, solvent ratios, and stoichiometry of reagents finally led to



2a **3a** (38%) **4a** (53%)

Scheme 1 Initial experiment setup

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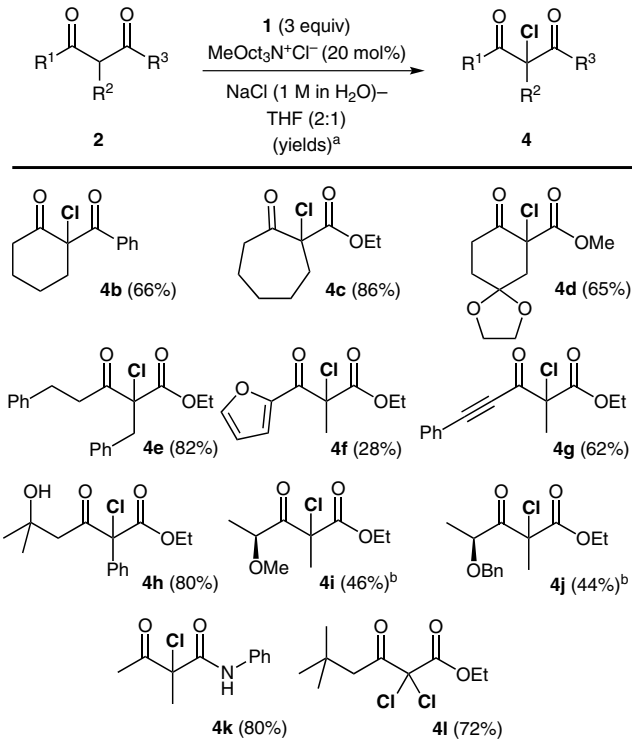
the identification of the following, easy-to-handle, reaction conditions for the oxidative chlorination of 1,3-dicarbonyl compounds with sodium chloride: substrate **2**, IBX–SO_3K (3 equiv), $MeOct_3NCl$ (0.2 equiv), 50 °C, 24 h, NaCl (1 M in H_2O)–THF (2:1). Again we would like to point out that in all our experiments IBX could be used instead of IBX–SO_3K to give nearly identical yields.

Several observations merit note: 1) In contrast to our previous disclosure on the azidation of 1,3-dicarbonyls,[10] the addition of catalytic amounts of sodium iodide was not required. 2) Under our optimized reaction conditions, the competing formation of the hydroxylated product **3a** is fully suppressed.

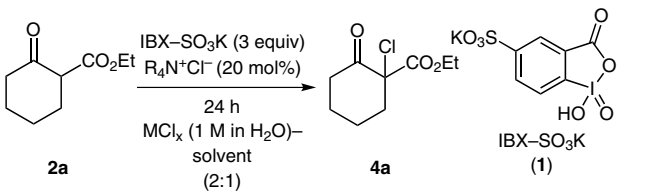
With the conditions from entry 12 (Table 1) in hand, we began to investigate the scope. As shown in Scheme 2, a great variety of 1,3-diketones and β-keto esters were smoothly chlorinated in yields ranging from moderate to high. Both cyclic and acyclic 1,3-dicarbonyl systems underwent clean chlorination with tertiary hydroxyl, acetal, amide, and alkyne functionalities being tolerated. When 1,3-dicarbonyls with no additional substituent at the 2-position were subjected to the reaction conditions, the dichlorinated product was formed.



Scheme 2 Scope of the chlorination of 1,3-dicarbonyls. Reactions were run at 50 °C. [a] Isolated yield after column chromatography. [b] Configuration of the stereogenic center was not assigned; product was obtained as a single diastereomer (dr >95:5).

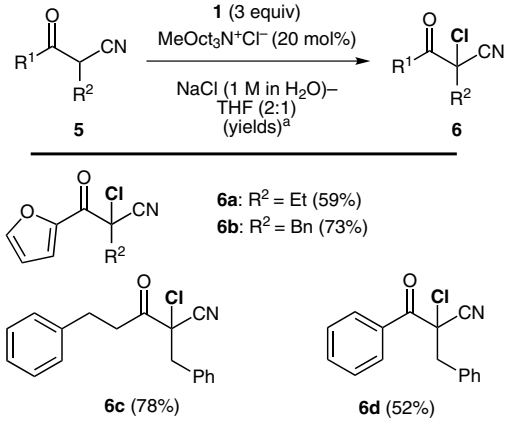
We next questioned whether our chlorination protocol might be mild enough to transfer chlorine onto α-cyano carbonyl substrates. Since we had previously observed that this class of substrates undergoes rapid dehydrogenation when treated with IBX in aqueous DMSO,[9b] our hope was that the use of IBX–SO_3K (**1**) as the oxidation agent under phase-transfer conditions might open the chlorination pathway while circumventing the dehydrogenation pathway. To our great delight, the chlorination of α-cyano carbonyls was indeed possible when employing IBX–SO_3K and 20 mol% of $MeOct_3NCl$ in a mixture of aqueous NaCl and THF. Various acyclic nitriles **5** were successfully chlorinated to result in the formation of the corresponding chlorides **6** in acceptable yields (Scheme 3).

Table 1 Optimization Studies for the Conversion **2a** → **4a**[a]



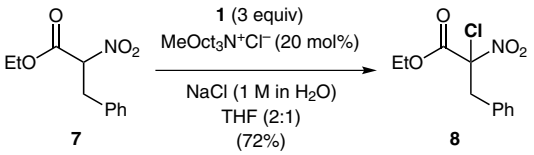
Entry	$R_4N^+Cl^-$	(°C)	Solvent	MCl_x[b]	Yield (%)[c]
1	$BnPh_3NCl$	23	THF	NaCl	no conv.
2	$BnPh_3NCl$	50	THF	NaCl	48
3	$BnPh_3NCl$	80	THF	NaCl	7
4	$BnPh_3NCl$	50	EtOAc	KCl	44
5	$BnPh_3NCl$	50	Et_2O	KCl	19
6	$BnPh_3NCl$	50	CH_2Cl_2	KCl	27
7	$BnPh_3NCl$	50	DMF	KCl	21
8	$BnPh_3NCl$	50	THF	NH_4Cl	46
9	$BnPh_3NCl$	50	THF	CuCl	43
10	$BnPh_3NCl$	50	THF	$SrCl_2$	32
11	$BnPh_3NCl$	50	THF	KCl	45
12	**$MeOct_3NCl$**	**50**	**THF**	**NaCl**	**57**
13[d]	–	50	THF	NaCl	27

[a] Conditions: **2a**, **1** (3 equiv), R_4NCl (0.2 equiv), 24 h, MCl_x (1 M in H_2O)–solvent (2:1).
[b] MCl_x was added as a 0.1 M solution in H_2O.
[c] Isolated yield after column chromatography.
[d] No phase-transfer catalyst was added.



Scheme 3 Chlorination of α-cyano carbonyls. Reactions were run at 50 °C. [a] Isolated yield after column chromatography.

Finally, it was briefly studied how α-nitro carbonyls behave under the chlorination conditions. The mild chlorination of those substrates might attract some interest, since they can be considered as α-amino acid precursors.[14] As exemplary shown for the conversion of **7** into **8**, chlorine can be transferred onto the α-nitro carbonyl skeleton under the reaction conditions in good yields (Scheme 4). However, further studies on this particular substrate class are recommended.



Scheme 4 Chlorination of α-nitro carbonyl compound **7**. Reaction was run at 50 °C.

In summary, a novel and operationally simple method for the direct chlorination of several types of activated methylene compounds (e.g., 1,3-dicarbonyls, β-keto esters, α-cyano carbonyls and α-nitro carbonyls) has been reported.[15] The method uses, under metal-free conditions, sodium chloride as universally available chlorine source and relies on the oxidation power of IBX–SO_3K that was found to be mild enough to tolerate a plethora of functional groups.[10] Further oxidative functionalization procedures making use of IBX–SO_3K will be reported in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of the ^{1}H NMR and ^{13}C NMR spectra of compounds **4a–i**, **6a–d**, and **8**.

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(15) **General Procedure**: The carbonyl substrate (1 equiv) was dissolved in a mixture of THF and aq 1 M NaCl solution (1:2, 0.3 M regarding substrate). Then, $MeOc_3NCl$ (20 mol%) and IBX–SO_3K (3 equiv) were added and the suspension was heated to 50 °C for 24 h. After the suspension was cooled to r.t., the organic phase and the aqueous phase were separated. The aqueous phase was extracted with Et_2O (3 ×). The combined organic phase was washed with aq sat. $NaHCO_3$ solution and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography. **Ethyl 1-Chloro-2-oxocyclohexanecarboxylate** (ref. 6a): Following the general procedure, **4a** was obtained from **2a** (25.0 mg, 147 μmol) in 57% yield (17.2 mg, 84.0 μmol) as a colorless oil (flash chromatography with cyclohexane–Et_2O, 95:5); R_f 0.35 (cyclohexane–Et_2O, 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.29 (qd, *J* = 7.1, 0.6 Hz, 2 H), 2.74–2.89 (m, 2 H), 2.39–2.46 (m, 1 H), 2.09–2.14 (m, 1 H), 1.81–2.00 (m, 3 H), 1.68–1.80 (m, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.8, 167.4, 73.6, 63.0, 39.8, 39.0, 26.8, 22.3, 14.0. HRMS (ESI): *m/z* [M + Na^+] calcd for $C_9H_{13}ClNaO_3^+$: 227.0445; found: 227.0451.

