Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201301012

The α-Chlorination of Aryl Methyl Ketones under Aerobic Oxidative Conditions

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Received: November 14, 2013; Revised: January 9, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201301012.

Abstract: The novel reaction system air/ammonium nitrate/iodine/hydrochloric acid [air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl] is introduced as a simple, safe, cheap, efficient and regioselective mediator for the α-chlorination of aryl, heteroaryl and alkyl methyl ketones under aerobic oxidative conditions. The inventive use of a catalytic amount of iodine enabled the moderate to quantitative, regioselective chlorination of a comprehensive scope of different methyl ketone derivatives including those bearing oxidizable heteroatom (S, N) substituents, some of which possess declared potential biological and pharmaceutical activity. Air oxygen under a slight overpressure plays the role of the terminal oxidant catalytically activated by redox cycles of nitrogen oxides released from the catalytic amount of ammonium nitrate (NH_4NO_3) under acidic conditions of hydrochloric acid (HCl) and co-catalyzed by elemental iodine (I_2), which was found to be essential for the high efficiency of the reaction system.

Keywords: air; ammonium nitrate; aryl methyl ketones; chlorination; iodine; nitrogen oxides

Introduction

Organic molecules containing a halogen atom are highly versatile synthetic intermediates and building blocks that are extensively employed in cross-coupling reactions, in nucleophilic substitutions, or utilized as precursors to organometallic reagents. Due to their useful properties, bromo-, chloro- and fluoroarenes are widely used as building blocks of fine chemicals, pharmaceuticals and agrochemicals, and are routinely elaborated in the synthesis of natural products and materials.[1] Moreover, iodinated compounds are widely used in medicinal diagnostics or as radioactively labelled markers.[2] Given the worldwide demand for these compounds there is an ever increasing need to synthesize them under environmentally more acceptable "green" conditions while at the same time achieving atom economy, selectivity and high yields.

α-Halocarbonyl derivatives are an important class of organic compounds and have always been receiving much attention due to their versatile building utilities in combinatorial synthesis. Their high reactivity makes them prone to react with a large number of nucleophiles producing numerous functionalized carbo- and heterocyclic compounds used in the design of novel, highly effective pharmaceuticals with a broad spectrum of bioresponses.[1,3] These complex bioactive molecules – pharmaceuticals – could significantly alter metabolic activities, have significant blood pressure effects or the ability to increase the bioavailability absorption factor of medications into the blood circulation system.[1b,4] Moreover, thienyl and phenyl α-halomethyl ketones, particularly chloro analogues, were found to be new, efficient non-ATP competitive inhibitors of glycogen synthase kinase 3β (GSK-3β), which is causing neurodegeneration in general and Alzheimer's disease in particular.[4a,b]

Over the last years and especially in the past two decades numerous methods and procedures were invented for the preparation of this highly important class of organic compounds. Traditionally, α-chloromethyl ketones have been prepared by chlorination of methyl ketones with molecular chlorine (Cl_2),[1a] or by using various inorganic or organic chlorinating agents such as metal halides,[5] *N*-chlorosuccinimide (NCS)[6] and related or similar reagents.[7] The above-mentioned methods exhibit quite a few drawbacks such as indirect chlorination over several steps, with low halogen atom economy, problems of over-chlorination,[7d] nuclear chlorination of activated aromatic

rings,[7e,8] non-reactivity with deactivated aromatic rings[8] and incompatibility with acid-sensitive or easily oxidizable groups.[7e] Microwaves, as ever popular in academic research, offer another interesting mode of activation for the synthesis of α-chloromethyl ketones. Carbonyl compounds are treated with [hydroxy(tosyloxy)iodo]benzene followed by magnesium halides under solvent-free microwave irradiation conditions.[9]

On the other hand in nature enzymatically supported oxidative halogenation processes, are co-catalyzed by high valence metal species and use oxygen or hydrogen peroxide as terminal oxidants. In these processes natural halo organic compounds, including α-halo carbonyl substituted molecules, are formed. In parallel, in classical organic synthesis, halo organic compounds should be produced by oxidative halogenation methodology using environmentally friendly oxidants leading to a minimum amount of waste after catalytic rather than non-catalytic processes. From the viewpoint of cost efficiency, atom economy and overall green and sustainable development, aqueous hydrogen peroxide and especially atmospheric molecular oxygen represent the most acceptable and superior choices in these tasks.[10] Hydrogen peroxide has some drawbacks such as a demand for certain safety precautions, when used in higher amounts or higher than 30% aqueous solutions since higher temperatures and/or impurities and traces of metallic catalysts can induce some undesirable decomposition to H_2O and O_2 during reactions.[11] In this manner efficient oxidative halogenating methods for α-chlorination were invented, exploiting hydrogen peroxide or its varieties such as urea-hydrogen peroxide[12] or commercially available Oxone®[13] ($KHSO_5$ – potassium hydrogen persulfate) as activator in combination with different halogen atom sources. Usually ammonium chloride, hydrochloric acid or aluminium chloride hexahydrate were used as a cheap source of halogen atom for α-chlorination of methyl ketones.[12–14] On the other hand molecular oxygen, especially when used in its natural diluted source as air, is the most abundant terminal oxidant and atom economical oxidant known today, giving great benefits from the viewpoints of cost efficiency and green chemistry. Transformations of organic substrates using molecular oxygen usually need transition metal catalysis to promote the reaction rate and selectivity to partial oxidation products. For this purpose organometallic complexes[15] or solid supported species[16] are often used, while nitrites ($NaNO_2$),[17] nitrates ($MgNO_3$,[18] NH_4NO_3[19]) or nitric(V) acid (HNO_3)[20] as transition metal-free catalysts for aerobic transformations of organic compounds were recently used.[17a,21] Nitric oxide donors play also an important role as reactive compounds useful in several chemical and biological applications.[21a,22] Over the last decade many articles have reported on efficient and selective iodination[10,23] and bromination[10,17e,24] of aryl methyl ketones at the alpha position and just recently the iodination of arenes[25] under aerobic oxidative conditions exploiting the NO/NO_2 oxidative catalytic redox cycle, while chlorination under the same conditions seems to be much less or not efficient. We can assume that the insufficient oxidative properties of molecular oxygen in combination with nitrogen oxides catalysts (NO/NO_2) and high redox potentials of chloride ions can be the reason for the insufficient generation of a critical amount of electrophilic chloro species for positive overall conversion.[26] Despite this reason a few articles do successfully report about efficient oxidative α-chlorination in different ionic liquids containing nitrate anion,[27] but to the best of our knowledge no data are available for α-chlorination under clear non-enzymatic aerobic oxidative conditions of organic compounds.

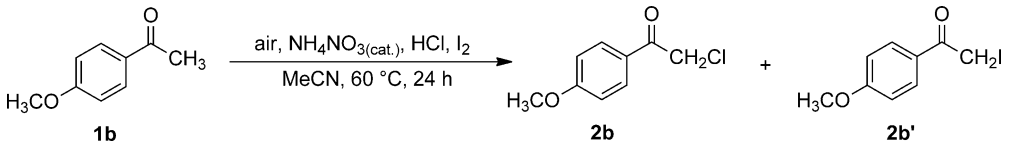
As a part of our continued interest in developing "greener" methods for halogenation[23,24,27a] we now report the discovery and the development of a system for side chain chlorination of methyl ketones under aerobic oxidative conditions using catalytic amounts of iodine (I_2) and ammonium nitrate (NH_4NO_3) as a cheap and readily accessible source of nitrogen oxides (NO/NO_2) under acidic conditions.

Results and Discussion

Primarily, the novel multi-component and cost-beneficial reaction system air/$NH_4NO_{3(cat.)}$/$HCl_{(cat.)}$/I_2 was tested on 1-(4-methoxyphenyl)ethanone **1b** used as a model compound. The reaction result of these tests are summarized in Table 1. In our initial mmol-scale experiment, the efficiency of the reaction system for iodination of **1b** was tested. To a solution of **1b** in acetonitrile, 20 mol% of NH_4NO_3, 50 mol% of I_2, and 20 mol% of HCl (aqueous 37% solution) were consecutively added in five minute intervals (Table 1, entry 1). The reaction vessel was closed with an air balloon (1 L) and the reaction mixture was stirred for 24 h at 60 °C. The ^{1}H NMR analysis of the isolated crude reaction mixture revealed regioselective side chain halogenation, 2-iodo-1-(4-methoxyphenyl)-ethanone **2b′** (21%) being the main product and, to our surprise, also 2-chloro-1-(4-methoxyphenyl)ethanone **2b** (13%) was formed as the side product, while no ring halogenated products were detected, but a low conversion of starting material observed. After that the α-chlorination reaction was investigated, in order to increase the efficiency and selectivity of this reaction.

First we performed a control experiment if a catalytic amount of I_2 (5 mol%) and stoichiometric amount of HCl (aqueous 37% solution, 1.1 mmol) with the

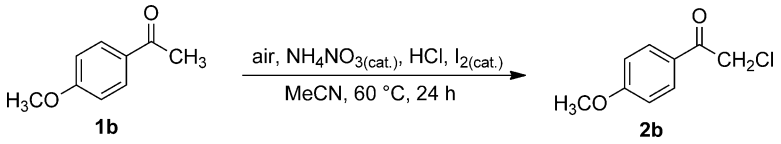
Table 1. Aerobic oxidative α-halogenation of 1-(4-methoxyphenyl)ethanone **1b** using the air/$NH_4NO_{3(cat.)}$/I_2/HCl reaction system.[a]



Entry	I_2 (mol%)	HCl (mmol)	MeCN (mL)	Relative distribution [%][b]		
				1b	**2b**	**2b′**
1	50	0.2	5	66	13	21
2	5	1.1	5	32	68	–
3	5	1.5	5	18	82	–
4	5	1.5	2	5	95	–

[a] *Reaction conditions:* 1-(4-methoxyphenyl)ethanone **1b** (1 mmol), NH_4NO_3 (20 mol%), I_2 (5 or 50 mol%), HCl (aqueous 37% solution), MeCN, 60 °C, 24 h, air balloon.
[b] Conversion of **1b** to **2b** and **2b′** determined from ^{1}H NMR spectra of the crude reaction mixtures.

Table 2. The role of each component in the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system.[a]



Entry	Reaction system variants: air or argon/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl	Conversion **1b**→**2b** [%][b]
1	argon/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl	18
2	air/$I_{2(cat.)}$/HCl	3
3	air/$NH_4NO_{3(cat.)}$/HCl	4
4	air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/H_2SO_4	0

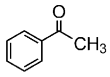
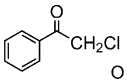
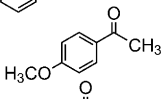
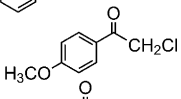
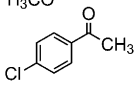
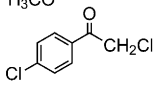
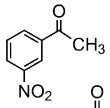
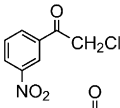
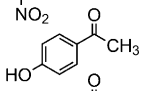
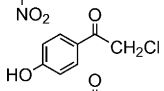
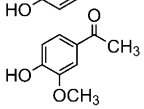
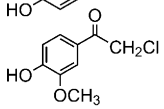
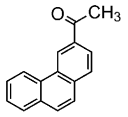
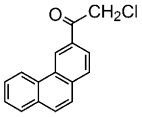
[a] *Reaction conditions:* **1b** (1 mmol), NH_4NO_3 (20 mol%), I_2 (5 mol%), HCl (aqueous 37% solution, 1.5 mmol), 2 mL MeCN, 60 °C, 24 h, air or argon balloon.
[b] Conversion of **1b** to **2b** determined from the ^{1}H NMR spectra of crude reaction mixtures.

same substrate **1b** would give the desired 2-chloro-1-(4-methoxyphenyl)ethanone **2b** in a reaction with 20 mol% NH_4NO_3 in 5 mL of acetonitrile (Table 1, entry 2). Air was again used as terminal oxidant and only **2b** was isolated with 100% selectivity in high yield. After this success we aimed to increase the efficiency of reaction to a quantitative level. By increasing the amounts of added acid HCl to 1.5 mmol (Table 1, entry 3) the conversion of starting material to **2b** was selectively increased, while almost quantitative formation of **2b** was achieved by decreasing the solvent volume to 2 mL (Table 1, entry 4).

The use of organic solvents in chemical processes is one of the most concerning issues from the green chemistry point of view.[28] Solvent losses are a major contributor to the high E (environmental) factor. The most desirable are solvent-free transformations or those performed in environmentally friendly alternatives such as water, lower alcohols, esters, some ethers or use of green renewable media such as ionic liquids. Several "greener" solvents and alternatives to acetonitrile were thus checked in order to improve a green profile of the investigated reaction and results are given in the Supporting Information (Table S1). Unfortunately chlorination under aerobic conditions with our reaction system under solvent-free reaction conditions as well as in H_2O failed, while the reaction barely took place and low conversion of substrate was observed in MeOH, 2-methyltetrahydrofuran, cyclopentyl methyl ether, Solkane® (1,1,1,3,3 pentafluorobutane, HFC 365), and an acetonitrile/water (4:1) mixture. Acetonitrile thus seems to be the best choice so far.

It is worth mentioning in order to illustrate the essential role of each component in the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system, i.e., air oxygen and HCl as reagent, and NH_4NO_3 and I_2 as catalysts, blank experiments were performed and are gathered in Table 2. Conversion up to 18% in an anaerobic experiment (Table 2, entry 1) is probably due to the presence of catalytic amounts of NO_2 and the absence of a redox cycle (re-oxidation of NO to NO_2). All

Table 3. Chlorination of aryl methyl ketones under aerobic oxidative conditions using the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system.[a]

Entry	Substrate		Product		Time [h]	Conversion [%][b]	Yield of **2** [%][c]
1		**1a**		**2a**	24	84	66
2		**1b**		**2b**	25	96	82
3		**1c**		**2c**	25	86	75
4		**1d**		**2d**	20	90	80
5		**1e**		**2e**	22	78	64
6		**1f**		**2f**	23	80	69
7		**1g**		**2g**	22	91	85

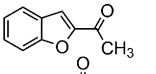
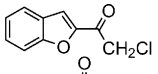
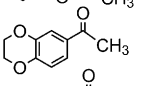
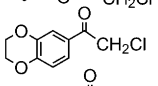
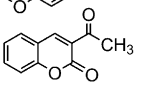
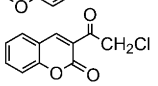
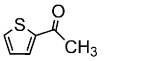
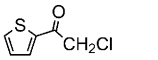
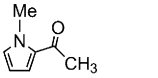
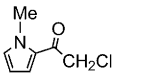
[a] *Reaction conditions:* aryl methyl ketone (1 mmol), NH_4NO_3 (20–25 mol%), HCl (aqueous 37% solution, 1.5 mmol), 2 mL MeCN, 60 °C, 24 h, air balloon.
[b] Conversion determined from the ^{1}H NMR spectra of crude reaction mixtures.
[c] Yield determined after purification by column chromatography (SiO_2; dichloromethane/petroleum ether) or by crystallization in hexane.

other experiments (entries 2, 3, 4, Table 2) gave negative results and 1-(4-methoxyphenyl)ethanone **1b** could not be successfully converted to 2-chloro-1-(4-methoxyphenyl)ethanone **2b** if any one of the components is absent.

Encouraged by these preliminary results, we applied the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system under the described reaction conditions for the α-chlorination of a series of aryl methyl ketones. As it can be seen from Table 3, a variety of structure types of aryl methyl ketones could be efficiently and selectively converted into their corresponding α-chloroaryl methyl ketones in relatively high isolated yields after 20–25 h. In general we found that electron-withdrawing as well as electron-donating substituents on the phenyl ring supported the transformation of tested compounds **1a–f** to their chloromethyl derivatives **2a–f**. The compound bearing a nitro substituent (**1d**, entry 4) was found to be slightly more reactive. Substrates bearing a phenol functionality (**1e** and **1f**, entries 5 and 6) as well as 1-(3,5-dihydroxyphenyl)ethanone were also efficiently α-chlorinated without any inconveniences, but the purification of the final product in the latter case caused some troubles. A phenanthrene derivative, 1-(phenanthren-3-yl)ethanone **1g** (entry 7) was readily converted to 2-chloro-1-(phenanthren-3-yl)ethanone **2g**. What is more, the methodology used enabled high chemoselectivity since no α-iodo aryl methyl ketone derivatives were detected.

The presence of functional groups bearing oxidizable or acid-sensitive heteroatoms such as sulfur or nitrogen in the target molecules could represent additional reaction centres for side reactions. We thus examined the efficiency and selectivity of the chlorination of some interesting heteroaryl methyl ketones in order to make the methodology more general. The results are collected in Table 4. Oxygen-containing heterocyclic methyl ketone derivatives such as 1-(benzofuran-2-yl)ethanone **3a** (entry 1) and 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanone **3b** (entry 2) were efficiently converted to their chloromethyl derivatives **4a** and **4b**, respectively. Acetyl-substituted coumarins as target molecules often exhibit potential bioactivity of pharmaceutical interest,[29] 3-acetyl-2*H*-chromen-2-one **3c** was successfully and selectively chlorinated and 3-(2-chloroacetyl)-2*H*-chromen-2-one **4c** was isolated (entry 3) in high yield. Moreover, we managed to chlorinate 1-(thiophen-2-yl)ethanone **3d** to the chloromethyl derivative **4d** which was declared to possess non-ATP competitive inhibitory activity on enzyme GSK-3β,[4a,b] and 1-(1-methyl-1*H*-pyrrol-2-yl)ethanone **3e** (entry 5) was chlorinated to 2-chloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone **4e** although in moderate yield.

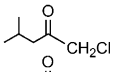
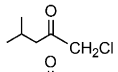
Table 4. Chlorination of heteroaryl methyl ketones under aerobic oxidative conditions using the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system.[a]

Entry	Substrate		Product		Time [h]	Conversion [%][b]	Yield [%][c]
1		**3a**		**3b**	24	83	75
2		**3b**		**4b**	22	85	79
3		**3c**		**4c**	21	98	90
4		**3d**		**4d**	24	69	61
5		**3e**		**4e**	25	56	45

[a] *Reaction conditions:* aryl methyl ketone (1 mmol), NH_4NO_3 (20–25 mol%), HCl (aqueous 37% solution, 1.5 mmol), 2 mL MeCN, 60 °C, 24 h, air balloon.
[b] Conversion determined from the ^{1}H NMR spectra of crude reaction mixtures.
[c] Yield determined after purification by column chromatography (SiO_2; dichloromethane/petroleum ether) or by crystallization.

Furthermore, limitations of the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system such as versatility, efficiency and selectivity for chlorination on branched dialkyl ketones at the alpha position were tested. The results are presented in Table 5. 4-Methylpentan-2-one **5a** (entry 1) was consumed in 80% and selectively chlorinated only on the alpha methyl position as determined from the crude reaction mixture. No other halogenated product was detected. Propiophenone **5b** (entry 2), as representative of more branched alkyl substrates, was chlorinated with decreased efficiency exclusively on the alpha position but a consumption of starting material not higher than 42% was achieved, while chlorination of its cyclic analogue 3,4-dihydronaphthalen-1(2*H*)-one (**5c**, entry 3) gave no positive result.

Table 5. Regioselectivity and limitations of the use of the air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl reaction system for the chlorination of different dialkyl or aryl alkyl ketones.

Entry	Substrate		Product		Conversion [%][b]
1		**5a**		**6a**	80
2		**5b**		**6b**	42
3		**5c**		**6c**	0
4		**5d**		**6d**	67(60)

[a] *Reaction conditions:* substrate (1 mmol), NH_4NO_3 (20–25 mol%), HCl (aqueous 37% solution, 1.5 mmol), 2 mL MeCN, 60 °C, 24 h, air balloon.
[b] Conversion determined from the ^{1}H NMR spectra of crude reaction mixtures. Value in bracket refers to pure product obtained after column chromatography.

We could only speculate that a larger steric hindrance at the alpha position to the carbonyl could be the cause of the lower or even no conversion rates of substrates **5b** and **5c** (Table 5, entry 2 and 3).

Furthermore, a representative of non-aryl substrates, 1-acetyladamantane **5d**, was chlorinated with the reaction system under aerobic conditions yielding selectively 1-chloroacetyladamantane **6d** in reasonable yield. It is a well-known that S_N2 substitution reaction rates are greatly increased and favored on primary methyl substrates at a position alpha to the carbonyl moiety when halide nucleophiles are involved. Further branching at the alpha position decreases the rate. Tertiary systems seldom react by the S_N2 type of reaction.[30]

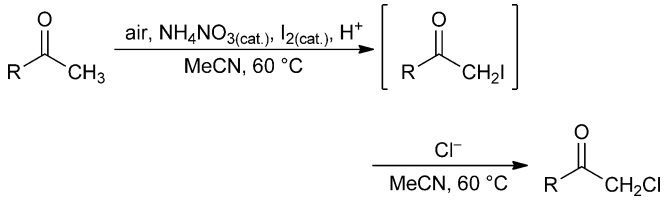
We also checked the practical applicability of our new procedure for possible use on a large scale. To demonstrate the practicality of scaling up the procedure, we treated 3 g (20 mmol) of 1-(4-methoxyphenyl)ethanone **1b** in MeCN (50 mL) solution with 25 mol% NH_4NO_3, 5 mol% I_2 and HCl (aqueous 37% solution, 30 mmol, 2.5 mL) in a flask (100 mL) equipped with condenser with attached balloon filled with air at 60 °C. After completion of the reaction, a white solid was filtered off and identified as ammonium chloride (NH_4Cl), solvent was distilled off under reduced pressure, the crude reaction mixture was extracted with ethyl acetate (3 × 10 mL) and analyzed by ^{1}H NMR spectroscopy. To examine the efficiency of reaction system under ambient pressure, exactly the

same reaction procedure was performed using a condenser open to the air. In the case of a closed system (balloon technique) 68% conversion was achieved, while in the case of the open air system quantitative and selective conversion to 2-chloro-1-(4-methoxyphenyl)ethanone **2b**, without the need for further purification of final product was achieved.

Mechanistic Discussion

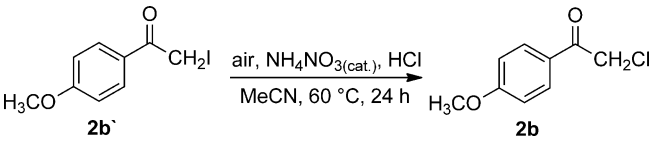
Oxidative iodination and bromination of organic compounds under aerobic oxidative conditions catalyzed by nitric oxides (NO/NO_2) with accompanying mechanistic elucidation, declared as an electrophilic process, have already been elaborated several times.[17e,23] The corresponding chlorination under the same conditions was found to be unsuccessful and attributed to the too high redox potential of chloride ions.[26] It has been assumed that the oxidative properties of molecular oxygen in combination with nitrogen oxides catalysts (NO/NO_2) are insufficient in the generation of a critical amount of electrophilic chloro species for the efficient chloro derivatization of organic target molecules through an electrophilic reaction process. As evident from Table 2 (entry 3) also our oxidative cocktail is not strong enough to produce electrophilic chlorine species from chloride anions, although we have demonstrated recently that, by enrichment with TEMPO co-catalyst, it could be used for the efficient aerobic oxidation of alcohols to aldehydes or ketones.[19] On the other hand the reaction system air/$NH_4NO_{3(cat.)}$/HCl seemed to be strong enough to oxidize iodide (see Table 1, entry 1) and thus enabling aerobic oxidative iodination of organic compounds, which will be elaborated in a forthcoming paper. On this basis we assumed the most probable reaction pathway resulting in the formation of chloromethyl aryl ketones using the reaction system air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl as aerobic oxidative iodination in the first and the a halogen exchange process in the second step of the reaction (Scheme 1).

From theory it is well known that the usual order of halide nucleophilicity in aprotic polar solvents decreases in the line: $Cl^- > Br^- > I^-$,[30] which makes S_N2 displacement of iodine from the iodomethyl moiety



Scheme 1. Chlorination of aryl and heteroaryl methyl ketones under aerobic oxidative conditions.

Table 6. The influence of air and NH_4NO_3 on the efficiency of S_N2 nucleophilic substitutions.[a]



2b` **2b**

Entry	Reaction system variants: air or argon/$NH_4NO_{3(cat.)}$/HCl	Conversion **2b′**→**2b** [%][b]
1	air/$NH_4NO_{3(cat.)}$/HCl	100
2	air/HCl	67
3	argon/$NH_4NO_{3(cat.)}$/HCl	98

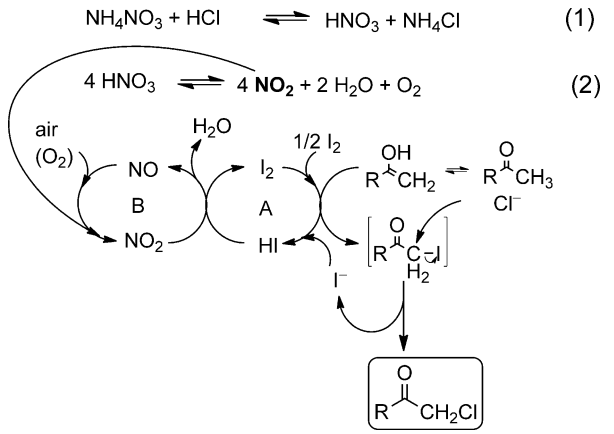
[a] *Reaction conditions:* **2b′** (1 mmol), NH_4NO_3 (20 mol%), HCl (aqueous 37% solution, 1.5 mmol), 2 mL MeCN, 60 °C, 24 h, air or argon balloon.

[b] Conversion of **2b′** to **2b** determined from the ^{1}H NMR spectra of crude reaction mixtures.

with chlorine thus forming chloromethyl derivative very reasonable. In order to confirm the S_N2 mechanism, a series of experiments was performed (Table 6). Firstly, pure 2-iodo-1-(4-methoxyphenyl)-ethanone **2b′** was reacted in MeCN with the air/$NH_4NO_{3(cat.)}$/HCl reaction system and 2-chloro-1-(4-methoxyphenyl)ethanone **2b** was readily obtained in 100% conversion (entry 1). Furthermore, the efficiency of the reaction system and role of each member in it was tested. Again, model compound **2b′** was used and reacted with the air/HCl reaction system, using no catalyst NH_4NO_3 this time. At the end 67% conversion of **2b** was achieved (entry 2). When using the argon/$NH_4NO_{3(cat.)}$/HCl reaction system, quantitative conversion (98%) was reached and pure 2-chloro-1-(4-methoxyphenyl)ethanone **2b** was obtained (entry 3). From the experiments performed it is evident that the presence of catalyst NH_4NO_3 and nitrogen oxides is essential for quantitative nucleophilic S_N2 substitution giving quantitative yields. We assume that role of nitrogen oxides (NO/NO_2) in particular in S_N2 substitution is the re-oxidation of released iodide (I^-) to iodine (I_2) thus consequently moving the halogen-exchange equilibrium more in the direction of formation of chlorinated product.

As the chlorofunctionalization of only methyl groups occurred efficiently (see Table 5), the halogen exchange process seems even more probable, since S_N2 displacements are favored on less hindered carbon atoms.

The essential role of each component of the system could be illustrated by Scheme 2 following the catalytic cycles already proposed to explain reaction pathways during air oxygen oxidative iodination and bromination of organic compounds catalyzed by nitrites.[17a,e,23a] In cycle A iodination of the enol form of ketone with I_2 at the alpha position to the carbonyl



Scheme 2. Plausible catalytic mechanism for the α-chlorination of aryl and alkyl methyl ketones.

occurs and I_2 is reduced to HI, while the halogen exchange process, thus forming chloromethyl derivative and releasing I^-, is a consecutive process. The re-oxidation of iodide to I_2 by NO_2 is illustrated as cycle B, which is the key for the catalytic amount of iodine in the reaction system. NO_2 is reduced to NO when it completes the oxidation of iodide while the oxidation of NO to NO_2 is a process accomplished with air oxygen. Acidic conditions are essential and have two main roles: the first role is to hydrolyze ammonium nitrate to HNO_3 [Eq. (1)] which is in thermally accelerated decomposing equilibrium with NO_2 [Eq. (2)] and the second is tuning the reactivity by increasing enolization of the ketone.

Conclusions

We have discovered and successfully developed a four-component reaction system of air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl for the efficient and selective chlorination of aryl and alkyl methyl ketones at the alpha position to the carbonyl moiety under mild conditions. The inventive use of a catalytic amount of iodine enabled the moderate to quantitative and regioselective chlorination of a comprehensive range of different methyl ketone derivatives including those with functional groups bearing oxidizable heteroatoms (S, N). To the best of our knowledge, the developed reaction system is a novel one used for the chlorination of organic compounds. Each member of the reaction system has an essential role in it. A plausible mechanistic interpretation of the reaction pathway as the sequence of aerobic oxidative iodination, followed by halogen exchange process was proposed. We believe that our invention could open new perspectives and improvements towards more economical, mild, simple and environmental friendly methodologies for selective halogenation of organic compounds.

Experimental Section

General Chemical Reagents and Inventory

All chemicals used in this study were of analytical grade, commercially available and used without further purification unless otherwise noted. Reactions were carried out in 10-mL glass flasks. Balloons (1-L) with 10 mil wall thickness were purchased from Sigma Aldrich and used as the air reservoir. Reactions were monitored with thin layer chromatography on TLC silica gel 60 F_{254} aluminium sheets (20 × 20 cm). Column chromatography (CC) and flash chromatography (FC) were performed using silica gel 60 (particle size: 0.063–0.200 mm) and preparative thin layer chromatography (preparative TLC) was done using PLC silica gel 60 F_{254}, 2 mm plates.

General Measurements

Conversions and yields were determined by NMR spectroscopy. NMR spectra were recorded on a Varian INOVA 300 NMR instrument (^{1}H: 303.0 MHz, ^{13}C: 76.2 MHz) using $CDCl_3$ as the solvent with $SiMe_4$ (TMS) as an internal reference. Mass spectra were measured with a high resolution mass spectrometer Q-TOF Premier using the ESI technique. Elemental analyses were performed on a Perkin–Elmer 2400-Series II apparatus. Melting points were determined with a Büchi 535 instrument.

Chlorination of Aryl Methyl Ketones under Aerobic Oxidative Conditions; General Procedure

A 10-mL glass flask equipped with magnetic stirring bar was charged with methyl or ethyl ketone (1 mmol) and acetonitrile (2 mL). To the thermostatted solution NH_4NO_3 (20–25 mol%) and I_2 (5 mol%) were added, followed after 10 min by the addition of hydrochloric acid (aqueous 37% solution, 1.5 mmol). The flask was further equipped with balloon filled with air (1-L) and magnetically stirred at 60 °C. The reaction system cyclically changed the colour from brown-red to yellow and back. The consumption of the starting material was monitored by TLC. After completion of the reaction, the reaction mixture was cooled down to room temperature and diluted with dichloromethane (10 mL). Insoluble material identified as ammonium chloride was filtered off, the filtrate washed with aqueous 10% solutions of $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) and the organic phase dried over anhydrous Na_2SO_4. Organic solvent was distilled off under reduced pressure and the crude product obtained was analyzed by ^{1}H NMR. Finally the crude product was purified using column chromatography (SiO_2, hexane/dichloromethane elution), preparative thin layer chromatography or crystallized out of pure hexane and hexane/ethyl acetate mixture to afford pure material which was compared to authentic samples. Detailed data, concerning catalyst loading, reaction times, yields of pure products and their spectroscopic and other identification data are given in Supporting Information, chapter: *Characterization Data of Isolated Final Products.*

Chlorination of 1-(4-Methoxyphenyl)ethanone with the Air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl System. Scaled-Up Procedure

A 100-mL glass reactor equipped with magnetic stirring bar and condenser (open or closed with balloon filled with air) was charged with 1-(4-methoxyphenyl)ethanone (0.02 mol; 3.0 g) and totally dissolved in acetonitrile (50 mL). The solution was thermostatted at 60 °C for 20 min and then co-catalyst I_2 (5 mol%; 253.8 mg), HCl (aqueous 37% solution; 30 mmol; 2.5 mL) and the first portion of catalyst NH_4NO_3 (12.5 mol%; 200 mg) were added in consecutive 4 min intervals. The reaction mixture was stirred (500 rpm) at 60 °C for 4 h under open air conditions and the second portion of catalyst NH_4NO_3 (12.5 mol%; 200 mg) was added. The reaction mixture was stirred for additional 68 h and then cooled to room temperature, insoluble material identified as ammonium chloride (375.6 mg recovered) was filtered off and washed with acetonitrile (5 mL). In order to obtain carry-over of the solvent, the filtrate was distilled under reduced pressure, the crude reaction mixture was washed with $NaHCO_3$ (aqueous 10% solution, 10 mL) and $Na_2S_2O_3$ (aqueous 10% solution, 10 mL) and extracted with ethyl acetate (3×10 mL). The organic phase was dried over anhydrous Na_2SO_4. The organic solvent was distilled off under reduced pressure and the crude product obtained was analyzed by ^{1}H NMR. Under the open air system 100% conversion was achieved and pure 2-chloro-1-(4-methoxyphenyl)-ethanone **2b** was obtained; yield: 3.61 g (98%). Using a condenser equipped with balloon filled with air, 68% conversion was achieved and a 60% yield of pure **2b** was obtained.

2-Chloro-1-(phenanthren-3-yl)ethanone (2g): One mmol of 1-(phenanthren-3-yl)ethanone, NH_4NO_3 (25 mol%, 20 mg), I_2 (5 mol%, 12.7 mg), HCl (aqueous 37% solution, 1.5 mmol, 124.6 μL), 2 mL MeCN, 60 °C, 22 h were used; crystallization in hexane and filtration under reduced pressure afforded a yellow solid; yield: 187.2 mg (85%); mp 90–92 °C. ^{1}H NMR (303.0 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.81 (s, 2H), 7.58–7.70 (m, 3H), 7.76–7.90 (m, 3H), 8.0 (dd, J = 1.61, 8.43 Hz, 1H), 8.64 (d, J = 8.09 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR (76.2 MHz, $CDCl_3$): δ = 46.3, 122.7, 124.3, 125.2, 126.2, 127.5, 127.6, 129.0, 129.2, 129.8, 130.4, 130.5, 131.8, 132.2, 191.1; MS (ESI): m/z = 257 [$(M+2+H)^+$, 33%], 255 [$(M+H)^+$, 100%]; HR-MS: m/z = 255.0572, calculated for $C_{16}H_{12}OCl$: 255.0577; anal. calculated for $C_{16}H_{11}OCl$: C 75.45, H 4.35; found: C 75.51, H 4.22.

2-Chloro-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanone (4b): One mmol of 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-ethanone, NH_4NO_3 (25 mol%, 20 mg), I_2 (5 mol%, 12.7 mg), HCl (aqueous 37% solution, 1.5 mmol, 124.6 μL), 2 mL MeCN, 60 °C, 22 h were used; crystallization in hexane/ethyl acetate/acetone (3/1/0.5) and filtration under reduced pressure afforded a white solid; yield: 168.0 mg (79%); mp 142–143 °C. ^{1}H NMR (303.0 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.27–4.36 (m, 4H), 4.63 (s, 2H), 6.91–6.96 (m, 1H), 7.47–7.52 (m, 2H); ^{13}C NMR (76.2 MHz, $CDCl_3$): δ = 45.9, 64.2, 64.9, 117.7, 118.2, 120.9, 128.1, 143.7, 149.0, 189.7; MS (ESI): m/z = 215 [$(M+2+H)^+$, 33%], 213 [$(M+H)^+$, 100%]; HR-MS: m/z = 213.0315, calculated for $C_{10}H_{10}O_3Cl$: 213.0318; anal. calculated for $C_{10}H_9O_3Cl$: C 56.49, 4.27; found: C 56.21, H 3.92.

3-(2-Chloroacetyl)-2*H*-chromen-2-one (**4c**): One mmol of 3-acetyl-2*H*-chromen-2-one, NH_4NO_3 (25 mol%, 20 mg), I_2 (5 mol%, 12.7 mg), HCl (aqueous 37% solution, 1.5 mmol, 124.6 μL), 2 mL MeCN, 60 °C, 24 h were used; flash chromatography (SiO_2, CH_2Cl_2) afforded a white solid; yield: 189.2 mg (85%); mp 178–180 °C. ^{1}H NMR (303.0 MHz, $CDCl_3$ with 2 drops of DMSO, 25 °C, TMS): δ = 4.96 (s, 2H), 7.39–7.44 (m, 2H), 7.70–7.79 (m, 2H), 8.70 (s, 1H); ^{13}C NMR (76.2 MHz, $CDCl_3$ with two drops of DMSO): δ = 49.9, 116.5, 117.8, 121.9, 125.2, 130.4, 135.1, 149.3, 155.0, 158.8, 188.6; MS (ESI): m/z = 225 [$(M+2+H)^+$, 33%], 223 [$(M+H)^+$, 100%]; HR-MS: m/z = 223.0164, calculated for $C_{11}H_8O_3Cl$: 223.0162.

Acknowledgements

We are grateful to the staff of the National NMR Centre at the National Institute of Chemistry, Ljubljana, Slovenia. The authors are also grateful to the Slovenian Research Agency (contracts: Programme ARRS P1-0134) and Young Researchers Fellowship (ARRS1000-08-310039), and CIPKeBiB (European Regional Development Fund) (OP 13.1.1.02.0005).

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