Tetrahedron Letters 52 (2011) 1217–1221

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

α-Halogenation of carbonyl compounds: halotrimethylsilane–nitrate salt couple as an efficient halogenating reagent system

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ARTICLE INFO

Article history:
Received 15 November 2010
Revised 3 January 2011
Accepted 10 January 2011
Available online 18 January 2011

Keywords:
PTP inhibitors
Direct α-halogenation
Chlorotrimethylsilane
Nitryl chloride
Density functional theory

ABSTRACT

A mixture of chloro/bromotrimethylsilane and nitrate salt is found to be an effective reagent system for the α-chlorination/bromination of carbonyl compounds. The reaction occurs under mild conditions yielding the products in moderate to good yields.

1. Introduction

The conversion of C–H bonds to C–X bonds (X = F, Cl, Br and I) has a variety of applications in medicinal chemistry. The C–X bonds can alter the metabolic activity as well as bioavailability significantly.[1] α-Halogenated carbonyl compounds are important synthetic intermediates and are used as precursors for various organic transformations.[2] α-Haloacetophenone derivatives, particularly the bromo analogs, have been investigated for their active participation in the inhibition of protein tyrosine phosphatases such as SHP-1 and PTP1B (Scheme 1).[3] Therefore, the development of a simple and convenient methodology for the synthesis of α-haloacetophenone derivatives is important.

There are relatively few reagents known that allow direct α-halogenation of carbonyl compounds. A significant number of halogenating reagents and methods are available for the preparation of these compounds.[4–9] Most of these protocols used *N*-halosuccinimides,[4a–r] molecular halogen,[4h–l] metal halides,[4m–s] as well as related or similar reagents.[5–9] Herein, we report α-chlorination/bromination of carbonyl compounds with chloro/bromotrimethylsilane–nitrate salt combination, as a source of mild chlorinating and brominating reagent.

Our group has previously reported the use of ammonium nitrate and chlorotrimethylsilane with a catalytic amount of $AlCl_3$ as a robust nitrating reagent for the electrophilic nitration of aromatic compounds.[10] Recently, we have achieved regioselective nitration of arylboronic acids using chlorotrimethylsilane and nitrate salts.[11] *ipso*-Substituted nitroaromatics were obtained in high yields and purity in most of these reactions (Scheme 2). Since most nitrating agents have been shown to possess oxidizing character, the oxidizing potential of the chlorotrimethylsilane–nitrate salt reagent system has also been closely examined.[12] As a result, chlorotrimethylsilane–nitrate salt system has been effectively employed in smooth oxidation of sulfide to sulfones and in the direct oxidative chlorination of thiols and disulfides to the corresponding sulfonyl chlorides (Scheme 2).[13] The major advantage of this protocol is that in most cases, products obtained need no further purification. Simple removal of the solvent from the reaction mixture provided analytically pure product in most cases.

Lee et al. have used a mixture of chlorotrimethylsilane (TMSCl) and nitrate/nitrite salts for the generation of nitryl/nitrosyl chloride in situ for deoximination of aldoximes/ketoximes in non-aqueous medium.[14] The chemistry of nitryl chloride (NO_2Cl) as a reagent has been extensively investigated for nitration of aromatic and aliphatic compounds.[4,9,15] It is well known that typical nitration reactions take place by electrophilic attack of NO_2^+ on the substrates facilitated by strong Lewis acids. Nitryl chlorides have been reported to react vigorously with ammonia to generate chloroamine suggesting that NO_2Cl can behave as a source of electrophilic chlorine.[16]

During the oxidation of sulfides and sulfoxides, we found that the reaction of substrates carrying α-H such as methyl phenyl

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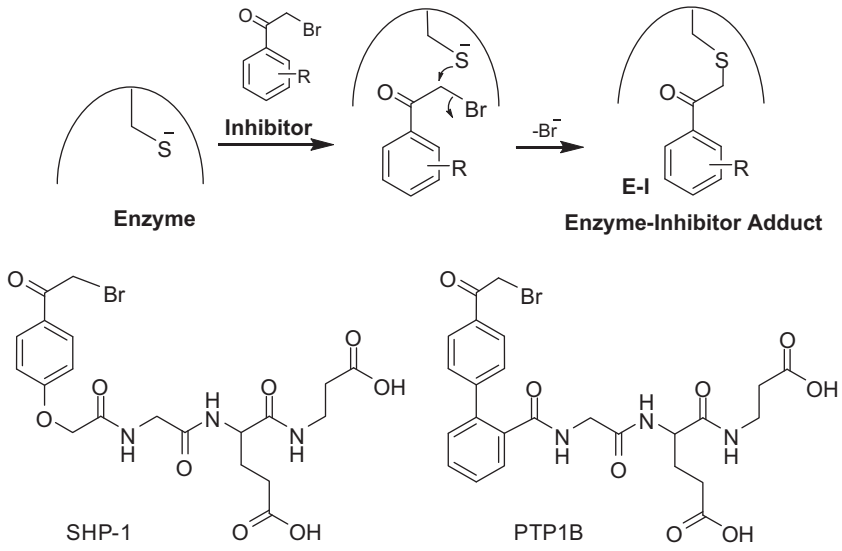
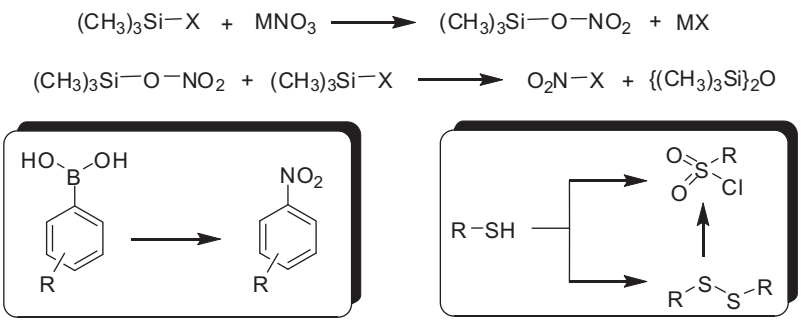
doi:10.1016/j.tetlet.2011.01.039



Scheme 1. α-Bromoacetophenone derivatives as potent PTP inhibitors.

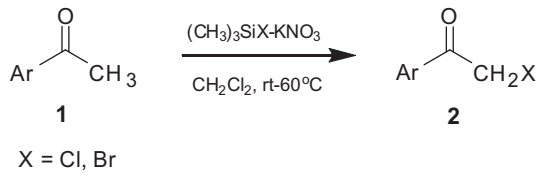


Scheme 2. Application of $(CH_3)_3SiX$–nitrate salt system in *ipso*-nitration and oxidative chlorination reactions.

sulfide and sulfoxide yielded a mixture with noticeable amounts of chlorine substituted products.[13] This is probably due to the formation of silyl-enol ether type intermediate from sulfoxide having α-H, which can undergo successive chlorination to give rise to a mixture of chlorinated products. In the case of dialkyl sulfides and sulfoxides also, the reactions were not clean resulting in a mixture of products due to the competing α-chlorination. However, this prompted us to screen the activity of the chlorotrimethylsilane–nitrate salt system for α-chlorination of ketones having α-H. Our initial attempts gave very promising results with significant amount of α-chlorinated products.

2. Results and discussion

As mentioned earlier, reaction of TMSCl with potassium nitrate in non-nucleophilic solvents such as dichloromethane leads to the formation of nitryl chloride. Generation of NO_2Cl is indicated by formation of brown gas in the reaction medium which results from



Scheme 3. α-Halogenation of acetophenones with $(CH_3)_3SiX$–nitrate system.

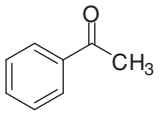
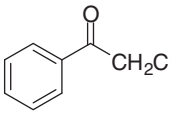
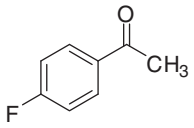
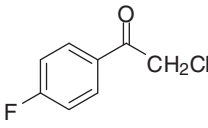
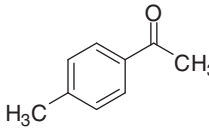
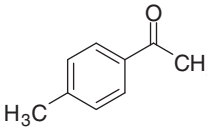
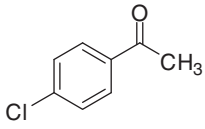
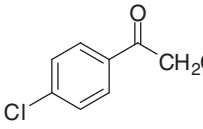
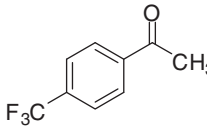
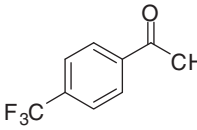
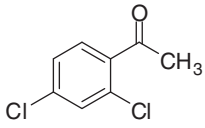
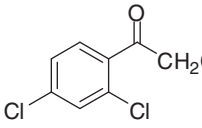
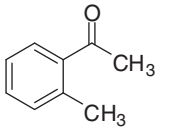
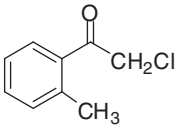
the possible decomposition of NO_2Cl.[16d] The α-chlorination of acetophenone derivatives was carried out at 60 °C for several hours, depending on the nature of the substrates (Scheme 3).[17]

The reactions were monitored by ^1H NMR spectroscopy by taking small aliquots from the reaction mixture. The products were purified by filtration to remove the insoluble salts, and then subjected to silica gel flash chromatography with hexane as eluent. The results are shown in Table 1. The chlorination of acetophenone derivatives took place at a relatively slower rate at 40 °C than at 60 °C, but with a higher selectivity (only 5% dichlorination product was formed). The reaction also took place in the absence of solvent but at a lower rate, and even after 16 h, significant amount of starting material remained unreacted.

In order to probe the versatility of this reagent system for other halogens, bromotrimethylsilane with potassium nitrate salt was reacted with acetophenone derivatives under similar conditions (Table 2). The formation of nitryl bromide is much faster and the reaction proceeds at room temperature with vigorous stirring. This reaction can be further accelerated by heating. The α-brominated products were obtained after filtering off the salt and evaporating the solvent. However, reaction with iodotrimethylsilane (prepared in situ from hexamethyldisilane and iodine) and nitrate salt was not clean.

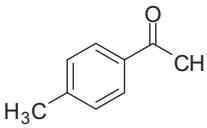
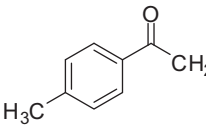
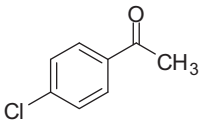
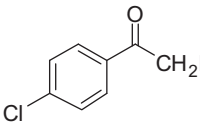
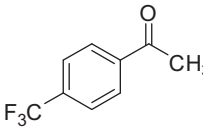
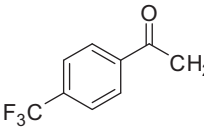
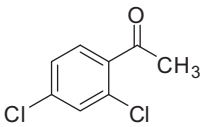
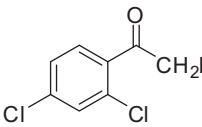
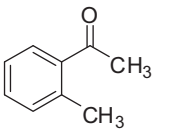
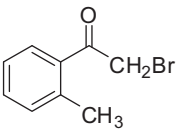
Taking into account the results of various studies on trimethylsilyl nitrate[10,11,18] and nitryl halide,[19] there are two plausible pathways in the mechanism of halogenation (Scheme 4). A mechanism involving trimethylsilyl nitrate (formed from trimethylsilyl halide and metal nitrate) and nitryl halide (formed from trimethylsilyl

Table 1
α-Chlorination of acetophenones with $(CH_3)_3SiCl$-nitrate system[a]

Entry	Substrate (**1a**–**g**)	Time (h)	Product (**2a**–**g**)	Yield (%)
a		16		43
b		48		67
c		16		63
d		16		42
e		16		64
f		16		73
g		18		68

[a] Reactions were carried out 60 °C, 7–22% dichloro products were obtained.

Table 2
α-Bromination of acetophenones with $(CH_3)_3SiBr$-nitrate system[a]

Entry	Substrate (**1c**-**g**)	Time (h)	Product (**2c′**–**g′**)	Yield (%)
c		16		35
d		20		72
e		16		63
f		48		72
g		16		47

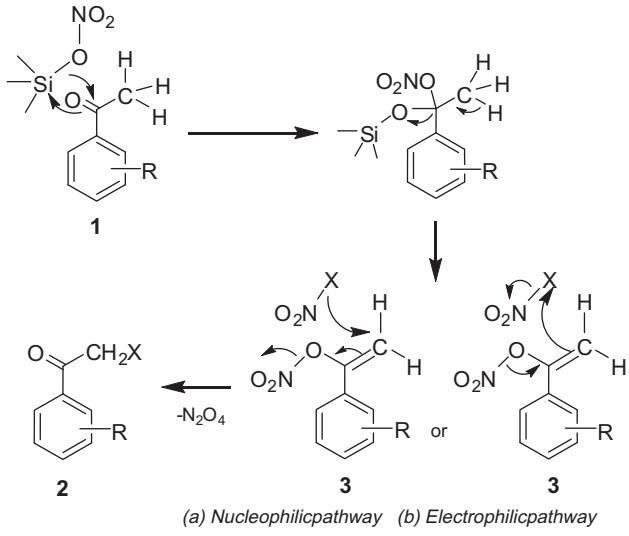
[a] Reactions were carried out at room temperature, 9–36% dibromo products were observed.

nitrate and another molecule of trimethylsilyl halide) is suggested. In solution, formation of an equilibrium involving trimethylsilyl nitrate and nitryl halide is possible. Similar to the addition of TMSCN, the addition of trimethylsilyl nitrate on the carbonyl function followed by elimination–addition step involving nitryl halide, where the halogen is acting as a nucleophile (pathway a), can provide the expected product. Alternatively, during the elimination–addition step, halogen in the nitryl halide can also act as an electrophile (pathway b), generating the expected product. Formation of NO_2Cl and its decomposition is clearly visible by the brownish yellow color formed during the reaction. In order to find the probability of the suggested pathways, calculations based on density functional theory (DFT) of both nucleophilic and electrophilic chlorination of the intermediate **3** have been carried out.

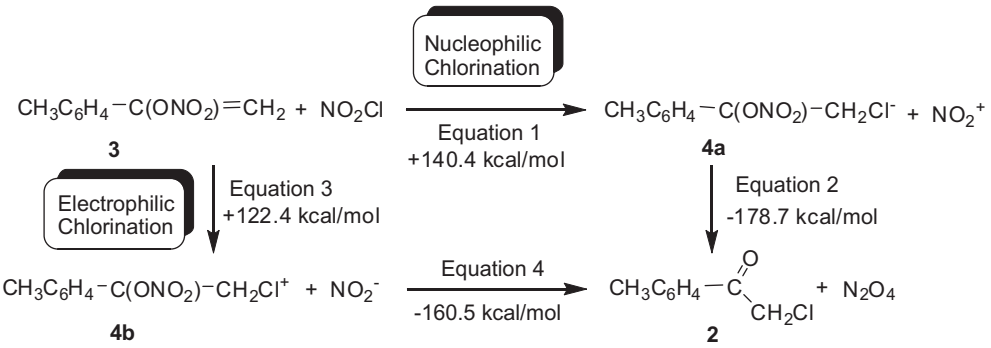
DFT study of nucleophilic versus electrophilic chlorination of $CH_3C_6H_4C(ONO_2)CH_2$ (3) by NO_2Cl

Calculations were performed using the GAUSSIAN 09 program.[20] Geometry optimizations and vibrational frequency calculations were performed at the B3LYP/6-31G** level. The geometries were further optimized at the higher B3LYP/cc-pVTZ level. Reaction of $CH_3C_6H_4C(ONO_2)$=CH_2 **3** and NO_2Cl to give isolated $CH_3C_6H_4C(O\text{-}NO_2)\text{–}CH_2Cl^-$ **4a** ion and nitronium ion (NO_2^+) was calculated at the B3LYP/cc-pVTZ//B3LYP/cc-pVTZ + ZPE (zero point vibrational energy) level (Scheme 5, Eq. 1). This nucleophilic chlorination reaction was found to be endothermic by 140.4 kcal/mol. The optimized structure of **4a** can be considered as loosely held complex of neutral $CH_3C_6H_4C(=O)\text{–}CH_2Cl$ **2** and nitrite ion (NO_2^-). Reaction of $CH_3C_6H_4C(ONO_2)\text{–}CH_2Cl^-$ **4a** and NO_2^+ to give $CH_3C_6H_4C(=O)\text{–}CH_2Cl$ **2** and neutral N_2O_4 was computed to be exothermic by 178.7 kcal/mol at the same level (Eq. 2). The overall reaction of **3** and NO_2Cl to give **2** through anionic intermediate **4a** is exothermic by 38.3 kcal/mol.

We have also computed the reaction of $CH_3C_6H_4C(ONO_2)$=CH_2 **3** (Fig. 1) and NO_2Cl to give isolated $CH_3C_6H_4C(ONO_2)\text{–}CH_2Cl^+$ **4b** ion and nitrite ion (NO_2^-). This electrophilic chlorination reaction



Scheme 4. Mechanism of α-halogenation of acetophenones involving (a) nucleophilic or (b) electrophilic pathway.



Scheme 5. Reaction of $CH_3C_6H_4C(ONO_2)$=CH_2 (**3**) and NO_2Cl (both nucleophilic and electrophilic chlorinations) and its thermochemical data calculated at the B3LYP/cc-pVTZ//B3LYP/cc-pVTZ + ZPE level.

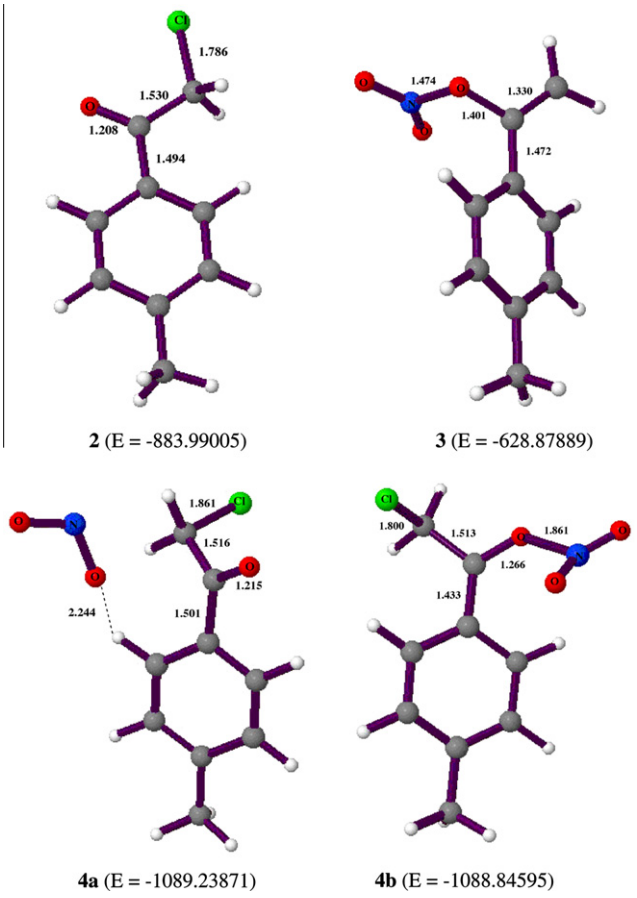


Figure 1. B3LYP/cc-pVTZ calculated structures and energies (Hartrees) of **2**–**4**.

was found to be endothermic by 122.4 kcal/mol at the same B3LYP/cc-pVTZ//B3LYP/cc-pVTZ + ZPE level (Eq. 3). The optimized structure of **4b** can be considered as a complex of neutral $CH_3C_6H_4C(=O)$–CH_2Cl **2** and nitronium ion (NO_2^+) with a carbonyl O–N distance of 1.861 Å. So, the reaction leading to formation of cationic intermediate $CH_3C_6H_4C(ONO_2)$–CH_2Cl^+ **4b** (Eq. 3) is 18.0 kcal/mol less endothermic than the reaction leading to formation of anionic intermediate $CH_3C_6H_4C(ONO_2)$–CH_2Cl^- **4a** (Eq. 1). On the other hand, reaction of $CH_3C_6H_4C(ONO_2)$–CH_2Cl^+ **4b** and NO_2^- to give neutral $CH_3C_6H_4C(=O)$–CH_2Cl **3** and neutral N_2O_4 was computed to be exothermic by 160.5 kcal/mol (Eq. 4). Again the overall reaction of **3** and NO_2Cl to give **2** through cationic intermediate **4b** is exothermic by 38.1 kcal/mol. Although the overall reaction for the nucleophilic process is slightly more exothermic (by 0.2 kcal/mol) than the electrophilic process, the formation of cationic intermediate (rate determining first step) $CH_3C_6H_4C(ONO_2)$–CH_2Cl^+ **4b** is more exothermic (by 18.0 kcal/mol) than the formation of anionic intermediate $CH_3C_6H_4C(ONO_2)$–CH_2Cl^- **4a**. These reactions indicate that the electrophilic chlorination reaction through cationic intermediate **4b** is likely more favorable than the nucleophilic chlorination reaction through anionic intermediate **4a**.

3. Summary

In summary, we have reported a simple and mild method involving chloro/bromotrimethylsilane–nitrate salt couple for α-chlorination/bromination of acetophenones. α-Bromination and chlorination occurred with good conversion. Calculational studies at the B3LYP/cc-pVTZ//B3LYP/cc-pVTZ + ZPE level showed that electrophilic halogenation is likely more favored in the present reaction protocol. This new method is very simple and convenient using less expensive and easily accessible reagents. α-Haloacetophenones with various substituents in the phenyl ring can be prepared under mild conditions and can be used for screening to investigate their therapeutic activity as PTP inhibitors.

Acknowledgment

The financial support by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

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17. *General experimental procedure for the halogenation reaction*: In a Nalgene® bottle, to acetophenone (2 mmol) in dichloromethane (10 mL), potassium nitrate (4 mmol) and chloro/bromotrimethylsilane (8 mmol) were added. The heterogeneous mixture was stirred vigorously at 60 °C (for chlorination) or room temperature (for bromination) until the reaction went to completion (monitored by ^{1}H NMR spectroscopy). The reaction mixture was then filtered and solvent removed under reduced pressure. The chlorinated/brominated acetophenone derivatives were obtained upon purification by flash chromatography (silica gel) with hexane as eluent. The products were characterized by comparing their spectroscopic data with those of the authentic samples.
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