



***N*-Halosuccinimide/SiCl₄ as general, mild and efficient systems for the α -monohalogenation of carbonyl compounds and for benzylic halogenation**

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ABSTRACT

Combinations of *N*-halosuccinimide and tetrachlorosilane in acetonitrile were found to be efficient systems for the selective α -monohalogenation of carbonyl compounds as well as for benzylic halogenation under mild conditions.

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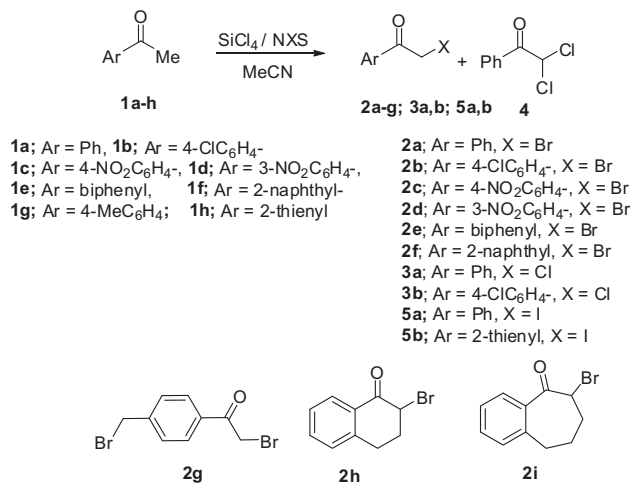
α -Halocarbonyl compounds are versatile building blocks for the synthesis of heterocycles,¹ natural products² and useful functionalized compounds.³ Moreover, a number of α -chloroketones possess biological activity and their properties have attracted considerable attention in medicinal chemistry.⁴ Direct conversion of carbonyl compounds into α -halocarbonyl derivatives is a widely applied synthetic transformation. Bromine, in the presence of protic or Lewis acids,⁵ is the typical reagent for the synthesis of α -bromoketones from ketones. However, its using as a brominating agent has several drawbacks arising from its toxic and corrosive nature, difficulty in handling and its high reactivity, which results in highly exothermic and non-selective reactions. α -Chloroketones have been prepared by direct chlorination of ketones with molecular chlorine or various inorganic or organic chlorinating agents.^{2a,6} Besides the hazards associated with chlorine, some of these methods suffer from problems of over-chlorination,^{6g} nuclear chlorination of activated aromatic rings,^{6f,h} non-reactivity with deactivated aromatic rings,^{6f,i} and incompatibility with acid-sensitive or easily oxidizable groups.^{6h} Molecular iodine as an iodinating agent^{7a} has been used for the synthesis of α -iodoketones, commonly in the presence of additional reagents such as SeO₂,^{7b} CuO,^{7c} urea/H₂O₂,^{7d} etc. In terms of accessibility and ease of handling,

N-halosuccinimides (NXS)⁸ are superior halogenating reagents, and transformations can be modulated under various reaction conditions in terms of catalysts,⁹ solvents,¹⁰ and mediators.¹¹ An alternative synthetic route to α -bromo/iodoketones was achieved from olefins employing NBS/NIS-IBX,¹² I₂/IBX,¹³ or BrOH.¹⁴ However, analogous routes have not been applied to the synthesis of α -chloroketones. On the other hand, halogenation of side chain aromatics represents a very useful route to benzyl halides which are widely used in synthetic organic chemistry and materials science.¹⁵ *N*-Haloimides are widely used for benzylic halogenation, but harsh conditions are usually required.¹⁶ For example, Wohl–Ziegler bromination, which is one of the most popular methods for obtaining α -brominated alkyl arenes, is usually performed with *N*-bromosuccinimide (NBS) in the presence of a radical initiator in boiling CCl₄.¹⁷ Little attention has been given to investigating the Wohl–Ziegler reaction at lower temperatures. An example employing a combination of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and ZrCl₄ under ambient conditions has been reported.¹⁸ The development of novel synthetic strategies for halogenations which have advantages with respect to using less expensive and readily available reagents, mild reaction conditions, cleaner reactions, and simple isolation of the product are of interest.

With this context and in conjunction with our interest¹⁹ in exploring the utility of in situ reagents based on tetrachlorosilane (TCS)²⁰ in organic synthesis, we report herein a general method that is not only applicable to α -chlorination, α -bromination and

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Scheme 1.

α -iodination of carbonyl compounds, but also to benzylic halogenation of side chain aromatics. The process involves sequential reaction of the carbonyl compound or substituted toluene with a combination of inexpensive and readily available tetrachlorosilane and NBS, NCS, or NIS under mild conditions.

The α -bromination of carbonyl compounds was performed smoothly at room temperature using acetonitrile as the solvent. The reaction of TCS/NBS with methylene ketones was previously reported using dichloromethane as the solvent yielding dibromo-derivatives.²¹ We decided to reinvestigate this reaction using acetonitrile as the solvent based on the reported important role of this solvent in such reactions,^{9c} envisaging that such a change may suppress the reaction to yield monobromo-derivatives. Thus, various active methylene ketones were stirred with 2 equiv of NBS and 2 equiv of TCS in acetonitrile at room temperature to afford the corresponding α -monobromo ketones in excellent yields (Scheme 1, Table 1). The procedure was successfully extended to both α -chlorination and α -iodination of carbonyl compounds employing combinations of tetrachlorosilane and *N*-chlorosuccinimide or *N*-iodosuccinimide under the same reaction conditions.

The results summarized in Table 1 show that the α -halogenation reaction proved to be general and quite efficient for aryl- and

Table 1
Reaction of ketones with the TCS-NXS reagent

Entry	Substrate	NXS	Temp (°C)	Time (h)	Product	Yield ^a (%)
1	1a	NBS	rt	5	2a	92
2	1a	NCS	rt	24	3a, 4	67, 28
			60–70	7	3a, 4	70, 22
3	1a	NIS	rt	22	5a	77
			60–70	6	5a	74
4	1b	NBS	rt	6	2b	90
5	1b	NCS	rt	23	3b	81
			60–70	7	3b	85
6	1c	NBS	rt	7	2c	89
7	1d	NBS	rt	7	2d	91
8	1e	NBS	rt	5	2e	90
9	1f	NBS	rt	6	2f	88
10	1g	NBS	rt	6	2g	87
11	1-Tetralone	NBS	rt	7	2h	85
12	1-Benzosuberone	NBS	rt	7	2i	91
13	1h	NIS	rt	22	5b	78
			60–70	7	5b	81

^a Isolated yield.

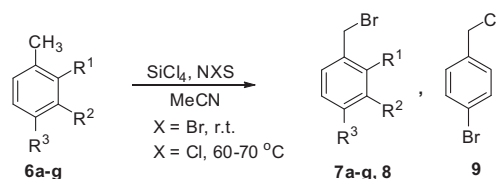
Table 2
Benzylic halogenation using TCS and NBS or NCS

Entry	Substrate	NXS	Time (h)	Product	Yield ^a (%)
1	6a	NBS	6	7a	82
2	6b	NBS	7	7b	74
3	6c	NBS	7	7c	69
4	6d	NBS	8	7d	75
5	6e	NBS	8	7e	84
6	6f	NBS	10	7f	72
7	6g	NBS	11	7g, 8	67, 28
8	6e	NCS ^b	8	9	75

^a Isolated yield.

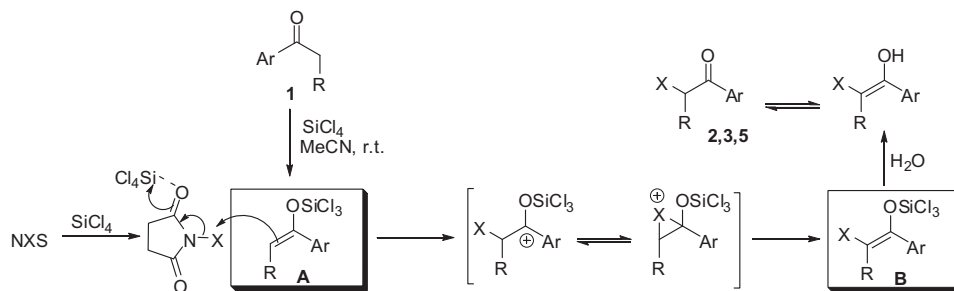
^b The reaction was conducted at 60–70 °C.

hetaryl-methyl ketones, as well as carbocyclic ketones such as 1-tetralone and 1-benzosuberone (entries 11 and 12), and tolerated a variety of functional groups on the phenyl ring regardless of whether electron-donating or electron-withdrawing in character. Thus, chloro, methyl, phenyl- and nitro-containing aromatic ketones were brominated selectively in good to excellent yields at room temperature (entries 4 and 6–10). Our procedure for the chlorination and iodination was studied further, and a number of active methylene ketones were reacted with a combination of SiCl₄ and NCS or NIS (2 equiv) in acetonitrile to give the corresponding α -haloketones in good yields. Both α -chlorination and α -bromination reactions were accomplished equally well along with somewhat reduced yields and longer reaction times (22–24 h) at room temperature, whilst heating the reaction mixture at 60–70 °C accomplished the halogenations in 6–7 h (entries 2, 3 and 13). Identification of the α -haloketones was carried out by spectroscopic analyses as well as by comparing their analytical properties with those reported. However, to our delight, the spectral data of the product from reaction of 4'-methylacetophenone (**1g**) with TCS/NBS (entry 10) showed it to be bromomethyl phenacyl bromide (**2g**), which has important applications in materials science,^{15f} instead of the anticipated 4'-methylphenacyl bromide. The formation of compound **2g** is the result of both α -bromination and benzylic bromination of 4'-methylacetophenone. This result led us to apply our procedure to the Wohl-Ziegler reaction at room temperature and various substituted toluenes were reacted with tetrachlorosilane and *N*-bromosuccinimide. Table 2 shows that treatment of methyl benzenes with TCS/NBS in the ratio 1:1.4:1.4 in either acetonitrile or dichloromethane at room temperature typically gave the respective bromomethyl benzene derivatives. A number of alkyl benzenes underwent the benzylic bromination efficiently (Scheme 2, Table 2). Benzylic chlorination was also examined, however, thermal activation of the reaction was needed. For example, reaction of 4'-bromotoluene with SiCl₄-NCS in acetonitrile at 60–70 °C gave a



6a, 7a: R¹ = R² = R³ = H
6b, 7b: R¹ = Cl, R² = R³ = H
6c, 7c: R¹ = R² = H, R³ = Cl
6d, 7d: R¹ = R³ = H, R² = Br
6e, 7e: R¹ = R² = H, R³ = Br
6f, 7f: R¹ = Cl, R² = Me, R³ = H
6g, 7g: R¹ = Me, R² = R³ = H
8: R² = R³ = H, R¹ = CH₂Br

Scheme 2.



Scheme 3.

good yield of the corresponding benzyl chloride **9** after aqueous work-up (Table 2, entry 8).

The structures of the isolated benzyl bromide derivatives were assigned based on spectral analyses as well as by comparison of their physical properties with reported analogues. Although the exact radical chain process is not quite clear, the reaction would appear to proceed via a radical mechanism under ambient conditions in the presence of light, in a manner similar to the reported Lewis acid catalyzed benzylic bromination.¹⁸ On the other hand, a reasonable pathway for the α -halogenation of carbonyl compounds may agree with that depicted in Scheme 3 involving reaction of enolisable ketone **1** with SiCl_4 to give chlorosilyl enolate **A**. The excess TCS may coordinate with the carbonyl oxygen of the *N*-halosuccinimide increasing the activity of the halogen atom. Next, attack of **A** on the halogen of NXS would produce the halogenated silyl enolate **B** which gives the desired product after aqueous work-up. This postulation is in agreement with the well-documented reaction of silyl enol ethers with *N*-halosuccinimides.²² A radical intermediate involving addition of the halogen to an enol silyl ether can also be similarly invoked.^{22,23}

In conclusion, we have developed a practical and efficient method for the α -monohalogenation of carbonyl compounds as well as for benzylic halogenation by using cheap and readily available tetrachlorosilane and *N*-halosuccinimides.²⁴ This method can be applied to a wide range of carbonyl compounds and alkyl benzene derivatives; the halogen atom can be introduced to the substrate with high regioselectivity. The mild reaction conditions, easy work-up procedure and simple operation are advantages of this procedure.

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24. Typical procedure for the halogenations of **1** or **6** with SiCl₄/NXS in the ratio 1:2:2 or 1:1.4:1.4, respectively: To a mixture of NXS and substrate (**1** or **6**) in CH₃CN at room temperature was added SiCl₄ and the mixture left to stir until TLC showed the disappearance of the starting material. The reaction was then poured onto H₂O and the mixture extracted with CH₂Cl₂. The extracts were combined, dried over MgSO₄ and evaporated. The residue was purified by recrystallization (pet. ether–Et₂O, 3:1) to give pure **2b–2g**, **3b**, or by silica gel column chromatography (hexane–EtOAc 10:1 or 30:1) to give pure **2a,h,i**, **3a–5** or **7–9**, respectively. Data for 4-bromomethyl phenacyl bromide^{15f} (**2g**) as a representative example: IR (KBr) ν 3070, 2860, 1687, 1620, 1371, 1295, 1185, 991, 843, 753, 706 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.50 (s, 2H), 4.43 (s, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 191.66, 139.23, 134.32, 129.42, 129.31, 32.98, 31.18 ppm; MS (*m/z*, %): 294 (1.8), 292 (M+, 3.8), 290 (1.9), 213 (17.6), 211 (18), 199 (96), 197 (100), 171 (15), 169 (17). Anal. Calcd for C₉H₈Br₂O: C, 37.02; H, 2.76. Found: C, 37.19; H, 2.82.