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Rapid and Catalyst-Free α-Halogenation of Ketones using *N*-Halosuccinamides in DMSO

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Abstract: α-Halogenation of various carbonyl compounds such as β-keto-esters, cyclic ketones, and lactams with *N*-halosuccinamides (NBS, NCS, NIS) in the presence of DMSO proceeded very smoothly to give the corresponding α-mono-halogenated products in good to excellent yields with high selectivity under catalyst-free conditions.

Keywords: carbonyl compounds, catalyst-free conditions, α-halogenation, NBS NCS, NIS

The central importance of halogenation reactions, in which organic molecules are formally oxidized, is a widely accepted fact in synthetic organic chemistry.[1] Halocarbon products are useful chemical intermediates serving as branch points in the synthesis of functionalized molecules. Within this context, α-bromination of 1,3-dicarbonyl compounds is an important transformation because the resulting α-brominated products are highly versatile intermediates in organic synthesis.[2] The most commonly used reagents for these transformations include molecular bromine in the presence of protic or Lewis acids,[3] copper(II) bromide,[4] and *N*-bromosuccinamide (NBS).[5] In terms of availability and the ease of handling, NBS is a superior brominating agent. The major advantage of NBS is that the by-product succinamide can be easily recovered and reconverted to NBS to be used in subsequent

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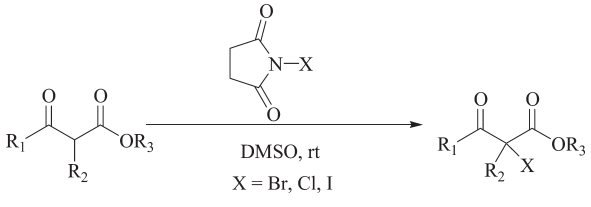
reactions. It has been reported that ketones are α-brominated by reactions with NBS initiated by azobisisobutyronitrile (AIBN) or dibenzylperoxide (BPO) in refluxing CCl_4,[6] NH_4OAc,[7] $MgClO_4$,[8] and amberlyst.[9] In addition, several methods have been developed for the α-chlorination and α-iodonation of β-keto-esters using *N*-chlorosuccinimide (NCS)[10] and *N*-iodosuccinimide (NIS),[11] respectively. Most of these methods generally employed strongly acidic and basic conditions and are accompanied by undesirable formation of α,α-dihalogenated products.

In the context of green chemistry, noncatalytic processes have attracted considerable attention. However, to the best of our knowledge, an efficient α-halogenation of carbonyl compounds without catalyst has not been reported so far.

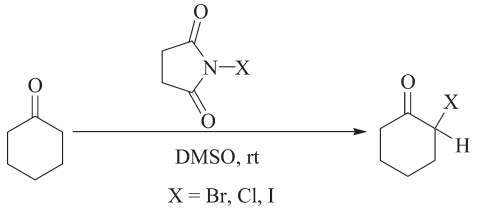
Recently, Watahiki et al. reported the cyanobenzylatiopn and hydrocyanation of aldehydes and silylation of alcohols using dimethyl sulfoxide (DMSO) as solvent under catalyst-free conditions.[12] Spontaneous aldol and Michael reaction of enoxytrimethylsilanes have been recently reported in DMSO.[13] We are interested in the properties of DMSO and envisioned the generation of halogen ions by activating the *N*-halosuccinamides.

From the point of view of green chemistry, a noncatalytic process is very significant and attractive for synthetic organic chemistry. Herein, we report an efficient and convenient method to selectively produce monohalogenated carbonyl compounds from various β-keto-esters and cyclic ketones with *N*-halosuccinamides under neutral conditions (Schemes 1 and 2).

At room temperature, when NBS is added to a DMSO solution of carbonyl compounds (β-keto-esters and cyclic ketones), an exothermic reaction takes place, and the temperature of the reaction mixture rises to



Scheme 1.



Scheme 2.

55–65°C within a minute. The reaction mixture was stirred for few minutes to obtain the corresponding α-monobrominated products in good to excellent yields. Under similar reaction conditions, NCS and NIS were also screened to obtain the corresponding α-monochlorinated and α-mono-iodinated products, respectively. Among these reactions, both α-bromination and α-chlorination reactions were accomplished equally well with somewhat reduced yields in the case of α-iodonation. However, increasing the reaction time gave good yields as illustrated in Tables 1 and 2, which may be attributed to the less electrophilic nature of iodine.

As shown in Table 1, various α-substituted and unsubstituted β-keto-esters were converted to their halogenated products in good yields (Table 1, entries 1–11). Among the substrates screened, 2-substituted β-keto-esters are less reactive than 2-unsubstituted β-keto-esters and require long reaction times (entries 5 and 6). Cyclic β-keto-esters also reacted smoothly and gave the corresponding product in good yield (entry 4). It is noteworthy that no dihalogenated products were observed while using 1.05 equiv. of *N*-halosuccinamides.

To extend the scope and general applicability of this reaction, several cyclic ketones were reacted with NXS (X=Br, Cl, I) in DMSO, and the results are tabulated in Table 2. As can be seen from Table 2, 2-methyl-cyclohexanone (entry 5) underwent halogenation predominantly at the highly substituted position. In addition, the system was also applied to 1,3-cyclicdiketones (entry 7). Further, the reaction of NBS with lactams gave the corresponding α-monobromo lactams in moderate yields (entries 8 and 9).

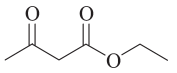
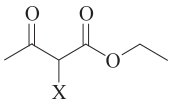
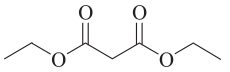
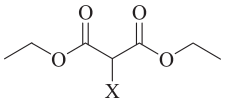
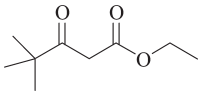
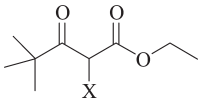
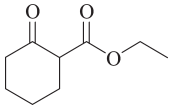
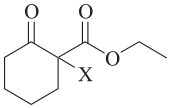
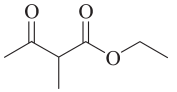
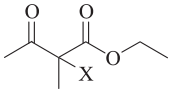
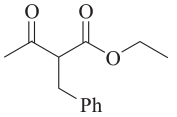
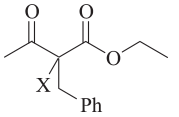
N-Halosuccinamides show enhanced reactivity in the presence of DMSO, thereby reducing reaction times and improving the yields. The rate of enhancement in DMSO, is probably due to increased polarization of the N-X bond in the polar DMSO solvent.

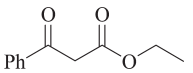
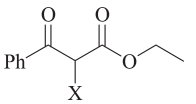
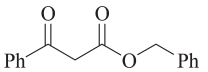
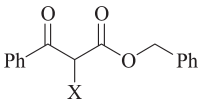
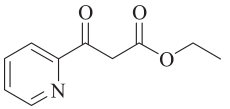
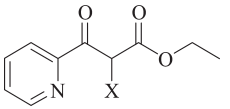
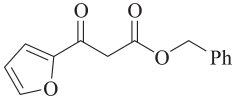
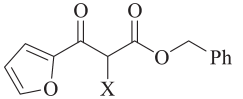
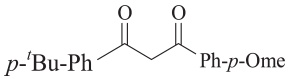
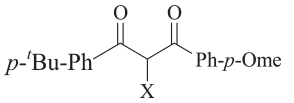
In summary, we have presented a highly efficient and convenient method for α-halogenation of various ketones with *N*-halosuccinamides (NBS, NCS, and NIS) in DMSO. This is the first example for the synthesis of 2-halogenated derivatives without using any catalyst. Accordingly, these reactions are very attractive from the standpoint of green chemistry.

GENERAL PROCEDURE FOR THE α-HALOGENATION OF KETONES

To the DMSO solution of 1,3-keto ester or cyclic ketone (1.0 mmol), *N*-halosuccinamide (1.05 mmol) was added, and the resultant mixture was stirred for an appropriate time at room temperature (see Tables 1 and 2). After completion of the reaction as indicated by thin-layer chromatography (TLC), the reaction mixture was washed with NH_4Cl solution. The product was extracted with

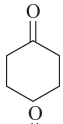
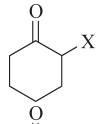
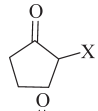
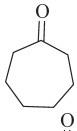
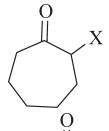
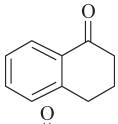
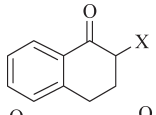
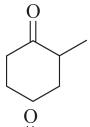
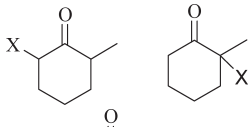
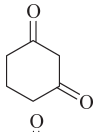
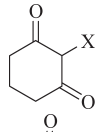
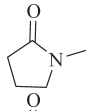
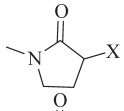
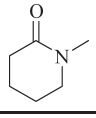
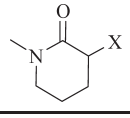
Table 1. 2-Halogenation of various β-ketoesters using *N*-halosuccinamides in DMSO[a]

Entry	β-keto-ester	Products[b] la: X = Br, lb: X = Cl, lc: X = **I**	Time (min)			Yield (%)[c]		
			NBS	NCS	NIS	NBS	NCS	NIS
1			20	20	50	92	90	86
2			20	20	50	90	90	80
3			25	25	60	86	80	75
4			40	45	90	92	90	85
5			45	45	120	85	80	75
6			45	45	120	85	82	70

7			20	25	45	90	85	78
8			25	30	60	90	88	80
9			25	30	60	85	80	80
10			25	30	60	85	80	75
11			40	40	120	95	92	90

[a]Reaction conditions as exemplified in the typical experimental procedure.
[b]All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[c]Isolated yields.

Table 2. 2-Halogenation of various cyclic ketones using *N*-halosuccinamides in DMSO[a]

Entry	Cyclic ketone	Product[b]	Time (min)			Yield (%)[c]		
			NBS	NCS	NIS	NBS	NCS	NIS
1			10	10	30	95	92	85
2			15	15	45	90	87	82
3			10	10	30	95	90	85
4			20	20	60	90	90	82
5			85	82	76	85	82	76
6			15	15	60	91	90	78
7			60	60	120	72	67	60
8			60	60	120	75	75	60

[a]Reaction conditions as exemplified in the typical experimental procedure.[14]
[b]All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[c]Isolated yields.

ethyl acetate, dried over sodium sulphate, and purified by column chromatography.

2-Chloro-3-oxo-3-pyridin-2-yl-propionic Acid Ethyl Ester (Table 1, Entry 9)

IR (neat): υ 2953, 2621, 1739, 1619, 1436, 751, 621 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.30 (m, 4H), 5.27 (s, 1H), 4.33–4.23 (q, 2H $J = 7.30$ Hz), 1.37–1.31 (t, $J = 7.3$ Hz). MS (EI) m/z: 229, 227 (M^+), 192, 151, 71.

1-Bromo-2-oxo-cyclohexanecarboxylic Acid Ethyl Ester (Table 1, Entry 4)

IR (neat): υ 2946, 2871, 1732, 1451, 1241, 755, 562 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 1.27 (t, 3H, $J = 7.4$ Hz), 1.66–1.75 (m, 1H), 1.82–1.96 (m, 3H), 2.03–2.11 (m, 1H), 2.30–2.39 (m, 1H), 2.67–2.74 (m, 1H), 2.75–2.83 (m, 1H), 4.23 (q, 2H, $J = 7.4$ Hz). MS (EI) m/z: 250 (M^{2+}), 248 (M^+), 169, 139, 43.

2-Bromo-1-(4-*tert*-butyl-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione (Table 1, Entry 11)

IR (neat): υ 3031, 2975, 2361, 1712, 1455, 1180, 751, 697, 637 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): 7.99–7.90 (4H, m), 7.46–7.41 (d, 2H, $J = 8.60$), 6.91–6.87 (d, 2H, $J = 8.60$), 6.59 (1H, s), 3.84 (3H, s), 1.33 (1H, s). MS (EI) m/z: 391 (M^{2+}), 369 (M^+), 309.

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