BULLETIN

OF THE

KOREAN CHEMICAL SOCIETY

ISSN 0253-2964 BKCSDE 24(4)
Volume 24, Number 4 April 20, 2003

Communications

Efficient α-Halogenation of Carbonyl Compounds by *N*-Bromosuccinimide and *N*-Chlorosuccinimde

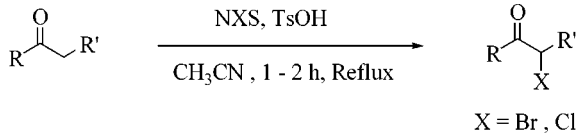
Jong Chan Lee,* Yong Hun Bae, and Suk-Kyu Chang

Department of Chemistry, Chung-Ang University, Seoul 156-756, Korea

Received December 20, 2002

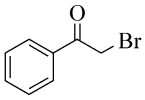
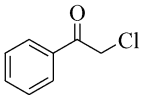
Key Words : Bromination, Chlorination, α-Halo carbonyl compounds, Ketones

Preparation of α-halocarbonyl compounds has always been receiving much attention due to their versatile utilities in the synthesis of a wide variety of useful organic compounds.[1] In general, α-bromo carbonyl compounds can be conventionally obtained by the reaction of carbonyl compounds with various reagents such as bromine,[2] copper (II) bromide,[3] dioxane dibromide,[4] tetrabutylammonium tribromide,[5] and polymer-supported pyridinium bromide perbromide.[6] In addition, the *N*-bromosuccinimide (NBS) has been classically utilized for the α-bromination of ketones *via* radical process promoted by radical initiators such as AIBN and benzoyl peroxide in CCl_4.[1] The α-chloro carbonyl compounds can be generally prepared from the reaction of carbonyl compounds with reagents such as sulfuryl chloride,[7] copper(II) chloride,[8] and trifluoromethanesulfonyl chloride.[9] Although some of these methods were successful for the preparation of α-bromo and α-chlorocarbonyl compounds, a number of these methods are practically inconvenient to use or employ rather harsh reaction conditions. Moreover, synthesis of α-halocarbonyl compounds utilizing these methods is often complicated by common but undesirable α,α-dihalocarbonyl by-products. Therefore, there is still a need for development of more convenient and efficient pathways for the transformation of carbonyl compounds to the corresponding α-halocarbonyl compounds. The utility of *N*-halosuccinimides (NXS) in the α-halogenation of aromatic ketones has received far less attention, whereas more efforts were devoted towards their uses in ring halogenation of activated alkylbenzenes in the presence of protic acids.[10-12] In this context, an example of α-iodination reaction of acetophenone as well as ring iodination of various alkylbenzenes with *N*-iodosuccinimide in trifluoromethanesulfonic acid has been briefly reported in literature.[13] In the course of our search for the efficient method for the preparation of α-haloketone precursors to be used for synthesis of heterocyclic compounds, we found that the acetophenone reacted with NBS in the presence of *p*-toluenesulfonic acid (TsOH) in acetonitrile to give α-bromoacetophenone in high yield. As far as we are aware, no previous studies on the application of NXS/TsOH/acetonitrile reaction systems for the preparation of α-bromo and α-chlorocarbonyl compounds have been undertaken. This prompted us to report in this communication on the *p*-toluenesulfonic acid promoted efficient reactions of *N*-halosuccinimides with various carbonyl compounds to provide α-bromo and α-chloro carbonyl compounds. In order to study the effects of the nature of acid on this reaction, variation of protic acids which included *p*-toluenesulfonic acid, trifluoroacetic acid (TFA), H_2SO_4, and trifluoromethanesulfonic acid (TfOH) has been attempted in combination with *N*-halosuccinimide in refluxing acetonitrile. It quickly revealed that the reaction is very dependent on the nature of protic acid employed as illustrated in Table 1. The acid of choice was *p*-toluenesulfonic acid among others in terms of reaction yields, reaction times, and easiness of manipulation. When reaction



Scheme 1

Table 1. Preparation of α-haloacetophenones promoted by NXS with various protic acids in acetonitrile

Product	% Yields[a] (h)[b]			
	TsOH	TFA	H_2SO_4	TfOH
	92 (2h)	83 (24h)	54 (5h)	42 (5h)
	85 (2h)	25 (24h)	47 (2h)	36 (2h)

[a]Isolated yields. [b]Reaction times.

solvent was changed to dichloromethane, instead of acetonitrile, the reactions required prolonged reaction times and the products were contaminated by increased amount of α,α-dihalocarbonyl side products in both reactions using NBS and NCS. When other aromatic ketones were treated with NBS and TsOH in acetonitrile by heating at reflux for 1-2 h, the corresponding α-haloketones were obtained in high yields as shown in the Table 2. In the absence of TsOH, no formation of appreciable amount of α-halogenated products was observed for all of the carbonyl compounds examined. It is worthy to note that α-bromoketones were obtained as single monobrominated ketones in most instances, whereas α,α-dichloroketones were formed in cases of chlorination as minor products along with desired α-chloroketones as revealed by GC analysis. These results clearly demonstrate the better reactivity and lower selectivity of NCS compared to those of NBS for the halogenation reactions. In the present reaction conditions, any halogenation directed to the aromatic ring was not observed. It also should be noted that the use of more than stoichiometric amounts (1.5 equiv.) of TsOH was required to ensure completion of the reactions, otherwise the yields of α-halocarbonyl compounds were considerably reduced. Having developed efficient method for the α-halogenation of aromatic ketones, attempts were made for the α-halogenation of 1,3-dicarbonyl compounds under the same reaction conditions. As illustrated in the Table 2, the reactions were also highly successful for the formation of 2-halo-1,3-dicarbonyl compounds (entries **7**-**9**). The formation of α-halocarbonyl compounds can be explained by the activation of NXS with TsOH *via* protonation of carbonyl oxygen of NXS to facilitate formation of halonium ions.[10] General procedure for bromination and chlorination is as follows: To a solution containing the carbonyl compound (1.00 mmol) and *p*-toluenesulfonic acid monohydrate (0.285 g, 1.5 mmol) in acetonitrile (50 mL) is slowly added NCS or NBS (1.0 mmol). The reaction mixture was stirred for 1-2 h with reflux. After reaction mixture was cooled down to room temperature, the solvent was evaporated. The residue was dissolved in dichloromethane (50 mL), washed with water (2 × 20 mL), and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel flash column chromatography using dichloromethane as eluent to give pure α-halocarbonyl compound.

Table 2. Preparation of α-halocarbonyl compounds promoted by NXS in the presence of TsOH

Entry	R	R'	Yield (%)[a]	
			X=Br	X=Cl
1	4-$CH_3OC_6H_4$	H	92	74
2	4-ClC_6H_4	H	91	82
3	4-$NO_2C_6H_4$	H	90	76
4	C_6H_5	CH_3	94	82
5	4-$CH_3OC_6H_4$	CH_3	96	72
6	4-ClC_6H_4	CH_3	95	78
7	CH_3	COOEt	72	82
8	Ph	COOEt	95	82
9	EtO	COOEt	95	64

[a]Isolated yields.

In summary, the selective α-halogenation of aromatic ketones and 1,3-dicarbonyl compounds has been accomplished efficiently utilizing NXS/TsOH/acetonitrile reaction conditions. The present protocol is operationally simple and requires only readily available starting materials. Hence it offers a useful alternative to the existing methods.

Acknowledgment. This research was supported by the Chung-Ang University special research grants in 2002.

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