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One-Pot Synthesis of α-Chloro Ketones from Secondary Alcohols Using N,N-Dichloro-p-toluenesulfonamide

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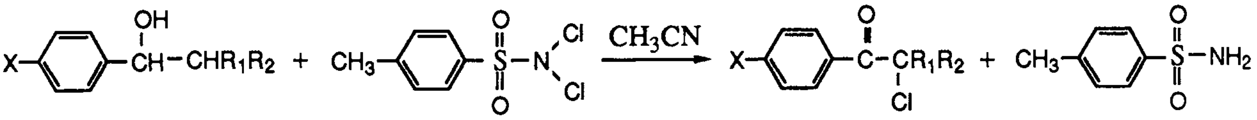
Various alkyl aryl secondary alcohols reacted with N,N-dichloro-p-toluenesulfonamide (N,N-dichloramine-T) in CH_3CN at 35 °C to give the corresponding α-chloro ketones in excellent yields under mild and neutral conditions.

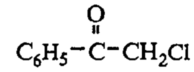
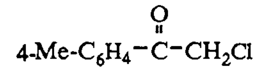
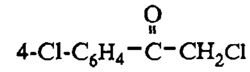
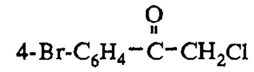
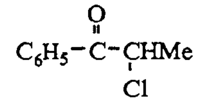
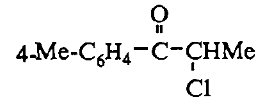
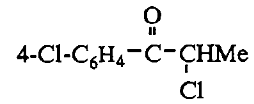
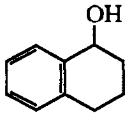
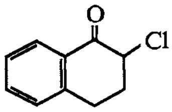
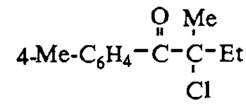
Since α-chloro ketones have been used as an important intermediate in organic synthesis, there has been considerable interest in the development of convenient methods for the synthesis of α-chloro ketones. A number of methods are available for the synthesis of α-chloro ketones, usually by the halogenation of the parent carbonyl compounds with chlorine,1) copper(II) chloride,2) selenium oxychloride,3) sulfuryl chloride,4) and benzyltrimethylammonium dichloroiodate.5) There have been also developed indirect routes for the synthesis of α-chloro ketones by oxidation of olefins with chromyl chloride,6) reaction of aldehydes with dichloromethyl lithium,7) and halogenation of enamines with hexachloroacetone.8)

These methods described above often require drastic conditions or toxic reagents such as chromyl chloride and nitrosyl chloride. Thus, a facile procedure has been desired. Recently, we have reported9) that various dialkyl sulfoxides or alkyl aryl sulfoxides reacted with N,N-dichloro-p-toluenesulfonamide (N,N-dichloramine-T ; 2)10) gave the corresponding α-chloro sulfoxides in excellent yields. In connection with a study of the utility of 2, we now report a new and convenient method for the one-pot synthesis of α-chloro ketones from the secondary alcohols : Various secondary alcohols reacted with 2 in CH_3CN at 35 °C to give the corresponding α-chloro ketones in excellent yields under mild and neutral conditions. In a typical experiment, a solution of 2 (144 mg, 0.6 mmol) in CH_3CN (2 ml) was added dropwise into a solution of 1-phenylpropan-1-ol (68 mg, 0.5 mmol) in CH_3CN (2 ml) with stirring at 35 °C under nitrogen atmosphere. After stirring for 1 h, the reaction mixture was



1 2 3 4

Table 1. Oxychlorination of Secondary Alcohols 1 with Dichloramine-T 2

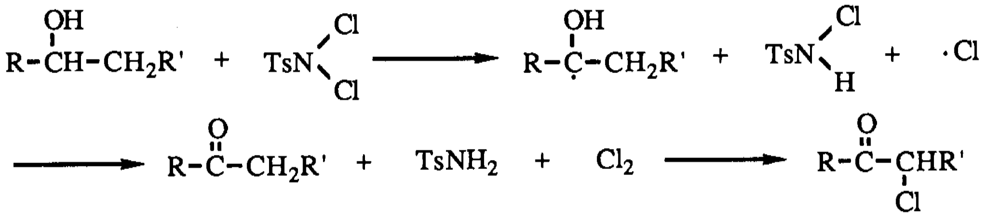
Run	Substrate			Ratio of	Temp	Time	Product	Yield[a)]
	R_1	R_2	X	2/1	°C	h		%
1	H	H	H	1.2	40	1.5	 $C_6H_5-\overset{O}{\overset{\Vert}{C}}-CH_2Cl$	80
2	H	H	CH_3	1.2	35	1.0	 $4\text{-}Me\text{-}C_6H_4-\overset{O}{\overset{\Vert}{C}}-CH_2Cl$	80
3	H	H	Cl	1.5	55	3.5	 $4\text{-}Cl\text{-}C_6H_4-\overset{O}{\overset{\Vert}{C}}-CH_2Cl$	79
4	H	H	Br	1.5	55	4.0	 $4\text{-}Br\text{-}C_6H_4-\overset{O}{\overset{\Vert}{C}}-CH_2Cl$	80
5	CH_3	H	H	1.2	35	1.0	 $C_6H_5-\overset{O}{\overset{\Vert}{C}}-\underset{\underset{Cl}{\vert}}{C}HMe$	94
6	CH_3	H	CH_3	1.2	30	1.0	 $4\text{-}Me\text{-}C_6H_4-\overset{O}{\overset{\Vert}{C}}-\underset{\underset{Cl}{\vert}}{C}HMe$	94
7	CH_3	H	Cl	1.5	55	8.0	 $4\text{-}Cl\text{-}C_6H_4-\overset{O}{\overset{\Vert}{C}}-\underset{\underset{Cl}{\vert}}{C}HMe$	91
8				1.2	40	1.5		92
9	CH_3	Et	CH_3	1.5	55	1.0		–[b)]
10	CH_3	Et	CH_3	1.2	55	27	 $4\text{-}Me\text{-}C_6H_4-\overset{O}{\overset{\Vert}{C}}-\underset{\underset{Cl}{\vert}}{\overset{Me}{\overset{\vert}{C}}}-Et$	19[c)]

a) Isolated yields. b) Major product ; Ketone (98%). c) Major product ; Ketone (80%).

concentrated under reduced pressure to give a mixture of α-chloropropiophenone and p-toluenesulfonamide which were separated by preparative TLC (silica gel, Merck, 60 GF$_{254}$, CHCl$_3$: hexane = 1 : 1, V/V) to give a pure product (79 mg, 94%), ^{1}H NMR (CDCl$_3$) δ1.83 (d, 3H), 5.15 (q, 1H), 7.4-8.0 (m, 5H) ; IR (NaCl) $\nu_{c=o}$ 1693 cm^{-1}. Other α-chloro ketones were isolated by preparative TLC or column chromatography (silica gel, Merck, Kieselgel 60, 70-230 mesh, 1 cm x 20 cm, $CHCl_3$: hexane = 1 : 6, V/V) and identified by comparing their IR, ^{1}H NMR, and GC-Mass spectral analyses with those of authentic samples. The results are summarized in Table 1.

The reaction appears to proceed via initial oxidation of secondary alcohols to the corresponding ketones followed by α-chlorination of the resulting ketones *in situ*. The formation of ketones from alcohols was confirmed by TLC monitoring during the oxychlorination of secondary alcohols to α-chloro ketones. In the cases of Run 9 and Run 10 where α-carbon of alcohols was disubstituted with two alkyl groups of Me and Et, the corresponding ketone was actually isolated together with **3**. From the Table 1, the reaction rate appears to be strongly dependent on the nature of substrates and substituents on the phenyl ring moiety. The formation of α-chloro ketones from phenethyl alcohol derivatives which have an electron withdrawing group at para position (Run 3, Run 4, and Run 7) was much slower and needed higher reaction temperature and longer time than that from substrates containing electron donating group (Run 2 and Run 6).

The lower yields observed in the cases of Run 9 and Run 10 may be due to the steric hindrance of R_1 (Me) and R_2 (Et) groups at α-position. It was reported11) that N,N-dihalo compounds decompose to RNX• and X• which converts to X_2. Thus, the secondary alcohols are initially oxidized by **2** to ketones12) and then the ketones appear to be chlorinated13) with Cl_2 formed *in situ* during the oxidation.



To check the solvent effects, the reaction of 1-phenylpropan-1-ol and **2** was carried out in various solvents such as CH_3CN, CCl_4, THF, and pyridine. The results are summarized in Table 2.

It is noteworthy that there are considerable different solvent effects between CH_3CN, CCl_4, THF, and pyridine. Among the four solvents, acetonitrile showed the best results in Table 2. The key to the success of this method appears to be the use of an aprotic polar solvent such as acetonitrile judging from the solvent effects.

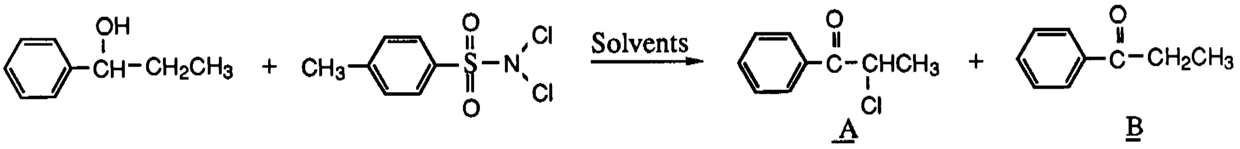
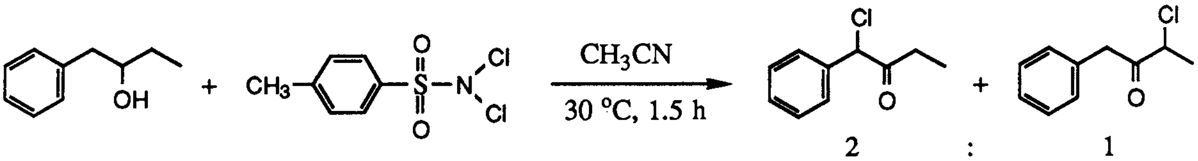


Table 2. Solvent Effects for the Synthesis α-Chloro Ketones

Solvent	Temperature/°C	Time/h	Yield/%[a]	
			A	B
CCl_4	17	48	-	>98
CCl_4	45	48	18	80
THF	45	48	-	81[b]
Pyridine	45	48	-	>98
CH_3CN	40	1.5	94	-

a) Isolated yield. b) Starting material was recoved in 16 %.

In order to see a selectivity in chlorination site between benzylic and methylene carbon position, 1-phenylbutan-2-ol was treated with the equimolar amount of 2. As a result, the ratio of the product chlorinated at benzylic and methylene position respectively was 2:1 as shown below.



2 : 1

(94 %)

This one-pot oxidative α-chlorination of secondary alcohols is simple and easy to work up. The dichloramine-T is commercially available and easy to handle. The scope and reaction mechanism are under investigation.

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