Chloramine-T-Mediated Oxidation of Benzylic Alcohols Using Indium(III) Triflate

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The efficient oxidation of benzylic alcohols to carbonyl compounds was performed using chloramine-T and a catalytic amount of indium(III) triflate. The primary benzylic alcohols were converted to the corresponding aldehydes in a good vield, and the secondary benzylic alcohols were oxidized to ketones in a high yield. The optimized reaction conditions required 0.3 eq of indium(III) triflate and the use of acetonitrile as a solvent.

Key words oxidation; alcohol; chloramine-T; indium(III) triflate

The oxidation of alcohol moieties to the corresponding carbonyl compounds is common in the field of organic synthesis. Various reagents and reactions have been reported in the oxidative reactions of alcohols.¹⁾ Particularly, two methods, Swern oxidation²⁾ and Dess-Martin oxidation³⁾ have been mainstays in organic and medicinal syntheses for decades.

When primary alcohols are subjected to Swern oxidation, they are transformed to the corresponding aldehydes, and the oxidation does not progress further to yield carboxylic acids. In Swern oxidation, however, the active intermediate derived from dimethyl sulfoxide and oxalyl chloride is thermally unstable, and strict control of the reaction temperature is required. Swern oxidation can be coupled with the generation of toxic carbon monoxide and dimethyl sulfide, which makes this reaction unsuitable for large-scale synthesis. Meanwhile, the reagent used in Dess-Martin oxidation includes a hypervalent state of iodine. Therefore, cautious treatment is required due to the risk that is magnified by increases in the reaction scale. Thus, this reagent must be handled with great care.

The oxidation of alcohols using metal-based reagents that include manganese,^{4,5)} ruthenium,⁶⁾ copper,⁷⁾ chromium,^{8,9)} and palladium^{10,11)} have been reported, but these are reactions using heavy transition metals, which are not considered environmentally friendly, at times. Therefore, our study was focused on an oxidative reaction of alcohols that could be performed using an indium reagent instead of transition metals, keeping with the latest trends toward more environmentally green chemistry. We have studied the catalyst effect of indium reagents for past several years, and have reported various chemical transformations using them.¹²⁻¹⁵⁾

Also, there exists a precedent study of selective oxidation of primary alcohols that results only the corresponding aldehyde compounds without the indication of over-oxidation to the carboxylic acids. The study must be a suitable evidence for the compatibility of chloramine-T and transition metal catalyst.¹⁶⁾ Another precedent notable study includes sulfonamide catalyzed oxidation of alcohols using chloramine-T derivatives. It is noteworthy that the oxidation was applicable not only

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CH₃CN

CH₃CN

37

N. R.

Table 1. Reactions during the Search for Optimal Conditions

H ₃ C CH ₃ Chloramne-1 Lewis acid reflux 3h H ₃ C CH ₃								
ntry	Lewis ac	id (eq.)	Chloramine-T (mmol)	Solvent	Yield (%)			
1	In(OTf) ₃	(0.2)	1	CH ₃ CN	81			
2	InCl ₃	(0.2)	1	$\rm CH_3CN$	50			
3	$InBr_3$	(0.2)	1	$\rm CH_3CN$	29			
4	In(OTf) ₃	(0.2)	1	toluene	N. R.			
5	In(OTf) ₃	(0.2)	1	$\mathrm{CH}_2\mathrm{Cl}_2$	N. R.			
6	In(OTf) ₃	(0.2)	1	THF	N. R.			
7	In(OTf)3	(0.1)	1	CH ₃ CN	44			
8	In(OTf)3	(0.3)	1	CH ₃ CN	85			

1

Ent

9

10

In(OTf)₃

(0.3)

Table 2. The Oxidation of Primary Benzylic Alcohols Using In(OTf)₃ as a Lewis Acid



to benzylic alcohols but also to aliphatic alcohols, such as 2-methylpentanol or octanol, with high yields.¹⁷⁾ Based on the outcome from our continuous research, we have attempted to elucidate that the starting benzylic alcohols could be subjected to a reaction with chloramine-T in order to be converted to the corresponding aldehyde or ketone functionalities by using indium(III) triflate as a Lewis acid. Herein, we wish to describe the details of our study.

Results and Discussion

Using 1 mmol of 1-(*para*-tolyl)ethanol as the starting substrate, we strived to find the optimal conditions for an oxidation reaction, as presented in Table 1.¹⁸⁾ Several commercially available indium salts were tested, and indium(III) triflate proved to be the most efficient Lewis acid when CH₃CN was used as a solvent (entries 1, 2, and 3). The entries using CH₃CN as the solvent afforded the expected product, whereas the entries using solvents such as toluene, CH₂Cl₂, and tetrahydrofuran (THF), all resulted in no reaction (entries 1, 4, 5, and 6). On the other hand, we have reported useful methodologies focused on indium(III) triflate using solvents such as CH₂Cl₂, THF, or MeOH, and thus these outcomes in terms of solvents need not to deny the compatibility of Lewis acids and solvents.^{19–21}

The use of a 0.3 eq of indium(III) triflate was discovered to be one of the key factors for the optimal reaction condition (entries 1, 7, 8, and 9). The reaction without Lewis acid gave a yield of 37% (entry 9), and thus the presence of indium(III) triflate must contribute for smooth reactions based on the previously suggested reaction mechanism in a similar manner.¹⁶) Attempts that avoid the use of a stoichiometric amount of chloramine-T resulted in no reaction, as predicted (entry 10). As a result, the maximum yield of the oxidation product was obtained by pairing a 0.3 eq of indium(III) triflate as a Lewis acids with CH₃CN as a solvent (entry 8).

With the optimal conditions for the oxidation of alcohols in hand, we next examined applicability. Various primary benzylic alcohols, phenylmethanol analogues, were subjected to the reaction using a 0.3 eq of indium(III) triflate with CH₃CN as a solvent, as shown in Table 2 (entries 1, 2, 3, and 4).^{22–25)} The reactions proceeded and generated the corresponding aldehyde compounds in 50–70% yields with no major perceptible byproduct, which could be due to the untoward decomposition occurring after the generation of newly formed aldehydes.

In further studies, secondary benzylic alcohols were used under the optimized oxidation reaction conditions. As shown in Table 3, these reactions proceeded smoothly to give the corresponding carbonyl compounds in good to high yields. The first attempt was the oxidation of the isomers of the methyl group at the meta-position which afforded a high yield, as the isomer with a methyl substituent at the para-position resulted in the higher yield (entries 1 and 2).18) Thus, the influence of the substituents at the meta and para positions was minimized in this case. Also, the oxidation of alcohols with a propanol moiety showed good results (entries 3 and 4).^{26,27)} Furthermore, this process was extended to compounds with two aromatic rings, and oxidation reactions starting with diphenylmethanol analogues were carried out.²⁸⁻³¹⁾ These reactions proceed smoothly to give the corresponding diphenylketone compounds in excellent yields. The electron-donating and electron-withdrawing substituents, such as halogens on the benzene ring, did not significantly influence the reaction efficacy of the diphenylmethanol analogues (entries 5, 6, 7, 8, and 9). However, the electron-donating methoxy group, where the oxygen atom can withdraw electron density inductively, at the para-position gave a reduced yield of 52% (entry 10).^{32,33)} Furthermore, comparison of entries 4 and 11 could suggest the steric hindrance of methyl group at the ortho-position was quite significant.34,35)

Table 3. The Oxidation of Secondary Benzylic Alcohols Using In(OTf)₃ as a Lewis Acid

Entry	Starting substrate	Product	Reflux Time (h)	Yield (%)
1	H ₃ C	H ₃ C CH ₃	3	85
2	H ₃ C CH ₃	H ₃ C CH ₃	2	70
3	CH ₂ CH ₃	CH ₂ CH ₃	3	66
4	H ₃ C	H ₃ C	3	84
5	OH		4	85
6	H ₃ C OH	H ₃ C	2	84
7	CI	CI CI CI	4	82
8	OH Br	Br	4	84
9	H ₃ C CH ₃	H ₃ C ^O CH ₃	3.5	90
10	H ₃ CO ^{OH} CH ₃	H ₃ CO	4	52
11	CH ₃ OH CH ₂ CH ₃	CH ₃ O CH ₂ CH ₂ CH ₃	3	50

Conclusion

In conclusion, we established an efficient method for the oxidation of benzylic alcohols to aldehydes or ketones in the presence of a stoichiometric amount of chloramine-T with a catalytic amount of indium(III) triflate. Many primary and secondary benzylic alcohols were applied to the optimized reaction conditions, and these furnished the corresponding carbonyl compounds in good to excellent yields. The reaction conditions were sufficiently mild and yielded only the expected products with no major byproducts.

Experimental

Materials and Instruments All reagents were of analytical grade. These were purchased commercially and used without purification. All reactions were carried out under an argon atmosphere using magnetic stirring unless otherwise noted. ¹H-NMR and ¹³C-NMR spectral data were recorded on JEOL JMTC-500 spectrometer using TMS as an internal standard.

General Experimental Procedure The starting 1-(para-tolyl)ethanol (1 mmol), chloramine-T (1 mmol), and $In(OTf)_3$ (0.3 mmol) were dissolved in CH₃CN (10 mL) in a 100 mL flask equipped with a magnetic stirrer and a reflux condenser. The reaction mixture was heated at reflux for 3h under an Argon atmosphere and was monitored for completion by TLC. After the reaction mixture was cooled to room temperature, the solvent was removed *via* rotary evaporation. The residue of the reaction mixture was separated through flash column chromatography on silica gel. The obtained product was con-

firmed by spectroscopy.

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Conflict of Interest The authors declare no conflict of interest.

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