Accepted Manuscript

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 PII:
 S0040-4039(17)30687-1

 DOI:
 http://dx.doi.org/10.1016/j.tetlet.2017.05.085

 Reference:
 TETL 48978

To appear in: Tetrahedron Letters

Received Date:18 April 2017Revised Date:19 May 2017Accepted Date:24 May 2017



Please cite this article as: Dip, I., Gethers, C., Rice, T., Straub, T.S., A rapid and convenient oxidation of secondary alcohols, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.05.085

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Tetrahedron Letters

journal homepage: www.elsevier.com

A rapid and convenient oxidation of secondary alcohols

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online A rapid (normally 20 minutes to 2 hours) and selective oxidation of secondary alcohols to ketones can be achieved using 0.4 equivalents trichloroisocyanuric acid and 1.2 equivalents pyridine at room temperature in ethyl acetate. A likely mechanism for the reaction is proposed.

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Keywords: alcohol oxidation selective mechanism

The oxidation of secondary alcohols has been well reviewed.^{1,2} The standard reagent for this oxidation is an aqueous solution of sodium hypochlorite, formerly known as "swimming pool chlorine", which normally is selective for secondary over primary alcohols.² This reaction is heterogeneous and usually requires several hours for completion. A homogeneous reaction with good yields and good selectivity using current "swimming pool chlorine", 1,3,5-trichloro-2,4,6triazinetrione (also known as trichloroisocyanuric acid, Symclosene, TCICA, 1) has been examined in order to provide an inexpensive, rapid general method for the oxidation of secondary alcohols.

TCICA was first used as a secondary alcohol oxidant by Mukawa³ for (1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2ol (borneol) and *rel*-(1R,2R,4R)-1,7,7trimethylbicyclo[2.2.1]heptan-2-ol (isoborneol), and several steroid alcohols, but no general method was proposed. Hiegel's group reexamined TCICA and studied its activity toward a variety of secondary alcohols.⁴ His study of the oxidation of secondary alcohols concluded with the statement, "The low cost of 1 (TCICA), the speed of the reaction, and the ease of isolation of the products may make **1** the oxidizing agent of choice for the conversion of secondary alcohols to ketones."⁴ TCICA has not become the reagent of choice although a few refinements in methodology may increase the popularity of this reagent.

TCICA is poorly soluble in most solvents. This led Mukawa, Hiegel, and others⁵ to choose acetone as the reaction media, and more recently, the reaction was examined in deuterated acetonitrile.⁶ TCICA is also reasonably soluble in ethyl acetate⁷, a choice that leads not only to a homogeneous reaction but to a clean reaction workup, near quantitative yields and few side reactions. The reaction conditions are quite gentle and convenient (see Scheme). Several alcohols were oxidized in twenty minutes following the addition of reagents, and all reactions were performed at room temperature and were isolated by solvent evaporation following acid, base, and salt washes.

The general procedure dissolves 0.01 mole alcohol and 1 milliliter (0.012 moles) pyridine in 10 milliliters ethyl acetate. 1.0 g (0.0043 moles) TCICA is dissolved in 10 milliliters ethyl acetate and added dropwise to the stirring alcohol solution (5 minutes). The reaction mixture becomes yellow as the TCICA is added, and a milky precipitate forms about halfway through the addition process. The reaction mixture is stirred until no detectable amount (gas chromatography) of the starting alcohol remains. The product mixture is filtered, washed with 10 milliliters 1M hydrochloric acid, 10 milliliters 5% sodium bicarbonate, 5 milliliters saturated sodium chloride and dried over anhydrous magnesium sulfate. Following filtration the solvent was evaporated. Normally no further purification is required.

Scheme I



All reactions (except that of benzoin due to poor solubility) were performed in the same fashion.¹⁰ When a base other than pyridine was employed, the molar amounts remained constant. Always a precipitate formed as TCICA was added. Attempts were made to isolate this precipitate, but a homogeneous material was never obtained.

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Table 1

			TCICA		R ₁		n of the
		нОн R ₂	base, ethyl aceta	⇒ ate	°)≡O R ₂		alcohol to the
	Alcohol	Base	Т	ime	% Yield	Lit, Solvent (ref)	e is the
	/ OH	pyridi	ne 20) min	100	· · · ·	step in
1		4-pico	line 20) min	100		mechanis
		4-met	nylmorpholine 20) min	0		m B, and
		collidi	ne 20) min	79		pyridine
2	ОН	pyridi	ne 20) min	96 ^a	68, acetone (4)	serves as general
3	\frown	pyridi	ne 20) min	100 ^a	83, acetone (4) 97, CD ₃ CN (6)	base to abstract
		óн					the proton
4	OH A L A	pyridi	ne 20) min	88	72, acetone (4)	in the formation
		OH			6		carbonyl.
				4			examinati
5		pyridi	ne 2	hr	91	82, acetone (4) 100, CD ₃ CN (6)	on of the results
	HO						summariz
	\checkmark	pyridi	ne 20) min	100		d in the
6 1		collidi	ne 24	4 hr	100		some
	Н						observatio
	\sim	pyridi	ne 60) min	100	86 acetone (4)	ns favor
	\mathbf{X}	4-nico	line 4) min	100		Mechanis
'L	П	collidi	ne 72	2 hr	100		mВ.
							ddition of
0				.	1008		TCICA ir
8		pyriai	ne ou	J min	100		solution t
Г							a pyridine
		nyridi	ne ?	hr	01		solution in
0		pyria		111	91		the
9	К /-СНОН						absence o
	2						an alcoho
10		nuridi	na 21) min	100	00 agatang (4)	results in
10	/=\ OH	pyriai 4 pice	lina 20) min	100	90, accione (4) 03, CD, CN (6)	precipitate
		4-pico		9 11111	100	$93, CD_3CN(0)$, the
11	OH	pyridi	ne 2	hr	88		spectra
		4-pico	line 20) min	100		consistent
							with a
-	OH _	pyridi	ne 2	hr	0		pyridiniu
12		4-pico	line 2	hr	0		m salt. ^{9,10}
		_/ 4-pico	line 2	hr	0^{b}		When a
	<u> </u>	4-pico	line 2	hr	0^{c}		TCICA
V		4-pico	line 24	4 hr	100 ^d		solution is
							added to

a. Crude liquid products contain trace reaction solvent; b. acetone solvent; c CH₃CN solvent; d. CH₂Cl₂ solvent

an alcohol/py ridine

The utilization of pyridine in this reaction is intriguing. Initially pyridine was added to capture the HCl produced, minimizing chlorination of the ketone product.⁵ Recent work has proposed a pyridinium chloride salt as the active oxidizing agent (Mechanism A).⁶ An alternate mechanism parallels the proposed oxidation mechanism using household bleach

solution, a yellow color is observed, consistent with the formation of a hypochlorite^{8a}, and a heavy white precipitate forms, consistent with the cyanuric acid/pyridinium chloride reaction product.

Mechanism A



Examples from the Table further support Mechanism B. Isoborneol and borneol (alcohols 6 and 7 in the Table) are oxidized at different rates with pyridine as the added base indicating a requirement for accessibility of the abstracted proton. Substituting for pyridine (pK_a 5.23) by the stronger base 4methylpyridine (4-picoline, $pK_a 5.96$)¹¹ increases the rate of oxidation. Using an even stronger but sterically encumbered base 2,4,6-trimethypyridine (collidine, pKa 7.45)¹¹ decreases the rate in all cases examined. The collidine experiment shows that there is a strong steric factor in the reaction. By comparing the *cis/trans* ratio of the starting material with the ratio after twenty minutes of reaction using collidine, cis-4-t-butylcyclohexanol is oxidized more rapidly than trans-4-t-butylcyclohexanol.¹¹ Replacing collidine by the equally basic but sterically compact tertiary amine 4-methylmorpholine $(pK_a 7.58)^{12}$ resulted in no oxidation as there was a strong exothermic reaction of 4methylmorpholine with TCICA. This also works against Mechanism A as a strong interaction with TCICA prevents oxidation. It appears that abstraction of the hydrogen attached to the alcohol carbon contributes substantially to the rate of reaction. This is seen by comparing the time required for complete oxidation of isoborneol and borneol using either pyridine or collidine as the base. Isoborneol was always oxidized in less time than borneol (typically, $\frac{1}{3}$ the time), and gas chromatographic analysis indicated that there were no side reactions.

The range and selectivity of this oxidation is excellent. Aliphatic reactants were oxidized in 20 minutes unless a steric problem was present (borneol, menthol). Reactants having aromatic rings close to the reaction site took longer with pyridine as the base but were often complete in 20 minutes with 4methylpyridine as base. Oxidation of diols with one primary and one secondary alcohol (2-ethylhexane-1,3-diol, 2-phenylethane-1,2-diol, alcohols 4 and 11 in Table) caused only the secondary alcohol to be oxidized. Benzoin was a special case (likely due to poor solubility in ethyl acetate) but was smoothly oxidized under appropriate conditions. Several solvents were tried for the benzoin oxidation, but only dichloromethane worked well. This reaction was slow likely due to poor solubility of the reagents. Benzyl alcohol was smoothly oxidized to benzaldehyde in 60 minutes with no evidence¹⁰ of benzoic acid in the reaction product.

The additional products of the reaction, 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (isocyanuric acid) and pyridinium chloride are solids that are filtered from the reaction solution and could be recycled. Thus the oxidation of secondary alcohols with TCICA and a pyridine base presents a rapid and gentle procedure that provides high yields of clean products from inexpensive starting materials.

Acknowledgments

We thank La Salle University for financial support. A portion of this work was accomplished on a sabbatical provided for the principal author. The nmr spectrometer used in this work was donated by Merck.

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Graphical Abstract

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Highlights

- A room temperature rapid oxidation of • secondary alcohols is proposed.
- Selectivity for secondary over primary alcohols ٠ is observed.
- Acctebrace A mechanism involving an oxychloride ٠