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Direct Conversion of Alcohols to α-Chloro Aldehydes and α-Chloro Ketones

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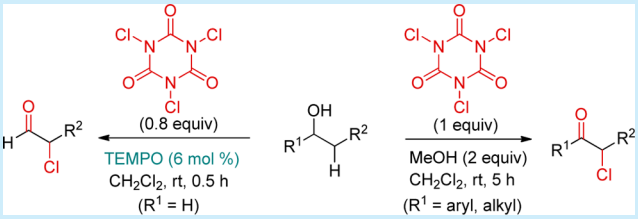
Supporting Information

ABSTRACT: Direct conversion of primary and secondary alcohols into the corresponding α-chloro aldehydes and α-chloro ketones using trichloroisocyanuric acid, serving both as stoichiometric oxidant and α-halogenating reagent, is reported. For primary alcohols, TEMPO has to be added as an oxidation catalyst, and for the transformation of secondary alcohols (TEMPO-free protocol), MeOH as an additive is essential to promote chlorination of the intermediary ketones.



α-Halo carbonyl compounds such as α-chloro aldehydes are versatile building blocks for natural product synthesis.[1] In general, these compounds are prepared via halogenation of the corresponding aldehydes or ketones.[2] Starting with alcohols, the targeted α-halo carbonyl derivatives are available by oxidation and subsequent α-halogenation in a two-step sequence, in which the intermediate aldehydes and ketones are generally isolated. In terms of process economy, one-pot oxidation with subsequent α-halogenation would be more appropriate. Along these lines, Christmann recently disclosed an elegant method for direct transformation of primary alcohols to the corresponding α-chloro aldehydes by TEMPO-catalyzed alcohol oxidation followed by chlorination using enamine catalysis as a one pot sequence.[3] An even more experimentally simple process would use the same reagent for both oxidation and α-halogenation.

In the literature, we found only a few reports where the oxidant currently acts as the halogenation reagent. Benzylic secondary alcohols are transformed to α-chloro acetophenones with *m*-chloroperbenzoic acid/HCl.[4] An example on the use of *N*-chlorosuccinimide for oxidation and chlorination of a secondary benzylic alcohol was disclosed,[5] and the same substrate class was oxidatively chlorinated to the corresponding α-chloro acetophenones with *p*-TosNCl$_2$.[6] In the *t*-BuOCl-mediated oxidation of 2-propanol, α-chloro acetone was observed in low yield.[7] We also found few reports on the analogous transformation comprising oxidation and α-bromination of alcohols.[8]

Herein we disclose highly practical direct conversion of various primary and secondary benzylic and aliphatic alcohols to the corresponding α-chloro carbonyl derivatives using commercially available and very cheap trichloroisocyanuric acid (TCCA)[9] as an oxidant and α-halogenating reagent (Scheme 1). For alcohols that are not oxidized by TCCA, TEMPO is added as a catalyst.[10]

During studies on the TEMPO-catalyzed oxidation of 1-phenylethanol (**1a**) to acetophenone (**2a**) with TCCA as stoichiometric oxidant (1 equiv)[11] we noted that α-chloro acetophenone (**3a**) was directly formed in the presence of alcohol additives. Initial experiments were conducted in dichloromethane at room temperature for 2 h. If the reaction was conducted in the absence of any additive, ketone **2a** was quantitatively obtained (Table 1, entry 1). However, upon addition of MeOH (1 equiv), the chlorinated ketone **3a** was formed as the major product (80%) along with 20% of acetophenone (entry 2). A good result was also achieved with 2,2,2-trifluoroethanol as additive (70%, entry 6), and EtOH supported ketone chlorination, albeit in a lower yield (49%, entry 3). With other alcohols such as *i*-PrOH, *t*-BuOH, and hexafluoro-2-propanol, the reaction stopped after a clean alcohol oxidation (entries 4, 5, and 7), and the same result was also obtained using DMF as an additive. Solvent screening revealed that the reaction did not work in THF or DMSO, and in acetone only a low-yielding oxidation to the ketone **2a** was achieved (entries 9, 10, and 12). EtOAc worked less efficiently than DCM (entry 11) and the best result was obtained in the presence of 2 equiv of MeOH (entry 13).

As a control experiment, we ran the reaction in the absence of TEMPO catalyst and noted slow transformation of **1a** to acetophenone (22%, entry 14). This experiment revealed that under the applied conditions (DCM, 1 equiv MeOH) TEMPO is not necessary for alcohol oxidation. However, oxidation in

Scheme 1. Direct Conversion of Alcohols to the Corresponding α-Halo Carbonyl Derivatives

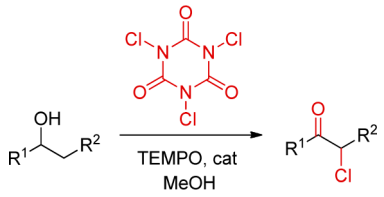


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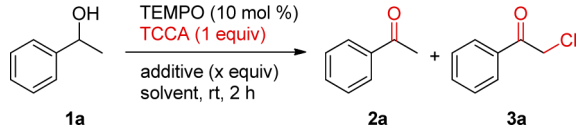
Table 1. Reaction Optimization Using 1a as Substrate[a]



entry	additive	equiv (additive)	solvent	yield (2a)[a] (%)	yield (3a)[a] (%)
1	none		DCM	100	0
2	MeOH	1.0	DCM	20	80 (78)[b]
3	EtOH	1.0	DCM	50	49
4	*i*-PrOH	1.0	DCM	100	0
5	*t*-BuOH	1.0	DCM	100	0
6	CF_3CH_2OH	1.0	DCM	25	70[c]
7	$(CF_3)_2CHOH$	1.0	DCM	100	0
8	DMF	1.0	DCM	100	0
9	MeOH	1.0	acetone	50	0
10	MeOH	1.0	THF	0	0
11	MeOH	1.0	EtOAc	53	36
12	MeOH	1.0	DMSO	0	0
13	**MeOH**	**2.0**	**DCM**	**13**	**87 (86)[b]**
14	MeOH	1.0	DCM	22	0[d]
15	MeOH	1.0	DCM	81	0[d,e]
16	**MeOH**	**2.0**	**DCM**	**18**	**82 (78)[d,e]**
17	MeOH	3.0	DCM	8	82 (78)[d,e,f]

[a]Determined by GC analysis of the crude reaction mixture using *n*-dodecane as an internal standard. [b]Isolated yield in parentheses. [c]Dichloroacetophenone was formed as a side product in 5% yield. [d]Without TEMPO. [e]Reaction for 5 h. [f]10% of α,α-dichloroacetophenone was formed.

the absence of nitroxide is far slower.[12] In fact, increasing the reaction time to 5 h provided acetophenone in 81% yield (entry 15). Surprisingly, repeating the reaction in the presence of 2 equiv of MeOH provided chloroacetophenone **3a** as the major product (82%) along with acetophenone (entry 16).[13] Upon extending the reaction time, we observed formation of α,α-dichloroacetophenone as a side product. We also ran an experiment with 3 equiv of MeOH for 5 h and got **3a** in 82% yield along with 8% of **2a** (entry 17). However, α,α-dichloroacetophenone as the product of overchlorination was also formed (10%). Therefore, reactions in the presence of MeOH (2 equiv) with 10 mol % of TEMPO (2 h, method A) or without TEMPO (5 h, method B) were deemed as the ideal conditions for direct transformation of secondary alcohols into the corresponding α-monochloro ketones (entries 13 and 16).

For the TEMPO-free process, reaction likely occurs by first transforming the alcohol into the corresponding hypochlorite which, upon HCl elimination, provides the ketone. HCl then reacts with TCCA, or its dichloro congener formed during reaction, to give Cl_2 which we assume to be the actual ketone chlorinating reagent. We do not fully understand the key role of the MeOH additive and currently assume that MeOH assists formation of the enol tautomer, which is probably the reactive intermediate to be chlorinated.

To study substrate scope, various secondary aromatic and aliphatic alcohols **1b–t** were reacted using methods A and B to provide the corresponding α-chlorinated ketones **3b–t** (Figure 1). In general, alcohol oxidation and chlorination using method A proceeds in good to high yields. However, in some cases only the nonchlorinated ketones were obtained by using the TEMPO-free protocol B, even after 24 h reaction time (see

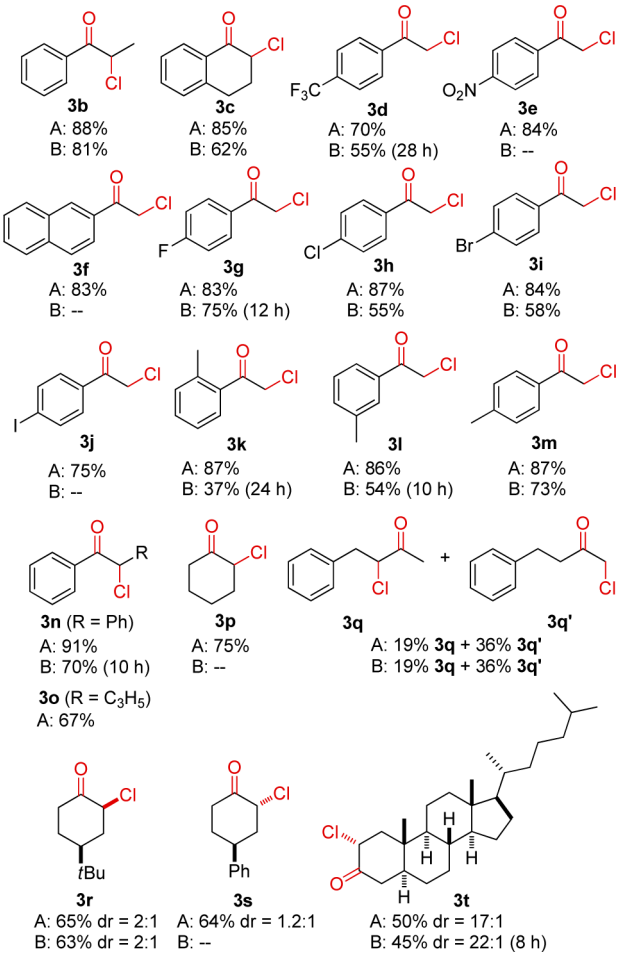


Figure 1. Oxidation and α-chlorination of various secondary alcohols using methods A and B (for **3r–t**, only major diastereoisomer drawn). Selectivity for **3r** and **3s** determined by GC analysis and selectivity of **3t** determined by ^{1}H NMR analysis.

3e,f,j,p,s). Importantly, α-chlorination is not restricted to aryl methyl ketones as shown by the successful preparation of ketones **3b**, **3c**, **3n**, and **3o**, which were isolated in good to excellent yields using either method A or B (62–91%). Notably, in the chlorination of 1-cyclopropylmethyl alcohol **1o** to **3o** we did not observe any ring-opening product, which indicates that chlorination does not occur via a radical pathway through the α-carbonyl radical supporting our ionic mechanism suggested above. For secondary benzylic alcohols we also looked at the effect of the arene substituent on the reaction outcome. Substrates bearing electron-withdrawing groups at the para-position, such as CF_3 and NO_2, could be smoothly converted to their corresponding products in high yields by using method A (**3d** 70%, **3e** 84%). Secondary benzylic alcohols carrying a halogen atom at the para-position of the arene ring were transformed to α-chlorinated ketones in good yields with method A (**3g–i**, 75–87%). However, for these substrates method B delivered either no product (**3j**) or slightly lower yields (55–75%). 1-(*o*-Tolyl)ethanol and 1-(m-tolyl)-ethanol gave similar results with method A (86–87%), but yields differed substantially by using the TEMPO-free protocol B (**3k** 37%, **3l** 54%, **3m** 73%). Applying method A, 1-naphthylethanol was successfully converted to **3f** (83%).

We next investigated whether aliphatic secondary alcohols are substrates for alcohol oxidation with subsequent α-

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chlorination. Pleasingly, under the above optimized conditions α-chloro cyclohexanone **3p** was isolated in 75% yield from cyclohexanol (method A). However, method B failed for this substrate. *trans*-4-*tert*-Butylcyclohexanol reacted with moderate diastereoselectivity (*cis*:*trans* = 2:1) and good yield to **3r** with either the A or B protocol. A similar result was achieved with *trans*-4-phenylcyclohexanol using method A (**3s**), but method B failed for this substrate.

We then studied regioselectivity of the α-chlorination using 4-phenyl-2-butanol as substrate. The corresponding chloro ketone **3q** and its regioisomer **3q′** were obtained in 55% combined yield. Chlorination at the sterically less hindered methyl group occurred with a 1.9:1 regioselectivity. Methods A and B delivered the same selectivity, revealing that TEMPO has no effect on the chlorination step.

We further applied this practical procedure to dihydrocholesterol **1t**, which was successfully transformed in an acceptable yield to **3t** (56% combined yield). The reaction occurred with 9:1 regioselectivity (2-chloro:4-chloro derivatives) and 17:1 α:β-diastereoselectivity for the 2-chloro regioisomers. The minor 4-chloro regioisomers were obtained with 2.7:1 diastereoselectivity (see the Supporting Information). A similar result was achieved with method B. The relative configuration of the isomers of **3t** was determined by NMR spectroscopy (see the Supporting Information). The structure of the major isomer of **3t** was further secured by X-ray analysis (Figure 2).

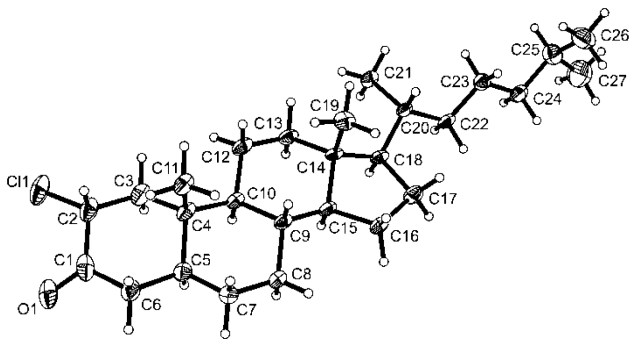


Figure 2. X-ray structure of the major isomer of **3t**.

We continued the studies by testing primary alcohols in the oxidative chlorination and found that the TEMPO-free protocol B failed for this substance class. For example, 2-phenylethanol (**1u**) remained unreacted by applying method B. Hence, primary alcohols are not oxidized by TCCA to the corresponding aldehydes. After some experimentation, we found that primary alcohols are best oxidized and in situ chlorinated in the presence of TEMPO (6 mol %) and 0.8 equiv of TCCA in dichloromethane at room temperature for 0.5 h. Notably, in contrast to the transformation of secondary alcohols, the reaction proceeded in the absence of MeOH additive and α-chloroaldehyde **3u** was isolated in 87% yield (Figure 3). TEMPO loading could be decreased to 3 mol % without diminishing yield to a large extent (80%); however, reaction time had to be extended to 2 h. By using 1 mol % of TEMPO, α-chlorination was not observed.

Under optimized conditions the primary alcohols **1v**–**y** were successfully converted to the corresponding α-chloro aldehydes **3v**–**y** in good to excellent yields (Figure 3, 80–96% yield).

To demonstrate the practicality of our novel method, a gram-scale experiment was carried out by employing 1.03 g of **1f**. In

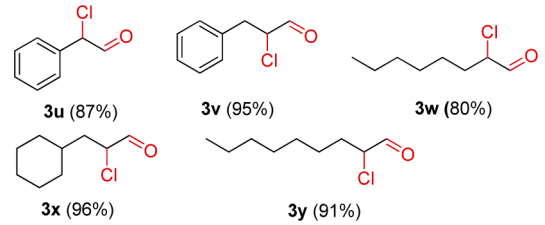
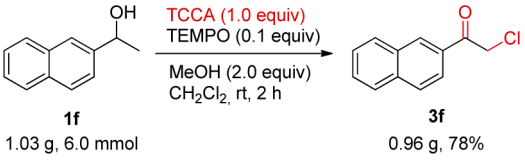


Figure 3. Oxidation and α-chlorination of various primary alcohols (6 mol % of TEMPO, 0.8 equiv of TCCA, 0.5 h).

the presence of 1.0 equiv of TCCA, 10 mol % of TEMPO and 2.0 equiv of MeOH in DCM this oxidative chlorination proceeded smoothly at room temperature to give the desired product **3f** in 78% yield (0.96 g) (Scheme 2).

Scheme 2. Gram-Scale Synthesis of 3f



In summary, we have reported a mild transformation of various alcohols into the corresponding α-chloro carbonyl derivatives. Trichloroisocyanuric acid was applied as a reagent that acts as both the alcohol oxidant and the Cl donor. Notably, TCCA is an attractive reagent because it is safe, commercially available, and inexpensive. It is produced on large scale and applied as a bleaching agent and disinfectant. We showed that TCCA in the presence of MeOH efficiently oxidizes secondary alcohols and in turn is also available for subsequent ketone α-chlorination. Notably, base addition is not required to conduct this two-step sequence, which renders the overall process cost economic. Although the exact role of MeOH additive is not understood, its presence is mandatory for the transformation of secondary alcohols to the corresponding α-chloro ketones. For primary alcohols, oxidation has to be conducted by using TEMPO as a catalyst, and the MeOH additive is not required for subsequent α-chlorination.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Britton, R.; Kang, B. *Nat. Prod. Rep.* **2013**, *30*, 227.

(2) Reviews on α-halogenation of carbonyl compounds: (a) Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324. (b) Shibatomi, K. *Synthesis* **2010**, 2679.
(3) Swatschek, J.; Grothues, L.; Bauer, J. O.; Strohmann, C.; Christmann, M. *J. Org. Chem.* **2014**, *79*, 976.
(4) Kim, H. J.; Kim, H. R.; Ryu, E. K. *Synth. Commun.* **1990**, *20*, 1625.
(5) Tripathi, C. B.; Mukherjee, S. *J. Org. Chem.* **2012**, *77*, 1592.
(6) Kim, Y. H.; Lee, I. S.; Lim, S. C. *Chem. Lett.* **1990**, 1128.
(7) Walling, C.; Mintz, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 1515.
(8) (a) Kruse, P. F., Jr.; Guerkink, N.; Grist, K. L. *J. Am. Chem. Soc.* **1954**, *76*, 5796. (b) Stuckwisch, C. G.; Hammer, G. G.; Blau, N. F. *J. Org. Chem.* **1957**, *22*, 1678. (c) Munavu, R. M. *J. Org. Chem.* **1980**, *45*, 3341. (d) Cami-Kobeci, G.; Williams, J. M. J. *Synlett* **2003**, 124. (e) Podgorsek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Green Chem.* **2007**, *9*, 1212.
(9) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.
(10) TEMPO-mediated oxidations: reviews: (a) Sheldon, R. A.; E. Arends, I. W. C.; Ten Brink, G.-T.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (b) Merbouh, N.; Bobbitt, J. M.; Brückner, C. *Org. Prep. Proced. Int.* **2004**, *36*, 3. (c) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979. (d) Bobbitt, J. M.; Brückner, C. In *Organic Reactions*; Denmark. S. E., Ed.; Wiley: New York, 2009; p 103. (e) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034. (f) Wertz, S.; Studer, A. *Green Chem.* **2013**, *15*, 3116. (g) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. J. *Chem. Commun.* **2014**, *50*, 4524. (h) Ryland, B. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 8824.
(11) TCCA-mediated alcohol oxidation with TEMPO as a catalyst: (a) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (b) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999. (c) Angelin, M.; Hermansson, N.; Dong, H.; Ramström, O. *Eur. J. Org. Chem.* **2006**, 4323. (d) Tomizawa, M.; Shibuya, M.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1829.
(12) Oxidation of alcohols with TCCA was reported to occur in acetone in the presence of pyridine; see: (a) Hiegel, G. A.; Nalbandy, M. *Synth. Commun.* **1992**, *22*, 1589. See also: (b) Kondo, S.; Kawasoe, S.; Kunisdada, H.; Yuki, Y. *Synth. Commun.* **1995**, *25*, 719.
(13) Ketone α-chlorination with TCCA was performed in acetic acid using BF_3 etherate as a catalyst using the ketone in excess; see: Hiegel, G. A.; Peyton, K. B. *Synth. Commun.* **1985**, *15*, 385.

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