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Intermolecular Reactions of Chlorohydrine Anions: Acetalization of Carbonyl Compounds under Basic Conditions

Michał Barbasiewicz and Mieczysław Mąkosza*

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warsaw, Poland

icho-s@icho.edu.pl

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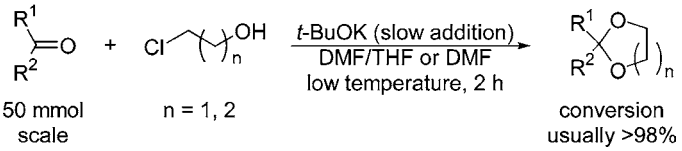
ABSTRACT

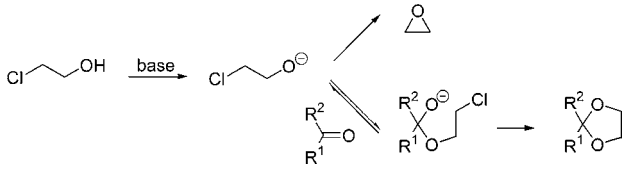


Nonenolizable aldehydes and ketones react with 2-chloroethanol and 3-chloropropanol under basic conditions (*t*-BuOK, DMF/THF) with formation of 2-substituted 1,3-dioxolanes and 1,3-dioxanes, respectively. Conversion of the two-step addition–alkylation process depends on the electrophilicity of the carbonyl group that governs the equilibrium of addition of chloroalkoxides. This method of protection of carbonyl groups in the form of cyclic acetals under kinetically controlled conditions is complementary to the acid-catalyzed reaction with diols.

γ-Halocarbanions undergo fast intramolecular substitution to give cyclopropanes; nevertheless, they can be efficiently trapped by appropriate electrophilic reagents such as aldehydes,[1,2] imines,[3] and Michael acceptors.[4] The resulting anionic adducts that possess electrophilic and nucleophilic centers in a 1,5-relation cyclize to five-membered rings of tetrahydrofurans, pyrrolidines, and cyclopentanes, respectively.

Ethylene chlorohydrine when treated with base forms the respective alkoxide anion that enters rapid 1,3-intramolecular substitution to ethylene oxide. This anion can be considered as an O-analogue of γ-halocarbanions, thus it may be expected that it can be trapped by sufficiently active electrophilic partners, e.g., aldehydes. The produced adducts shall enter intramolecular substitution giving 1,3-dioxolanes—cyclic acetals of carbonyl compounds (Scheme 1).[5]

Scheme 1. Competition of Intramolecular and Intermolecular Processes: Cyclization to Oxirane and Formation of 1,3-Dioxolane



Protection of carbonyl groups is widely used in the synthesis of multifunctional molecules, and its many efficient methods were described.[6] Among them, acetalization is a primary solution and was applied from early times.[7,8] The general methodology for the acetal formation consists of acid-catalyzed reaction of carbonyl compounds with diols, where the equilibrium of the reaction is shifted by azeotropic water removal or dissicators or by reaction with oxiranes catalyzed

(1) (a) Mąkosza, M.; Judka, M. *Chem.−Eur. J.* **2002**, *8*, 4234−4240. (b) Mąkosza, M.; Przyborowski, J.; Klain, R.; Kwast, A. *Synlett* **2000**, 1773−1774. (c) Barbasiewicz, M.; Judka, M.; Mąkosza, M. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1846−1858 (review).

(2) Fleming, F. F.; Gudipati, V.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 3943−3946.

(3) Mąkosza, M.; Judka, M. *Helv. Chim. Acta* **2005**, *88*, 1676−1681.

(4) Mąkosza, M.; Judka, M. *Synlett* **2004**, 717−719.

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by Lewis acids[9] and tetraalkylammonium halides.[10] The last of these reactions proceeds via nucleophilic opening of the oxirane ring with formation of 2-haloethoxide, which subsequently adds to the carbonyl group with the formation of an O-anion of the hemiacetal. All these steps are reversible except the last one, cyclization of an anion with the formation of 2-substituted 1,3-dioxolanes, that drives the reaction to completion.[11] The main drawback of this protocol is the necessity of operation with highly toxic gaseous ethylene oxide, thus limiting its routine use. Application of 2-chloro- and 2-bromoethanol as sources of 2-haloalkoxide anions was reported[12] but was limited to highly electrophilic carbonyl groups, such as, e.g., 4-nitrobenzaldehyde,[13] 1,2-dicarbonyl compounds,[14] and highly chlorinated[15] or fluorinated ketones.[16] For the less-electrophilic carbonyl compounds, such as benzaldehyde, irreversible intramolecular substitution to ethylene oxide dominates, making formation of 1,3-dioxolanes unsuccessful.[17]

In this communication, we present a practical protocol for the protection of nonenolizable aldehydes and ketones under basic, kinetically controlled conditions.[18]

For our initial attempts of synthesis of 1,3-dioxolanes, benzaldehyde was chosen as a model carbonyl compound possessing intermediate electrophilicity. On the basis of our early studies of reactions of γ-halocarbanions and optimization of the reaction conditions, we have found that *t*-BuOK in a DMF/THF mixture at low temperature ensures good results of the desired process. A series of reactions with aldehydes were carried out on the preparative 50 mmol scale, and the products were isolated by distillation (Table 1).[19,20]

In most cases, aldehydes were cleanly converted into dioxolanes, without competing side processes, thus conversions and purities of products were determined by ^{1}H NMR (integration of formyl and benzylidene protons). We observed that the total conversion of an aldehyde is strongly dependent on temperature. At −60 °C, it reaches the optimum. At higher temperatures, conversions are lower, and at lower temperatures, problems with efficient stirring occurred as a consequence of the viscosity of the mixture.[21] An interesting influence of substituents on conversion was noticed. In this system, two competing processes operate (Scheme 1)—intra- and intermolecular—and only the latter depends on the electrophilicity of the aldehyde carbonyl group. Thus, the results obtained correlate with the "effective electrophilicity" of the carbonyl group as a superposition of electronic and steric effects of the substituents. A methoxy group located at the para position (entry 1) retards the reaction strongly, whereas at the ortho position (entry 3), this mesomeric influence is diminished. Finally, the *m*-MeO substituent (entry 2) exhibits the weakest deactivating effect as can be expected from simple resonance considerations. It should be emphasized that even a weak donor-like methyl group (entries 4 and 5) induced a measurable effect on the conversion. Most other aldehydes reacted quantitatively, and in some cases, isolated yields were affected by the isolation procedure.[22] Nonenolizable aliphatic aldehyde (entry 19) reacted quantitatively, whereas enolizable 2-methylbutanal underwent self-condensation as determined by GC/MS analysis of the reaction mixture.[23]

(5) For carbanions, cyclization to a three-membered ring is faster than that to a five-membered ring, whereas for O-anions, the opposite is true: Gronert, S.; Azizian, K.; Friedman, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3220−3226.

(6) For a review of protecting group chemistry, see, for example: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999. (b) Kocieñski, P. J. *Protecting Groups* 3rd ed.; Thieme Verlag: New York, 1994.

(7) (a) Showler, A. J.; Darley, P. A. *Chem. Rev.* **1967**, *67*, 427−440. (b) Klausener, A.; Fraunrath, H.; Mikhail, G. K.; Lange, W.; Schneider, S.; Schröder, D. In *Houben-Weyl Methoden der organischen Chemie*; Hagemann, H., Klamann, D., Eds.; Georg Thieme Verlag Stuttgart: 1991; Vol. E14a, Part 1, pp 232−234. (c) MacPherson, D. T.; Rawi, H. K. In *Function Bearing Two Oxygens $R^1{}_2C(OR^2)_2$ in Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, Ch. W., Eds.; Pergamon Elsevier Science: Oxford, 1995; Vol. 4, pp 159−214. (d) Hoffman, W. Ch. Ethylene Glycol. In *Handbook of Reagents for Organic Synthesis. Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. J., Eds.; Wiley: Chichester, 1999.

(8) For recent examples, see: (a) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765−2771. (b) Chen, Ch.-T.; Weng, S.-S.; Kao, J.-Q.; Lin, Ch.-Ch.; Jan, M.-D. *Org. Lett.* **2005**, *7*, 3343−3346. (c) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220−4224. (d) Kim, Y. J.; Varma, R. S. *Tetrahedron Lett.* **2005**, *46*, 7447−7449. (e) Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 8319−8323.

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(11) Font, J.; Galán, M. A.; Virgili, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 75−78 and references therein.

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(13) Schmitz, E. *Ber.* **1958**, *91*, 410−414.

(14) (a) Kuhn, R.; Trischmann, H. *Ber.* **1961**, *94*, 2258−2263. (b) Abe, M.; Adam, W.; Borden, W. T.; Hattori, M.; Hrovat, D. A.; Nojima, M.; Nozaki, K.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 574−582. (c) Magnus, Ph.; Giles, M.; Bonnert, R.; Kim, Ch. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403−4405. (d) Magnus, Ph.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, Ch. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116−8129.

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(16) (a) Simmons, H. E.; Wiley, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 2288−2296. (b) He, Y.; Junk, Ch. P.; Cawley, J. J.; Lemal, D. M. *J. Am. Chem. Soc.* **2003**, *125*, 5590−5591. (c) Ref 7b and references therein.

(17) Attempts to protect benzaldehyde as 1,3-dioxolane with bromoethanol were unsuccessful; see footnote 12 in: Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, *65*, 974−978.

(18) Some specific methods of formation of acetals under basic conditions were described. (a) Base-promoted acetal formation with phenyl salicylates: Perlmutter, P.; Puniani, E. *Tetrahedron Lett.* **1996**, *37*, 3755−3756. (b) Acetalization of aldehydes catalyzed by $TiCl_4$ in a basic medium: Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **1998**, *54*, 15679−15690. (c) Synthesis of acetals from phenols and 1,1-dihaloalkanes: Dehmlow, E. V.; Schmidt, J. *Tetrahedron Lett.* **1976**, 95−96.

(19) **Typical procedure:** To a vigorously stirred solution of benzaldehyde (5.30 g; 50 mmol) and 2-chloroethanol (6.04 g; 75 mmol) in DMF (20 mL) and THF (10 mL) at −60 °C under argon was added dropwise a solution of *t*-BuOK (8.40 g; 75 mmol) in DMF (15 mL) for 30 min. Then, the mixture was stirred for 90 min and aqueous NH_4Cl, brine, and water were added. The mixture was extracted with ethyl acetate (5 × 70 mL), and combined organic phases were washed with brine (3 × 100 mL) and dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was distilled under reduced pressure (see Supporting Information for details).

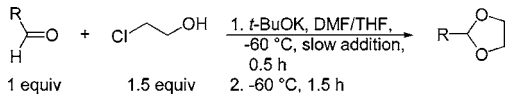
(20) *p*-NO_2- and *p*-NMe_2-substituted benzaldehydes and terephthalaldehyde were unsoluble under the reaction conditions. Cinnamaldehyde substantially polymerized during the reaction; however, small amounts of the acetal were obtained.

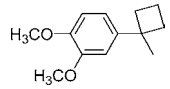
(21) A substantially decreased temperature (−60 °C) favors addition of a 2-haloethoxide anion to the carbonyl group; however, for more electrophilic aldehydes, such as *p*-bromobenzaldehyde, complete conversion of the substrate is reached also at higher temperatures, e.g., −30 °C.

(22) E.g., solubility of products in the water phase containing DMF during workup or small differences of boiling points of ingredients of the reaction mixture.

(23) In the reaction with pivalaldehyde, we were unable to separate the acetal from the mixture of solvents in a pure form.

Table 1. Formation of 1,3-Dioxolanes from Aldehydes under Basic Conditions

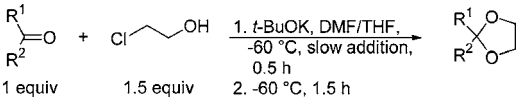


entry	R	conversion (^{1}H NMR)[a]	isolated yield (purity)
1	*p*-MeO−C_6H_4	32%	–
2	*m*-MeO−C_6H_4	85%	68% (98%)
3	*o*-MeO−C_6H_4	78%	45% (95%)
4	*p*-Me−C_6H_4	67%	52% (93%)
5	*o*-Me−C_6H_4	83%	64% (95%)
6	C_6H_5	95%	80% (>98%)
7	*p*-Cl−C_6H_4	>98%	89% (98%)
8	*m*-Cl−C_6H_4	96%	86% (95%)
9	*o*-Cl−C_6H_4	>98%	87% (>98%)
10	*p*-Br−C_6H_4	>98%[b]	93% (>98%)
11	*o*-Br−C_6H_4	>98%	92% (>98%)
12	*m*-NO_2−C_6H_4	>98%[b]	86% (>98%)[c]
13	*o*-NO_2−C_6H_4	95%	92% (98%)
14	2-furyl	>98%	63% (>98%)
15	2-thienyl	90%	66% (98%)
16	2-Py	98%	75% (>98%)
17	*m*-MOM−O−C_6H_4	87%	78% (95%)
18	*p*-H_2C=CH−C_6H_4	75%	70% (98%)[d]
19		>98%	93% (>98%)

[a] The description ">98%" means that substrate was not detected in the reaction mixture. [b] Reaction was performed at −30 °C to ensure solubility of the aldehyde in the reaction mixture. [c] Isolated by recrystallization from ethanol. [d] Reaction was performed on a 10 mmol scale, and product was isolated via column chromatography.

The influence of substituents on conversion was also observed for a series of ketones (Table 2). Less-electrophilic

Table 2. Formation of 1,3-Dioxolanes from Ketones under Basic Conditions



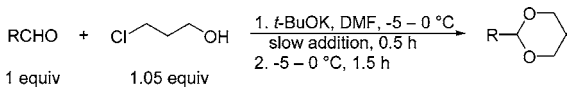
entry	R^1	R^2	conversion (GC)[a]	isolated yield (purity)
1	C_6H_5	C_6H_5	12%[b]	–
2	*p*-Cl−C_6H_4	C_6H_5	60%[b]	–
3	2-Py	2-Py	>98%[b]	62% (>98%)[c]
4	CO_2Me	C_6H_5	97%	67% (mixture of esters)[d]
5	CF_3	C_6H_5	>98%	75% (>98%)

[a] The description ">98%" means that substrate was not detected in the reaction mixture. [b] Reaction was performed on a 10 mmol scale. [c] Isolated by recrystallization from hexanes/ethyl acetate 5:1 [d] Mixture of methyl and *tert*-butyl esters from transesterification with base (86:14, according to GC).

benzophenone gave only 12% of the respective acetal, whereas the *p*-chloro analogue gave 60%. 2,2′-Bipyridyl ketone, described by Newkome[12] to be acetalized with difficulty under acidic conditions, reacted quantitatively.[24]

Next, we investigated the behavior of 3-chloropropanol,[25] a homologue of 2-chloroethanol, in this reaction, as 1,3-dioxanes that should be produced are also applied as carbonyl protecting groups.[6] As cyclization to the six-membered ring proceeds slower than that to the five-membered ring, a much higher temperature (−5 to 0 °C) was necessary for this reaction to be completed (Table 3).

Table 3. Formation of 1,3-Dioxanes from Aldehydes under Basic Conditions



entry	R^1	R^2	conversion (^{1}H NMR)[a]	isolated yield (purity)[b]
1	C_6H_5	H	>98%	90% (95%)
2	*p*-MeO−C_6H_4	H	85%	72% (93%)
3	2-Py	H	>98%	52% (85%)[c]
4	*o*-Br−C_6H_4	H	>98%	79% (>98%)

[a] Description ">98%" means that substrate was not detected in the reaction mixture. [b] 1,3-Dioxanes were contaminated with traces of unreacted 3-chloropropanol and/or its oligomers. [c] Partial decomposition of product under the reaction conditions was observed.

Synthesis of acetals under nonequilibrating basic conditions elaborated in this paper is particularly useful when acid-catalyzed processes give mixtures of products.[26] For instance, acid-catalyzed reaction of benzaldehyde with glycerol gives all possible diastereoisomers of 1,3-dioxolanes and 1,3-dioxanes.[27] We expected that in the model reaction of benzaldehyde with 3-chloro-1,2-propanediol only 1,3-dioxolanes would be produced. Equilibration of the isomeric alkoxide anions and the reversibility of the addition of these anions to the carbonyl group, which connected with much faster 1,5-substitution leading to 1,3-dioxolanes than 1,6-substitution leading to 1,3-dioxanes, should drive the system to produce the former. Indeed, treatment of a mixture of benzaldehyde and 3-chloro-1,2-propanediol in DMF with *t*-BuOK at −5 to 0 °C gave the expected 1,3-dioxolane in good yield as a 1:1 mixture of diastereoisomers. Finally, we applied in this reaction enantiomerically enriched (*R*)-

(24) The mechanism of the reaction of 2,2′-bipyridyl ketone with 2-bromoethanol with Li_2CO_3 at reflux temperature postulated by Newkome (ref 12a) included the assistance (initiated by quaternization) of one ring nitrogen atom in the acetalization process. This idea was further presented elsewhere (ref 17). However, these conditions differ substantially from ours; we assume that the main effect of nitrogen atoms in pyridine rings is inductive in nature.

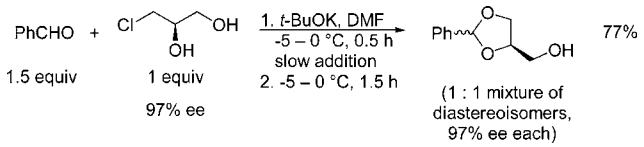
(25) Reaction of 3-bromopropanol with benzaldehyde at −60 °C gave uncomplete conversion.

(26) Strong substituent effects and nonequilibrating conditions may be applied, e.g., for protection of one of the two distinct carbonyl groups (see Supporting Information for details).

(27) Compare, for example: (a) Piantadosi, C.; Anderson, C. E.; Brecht, E. A.; Yarbro, C. L. *J. Am. Chem. Soc.* **1958**, *80*, 6613−6617. (b) Carlsen, P. H. J.; Sørbye, K.; Ulven, T.; Aasbø, K. *Acta Chim. Scand.* **1996**, *50*, 185−187.

3-chloro-1,2-propanediol[28,29] obtained from reaction of epichlorohydrine with water under kinetic resolution conditions with the Jacobsen cobalt−salen complex.[30] The resulting product possessed the same optical purity as the substrate (Scheme 2), whereas its preparation[31] under acidic conditions

Scheme 2. Reaction of Benzaldehyde with 3-Chloro-1,2-propanediol Giving Substituted 1,3-Dioxolane



is obviously impossible as a consequence of equilibration and the achiral character of the glycerol.[32]

(28) For reactions of a nonracemic γ,δ-epoxycarbanion precursor with aldehydes, see: Mąkosza, M.; Barbasiewicz, M.; Krajewski, D. *Org. Lett.* **2005**, *7*, 2945−2948.

(29) Both enantiomers of this compound are commercially available.

(30) (a) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776−6777. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(31) Compare: Carman, R. M.; Kibby, J. J. *Aust. J. Chem.* **1976**, *29*, 1761−1767.

In conclusion, we presented a practical protocol for the synthesis of 1,3-dioxolanes and 1,3-dioxanes from nonenolizable carbonyl compounds under basic conditions. This approach, extended to a wide range of substrates, opens up new possibilities based on different reaction mechanisms, irreversibility of process, and functional group tolerance.

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Supporting Information Available: Experimental procedures and characterization data for all compounds with reprints of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) This product can be easily transformed via DIBAL reduction into *sn*-1-*O*-benzylglycerol, an interesting intermediate in biological research: Marguet, F.; Cavalier, J.-F.; Verger, R.; Buono, G. *Eur. J. Org. Chem.* **1999**, 1671−1678 and references therein.