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General and Practical Conversion of Aldehydes to Homologated Carboxylic Acids

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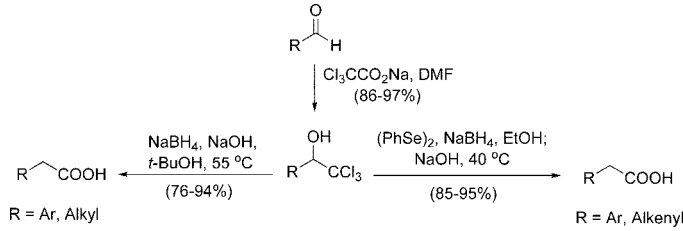
ABSTRACT

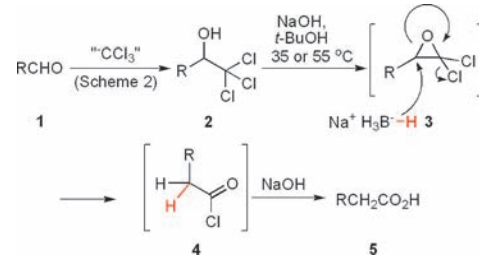


The reaction of aldehydes with trichloromethide followed by sodium borohydride or sodium phenylseleno(triethyl)borate under basic conditions affords homologated carboxylic acids in high yields. This operationally simple procedure provides a practical, efficient alternative to other homologation protocols. The approach is compatible with sensitive aldehydes including enals and enolizable aldehydes. It also offers convenient access to α-monodeuterated carboxylic acids.

Few general processes exist for the one-carbon homologation of aldehydes to carboxylic acids.[1] Reported methods generally require special reagents or complex procedures, and all are limited in scope, especially regarding homologation of enals or aldehydes bearing α-stereocenters. We have devised a two-step homologation of aldehydes to one-carbon extended carboxylic acids by way of trichloromethyl carbinols in a Jocic-type reaction.[2] Treatment of a carbinol with sodium borohydride or a sodium phenylseleno(triethyl)borate complex in a basic alcohol solvent generates the homologated carboxylic acid. The approach is operationally convenient, more economical, and higher yielding than alternative homologation protocols. It also results in a net oxidation of the original carbonyl substrate without employing a traditional oxidant.

Recognizing the potential for the reactive *gem*-dichloroepoxide (**3**) formed during a Jocic reaction to undergo reductive ring opening via a hydride delivery agent (Scheme 1), we considered conditions suitable for the process. The

Scheme 1. Conversion of Aldehydes to Homologated Carboxylic Acids via Trichloromethyl Carbinols



(1) (a) Dinizo, S. I.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Am. Chem. Soc.* **1977**, *99*, 182. (b) Doleschal, G. *Tetrahedron Lett.* **1980**, *21*, 4183. (c) Hiyashi, S.; Ishikawa, N. *Chem. Lett.* **1980**, *6*, 651. (d) Takashi, K.; Shibasaki, K.; Ogura, K.; Lida, H. *J. Org. Chem.* **1983**, *48*, 3566. (e) Katritzki, A. R.; Toader, D.; Xie, L. *Synthesis* **1996**, *12*, 1425. (f) Satoh, T.; Nakamura, A.; Iriuchijima, A.; Hayashi, Y.; Kubota, K.-I. *Tetrahedron* **2001**, *57*, 9689. For a review of other types of carbonyl homologation reactions, see: (g) Badham, N. F. *Tetrahedron* **2004**, *60*, 11.

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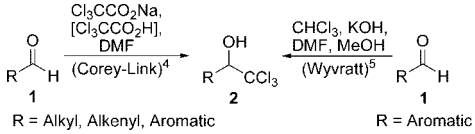
protic solvent required to form **3** from **2** limited our selection of viable hydride sources.[3] Sodium borohydride was particularly attractive due to its affordability, ease of handling, and stability in basic protic media.

All classes of aldehydes were readily trichloromethylated using the method of Corey and Link, providing rapid access to **2** (Scheme 2).[4] The solution of sodium trichloroacetate,

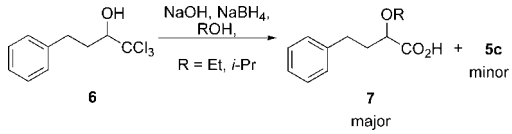
Scheme 2. Preparation of Trichloromethyl Carbinols



optionally buffered with trichloroacetic acid, in DMF allows trichloromethylation to occur without aldehyde enolization, vide infra. We found the procedure of Wyvratt and coworkers generally afforded aryl trichloromethyl carbinols with improved efficiency relative to the Corey−Link method, perhaps due to hydrogen bond activation of the conjugated carbonyl group.[5] However, the Wyvratt procedure is not compatible with aliphatic aldehydes because the enolizable substrates often generate aldol products under the basic reaction conditions during trichloromethylation.

Initially, we examined ethanol as the protic solvent for the conversion of trichloromethyl carbinols (**2**) to carboxylic acids (**5**). The nucleophilicity of ethanol and the ability to slowly consume the borohydride resulted in exclusive ethoxide addition to the *gem*-dichloroepoxide, thereby affording α-ethoxy carboxylic acids (Scheme 3). Employment

Scheme 3. Alkoxide Addition on Treatment of Trichloromethyl Carbinol with $NaBH_4$ and NaOH in ROH

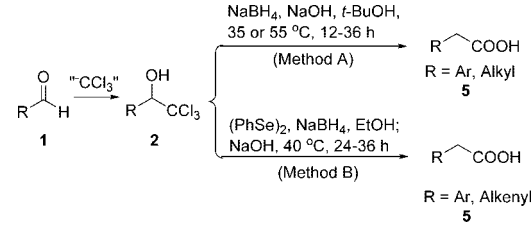


of the less nucleophilic isopropyl alcohol yielded approximately a 1:1 mixture of α-isopropoxy carboxylic acid and the desired homologation product **5c**. Reactions conducted with $NaBH_4$ in basic DME/H_2O (1:1 v/v) resulted in predominantly hydroxide addition to form the α-hydroxy carboxylic acids. Meanwhile, use of poorly nucleophilic 2,2,2-trifluoroethanol offered nearly complete recovery of trichloromethyl carbinol, even after several days of heating.

Brown reported that $NaBH_4$ is a stable yet effective reductant in poorly nucleophilic *tert*-butyl alcohol.[6] Given the tolerance of our designed reaction to moisture, standard *tert*-butanol served beautifully as the medium for hydride delivery/acylation. Its sole limitation is the reduced reactivity of $NaBH_4$ in the solvent at 25 °C. This limitation is mitigated by conducting the reaction at 35 or 55 °C, the latter of which increases the reaction rate but offers no marked benefit in yield (Scheme 1).

Treatment of both aliphatic and aromatic trichloromethyl carbinols with 3.3 equiv of NaOH and 1.5 equiv of $NaBH_4$ in *tert*-butyl alcohol afforded one-carbon extended carboxylic acids in uniformly high yields (Table 1). The intermediate

Table 1. Two-Step Conversion of Aldehydes to Homologated Carboxylic Acids



compd	R	**2**, yield[a] (%)	method[b,c]	**5**, yield[a] (%)
a	C_7H_{15}	93	A	94
b	$TBSOC_4H_8$	93	A	89
c	$PhCH_2CH_2$	89	A	93
d	C_6H_{11}	87	A	85
e	$PhCH(CH_3)$	90	A	85
f	Ph	96	A	92
g	4-CH_3OPh	97	B	90
h	4-NO_2Ph	95	A	76
			B[d]	85
i	2-naphthyl	93	A	78
			B	94
j	2-furyl	95	A[e]	82
			B	92
k	thiophen-2-yl	93	A[e]	83
			B	94
l	$(CH_3)_2C{=}CH$	87	B	95
m	*E*-$C_2H_5CH{=}CH$	90	B	95
n	*E*-$C_2H_5CH{=}C(CH_3)$	86	B	87

[a] Yield of purified material. [b] Method A: 3.3 equiv of NaOH, 1.5 equiv of $NaBH_4$, *t*-BuOH, 55 °C, 12−36 h. [c] Method B: 1.05 equiv of $(PhSe)_2$, 2.1 equiv of $NaBH_4$, abs EtOH, 30 min, then 6.0 equiv of NaOH, 40 °C, 24−36 h. [d] Reaction time was 48 h. [e] Reaction conducted at 35 °C for 48 h.

acid chlorides (**4**) were hydrolyzed faster than sodium borohydride reduction could occur, thus carboxylic acids were furnished rather than the corresponding alcohols. Homologations were conducted on trichloromethyl carbinols **5j** and **5k** at 35 °C due to their propensity to undergo some decomposition at 55 °C.

Although the homologation of aliphatic and aryl aldehydes worked well using $NaBH_4$ in basic *t*-BuOH (method

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(3) (a) Blanchet, J.; Zhu, J. *Tetrahedron Lett.* **2004**, *45*, 4449. (b) Shamshina, J.; Snowden, T. S. *Org. Lett.* **2006**, *8*, 5881.

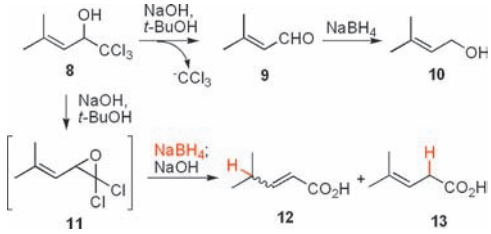
(4) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435.

(5) Wyvratt, J. M.; Hazen, G. G.; Weinstock, L. M. *J. Org. Chem.* **1987**, *52*, 944.

(6) Brown, H. C.; Mead, E. J.; Suba Rao, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 6209.

A), trichloromethylated enals afforded several products under corresponding conditions at a variety of reaction temperatures and reagent concentrations. The predominant product was the allylic alcohol (**10**) resulting from detrichloromethylation−reduction (Scheme 4).[7] The other

Scheme 4. Fate of Allylic Trichloromethyl Carbinols Using $NaBH_4$ in Basic *t*-BuOH



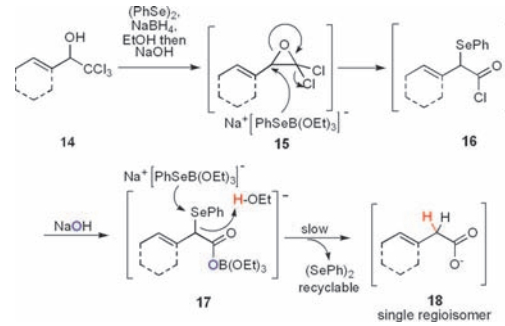
major products resulted from poor regioselectivity during the borohydride reduction of the vinyl *gem*-dichloroepoxide intermediate. Thus, approximately equal mixtures of α,*β*-(**12**) and *β*,*γ*-unsaturated homologated acids (**13**) were obtained.

Results from our investigation into the regioselective substitution of alkenyl *gem*-dichloroepoxides with various nucleophiles revealed a possible solution to the issues encountered in the homologation of enals using method A.[3b] We recognized that employing a better hydrogen-bond donating solvent than *t*-BuOH would likely prevent the detrichloromethylation plaguing the conditions depicted in Scheme 4. We also were aware that a polarizable nucleophile, such as a thiolate or selenide, would offer excellent regioselectivity in the addition to the alkenyl *gem*-dichloroepoxide (**11**) via an S_N2 pathway rather than the mixture of S_N2 and S_N2' pathways elicited with $NaBH_4$. Sharpless' sodium phenylseleno(triethyl)borate complex offered a possibility for resolving the issues with the enals.[8] Miyashita et al. used this reagent for regioselective addition to oxiranes of α,*β*-epoxycarbonyl compounds in high yields.[9] The resultant *β*-hydroxy-α-phenylselenyl ketones and esters were then deselenylated in situ by a second equivalent of the phenylseleno(triethyl)borate complex leaving an enolate subject to protonation. Because ethanol was the solvent employed in the Miyashita protocol, this procedure offered a suitable medium for *gem*-dichloroepoxide formation with probable minimization of the problematic detrichloromethylation witnessed using *t*-BuOH. The intermediate α-phenylselenyl carbonyl intermediates observed by Miyashita were also expected to be analogous to those generated in our desired reaction, thereby offering the possibility for α-deselenylation−protonation with subsequent formation of the homologated carboxylic acid.

The phenylseleno(triethyl)borate complex, easily prepared by mixing diphenyldiselenide and $NaBH_4$ in argon-purged EtOH, served perfectly in the regioselective opening of alkenyl *gem*-dichloroepoxides, allowing for subsequent in situ deselenylation and acyl substitution. No alkene isomerization was observed in any of the substrates examined (**5l**−**5n**). This alternative method (method B) also featured slightly improved yields in the homologation of aromatic aldehydes relative to those obtained using method A (compare results in Table 1).

A plausible mechanism for method B, based upon our observations and the mechanism reported by Miyashita, is shown in Scheme 5. Support for this mechanism includes

Scheme 5. Proposed Mechanism for Sodium Phenylseleno(triethyl)borate Conversion of **14** to **18**



the appearance of the α-phenylselenylcarboxylic acid (from protonated **17**) as an isolable intermediate and complete recovery of introduced diphenyldiselenide after workup.[10] We have taken advantage of this last fact by reusing the recycled diphenyldiselenide in subsequent homologations with no decrease in reaction efficiency. Hence, this approach, like that employing $NaBH_4$ in *t*-BuOH, is remarkably economical. Unfortunately, the diphenyldiselenide cannot be used catalytically under these conditions because of the consumption of nearly 1 equiv of phenylseleno(triethyl)borate complex in the relatively rapid formation of **17**, with the need for additional phenylseleno(triethyl)borate to promote rate-limiting α-deselenylation leading to **18**.

Given the mild buffered reaction conditions featured in the Corey−Link aldehyde trichloromethylation protocol[4] and that enolizable aldehydes do not readily undergo aldol reactions under such conditions, we reasoned that aldehydes bearing α-stereocenters should be amenable to the one-carbon homologation to carboxylic acids without racemization. Neither the trichloromethyl carbinol nor the homologation product should be susceptible to racemization at the original stereocenter as the stereogenic hydrogen is no longer activated by an adjacent electron-attracting substituent in either compound. Hence, the only step of concern was the initial trichloromethylation of the asymmetric aldehyde.

(7) For a direct application see: Cafiero, L. R.; Snowden, T. S. *Tetrahedron Lett.* **2008**, *49*, 2844.

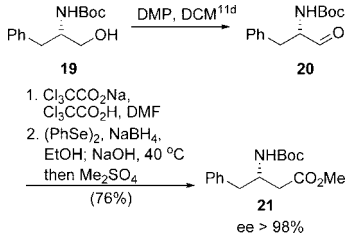
(8) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(9) Miyashita, M.; Suzuki, T.; Hoshina, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469.

(10) Formation of a discreet enolate after deselenylation seems unlikely given that no olefin isomerization to the conjugated enoic acid is observed even at 40 °C and that the first pK_a of the conjugate acid of the carboxylate enolate would be prohibitively high to be compatible with protic media.

We evaluated the compatibility of homologation method B with sensitive[11] (*S*)-amino aldehyde **20** as depicted in Scheme 6.[12] A diastereomeric mixture of amino trichloro-

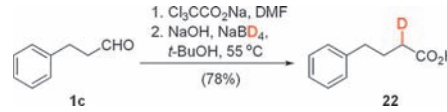
Scheme 6. Homologation of Asymmetric α-Aminoaldehyde **20**



methylcarbinols was formed upon treatment of freshly prepared **20** with a 1:1 mixture of trichloroacetic acid and sodium trichloroacetate in DMF. The resulting material was passed through a silica plug and then subjected to the phenylselenylation−deselenylation protocol in basic ethanol (method B). The crude product was esterified in situ by addition of excess dimethylsulfate to facilitate product isolation through β-amino ester **21**. The overall yield for the conversion of **20** to **21**, including the esterification, was 76%. Following the procedure of Mazaleyrat et al., the amine of **21** was deprotected and subsequently converted to the Mosher amide.[13] Analyses (^{1}H, ^{13}C, and ^{19}F NMR spectroscopies and comparison of specific rotation[14]) confirmed that stereochemical fidelity (>98% ee) was retained during the conversion of **19** to **21**.

A further application of these homologation reactions involves the preparation of α-monodeuterated carboxylic acids in high yield (Scheme 7). Such acids may serve as

Scheme 7. Formation of α-Deuterocarboxylic Acids



convenient precursors to deuterated carboxylic acid derivatives, ketones, or alcohols by simple functional group transformations from the α-deutero acid. The procedure involves substituting $NaBD_4$ for $NaBH_4$ (or EtOD in the place of EtOH using method B), thereby resulting in access to the monodeuterated acid. Aside from operational simplicity, this approach alleviates any substrate susceptibility to undesirable polydeuteration.

The first conversion of aldehydes to one-carbon homologated carboxylic acids by way of trichloromethyl carbinols was explored. The low cost and commercial availability of all reagents, operational simplicity, broad substrate scope, uniformly high yields, and innocuous byproducts generated using method A make these approaches particularly attractive relative to other carbonyl homologation protocols. Even sensitive substrates, such as asymmetric α-amino aldehydes and enals, are cleanly homologated without incident.

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Supporting Information Available: Full experimental procedures, characterization data, and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Compound **20** was used directly after oxidation without purification. (b) Homologation of **20** was also conducted using method A in 63% yield (unoptimized) without product racemization.

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(14) Gordon, E. M.; Godfrey, J. D.; Delaney, N. G.; Asaad, M. M.; Von Langen, D.; Cushman, D. W. *J. Med. Chem.* **1988**, *31*, 2199.