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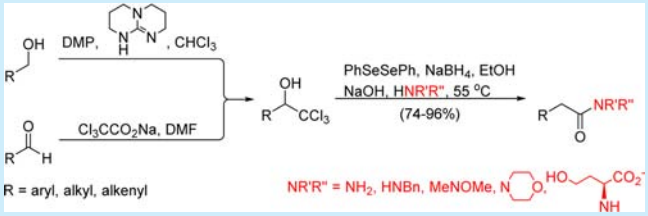
Preparation of One-Carbon Homologated Amides from Aldehydes or Primary Alcohols

Manoj K. Gupta, Zhexi Li, and Timothy S. Snowden*

Department of Chemistry, The University of Alabama, Box 870336, Tuscaloosa, Alabama 35487-0336, United States

Supporting Information

ABSTRACT: Aldehydes and primary alcohols can be converted to one-carbon homologated primary, secondary, or tertiary amides in two operational steps. The approach offers several unique features including compatibility with (hetero)-aryl, alkyl, alkenyl, and racemizable chiral substrates, the ability to prepare Weinreb amides from aryl and unhindered aliphatic substrates, and the opportunity to employ unprotected amino acids as amine sources in the amidation step.



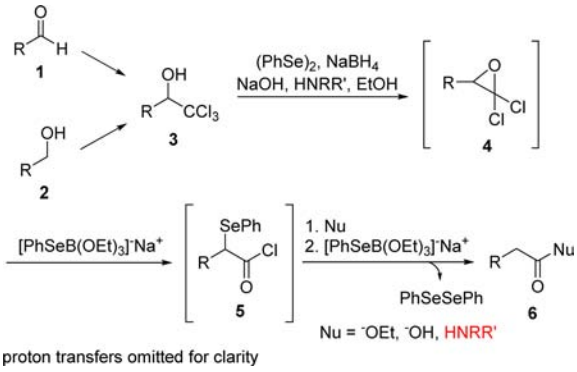
One-carbon homologation−functionalization reactions of carbonyl compounds have a rich history, particularly with regard to conversions of aldehydes and ketones to one-carbon extended carbonyl derivatives.[1] Several useful methods for the homologation−amidation of aldehydes have been reported;[2] however, all except the classic three-step approach by Watt[2a] are limited in the types of aldehydes usable as substrates, the types of amides formed (i.e., primary, secondary, or tertiary), or the commercial availability of required reagents. We reasoned that an extension of our conversion of aldehydes to one-carbon homologated carboxylic acids by way of trichloromethyl carbinols[3] might be modified to afford primary, secondary, or tertiary amides with a broad substrate scope and through the implementation of commercial reagents.

The key to such an approach was to establish conditions that took advantage of the relative reactivities of seven potential nucleophiles ($PhSeB(OEt)_3^-$,[4] HO^-, H_2O, EtO^-, EtOH, Cl^-, and HNRR′) that would compete in consecutive substitution reactions with two electrophilic intermediates, a *gem*-dichloroepoxide **4** and an acid chloride **5**, in a modification of a Jocic−Reeve-type reaction (Scheme 1).[5] Assuming we could convert trichloromethyl carbinols to the corresponding amides in high yields, our reported one-pot preparation of trichloromethyl carbinols from primary alcohols[6] would allow both aldehydes and alcohols to be used as substrates in one-carbon homologated amide preparations involving just two operational steps.

We synthesized 10 trichloromethyl carbinols as test substrates for the amide preparations starting from aldehydes (Table 1, method A)[7] and primary alcohols (Table 1, method B).[6] The carbinols were selected to feature functionality including electron-rich and electron-poor arenes, heteroarenes, aliphatic and alicyclic moieties, and conjugated and non-conjugated alkenes.

With compounds **3a−j** in hand, we conducted a series of reactions with **3a** and benzylamine to determine the optimum temperature and quantities of hydroxide and amine required to form the corresponding amide **6k** (Table 2). Reactions

Scheme 1. Planned Two-Pot Homologation−Amidation of Aldehydes and Primary Alcohols



conducted at either 65 or 55 °C external bath temperatures gave comparable results after 36 h (entries 1 and 2). However, the reaction was not complete even after 60 h when the system was heated at 45 °C (entry 3). Additional studies revealed that the number of equivalents of NaOH used had a dramatic effect on the product distributions at 55 °C. High yields of **6k** were obtained when either 3.0 (entry 2) or 2.5 equiv of NaOH (entry 6) were employed, and neither reaction showed evidence of byproduct formation. However, when 4.0 equiv of NaOH was used, phenylacetic acid was the major product isolated (entry 4). Meanwhile, use of 2.0 equiv of NaOH resulted in incomplete consumption of **3a** even after 60 h (entry 5). We also established that addition of more than 1.1 equiv of benzylamine did not increase the yield of **6k** (entries 6 and 7).

After establishing optimal reaction conditions, we explored the preparation of primary, secondary, and tertiary amides from **3a−j** (Table 3). Ammonia-saturated ethanol was used to

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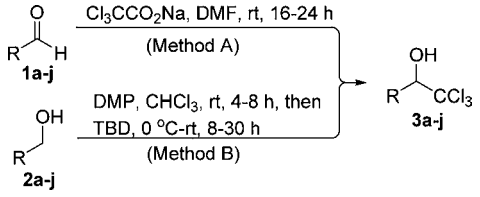
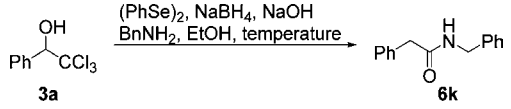
Table 1. Preparation of Trichloromethyl Carbinols from Aldehydes 1a–j or Primary Alcohols 2a–j



reactant	R	method[a,b]	product	yield[c] (%)
1a	Ph	A	**3a**	96
1b	4-CF_3Ph	A	**3b**	92
1c	4-CH_3OPh	A	**3c**	97
1d	$PhCH_2CH_2$	A	**3d**	89
1e	$CH_3(CH_2)_{10}$	A	**3e**	88
1f	Cy	A	**3f**	87
1g	2-furyl	A	**3g**	95
1h	thiophene-2-yl	A	**3h**	93
1i	(*E*)-$(CH_3)_2$CHCH=CH	A	**3i**	93
1j	(*E*)-PhCH=CH	A	**3j**	90
2a	Ph	B	**3a**	87
2b	4-CF_3Ph	B	**3b**	86
2c	4-CH_3OPh	B	**3c**	83
2d	$PhCH_2CH_2$	B	**3d**	71
2e	$CH_3(CH_2)_{10}$	B	**3e**	60
2f	Cy	B	**3f**	73
2g	2-furyl	B	**3g**	70
2h	thiophene-2-yl	B	**3h**	61
2i	(*E*)-$(CH_3)_2$CHCH=CH	B	**3i**	68
2j	(*E*)-PhCH=CH	B	**3j**	62

[a]Method A: 1.5 equiv of Cl_3CCO_2Na, 1.5 equiv of Cl_3CCO_2H, 0 °C to rt, 6–24 h. [b]Method B: 1.2 equiv of Dess–Martin periodinane (DMP), $CHCl_3$, 4–8 h, and then 3.3 equiv of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 0 °C to rt, 8–30 h. [c]Yield of purified product.

Table 2. Optimization of Formation of Amide 6k

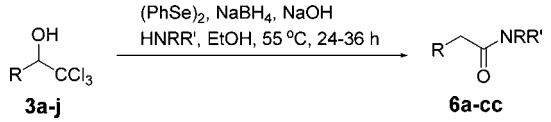


entry[a]	NaOH (equiv)	$BnNH_2$ (equiv)	temp (°C)	yield[b] (%)
1	3.0	2.2	65	87
2	3.0	2.2	55	86
3	3.0	2.2	45	63[c]
4	4.0	2.2	55	25[d]
5	2.0	2.2	55	54[c]
6	2.5	2.2	55	87
7	2.5	1.1	55	89

[a]1.3 equiv of $(PhSe)_2$, 2.8 equiv of $NaBH_4$, abs EtOH, rt, 30 min, then *x* equiv of NaOH, *y* equiv of $BnNH_2$, 45–65 °C, 36 h. [b]Yield of purified product. [c]Reaction not completed after 60 h. [d]Phenylacetic acid (44%) was the major product.

prepare primary amides, while benzylamine and morpholine were employed to afford representative secondary and tertiary amides, respectively. Gratifyingly, all amide types could be formed in high yields (>73%) with all tested substrates. Only substrate **3j**, which also generated 6–10% of the corresponding *α,β*-unsaturated amide as a byproduct in each reaction, and

Table 3. Conversions of Trichloromethyl Carbinols to Primary, Secondary, and Tertiary Amides



cmpd	R	HNRR′[a]	amide	yield[b] (%)
3a	Ph	NH_3[c]	**6a**	88
3b	4-CF_3Ph	NH_3[c]	**6b**	90
3c	4-CH_3OPh	NH_3[c]	**6c**	86
3d	$PhCH_2CH_2$	NH_3[c]	**6d**	85
3e	$CH_3(CH_2)_{10}$	NH_3[c]	**6e**	80
3f	Cy	NH_3[c]	**6f**	92
3g	2-furyl	NH_3[c]	**6g**	75
3h	thiophene-2-yl	NH_3[c]	**6h**	90
3i	(*E*)-$(CH_3)_2$CHCH=CH	NH_3[c]	**6i**	86
3j	(*E*)-PhCH=CH	NH_3[c]	**6j**	74
3a	Ph	$BnNH_2$	**6k**	89
3b	4-CF_3Ph	$BnNH_2$	**6l**	95
3c	4-CH_3OPh	$BnNH_2$	**6m**	87
3d	$PhCH_2CH_2$	$BnNH_2$	**6n**	85
3e	$CH_3(CH_2)_{10}$	$BnNH_2$	**6o**	96
3f	Cy	$BnNH_2$	**6p**	93
3g	2-furyl	$BnNH_2$	**6q**	83
3h	thiophene-2-yl	$BnNH_2$	**6r**	92
3i	(*E*)-$(CH_3)_2$CHCH=CH	$BnNH_2$	**6s**	96
3j	(*E*)-PhCH=CH	$BnNH_2$	**6t**	82
3a	Ph	morpholine	**6u**	88
3b	4-CF_3Ph	morpholine	**6v**	88
3c	4-CH_3OPh	morpholine	**6w**	81
3d	$PhCH_2CH_2$	morpholine	**6x**	84
3f	Cy	morpholine	**6y**	95
3g	2-furyl	morpholine	**6z**	75
3h	thiophene-2-yl	morpholine	**6aa**	91
3i	(*E*)-$(CH_3)_2$CHCH=CH	morpholine	**6bb**	82
3j	(*E*)-PhCH=CH	morpholine	**6cc**	78

[a]1.3 equiv of $(PhSe)_2$, 2.8 equiv of $NaBH_4$, abs EtOH, rt, 30 min, then 2.5 equiv of NaOH, 1.1 equiv of amine (HNRR′), 55 °C, 24–36 h. [b]Yield of purified product. [c]Reaction conducted in NH_3-saturated abs EtOH.

sensitive substrate **3g**, which also produced colored polymeric byproducts, resulted in yields less than 80%.

With the ability to form homologated primary, secondary, or tertiary amides from aryl, alkyl, or alkenyl substrates, we expanded our investigation to the generation of Weinreb amides.[8] To our knowledge, no homologation–Weinreb amidation method that requires fewer than four operational steps is reported.[9] However, using the outlined method, trichloromethyl carbinols **3a–f**, derived from **1a–f** or **2a–f**, were converted to the corresponding Weinreb amides in 75–89% yields (Table 4).

Although Weinreb amide preparations worked well with the aryl and aliphatic trichloromethyl carbinols, attempted preparations of Weinreb amides from substrates **3g–j** unexpectedly afforded the secondary *N*-methylamides as the major products (Figure 1). On the basis of the results of our investigations and Graham's reported studies of base-promoted elimination of formaldehyde from Weinreb amides leading to the corresponding *N*-methylamides,[10] the substrates must satisfy one of two criteria to allow formation of **7** in reasonable

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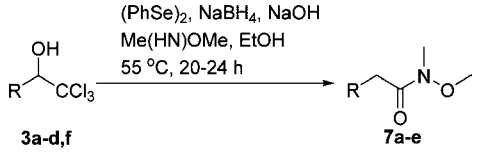
Table 4. Conversion of Trichloromethyl Carbinols to Weinreb Amides



compd	R	product[a]	yield[b] (%)
3a	Ph	**7a**	83
3b	4-CF_3Ph	**7b**	89
3c	4-CH_3OPh	**7c**	76
3d	$PhCH_2CH_2$	**7d**	87
3f	Cy	**7e**	75

[a]1.3 equiv of $(PhSe)_2$, 2.8 equiv of $NaBH_4$, abs EtOH, rt, 30 min, then 3.3 equiv of NaOH, 1.1 equiv of MeONHMe·HCl, 55 °C, 20−24 h. [b]Yield of purified product.

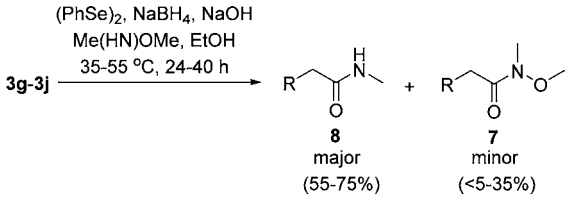


Figure 1. Preferential formation of *N*-methylamides **8** during attempted formation of Weinreb amides **7** from **3g−j**.

yields. Either the Weinreb amide intermediates or products, once formed, must readily enolize to suppress elimination (e.g., **3b** and **3d**) or the corresponding trichloromethyl carbinols must be converted to **7** within 18−24 h. Compounds **3g−j** all required 36−40 h for complete consumption, and during that extended reaction time, the Weinreb amide products created were largely demethoxylated leading to **8**. Reactions attempted at 35 or 45 °C did not offer improved yields. Even with these results, the examples in Table 4 show that substituted benzyl alcohols, benzaldehydes, and aliphatic alcohols and aldehydes can now be converted to homologated Weinreb amides in attractive yields in just two operational steps.

We challenged the method further by using an unprotected *α*-amino acid, L-homoserine, with its unhindered hydroxyethyl side chain and its carboxylate group available to compete with the 2-amino group, in the homologation−functionalization of **3e**. The reaction generated the *N*-acylated homoserine **9** as the only observed product in 89% yield (Figure 2).[11]

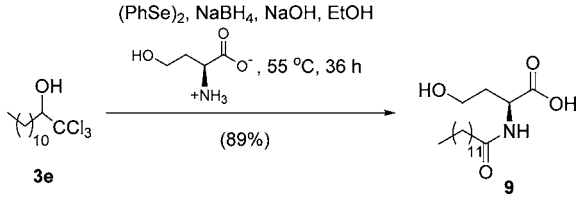
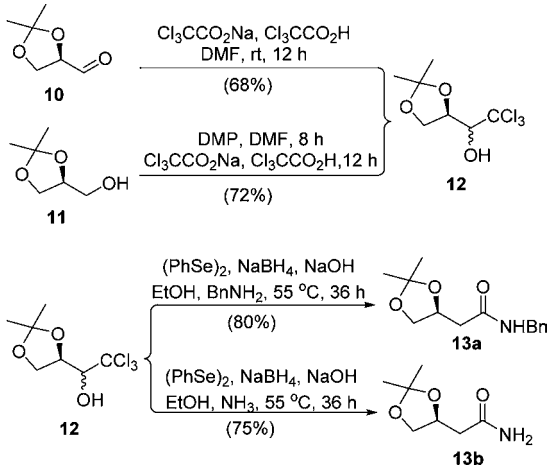


Figure 2. Amide formation using unprotected L-homoserine.

We also tested the utility of the method in a one-carbon homologation−amidation of a chiral enolizable aldehyde **10** and the corresponding alcohol **11**, which becomes **10** in the one-pot trichloromethylation step (Scheme 2). Both substrates were converted to trichloromethyl carbinol **12** in one pot using sodium trichloroacetate buffered with trichloroacetic acid in

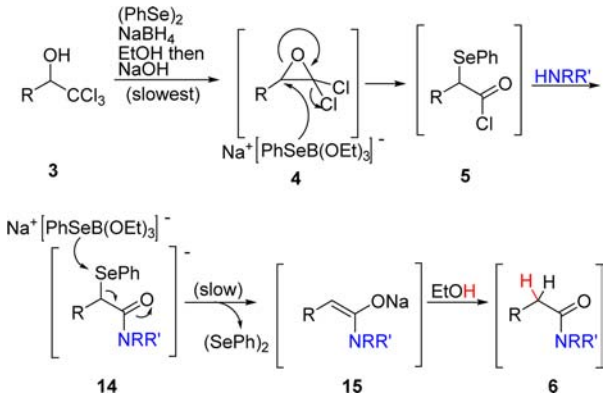
Scheme 2. Two-Step Preparation of Chiral Amides 13a and 13b from Racemizable 10 and 11 (Racemizable via Intermediate 10)



DMF as the source of trichloromethide.[7] The products generated from the two substrates featured identical characterization data and showed no evidence of racemization.[5d,6] Compound **12** was then treated separately with ammonia-saturated ethanol and with benzylamine to afford known chiral amides **13a** and **13b**.[12] The enantiopurity of both compounds was confirmed by Mosher diester analysis of the deprotected dihydroxyamides, thereby affirming the compatibility of the two-step protocol with sensitive chiral substrates. This appears to be the first reported example of a homologation−amidation of a chiral alcohol or aldehyde in two or fewer operational steps. Unfortunately, attempted conversion of **12** to the corresponding Weinreb amide resulted in predominant formation of the undesired *N*-methylamide.

A plausible mechanism for the transformation of **3** to **6** deduced from known reactions involving *gem*-dichloroepoxide intermediates, the possible isolation of significant quantities of intermediate **14**, and the complete recovery of the diphenyldiselenide after workup of reactions that are allowed to go to completion, is outlined in Scheme 3. No compounds other than **3**, **14**, and **6** were detected during the reactions. Upon deprotonation of the trichloromethyl carbinol **3**, a reactive *gem*-dichloroepoxide **4** is formed in the requisite protic media. Generation of **4** is the slowest step of the reaction,

Scheme 3. Proposed Mechanism of Amide Formation



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generally requiring 12−24 h for full conversion of the conjugate base of **3** to **4** depending upon the substrate used.

Once formed, intermediate **4** quickly undergoes nucleophilic substitution by the poorly solvated phenylseleno(triethyl)-borate complex. Opening of the epoxide leads to formation of an acid chloride intermediate **5** that is subject to rapid preferential nucleophilic acyl substitution with the available amine in a Schotten−Baumann-type reaction.[13,14] The resultant α-phenylselenoamide intermediate **14** slowly undergoes α-dephenylselenation (this step requires 4−16 h depending upon the structure of **14** and the amount of phenylseleno(triethyl)-borate complex remaining) followed by rapid protonation of the ensuant enolate **15** in the protic media to afford the amide product **6**. The only byproducts identified from these reactions, with the exception of the demethoxylated product described during some attempted Weinreb amide preparations and the small amount of α,β-unsaturated amide obtained in reactions involving **3j**, are **14** if the reactions are quenched too early. We also noted small amounts of α-aminoamide formation when older sources of $NaBH_4$ were used (due to incomplete formation of phenylseleno(triethyl)borate complex) or when oxygen was inadvertently introduced to the system (due to regeneration of diphenyldiselenide) prior to complete conversion of **3** to intermediate **5**.

In summary, we developed a novel two-step preparation of one-carbon homologated amides from primary alcohols or aldehydes. The approach offers unmatched versatility in terms of substrate compatibility and its capacity to furnish disparate primary, secondary, or tertiary amides with comparable facility. Aryl and unhindered aliphatic primary alcohols and aldehydes can also be transformed into one-carbon homologated Weinreb amides.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds and products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: snowden@bama.ua.edu.

Notes

The authors declare no competing financial interest.

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(11) The stereochemical integrity of **9** was confirmed by Mosher ester analysis. See the Supporting Information for details.

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(14) GC−MS analysis of reaction aliquots at various time points showed no evidence of acylselenium intermediates, although generation of such species cannot be unequivocally dismissed.