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Copper Catalyzed Chlorine Transfer Cyclizations of Glycine and Glycolic Acid Derivatives

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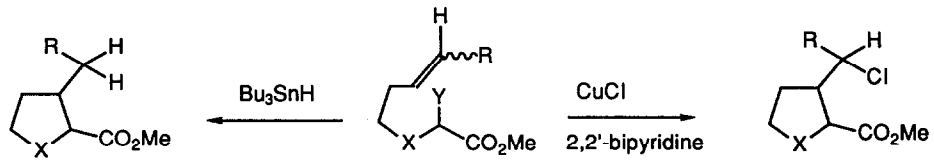
Key Words: radical cyclization; 3-substituted prolines; 3-substituted 2-tetrahydrofurancarboxylic esters; cuprous chloride 2,2'-bipyridine complex; methyl glyoxylate adducts

Abstract: *Chloroglycine and chloroglycolic acid derivatives smoothly cyclize in the presence of a catalytic amount of cuprous chloride and 2,2'-bipyridine to produce functionalized proline and 2-tetrahydrofurancarboxylic esters, respectively, in an atom transfer process.*

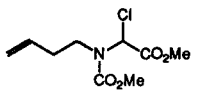
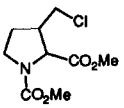
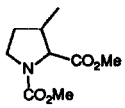
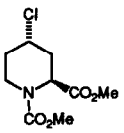
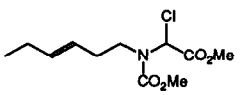
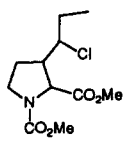
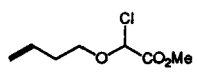
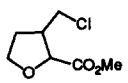
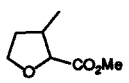
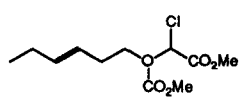
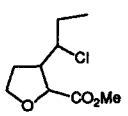
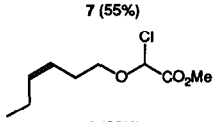
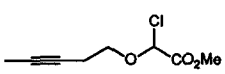
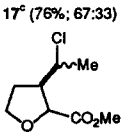
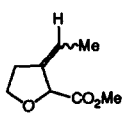
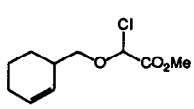
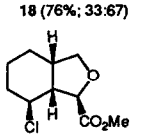
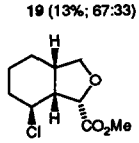
Radical mediated C-C bond formation between a halogen bearing carbon atom and an olefinic double bond has become an important cyclization method in organic synthesis.[1] Of the various available techniques the atom transfer method has the synthetic advantage that it avoids the reductive termination step of the tin hydride process, thus preserving functionality for further synthetic transformations.[2,3] Recently, we described the use of glycine and glycolic acid derived radical precursors **1a** (X = NCO_2Me or O) for cyclization processes to proline[4] and 2-tetrahydrofurancarboxylic acid[5] derivatives **2** (see eq 1). We herewith report that the corresponding chlorides **1b** undergo chlorine transfer cyclization, catalyzed by Cu(I), to give the more highly functionalized heterocycles **3**. The use of precursors of type **1b** in this manner finds, as far as we know, only precedent in the $Pd(PPh_3)_4$ catalyzed ene-halogenocyclization to bicyclic β-lactam systems.[6]



2 **1a** Y = SPh, **1b** Y = Cl **3** (1)

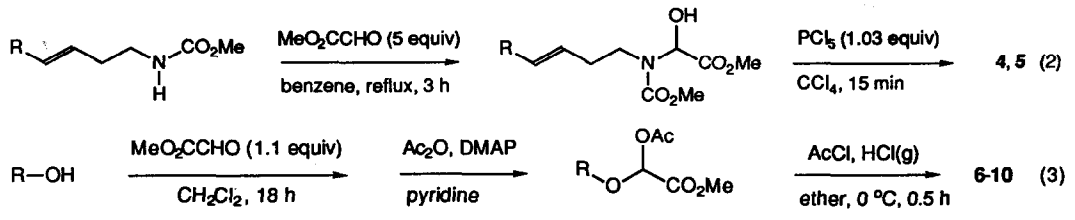
The cyclization precursors **4** and **5** (see Table), leading to proline derivatives, were synthesized from methyl 3-butenyl- and methyl 3-(*E*)-hexenylcarbamate, respectively, in two steps (eq 2). Addition of the latter carbamates to methyl glyoxylate[7] led to stable hemiacetals, which were purified by using flash chromatography. Treatment of these glyoxylate adducts with PCl_5 in CCl_4[8] gave the chlorides **4** and **5** as moisture sensitive oils, virtually pure according to NMR.[9] The tetrahydrofuran precursors **6-10** were prepared from the corresponding alcohols as shown in eq 3. Synthesis of the acetates of the glyoxylate adducts from the alcohols has been published before.[10] Their conversion into the chlorides required treatment with excess acetyl chloride and hydrogen chloride in ether,[11] and evaporation of the volatiles, to give **6-10** as virtually pure oils (according to NMR)[12], which were less moisture sensitive than nitrogen analogues **4** and **5**.

Table

entry	cyclization precursor (yield)[a]	solvent	reaction time (h)	products (yield[b]; cis:trans or Z:E ratio)		
						
1	**4** (86%)	DME	17	**11** (47%; 30:70)	**12** (4%)	**13** (12%)
2		THF	17	(41%; 30:70)	(4%)	(27%)
3		$(CH_2Cl)_2$	16	(50%; 30:70)		(25%)
						
4	**5** (81%)	acetone	18	**14**[c] (83%; 11:89)		
						
5	**6** (48%)	THF	18	**15** (65%; 57:43)	**16** (7%; 60:40)	
6		CH_2Cl_2	48	(84%; 71:29)		
7		$(CH_2Cl)_2$	16	(80%; 66:34)		
						
8	**7** (55%)	THF	72	**17**[c] (85%; 60:40)		
						
9	**8** (66%)	MeOAc	18	**17**[c] (76%; 67:33)		
						
10	**9** (57%)	MeOAc	18	**18** (76%; 33:67)	**19** (13%; 67:33)	
						
11	**10** (35%)	CH_2Cl_2	72	**20** (18%)	**21** (45%)	

[a] Overall yields from NH-carbamate or alcohol (see text). [b] Isolated yield, unless otherwise stated; however, **11** and **12**, **15** and **16**, and **18** and **19** were inseparable mixtures. [c] Mixture of four diastereomers .

The cyclization reactions of precursors **4-10** were carried out in the presence of 0.3 equiv of cuprous chloride and 0.3 equiv of 2,2'-bipyridine[3c] under reflux in the solvent, indicated in the Table. As a representative procedure the cyclization of **7** is detailed in a note.[13]



An important aspect of the methodology was the choice of the solvent. Firstly, the copper bipyridine complex had to be in solution, and secondly, the solvent should not contain reactive hydrogen atoms that might lead to reduction, thus competing with chlorine transfer. Entries 1, 2, 5 and 10 show that reduction took place to a small extent in DME, THF and MeOAc, leading to byproducts **12**, **16**, and **19**.[3] These compounds were already characterized after tin hydride mediated radical cyclizations.[4,5] Best chlorine transfer results were obtained in dichloromethane and 1,2-dichloroethane as solvent,[3g] giving no trace of reduction products (entries 3, 6, 7, and 11). 1,2-Dichloroethane is preferred because of its higher boiling point (82 °C), giving rise to complete cyclization of **6** after reflux overnight (18 h reflux in CH_2Cl_2 gave only 74% conversion, cf entries 6 and 7). Acetonitrile was unsuitable in our case, because in this polar solvent cationic processes became competitive, leading to the formation of considerable amounts of the *trans*-4-acetamidopipecolic ester derivative from **4**.[14] The apolar solvent benzene also failed to give atom transfer cyclization, probably because of the insolubility of the catalyst.[15]

The chlorine transfer processes occurred with comparable regio- and stereoselectivity as the tin hydride mediated cyclizations.[4,5] Thus, all substrates mentioned only produced the 5-exo products, except for **4** which gave 6-endo product **13** as a minor regioisomer. The stereochemical assignment of the cyclization products with respect to 5-membered ring substitution was mainly based on comparison of their NMR data with data for the reduced products.[4,5] Chlorine transfer occurred with little stereoselectivity in the formation of **14**, **17**[16] and **18**[16], but **13**,[14] **20**,[16] and **21**[16] were obtained as single stereoisomers with equatorial chlorine substituents.

Comparison of the regio- and stereochemical course of the chlorine transfer processes reported herein with tin hydride mediated cyclizations[4,5] strongly suggest the intermediacy of radicals. The relatively[3] low temperatures required for chlorine transfer indicate that the initially formed radical intermediates are considerably stabilized, possibly due to the capto-dative effect.[17] Further elaboration and applications of the present methodology will be described in due course.

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7. Generated from the commercially available methyl hemiacetal of methyl glyoxylate through distillation from phosphorus pentoxide (cf. Hook, J. M. *Synth. Commun.* **1984**, *14*, 83).
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9. Data for chloride **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.25-2.50 (m, 2 H, $=CCH_2$), 3.24-3.64 (m, 2 H, NCH_2), 3.78 (s, 3 H) and 3.81 (s, 3 H, 2 × OCH_3), 5.00-5.13 (m, 2 H, $=CH_2$), 5.63-5.80 (m, 1 H, =CH), 6.41 (s, ClCH). ^{13}C NMR (63 MHz, $CDCl_3$): δ 32.9 ($=C\underline{C}H_2$), 45.5 (NCH_2), 53.4 and 53.5 (2 × OCH_3), 70.1 (ClCH), 116.8 ($=CH_2$), 134.5 (=CH), 155.3 (NC=O), 165.6 (C=O).
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12. Data for chloride **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37-2.50 (m, 2 H, $=CCH_2$), 3.56-4.08 (m, 2 H, OCH_2), 3.85 (s, 3 H, OCH_3), 5.06-5.18 (m, 2 H, $C=CH_2$), 5.69-5.90 (m, 1 H, C=CH), 5.83 (s, 1 H, ClCH). ^{13}C NMR (63 MHz, $CDCl_3$): δ 32.8 ($=C\underline{C}H_2$), 52.9 (OCH_3), 69.5 (OCH_2), 88.2 (CHCl), 117.2 ($=CH_2$), 133.4 (=CH), 165.4 (C=O).
13. To a solution of **7** (0.994 g, 4.81 mmol) in 16 mL of THF under a nitrogen atmosphere was added 2,2'-bipyridine (0.225 g, 1.44 mmol) and cuprous chloride (0.143 g, 1.44 mmol). The mixture was heated under reflux for three days. After removal of the solvent in vacuo, the residue was subjected to flash chromatography (EtOAc/hexanes 1:6) to give **17** as a 60:40 mixture of *cis*- and *trans*-3-(1-chloropropyl)-2-tetrahydrofurancarboxylic acid methyl ester (0.840 g, 4.07 mmol, 85%): R_f 0.50 (*cis*) and 0.35 (*trans*), IR ($CHCl_3$): 1738 cm^{-1} (C=O). Accurate mass 206.0712 (calcd for $C_9H_{15}O_3Cl$ 206.0715). Data for *cis*-**17**: ^{1}H NMR (200 MHz, $CDCl_3$): mixture of stereoisomers (1:1), δ 1.04 (t, J = 7.2 Hz, 3 H), 1.62-2.22 (m, 4 H), 2.69-2.82 (m, 1 H, H-3), 3.74 (s, 3 H), 3.71-4.05 (m, 2 H), 4.24 (dt, J = 8.5, 2.9 Hz, 1 H), 4.47 (d, J = 8.0 Hz) and 4.60 (d, J = 7.3 Hz), 1 H, H-2). ^{13}C NMR (63 MHz, $CDCl_3$): δ 10.3, 11.0 ($CH_2\underline{C}H_3$), 28.8, 30.1, 31.2 ($\underline{C}H_2CH_3$, C-4), 49.6, 50.7 (C-3), 51.7, 52.0 (OCH_3), 63.2, 64.1 (CCl), 68.5, 69.1 (C-5), 78.2, 79.4 (C-2), 171.69, 171.72 (C=O). Data for *trans*-**17**: ^{1}H NMR (200 MHz, $CDCl_3$): mixture of stereoisomers (1:1), δ 1.05, 1.06 (2 × t, J = 7.2 Hz, 3 H), 1.67-2.18 (m, 4 H), 2.63-2.75 (m, 1 H, C-3), 3.75, 3.76 (2 × s, 3 H), 3.68-4.11 (m, 3 H), 4.38 (d, J = 6.8 Hz) and 4.47 (d, J = 5.1 Hz, 1 H, H-2). ^{13}C NMR (63 MHz, $CDCl_3$): δ 11.1, 11.4 ($CH_2\underline{C}H_3$), 27.6, 30.1 ($\underline{C}H_2CH_3$), 29.7, 30.6 (C-4), 49.6, 50.0 (C-3), 52.0, 52.2 (OCH_3), 66.0, 66.8 (CCl), 68.5, 69.1 (C-5), 79.1, 79.2 (C-2), 173.1, 173.3 (C=O).
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15. The ruthenium(II) complex $RuCl_2(PPh_3)_3$[3] could, however, be used as catalyst in refluxing benzene, to give **15** in good yield (NMR) from **6** (48 h, 0.1 equiv of catalyst).
16. Stereochemistry was assigned by using the NOE difference technique.
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