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First Direct Reductive Amination of Mucochloric Acid: A Simple and Efficient Method for Preparing Highly Functionalized α,β-Unsaturated γ-Butyrolactams

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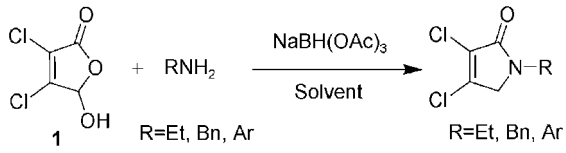
ABSTRACT



The first direct reductive amination of mucochloric acid (1) has been accomplished. Reaction of 1 with various alkyl, aryl, and benzylamines, followed by reduction in the same pot, provides an efficient method of obtaining *N*-benzyl-3,4-dichloro-1,5-dihydro-pyrrol-2-one and *N*-aryl (or alkyl)-3,4-dichloro-1,5-dihydro-pyrrol-2-ones.

The γ-butyrolactam (pyrrolidinone or γ-lactam) skeleton exists throughout nature and is present in many bioactive natural products;[1] it also serves as a key intermediate in the synthesis of biologically and pharmaceutically useful molecules.[2] For example, Ennis and co-workers[3] used a chiral polycyclic lactam to prepare cis-fused bicyclic pyrrolidine U-93385, a potent serotonin 1A agonist. Recently, Snider and his team[4] finished the total synthesis of racemic martinellic acid, a novel non-peptide antagonist for the bradykinin (BK) B_1 and B_2 receptor. Reduction of the pyrrolidinone to an amino alcohol, a key step, was achieved by careful selection of the reducing agent. A short time ago, Duan and co-workers[5] reported development of a new series of selective TACE inhibitors based on a γ-lactam scaffold. These compounds may have potential use in the treatment of rheumatoid arthritis.

The γ-butyrolactam skeleton can be viewed as the dehydration product of γ-aminobutyric acid (GABA),[6] one of the most abundant inhibitory neurotransmitters. Several successful pharmaceutical products and drug candidates such as Neurontin, (*R*)-Baclofen, and CI-1008 (Pregabalin) are γ-amino acids.[7] The γ-lactams Rolipram and Rolicyprine are antidepressant agents.[8] Generally speaking, γ-amino acids

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serve as precursors to γ-lactams,[9] but in some cases γ-lactams can be transformed into the corresponding γ-amino acid.[10]

Furthermore, the γ-butyrolactam can be converted to pyrrolidine by reduction.[11] Pyrrolidines are ubiquitous structural motifs in drugs and potential drug candidates such as antidepressants,[12] antimicrobials,[13] antihypertensives,[14] antiarthritics,[15] antivirals,[16] and antinociceptive agents.[17] Singaram and co-workers recently reported the facile reduction of *N*-alkyl lactams to the corresponding pyrrolidines in excellent yields using lithium aminoborohydrides.[18]

Considering the close relationship among γ-lactams, γ-amino acids, and pyrrolidine and their potential benefit in drug discovery and development, we set out to develop a method for preparing highly functionalized α,β-unsaturated γ-butyrolactams.[19] Mucochloric acid (**1**, 3,4-dichloro-5-hydroxy-5*H*-furan-2-one) is a commercially available and inexpensive starting material with multiple functional groups and has attracted our attention recently.[20] It has one carbon−carbon double bond with (*Z*)-configuration, two halogen atoms, and two carbonyl groups possessing different reactivity. Surprisingly, this C-4 building block is not often used in organic synthesis, presumably for reasons of its many reactive sites, poor stability under basic conditions, and assumed difficulty in the selective manipulation of its halogen atoms. Therefore, we sought to develop a manifold for selective manipulation of this densely functionalized molecule.

It has long been known that **1** and **2** (mucobromic acid) react with hydrazine (**3**) or arylhydrazines **4** to form pyridazinones **5** in acetic acid medium (Figure 1).[21] This prompted us to investigate the reactions of **1** or **2** with aniline or benzylamine in acetic acid, including reductive amination. The reaction products would be useful as intermediates in organic synthesis, especially in the synthesis of many biologically active heterocycles such as substituted 1,5-dihydro-pyrrol-2-ones,[22] other γ-lactams,[23] and pyrrolidines.[24] Herein we report the first direct reductive amination of mucochloric acid (**1**).

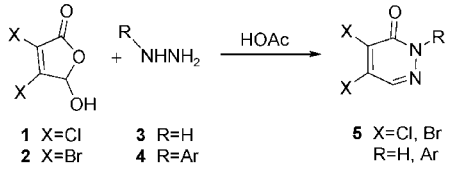
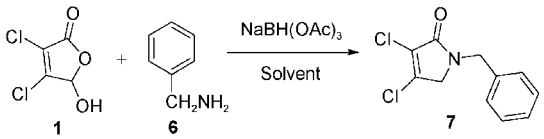


Figure 1. Condensation of mucohalic acids with hydrazines.

The reaction between **1** and benzylamine (**6**) was selected initially (Table 1). A 1:1 v/v mixture of dichloromethane

Table 1. Reductive Amination in Different Solvents[a]



entry	solvent	yield (%)[b]
1	1:1 CH_2Cl_2/HOAc	46
2	1,4-dioxane	48
3	THF	52
4	CH_3CN	49
5	DCE	68
6	$CHCl_3$	66
7	CH_3NO_2	35
8	$CHCl_3$	76

[a] Reaction conditions: 1 equiv of **1**, 1.1 equiv of **6**, 1.5 equiv of $NaBH(OAc)_3$, 24 h at room temperature. A catalytic amount of HOAc was used in entries 2−8. The reaction time was not optimized. A reaction time of 48 h and 1.5 equiv of **6** was used in entry 8. [b] Products were isolated and purified by silica gel chromatography and/or crystallization. Isolated yields are averages of two runs, and products are estimated to be >95% pure by ^{1}H NMR and elemental analysis. All compounds gave satisfactory elemental analysis data.

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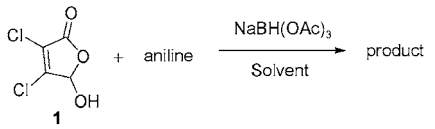
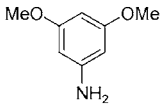
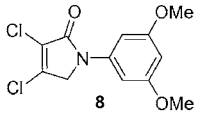
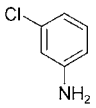
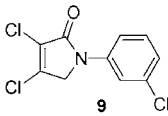
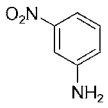
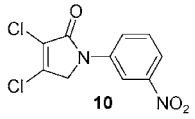
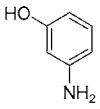
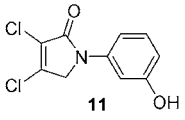
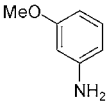
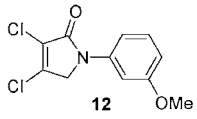
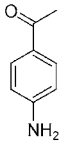
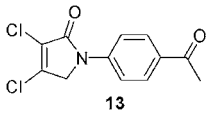
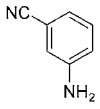
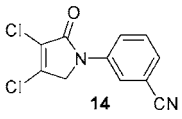
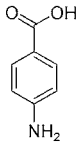
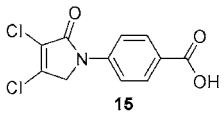
Table 2. Reductive Amination with Different Anilines[a]



entry	aniline	product	yield (%)[b]
1			55
2			65
3			42
4			40
5			60
6			68
7			75
8			53

[a] Reaction conditions (except for entry 1): 1 equiv of **1**, 1.0 equiv of aniline, 3.0 equiv of $NaBH(OAc)_3$, 5:3 v/v CH_2Cl_2/HOAc, 24 h at room temperature. Reaction conditions for entry 1: 1 equiv of **1**, 1.1 equiv of aniline, 1.5 equiv of $NaBH(OAc)_3$, $CHCl_3$ (cat. HOAc), 24 h at room temperature. The reaction time was not optimized. [b] Products were isolated and purified by silica gel chromatography and/or crystallization. Products are estimated to be >95% pure by ^1H NMR and elemental analysis. All compounds gave satisfactory elemental analysis data.

and acetic acid was chosen as the solvent to maintain the stability and solubility of both starting materials. A mild reductive amination reagent, sodium triacetoxyborohydride,[25] was used, and the reactions were conducted at room temperature. Initially γ-lactam **7** was isolated in 46% yield, but a solvent screen revealed that **7** could be obtained in 66−76% yield once the amount of acetic acid was reduced.

The reaction has been further extended to anilines, with electron-donating, electron-withdrawing, and neutral substituents (Table 2).[26] Electron-deficient (entries 2, 3, and 7) and electron-rich (entries 1, 4, and 5) anilines reacted with almost equal facility.

Mucochloric acid (**1**) can exist as the open or cyclic form (Figure 2).[27] However, the ultraviolet spectrum in $CHCl_3$ indicates that **1** exists predominantly in the lactone form.[28]

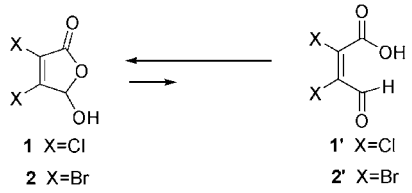


Figure 2. Equilibria of mucochloric and mucobromic acids.

Additional spectral data, i.e., vibrational (IR, Raman)[29] and others (NMR and NQR)[30] suggest that the lactone is the dominant form in both the liquid and solid states. Experi-

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(27) It is interesting to note that several fine chemical manufacturers' catalogs list **1** only as the open form, whereas The Merck Index suggests the existence of an equilibrium between the open and cyclic forms: (a) *The Merck Index*, 12th ed.; Merck & Co., Inc.: Whitehouse, NJ, 1996; p 1079. (b) *2003−2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 2003; p 1313. (c) *Acros Organics 2002/03 Catalog of Organics and Fine Chemicals*; Fisher Scientific Company, L.L.C.: Pittsburgh, PA, 2002; p 1523. (d) *Lancaster 2002−3 Research Chemicals Catalog*; Lancaster Synthesis, Inc.: Windham, NH, 2002; p 1304.

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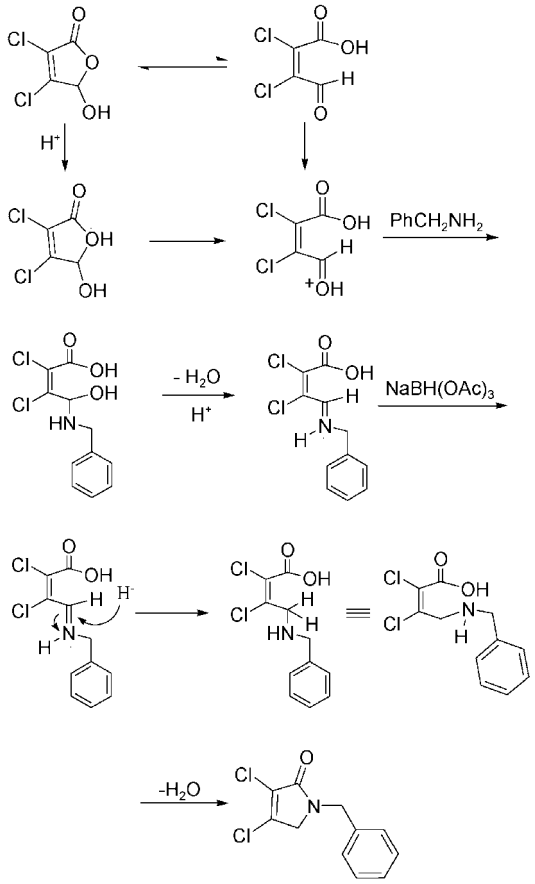
(30) Valente, E. J.; Fuller, J. F.; Ball, J. D. *Acta Crystallogr., Sect. B. Struct. Sci.* **1998**, *B54*, 162.

mental results further support these observations. Thus, a possible mechanism for forming lactam **7** is proposed in Scheme 1.

Scheme 1. Proposed mechanism of reductive amination

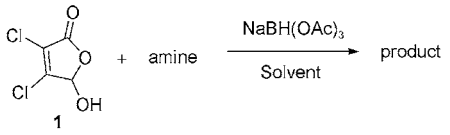


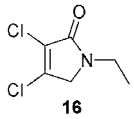
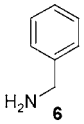
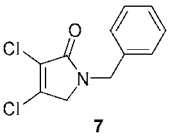
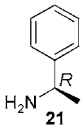
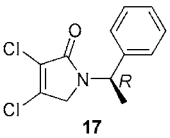
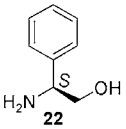
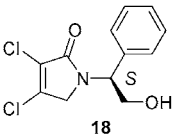
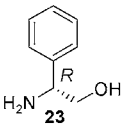
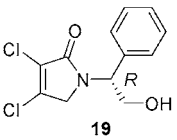
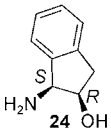
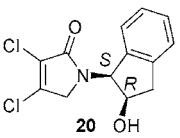
In accordance with the proposed mechanism, removing water will favor formation of the desired lactams. Therefore, 4 Å molecular sieves were added to the reaction mixture and the chemical yield was increased from 76 to 85% (Table 1, entry 8; Table 3, entry 2). We also successfully introduced chirality into the lactam system by using chiral amines **21**−**24**.

In summary, we have developed a simple, efficient, and selective method for preparing *N*-benzyl-3,4-dichloro-1,5-dihydro-pyrrol-2-one and *N*-aryl (or alkyl)-3,4-dichloro-1,5-dihydro-pyrrol-2-ones.[31] These products possess a geometrically defined tetrasubstituted olefin and two differentiated vinyl halides, and could be used in the synthesis of a variety of compounds. Further investigations, including extension of the use of these building blocks, will be reported in due course.

(31) Mucobromic acid (**2**) gave the corresponding bromides when subjected to similar reaction conditions. Unpublished results.

Table 3. Reductive Amination with Different Amines[a]



entry	amine	product	yield (%)[b]
1		 **16**	67
2	 **6**	 **7**	85[c]
3	 **21**	 **17**	89
4	 **22**	 **18**	89[c]
5	 **23**	 **19**	92[c]
6	 **24**	 **20**	79[c]

[a] Reaction conditions: 1 equiv of **1**, 1.1 equiv of amine, 1.5 equiv of $NaBH(OAc)_3$, $CHCl_3$ (cat. HOAc), 24 h at room temperature. The reaction time was not optimized. [b] Products were isolated and purified by silica gel chromatography and/or crystallization. Products are estimated to be >95% pure by ^1H NMR and elemental analysis. All compounds gave satisfactory elemental analysis data. [c] Used 4 Å molecular sieves.

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Supporting Information Available: Experimental procedures, spectral and analytical data for all products, and additional structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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