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Easy approach to 3-benzylimino-2-pyrrolidinones from 3-chloro-4-chloromethyl-2-pyrrolidinones

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Abstract

3-Benzylimino-2-pyrrolidinones can be prepared in good yield by heating 3-chloro-4-chloromethyl-2-pyrrolidinones, benzylamine and NaI in THF at 80°C. An *endo*-dehydrohalogenation followed by a SN_2' substitution on the intermediate allyl chloride, and finally a shift of the *exo*-double bond to Δ^3 with attendant tautomerization, appears to be the most probable reaction mechanism.

Keywords: amino acids; amino acid derivatives; imines; lactams; pyrrolidinones.

3-Amino-2-pyrrolidinones are appealing structures that are capturing the attention of many researchers.[1] The interest is stimulated by their biological activity and their use as building-blocks for conformationally-constrained peptides:[2] and indeed, pharmaceutically-active compounds with this substructure frame are well-known.[3] 3-Amino-γ-lactams can also be considered derivatives of α,γ-diaminoacids, which are substances found in natural products, like ornithine, polymyxin and aerosporin.[1c,4] Moreover, appendages important for increasing the activity of antibacterial drugs, such as the C-7 substituent of quinolone agents, could easily be obtained by reduction of the 3-amino-2-pyrrolidinone nucleus to 3-amino-pyrrolidine.[5]

Cyclization of glycinyl radical, generated by irradiation of modified dipeptides[1a] or through the protection/radical translocating group,[1b] and Raney-Ni catalyzed hydrogenation of 1-pyrazoline-3-carboxylic acid derivatives[1c] are the most recent methods devised for synthesizing 3-amino-2-pyrrolidinones. Here, we report an efficient one-pot conversion of 3-chloro-4-chloromethyl-2-pyrrolidinones to 3-imino-2-pyrrolidinones. Owing to the easy reduction of the imino group[6] and the selectivity and efficiency of the nucleophilic addition of organometallic reagents to the C=N bond,[7] our proposal can be viewed as an alternative and versatile route to 3-amino-γ-lactams.

Recently, we have reported the use of CuCl–TMEDA as a promoter for halogen atom transfer via radical rearrangement of *N*-allyl-*N*-protected-2,2-dihaloamides to 2-pyrrolidinones.[8] With the aim

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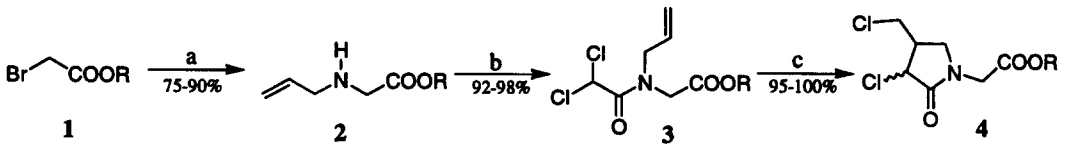
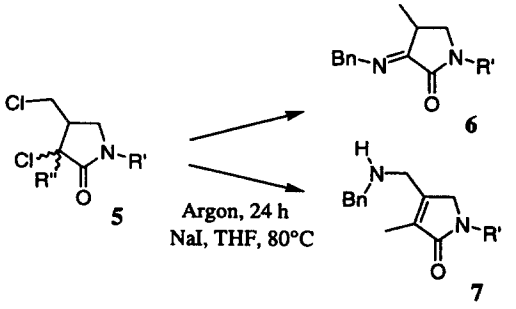
of preparing Freidinger dipeptides,[2] we have synthesized in good yields *N*-alkyl-carboxymethyl-3-chloro-4-chloromethyl-2-pyrrolidinones (Scheme 1), which are potential candidates as conformationally constrained segments.



Scheme 1. (a) Allylamine, Et_3N, DMSO, rt; (b) Dichloroacetylchloride, Et_3N, CH_2Cl_2, 0°C; (c) CuCl/TMEDA 20%, CH_3CN, 80°C, argon

To replace the more mobile *endo*-chlorine[9] with a nucleophilic nitrogen source, several protocols were followed, but the results were generally unsatisfactory. However, when **5a** was treated with benzylamine (3 equiv.) and NaI in THF at 80°C, we observed formation of the 3-benzylimino derivative **6a**, as a single *anti* stereoisomer, in good yields (Scheme 2).[10] Good results were also obtained when using *N*-protections of different sizes **5b** and **5c** (Table 1), whereas when replacing the C(3)-H with a C(3)-CH_3 (**5d**), the major product isolated, albeit in modest yields (conv. 56%, yield 26%) was the *N*-benzyl-4-benzylaminomethyl-3-methyl-3-pyrrolin-2-one **7**. This clearly rules out a 1,3-shift of the C(3) substituent in the conversion of **5** to **6**. It is likely that the reaction proceeds through an *endo*-dehydrohalogenation followed by a SN_2' substitution on the intermediate allyl chloride and a final shift of the *exo*-double bond to Δ^3 with attendant tautomerization.



Scheme 2.

The easy elimination of 3-chloro-4-methyl-2-pyrrolidinone to the corresponding 3-pyrrolin-2-one under the same reaction conditions (conv. 100%, yield 76%), in contrast to the more difficult dehydrohalogenation of the 4-chloromethyl-2-pyrrolidinone (after 24 h, conv. 33%, mixture of dehydrohalogenated and substituted adducts), supports the previous hypothesis.

Table 1
Reaction of benxylamine with **5**

R'	R''		Yield (%)[a]
$CH_2COOCH_2CH_3$	H	**a**	67
$CH_2COOCH(CH_3)_3$	H	**b**	65
$CH_2(C_6H_5)$	H	**c**	75
$CH_2(C_6H_5)$	CH_3	**d**	26[b,c]

a) Yield of isolated product; b) *N*-benzyl-4-benzylaminomethyl-3-methyl-3-pyrrolin-2-one **7**; c) GC value.

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10. Synthesis of *N*-ethyl-carboxymethyl-3-benzylimino-4-methyl-2-pyrrolidinone: *N*-ethyl-carboxymethyl-3-chloro-4-chloromethyl-2-pyrrolidinones (0.254 g, 1 mmol) and NaI (0.15 g, 1 mmol) were weighed in a Schlenk tube; then THF (5 ml) and benzylamine (0.321 g, 3 mmol) were added by syringe under argon. The mixture was stirred at 80°C and after 24 h diluted with H_2O (5 ml), and extracted with CH_2Cl_2 (2×6 ml). The organic layer was dried over $MgSO_4$ and evaporated. The crude **6a** was purified by silica gel chromatography, using petroleum ether (bp 40–60°C)/diethyl ether gradient; yield ~70%. IR (film): ν=1745 and 1680 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.28 (3H, t, J=7.1 Hz, CH_3CH_2O), 1.36 (3H, d, J=7.2 Hz, CH_3CHCH_2), 2.37 (1H, dd, J=1 8, 7.7 Hz, CH_3CHCH_2), 2.98 (1H, dd, J=7.7, 8.8 Hz, CH_3CHCH_2), 3.30 (1H, m, CH_3CHCH_2), 4.21 (2H, q, J=7.1 Hz, CH_3CH_2O), 4.40 (2H, s, CH_2COO), 4.68 (2H, m, benzyl H), 7.22–7.40 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 288 (82%); 259 (7); 201 (32); 187 (22); 106 (13); 91 (100). Found: C, 66.7; H, 7.1; N, 9.6. $C_{16}H_{20}N_2O_3$ requires: C, 66.65; H, 6.99; N, 9.72. Oil. The *anti* stereochemistry was assigned by NOE between the methyl on C(4) and the CH_2 linked to the imino group.