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Conformationally Constrained Amino Acids: a Convenient Approach to *cis*-2,3-Methano-GABAs

Luca Forti,[1]* Franco Ghelfi, Stefano Levizzani and Ugo M. Pagnoni

Dipartimento di Chimica, Università di Modena e Reggio Emilia, Via Campi 183, 41100 Modena (Italy)

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Abstract

3-Aza-2-oxo-bicyclo[3.1.0]hexanes, which are opened to 2,3-methano-γ-aminobutyric acids, are obtained in very high yields by a two step procedure from *N*-protected-*N*-allyl-α-Br-amides.

Keywords: amino acids and derivatives; cyclopropanation; lactams; radicals and radical reactions.

Cyclopropyl amino acids have been used to obtain conformationally constrained peptides [1]. In fact, if such a structure is present in a peptide chain, severe changes in the neighbouring framework are expected affecting the ability to fit a biologically active site. Recently, γ-peptides have received considerable attention because they can give rise to stable right-handed helical secondary structures [2,3]. For these reasons, we here report a straightforward preparation of cyclopropyl γ-amino acids.

It has been reported that 2,3-methano-4-aminobutyric acids can be obtained from 3-aza-2-oxobicyclo[3.1.0]hexanes [4], usually prepared *via* α-diazo amides [5] or by a tandem Michael-S_N2 reaction [6]; two other methodologies, based on a tandem radical cyclization-intramolecular S_N2 reaction of ∂-ethylenic α,α-dichloromalonamides [7] or by an intramolecular alkylation of 4-methanesulphonylpyrrolidin-2-one [4], have been reported.

As a part of a program aimed at applying the halogen atom transfer radical cyclization to the synthesis of heterocyclic compounds with biological activity, we found that 3-aza-2-oxo-bicyclo[3.1.0]hexane, a latent form of 2,3-methano-4-aminobutyric acid (2,3-methano-GABA), may be conveniently synthesized from *N*-protected-*N*-allyl-α-Br-amides. Our approach is based on the two step procedure reported in scheme 1. Monobromo amides **1** are first quantitatively converted into the two diastereomeric lactams **2a,b**, by halogen atom transfer radical cyclization promoted by a catalytic amount (0.075 mol/mol substrate) of $Cu(bipy)_2Br$ in CH_3CN under Ar in a Schlenk vessel. Then, the isolated primary alkyl bromides are dehydrobrominated by DBU (1.5 mol/mol substrate) in CH_3CN, affording the bicyclic system **3** in overall high yield (91-96 mol%); a number of 3-aza-2-oxobicyclo[3.1.0]hexanes are thus conveniently synthesized (scheme 1) [8].

By comparison, *N*-deprotection is a rather difficult step, giving rise to relatively low yields. Different deprotection methods have been tried both for benzyl and tosyl groups; the best results have

[1] To whom correspondence should be addressed; Fax: (+39) 059 373543; E-mail: forti@pascal.unimo.it

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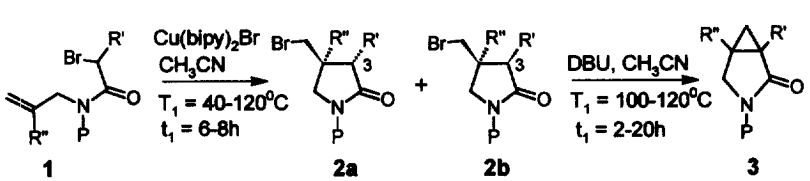
been obtained with Li (5 equivalents)-NH_3 (ca. 7ml/mmol substrate) at -78°C in THF/*t*-BuOH 9:1 (3 ml/mmol substrate) and with Li (14 equivalents)-naphthalene (0.04 equivalents) at -15°C in THF.

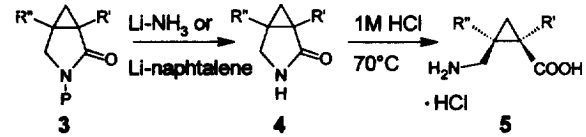


Scheme 1

R'	R"	P
C_6H_5	H	Bn
CH_3	CH_3	Bn
$(CH_3)_2CH$	CH_3	Bn
CH_3	H	Ts
$(CH_3)_2CH$	H	Ts

Bn = benzyl; Ts = toluene-p-sulphonyl

N-Deprotection of the benzyl group by Li-NH_3 occurs without affecting the cyclopropane ring only if R' = alkyl or H; when R' = phenyl the cyclopropane is opened. The *N*-deprotected derivatives **4** have been purified by silica gel chromatography (ethyl acetate); finally, the lactam ring is opened by 1M HCl at 70°C with high yield, without cleavage of the cyclopropane group, affording the 2,3-methano-4-aminobutyric acids **5** (scheme 2 and table).



Scheme 2

Table
Synthesis of 2,3-methano-4-aminobutyric acids **5**.[a]

R'	R"	P[b]	3 → 4[c]	4 → 5[d]
CH_3	CH_3	Bn	64	85
$(CH_3)_2CH$	CH_3	Bn	62	84
CH_3	H	Ts	72	88
$(CH_3)_2CH$	H	Ts	69	86

[a]Reactions were performed on 5 mmol of lactams **3**. [b]Bn = benzyl; Ts = toluene-p-sulphonyl. [c]Isolated yields based on **3**, mol%; all products have been characterized by NMR, GC-MS and elemental analysis [9]. [d]Isolated yields based on **4**, mol%; all products have been characterized by NMR spectroscopy and elemental analysis [9]

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[8] Substituents (R'=C_6H_5 or P=Ts) which stabilize the carbanion at C3 give rise to cyclopropanation under milder conditions. However, the great basicity of DBU (pKa = 11.5) affords a high yielding ring-closure also when R'= alkyl and P = Bn, though higher temperatures, longer reaction times, R" = alkyl and a greater excess of DBU are required. On treating the diastereomeric mixture **2a,b** with a catalytic amount of DBU (10 mol%) in refluxing CH_3CN, the **2b/2a** ratio increases significatively through C3-epimerization, indicating that the *trans* lactams **2b** are substrates of cyclopropanation.
[9] Representative data for compounds **4** and **5**. *1,5-dimethyl-3-aza-2-oxobicyclo[3.1.0]hexane*, white solid: ^{1}H-NMR ($CDCl_3$, 200MHz) δ: 0.68 (d, 1H, J = 4.32 Hz); 0.85 (d, 1H, J = 4.32); 1.26 (s, 3H); 1.30 (s, 3H); 3.19 (d, 1H, J = 9.85 Hz); 3.35 (d, 1H, J = 9.85); 5.93 (bs, 1H). GC-MS (EI, 70 eV): m/z 125 (18%, M^+), 110 (13%), 97 (77%), 82 (100%), 67 (48%), 41 (47%). Elemental analysis for $C_7H_{11}NO$: Calcd. C, 67.17%; H, 8.85%; N, 11.19%. Found. C, 67.13%; H, 8.92%; N, 11.18% *cis-1-Aminomethyl-1,2-dimethyl-2-carboxycyclopropane hydrochloride*, white crystals: ^{1}H-NMR (D_2O, 200MHz) δ: 0.86 (s, 2H); 1.25 (s, 3H); 1.34 (s, 3H); 3.30 (d, 1H, J = 10.80 Hz); 3.45 (d, 1H, J = 10.80 Hz). Elemental analysis for $C_7H_{14}ClNO_2$: Calcd. C, 46.80%; H, 7.85%; N, 7.80%. Found. C, 46.83%; H, 7.89%; N, 7.78%.