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Intramolecular Nicholas Reaction: Stereoselective Synthesis of 5-Alkynylproline Derivatives

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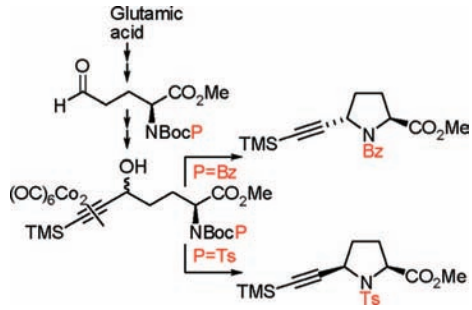
ABSTRACT



The intramolecular Nicholas reaction of propargylic alcohols derived from *N,N*-acyl-diprotected ω-semialdehydes obtained from glutamic acid provided stereoselectively 5-alkynylproline derivatives. The suitable choice of the N-protecting group (tosyl or benzoyl derivative) permitted control of the stereochemistry during the ring formation. Semiempirical calculations of the species involved in the cyclization support the observed stereochemistry.

2,5-Disubstituted pyrrolidines are frequently encountered components of natural and bioactive products.[1] In particular, 5-alkylproline derivatives have been used as constrained peptidomimetics.[2] Much effort has been expended in the development of suitable synthetic methods to make these structural fragments available.[3] 5-Alkynylproline derivatives **1** are versatile intermediates that can be easily transformed into a wide variety of related molecules simply taking advantage of their acetylenic and carboxylic reactivity.[2c,4] Typically, these acetylenic heterocycles are obtained by Lewis acid catalyzed addition of TMS-acetylenes to 5-methoxyproline esters available by anodic oxidation of proline esters as a diastereomeric mixture.[2c,5]

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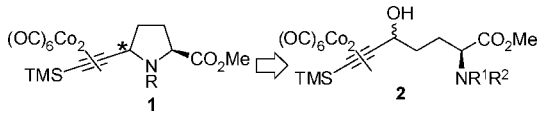
The intramolecular nucleophilic attack of a hydroxy group on a $Co_2(CO)_6$-propargylic cation (Nicholas reaction) is a robust method for the synthesis of cyclic ethers.[6] Given the similar chemical reactivity of the acyl amide and the alcohol, we investigated the possibility of obtaining the title compounds **1** from suitable amino alcohol derivatives **2** (Scheme 1).[7] Taking advantage of our general method to gain access

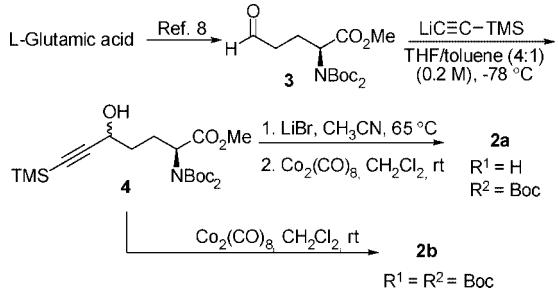
Scheme 1. Stereoselective 5-Alkynylproline Synthesis Using the Nicholas Reaction



to ω-semialdehydes from α-amino diacids,[8] we now report a new method to obtain 5-alkynylproline derivatives from glutamic acid. Stereochemical control of the ring substituents was achieved by tuning the nature of the protecting acyl group at the nitrogen.

To evaluate our approach the key intermediate **2** (R^1 = H, R^2 = Boc) was prepared from L-glutamic acid (Scheme 2). Semialdehyde **3** was prepared by controlled reduction

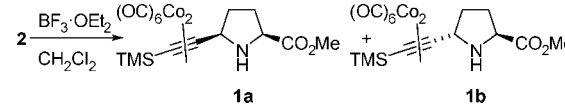
Scheme 2. Synthesis of $Co_2(CO)_6$-δ-propargylic Alcohols Derived from L-Glutamic Acid



from dimethyl *N*,*N*-diBoc-glutamate[8] and submitted to the lithium acetylide of trimethylsilylacetylene. To avoid possible racemization and interaction with the ester function, low temperatures were used (−78 °C). Special care must be taken with the concentration of the reaction mixture since the use of low to medium concentration conditions (0.02−0.05 M) in THF or THF−toluene mixtures provided low conversions and yields. Fortunately, using a high concentration (0.2 M) of the reaction mixture in a toluene/THF mixture (4:1) provided the propargylic alcohol **4** in excellent yields.[9] Selective cleavage of an *N*-Boc group[10] and alkyne complexation provided **2** (R^1 = H, R^2 = Boc). Alternatively, the *N*,*N*-diBoc-derivative **2** was also obtained by direct treatment of **4** with the $Co_2(CO)_8$ complex.

The acidic treatment of both *N*-Boc and *N*,*N*-diBoc-**2** (BF_3·OEt_2, CH_2Cl_2) was performed at different temperatures (Table 1). The corresponding complexed 5-alkynylproline

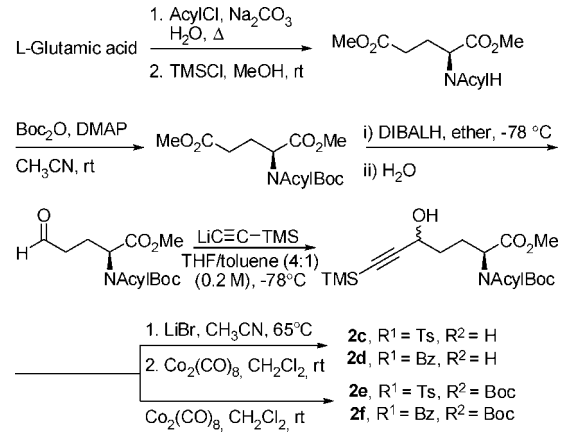
Table 1. Acidic Cyclization of $Co_2(CO)_6$-δ-propargylic Alcohols α-Amino Acid Derivatives to 2,5-Disubstituted Pyrrolidines



entry	**2**	T (°C)	time (h)	yield	**1a**:**1b**
1	**2a**	rt	0.2	85	2.4:1
2	**2a**	0	10	84	2.5:1
3	**2a**	−20	36	90	2.7:1
4	**2b**	rt	0.2	83	2.4:1
5	**2b**	0	10	82	2.5:1
6	**2b**	−20	36	91	2.2:1

esters were obtained with very good yields, the *cis*-isomer **1a** being predominant, in a ratio of approximately 2.5:1. Both yield and stereochemistry were essentially independent of

Scheme 3. Preparation of $Co_2(CO)_6$-δ-propargylic Alcohols *N*,*N*-Acyl Boc-α-amino Acid Derivatives



temperature and whether the nitrogen is mono- or diprotected. In both cases, the final product was the unprotected pyrrolidine.[11] So considering step economy, the use of *N*,*N*-

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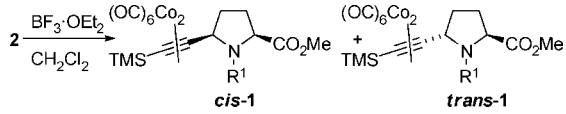
(9) ^{1}H NMR of the reaction mixture after workup shows virtually pure samples of the propargylic alcohols even at 0.1 M scale.

(10) Hernández, J. N.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2003**, *68*, 743–746.

(11) When performing the reaction at −20 °C, the protected *N*-Boc-pyrolidine is detected in the reaction mixture that gives rise to the unprotected amine.

Table 2. Stereocontrolled Synthesis of 2,5-Disubstituted Pyrrolidines



entry	**2**	*T* (°C)	time (h)	yield	product	*cis*:*trans*
1	**2c**, R^1 = Ts, R^2 = H	rt	0.25	88	**1c**	>99:1
2		0	2	85		>99:1
3		−20	2	84		>99:1
4	**2d**, R^1 = Bz, R^2 = H	rt	2	86	**1d**	1:10
5		0	2	85		1:10
6		−20	2	82		1:10
7	**2e**, R^1 = Ts, R^2 = Boc	rt	1	87	**1c**	>99:1
8		0	20	-[a]		
9	**2f**, R^1 = Bz, R^2 = Boc	rt	17	88	**1d**	1:10
10		0	30	-[a]		

[a] Almost all of the starting material was recovered.

diprotected α-amino acids having at least one Boc-group looks promising.

These results were encouraging, as they provide access to a very important kind of molecules; however, the low stereoselectivity and absence of control at the newly created stereocenter prompted us to study the influence of additional *N*-protected groups on the cyclization reaction. The *p*-methylbenzenesulfonyl and -benzoyl groups were chosen as acid-resistant protecting groups. The necessary precursors **2c** and **2d** were also prepared from L-glutamic acid following a similar scheme to that outlined before (Scheme 3). In addition, considering the lability of the Boc group in acidic conditions, the *N*,*N*-acyl-Boc-diprotected precursors **2e** and **2f** were also prepared.

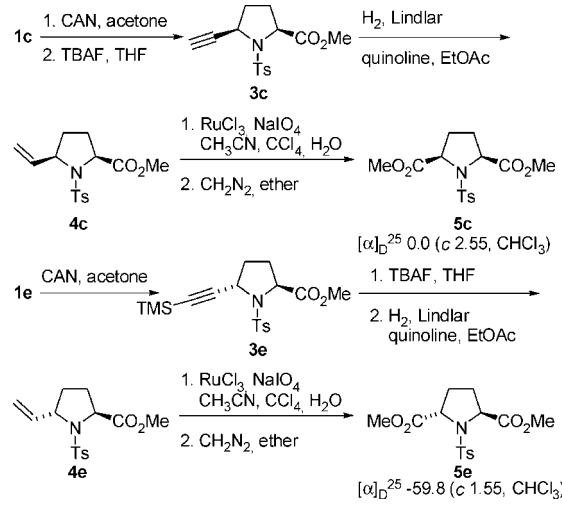
To our delight, we found the cyclization reaction to be highly stereoselective and the stereochemistry at the newly created stereocenter to be *N*-acyl-protecting group dependent (Table 2). Thus, when **2c** was submitted to acidic conditions at room temperature, the *cis*-5-alkynylproline ester **1c** was formed as the only detected diastereoisomer (entry 1).[12] Alternatively, the benzamide **2d** provided the *trans*-isomer **1d** in a 10:1 ratio (entry 2). As before, treating *N*,*N*-Boc-acyl-protected derivatives **2e** and **2f** yielded the corresponding 2,5-pyrrolidines **1c** and **1d** with excellent stereocontrol, although in these cases the reaction rate is strongly dependent on temperature (entries 8 and 10).

(12) Only one stereoisomer was detected by NMR analysis.

(13) The deposit numbers for compounds **3c** and **3e** are CCDC 676614 and 676613, respectively. Crystallographic data for **3c**: $(C_{15}H_{17}NO_4S$, M_w = 307.4), monoclinic, space group $P2_1$, a = 7.520(3) Å, b = 11.111(4) Å, c = 9.544(5) Å, β = 96.004(1)°, V = 793.1(6) Å^3, Z = 2, μ(Mo K$_\alpha$) = 0.22 mm^{-1}, ρ_{calc} = 1.29 g·cm^{-3}; S = 1.14, final R indices: R_1 = 0.0481 and R_w = 0.127 (for 1595 observed reflections (θ_{max}=26.4° and $I > 2\sigma(I)$ criterion) and 191 parameters); maximum and minimum residues are 0.31 and 0.27, respectively. Crystallographic data for **3e**: $C_{18}H_{25}NO_4SSi$, M_w = 379.6), orthorhombic, space group $P2_12_12$, a = 9.540(4) Å, b = 29.793(8) Å, c = 7.571(3) Å, V = 2151.87(14) Å^3, Z = 4, μ(Cu K$_\alpha$) = 1.94 mm^{-1}, ρ_{calc} = 1.17 g·cm^{-3}; S = 1.07, final R indices: R_1 = 0.0537 and R_w = 0.157 (for 2523 observed reflections (θ_{max} = 73.9° and $I > 2\sigma(I)$ criterion) and 228 parameters); maximum and minimum residues are 0.38 and 0.29, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre viawww.ccdc.cam.ac.uk/data_request/cif.

NMR data did not provide an unambiguous configuration of the newly created stereocenter. A series of correlations were performed to clarify the relative stereochemistry (Scheme 4). The tosyl pyrrolidine **1c** was submitted to CAN oxidation to give the uncomplexed acetylene. The corresponding silyl derivative was treated with TBAF to yield the terminal acetylene **3c**. Hydrogenation using Lindlar catalysis provided known **4c**.[5] Additional information regarding the *trans*-relationship between the 2,5-substituents was obtained by oxidative double-bond cleavage with RuO_4 and methyl esterification of the resulting carboxylic acid, providing the meso diester **5c**. In parallel, a similar sequence using

Scheme 4. Determination of the Relative Configuration



1e, obtained by tosylation of **1b**, afforded the known **4e** and the chiral pyrrolidine **5e**. In addition, X-ray analysis of both **3c** and **3e** were performed, confirming the correct stereochemistry (Figure 1).[13]

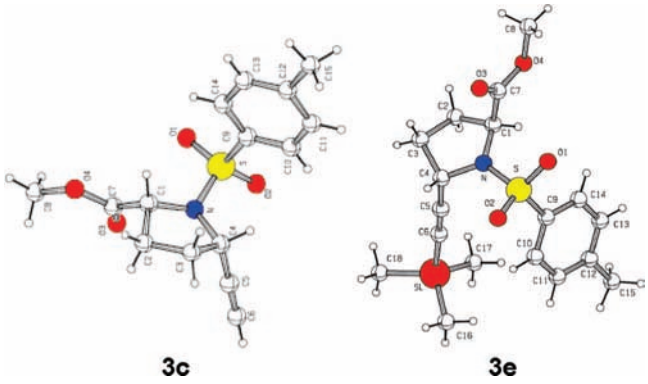


Figure 1. X-ray crystallographic structures of *cis*- and *trans*-tosylpyrrolidines **3c** and **3e**.

Semiempirical calculations with PM3(tm) Hamiltonian were performed to investigate the stereochemical preferences of the cyclization to obtain **1c** and **1d** (Figure 2).[14] The geometry of the reactants, products and transition states (TS) were fully optimized for both *N*-tosyl (Ts) and *N*-benzoyl (Bz) derivatives. Stereochemical results are in agreement with relative energies of the final products in both N-protonated and free species.[13] In addition, the relative energies of the transition states assuming the stereoselective trapping of a preordered propargylic cation by the electron pair of the nitrogen are also in agreement with the stereochemical outcome of the cyclization. Although the overall processes are exothermic, it should be considered that the calculations are performed considering gaseous state, and the protonated final products are highly energetic species. The distribution of the relative energies could be the result of a combination of steric interactions between the bulkiest groups and electrostatic interactions between the highly polarized carbonyl group of the cobalt complex and the oxygens of the acyl substitutents of the nitrogen.

In summary, we have developed a simple, practical method for the preparation of 5-alkynyl derivatives via an intramolecular Nicholas reaction. The suitable choice of the protecting group on the nitrogen permits control of the stereochemistry in the cyclization. The procedure offers a straightforward way to construct 2,5-dialkylpyrrolidines in their enantiomeric forms. Semiempirical theoretical calculations support the stereochemical preferences.

Acknowledgment. This research was supported by the Ministerio de Educación y Ciencia of Spain, cofinanced by the European Regional Development Fund (CTQ2005-09074-C02-01/BQU) and the Canary Islands Government.

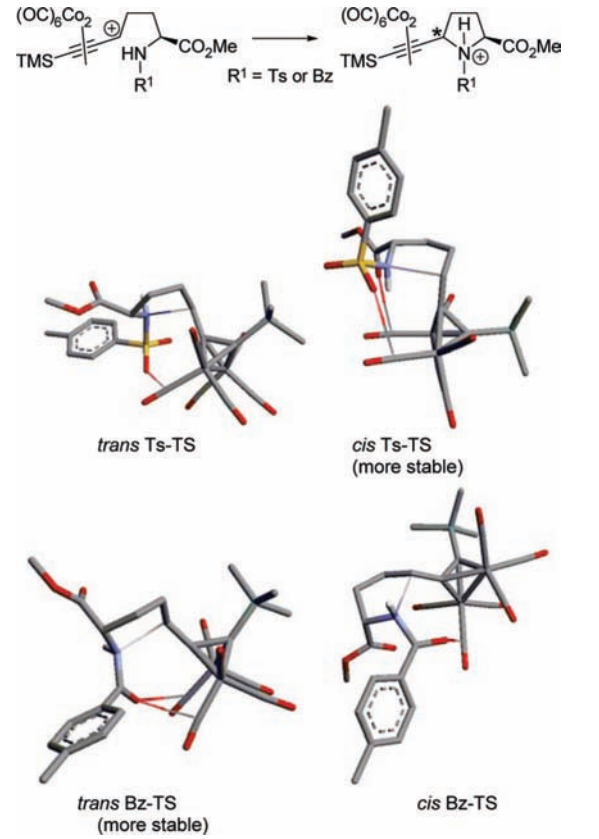


Figure 2. Geometries of the optimized transititon states (hydrogens were omitted by clarity) for the cyclization to protonated **1c** and **1d**. Red thinner lines denote electrostatic interactions between the carbonyl group of the cobalt complex and the oxygens of the sulfonamide and benzamides groups.

Supporting Information Available: Experimental details, ^{1}H NMR and ^{13}C NMR spectra for all new compounds, and geometries of the optimized minima and transititon states (Figure 2). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Semiempirical quantum mechanics method using a minimal valence basis set of Slater-type orbitals. Spartan'06 package, Wavefunction, Inc. (http://www.wavefun.com).