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The Reaction of Propiolate Acetylides with Nitrones. Synthesis of γ-Amino-α,β-ethylenic Acid Derivatives

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Abstract: Nitrones react with the lithium anions of ethyl and *t*-butyl propiolates to give acetylenic *N*-hydroxylamines. The reduction of these compounds with Zn in the presence of an acid leads to *E* and *Z* α,β-ethylenic-γ-aminoacids derivatives. The stereoselectivity of these reactions was studied.
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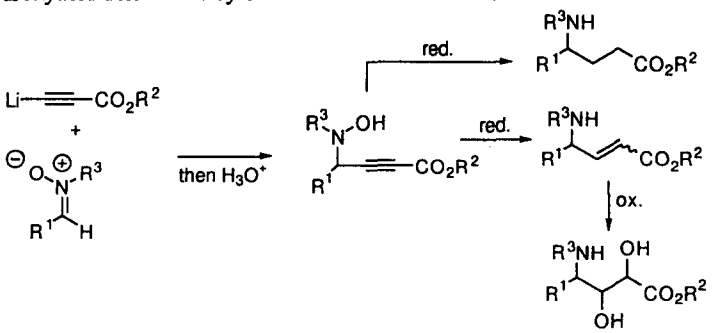
In contrast with imines, which are often poorly stable, nitrones are easily synthesized, stable and often crystalline compounds which react readily with organometallics.[1] If the organometallic reagent is a propiolate ester anion, the expected products are acetylenic *N*-hydroxylamines which may then be totally reduced to γ-aminoesters, or partially reduced into α,β-ethylenic-γ-aminoesters.

The fact that γ-aminobutyric acid (GABA) is a major neurotransmitter, known to prevent epilepsy, has created an important demand for the synthesis of γ-aminoacids. GABA is degraded by the enzyme GABA-transaminase and when its concentration in the brain falls under a threshold level, epileptic seizures appear.[2] Various GABA-analogues have been synthesized and tested as GABA-transaminase inhibitors, the most important being 4-amino-5-hexenoic acid (Vigabatrin)[3] and 4-amino-5-hexynoic acid.[4] In this communication we present a convenient approach towards α,β-ethylenic-γ-aminoacids,[5] which are examples of 'conformationaly restricted'[6] GABA-analogues. This method also allows the diastereoselective synthesis of γ-amino-α,β-dihydroxyacid derivatives by oxidation of the obtained C=C double bond.[7]



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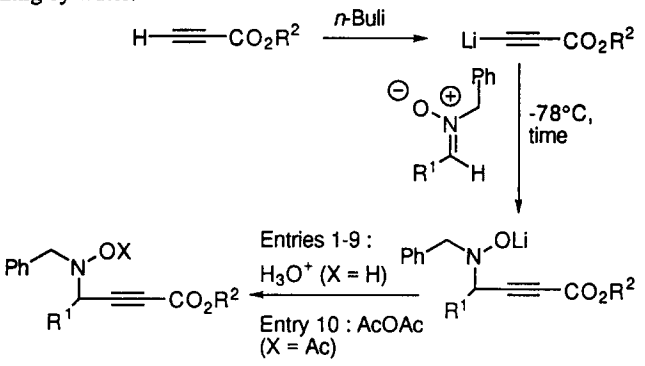
The lithium anions of ethyl and *t*-butyl propiolates, obtained from the reaction of the acetylenic compound with *n*-butyllithium at low temperature in THF, reacted with various nitrones at -78°C.[8] Representative results are summarized in the Table. Yields were generally good with alkyl nitrones, eventhough the reactions were sometime rather slow (entries 6-8). This was the case in particular for the tested aromatic nitrone, for which we were unable to reach an acceptable yield (entry 9). Entry 10 gives an example of a one-pot synthesis of a *O*-acylated hydroxylamine obtained by addition of acetic anhydride to the reaction mixture before quenching by water.

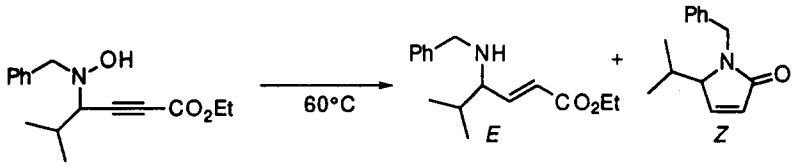


Table

Entry	R^1	R^2	time (h)	yield %[a]	Entry	R^1	R^2	time (h)	yield %[a]
1	Me	Et	1	81	6	*t*-Bu	Et	0.5	17[b]
2	Et	"	2.5	60	7	"	"	2.5	50[b]
3	"	*t*-Bu	3	85	8	"	"	14	67
4	*i*-Pr	Et	1	76	9	Ph	"	14	10[b]
5	"	*t*-Bu	1.66	94	10[c]	*i*-Pr	"	1	85

[a] Isolated yield. [b] Estimated by NMR. [c] In this case, acetic anhydride was added prior to water. The isolated product is the *O*-acetylated hydroxylamine.

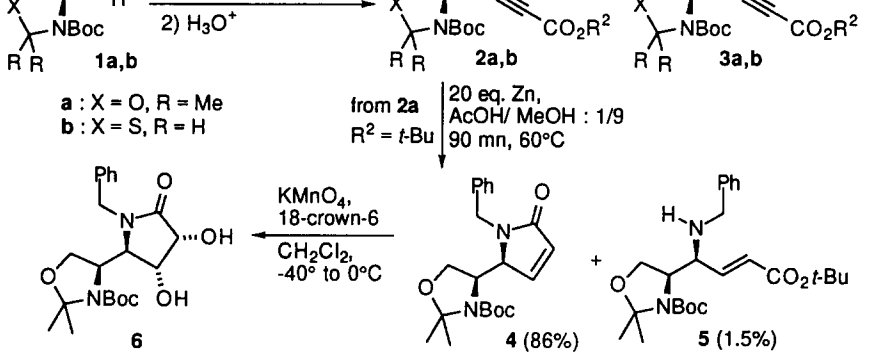
One of the known methods for the reduction of hydroxylamines into amines is their treatment by zinc in an acidic medium.[9] In our case, the action of zinc on the obtained acetylenic hydroxylamines reduced not only the hydroxylamine function, but also the C≡C triple bond, which was transformed into a C=C double bond. Thus, this method is a convenient way for obtaining γ-amino-α,β-ethylenic acid derivatives, however, as a mixture of *E* and *Z* isomers. Fortunately, the *Z* compounds cyclized to γ-lactams and thus were easily separated by liquid chromatography from the *E*-esters.[10] The *E*/*Z* ratio was very sensitive to any changes in the reaction conditions. Particularly crucial was the choice of the acidic solvant mixture. This is obvious from the data given below for the reduction of a representative hydroxylamine. Reactions were generally complete in *ca.* 30 mn at 60°C. Good yields of the lactam can be obtain by using low AcOH/H_2O or AcOH/MeOH ratios. We were able to isolate reasonnable quantities of the *E*-esters using high AcOH/H_2O ratios. The use of a Copper-Zinc couple or substitution of formic acid for acetic acid does not allow us to get higher *E*/*Z* ratios. We have no conclusive explanation about the effect of the acid on the *E*/*Z* ratio.



Conditions and Reagents	E/Z ratio[a]	Yield[b]
20 eq. Zn, AcOH/H_2O : 1/9, 30mn	7/93	70% (*Z*)
20 eq. Zn, AcOH/MeOH : 1/9, 45mn	11/89	75% (*Z*)
20 eq. Zn, AcOH/H_2O : 4/1, 30mn or 240mn	60/40	50% (*E*)
5 eq. Zn + 0.1 eq. $CuSO_4$, AcOH/H_2O : 3/1, 30mn	50/50	40% (*E*)
20 eq. Zn, HCOOH/H_2O : 4/1, 30mn	67/33	50% (*E*)

[a] Determined by ^1H NMR of the crude reaction mixture. [b] Isolated yield of one pure isomer.

The diastereoselectivity of the reactions of acetylides with nitrones has been poorly studied. Recently, Merino *et al.* reported good stereoselectivities in the condensation of Li-C≡CSiMe3 with a chiral nitrone derived from glyceraldehyde.[11] We have synthesized two nitrones derived from cyclic chiral α-amino-aldehydes.[12] These nitrones **1a,b** were treated with the lithium anion of *t*-butyl propiolate. The addition was stereoselective and the *syn* products **2a,b** (R^2 = *t*-Bu)[13] were isolated in 78 and 72% yield respectively.[14] Under these conditions, the *anti* adducts were not detected. Similar results were obtained with R^2 = Et (**2a** 59%, **2b** 55%). Interestingly, when MgBr2 was added to the nitrone **1b** prior to the acetylide, the major product was the *anti* adduct (R^2 = Et, **2b/3b** = 13/87). Such a reversal of selectivity has previously been noticed in a similar case.[11] Treatment of **2a** by Zn in a AcOH/MeOH (1/9) mixture, gave lactam **4**[13] in 86% yield. This reduction was highly stereoselective, the *E*-ester **5** being isolated in only 1.5% yield. Finally, we have tested the synthesis of γ-amino-α,β-dihydroxy acid derivatives. Oxidation of **4** by $KMnO_4$ gave the dihydroxy compound **6** in 55% yield.[13,15]



Thus we have demonstrated that the reaction of Li-C≡CCO_2R with nitrones is an efficient way to γ-amino acids derivatives. We are currently pursuing the study of stereoselectivity problems related to this condensation and the following reduction and oxidation steps.

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10. However, in one case (R^1 = *i*-Pr, R^2 = *t*-Bu), we were able to isolate the non-cyclized *Z*-amino ethylenic ester in 60% yield (conditions : 20 eq. Zn, AcOH/MeOH : 1/9, 100mn, 60°C)
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12. Dondoni, A.; Franco, S., Junquera, F. L.; Merchàn, F., Merino, P.; Tejero, T. *Synth. Commun.*, **1994**, *24*, 2537-2550.
13. **2a** (R^2 = *t*-Bu) : $[\alpha]_D^{20}$ = +67 (c 2.4, $CHCl_3$) ; ^{1}H NMR (300 MHz, $CDCl_3$) : 7.60 (s, 1H, OH), 7.3-7.2 (m, 5H, C_6H_5), 4.32-4.27 (m, 1H, CHNBoc), 4.22 and 3.90 (2d AB, 2H, J_{AB} = 13 Hz, CH_2), 4.03-3.94 (m, 2H, CH_2O), 3.52 (d, 1H, J = 10 Hz, C<u>H</u>NOH), 1.53 (s, 9H, $(CH_3)_3C$), 1.52 (s, 9H, $(CH_3)_3C$), 1.47 and 1.31 (2s, 6H, $(CH_3)_2C$) . **4** : $[\alpha]_D^{20}$ = -58 (c 0.2, $CHCl_3$) ; ^{1}H NMR (200 MHz, $CDCl_3$) : 7.4-7.0 (m, 6H, C_6H_5 and CH=), 6.31 (dd, 1H, J = 5.8 and 12.8 Hz, CH=), 4.74-4.05 (m, 4H, CH_2, CHNBoc and CHN), 3.56-3.2 (m, 2H, CH_2O), 1.64-1.30 (m, 15H, $(CH_3)_3C$ and $(CH_3)_2C$). **6** : $[\alpha]_D^{20}$ = +24 (c 2, $CHCl_3$) ; ^{1}H NMR (200 MHz, toluene-d8, 70°C) : 7.01-6.9 (m, C_6H_5), 4.82 and 4.14 (2d AB, 2H, J_{AB} = 15 Hz, CH_2), 4.22-4.1 (m, 2H, C<u>H</u>OH and CHNBoc), 3.64 (s, 1H, C<u>H</u>OH), 3.75-3.6 (m partly masked by the singlet at 3.64, 1H, CHN), 3.33-3.19 (m, 2H, CH_2O), 1.53 and 1,30 (2s, 6H, $(CH_3)_2C$), 1.28 (s, 9H, $(CH_3)_3C$).
14. The *syn* structure of **2a** (R^2 = *t*-Bu) was determined by X-ray analysis of a single crystal. This structure will be published soon.
15. The configuration of **6** was determined by ^{1}H NMR ($^3J_{\underline{C}HOH,\underline{C}HN} \approx 0$ Hz) : Gaudemer, A. in *Stereochemistry, Fundamentals and Methods*, Kagan, H, Ed., Georg Thieme Publishers : Stuttgart, **1977**, vol. 1, pp. 44-136. See also : Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L.; Fava, G. G.; Ferrari, M. B.; Pelosi, G. *Tetrahedron : Asym.*, **1992**, *3*, 1035-1048.

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