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Direct Vinylation of 2-Substituted N-(Benzylidene)glycinonitriles Under Basic Conditions

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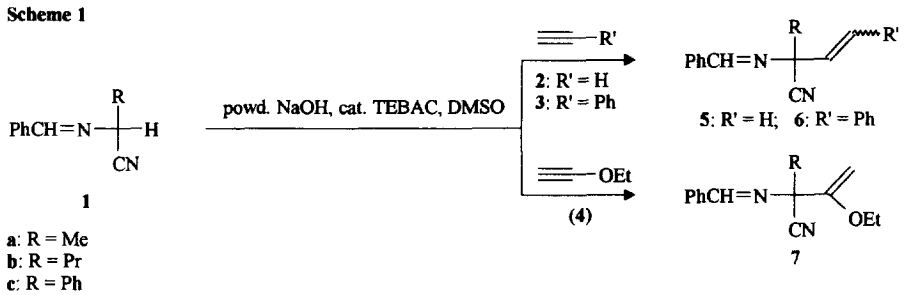
Abstract: *α-Vinyl substituted nitriles 5 - 7 were prepared via addition of carbanions generated from nitriles 1, to acetylene (2) and its derivatives 3 and 4. Subsequent cleavage of nitriles 6 and 7 afforded α,β-unsaturated ketones 8 and 9.*

Recent papers on base catalyzed addition of ethyl 2-substituted N-diphenylmethyleneglycinate to ethyl propiolate, and further transformations of the products thus formed,[2,3] prompted us to report preliminary results on the reaction of carbanions generated from nitriles **1a,b**[4] and **1c**[5] with unactivated acetylenes **2 - 4**.

Searching of literature reveals that addition of glycinonitrile anion equivalents to acetylenes has not been reported yet while base catalyzed reaction of 2-phenylalkanenitriles[6] or 2-(dialkylamino)arylacetonitriles[7,8] with acetylene, its mono and disubstituted derivatives, has been thoroughly investigated.

Scheme 1



The reaction of nitrile **1a** with phenylacetylene (**3**) which we selected for optimization experiments, carried out in the presence of powdered NaOH and benzyltriethylammonium chloride (TEBAC) as a catalyst, in DMSO (phase - transfer catalysis, PTC[9,10]), revealed that the expected addition product **6a** was formed indeed, in moderate yield (**Table**). Of a few base - solvent systems studied,[11] this mentioned above afforded **6a** in the highest yield. Due to limited stability of carbanions $\mathbf{1}^-$ (particularly $\mathbf{1a}^-$) thus generated, the reaction with liquid

acetylenes **3** and **4** were carried out by addition of nitriles **1** to the mixture of all other components, dissolved and / or suspended in small amount of DMSO.[12] Under these conditions, the products **5** - **7** were formed in low to good yields, usually after short reaction time (**Scheme 1**, **Table**).

Table. Reaction of nitriles **1** with acetylenes **2** - **4**.[13]

Reagents	Reaction time (min)	Product[a]	Yield[b] (%)	Reagents	Reaction time (min)	Product[a]	Yield[b] (%)
1a + **2**	60	**5a**	15	**1a** + **4**	15	**7a**	70
1b + **2**	15	**5b**	30	**1b** + **4**	15	**7b**	55
1a + **3**	15	**6a**[c]	42	**1c** + **4**	15	**7c**	20
1b + **3**	15	**6b**[d]	45				

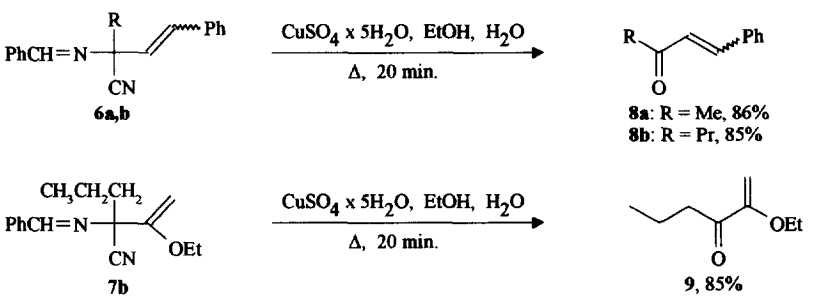
[a]Isolated by column chromatography (neutral aluminum oxide, eluted with hexane - ethyl acetate mixture), and fully characterized by standard techniques. [b]Large amount of tarry products were formed. [c]E / Z ≅ 1 : 3.5. [d]E / Z ≅ 1 : 5.3.

We have noticed different regiochemistry of addition of carbanions from **1** to acetylenes **3** and **4**, respectively. The presence of electron-donating oxygen atom in **4** which poorly stabilizes adjoining negative charge,[14] results in the addition of **1**$^-$ to C-1 of ethoxyacetylene (**4**).

Concerning the stereochemistry, the products **6** were formed as mixtures of E and Z isomers, with the latter in excess. This observation confirms that *trans* addition of carbanions generated from **1** to **3**, with formation of Z isomers of **6**, significantly prevails.[6,8]

Due to low electrophilicity of acetylenes studied (in contrast with ethyl propiolate[2,3] which possesses strongly electron-withdrawing ethoxycarbonyl group), satisfactory results gave the active carbanions **1a**$^-$ and **1b**$^-$ only, derived from rather weak C-H acids **1a,b**. On the other hand, the best stabilized carbanions **1c**$^-$ is unsufficiently nucleophilic, and its decomposition competes with addition to acetylene **4**, and particularly **3** (in the latter case, addition product has not been formed, at all).

Scheme 2



Chemical modifications of Schiff bases derived from glycine esters afforded products which are valuable precursors of α-aminoacids.[15] α-Aminonitriles are also prone to enter many interesting chemical

transformations.[16,17] Based on these informations, the products **6a,b** were allowed to react with variety of reagents, but these attempted transformations of **6** generally failed.[18] Only the system $CuSO_4$ / H_2O / EtOH assured clean and efficient conversion of **6a,b** into the corresponding α,β-unsaturated ketones **8**, and nitrile **7b** into α-ketoenolether **9**[19,20] (**Scheme 2**). So far, we were not able to cleave simultaneously azomethine bond and to hydrolyze cyano group in the products **6** - **7**, to obtain β,γ-unsaturated-α-aminoacids.

The results of our investigations indicate that under basic conditions, direct vinylation of chemical equivalent of glycinonitrile derivatives by means of weakly electrophilic acetylenes, is possible. Further work is directed toward modification of molecules of **1** to increase yields of vinyl derivatives, and to cleave them into β,γ-unsaturated-α-aminoacids.

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References and Notes

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2. Rubio, A.; Ezquerra, J. *Tetrahedron Lett.*, **1995**, *36*, 5823 - 5826.
3. López, A.; Moreno-Manas, M.; Pleixats, R.; Roglans, A.; Ezquerra, J.; Pedregal, C. *Tetrahedron*, **1996**, *52*, 8365 - 8386.
4. **1a** (oil, yield 93%) and **1b** (oil, yield 81%) were prepared as described for similar compounds (Stork, G.; Leong, A.Y.W.; Touzin, A.M. *J. Org. Chem.*, **1976**, *41*, 3491 - 3493), and fully characterized.
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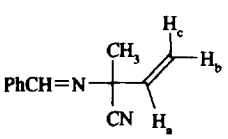
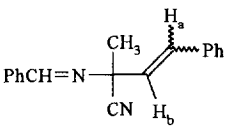
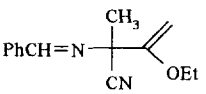
11. With LDA in THF (r.t., 24 h) yield of **6a** was only 14%, while with solid K_2CO_3, tetrabutylammonium bromide as a catalyst, in acetonitrile solution (reflux, 6 h) none of **6a** was formed.
12. **General procedure**: Powdered NaOH (2.4 g), TEBAC (0.5 g), DMSO (2 mL) and **3** or **4** (20 mM) were stirred at 15-20°C while **1a-c** (5.0 mM) was immediately added. The reaction was carried out at r.t. for 15 min., conventionally worked-up, and the products were isolated by column chromatography (**Table**). Reaction with **2** was carried out as above (20 mL DMSO was used) in an apparatus described by one of us.[6] All compounds gave satisfactory HR-MS.
13. Typical NMR data (recorded with a Varian AC-200 spectrometer at 200 MHz with TMS as internal standard):



5a: ^{1}H NMR ($CDCl_3$), δ 8.57 (s, 1H, PhC*H*), 6.03 (dd, 1H, $J_{Ha,Hb}$ 10.4, $J_{Ha,Hc}$ 16.9 Hz, H_a), 5.52 (d, 1H, H_c), 5.26 (d, 1H, H_b), 1.74 (s, 3H, CH_3).



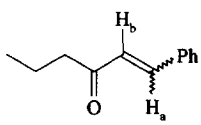
6a: ^{1}H NMR ($CDCl_3$), δ *cis* isomer: 8.40 (s, 0.22H, PhC*H*), 6.80 (d, 0.22H, $J_{H_aH_b}$ 11.9 Hz, H_a), 5.82 (d, 0.22H, H_b), 1.75 (s, 0.66H, CH_3); *trans* isomer: 8.63 (s, 0.78H, PhC*H*), 6.83 (d, 0.78H, $J_{H_aH_b}$ 16.0 Hz, H_a), 6.34 (d, 0.78H, H_b), 1.84 (s, 2.34H, CH_3). ^{13}C NMR ($CDCl_3$), δ *cis* isomer: 160.00 (PhCH), 119.23 (CN), 61.46 (C), 30.19 (CH_3); *trans* isomer: 64.74 (C), 29.28 (CH_3).



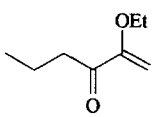
7a: ^{1}H NMR ($CDCl_3$), δ 8.63 (s, 1H, PhC*H*), 4.47 (d, 1H, *J* 3.0 Hz, =CH), 4.17 (d, 1H, =CH), 3.85 (q, 2H, *J* 7.0 Hz, OCH_2), 1.84 (s, 3H, CH_3), 1.36 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ 161.09 (PhCH), 159.13 (=C-O), 118.90 (CN), 83.43 (=CH_2), 65.46 (C), 64.13 (OCH_2), 27.01 (CH_3), 14.25 (CH_3).

14. Observed regiochemistry of addition of nucleophiles to **4** has been explained by the following polarization (Krishnamurthy, V.N.; Soundararajan, S. *J. Org. Chem.*, **1966**, *31*, 4300 - 4301):

15. α-Amino acids synthesis: O'Donnell, M.J. (Ed.), *Tetrahedron*, **1988**, *44*, 5253 - 5614.
16. Albright, J.D. *Tetrahedron*, **1983**, *39*, 3207 - 3233.
17. Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Organic Reactions*, John Wiley & Sons, **1984**, *31*.
18. The following reactions of **6** selected from an array of chemical transformations of α-aminonitriles, have been tried:
    reduction of **6b** by $LiAlH_4$ - decomposition of substrate;
    reduction of **6a** by $NaBH_4$ or $NaBH_4$ / $NiCl_2$ system - unchanged substrate;
    hydrolysis of **6a** by $AgNO_3$ / THF / H_2O - very slow, practically unuseful process;
    hydrolysis of **6a,b** by 1M HCl / hexane - formation of tars, already in room temp.;
    hydrolysis of **6a,b** by 20% NaOH in water or methanol at r.t. - unchanged substrate.
19. **General procedure**: A mixture of **6b** (9 mM), ethanol (30 mL), $CuSO_4 \times 5H_2O$ (13.5 mM) and water (10 mL) was refluxed for 1 h. Filtration followed by evaporation and column chromatography (hexane - ethyl acetate, 10 : 1) gave **8b** (85%).
20. Typical NMR data: (recorded with a Varian AC-200 spectrometer at 200 MHz with TMS as internal standard):



8b: ^{1}H NMR ($CDCl_3$), δ *cis* isomer: 6.90 (d, 0.35H, $J_{H_aH_b}$ 10 Hz, H_a), 6.22 (d, 0.35H, H_b); *trans* isomer: 7.32 - 7.72 (m, Ph, H_a), 6.80 (d, 0.65H, $J_{H_bH_a}$ 15 Hz, H_b), 2.66, 1.80 and 0.95 (3m, 7H, $CH_3CH_2CH_2$).



9: ^{1}H NMR ($CDCl_3$), δ 5.16 (d, 1H, *J* 2.4 Hz, =CH), 4.40 (d, 1H, =CH), 3.80 (q, 2H, *J* 7.0 Hz, OCH_2), 2.65 (t, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.39 (t, 3H, CH_3), 0.94 (t, 3H, CH_3).

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