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Synthesis of α-Amino Acids by Addition of Putative Azido Radicals to α-Methoxy Acrylonitriles Derived From Aldehydes and Ketones

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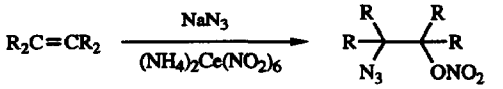
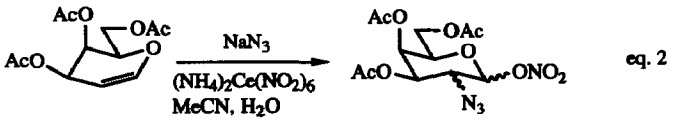
Summary : α-Methoxy acrylonitriles, available from aldehydes and ketones, react with sodium azide in the presence of ceric ammonium nitrate to give azido nitrates; from these compounds, α-amino acids are obtained by sequential treatment with sodium acetate in acetic acid and then methanolic potassium carbonate, followed by hydrogenation.

Formation of azido nitrates by reaction of olefins with sodium azide in the presence of ceric ammonium nitrate (eq 1) was reported many years ago,[1] and the process, which is suspected (but not proved) to involve



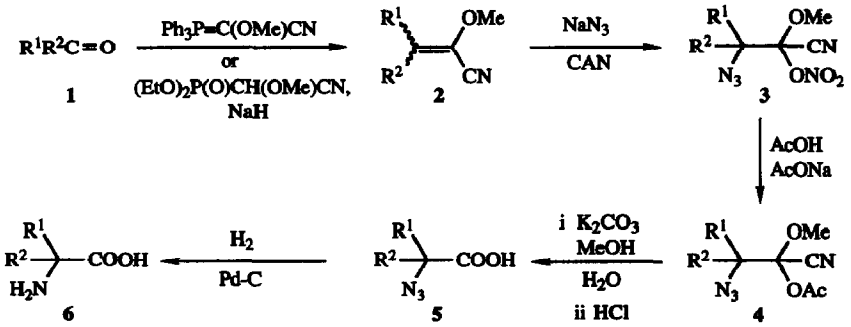
eq. 1



eq. 2

azido radicals,[1,2a] has been used in synthesis,[2,3] especially in the area of carbohydrate chemistry (e.g. eq 2[2a]). We report here an application of the technique to the construction of amino acids (Scheme 1).[4,5]

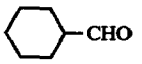
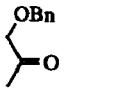
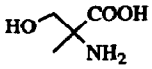
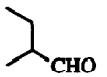
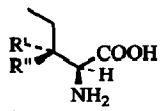
Scheme 1



α-Oxygenated acrylonitriles **2** were made by standard methods that involve using a Wittig reagent

[$Ph_3P^+CH(OMe)CN.Br^-$ / Et_3N / CH_2Cl_2[6]] or a phosphonate [$(EtO)_2P(O)CH(OMe)CN$ / NaH / THF (tetrahydrofuran)[7]]. Sometimes one or other of the methods was very much better (see Table 1 entries i, iii, and iv). We have generally started with aldehydes (**1**, R^2 = H); however, the sequence can also be used in the ketone series (Table 1, entry v). For this preliminary work we restricted our experiments to the *O*-methyl enol ethers **2**, but corresponding silyl ethers[8,9] and *O*-acetates[9,10] are related and known compound types that, in principle, might be suitable.

Table 1

Entry	Carbonyl compound **1**	α-Methoxy acrylonitrile **2** (%)[a]	Azido acid **5** (%)[b]	Amino acid **6** (%)[c]	
i	EtCHO	77[d,e] ≤41[f]	50[g]	$EtCH(NH_2)COOH$	76
ii	$PhCH_2CHO$	78[e]	65	$PhCH_2CH(NH_2)COOH$	75
iii	*t*-BuCHO	81[f] <5[e]	40	*t*-$BuCH(NH_2)COOH$	76
iv		85[f] 45[e]	59	*c*-$C_6H_{11}CH(NH_2)COOH$	86 69[h]
v		67[f]	57[i]		79[j]
vi		87[f]	54	 **6a** R'= H, R"= Me **6b** R'= Me, R"= H	83[k]
vii	PhCHO	49[e,l]	–		

[a] Yield from **1**. [b] Yield from **2**. [c] Yield from **5**; use of Pd/C/H_2, unless otherwise stated. [d] Material contained 5w/w% of $MeOCH_2CN$. [e] Use of Ph_3P=C(OMe)CN. [f] Use of $(EtO)_2P(O)CH(OMe)CN$/NaH. [g] Uncorrected for fact that **2** contained $MeOCH_2CN$. [h] Use of Ph_3P/H_2O. [i] Contains some (≤6 mole%) impurity. [j] Yield not corrected for fact that **5** was not pure. [k] **6a**:**6b** = 1:1.7. [l] The next step (reaction with azido radical) was unsuccessful.

The α-methoxy acrylonitriles **2** react[11] below room temperature with sodium azide in the presence of ceric ammonium nitrate to form azido nitrates **3**. We were unable to purify the latter compounds and so they were converted directly into the corresponding acetates **4** by heating (100°C) with sodium acetate in acetic acid. Mild base hydrolysis (aqueous methanolic potassium carbonate, room temperature) of the acetates, again without purification, gave azido acids **5**. Finally, the standard method[12] of catalytic hydrogenation served to generate

the amino acids (**5**→**6**).

We routinely transformed the starting acrylonitriles directly to the azido acids, but we sometimes isolated the (unstable) intermediates **3** and **4** which, although not pure, did have spectral characteristics (IR, ^{1}H NMR, ^{13}C NMR) consistent with the proposed structures.

Most of our results are summarized in the Table. As shown, the azide addition did not work for benzaldehyde (entry vii), which was the only example we tried with a conjugated carbonyl group. Steric factors do not seem to be very significant (see entry iii), and a related observation is that the method works in the case of a ketone (entry v) which, of course, gives an α-alkylated amino acid. In this particular example we specifically wished to deprotect the ether oxygen, and this was achieved at the same time as azide reduction, by catalytic hydrogenation. Other more selective methods for azide reduction are available however, and, for generation of α-cyclohexyl glycine (entry iv), we also used triphenylphosphine/water.[13] Finally, the synthesis (entry vi) of isoleucine (**6a**) and alloisoleucine (**6b**), which were produced in a ratio of 1:1.7, shows that the method can display appreciable levels of diastereoselectivity even in a minimally biased case.

All new compounds indicated in Table 1 were fully characterized by spectroscopic methods. Acknowledgement is made to the Natural Sciences and Engineering Research Council of Canada and to Merck Frosst (Canada) for financial support.

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11 *Typical procedure*: A solution of the α-methoxy nitrile (0.2 M, 1 mmol) in acetonitrile was added to a cooled (ca. -15°C) flask containing ceric ammonium nitrate (3 mmol) and sodium azide (1.5 mmol). Stirring was then (and only then) started, and was continued overnight at -15 to -5°C. The mixture was partitioned between water and ether at ca. 0°C. The residue obtained by evaporation of the solvent below 20°C was dissolved in glacial acetic acid (4 mL), and sodium acetate (4.0-5.5 mmol) was added. The solution was heated at 100°C for 1 h. The crude azido acetate, obtained by partitioning the mixture between water and dichloromethane, and evaporation of the solvent, was dissolved in 75% aqueous methanol (4 mL), and the solution was stirred overnight with potassium carbonate (4.0-5.5 mmol). Non-acidic material was removed by extraction (dichloromethane) and acidification (4 *N* HCl) of the aqueous phase gave the azido acid, which was isolated by extraction into dichloromethane.

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