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Unexpected 1,2,3-triazole formation in the reaction of diethylaluminum azide with α′-amino-α,β-unsaturated ketones

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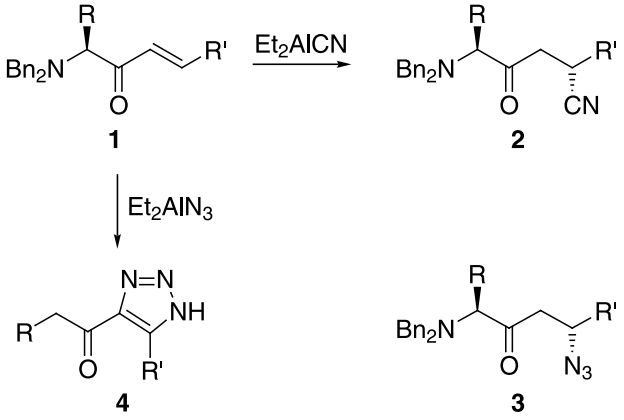
Abstract—4-Acyl-1*H*-1,2,3-triazoles are formed from diethylaluminum azide and α′-(*N*,*N*-dibenzylamino)-α,β-unsaturated ketones by [3+2] cycloaddition of azide, followed by 1,5 hydride transfer to the β carbon of the triazoline side chain and fragmentation of the tertiary amino group promoted by coordination of the latter to the Lewis acid. The structure of a triazole product is confirmed by X-ray crystallography.

We have recently shown that highly stereoselective conjugate addition of cyanide to chiral α′-(*N*,*N*-dibenzylamino)-α,β-unsaturated ketones **1** can be achieved using Nagata's reagent (Et_2AlCN) as cyanide donor.[1] We have proposed that the reaction takes place by chelation of an aluminum species between the carbonyl and the dibenzylamino group which directs attack of the incoming nucleophile to the less hindered *si* face of the double bond.

Prompted by this result, and based on a previous report describing the conjugate addition of diethylaluminum azide to α,β-unsaturated carbonyl compounds,[2] we decided to investigate the reaction of the same α,β-unsaturated aminoketones **1** with Et_2AlN_3. We thus hoped to obtain a stereoselective 1,4-azidation of aminoketones **1** in a similar fashion to the reaction shown in Scheme 1. However, when the α,β-unsaturated aminoketone **1a**[1] was reacted with Et_2AlN_3, obtained in situ from diethylaluminum chloride and sodium azide,[3] no linear adduct **3a** was detected. The only product isolated was the triazole **4a** in 41% yield (Scheme 1). The latter derives from a [3+2] cycloaddition of azide to the double bond followed by aromatization and loss of the dibenzylamino group. The structure of compound **4a** was unambiguously confirmed by a X-ray analysis (Fig. 1).[4]

1,3-Dipolar cycloaddition of azides and acetylenes is a classical method for the synthesis of 1*H*-1,2,3 triazoles.[5] [3+2] Cycloaddition of azides to activated alkenes proceeds in a similar fashion giving Δ^2 1,2,3-triazolines which can then be aromatized under oxidative conditions.[6] Triazoles can also be obtained by the cycloaddition of azides and electron deficient alkenes with a suitable leaving group positioned on the double bond.[6,7] While both organic azides and metal azides, or hydrazoic acid, can be used in the cycloaddition with alkynes to obtain 1-substituted triazoles and the parent unsubstituted compounds, respectively, the corresponding reaction with alkenes is limited to organic azides,[7] as 1,4-conjugate addition and formation of linear



R,R' = **a**: *i*Pr,Me; **b**: Bn,Me; **c**: Bn,Bn; **d**: Bn,*i*Pr

Scheme 1. Diethylaluminum cyanide addition to α,β-unsaturated aminoketones.

Keywords: [3+2]cycloaddition; diethylaluminum azide; hydride transfer; 1*H*-1,2,3-triazole.

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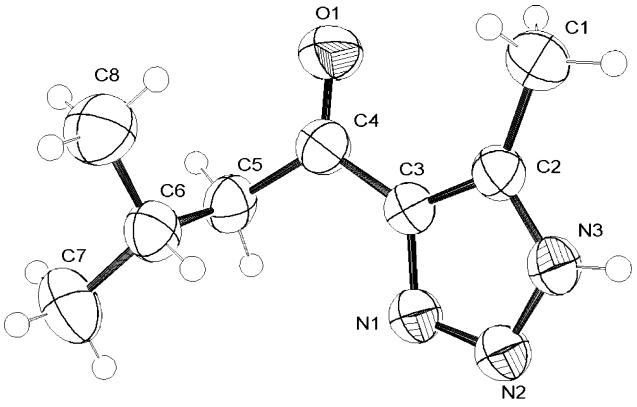
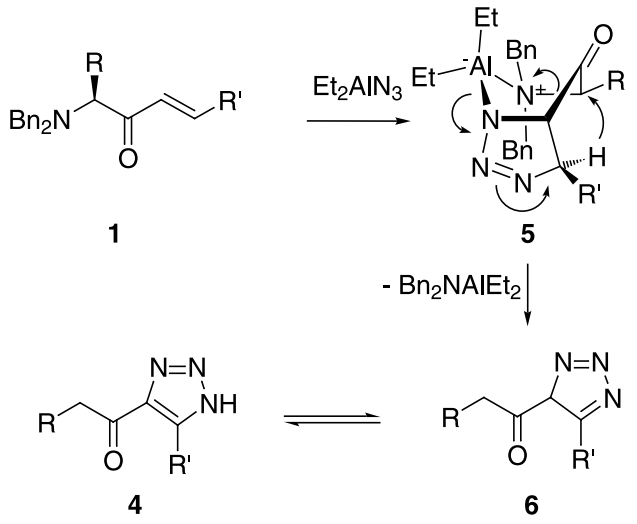


Figure 1. X-Ray crystal structure of triazole **4a** showing the crystallographic numbering scheme.



Scheme 2. [3+2] Cycloaddition of diethylaluminum azide and α,β-unsaturated aminoketones **1**.

Table 1. Yields of triazoles **4** from the reaction of enones **1** and diethylaluminum azide

Triazole	R	R′	Yield (%)
4a	*i*-Pr	Me	41[a]
4b	Bn	Me	37[a]
4c	Bn	Bn	40[a]
4d	Bn	*i*-Pr	10[a]
4e	Ph	Me	—[b]

[a] Remainder was a mixture of unidentified products.
[b] 1-Dibenzylamino-4-methyl-1-phenylhexan-2-one (from addition of an ethyl group to **1e**) was the main product.

adducts is generally preferred with azide ions and hydrazoic acid.[8] The formation of triazoles **4** from alkenes **1** (Scheme 1) is an exception to this general pattern of reactivity.

Based on the established dipolar reactivity of azides, the mechanism shown in Scheme 2 can be proposed for the reaction between α,β-unsaturated ketones **1** and diethylaluminum azide.

[3+2] Cycloaddition of **1** and Et_2AlN_3 leads, either directly or after reorganization of the initial adduct, to the intermediate **5**, in which the metal is chelated between the triazoline N-1 and the dibenzylamino group. In **5**, the two rings are optimally aligned for an intramolecular migration of hydride from the triazoline C-4 to the α-carbon with displacement of the *N*,*N*-dibenzylamino group, activated by complexation with aluminum. This leads to the formation of the triazole **6**, which then tautomerizes to **4**. A similar mechanism is likely to operate in the cycloaddition of phenylazide to α,β-unsaturated epoxyketones in which reductive ring opening of the epoxide, presumably by hydride migration from the β-carbon, is reported to partially accompany aromatization of the triazoline adduct.[9] Spontaneous aromatization of triazolines to triazoles, on the other hand, is exceedingly slow at room temperature.[10] Consistent with the proposed mechanism, dibenzylamine is isolated, after aqueous workup, in equimolar amount to triazoles **4**.

In order to assess its generality, the same reaction was carried out on several substrates (**1a**–**e**)[11] with different substituents R, R′ (Scheme 1).[12,13] The results collected in Table 1 indicate that the reaction is sensitive to the substituents: triazoles **4a**–**c** are the main products in the reaction with alkenes **1a**–**c**, while **4d** is formed only in minor amounts from substrate **1d**, and no triazole **4e** could be detected in the reaction of **1e**. In the latter case the amino ketone resulting from 1,4-addition of an ethyl group to the enone was the main reaction product, as a 1:1 mixture of diastereoisomers.

Triazolines deriving from the [3+2] cycloaddition of azides to electron-deficient alkenes have been reported to be in equilibrium with the corresponding diazo amines (open chain tautomers) which, in turn, may further react by several pathways.[14] This may explain the formation of a number of unidentified products, accompanying triazoles **4a**–**d**.

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4. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 215076. Copies of the data can be obtained, free of charge, on application to

CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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12. *Typical procedure*: 5.6 mL of a 1 M solution of diethylaluminum chloride in hexane was added to a stirred suspension of sodium azide (472 mg, 7.25 mmol) in 5 mL dry toluene and stirring was continued for 4 h. Enone **1a** (600 mg, 1.86 mmol) in 3 mL dry toluene was added and the mixture was stirred for 1 h (48 h for **1c** and **1d**). NaF (1.65 g) and water (0.7 mL) were added and the mixture was stirred for 30 min and then filtered over a pad of anhydrous sodium sulfate. Solvent evaporation and column chromatography of the residue (ether/petroleum ether 1:1) gave crude **4a**.
13. **4a**: mp 93–94°C (toluene); ^{1}H NMR ($CDCl_3$; 400 MHz) δ: 1.00 (d, $J=6.8$ Hz, 6H), 2.29–2.36 (m, 1H), 2.61 (s, 3H), 2.96 (d, $J=7.1$ Hz, 2H), 11.5 (broad, NH); ^{13}C NMR (100.4 MHz) δ: 10.4, 22.7, 25.1, 48.9, 141.4, 142.0, 196.8. Anal. calcd for $C_8H_{13}N_3O$ (167.21): C, 57.5; H, 7.84; N, 25.1%. Found: C, 57.3; H, 8.14; N, 25.3%. **4b**: mp 106–107°C (toluene): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.60 (s, 3H), 3.07 (t, $J=7.7$ Hz, 2H), 3.45 (t, $J=7.7$ Hz, 2H), 7.15–7.28 (m, 5H), 11.1 (broad, NH); ^{13}C NMR (100.4 MHz) δ: 10.4, 29.8, 41.6, 126.2, 128.5 (2C), 140.9, 141.7, 142.5, 195.6. Anal. calcd for $C_{12}H_{13}N_3O$ (215.25): C, 67.0; H, 6.09; N, 19.5%. Found: C, 66.7; H, 6.03; N, 19.0% **4c**: mp 114–115°C (toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.05 (t, $J=7.7$ Hz, 2H), 3.43 (t, $J=7.7$ Hz, 2H), 4.36 (s, 2H), 7.2–7.3 (m, 10H); 12.5 (broad, NH); ^{13}C NMR (100.4 MHz) δ: 29.7, 30.9, 41.6, 126.2, 127.2, 128.49, 128.51, 128.9, 129.0, 136.8, 140.9, 141.8, 144.9, 195.2. Anal. calcd for $C_{18}H_{17}N_3O$ (291.35): C, 74.2; H, 5.88; N, 14.4%. Found: C, 74.0; H, 5.81; N, 14.3%. **4d**: mp 106–108°C (toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (d, $J=7.0$ Hz, 6H), 3.07 (t, $J=7.7$ Hz, 2H), 3.45 (t, $J=7.7$ Hz, 2H), 3.69–3.72 (m, 1H), 7.15–7.28 (m, 5H); 12.05 (broad, NH); ^{13}C NMR (100.4 MHz) δ: 21.4, 25.0, 29.9, 41.8, 126.1, 128.5 (2C), 139.1, 141.1, 141.5, 195.5. HRMS calcd for $C_{14}H_{17}N_3O$: 243.1372. Found: 243.1399.
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