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Dialkylzinc-Assisted Alkynylation of Nitrones

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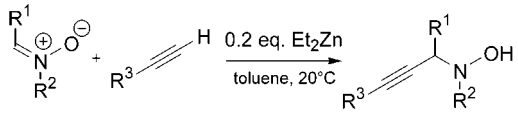
ABSTRACT



Reaction of nitrones with terminal alkynes takes place readily in the presence of a substoichiometric amount of diethylzinc in toluene, affording *N*-propargyl-hydroxylamines in excellent yields and purity.

We recently published[1] a study of the vinylation of nitrones by vinylzinc reagents. The latter were prepared by hydrozirconation of terminal alkynes followed by zirconium-to-zinc exchange according to the procedures of Wipf.[2] In some of our runs, we found that the desired *N*-allyl-hydroxylamine was contaminated by *N-propargyl*-hydroxylamine, issued from unreacted alkyne. Checking the outcome of this side reaction led us to the present communication of a new reaction of terminal alkynes with nitrones, in the presence of substoichiometric amounts of diethylzinc.

The versatility of propargylic amines has been widely exemplified.[3] One of the ways to these reagents is the addition of an acetylide onto a C=N double bond. Usually the acetylides are prepared by the action of a stoichiometric base on terminal alkynes; asymmetric versions have been developed.[4,5] However, as far as the use of organozinc reagents is concerned, the reports are few compared to the related reactions of aldehydes and 1-alkynylzinc (separately prepared by action of dialkylzinc to terminal alkynes). These additions to aldehydes are catalyzed by several types of ligands, allowing enantioselective versions.[6]

Another interesting trend of these additions to aldehydes is the feasibility of the nucleophilic addition of terminal alkynes in the presence of weak bases and/or substoichiometric amounts of bases.[7] The recent Meerwein−Ponndorf−Verley alkynylation of aldehydes should also be quoted.[8]

Carreira et al. recently found[9] that the combined action of small amounts of a zinc salt and a tertiary amine onto a

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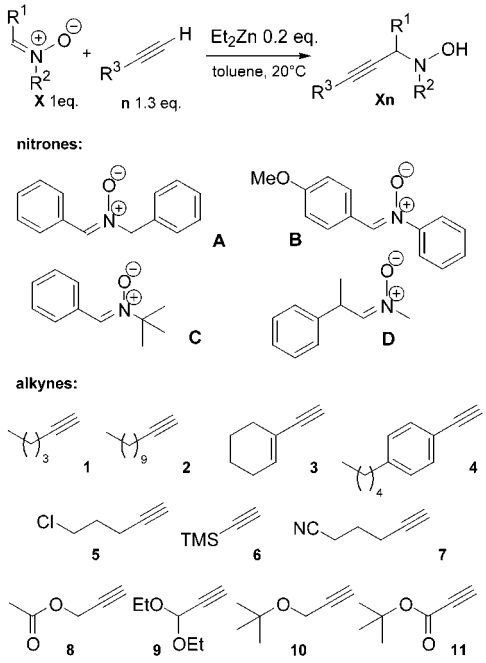

Figure 1. Reaction of nitrones and alkynes in the presence of 0.2 equiv of Et_2Zn in toluene at 20 °C.

mixture of a terminal alkyne and an aldehyde[9,10] or a nitrone[11] leads smoothly and efficiently to the propargyl adduct. In the case of nitrones the addition of alkynes is best run in the presence of zinc trifluoromethanesulfonate and a tertiary amine in dichloromethane or acetonitrile at 23 °C.[11]

Since our own study began with the identification of this addition as a side reaction in dichloromethane, we first worked in this solvent. We found that in dry dichloromethane, a slow reaction of benzylidene-benzylamine-*N*-oxide, 1-hexyne, and diethylzinc in a 1:2:1 ratio[12] proceeds to completion overnight at 20 °C, leading to the propargylic *N*-hydroxylamine. The addition is more sluggish if benzylidene-*aryl*amine-*N*-oxide or benzylidene-*tert*-*butyl*amine-*N*-oxide, or *O*-protected propargyl alcohols are used. In some instances, on standing, a cyclization of the product propargylic *N*-hydroxylamine into 2,3-dihydroisoxazole (see below) was observed.

A dramatic improvement was brought by changing from dichloromethane to toluene. In this solvent, not only is the reaction much quicker, but it can be completed in the presence of only 0.2 equiv of diethylzinc (use of 0.1 equiv is possible, but the results are less reproducible) within 4 h at 20 °C.

In such conditions, the reaction becomes highly efficient and general, as exemplified in Figure 1 and Table 1.

Table 1. Reaction Time and Yields of the Additions

nitrone	alkyne	time (h)	yield (%)	notes
A	**1**	6	92	*a*
A	**2**	30	82	
A	**3**	2	88	
A	**4**	3	92	
A	**5**	6	96	
A	**6**	23	90	
A	**7**	8	78	*b*
A	**8**	30	62	*c*
A	**9**	20	90	
A	**10**	8	82	
A	**11**	9	<42	*d*
B	**1**	1.5	72	
B	**4**	1.5	56	
B	**5**	2	61	
C	**8**	19	quant	*e*
D	**1**	4.5	94	dr 78/22 [f]
D	**1**	24 (−10 °C)	83	dr 81/19
D	**3**	3	97	dr 74/26
D	**6**	4	87	dr 76/24
D	**8**	3	91	dr 77/23

[a] Nitrone (1 mmol), terminal alkyne (1.3 mmol), and diethyl zinc (1 M solution in hexanes, 0.2 mmol) in anhydrous toluene (4 mL) were stirred in a Schlenk tube under N_2. [b] 0.3 equiv of diethylzinc was used. [c] Deprotected **A8** was isolated as a side product (21% yield). [d] In one run, after 9 h, the crude mixture contained 42% product **A11**, 33% nitrone **A**, 7% 2-benzyl-3-phenyl-2,3-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester, and 18% 2-benzyl-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid *tert*-butyl ester. [e] Product is obtained solely as 2,3-dihydroisoxazole (Figure 2). [f] dr: diastereoisomeric ratio

In most cases, the propargylic *N*-hydroxylamines are obtained pure after a simple washing of the crude material in pentane. Contamination by a product that would be issued from addition of an ethyl moiety[1] onto the nitrone is never observed (^{1}H NMR). Carreira et al.[13] observed that the products are prone to cyclization to form 2,3-dihydroisoxazoles. In our conditions, this side product remains beyond NMR detection after workup. A curious exception is observed when a *tert*-butyl substituent is on the nitrogen atom: the reaction of **C** and **8** leads to complete cyclization

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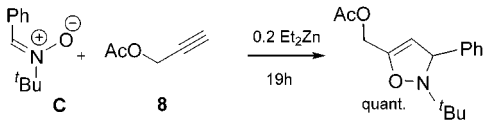

Figure 2. Cyclization of the primary adduct of a *N*-*tert*-butyl-nitrone.

after 19 h (Figure 2). In the case of *N*-aryl-hydroxylamines, we observed that the product is particularly unstable, even after purification. Although the nitrone **B** is fully consumed, isolated yields of products **B1**, **B4**, and **B5** are lower.

In the case of the *tert*-butyl propiolate (run **A11**), the reaction is very sluggish; the transformation of the nitrone cannot be completed, and the expected hydroxylamine **A11** is contaminated with side products (in variable proportions) that we suppose (on ^{1}H NMR basis) to be 2-benzyl-3-phenyl-2,3-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (issued from cyclization of **A11**) and its isomer 2-benzyl-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid *tert*-butyl ester (issued from thermal 1,3-dipolar cycloaddition).

The propargylic *N*-hydroxylamines can be easily reduced[5] to provide the expected *N*-propargylamines in good yields, as shown in Figure 3.

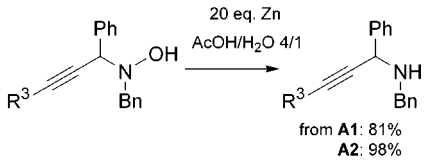

Figure 3. Reduction of the hydroxylamines.

Thus, the conditions are compatible with a large array of functional groups. Versatile acetylenic moieties, including propargylic ethers, acetates, and acetals, can be introduced. The addition of trimethylsilylacetylene (**A6**) followed by desilylation,[14] provides an easy way to the formal addition of acetylene.

Discussion of the Mechanism. To get insight into the mechanism, we first checked that in our conditions zinc triflate alone does not catalyze the reaction (20 °C, 24 h, no reaction). It could also be supposed that the hydroxylamine produced in the reaction could replace the tertiary amine used in Carreira's system. However, a mixture of alkyne **1**, nitrone **A**, zinc triflate (0.2 mole equiv) and 0.2 mole equiv of product **A1 (**from a previous run) does not show any change in toluene at 20 °C for 24 h.

The reactions were then followed by NMR in d_8-toluene. Dimethylzinc was used instead of diethylzinc. A solution of 80 μmol of dimethylzinc shows a sharp singlet at −0.75 ppm.[15] On addition of 160 μmol of alkyne **10**, this signal does not shift, but its intensity immediately decreases 16% (loss of 25 μmol dimethylzinc). Comparison of the integral of the acetylenic proton (1.92 ppm) and the integrals of other signals of the alkyne show an apparent lack of terminal H (33%, ∼60 μmol H). The remainder of the dimethylzinc is then very slowly consumed (more than 6 h for completion). Our best explanation is that the first rapid incomplete reaction is assisted by some impurity (moisture?) that is present at the start but is rapidly consumed. Then, the observation of a single set of signals hints for a rapid exchange of the acetylenic protons, as already proposed by others.[9]

When increasing amounts of nitrone **A** are added to a solution of dimethylzinc in d_8-toluene, nucleophilic addition is not observed after 15 min. The intensity of the methyl signal does not change, but a downfield shift is observed for both the methylzinc signal and the nitrone benzylic methylene (0.2 and 0.1 ppm, respectively)

Another reaction was run with a 1.8:1:0.1 ratio of alkyne **10**, nitrone **A**, and dimethylzinc in d_8-toluene. On addition of the alkyne to the dimethylzinc solution at 23 °C, the dimethylzinc signal decreases by 40%, without shift. The acetylenic H is at 1.98 ppm. On addition of the nitrone, the dimethylzinc signal disappears within 2 min, and the acetylenic H shifts to 2.10 ppm. Such a shift again indicates that a rapid exchange of the corresponding proton is taking place. The reaction proceeds slowly (12% after 1 h). As the amount of product increases, the basicity of the medium changes. Remarkably, this causes not only shifts of the acetylenic H resonance (from 2.10 to 2.01 ppm) but also of the nitrone signals (benzylic singlet of **A**, from 4.58 to 4.43 ppm).

Finally, the fate of dimethylzinc was more closely examinated. A mixture of 200 μmol of dimethylzinc and 290 μmol of alkyne **10** shows a methyl signal at −0.71 ppm. On addition of 200 μmol of nitrone **A**, it shifts to −0.60 ppm and broadens. Then, all three reagents are consumed in about 1 h, and noticeably, the methylzinc and nitrone signals decrease in the same proportions (Figure 4). At this stage,

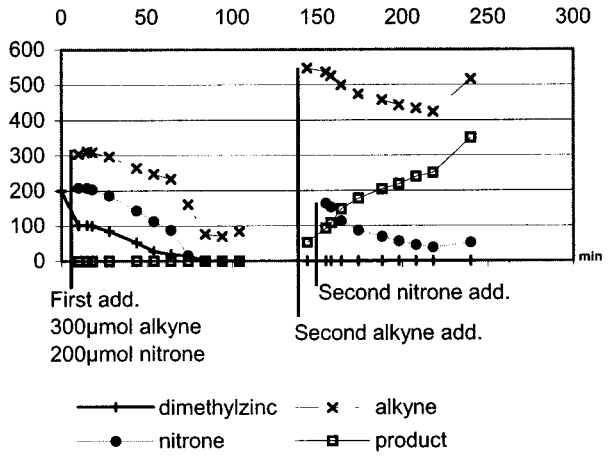

Figure 4. Plot of amounts/time in a NMR-tube experiment.

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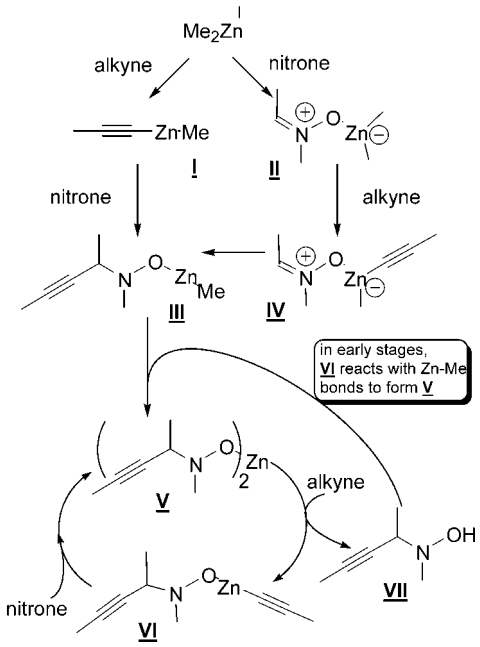
Scheme 1. Postulated Mechanism[16]



the free hydroxylamine product **A10** is not observed. Instead, several very broad bands grow (1−1.4, 3.9−4.8, 7.1−7.8 ppm), which we attribute to oligomeric zinc salts of **A10**. After completion of this first step, more (460 μmol) alkyne **10** is added. Immediately, the presence of *free* hydroxylamine **A10** is observed. This proves that an acido-basic reaction between the zinc salts of **A10** and alkyne **10** is effective. After 10 min, nitrone **A** (200 μmol) is added again; it is consumed with a concomitant formation of *free* product **A10**. Finally, the solution is treated with 0.2 mL of d_4-methanol. The broad bands disappear, and the amount of product **A10** significantly rises.

From these observations, some hypotheses can be gathered as shown in Scheme 1. In an initiation step, a MeZn−**A10** specie (**III**) would be formed by the reaction of some alkynyl-methylzinc (**I**) with A. Alternatively, the dimethylzinc−nitrone complex could be a better metallation agent than dimethylzinc and would produce **IV**, which would give **III**. **III** would react with the alkyne to form **VI** or with free hydroxylamine **VII** to give **V**. Then the reaction would proceed through the bottom cycle.

Thus, the present work presents a very mild, high-yielding, clean, and chemoselective access to secondary propargylic *N*-hydroxylamines and amines, which is of obvious interest in synthesis. Further studies about a possible autocatalysis and its implications in asymmetric versions are currently underway.

Supporting Information Available: Experimental procedures, descriptions of spectra of nitrones **B** and **D**, and all adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Substituents are omitted for clarity

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