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Tetrahedron Letters 48 (2007) 1457–1459
Tetrahedron Letters

Trimethylaluminum-assisted alkynylation of nitrones

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Received 29 November 2006; accepted 13 December 2006
Available online 16 January 2007

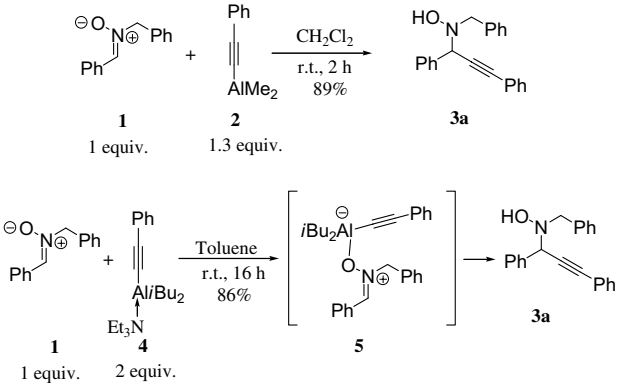
Abstract—Reaction of nitrones with terminal alkynes occurs in the presence of 1 equiv of trimethylaluminum and leads to the corresponding propargylic hydroxylamines in yields ranging from 49 to 90%.

Nitrones are powerful tools in organic synthesis, not only as 1,3-dipolar reagents in cycloadditions[1] or electrophiles toward organometallic compounds,[2] but also in many other reactions, as recently highlighted.[3] During our investigations on the preparation and the use of mixed alkynylaluminum reagents,[4] we were surprised to see that the reactivity of nitrones toward alanes was almost unknown, despite numerous reports on aluminum-based Lewis acid activation of nitrones.[5] We report in this Letter our investigations in this field.

Preliminary experiments were conducted with nitrone **1** and mixed alane **2** prepared by triethylamine-catalyzed metalation (Scheme 1).[4c] These two components reacted in a fast manner to deliver the corresponding hydroxylamine **3a** in an 89% yield.

More surprisingly, we found that stoichiometric complex **4**, generally not reactive with aldehydes or oxazolidines, was also able to react in a similar manner with nitrone **1**. This result could be explained by a complexation shift between complex **4** and intermediate **5**, leading to the final product **3a** by an intramolecular delivery of the alkynyl group. We then realized that nitrone itself could act as a Lewis base in the metalation step, enabling a one-pot transformation, as proposed by Chavant and Vallée in closely related studies on dialkylzinc-assisted alkynylations.[6]

First experiments were conducted in toluene at 70 °C with a stoichiometric amount of trimethylaluminum



Scheme 1.

(Table 1). Propargylic hydroxylamines **3a–d** were obtained in 48–86% yield after a hydrolytic work-up.

A significant improvement was found by changing the solvent from toluene to refluxing methylene chloride, leading to a better solubility of nitrone **1** (and probably its metallic complexes) under these conditions. Thus, a wide range of propargylic hydroxylamines were obtained under very simple experimental conditions from aromatic nitrone **1** (Table 2).[7]

In such conditions, the reaction becomes efficient and general with various nitrones, as exemplified in Table 3. Interestingly, even functional groups possessing a Lewis base character such as pyridine (Table 1, entry 4 or Table 2, entry 4) or furan (Table 3, entry 5) are well tolerated, as well as aliphatic (Table 1 or 2, entry 3) or aromatic (Table 2, entries 5 and 6) halogens.

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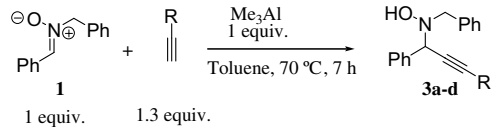
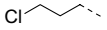
doi:10.1016/j.tetlet.2006.12.086

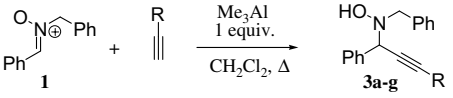
Table 1. One-pot alkynylation of nitrone **1** in toluene

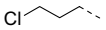
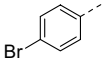


Entry	R	Compound	Yield[a] (%)
1	Ph	**3a**	86
2		**3b**	60
3		**3c**	48
4		**3d**	49

[a] Isolated chemical yield.

Table 2. One-pot alkynylation of nitrone **1** in CH_2Cl_2



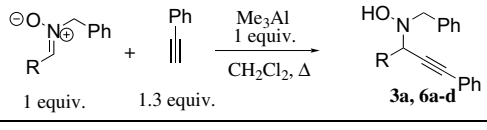
Entry	R	Time (h)	Compound	Yield[a] (%)
1	Ph	2	**3a**	88
2		4	**3b**	81
3		7	**3c**	64
4		5	**3d**	46
5		5	**3e**	75
6		16	**3f**	68
7	$(CH_3)Si$	16	**3g**	57
8	$(CH_3)Si$	48	**3g**	70

[a] Isolated chemical yield.

Although the mechanism of this transformation was not fully investigated, it might be slightly different from the one proposed for the dialkylzinc-assisted alkynylation (Scheme 2). Only 0.2 equiv of dialkylzinc is indeed required for the transformation of 1 equiv of nitrone,[6e] whereas all attempts to perform our reaction with less than 1 equiv of trimethylaluminum led to a significant decrease of a chemical yield.

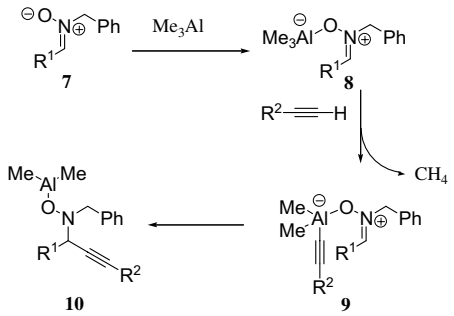
Thus, the initial complexation of trimethylaluminum by the nitrone activates the metalation of the alkyne and leads, probably in an intramolecular way, to the metalated hydroxylamine **10**, which is not able to enter a catalytic metalation–alkynylation process, as proposed with dialkylzinc. This compound is however, probably able to release some trimethylaluminum by disproportionation since nitrone **3a** was isolated in a 49% yield when alkynylation was conducted with **1** in the presence of only 0.4 equiv of trimethylaluminum.

Table 3. Nitrone variation in one-pot alkynylation



Entry	R	Time (h)	Compound	Yield[a] (%)
1	Ph	2	**3a**	88
2		7	**6a**	62
3		7	**6b**	47
4		4	**6c**	90
5		7	**6d**	75

[a] Isolated chemical yield.



Scheme 2.

In conclusion, we have shown in this study that mixed alkynylalanes readily react with nitrones. Furthermore, the Lewis basicity of these electrophiles promotes the in situ metalation of alkynes, enabling a simple one-pot procedure.[8] Once again, the preparation of acetylides using a widely available, non-toxic metal source can provide a useful alternative route to reactive acetylides generally prepared with strongly basic reagents, and might present an attractive functional group tolerance.

Acknowledgments

T.B. thanks the Alexander von Humboldt Foundation for a Feodor Lynen Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.086.

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7. *Typical procedure*: The preparation of **3a** is representative. A dry and argon-flushed flask equipped with a magnetic stirrer and condenser was charged with *N*-benzylidene-benzylamine *N*-oxide (0.22 g, 1 mmol) and phenylacetylene (0.14 mL, 1.3 mmol) in distilled CH_2Cl_2 (1.5 mL), and $AlMe_3$ (0.5 mL, 1 mmol, 2 M in toluene) was added dropwise. The reaction mixture was refluxed, until the gas evolution ceased. A 2 M aqueous solution of Rochelle's salt (4 mL) was added and stirred for 1 h at rt, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (5% EtOAc in cyclohexane) yielded **3a** (0.275 g, 88%) as a white solid. *N-Benzyl-N-(1,3-diphenyl-prop-2-ynyl)-hydroxylamine* (**3a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70–7.58 (m, 4H), 7.50–7.26 (m, 11H), 6.14 (br s, 1H), 4.86 (s, 1H), 4.03 and 3.85 (2d, $J_{AB} = 12$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 137.4, 137.1, 132.0, 129.8, 129.0, 128.4, 128.2, 127.6, 122.9, 88.7, 84.6, 62.9, 60.4.
8. This one-pot procedure is mechanistically different from the well established Carreira's method, which is based on an in situ metal-assisted deprotonation of alkyne by an organic base, whereas this work is based on an organic base-assisted metalation of alkyne by a Lewis acid. For mechanistic details of the Carreira's procedure, see: Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5843–5845, and references cited.