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A Highly Effective Quenching Method of 1,3-Dipolar Cycloadditions of Nitrile Oxides or Nitrile Oxide/Lewis Acid Complexes by Use of 2-Propenyloxymagnesium Bromide

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Abstract: *2-Propenyloxymagnesium bromide, readily prepared by treating 2-propen-1-ol with EtMgBr, is a highly effective quencher of nitrile oxide cycloadditions since this alkoxide is much more reactive to nitrile oxides than any other ever known dipolarophiles of the electron-deficient, electron-rich, and strained types, including 3-buten-2-one, ethyl vinyl ether, and norbornene, respectively. This quencher is also effectively utilized to terminate the dipolar cycloadditions of nitrile oxide/Lewis acid complexes.*

Nitrile oxide cycloadditions to olefinic and acetylenic dipolarophiles lead to 2-isoxazolines and isoxazoles, respectively. These are regarded as highly functionalized heterocycles since they mask a variety of synthetically important building blocks, such as β-hydroxy ketones (aldols), α,β-unsaturated ketones, γ-amino alcohols, β-diketones, and so on, which are then demasked through the reductive N-O bond cleavage.[1] Based on the synthetic viewpoint, much attention has been enthusiastically focussed on the stereo- and regiocontrol as well as enantiocontrol of nitrile oxide cycloadditions.[2-4] To attain a higher stereoselectivity under milder reaction conditions, nitrile oxide cycloadditions, especially enantio-controlled asymmetric reactions using chiral dipolarophiles, will be performed at a low temperature.[5]

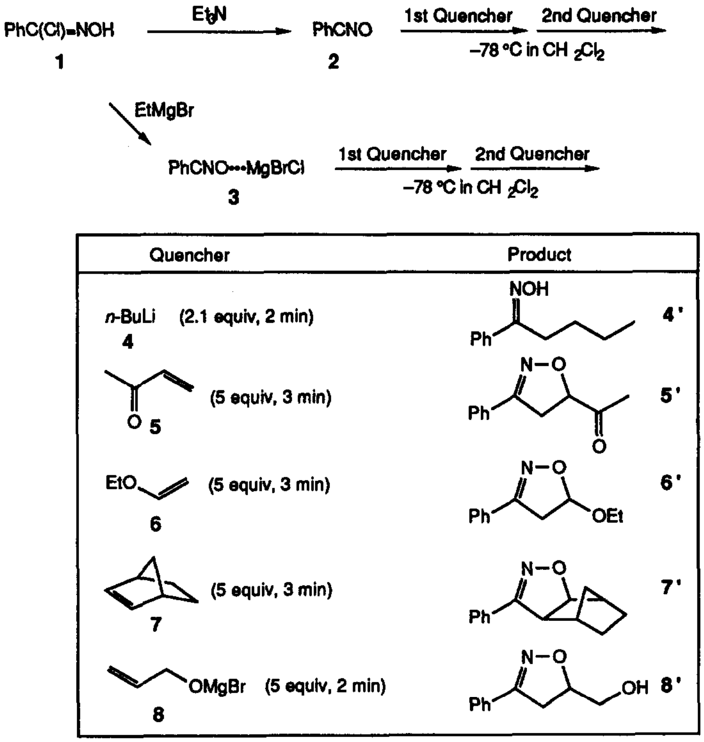
One of the recent advances in the related field involves the highly *syn*-selective nitrile oxide cycloadditions to allylic alcohol dipolarophiles in which nitrile oxide/Lewis acid complexes are responsible for the high stereocontrol.[2] Use of the magnesium alkoxides of allylic alcohols leads to high rate enhancement and absolute regiocontrol.[3] However, the metal-assisted stereo- and regiocontrol of 1,3-dipolar cycloadditions to electron-deficient dipolarophiles, as typical conventional acceptor molecules, remain unsolved.[6-8]

In the course of our kinetic study on the rate acceleration in chelation-controlled nitrile oxide cycloadditions, we needed an effective termination method of nitrile oxide cycloadditions. Quenching with aqueous salts such as ammonium chloride has been most widely employed. However, this procedure often arouses criticisms when one tries to terminate the nitrile oxide reactions performed at a low temperature such as –78 °C. Quenching becomes ineffective due to the freeze of aqueous quencher at this temperature. Nitrile oxides are not always instaneously consumed under these conditions, and hence cycloaddition to the remaining dipolarophile still proceeds under the workup conditions. Especially, the cycloaddition rate increases as the reaction mixture is concentrated in a condensation procedure. On the hydrolytic termination of the chelation-controlled cycloadditions to electron-deficient dipolarophiles, free nitrile oxides, presumably more reactive than the complex, are liberated. They are hydrolyzed, but at the same time they undergo a competitive cycloaddition with the unreacted dipolarophile during the workup procedure.

We would like to present in this communication letter a highly effective quenching method of nitrile oxide cycloadditions by the aid of 2-propenyloxymagnesium bromide. This termination method can be applied to a wide variety of nitrile oxide cycloadditions to any kinds of dipolarophiles.

A very reactive dipolarophile is suitable as an efficient quencher for nitrile oxide cycloadditions. Inexpensive and volatile compounds are desired so that they can be employed in a large excess and removal of the remaining quencher may be readily undertaken by evaporation. Also desirable is the ready separation of the cycloadduct derived from the quencher employed from the target cycloadduct.

Selected quenchers here in the present work include butyllithium (**4**), 3-buten-2-one (**5**), ethyl vinyl ether (**6**), bicyclo[2.2.1]hept-2-ene (norbornene, **7**), and 2-propenyloxymagnesium bromide (**8**). Dipolarophiles **5**,**6**,**7** are each the most reactive dipolarophiles of the electron-deficient, electron-rich, and strained types.[9] Nucleophile **4** adds to nitrile oxides to give alkylated oximes; alkoxide **8** undergoes a rapid cycloaddition to give 2-isoxazoline-5-methanols. One anxious thing is that termination with **4** as a strong base may cause some serious decomposition of product cycloadducts, especially when a leaving group is attached at 5-position of 2-isoxazoline ring.



Scheme 1.

In general, termination of a reaction is desired to be done in a few minutes at a low temperature, more desirablly in a few second. Accordingly, appropriate two quenchers of the above **4**-**8**, in excess as much as 5 equivalents (2.1 equivalents for **4**), were employed in order in an interval of 3 min (2 min for **4**, **8**). As a general procedure, a nitrile oxide was allowed to react with the first quencher for 3 min at –78 °C and this reaction was terminated with the second quencher. The efficiency of quenchers was evaluated based on the product ratios. Results are summarized in Table 1.

Table 1. Reactions of Benzonitrile Oxide 2 or Benzonitrile Oxide/MgBrCl Complex 3 with Various Quenching Agents 4-8[a]

Entry	Nitrile oxide or complex	1st Quencher[b,c]	2nd Quencher[b,c]	Product (yield/%)[d]
1	PhCNO[e]	**4**	none	**4'** (76)
2		**5**	none	**5'** (97)
3		**4**	**5**	**4'** (95), **5'** (5)
4		**5**	**4**	**5'** (85), **4'** (6)
5		**5**+**7**[f]	none	**5'**+ **7'** (100, 42:58)
6		**6**	**4**	**6'** (0), **4'** (92)
7		**7**+**8**	none	**7'** + **8'** (97, only **8'**)
8	PhCNO•MgBrCl[e]	**4**	**5**	**4'** (15), **5'** (50)
9		**5**	**4**	**5'** (86), **4'** (trace)
10		**5**+**7**[f]	none	**5'**+ **7'** (78, 45:55)
11		**6**	**4**	**6'** (25), **4'** (16)
12		**7**+**8**	none	**7'** + **8'** (86, 2:98)

[a] All reactiones were performed in CH_2Cl_2 (entries 1-7) and CH_2Cl_2/THF (10:1 v/v, entries 8-12). [b] Unless otherwise referred, a quencher was added and allowed to stir at –78 °C for 2-3 min. [c] Quencher **4** was used in 2.1 equivalents and the other ones **5-8** in 5 equivalents. [d] Yield of isolated products. Product ratio was based on the ^1H NMR spectrum of the crude reaction mixture. [e] Hydroximoyl chloride **1** was treated with Et_3N (0 °C, 3 min) or EtMgBr (1M in THF, 0 °C, 5 min) and cooled down to –78 °C. [f] A mixture of each 5 equivalents was used.

Free benzonitrile oxide (**2**), generated from hydroximoyl chloride **1** and triethylamine at 0 °C, was first examined in quenching experiments. In reactions with **2**, nucleophile **4** and enone **5** are smoothly consumed in a few minutes at –78 °C to give adduct **4'** and cycloadduct **5'**, respectively, in good yields (Table 1, entries 1, 2). The successive use of **4** and **5** in an interval of 2 or 3 min indicates that these two can be excellent quenchers at –78 °C (entries 3, 4); the competitive cycloaddition between **5** and **7** indicates that they have nearly equal reactivities to nitrile oxide **2** (entry 5). However, vinyl ether **6** does not show a sufficient reactivity toward **2** in a reaction within a few minutes at –78 °C (entry 6).

To our great surprise, the competitive cycloaddition of free nitrile oxide **2** between norbornene (**7**) and 2-propenyloxymagnesium bromide (**8**)[10], each 5 equivalents, at –78 °C results in the exclusive formation of cycloadduct **8'** as the sole product in a quantitative yield (entry 7). It is later found that the latter is about 130 times reactive than the former. As a result, allyl alkoxide **8** is recognized to be the best quenching agent for nitrile oxide cycloadditions so as to be effectively utilized in the nitrile oxide cycloadditions to any kinds of dipolarophiles.[11]

Quenching of the cycloadditions of a nitrile oxide/Lewis acid complex has to be done carefully. Among the quenching agents employed in the cycloadditions of benzonitrile oxide/MgBrCl complex (**3**), as a representative for nitrile oxide/Lewis acid complexes, alkyllithium **4** and vinyl ether **6** are not promising (entries 8, 11): Vinyl ether **6** is a little more activated in the reaction with **3** than in the reaction with **2**, but still too poor in reactivity (entries 6, 11). In the case of **4**, two equivalents are consumed in the transmetalation with the Lewis acid part (MgBrCl) of complex **3**, but yet use of a large excess of such a strong base **4** would cause some undesired side reactions. Nucleophilic addition to carbonyl-functionalized 2-isoxazolines may be a case. As a trouble actually observed, when **6** and **4** are employed in this order (entry 11), the reaction produces mixture of complex products and part of cycloadduct **6'** suffers from the elimination of ethanol.

Enone **5** and strained olefin **7** show reactivities comparably high enough to consume complex **3** within a few minutes at –78 °C (entries 9, 10). However, allyl alkoxide **8** is much more reactive than norbornene (**7**) (entry 12), and hence than **5** as well, indicating that **8** may be effectively utilized again as a powerful terminating agent for the cycloadditions of nitrile oxide/Lewis acid complexes to any kinds of dipolarophiles.

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10. Magnesium alkoxide **8** was prepared as follows: Weighed 2-propen-1-ol was treated with an equivalent amount of EtMgBr at 0 °C in dichloromethane and the resulting solution was evaporated to dryness in vacuo. The residual solid was dissolved in another portion of dry dichloromethane and used for the reaction.
11. Norbornene is known to be the most reactive dipolarophile toward benzonitrile oxide but enamines (Caramella, P.; Grünanger, P. "Nitrile Oxides and Imines," as Chapter 3 of "1,3-Dipolar Cycloaddition Chemistry," ed by Padwa, A. John Wiley & Sons, New York (1984), Vol 1, pp. 327.)

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