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INTRAMOLECULAR [3+2] NITRONE-ALKYNE CYCLOADDITION

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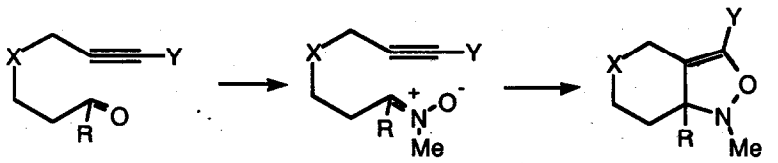
Abstract: It is demonstrated that the [3+2] cycloaddition of a nitrone to an alkyne is facile when the lengh of the tether connecting the two reacting sites is appropriate. The resulting [3+2] cycloaddition products, isoxazolidines can be further converted to 3-hydroxy-3-pyrrolin-2-ones and α-keto-β,γ-unsaturated esters by reductive and oxidative cleavage, respectively.

The [3+2] nitrone addition to an olefin has been established as a useful synthetic method.[1] Numerous applications of both inter- and intramolecular [3+2] nitrone additions to the synthesis of various natural products have been reported as well. Some examples, albeit limited, for the [3+2] cycloaddition of a nitrone to an alkyne in intermolecular mode have also been presented in the literature.[2] However, the *intramolecular* [3+2] nitrone addition to an alkyne has attracted little attention. In 1970, Le Bel and coworkers[3] reported the intramoleular [3+2] cycloaddition of an acetylenic nitrone generated from a reaction between 6-octyne-2-one and *N*-methylhydroxylamine and this has been the lone example in this category of reactions. In their report they documented the difficulty in directly isolating the cycloadduct, which was presumably due to the instablity of the cycloadduct. Consequently, they were only able to isolate the cycloadduct as a solvent addition product in unreported yield. No further works on the study of the nitrone additon to an alkyne in intramolecular mode have been reported during the last two decades.

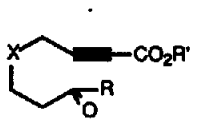
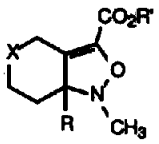
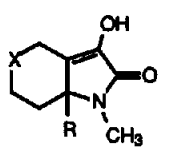
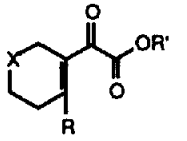
Here we wish to communicate our successful results from an investigation on the intramolecular [3+2] nitrone addition to an alkyne shown in the following equation (1).



1 2 3

The methanolic solution of *N*-methylhydroxylamine was added to a solution of 1 in benzene. The resulting solution was stirred at room temperature for ca. 30 min. After concentration of the solution the residue was dissolved in benzene and heated at reflux for 2 ~ 3 h. Purification by chromatography afforded the desired cycloadditon product 3. Concentration of the solvent followed by dissolving the residue into benzene before reflux is crucial for obtaining the resonable yields of the [3+2] cycloadducts. Omission of this step

Table 1. Intrmolecular [3+2] nitrone-alkyne cycloaddition[5]

entry	starting material (% yield)	cycloadduct (% yield)	hydrogenation product (% yield)	after mCPBA oxidation (% yield)
				
1	**1a** (R = H; R'= Me; X = CH_2)	**3a** (54%)	**4a** (94%)	**5a** (66%)
2	**1b** (R = Me; R'= Me; X = CH_2)	**3b** (40%)	**4b** (89%)	**5b** (68%)
3	**1c** (R = H; R'= Me; X = O)	**3c** (47%)	**4c** (86%)	**5c** (69%)
4	**1d** (R = H; R'= Benzyl; X = CH_2)	**3d** (76%)	**4a** (82%)	**5d** (61%)
5	**1e** (R = H; R'= *p*-Nitrobenzyl; X = CH_2)	**3e** (78%)	**4a** (72%)	**5e** (62 %)

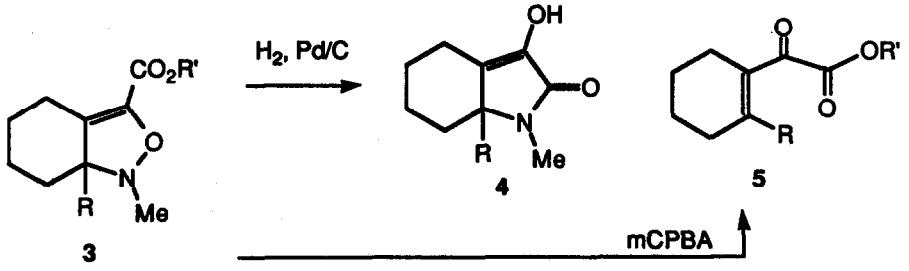
results in low yields of the cycloadduct (ca. < 10%).

The results of the intramolecular [3+2] nitrone-alkyne cycloaddition are summarized in Table 1. It is understood that the [3+2] cycloadditions take place with ease when the terminal site of the alkyne triple bond is substituted with an electron withdrawing group, in our case, alkoxycarbonyls (Y = CO_2R). Thus, when Y is H, trimethylsilyl, or methyl, no cycloaddition products, in contrast to reports by Le Bel and coworkers,[3] were observed. The feasibility of the [3+2] cycloaddition depended also on the length of the tether chain. Thus, under the same conditions described as above, the cycloaddition was not successful in the case of X = CH_2 and n = 0, which would provide five-membered ring compounds fused to the isoxazolidine, presumably due to ring strain involved in the transition state.[4]

The facile cycloaddition was observed when X = CH_2 and n = 1. Similarly, when the tether chain contained oxygen (X = O), the cycloadditon could also be performed easily.

The yields of the cycloaddition were only moderate in the case of R' = Me [54% and 40% for **3a**(entry 1) and **3b**(entry 2), respectively]. However, switching of the R' group to benzyl or nitrobenzyl increased the cycloaddition yields [76% and 78% for **3d**(entry 4) and **3e**(entry 5), respectively]. It appears that the aldonitrones are more reactive than ketonitrones. Thus, the yield of the cycloadduct **3b** (entry 2) is lower than that of **3a**(entry 1). A moderate yield was

obtained from the aldonitrone derived from 1c(entry 3; R = H, R' = Me, X = O), in which the tether chain contained an oxygen atom, whereas no cycloaddition product was isolated from the corresponding ketonitrone derived from the educt 1(R = R' = Me, X = O)](entry not shown in Table 1). All of the cycloadducts 3a ~ 3e were stable, and no problems arose during isolation and handling.[3]



Unambiguous evidences for formation of the desired intramolecular [3+2] nitrone-alkyne cycloadduct were obtained from the following reactions. The catalytic hydrogenation of cycloadduct 3a afforded a crystalline product 4a in good yield. The structure of 4a was rigorously established by spectral as well as single crystal X-ray diffraction analysis.[5] These analyses confirm that 4a exists as an enol form,[6] which is consistent with the phenomenon known in cyclopentane-1,2-dione and 2,3-dioxopyrrolidines cases.[7]

Another transformation of the cycloadduct 3 was performed with the reaction with m-chloroperbenzoic acid(mCPBA). Therefore, the treatment of 3 with mCPBA provided the expected α-keto-β,γ-unsaturated esters 5 in good yields.[8] The results of the two transformations are also listed in Table 1. The facile formation of the reduction and oxidation products from the cycloadducts proves that the intramolecular [3+2] nitrone–alkyne cycloaddition could be used as an expeditious entry to the compounds such as 4 and 5.

In summary, we have established that the intramolecular [3+2] nitrone-alkyne cycloadditions can be performed with ease. It has also been confirmed that the yields of the cycloadditon can reach a synthetically acceptable level, when the terminal site of the alkyne is substituted with an appropriate electron withdrawing group and, of course, the length of the tether chain connecting the two reaction sites is proper. The synthetic value of the intramolecular cycloaddition of acetylenic nitrones was demonstrated further by reduction as well as oxidation of the cycloadducts, which provided 3-hydroxy-3-pyrrolin-2-ones and α-keto-β,γ-unsaturated ester, respectively.

References and Notes

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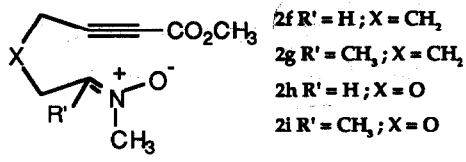
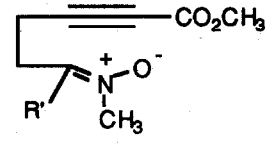
4. Subjecting **2f** and **2g** to our cycloaddition conditions(reflux in benzene) led to gradual decomposition. Ketonitrone **2g** under forcing conditions (reflux in toluene), however, provided two products(ca. 1:1 ratio; total yield ca. 50%). Aldonitrone **2f** in toluene at reflux also provided a product(ca. 20%). These products are clearly not the anticipated cycloadducts and the structures are under investigation. When an oxygen atom is within the chain (e. g., nitrones **2h** and **2i**) or if the length of the tether is further reduced(e. g., nitrones **2j** and **2k**), no detectable products were observed.



2f R' = H ; X = CH_2
2g R' = CH_3 ; X = CH_2
2h R' = H ; X = O
2i R' = CH_3 ; X = O



2j R' = H
2k R' = CH_3

5. Spectral data: **3a**; ^{1}H NMR($CDCl_3$, 200 MHz) δ 1.26~1.51 (3H,m), 1.79~1.98 (4H, m), 2.82 (3H, s, N-CH_3), 3.15~3.23 (1H, br d, J = 14 Hz, CH-C=CCO_2CH_3), 3.60~3.66 (1H, m, CHNCH3), 3.75 (3H, s, OCH_3); ^{13}C NMR($CDCl_3$, 50 MHz) δ 23.5, 24.4, 26.3, 33.5, 46.7, 51.7, 74.6, 126.7, 135.0, 160.2; MS (*m/e*, rel intensity) 197 (M^+, 11.7), 138 (100). **4a**; ^{1}H NMR($CDCl_3$, 200 MHz) δ 0.83~1.08 (1H, m), 1.10~1.52 (2H, m), 1.75~2.20 (3H, m), 2.40~2.60 (1H, m, CH-C=C-OH), 2.83~3.11 (4H, m, CH-NCH_3), 3.35~3.50 (1H, m, CH-C=C-OH); ^{13}C NMR($CDCl_3$, 50 MHz) δ 23.8, 24.1, 27.2, 27.8, 33.3, 59.9, 124.7, 139.3, 168.5; MS (*m/e*, rel intensity) 167(M^+, 100). **5a**; ^{1}H NMR($CDCl_3$, 200 MHz) δ 1.32~1.74 (4H, m, CH_2-CH_2), 2.23 ~ 2.73 (4H, m, CH_2-C=C-CH_2), 3.88 (3H, s, OCH_3), 6.97 ~ 7.00 (1H, m, C=CH); ^{13}C NMR($CDCl_3$, 50 MHz) δ 22.0, 22.7, 27.2, 52.9, 83.0, 136.8, 149.9, 165.7, 188.6; MS (*m/e*, rel intensity) 168 (M^+, 1.7), 109 (100).
6. Both **4a** and **4b** exist exclusively as the enol forms in solution. In the case of **4c** a ratio of 1:3(keto vs enol form) was observed(by NMR spectral analysis).
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