



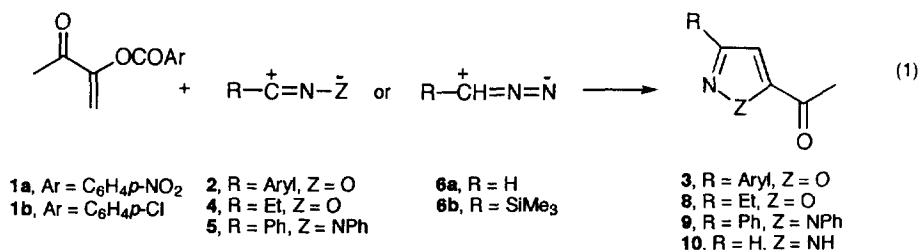
Highly Selective 1,3-Dipolar Cycloadditions of Captodative Olefins 1-Acetylvinyl Carboxylates to Diverse Dipoles

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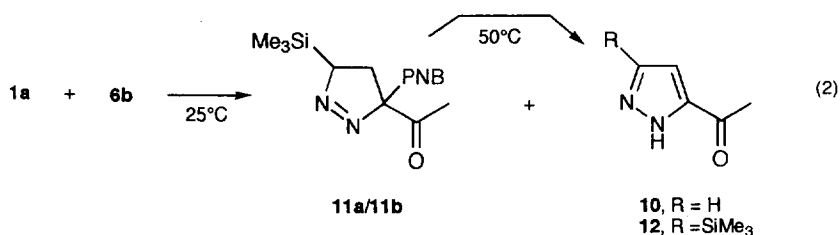
Abstract: Regioselective 1,3-dipolar cycloadditions of captodative 1-acetylvinyl *p*-nitrobenzoyloxy (**1a**) with propionitrile oxide, diphenylnitrile imine and diazoalkanes provided the corresponding 5-acetyl- isoxazoles and pyrazoles. Evidence to support the formation of the initial cycloadducts was obtained. The addition of nitrones also proved to be highly regio- and stereoselective.
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1,3-Dipolar cycloadditions have been extensively studied with numerous substituted olefins, bearing substituents of diverse electron-demand, in order to establish the factors responsible for the regio- and stereoselectivity in these processes.¹ On the other hand, captodative olefins have attracted especial attention in Diels-Alder reactions, due to the opposite electronic effect displayed by their geminally substituted functional groups.² Nevertheless, no studies have been devoted to this kind of olefin in 1,3-dipolar cycloadditions and only isolated examples have been reported.^{2a,3} Recently, we described the 1,3-dipolar cycloaddition of captodative olefins **1** with aryl nitrile oxides **2**,⁴ giving exclusively isomers 5-acetyl-3-arylisoxazoles **3** (eq. 1). This result prompted us to examine the reactivity and selectivity of these olefins with various dipoles. Herein, we disclose the results of the cycloadditions with propionitrile oxide (**4**),⁵ diphenylnitrile imine (**5**),⁶ diazomethane (**6a**), trimethylsilyl diazomethane (**6b**)⁷ and nitrones **7a-7g**.⁸

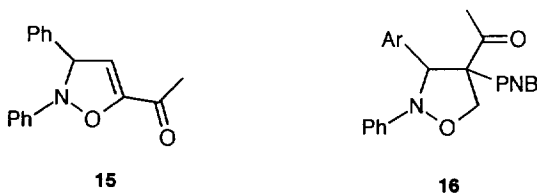


As observed for the series of aryl nitrile oxides **2**, the reaction of **1a** with **4** (C₆H₆, reflux, 2 h) provided single isoxazole **8**⁹ in 85% yield (eq. 1). Similarly, the addition of nitrile imine **5** (dioxane, reflux, 2 h) afforded *N*-phenyl pyrazole **9** as the only product in 80% yield. Diazomethane (**6a**) (ether, 25°C, 5 h) yielded 5-acetyl pyrazole (**10**) (68%). These aromatic heterocycles might have been formed as a result of β-elimination of the *p*-nitrobenzoyloxy group (PNB) from the initial cycloadducts; however, no evidence of the latter was found.

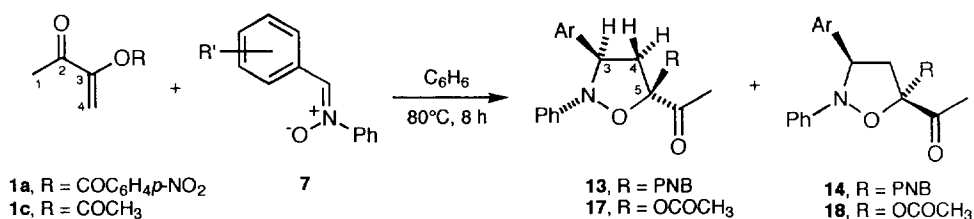
The reaction of **1a** with **6b** was carried out in ether at room temperature for 24 h, giving a mixture of stereoisomeric adducts **11a/11b** (79:21) and pyrazole **10** in a ratio of *ca.* 1:1 (eq. 2). When the reaction mixture was heated to 50°C for 30 min, the conversion of adducts **11** to the aromatic product **10** was complete. No traces of 3-(trimethylsilyl)-5-acetyl pyrazole (**12**) were detected. Thus, this reaction gives evidence that the cycloadduct is initially formed and transformed into the more stable aromatic product. The same explanation could be extended to the reaction with the other dipoles, including nitrile imine and nitrile oxides.



Therefore, it appears that the presence of a double bond in the initially formed cycloadducts facilitates the elimination of the PNB group, leading to the aromatic compound. This was additionally supported by the fact that the reaction of **1a** with diphenyl nitron (**7a**) provided isoxazolidines **13a/14a** in 80% yield, as a mixture of stereoisomers *endo/exo* in a ratio of 89:11. Other *C*-aryl-*N*-phenyl nitrones were assessed and the isomer ratios are shown in Table 1. The NMR spectra of crude mixtures revealed the presence of a mixture of diastereomeric isoxazolidines **13/14**. NOE experiments established the relative configuration of the major isomer, indicating that an *endo* transition state was favored¹⁰ and probably stabilized by secondary orbital interactions¹¹ (Figure 1). It is also noteworthy that neither the elimination product, i.e. dihydroisoxazole **15**, nor the possible C-4 regioisomers **16** were present in the crude mixture.

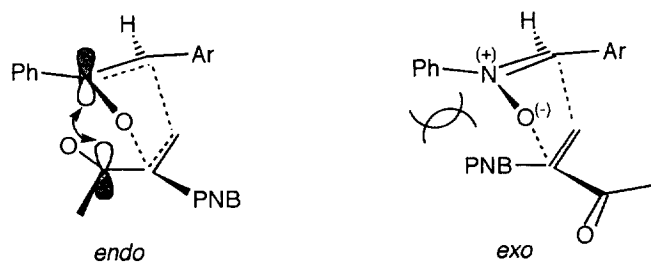


In order to evaluate the steric effect of the PNB group as a factor in contributing to the high stereoselectivity observed in the cycloaddition with nitrones, we carried out the reaction of nitron **7c** with the sterically less hindered captodative olefin **1c**. Only a mixture of C-5 disubstituted isoxazolidines **17/18** (73:27) (Table 1) was observed. The lower stereoselection for olefin **1c** in comparison with **1a** would suggest that the steric hindrance between the *N*-phenyl group of the nitron and the carboxylate substituent in the dipolarophile could affect the stereochemical outcome of these reactions.¹¹ Indeed, the more crowded *exo* transition state for **1a** would lead to the preferential *endo* approach, improving **13/14** ratio (Figure 1), as observed.

Table 1. Cycloadditions between nitrones **7** and olefins **1a** and **1c**.

Olefin	Nitrone	Products (ratio) ^a	mp (°C) ^b	Yield (%) ^c
1a	7a (R' = H)	13a/14a (89:11)	101-102	70
1a	7b (R' = 4-Cl)	13b/14b (90:10)	57-58	75
1a	7c (R' = 4-Br)	13c/14c (87:13)	126-127	70
1a	7d (R' = 4-NO ₂)	13d/14d (85:15)	120-121	70
1a	7e (R' = 4-OCH ₃)	13e/14e (83:17)	112-113	80
1a	7f (R' = 4-CH ₃)	13f/14f (95:5)	67-68	80
1a	7g (R' = 3-NO ₂)	13g/14g (89:11)	137-138	75
1c	7c (R' = 4-Br)	17/18 (73:27)	122-123	70

^a Determined by NMR (300 MHz). ^b Of the major isomer **13** or **17**. ^c Of the major isomer after recrystallization.

Figure 1. Transition states of the cycloaddition of nitrones towards olefins **1a**.

The high C-5 regioselectivity observed in these cycloadditions with all the dipoles could be explained by a steric control, keeping the bulkier aryl group of the nitrone and the geminally substituted carbon C-3 of the olefin as far away from each other as possible. However, this regioselectivity could not be explained only by steric interactions,^{3c,12,13} since the more crowded C-4 substituted isomers have mainly been generated depending on the electronic demand¹⁴ of the dipolarophile substituents.¹⁵ Factors such as the captodative effect,^{2a} involving diradicaloid intermediates or transition states,^{3a,b} could also be considered in controlling the orientation of the cycloaddents.¹⁶

In summary, these results demonstrated that captodative olefins **1** were highly selective in 1,3-dipolar additions with diverse dipoles, since only the 5-acetyl isomer was formed, in agreement with other 1,1-disubstituted olefins, which give rise to similar high regioselectivity.^{16b,17} Moreover, by giving access to acetyl

substituted aromatic heterocycles, **1a** behaves as an acetyl acetylene equivalent, improving the selectivity shown by dipolarophiles such as 3-butyne-2-one.¹⁸

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9. The products were characterized by ¹H and ¹³C NMR, IR spectral data and by elemental analysis. The yields were calculated after recrystallization or purification by column chromatography. **10**: ¹H NMR (CDCl₃) δ 2.62 (s, 3H, CH₃CO), 6.87 (d, *J* = 2.3 Hz, 1H, H-4), 7.71 (d, *J* = 2.3 Hz, 1H, H-3), 10.91 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 27.5, 108.0, 134.7, 148.0, 192.5.
10. The *Z* configuration of nitrone **7c** was suggested by NOE experiments, which would agree with previous reports.^{3c} **13c**: ¹H NMR (CDCl₃) δ 2.52 (s, 3H, CH₃CO), 2.93 (dd, *J* = 14.1, 6.3 Hz, 1H, H-4β), 3.29 (dd, *J* = 14.1, 9.0 Hz, 1H, H-4α), 4.65 (dd, *J* = 9.0, 6.3 Hz, 1H, H-3), 6.96-7.11 (m, 3H, Ph), 7.26 (m, 2H, Ph), 7.40 (m, 2H, Ar), 7.52 (m, 2H, Ar), 8.05 (m, 2H, PNB), 8.28 (m, 2H, PNB); NOE (enhancement %): {H_{4β}}-H_{4α} (25.5), {H_{4α}}-H₃ (10.0), {H_{4β}}-Ar (3.7), {H_{4β}}-PNB (0.7), {H₃}-COCH₃ (0.5), {H₃}-Ph (4.3), {H₃}-Ar (5.3).
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