Pergamon

Tetrahedron Letters, Vol. 37, No. 38, pp. 6835-6838, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01546-8

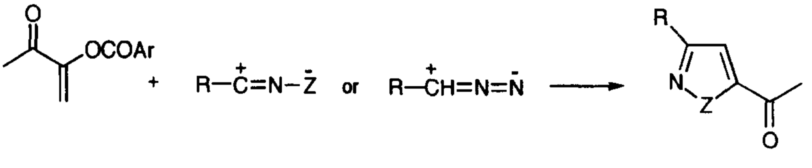
Highly Selective 1,3-Dipolar Cycloadditions of Captodative Olefins 1-Acetylvinyl Carboxylates to Diverse Dipoles

Arumugam Nagarajan, Gerardo Zepeda and Joaquín Tamariz*

Department of Organic Chemistry, Escuela Nacional de Ciencias Biológicas, IPN,
Prol. Carpio y Plan de Ayala, 11340 Mexico, D.F., Mexico

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.

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 arylnitrile 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]



(1)

1a, Ar = C_6H_4*p*-NO_2
1b, Ar = C_6H_4*p*-Cl

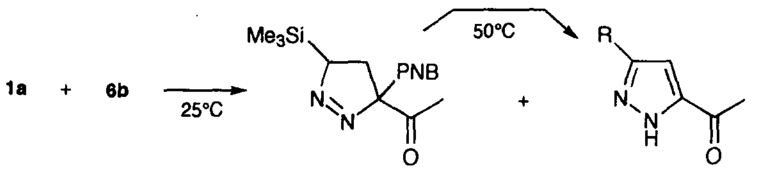
2, R = Aryl, Z = O
4, R = Et, Z = O
5, R = Ph, Z = NPh

6a, R = H
6b, R = $SiMe_3$

3, R = Aryl, Z = O
8, R = Et, Z = O
9, R = Ph, Z = NPh
10, R = H, Z = NH

As observed for the series of arylnitrile oxides **2**, the reaction of **1a** with **4** (C_6H_6, 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.

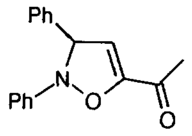


11a/11b

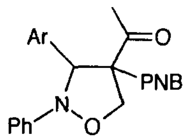
10, R = H
12, R = SiMe$_3$

(2)

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 coupound. This was additionally supported by the fact that the reaction of **1a** with diphenyl nitrone (**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 favored[10] and probably stabilized by secondary orbital interactions[11] (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.



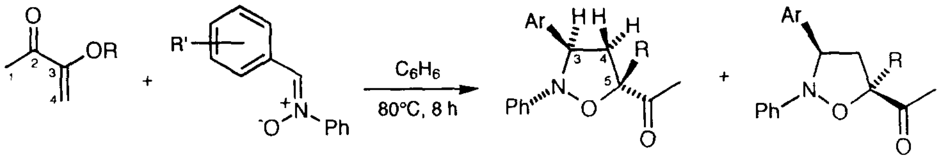
15



16

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 nitrone **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 nitrone and the carboxylate subtituent 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**.



1a, R = $COC_6H_4p\text{-}NO_2$
1c, R = $COCH_3$

7

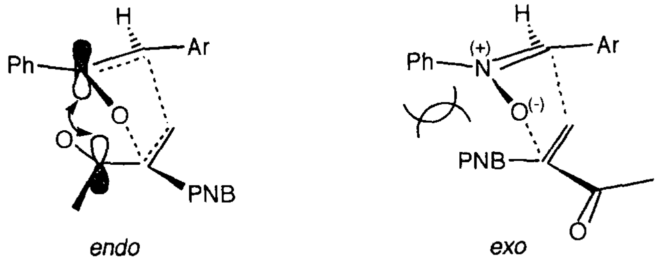
13, R = PNB
17, R = $OCOCH_3$

14, R = PNB
18, R = $OCOCH_3$

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**.



endo

exo

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 demand[14] 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]

Acknowledgments. We are grateful to Fernando Labarrios for his help in spectrometric measurements. We thank DEPI/IPN (Grant 921769) and CONACYT (Grant 1570P-E9507) for financial support. A.N. wishes to thank CONACYT for a postdoctoral fellowship awarded (Cátedra Patrimonial Nivel II, No 920347).

References and Notes

1. *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990; pp 269-331; Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607, and references cited therein.
2. a) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148; b) Cativiela, C.; Fraile, J. M.; García, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F.; de Ménorval, L. C. *Tetrahedron* **1993**, *49*, 4073; c) Odenkirk, W.; Rheingold, A. L.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 6392; d) Boucher, J.-L.; Stella, L. *Tetrahedron* **1986**, *42*, 3871; e) Seerden, J.-P. G.; Scheeren, H. W. *Tetrahedron Lett.* **1993**, *34*, 2669; f) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115; g) Reyes, A.; Aguilar, R.; Muñoz, A. H.; Zwick, J.-C.; Rubio, M.; Escobar, J.-L.; Soriano, M.; Toscano, R.; Tamariz, J. *J. Org. Chem.* **1990**, *55*, 1024.
3. a) Baran, J.; Mayr, H. *J. Org. Chem.*, **1989**, *54*, 5774; b) Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603; c) Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *J. Org. Chem.* **1987**, *52*, 3909; d) Jaroskova, L.; Fisera, L.; Matejkova, I.; Ertl, P.; Prónayová, N. *Monatsh. Chem.* **1994**, *125*, 1413; e) Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1041; f) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397; g) M'Sadek, M.; Rammah, M.; Schmitt, G.; Vebrel, J. *Bull. Soc. Chim. Belg.* **1992**, *101*, 323; h) Döpp, D.; Henseleit, M. *Chem. Ber.* **1982**, *115*, 798.
4. Jiménez, R.; Pérez, L.; Tamariz, J.; Salgado, H. *Heterocycles* **1993**, *35*, 591.
5. Propionitrile oxide was generated by the general method of Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
6. Diphenylnitrile imine was generated following the procedure of Hemming, K.; Luheshi, A.-B. N.; Redhouse, A. D.; Smalley, R. K.; Thompson, J. R.; Kennewell, P. D.; Westwood, R. *Tetrahedron* **1993**, *49*, 4383.
7. Trimethylsilyl diazomethane was used as received from Aldrich Chem. Co.
8. Nitrones **7** were prepared by condensing *N*-phenyl hydroxylamine with the corresponding benzaldehyde, see: Black, D. S. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205; Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123.
9. The products were characterized by ^1H and ^{13}C NMR, IR spectral data and by elemental analysis. The yields were calculated after recrystallization or purification by column chromatography. **10**: ^1H NMR ($CDCl_3$) δ 2.62 (s, 3H, CH_3CO), 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) δ 2.52 (s, 3H, CH_3CO), 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 %): $\{H_{4\beta}\}$-$H_{4\alpha}$ (25.5), $\{H_{4\alpha}\}$-H_3 (10.0), $\{H_{4\beta}\}$-Ar (3.7), $\{H_{4\beta}\}$-PNB (0.7), $\{H_3\}$-$COCH_3$ (0.5), $\{H_3\}$-Ph (4.3), $\{H_3\}$-Ar (5.3).
11. Padwa, A.; Fisera, L.; Koehler, K. F.; Rodriguez, A.; Wong, G. S. K. *J. Org. Chem.* **1984**, *49*, 276. Tsuge, H.; Okano, T.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2761.
12. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1.
13. Captodative olefin **1a** was added to substituted dienes in Diels-Alder reactions to give, however, preferentially the more hindered adducts; see Ref. 2g.
14. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301; Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.
15. DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309; Mullen, G. B.; Bennett, G. A.; Swift, P. A.; Marinyak, D. M.; Dormer, P. G.; Georgiev, V. St. *Liebigs Ann. Chem.* **1990**, 105; Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.
16. Regioselectivity in 1,3-dipolar cycloadditions has usually been explained by an FMO control.[12] However, this model has not provided satisfactory rationalization with our molecules,[4] and with other captodative dipolarophiles: a) Sustmann, R.; Sicking, W. *Chem. Ber.* **1987**, *120*, 1653; b) Fisera, L.; Konopíkova, M.; Ertl, P.; Prónayová, N. *Monatsh. Chem.* **1994**, *125*, 301; see also Ref. 3c. Improved calculations are in progress and will be reported in due course.
17. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1995**, *60*, 4697; Yang, S.; Hayden, W.; Griegl, H. *Monatsh. Chem.* **1994**, *125*, 469; Kelly-Basetti, B. M.; Mackay, M. F.; Pereira, S. M.; Savage, G. P.; Simpson, G. W. *Heterocycles* **1994**, *37*, 529; Buñuel, E.; Cativiela, C.; Diaz-de-Villegas, M. D.; Jimenez, A. I. *Synlett* **1992**, 579; Srivastava, V. P.; Roberts, M.; Holmes, T.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 5866.
18. Bianchi, G.; Gandolfi, R.; Grünanger, P. *Recent Developments on Nitrile Oxides, Nitrile Sulphides and Nitrile Selenides*, In *The Chemistry of Functional Groups, Supplement C*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1983; pp. 737-804; Bianchi, G.; Gandolfi, R.; de Micheli, C. *J. Chem. Res. (S)* **1981**, 6.

(*Received in USA* 19 *June* 1996; *revised* 26 *July* 1996; *accepted* 1 *August* 1996)