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Aryl Nitrile Oxide Cycloaddition Reactions in the Presence of Baker's Yeast and β-Cyclodextrin

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Abstract: Contrary to recent reports, baker's yeast is not required for reactions of nitrile oxides with either ethyl cinnamate or 4-vinylpyridine to give isoxazolines. β-Cyclodextrin may alter the ratio of isomers isolated from the reactions of the cinnamate but only at concentrations of reactants much lower than those reported, and this effect is most likely due to selective product complexation rather than selective product formation.

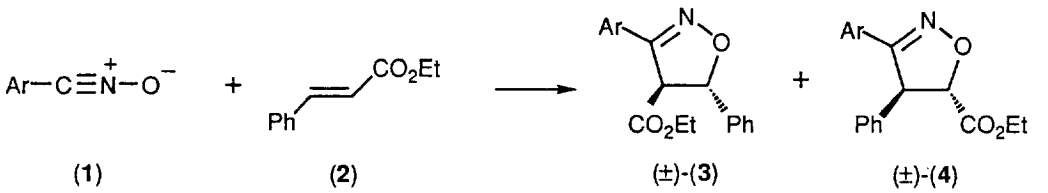
In recent articles,[1-5] that have often been cited,[6] it has been reported that baker's yeast catalyses 1,3-dipolar cycloaddition reactions of nitrile oxides with cinnamates,[1,2] vinylpyridines,[2,3] acrylates[4] and vinylcarbazoles,[5] furthermore β-cyclodextrin (βCD) influences the regioselectivity and stereoselectivity of some of these reactions.[1-3] Our interest in the chemistry of nitrile oxide cycloadditions,[7-9] yeast-catalysed reactions,[10] and cyclodextrins,[11] led us to examine these effects. We began by repeating a selection of the reported[1,2] experiments with ethyl cinnamate **2**. The results of these studies and comparable literature data are shown in Table 1, together with results of experiments performed in the absence of yeast but otherwise under identical conditions.[12]

Table 1. Ratio of the Cycloadducts **3** and **4** Formed in Reactions of the Nitrile Oxides **1** with Ethyl Cinnamate **2**.

Nitrile Oxide	Ratio of the Cycloadducts 3:4[a]			
	Yeast[b] No βCD	No Yeast No βCD	Yeast[b] βCD	No Yeast βCD
1a	94:6 (100:0)[c]	87:13	97:3 (100:0)[c]	87:13
1b	57:43 (65:35)[c]	61:39	59:41 (0:100)[c]	60:40

[a] Determined by integration of 200 MHz ^{1}H NMR spectra.[13]
[b] Fermipan®, Gist-brocades, Holland (*sp. Saccharomyces cerevisiae*).
[c] Data from reference 1 shown in brackets.

Contrary to specific reported statements that cycloaddition reactions of the nitrile oxides **1a** and **1b** with ethyl cinnamate **2** (Scheme 1) do not proceed in aqueous media in the absence of yeast,[1,2] we found that yeast was not required for these reactions. Further, yeast had little effect on the ratio of the regioisomeric cycloadducts **3** and **4** or on the yields of these reactions, which were consistently of the order of 50%.[14] Our results are in accord with earlier literature reports describing cycloadditions of nitrile oxides with cinnamates and acrylates occurring without the need for a biocatalyst.[15,16]



(1) (2) (±)-(3) (±)-(4)

a) Ar = 2,6-dichlorophenyl
b) Ar = 2,4,6-trimethylphenyl

Scheme 1

We observed formation of the cycloadduct **4a**, in addition to the regioisomer **3a** reported previously.[1,2] Using X-ray crystallographic analysis, the regioisomer **3a** (Figure 1)[17] was confirmed to be that previously proposed[1,2] on the basis of ^{1}H NMR spectral data.[15] In the absence of yeast we observed the reported effect of βCD,[1,2] to alter the ratio of the cycloadducts **3b** and **4b** isolated from the reaction of 2,4,6-trimethylbenzonitrile oxide **1b** with ethyl cinnamate **2**. The magnitude of the effect was less than that reported, however, unless much reduced concentrations of the reactants **1b** and **2** were used (Table 2). In the present study, βCD also changed the observed ratio of the isolated cycloadducts **3a** and **4a**.

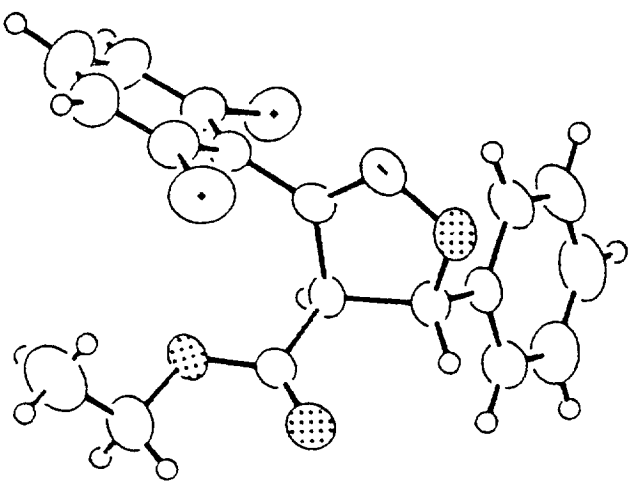


Figure 1. Molecular structure of **3a**

Table 2. Effect of Varying the Ratio of the Reagents **1** and **2**[a] to βCD[b] on the Ratio of the Cycloadducts **3** and **4**.

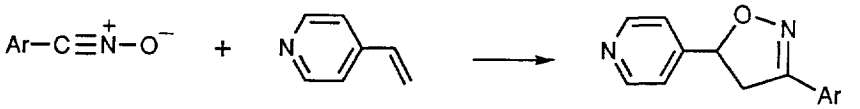
Nitrile Oxide (mmol)	Ratio 3:4
1a (1.5)	87:13
1a (0.25)	80:20
1b (1.5)	60:40
1b (1.0)	46:54
1b (0.25)	26:74

[a] Mole ratio of 1:2 – 1:1.
[b] The amount of βCD was 1.5 mmol in each experiment.

In a separate experiment, we treated a *ca.* 1:1 mixture of the regioisomers **3b** and **4b** (0.1 mmol) with βCD (1.5 mmol) under the conditions used for the cycloadditions. The sample recovered through work-up in the usual manner[12] was a 1:4 mixture of the regioisomers **3b** and **4b**, however, further extractions of the aqueous βCD solution with chloroform, then ethyl acetate, afforded samples increasingly enriched in the cycloadduct **3b**. The final ethyl acetate extracts contained only the regioisomer **3b**. On this basis, the effect of βCD on the ratio of the isomers **3b** and **4b** obtained from the reactions of the nitrile oxide **1b** with the cinnamate **2** can be solely attributed to the isolation procedure, and it is unlikely that βCD affects the ratio of formation of the products **3b** and **4b**.[1,2]

Mixtures of the regioisomers **3** and **4** (0.1 mmol) were treated with yeast under the conditions used for the cycloadditions. In recovered material the ratio of **3a** to **4a** had increased but the ratio of **3b** to **4b** was not affected. This probably results from the yeast either selectively consuming the isoxazoline **4a** or affecting the relative ease with which the isomers **3a** and **4a** are extracted from the aqueous solution.

In our hands the nitrile oxides **1a** and **1b** reacted with 4-vinylpyridine **5** (Scheme 2) in the absence of yeast. Further, the products **6a** and **6b** from reactions carried out in the presence of either yeast, βCD or both, were optically inactive. Again these results are in contrast to the literature[2,3] where it is stated that yeast is required for this reaction to proceed, that reaction in the presence of yeast gives optically active products, and that the optical activity of the products is enhanced by conducting the reactions in the presence of β-cyclodextrin.



(1) (5) (6)

a) Ar = 2,6-dichlorophenyl
b) Ar = 2,4,6-trimethylphenyl

Scheme 2

References and Notes

1. Rama Rao, K.; Bhanumathi, N.; Srinivasan, T. N.; Sattur, P. B. *Tetrahedron Lett.* **1990**, *31*, 899.
2. Rama Rao, K. *Pure Appl. Chem.* **1992**, *64*, 1141.
3. Rama Rao, K.; Bhanumathi, N.; Sattur, P. B. *Tetrahedron Lett.* **1990**, *31*, 3201.
4. Rama Rao, K.; Nageswar, Y. V. D.; Bhanumathi, N.; Srinivasan, T. N. *Indian J. Chem.* **1994**, *33B*, 171.
5. Rama Rao, K.; Nageswar, Y. V. D.; Sampathkumar, H. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3199.
6. For examples see: Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631; Fronza, G.; Fuganti, C.; Mele, A.; Pedrocchi-Fantoni, G.; Servi, S. *J. Org. Chem.* **1992**, *57*, 999; Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071; Suckling, C. J.; Tedford, M. C.; Bence, L. M.; Irvine, J. I.; Stimson, W. H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1925; Moriya, O.; Takenaka, H.; Iyoda, M.; Urata, Y.; Endo, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 413; Turner, N. J. *Natural Prod. Rep.* **1994**, 1; Takahashi, K.; Hattori, K. *J. Inclusion Phen. Molecular Recognition Chem.* **1994**, *17*, 1.
7. Easton, C. J.; Hughes, C. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocyclic Chem.* **1994**, *60*, 261.
8. Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T., Lubin, C. E.; Savage, G. P.; Simpson, G. W., *Tetrahedron Lett.* **1994**, *35*, 3589.
9. Kelly-Basetti, B. M.; Mackay, M. F.; Pereira, S. M.; Savage, G. P.; Simpson, G. W. *Heterocycles* **1994**, 529; Pereira, S. M.; Savage, G. P; Simpson, G. W.; Greenwood, R. J.; Mackay, M. F. *Aust. J. Chem.* **1993**, *46*, 1401.
10. Easton, C. J.; Hughes, C. M.; Kirby, K. D.; Savage, G. P.; Simpson, G. W.; Tiekink, E. R. T. *J. Chem. Soc., Chem. Comm.* **1994**, 2035.
11. For examples see: Brown, S. E.; Coates, J. H.; Duckworth, P. A.; Lincoln, S. F.; Easton, C. J.; May, B. L. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1035; Brown, S. E.; Coates, J. H.; Easton, C. J.; van Eyk, S. J.; Lincoln, S. F.; May, B. L.; Stile, M. A.; Whalland, C. B.; Williams, M. L. *J. Chem. Soc., Chem. Comm.* **1994**, 47.
12. A solution of the nitrile oxide **1** (*ca.* 1.5 mmol), ethyl cinnamate **2** (1 mole equiv.) and βCD (1 mole equiv.) in 30% aqueous ethanol (20 ml) was added to a mixture of yeast (0.5 g) in phosphate buffer (0.5 M, pH 7.2, 12.5 ml). The suspension was incubated at 37 °C with gentle stirring for 30 h, then it was extracted with chloroform (2 x 20 ml). The extracts were combined and dried ($MgSO_4$), then concentrated under reduced pressure to give the crude product.
13. ^1H NMR ($CDCl_3$) data for the isoxazoline ring hydrogens: **3a**, δ 4.57 and 6.26, J = 9 Hz; **4a**, δ 5.24 and 5.27, J = 6 Hz; **3b**, δ 4.37 and 6.10, J = 9.5 Hz; **4b**, δ 4.81 and 5.32, J = 4 Hz.
14. No yields were reported[1,2] for these reactions.
15. Christl, M; Huisgen, R. *Tetrahedron Lett.* **1968**, 5209; Christl, M; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3275.
16. Weidner-Wells, M. A.; Fraga, S. A.; Demers, J. P. *Tetrahedron Lett.* **1994**, *35*, 6473.
17. Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W.; Tiekink, E. R. T. *Z. Krist.* in press.

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