Pergamon

Tetrahedron Letters, Vol. 37, No. 25, pp. 4341-4344, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00824-6

Chemo-, Regio- and Stereoselective Addition of Nitrile Oxides to Cobalt-Coordinated 1,3-Enynes

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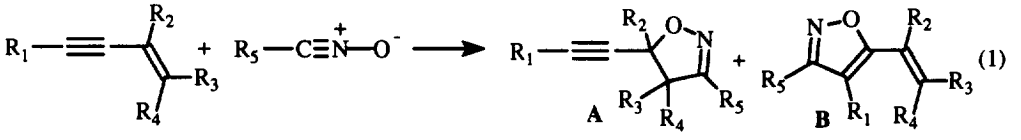
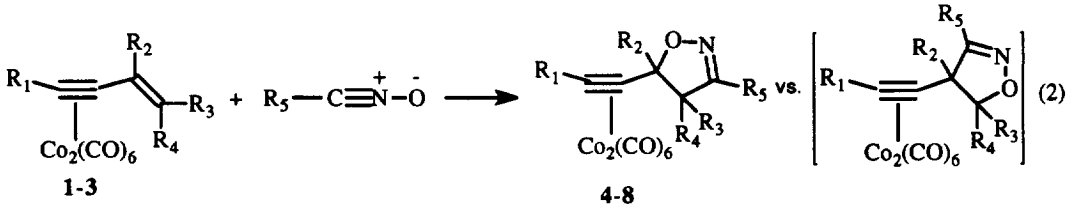
Abstract. Unlike the frequently unselective reactions of 1,3-enynes with 1,3-dipoles, nitrile oxides add chemo-, regio- and stereoselectively to the free double bond of (1,3-enyne)$Co_2(CO)_6$ complexes to provide 5-alkynyl-2-oxazoline derivatives in moderate to excellent yield.

The 1,3-dipolar cycloaddition reaction of unsaturated C-C and C-N bonds provides a powerful and synthetically versatile entry to various classes of heterocyclic compounds.[1] If the dipolarophile possesses more than one site of unsaturation, e.g. as in an en-yne, addition to either (or both) site(s) may occur. Indeed, with nitrile oxides as dipoles[2] and 1,3-en-ynes as substrates[3] the chemoselectivity is very sensitive to the substitution pattern of the en-yne; either product, A or B, may predominate and mixtures have been reported in several cases (eq. 1).[4] In this contribution we describe a potentially general solution to the chemoselectivity problem



(1)

associated with dipolar cycloadditions of ene-yne substrates which utilizes the readily introduced and removed -$Co_2(CO)_6$ unit as a protecting group for the triple bond,[5] allowing selective additions to the C-C double bond according to eq. 2.



1-3 4-8 (2)

Reactions of enyne complexes 1-3[6] with an excess of the unstable dipoles, PhCNO and MeCNO,

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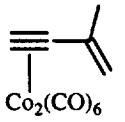
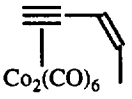
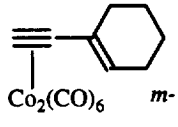
were carried by *in situ* generation from PhC(Cl)=NOH/Et_3N[8] and $MeCH_2NO_2$/PhNCO/Et_3N[9] (20° C, 12-48 hr) respectively; the stable nitrile oxide *m*-NO_2-C_6H_4CNO[10] was employed (20 °C, acetone, 12-48 hr) following isolation. The reactions were monitored conveniently by TLC and the dark red adducts **4-8** were isolated after flash chromatography (silica/ethyl acetate-hexane) and identified spectroscopically.[11] Enyne complexes **1** and **2** thus were found to undergo chemoselective addition to the uncoordinated double bond, the -$Co_2(CO)_6$ group effectively blocking reaction at the triple bond (Table); compound **3** was unreactive under ambient conditions. The selective C=C additions to **1** should be contrasted with the corresponding reactions of 2-methyl-1-buten-3-yne itself in which addition to both the double and triple bonds occurs.[4a] The order of reactivity of the three complexes, **1** > **2** > **3**, decreases according to the position and degree of substitution on the double bond, in keeping with the general sensitivity of nitrile oxide additions to the steric accessibility of the double bond.[2] In each reaction a single regioisomer was obtained whose structure was tentatively, but not unambiguously, assigned as **4-8** on the basis of ^1H NMR spectroscopy, e.g. the -CH_2 AB quartets of **4-6** (R_3=R_4=H) appeared in the region δ 3.3 - 3.5 ppm.

Table. Addition of Nitrile Oxides to (1,3-Enyne)$Co_2(CO)_6$

complex	dipole	adduct	% yield[a](conv.)
 **1**	PhC≡N-O	**4** R= Ph	80(99)
	m- NO_2-C_6H_4C≡N-O	**5** R=*m*- NO_2-C_6H_4	78(77)
	MeC≡N-O	**6** R = Me	91(55)
 **2**	PhC≡N-O	**7** R = Ph	ca. 50[b](40)
	m- NO_2-C_6H_4C≡N-O	**8** R =*m*- NO_2-C_6H_4	40(51)
 **3**	MeC≡N-O	------[c]	----
	m- NO_2-C_6H_4C≡N-O	------	----

[a] isolated yield based on recovered **1-3**; [b] 4:1 cis/trans; [c] no adduct formed

The regiochemistry was firmly established by X-ray crystallographic analysis of **5** (Figure 1). The observed regioselectivity is that generally, but not exclusively, found in nitrile oxide additions to unsymmetrical

alkenes[2] and can be rationalized on the basis of minimizing steric effects (between the bulky (alkyne)$Co_2(CO)_6$ group and R[5] of the nitrile oxide) while maximizing frontier orbital overlap. The result is also consistent with polarity matching of the dipole with the C-C double bond polarized by the electron donating (alkyne)$Co_2(CO)_6$ unit.[5]

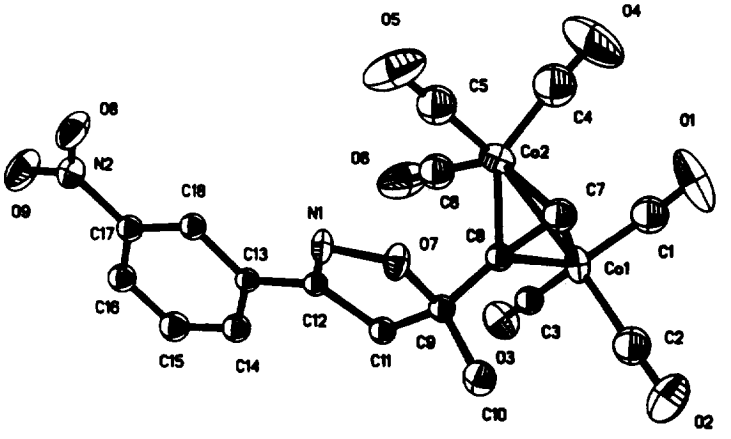


Figure 1. X-ray structure of **5**

Cycloadditions to the Z-complex **2** allowed assessment of the stereochemistry of addition as well. Reaction of **2** with either PhCNO or *m*-NO_2-C_6H_4CNO occurred slowly giving single regioisomeric products **7**, **8** as judged by NMR. The latter product (**8**) was also clearly a single stereoisomer, assigned as *cis* based on the $J_{H4\text{-}H5}$ = 8.1 Hz (J_{cis} 8-10 Hz, J_{trans} 3-6 Hz[12]). Surprisingly, the product **7** was apparently produced as a mixture of stereoisomers which could be separated in impure form (contaminated with nitrile oxide dimer); the major product (ca. 80 %) was found to be the *cis* isomer (J = 8 Hz), accompanied by less of the *trans* derivative (J = 4 Hz). The observed preference for the adduct which preserves the stereochemistry of the dipolarophile is characteristic of dipolar cycloadditions[1,2] but formation of a significant amount of the *trans* isomer of **7** was unexpected. At present it is not clear whether this stereochemical leakage is the direct result of the reaction of **2** with PhCNO or whether product isomerization occurs under the reaction conditions (e.g. via reversible Co-assisted ionization of the C-O bond). Unreacted **2** was recovered stereochemically intact from the reaction with PhCNO, excluding starting material isomerization as the source of the trans product.

The -$Co_2(CO)_6$ unit has thus been found to be effective in directing the chemo-, regio-, and stereoselective [3 + 2]-cycloaddition of nitrile oxides to 1,3-enynes. The 5-alkynyl-2-oxazolines derived from demetallation[5b,c] are potentially versatile intermediates for the general synthesis of 5-substituted 2-oxazolines.

Acknowledgements.

We thank Dr. M. A. Khan for determination of the X-ray structure of **5**. Partial financial support from the A.C.S. Petroleum Research Fund (27375 AC1) and E.N.S.C.C.F. is greatly appreciated.

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6. Dark red liquids **1** (96%) and **2** (85%) were prepared by treatment of the enyne with $Co_2(CO)_8$ in Et_2O (20 °C, 4 hr) followed by chromatography over alumina (petroleum ether); spectroscopic data were identical to those reported previously.[7] Dark red oil **3** was prepared (50% yield) by acid (CF_3CO_2H)-catalyzed dehydration of the ethynylcyclohexyl carbinol complex in benzene (20 °C, 12 hr)[7] followed by chromatography over silica gel (petroleum ether); spectroscopic data were identical to those reported previously.[7]
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11. Products **5-8** were characterized by IR, ^1H NMR and MS: (**4**) (oil) ^1H NMR (δ): 7.65 (m, 2H), 7.40 (m, 3H), 6.15 (s, 1H), 3.45 (d, J=16 Hz, 1H), 3.35 (d, J=16 Hz, 1H), 1.85 (s, 3H); IR (cm^{-1}) 3053, 2986, 2096, 2060, 2030, 1635; MS (12 eV, DIP, m/e) 443 (25, M-CO), 303 (100, M-6CO); HRMS (FAB) 471.9279 ($M+H^+$); (**5**) mp 103 °C; ^1H NMR: 8.42 (s, 1H), 8.30 (d, J= 8 Hz, 1H), 8.05 (d, J= 8 Hz, 1H), 7.60 (t, J= 8 Hz, 1H), 6.15 (s, 1H), 3.45 (d, J= 16.2 Hz, 1H), 3.40 (d, J=16 Hz, 1H), 1.80 (s, 3H); IR 2093, 2060, 2029, 1535; MS: 488 (M-CO), 348 (M-6CO); (**6**) ^1H NMR: 4.10 (s, 1H), 3.10 (d, J = 17 Hz, 1H), 2.95 (d, J= 17 Hz, 1 H), 2.00 (s, 3H), 1.75 (s, 3H); IR 2095, 2059, 2028, 1603; MS 381 (M-CO), 241 (M-6CO); (**7**) *trans* (less polar) ^1H NMR: 7.8-7.3 (cm, 5H), 5.90 (s, 1H), 4.48 (d, J= 3.9 Hz, 1H), 3.12 (dq, J= 4, 7 Hz, 1 H), 0.85 (d, J= 7Hz, 3 H); (**7**) *cis* (more polar) ^1H NMR: 7.8-7.3 (cm, 5H), 6.13 (s, 1H), 5.88 (d, J= 7.8 Hz, 1H), 3.85 (m, 1H), 1.60 (d, J= 8 Hz, 3H); MS: 443 (M-CO), 303 (M-5CO); (**8**) ^1H NMR: 8.50 (s, 1H), 8.30 (d, J= 8 Hz, 1H), 8.10 (d, J= 8 Hz, 1H), 7.65 (t, J= 8 Hz, 1 H), 6.20 (s, 1H), 5.86 (d, J= 8 Hz, 1H), 3.80 (m, 1H), 0.90 (d, J = 7 Hz, 3 H); X-ray data tables for **5** are available from the Cambridge Crystallographic Data Base.
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(*Received in USA* 18 *March* 1996; *accepted* 24 *April* 1996)