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CYCLOADDITIONS WITH CAPTO-DATIVE OLEFINS, III[1]
ADDITION OF 2-MORPHOLINO-ACRYLONITRILE TO VARIOUS ALDONITRONES[2]

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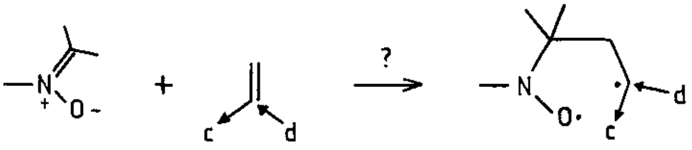
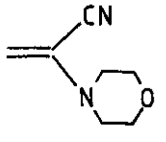
Abstract: —— With very high regioselectivity, 2-morpholino-acrylonitrile (1) is added to aldonitrones to form unstable 5-morpholino-isoxazolidine-5-carbonitriles; the latter generally tend to form α,ß-unsaturated carboxylic acid morpholides with ring opening and elimination of hydrogen cyanide.

Capto-dative3) substituent effects are a field of considerable current interest[1-7]. We[1,2,4] and others[7] have especially been intrigued by the question what (if any) effect a capto-dative (and thus highly radicophilic3)) substitution on one terminus of an olefinic dipolarophile might exert on the course of the 1,3-dipolar cycloaddition. Especially, could an *a priori* possible 1,5-diradical intermediate - as advocated by *Firestone*[8] and impressively rejected by *Huisgen*[9] - electronically (but not necessarily kinetically) be stabilized by capto-dative[3] substitution (or "push-pull-"[10] or "merostabilization"[11]) at one terminus so that the diradical pathway could become competitive to the concerted one? The principle may be illustrated by the addition of a capto-dative (c,d-) olefin to a nitrone (in which case the other terminus of the hypothetical diradical would be an aminyl oxide):



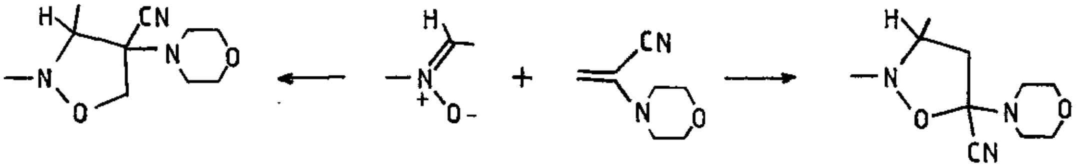
(c = electron acceptor, d = electron donor)



1

Our earlier experiments[4] had indicated that the additions of c,d-olefins to nitrones were complicated by the instability of the primary adducts. Recently *Stella*[6] reported about Diels-Alder additions of such olefins and stressed their usefulness as ketene equivalents. In this study, we report 1,3-dipolar cycloadditions of 2-morpholino-acrylonitrile (1) with selected aldonitrones. Ketonitrones so far have been found to be unreactive towards 1.

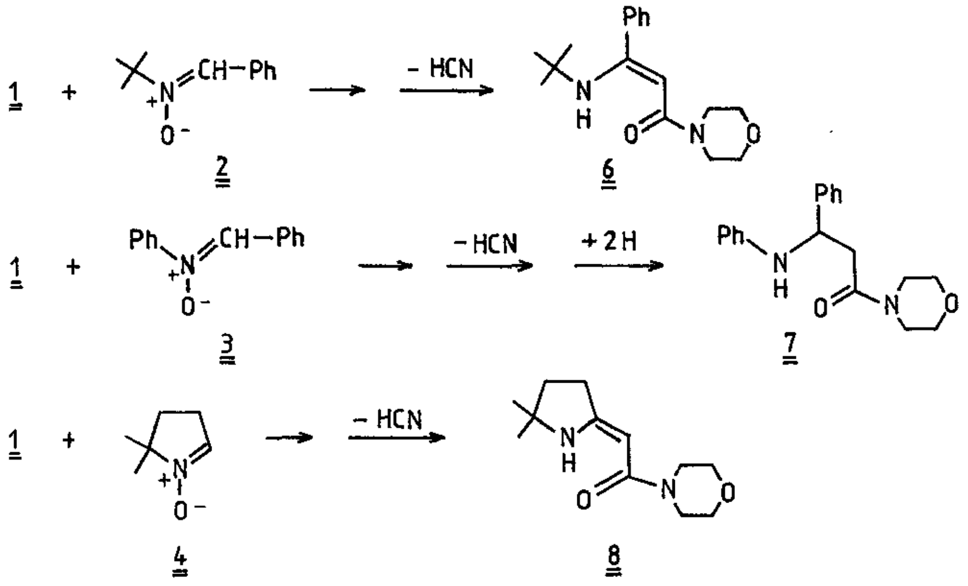
Generally, one should expect two regioisomeric isoxazolidines (A and B), each as a pair of diastereomers, resulting from the addition of 1 to an aldonitrone, similar to the product distribution observed in the cycloaddition of 2-tert-butylthio-acrylonitrile to α,N-diphenylnitrone[1a].



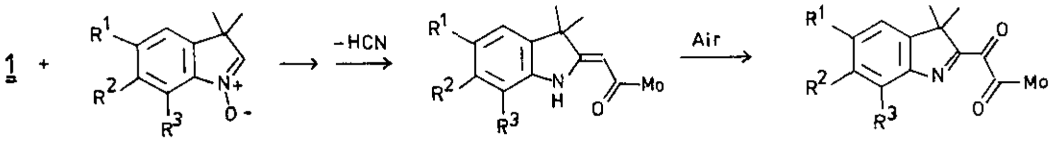
A 1 B

A value of 8.68 eV has been determined[12] for the first I.P. of 1. As judged solely from this value, 1 should behave more like an enamine (e. g. morpholinocyclopentene, first I.P. = 8.80 eV[13]) than like acrylonitrile (First I.P. = 10.91 eV[13]). Since both electron rich and moderatly electron poor alkenes add unidirectionally to nitrones to yield 5-donor- (or acceptor-) substituted isoxazolidines[14], a strong tendency of 1 to form B-type adducts should be expected.

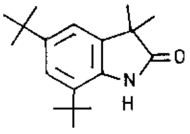
When 1 was allowed to react with aldonitrones 2; 3; 4 and 5a,b in benzene solution at ambient or elevated temperature, neither A- nor B-type adducts were obtained. Instead, varying yields of ring-opened follow-up products (6; 7; 8; 9a,b; 10a,b) derived solely from the B-type 5,5-disubstituted isoxazolidines, could be isolated by chromatographic work-up.



In addition, small amounts of 5b are isomerized to 11 under the reaction conditions.



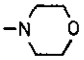
5a,b 9a,b 10a,b



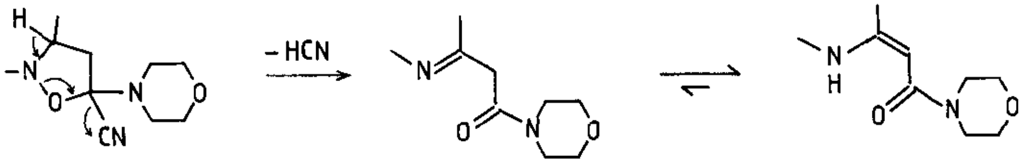
11

5,9,10: a: $R^1=R^3=H$, $R^2= t\text{-}C_4H_9$ b: $R^1=R^3= t\text{-}C_4H_9$, $R^2=H$

9a,b; 10a,b: Mo =



Among B-type isoxazolidines, there seems to exist a pronounced tendency to eliminate hydrogen cyanide along with ring opening to form α,ß-unsaturated carboxylic acid morpholides D:



B C D

The tautomeric relationship between C and D is demonstrated by hydrogen-deuterium exchange, which involves not only the NH proton but also the vinylic proton, as exemplified with compounds 6 and 8. The reason for the formation of a saturated carboxylic acid morpholide (7) in one case is not yet understood. The pronounced tendency of 9a,b to undergo autoxidation is noteworthy and 9b was quantitatively oxidized to 10b when adsorbed on silica and exposed to air overnight. All structures of the products have been assigned on the basis of their spectral data and the unambiguous demonstration of absence of CN-groups. The Z-configuration (type D) of 6, 8, and 9a,b was assigned on the basis of intramolecular $>N\text{-}H\cdots O=C<$ bridges detected by IR or ^{1}H-NMR (see experimental part). It should be noted though, that, since D and C are tautomers and there is free rotation in C, the corresponding E-tautomers may also be present in solution.

The complications observed with the additions of 1 to aldonitrones make 1 a less useful candidate for the quantitative study of cycloadditions of c,d-olefins.

It should be mentioned that both hydrogen cyanide and hydrogen chloride are eliminated in the cycloaddition of 2-chloroacrylonitrile to 2,5,5-trimethyl-Δ^1-pyrroline-1-oxide[15].

EXPERIMENTAL

Starting materials: 2-Morpholinoacrylonitrile (1)[16a], N-tert-butyl-α-phenylnitrone (2)[16b], α,N-diphenylnitrone (3), 5,5-dimethyl-Δ^1-pyrroline-1-oxide (4)[16c], 6-tert-butyl-3,3-dimethyl-3H-indole-1-oxide (5a)[16d] and 5,7-di-tert-butyl-3,3-dimethyl-3H-indole-1-oxide (5b)[16e] were prepared according to literature procedures. - Chromatography: 48 cm x 20 cm glass plates, coated with 1 mm thick layers of silica gel PF_{254}, air-dry, were used with either toluene/ethyl acetate 1:1 (solvent I) or toluene/ethyl acetate 5:1 (solvent II). The individual zones have been characterized by approximate R_F-values, materials were extracted using acetone. - Spectra: IR: Perkin-Elmer 397 and 283. - 60 MHz-^{1}H-NMR-spectra were recorded at ambient temperature on a Varian EM 360 spectrometer, using $CDCl_3$ (TMS) throughout. mc = multiplet centered at... . - 70 eV - EI-mass spectra (temp. of inlet system and relative intensities given in brackets): MAT 311 A.

ß-(N-tert-Butylamino)cinnamic acid morpholide (6): Run: 247 mg (1.8 mmoles) of 2, 359 mg (2.0 mmoles) of 1, 1 ml of benzene, 80 °C for 36 h; 3 plates, solvent I. - Zones at R_F = 0.52 and 0.39 contained very little material and were discarded. The third zone (R_F = 0.14) gave 406 mg of a mixture of 31% product 6 and starting material 2 (as determined by NMR-analysis). Thus it was estimated that 79 mg of 2 had been converted and 126 mg of 6 (98%, based on converted 2) had been formed. - IR (film) 3220 broad, NH. - ^{1}H-NMR: δ = 1.11 (s, 9H), 3.62 (mc, 8H, morpholido group), 4.60 (broadened s, 1H, vinyl), 7.30 - 7.88 (several m, 10H, phenyl), 9.90 (broad, 1H, NH). Both the δ 9.90 and 4.60 signals faded upon treatment of the $CDCl_3$-solution with D_2O. - The compound could not be fully separated from accompanying 2.

ß-Anilino-dihydrocinnamic acid morpholide (7): Run: 631 mg (3.2 mmoles) of 3, 489 mg (3.5 mmoles) of 1, 2 ml of benzene, 40 °C for 3 h; 4 plates, solvent II. Zone 1 (R_F = 0.40) contained a decomposition product of 1, zone 2 gave 177 mg of 3. The material from the slowest zone gave 241 mg (34%) colourless crystals, mp 153 °C (from ethanol). - IR (KBr): 3350 (NH), 1628 (C=O), 1601 cm^{-1} (CCl_4, d= 3.0 cm): 3375 cm^{-1} (NH). - ^{1}H-NMR: δ = 2.87 (pseudo-d, $\Delta\nu$ = 6 Hz, 2H, CH_2), 3.23 and 3.54 (two broadened bands, together for 8H, morpholido group), 4.84 (mc, 1H, $>$CH-), 5.20 (broad, 1H, NH, signal fades upon D_2O treatment), 6.43 - 7.62 (several m, 10H, phenyl). - MS (144 °C): m/e = 310 (M^+, 36), 195 (8), 194 (9), 182 (100), 181 (9), 180 (10), 114 (11), 104 (9). - $C_{19}H_{22}N_2O_2$ (310.4): Calcd. C 73.52, H 7.14, N 9.03; found C 73.36, H 7.18, N 9.18.

(5,5-Dimethylpyrrolidin-2-ylidene)acetic acid morpholide (8): Run: 1.05 g (9.3 mmoles) of 4 and 850 mg (6.2 mmoles) of 1, 23 h at 80 °C; 6 plates, solvent I. - From the first zone (R_F = 0.61), 311 mg of 4 were recovered. The material from the intense zone at R_F=0.46 was subjected to bulb-to-bulb destillation at 0.03 mm Hg and 150 °C to yield 473 mg (32%, based on converted 4). IR (film between NaCl plates): 3305 (broadened, NH), 1645 (tert. amide CO, free), 1617 (tert. amide CO, in intramolecular H-bridge). (CCl_4, 10^{-3} M, d = 3 cm): 3430 (NH, free) and 3300 (broad, NH assoc.)

^{1}H-NMR: δ = 1.28 (s, 6H), 1.75 and 2.67 (two mc for 2H each, methylene groups in five membered ring), 3.57 (mc, 8H, morpholido group), 4.60 (broadened s, 1H, vinyl), 8.60 (broad, 1H, NH). The latter two signals fade upon treatment of the $CDCl_3$-solution with D_2O.

Addition of 1 to 5a: Run: 220 mg (1.0 mmole) of 5a, 150 mg (1.09 mmole) of 1, 3 ml of benzene, 12 h at room temp. - The oily residue was treated with pentane and 48 mg (15%) of colourless crystals, mp 183 °C, were filtered off and recrystallized from cyclohexane. From the elemental analysis (calcd. C 73,13, H 8.59, N 8.53; found C 73.10, H 8.60, N 8.49), its IR (KBr), showing an intense band at 1649 cm^{-1} (C=O) and its ^{1}H-NMR, showing signals at δ = 1.32 (s, 12H, CH_3 and tert-butyl), 1.70 (s, 3H, CH_3), 2.8 - 4.0 (complex m with prominent peaks at δ = 2.95, 3.50 and 3.78), 7.10 (mc, 2H, aryl), 7.30 (mc, 1H, aryl) it was deduced that this byproduct is an isomer of the main product. No more crystalline fractions were obtained from the concentrated mother liquors. Chromatography (4 plates, toluene/cyclohexane 2:1) gave one intense zone at R_F 0.40 which yielded 272 mg (83%) of oily (6-tert-butyl-3,3-dimethyl-2-indolinylidene)acetic acid morpholide (9a), which did not crystallize. - IR: 3260 cm^{-1} (broad, NH). - ^{1}H-NMR: δ = 1.31 (s, 9H), 1.38 (s, 6H), 3.66 (broadened, 8H, morpholido group), 5.02 (1H, vinyl), 7.00 (mc, 3H, aryl); 11.0 (broad, 1H, NH).

2-Oxo-2-(6-tert-butyl-3,3-dimethyl-3H-indol-2-yl)acetic acid morpholide (10a): Upon prolonged standing with admission of air, yellow crystals precipitated from the oily residue of 9a. Crystallization from cyclohexane gave 202 mg (61%), mp 165 °C. - IR (KBr): 1674, 1660, 1654, 1646 cm^{-1}. - ^{1}H-NMR: δ = 1.39 (s, 9H), 1.52 (s, 6H), 3.36 (mc, 2H, $-CH_2-N<$), 3.75 (mc, 2H, $-CH_2-O-$), 3.82 (broad s, 4H, $>N-CH_2-CH_2-O-$), 7.46 (mc, 2H, aryl), 7.98 (mc, 1H, aryl). - MS (87 °C): m/e 342 (M^+, 47, 327 (M-15, 100). $C_{20}H_{26}N_2O_3$ (342.4): Calcd. C 70.15, H 7.65, N 8.18; found C 70.19, H 7.79, N 7.99.

(5,7-Di-tert-butyl-3,3-dimethyl-2-indolinylidene)acetic acid morpholide (9b): Run: 273 mg (1.0 mmole) of 5b, 150 mg (1.09 mmole) of 1, 1 ml of benzene, 3 h at room temp. - The oily residue was treated with 3 ml of pentane and left standing overnight. 150 mg of crystals were separated off. Crystallization from cyclohexane gave 138 mg (44%) of colourless crystals, mp 184 °C. - IR (KBr): 3260 (broad, NH), 1628 cm^{-1} (C=O). - ^{1}H-NMR: δ = 1.32 (s, 9H), 1.39 (s, 6H), 1.49 (s, 9H), 3.69 (broadened, 8H, morpholido group), 5.00 (s, 1H, vinyl), 7.17 (mc, 2H, aryl), 11.05 (broad, 1H, NH). MS (155 °C): m/e = 384 (M^+, 100), 369 (17), 355 (22), 354 (28), 340 (28), 299 (39), 298 (39), 282 (50). - $C_{24}H_{36}N_2O_2$ (384.5): Calcd. C 74.96, H 9.44, N 7.29; found C 75.01, H 9.43, N 7.56.

2-Oxo-2-(5,7-di-tert-butyl-3,3-dimethyl-3H-indol-2-yl)acetic acid morpholide (10b): The mother liquor of 9b was separated (4 plates, solvent II) into 6 zones (R_F and weight given): (1) 0.64, 8 mg; (2) 0.50, 10 mg; (3) 0.40, < 5 mg; (4) 0.19, 37 mg (17%) of 5,7-di-tert-butyl-3,3-dimethyl-2-indolinone (11), mp 241 °C, mp lit.[16e,f] 241 °C; (5) 0.13, 68 mg of yellow crystals; (6) 0.05, 52 mg

(19%) of contaminated starting material 5b. Zones 1 - 3 were discarded. Zone 5 was crystallized from ethyl acetate/pentane to give 55 mg (17%) of yellow crystals, mp 221 °C. - IR (KBr): 1688, 1654, 1645 cm^{-1}. - ^1H-NMR: δ = 1.39 (s, 9H), 1.51 (s, 6H), 1.56 (s, 9H), 3.33 (mc, 2H, $-CH_2-N<$), 3.70 (mc, 2H, $-CH_2-O-$), 3.80 (broadened s, 4H, $>N-CH_2-CH-O-$), 7.36 (mc, 2H, aryl). - MS (124 °C): m/e = 398 (M^+, 23), 384 (6), 383 (10), 285 (66), 258 (23), 257 (100), 256 (12), 255 (12), 241 (20), 230 (22), 201 (65), 115 (50), 70 (40), 57 (24). - $C_{24}H_{34}N_2O_3$ (398.5): Calcd. C 72.33, H 8.60, N 7.03; found: C 71.97, H 8.51, N 7.20.

Air oxidation of 9b to 10b on a chromatographic plate: A 25 mg sample of 9b was chromatographed on 1 plate using solvent II. The dried plate was exposed to air for 16 h. Recovery of the material in the usual way gave a quantitative yield of 10b, mp 221 °C, identical in its IR with that of a sample described above.

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