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POLAR *VS* STERIC EFFECTS IN THE 1,3-DIPOLAR CYCLOADDITION REACTIONS OF ACETONITRILE OXIDE AND 2-*ENDO*-ACETOXY-5-HALO-7-OXABICYCLO[2.2.1]HEPT-5-EN-2-*EXO*-CARBONITRILE

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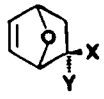
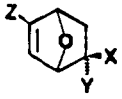
Abstract: The regioselectivity of the cycloaddition reactions between acetonitrile oxide and a number of 7-oxabicyclo[2.2.1]hept-5-enes is discussed. Acetonitrile oxide adds with complete regioselectivity to 2-*endo*-acetoxy-5-halo-7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-carbonitriles. Kinetic measurements indicate a more polar transition state for **2a** than for the unsubstituted substrate **1a**.

Bicyclic derivatives such as **1**, undergo Diels-Alder[1] and 1,3-dipolar cycloadditions reactions[2]. During the course of our investigations on new methods of functionalization of C-5 and C-6 in 7-oxanorbornenic systems[2c-e,3], we studied the regioselectivity of the 1,3-dipolar cycloadditions between substrates **1-3** and several nitrile oxides[2c,2e]. The resulting isoxazolines are versatile intermediates[4], which could be converted to γ-amino alcohols, β-hydroxy ketones and various other functional groups. The cycloaddition reactions of compounds **1** were not regioselective. However, 7-oxanorbornenic derivatives bearing substituents at the double bond[5], displayed regioselectivity in their reactions with mesitonitrile and benzonitrile oxides[2e] yielding the least sterically crowded cycloadducts **4** or **5** exclusively (Scheme I). Aside from electronic factors, the steric bulk of the substituent on the nitrile oxide appears to be of little relevance in additions of nitrile oxides to alkenes[6], on the other hand when one end of the double bond is significantly more congested than the other, the cycloaddition proceeds with high selectivity such that the oxygen of the nitrile oxide becomes bonded to the more hindered terminus of the double bond. However, steric effects caused by dipole and dipolarophile simultaneously cannot be ruled out. Are steric effects solely responsible for the high regioselectivity observed?.

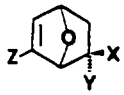
Dedicated to the memory of Prof. Francisco Gaviña.



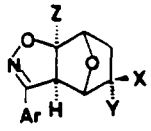
1a X=CN, Y=OAc
1b X,Y=O
1c X,Y=OCH_2CH_2O



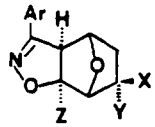
2a X=CN, Y=OAc, Z=Cl
2b X=CN, Y=OAC, Z=Br
2c X,Y=OCH_2CH_2O, Z=Br



3a X=CN, Y=OAc, Z=SO_2Ph
3b X,Y=O, Z=Br
3c X,Y=OCH_2CH_2O, Z=SO_2Ph



4a X=CN, Y=OAc, Z=Cl
4b X,Y=OCH_2CH_2O, Z=Br

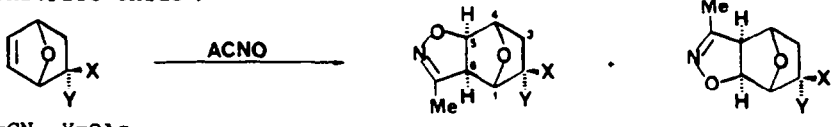


5a X=CN, Y=OAc, Z=SO_2Ph
5b X,Y=OCH_2CH_2O, Z=SO_2Ph

Scheme I

The results obtained from the reaction between compounds **1** and acetonitrile oxide (ACNO) are summarized in Table I.

Table I.- Cycloaddition Reactions of 7-Oxanorbornenic Substrates with Acetonitrile Oxide[a].



1a X=CN, Y=OAc
1b X,Y=O
1c X,Y=OCH_2CH_2O

6 7

Entry	Substrate	Products	Ratio(a/b)[b]	Yield(%)[c]
1	1a	6a, 7a	75:25	75
2	1b	6b, 7b	52:48	80
3	1c	6c, 7c	60:40	75

[a] The reaction was performed with 1.2 equiv. of ACNO ; [b] Determined by ^1H NMR (300 MHz); [c] Overall yield of mixtures of pure products.

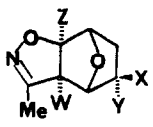
The reaction of cyanacetoxy derivative **1a** with ACNO (entry 1), affords a 75:25 mixture of cycloadducts **6a** and **7a** respectively. This is the highest regioselectivity observed in cycloadditions of nitrile oxides with compounds **1a**, **1b** and **1c**.

Introduction of a halogen atom in position 5 of the 7-oxanorbornenic substrate changes dramatically the observed regioselectivity. Thus, the reaction of compounds **2a** and **2b** (table II, entries 1 and 2) with one equivalent of ACNO affords only adducts **8a** and **8b** respectively. When the reaction was carried out with an excess (2.1 equivalents) of ACNO, compound **2a** afforded **8a** and **10a** in a 66:33 ratio, and **2b** afforded **8b** and **10b** in a 70:30

ratio (table II, entries 3 and 4). It should be pointed out that 1,3-dipolar cycloadditions of nitrile oxides to the C≡N triple bond are known only for aromatic and heteroaromatic nitriles, and for those activated with electron withdrawing groups; in contrast, for aliphatic nitriles the use of BF_3OEt_2 as a catalyst is necessary[7]. This unexpected tendency to the uncatalyzed cycloaddition to the C≡N triple bond was confirmed by the reaction of pure **4a** (Ar = 2,4,6, $Me_3C_6H_2$) with ACNO to give cycloadduct **10c** under mild reaction conditions (table II, entry 7).

In conclusion, the reluctance of the cianacetoxy derivatives to give the opposite regioisomer is noteworthy; when we examined the reactivity of other substrates as ketone **3b** or derivative **2c**, mixtures of regioisomers **8c**, **9c** and **8d**, **9d** were obtained respectively (table II, entries 5 and 6).

Table II.- Cycloaddition Reactions of 5-Halo-7-oxanorbornenic Substrates with Acetonitrile Oxide.



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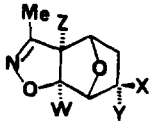

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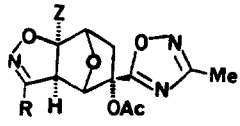

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a: X=CN, Y=OAc, Z=Cl, W=H
b: X=CN, Y=OAc, Z=Br, W=H
c: X,Y=O, Z=H, W=Br
d: X,Y=OCH_2CH_2O, Z=Br, W=H

a: Z=Cl, R=Me
b: Z=Br, R=Me
c: Z=Cl, R=2,4,6,$Me_3C_6H_2$

Entry	Substrate	Products	Ratio[a]	Yield%
1[d]	**2a**	**8a**	100	70[b]
2[d]	**2b**	**8b**	100	80[b]
3[e]	**2a**	**8a,10a**	66:33	75[c]
4[e]	**2b**	**8b,10b**	70:30	85[c]
5[e]	**2c**	**8d,9d**	60:40	89[c]
6[e]	**3b**	**8c,9c**	47:53	90[c]
7[e]	**4a**	**10c**	100	65[b]

[a] Determined by ^{1}H-NMR (300 MHz). [b] Yield of pure isolated product; [c] Overall yield of mixtures of pure products; [d] The reaction was performed with 1.1 equiv. of ACNO; [e] The reaction was performed with 2 equiv. of ACNO. The products were separated and characterized independently.

The structural assignment of cycloadducts **6** and **7** was derived from their ^{1}H NMR spectra with the help of NOE measurements, similarly to other analogous cases[2e]. Data of cycloadducts **8-10** were consistent with *exo* structures[8], the isoxazoline proton H-5 or H-6 occurred as a singlet thus evidencing the *exo* stereochemistry; H-1 appeared as a broad singlet or doublet (J = 1 Hz) due to a small coupling with H-4. The regiochemistry was unequivocally assigned by the ^{13}C NMR spectrum, for cycloadducts **8** and **10** C-5 appeared clearly deshielded (table III, entries 1-5) and C-6 appeared at 66.6-64.2 ppm wich are

typical values of this carbon when it does not bear any heteroatoms. On the other hand, in compound 9 C-5 appeared as a cuaternary carbon joined to halogen (table III, entry 6), and C-6 appeared as a carbon atom adjacent to the isoxazoline oxygen (87.9 ppm).

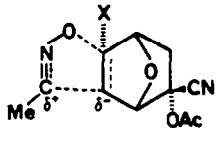
Table III.- Selected ^{1}H NMR and ^{13}C NMR Data for Cycloadducts 8,9 and 10.

Entry	Product	^{1}H-NMR (δ ppm)		^{13}C-NMR (δ ppm)	
		H-1	H-6	C-5	C-6
1	8a	5.09(br)	3.59(s)	105.8	64.2
2	8b	5.10(br)	3.72(s)	98.5	65.8
3	8d	4.09(d)[a]	3.94(s)	101.0	66.6
4	10a	4.94(br)	3.85(s)	106.6	65.1
5	10b	4.95(br)	4.01(s)	99.4	66.6
6	9d	4.30(br)	5.08(s)	87.9	72.3

[a] J = 1.0 Hz

Thus, the regioselectivity of the cycloaddition depends on the substituent on C-2 and steric effects alone do not explain the experimental results.

The halogen attached to C-5 renders this position an electrophilic center. Thus, a transition state with a highly asynchronous character (11, Scheme II) may be envisaged for the cycloaddition reaction of the polar nitrile oxide[9] to 2a or 2b. Additionally, the homoconjugated cyanacetoxy group stabilizes a partially carbanionic center on position C-6[10]. The homodonating character of the ethylenedioxy group of 2c[10] destabilizes an analogous transition state for 2c, and this could account for the reduced selectivity encountered.



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Scheme II

The asynchrony of transition states must be reflected in the solvent effects on cycloaddition rates[11] regardless of the nature of the hydrocarbon moiety in the nitrile oxide. Kinetic measurements of the cycloaddition of mesitonitrile oxide to 1a and 2a are indicated in table IV. In the case of 1a a decrease of the rate constant with the polarity of the solvent was observed; this means a reduction of polarity in going from the initial to the transition state. In this case the asynchrony of the transition state does not balance the disappearance of the formal charges of the 1,3-dipole. In the case of 2a an increase of rate constant with the solvent polarity is the result of the kinetic measurement. Thus, the transition state for the 5-haloderivative must be more polar relative to the unsubstituted compound.

Table IV.- Second Order Rate Constants for the Reaction of 1a and 2a with mesitonitrile oxide at 21.0 ± 0.5°C.

Entry	Substrate	Solvent	$k_2 \times 10^{-4}$ (L mol^{-1} s^{-1})
1	1a	$CDCl_3$	26.5 ± 0.1
2	1a	CD_3CN	10.40 ± 0.05
3	1a	CD_3OD	5.94 ± 0.05
4	2a	$CDCl_3$	0.66 ± 0.01
5	2a	CD_3CN	1.74 ± 0.07
6	2a	CD_3OD	3.74 ± 0.05

In conclusion, a combination of polar and steric effects appears to be responsible for the observed regioselectivity of the 1,3-dipolar cycloaddition of acetonitrile oxide and 5-halo substituted 7-oxanorbornenic derivatives 2.

EXPERIMENTAL

General. Analytical TLC was carried out on 0.20 mm E. Merck precoated silica gel plates (60 F-254), with detection by UV light, iodine or acidic vanillin solution. Column chromatography was performed using E. Merck 230-400 mesh or 70-230 mesh silica gel. Melting points were determined on a Büchi 512 apparatus an are uncorrected. Infrared spectra were recorded on either a Perkin Elmer 781 or 257 grating spectrophotometers; band positions are indicated in wavenumbers. ^{1}H NMR spectra were recorded on a Varian T-60A, Brüker AM-200 or Varian VXR-300 instrument, using $CDCl_3$ as solvent. ^{13}C NMR spectra were measured on a Varian FT-80A or Varian VXR-300 instrument, using $CDCl_3$ as solvent, and are completely decoupled. In both, ^{1}H NMR and ^{13}C NMR, chemical shifts are reported in δ units downfield from tetramethylsilane. The following abbreviations are used to describe peak patterns when appropiate: br = broad, s = singlet, d = doublet, t = triplet, m = multiplet. All new compounds described are racemic. 1a, 1b, 1c, 2a, 2b, 2c and 3b were prepared by previously described methods[1,2e].

General procedure for generation of acetonitrile oxide and 1,3-dipolar cycloadditions with 7-oxanorbornenic systems.

To a solution of the alkene (5 mmol) and nitroethane (5.1 mmol) in 10 ml of dry benzene, were added one drop of triethylamine and phenylisocyanate (10.2 mmol) in 5 ml of dry benzene. The reaction started, evolving carbon dioxide, and *sym*-diphenylurea precipitated. After shaking the reaction mixture for one hour, it was refluxed for an additional hour, cooled and filtered, and concentrated under reduced pressure.

Cycloaddition between 1a and ACNO (6a, 7a).

From 1a and 1.2 equivalents of ACNO 6a and 7a were obtained as a 75:25 inseparable mixture (white solid after crystallization from hexane:ethyl acetate, 1:1; yield: 75%). IR (KBr) ν 2250, 1750, 1630, 1175, 1020 cm^{-1}. 6a: ^{1}H-NMR ($CDCl_3$) δ 5.12 (s, 1H, H-1), 4.86 (d, 1H, J = 5.5 Hz, H-4), 4.70 (d, 1H, J = 8.0 Hz, H-5), 3.61 (d, 1H, J = 8.0 Hz, H-6), 2.73 (dd, 1H, J = 15.0, 5.5 Hz, H-3$_{exo}$), 2.20 (s, 3H, $COCH_3$), 2.00 (s, 3H, CH_3), 1.60 (d, 1H, J = 15.0 Hz, H-3$_{endo}$) ppm; ^{13}C NMR (DMSO-d6) δ 169.4, 152.6, 118.6, 83.1, 82.9, 80.7, 72.7, 55.6, 38.5, 20.4, 11.1 ppm. 7a: ^{1}H NMR ($CDCl_3$) δ 5.22 (s, 1H, H-1), 4.97 (d, 1H, J = 8.0 Hz, H-6), 4.75 (d, 1H, J = 5.5 Hz, H-4), 3.48 (d, 1H, J = 8.0 Hz, H-5), 2.81 (dd, 1H, J = 15.0, 5.5 Hz, H-3$_{exo}$), 2.17 (s, 3H, $COCH_3$), 2.00 (s, 3H, CH_3), 1.93 (d, 1H, J = 15.0 Hz, H-3$_{endo}$) ppm; ^{13}C NMR (DMSO-d6) δ 169.4, 153.7, 118.5, 85.7, 79.5, 77.6, 71.8, 60.7, 38.5, 20.4, 11.1 ppm; Anal. Calcd. for $C_{11}H_{12}O_4N_2$: C, 57.83; H, 5.24; N, 11.24. Found: C,57.71; H, 5.33; N, 11.45.

Cycloaddition between 1b and ACNO (6b, 7b).

From **1b** and 1.2 equivalents of ACNO, **6b** and **7b** were obtained as a 52:48 inseparable mixture (white solid after crystallization from hexane:ethyl acetate, 1:1; yield: 80%). IR (KBr) ν 1775, 1635, 1020 cm^{-1}. **6b**: ^1H NMR ($CDCl_3$) δ 5.04 (d, 1H, J = 4.8 Hz, H-4), 4.90 (d, 1H, J = 8.0 Hz, H-5), 4.40 (s, 1H, H-1), 3.58 (d, 1H, J = 8.0 Hz, H-6), 2.30 (dd, 1H, J = 17.5, 4.8 Hz, H-3$_{exo}$), 2.16 (d, 1H, J = 17.5 Hz, H-3$_{endo}$), 2.08 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 207.5, 152.9, 84.2, 82.3, 79.7, 56.4, 38.8, 11.2. **7b**: ^1H NMR ($CDCl_3$) δ 5.02 (d, 1H, J = 4.8 Hz, H-4), 4.94 (d, 1H, J = 8.0 Hz, H-6), 4.60 (s, 1H, H-1), 3.63 (d, 1H, J = 8.0 Hz, H-5), 2.28 (dd, 1H, J = 17.5, 4.8 Hz, H-3$_{exo}$), 2.13 (d, 1H, J = 17.5 Hz, H-3$_{endo}$), 2.04 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 207.6, 151.2, 86.3, 81.1, 77.6, 61.4, 42.5, 11.3 ppm; Anal. Calcd. for $C_8H_9O_3N$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.75; H, 4.82; N, 8.31.

Cycloaddition between 1c and ACNO (6c, 7c).

From **1c** and 1.2 equivalents of ACNO, **6c** and **7c** were obtained as a 60:40 inseparable mixture (white solid after crystallization from hexane:ethyl acetate, 1:1; yield: 75%). IR (KBr) ν 1630, 1330, 1120, 1020 cm^{-1}. **6c**: ^1H NMR ($CDCl_3$) δ 4.72 (m, 2H, H-4, H-5), 4.12 (s, 1H, H-1), 4.09-3.85 (m, 4H, OCH_2CH_2O), 3.81 (d, 1H, J = 8.7 Hz, H-6), 2.13 (dd, 1H, J = 13.9, 5.8 Hz, H-3$_{exo}$), 2.00 (s, 3H, CH_3), 1.66 (d, 1H, J = 13.9 Hz, H-3$_{endo}$) ppm; ^{13}C NMR ($CDCl_3$) δ 152.7, 113.1, 84.4, 82.5, 79.6, 64.9, 64.4, 56.1, 38.6, 11.4 ppm. **7c**: ^1H NMR ($CDCl_3$) δ 5.15 (d, 1H, J = 8.7 Hz, H-6); 4.65 (d, 1H, J = 5.8 Hz, H-4), 4.40 (s, 1H, H-1), 4.09-3.85 (m, 4H, OCH_2CH_2O), 3.45 (d, 1H, J = 8.7 Hz, H-5), 2.22 (dd, 1H, J = 13.9, 5.8 Hz, H-3$_{exo}$), 2.00 (s, 3H, CH_3), 1.78 (d, 1H, J = 13.9 Hz, H-3$_{endo}$) ppm; ^{13}C NMR ($CDCl_3$) δ 152.8, 112.0, 85.1, 81.4, 77.2, 64.9, 64.0, 61.1, 41.9, 11.3 ppm; Anal Calcd. for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.91; H, 6.17; N, 6.75.

Cycloaddition between 2a and ACNO (8a, 10a).

From **2a** and 1.1 equivalents of ACNO **8a** was obtained as a white solid after column chromatography (hexane:ethyl acetate, 3:1) and crystallization from EtOH (yield: 70%); **8a**: Mp 128-129°C; IR (KBr) ν 2265, 1770, 1635, 1375, 1210, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.09 (s, 1H, H-1), 4.81 (d, 1H, J = 5.9 Hz, H-4), 3.59 (s, 1H, H-6), 2.76 (dd, 1H, J = 14.8, 5.9 Hz, H-3$_{exo}$), 2.55 (d, 1H, J = 14.8 Hz, H-3$_{endo}$), 2.15 (s, 3H, $COCH_3$), 2.01 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 168.8, 154.4, 117.0, 105.8, 84.7, 83.1, 73.0, 64.2, 39.6, 20.2, 11.4 ppm; Anal. Calcd. for $C_{11}H_{11}O_4N_2Cl$: C, 48.81; H, 4.10; N, 10.35; Cl, 13.10. Found: C, 48.82; H, 4.05; N, 10.41; Cl, 13.40.

From **2a** and 2.1 equivalents of ACNO a 66:33 mixture of **8a**:**10a** was obtained (yield: 75%). The products were separated by column chromatography (hexane:ethyl acetate, 3:1) and purified by crystallization from EtOH, (**8a**, yield: 50%; **10a**, yield: 25%). **10a**: Mp 168-169°C; IR (KBr) ν 1770, 1580, 1220, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.94 (s, 1H, H-1), 4.84 (d, 1H, J = 6.0 Hz, H-4), 3.85 (s, 1H, H-6), 3.00 (dd, 1H, J = 14.8, 6.0 Hz, H-3$_{exo}$), 2.63 (d, 1H, J = 14.8 Hz, H-3$_{endo}$), 2.34 (s, 3H, CH_3), 2.13 (s, 3H, $COCH_3$), 2.01 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 177.1, 169.6, 167.5, 154.8, 106.6, 85.5, 83.5, 79.3, 65.1, 38.5, 20.6, 11.7, 11.5; Anal. Calcd. for $C_{13}H_{14}O_5N_3Cl$: C, 47.63; H, 4.30; N, 12.82; Cl, 10.82. Found: C, 47.68; H, 4.32; N, 12.75; Cl, 10.90.

Cycloaddition between 2b and ACNO (8b, 10b).

From **2b** and 1.1 equivalents of ACNO **8b** was obtained as a white solid after column chromatography (hexane:ethyl acetate, 3:1) and crystallization from EtOH (yield: 80%). **8b**: Mp 153-154°C; IR (KBr) ν 2260, 1780, 1640, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10 (s, 1H, H-1), 4.93 (d, 1H, J = 5.7 Hz, H-4), 3.72 (s, 1H, H-6), 2.84 (dd, 1H, J = 15.0, 5.7 Hz, H-3$_{exo}$), 2.73 (d, 1H, J = 15.0 Hz, H-3$_{endo}$), 2.22 (s, 3H, $COCH_3$), 2.09 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 168.7, 154.7, 116.9, 98.5, 85.7, 83.1, 73.0, 65.8, 40.7, 20.3, 11.4 ppm; Anal. Calcd. for $C_{11}H_{11}O_4N_2Br$: C, 41.91; H, 3.51; N, 8.88; Br, 25.35. Found: C, 42.15; H, 3.51; N, 8.91; Br, 25.17.

From **2b** and 2.1 equivalents of ACNO a 70:30 mixture of **8b**:**10b** was obtained (yield:85%). The products were separated by column chromatography

(hexane:ethyl acetate, 3:1) and purified by crystallization from EtOH (**8b**, yield: 60%; **10b**, yield: 25%). **10b**: Mp 170-171°C; IR (KBr) ν 1770, 1590, 1390, 1240, 1220, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.97 (d, 1H, J = 6.0 Hz, H-4), 4.95 (s, 1H, H-1), 4.01 (s, 1H, H-6), 3.09 (dd, 1H, J = 14.7, 6.0 Hz, H-3$_{exo}$), 2.79 (d, 1H, J = 14.7 Hz, H-3$_{endo}$), 2.40 (s, 3H, CH_3), 2.20 (s, 3H, $COCH_3$), 2.11 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 176.9, 169.5, 167.4, 155.1, 99.4, 86.4, 83.3, 79.2, 66.6, 39.4, 20.5, 11.4; Anal. Calcd. for $C_{13}H_{14}O_5N_3Br$: C, 41.94; H, 3.79; N, 11.28; Br, 21.46. Found: C, 41.89; H, 3.57; N, 11.31; Br, 21.37.

Cycloaddition between 2c and ACNO (8d, 9d).

From **2c** and 2.1 equivalents of ACNO a 60:40 mixture of **8d**:**9d** was obtained (yield: 89%), the products were separated by column chromatography (hexane:ethyl acetate, 3:1) and purified by crystallization from Et_2O:hexane at -10°C, (**8d**, yield: 53%; **9d**, yield: 35%). **8d**: Mp 240-241°C; IR (KBr) ν 1650, 1600, 1550, 1450, 1320, 1240, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.82 (d, 1H, J = 6.1 Hz, H-4), 4.06 (m, 1H, OCH_2CH_2O), 4.09 (d, 1H, J = 1.0 Hz, H-1), 3.90 (m, 3H, OCH_2CH_2O), 3.94 (s, 1H, H-6), 2.51 (d, 1H, J = 14.0 Hz, H-3$_{endo}$), 2.27 (ddd, 1H, J = 14.0, 6.1, 1.0 Hz, H-3$_{exo}$), 2.09 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 155.9, 113.1, 101.0, 86.2, 82.1, 66.6, 65.7, 65.0, 40.3, 11.8 ppm; Anal. Calcd. for $C_{10}H_{12}O_4NBr$: C, 41.40; H, 4.17; N, 4.82; Br, 27.54. Found: C, 41.36; H, 4.17; N, 5.02; Br, 27.23. **9d**: Mp 245-246°C; IR (KBr) ν 1620, 1440, 1280, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.08 (s, 1H, H-6), 4.56 (dd, 1H, J = 5.9, 0.6 Hz, H-4), 4.30 (s, 1H, H-1), 4.08 (m, 1H, OCH_2CH_2O), 3.92 (m, 3H, OCH_2CH_2O), 2.67 (d, 1H, J = 13.9 Hz, H-3$_{endo}$), 2.28 (ddd, 1H, J = 13.9, 5.9, 0.6 Hz, H-3$_{exo}$), 2.08 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 153.2, 112.0, 87.9, 87.0, 80.7, 72.3, 65.4, 64.4, 39.6, 9.0 ppm; Anal. Calcd. for $C_{10}H_{12}O_4NBr$: C, 41.40; H, 4.17; N, 4.82; Br, 27.54. Found: C, 41.52; H, 4.20; N, 4.70; Br, 27.31.

Cycloaddition between 3b and ACNO (8c, 9c).

From **3b** and 2.1 equivalents of ACNO a 47:53 mixture of **8c**:**9c** was obtained (yield:90%), the products were separated by column chromatography (hexane:ethyl acetate, 2:1) and purified by crystallization from Et_2O:hexane at -10°C, (**8c**, yield: 45%; **9c**, yield: 47%). **8c**: Mp 147-148°C; IR (KBr) ν 1775, 1665, 1610, 1320, 1250, 1175, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.07 (d, 1H, J = 6.6 Hz, H-4), 4.91 (s, 1H, H-5), 4.26 (s, 1H, H-1), 2.64 (dd, 1H, J = 18.0, 6.6 Hz, H-3$_{exo}$), 2.31 (d, 1H, J = 18.0 Hz, H-3$_{endo}$), 2.09 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 202.6, 151.5, 91.6, 83.6, 82.3, 64.9, 38.4, 9.3 ppm. Anal. Calcd. for $C_8H_8O_3NBr$: C, 39.05; H, 3.27; N, 5.69; Br, 32.47. Found: C, 38.86; H, 3.31; N, 5.50; Br, 32.39. **9c**: Mp 151-152°C; IR (KBr) ν 1780, 1355, 1215, 1080, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.04 (d, 1H, J = 6.0 Hz, H-4), 4.62 (s, 1H, H-1), 3.81 (s, 1H, H-5), 2.66 (dd, 1H, J = 18.0, 6.0 Hz, H-3$_{exo}$), 2.35 (d, 1H, J = 18.0 Hz, H-3$_{endo}$), 2.13 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 202.1, 155.9, 93.2, 87.8, 78.7, 72.1, 41.2, 11.4 ppm. Anal. Calcd. for $C_8H_8O_3NBr$: C, 39.05; H, 3.27; N, 5.69; Br, 32.47. Found: C, 39.17; H, 3.18; N, 5.56; Br, 32.00.

Cycloaddition between 4a and ACNO (10c).

From **4a** and 2 equivalents of ACNO, **10c** was obtained (yield:65%). Mp 197-198°C; IR (KBr) ν 1770, 1660, 1605, 1565, 1510, 1330, 1200; ^1H NMR ($CDCl_3$) δ 6.94 (s, 2H, H-Ar), 4.96 (d, 1H, J = 6.0 Hz, H-4), 4.72 (s, 1H, H-1), 4.38 (s, 1H, H-6), 3.23 (dd, 1H, J = 15.0, 6.0 Hz, H-3$_{exo}$), 2.69 (d, 1H, J = 15.0 Hz, H-3$_{endo}$), 2.36, 2.30, 2.28, 2.13 (4s, 15H, 5CH_3); ^{13}C NMR ($CDCl_3$) δ 177.2, 169.1, 167.8, 157.0, 139.9, 136.9, 129.0, 123.0, 106.7, 86.1, 83.7, 79.3, 66.0, 38.4, 21.1, 20.5, 19.9, 11.6. Anal Calcd. for $C_{21}H_{22}O_5N_3Cl$: C, 58.40; H, 5.13; N, 9.73; Cl, 8.21. Found: C, 58.52; H, 5.20; N, 9.69; Cl, 8.34.

Kinetics.

Kinetic measurements were performed by ^1H-NMR on a Varian VXR-300 spectrometer The absolute intensity mode was used to measure integrals of relevant peaks, which were well separated. The ratio of the concentration of the reactants was determined by integration of the H-1 signals of **1a** or **2a** and OCH_3 of internal standards, 2,2-dimethoxypropane or anisol respectively.

Spectra at different times for the kinetic runs were obtained by arraying the pre-acquisition delay time. The second order constants were determined by linear regression analysis of the data at 21.0 ± 0.5°C, it was reproducible within 5%. The kinetics were followed up to 40-70% of chemical conversion.

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