Face Selectivity in the 1,3-Dipolar Cycloaddition Reactions of Benzonitrile Oxide with 5-Substituted Adamantane-2-thiones and 2-Methyleneadamantanes

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Received February 27, 1997

The 1,3-dipolar cycloaddition reactions of benzonitrile oxide with 5-substituted adamantane-2-thiones (2-X) and 2-methyleneadamantanes (3-X) produced two geometrically isomeric $\Delta^1$-4,2-oxathiazolines (5-Xs) and two $\Delta^2$-isoxazolines (6-Xs), respectively. The substituent was varied from fluoro, chloro, bromo, to phenyl. X-ray single-crystal analysis confirmed the configuration of (Z)-5-F. The product formation bias resulting from the favored attack of nitrile oxide on the zu-face is discussed in terms of transition-state hyperconjugation and frontier molecular orbital theory.

1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of a variety of complex five-membered heterocycles that are synthetically useful compounds.1 Nitrile oxide cycloadditions to terminal alkenes proceeded regioselectively to give 5-substituted $\Delta^2$-isoxazolines as single products.1b The cycloaddition of nitrones and nitrile oxides to thiones leading to $\Delta^2$,1,4,2-oxathiazolines and $\Delta^1$,4,2-oxathiazolines, respectively, have also drawn much attention recently.2 Because of their extremely high reactivity toward 1,3-dipoles, thiones have been called superdipolarophiles by Huisgen.2a,b

5-Substituted adamantane-2-ones 1-X and their derivatives have proven to be useful probes in research aimed at understanding the electronic factors in face selection.3 Studies by le Noble et al.3a of a variety of reactions indicate that the reagent prefers to attack the face that is antiperiplanar to the more electron-rich vicinal bonds (zu and en face preference in 1 when X equals an electron-withdrawing and electron-donating group, respectively). Their results have been reconciled with Cieplak’s transition-state hyperconjugation model.4

The Diels–Alder reaction of 2,3-dimethylbuta-1,3-diene with 5-fluoroadamantane-2-thione (2-F) has been reported to follow Cieplak’s prediction.5 When frontier molecular orbital (FMO) theory is applied to this Diels–Alder reaction, the diene functions as the donor, and the reaction is controlled by the HOMO (dienophile)–LUMO (dipolarophile) interaction. In other words, this is a normal Diels–Alder-type reaction.1a,2d,6 On the other hand, 1,3-dipolar cycloadditions of benzonitrile oxide with thiones 2, or terminal alkenes 3, are controlled mainly by the LUMO (dipole)–HOMO (dipolarophile) interaction (an inverse electron-demand type of reaction). Thus, 1,3-dipolar cycloaddition reactions to 2 and 3 provide an important test of the transition-state hyperconjugation model because Cieplak’s model stresses that, regardless of the type of reaction (nucleophilic, electrophilic, radical addition, etc.), the newly developing $\sigma^*$ orbital should attract electron density with the same directional preference provided the transition states are electron deficient.3a,4c We report here our study of the 1,3-dipolar cycloaddition reactions of benzonitrile oxide with 5-substituted adamantane-2-thiones (2-X) and 2-methyleneadamantanes (3-X). We find that the favored approach is indeed syn as predicted, in all instances.

Results and Discussion

The reaction of thione 2-F with benzonitrile oxide generated in situ from benzhydroximoyl chloride (4) and

References


The assignment of the epimers of 5-fluoro-3-phenyladamantane-2-spiro-5-(1,4,2-oxathiazolines) was not straightforward. We were initially misled by the X-ray crystal structure of (E)-5-Br, which was sluggish at room temperature but was accelerated by refluxing in THF for 24 h to give two isoxazolines in 72–88% isolated yield (Scheme 2). Again, these products were proven to be stable under the reaction conditions; i.e., both products are formed in kinetically controlled processes. In all instances examined, the major product is assumed to have the E-configuration, whereas deviations of several ppm are found when the opposite assumption is used (Table 1). Finally, the configuration of (Z)-5-F was established independently by means of an X-ray structural determination (see Figure 1).

The reaction of benzonitrile oxide with 5-substituted methyleneadamantanes in 82% yield after chromatography (Scheme 1). Both adducts are stable to the reaction conditions, and they are characterized as 5-fluoro-3-phenyladamantane-2-spiro-5-(1,4,2-oxathiazolines) on the basis of their mass and NMR spectroscopy. In all instances examined, the major isomer was (E)-5-X, which results from syn attack of the nitrile oxide on 2-X (Scheme 1). The configurational assignment of the epimers 5-X was based on the relative shielding power of oxygen vs sulfur directly "above" the flanking methylene groups. The shielding effect of an oxygen atom on these CH bonds in a series of spirocyclohex-4-ene was found to be 0.6 ppm in 5-fluorospiro[adamantane-2,2'-thioxodihexy-4'-ene]. Thus, C-4 and C-9 (identified by their 19F coupling), which are syn to the oxygen in the parent compound 5-H, are determined to be shielded vs C-8 and C-10 by a margin of ≥2 ppm. Moreover, application of the 13C NMR additivity scheme to the oxathiazolines furthered led to carbon resonances correctly predicted to be within ±0.4 ppm if the major product is assumed to have the E-configuration, whereas deviations of several ppm are found when the opposite assumption is used (Table 1).

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Moreover, application of the 13C NMR additivity scheme to the oxathiazolines furthered led to carbon resonances correctly predicted to be within ±0.4 ppm if the major product is assumed to have the E-configuration, whereas deviations of several ppm are found when the opposite assumption is used (Table 1). Finally, the configuration of (Z)-5-F was established independently by means of an X-ray structural determination (see Figure 1).

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The reaction of benzonitrile oxide with 5-substituted methyleneadamantanes 3-X was sluggish at room temperature but was accelerated by refluxing in THF for 24 h to give two isoxazolines 6-Xs in 72–88% isolated yield (Scheme 2). Again, these products were proven to be stable under the reaction conditions; i.e., both products are formed in kinetically controlled processes. In all instances examined, the major product is assumed to have the E-configuration, whereas deviations of several ppm are found when the opposite assumption is used (Table 1). Finally, the configuration of (Z)-5-F was established independently by means of an X-ray structural determination (see Figure 1).

(7) All compounds mentioned in this paper have been completely characterized; see the Experimental Section. The final structural assignment of oxathiazolines was not straightforward. We were initially misled by the X-ray crystal structure of (Z)-5-Br, which crystallized from a 95:5 mixture of (E)-5-Br (due to poor separation). Fortunately, (Z)-5-F can be separated in pure form by means of column chromatography, and this finally revealed the fact that only the Z-form of oxathiazoline produced single crystals.


The present study provides strong support for the Cielplak transition-state hyperconjugation model: while the dipolarophiles 1-3 behave as electron donors in an inverse electron-demand-type 1,3-dipolar addition, the Dienophiles 2 and 3 behave as electron acceptors in a normal Diels–Alder reaction. Nevertheless, both the diene (in a Diels–Alder reaction) and the dipole (in a 1,3-dipolar cycloaddition) approach the trigonal carbon from the same direction antiparallel to the most electron-rich bonds. Although the involvement of electrostatic effects in face-selectivity is not excluded, claims to that effect have relied mainly on calculations. Ab initio and semiempirical calculations of the transition states for 1,3-dipolar cycloaddition reactions of 5-substituted adamantane-2-thiones and 2-methyleneadamantanes are now in progress and will be reported in due course. We are presently studying the electronic effect of para-substituted phenylnitrile oxides in 1,3-dipolar cycloaddition reactions.

Experimental Section

General Procedure for the Synthesis of 5-Substituted 3'-Phenylandamantane-2-spiro-5'(1,4,2'-oxathiazoles) 5-X. All 5-substituted 3'-phenyladamantane-2-spiro-5'(1,4,2'-oxathiazoles) were prepared from the corresponding adamantane-2-thiones 2-X with a standard procedure described below for the fluoro derivative (X = F). Triethylamine 0.124 g (1.22 mmol) was added gradually at 0 °C to a stirred solution of 2-F (0.15 g, 0.82 mmol) and benzohydroxymethyl chloride (0.19 g, 1.22 mmol) in 10 mL of dry dichloromethane. After being stirred for 3 h at rt, the mixture was poured into 15 mL of water. Following removal of the organic solvent, the solid residue was purified on a silica gel column by elution with n-hexane/dichloromethane to give two isomeric adducts (E)- and (Z)-5-F. The isolated yields based on converted starting materials are as follows: 5-F 82%, 5-Cl 78%, and 5-Br 75%. For all 13C NMR spectra data, see Table 1; all 1H NMR spectra were measured at 300 MHz in CDCl3.

(E)-5-F: colorless solid; mp 91.5–92.5 °C; δH 1.72–2.0 (m, 8 H), 2.0–2.3 (m, 1 H), 2.4–2.6 (bs, 2 H), 2.7 (bs, 2 H), 7.3–7.5 (m, 3 H), 7.6–7.7 (m, 2 H); MS (EI, m/z) 303 (M + 1, 81), 184 (59), 168 (11), 135 (100), 91 (18), 29 (16); HRMS calc for C17H18ONSCl 319.0799, found 319.0798.

(Z)-5-F: colorless solid; mp 82.5–83 °C; δH 1.5–1.7 (m, 2 H), 1.9–2.2 (m, 6 H), 2.2–2.4 (m, 3 H), 2.65 (bs, 2 H), 7.3–7.5 (m, 3 H), 7.6–7.7 (m, 2 H); MS (EI, m/z) 303 (M + 6), 184 (29), 168 (9), 135 (100), 91 (81), 29 (9); HRMS calc for C17H18ONSF 303.1094, found 303.1095.

(E)-5-Cl: colorless solid; mp 147–148 °C; δH 1.75–2.2 (m, 9 H), 2.62 (bs, 2 H), 2.65–2.80 (m, 2 H), 2.65 (bs, 2 H), 7.3–7.5 (m, 3 H), 7.60–7.75 (m, 2 H); MS (EI, m/z) 321 (M + 2, 13), 319 (M + 3), 200 (26), 184 (8), 135 (100), 91 (14), 79 (17); HRMS calc for C17H18ONSCl 319.0799, found 319.0789. Anal. Calc for C17H18ONSCl: C, 63.64; H, 5.67; N, 4.38; S, 10.03. Found: C, 64.02; H, 5.6; N, 4.43; S, 10.12.

(Z)-5-Cl could not be isolated; however, the 1H and 13C NMR spectra can be obtained from the (E)- and (Z)-5-Cl mixture: MS (EI, m/z) 321 (M + 2, 5), 319 (M + 14), 200 (19), 184 (13), 135 (100), 91 (29), 79 (40).

An attempt to react nitrile oxide with adamantane 1-H was unsuccessful even at high temperature and with a long reaction time. Kinetic studies of 1,3-dipolar additions of nitrones to thiones revealed that the weakness of the C=S π bond was not responsible for the high reaction rates; instead, the low HOMO–LUMO energy gap of the C=S π bond was suggested to be the decisive factor. AM1 calculations of the HOMO–LUMO energy of 1-3 reveal that all of the 1,3-dipolar reactions described here are LUMO (dipole)–HOMO (dipolarophile) controlled reactions, and the rates diminish in the order k(C=S) > k(C=CH3) > k(C=O).

Figure 1. ORTEP drawing of oxathiazoline Z-5-F.

Scheme 2

Figure 1. ORTEP drawing of oxathiazoline Z-5-F.
Isolated yields based on converted starting materials are as follows: Cycloaddition Reactions of Benzonitrile

(E)-5-Brc: colorless solid; mp 181–182 °C; δH 1.80–2.00 (m, 4 H), 2.12 (bs, 1 H), 2.15–2.30 (m, 2 H), 2.38 (bs, 2 H), 2.58 (bs, 2 H), 2.85–3.00 (m, 2 H), 7.3–7.75 (m, 3 H), 7.70–7.75 (m, 2 H); MS (EI, m/z) 365 (M+ + 2, 53), 363 (M+, 51), 246 (M+ + 2 – PhCNCO, 22), 244 (M+ – PhCNCO, 21), 165 (40), 135 (100), 91 (28), 79 (36); HRMS calcd for C17H18ONS79Br 363.0293, found 363.0291. Anal. Calcd for C17H18ONSBr: C, 56.05; H, 2.85; Br, 2.12; N, 18.43.

(Z)-5-Brc: colorless solid; mp 158–158.5 °C; δH 1.65–1.75 (m, 2 H), 2.10 (bs, 1 H), 2.3–2.6 (m, 10 H), 7.35–7.50 (m, 3 H), 7.65–7.70 (m, 2 H); MS (EI, m/z) 365 (M+ + 2, 27), 363 (M+, 26), 246 (M+ + 2 – PhCNCO, 9), 244 (M+ – PhCNCO, 9), 165 (17), 135 (100), 91 (13), 79 (18); HRMS calcd for C17H18ONS79Br 363.0293, found 363.0297.

Anal. Calcd for C18H20ONBr: C, 62.44; H, 5.82; Br, 17.68.

Cycloaddition Reactions of Benzonitrile

(E)-6-Fr: colorless solid; mp 142–143 °C; δH 1.52 (m, 4 H), 1.56 (bs, 1 H), 1.68–2.10 (m, 6 H), 2.15–2.35 (m, 5 H), 3.21 (s, 2 H), 7.32–7.50 (m, 3 H), 7.60–7.75 (m, 2 H); MS (EI, m/z) 285 (M+ + 100), 268 (38), 117 (M+ – C10H13OF, 33), 91 (12), 77 (28); HRMS calcd for C18H17OBr 285.1530, found 285.1523. Anal. Calcd for C18H17OBr: C, 75.76; H, 7.06; N, 4.91. Found: C, 75.55; H, 7.03; N, 5.09.

(Z)-6-Fr: colorless solid; mp 146–147 °C; δH 1.65–1.90 (m, 4 H), 1.99 (bs, 1 H), 2.03 (bs, 1 H), 2.05–2.25 (m, 5 H), 2.71 (bs, 1 H), 2.75 (bs, 1 H), 3.16 (bs, 2 H), 3.75–4.55 (m, 3 H), 7.60–7.75 (m, 2 H); MS (EI, m/z) 303 (M+ + 2, 32), 301 (M+, 100), 286 (15), 284 (44), 266 (M+ – 3Cl, 7), 117 (40), 91 (58), 77 (92); HRMS calcd for C18H17O3Br 310.1235, found 310.1237. Anal. Calcd for C18H17O3Cl: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.54; H, 6.64; N, 4.69.

(E)-6-Cl: colorless solid; mp 122–123 °C; δH 1.62 (bs, 1 H), 2.10–2.35 (m, 12 H), 3.22 (s, 2 H), 3.75–4.55 (m, 3 H), 7.60–7.70 (m, 2 H); MS (EI, m/z) 303 (M+ + 2, 32), 301 (M+, 24), 286 (4), 284 (12), 117 (32), 91 (47), 77 (100); HRMS calcd for C18H17O3Cl 310.1235, found 310.1230. Anal. Calcd for C18H17O3Cl: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.54; H, 6.66; N, 4.69.

(Z)-6-Br: colorless solid; mp 152–154 °C; δH 1.60–1.95 (m, 4 H), 2.17 (bs, 3 H), 2.24 (bs, 1 H), 2.38 (bs, 1 H), 2.91 (bs, 1 H), 2.95 (bs, 1 H), 3.14 (s, 2 H), 7.35–7.50 (m, 3 H), 7.65–7.72 (m, 2 H); MS (EI, m/z) 347 (M+ + 2, 68), 345 (M+, 69), 330 (8), 328 (8), 266 (M+ – 3Br, 100), 117 (M+ – C18H12OBr, 31), 91 (43), 77 (48); HRMS calcd for C18H17O3Br 345.0729, found 345.0731. Anal. Calcd for C18H17O3Br: C, 62.44; H, 5.82; N, 4.04. Found: C, 62.39; H, 5.87; N, 4.04.

(E)-6-Br: colorless solid; mp 106–108 °C; δH 1.63 (bs, 1 H), 1.67 (bs, 1 H), 2.02–2.16 (m, 3 H), 2.20–2.50 (m, 8 H), 3.22 (s, 2 H), 7.30–7.45 (m, 3 H), 7.60–7.70 (m, 2 H); MS (EI, m/z) 347 (M+ + 2, 90), 345 (M+, 91), 330 (14), 328 (12), 266 (M+ – 3Br, 90), 117 (M+ – C18H12OBr, 42), 91 (73), 77 (100); HRMS calcd for C18H17O3Br 345.0729, found 345.0731. Anal. Calcd for C18H17O3Br: C, 62.44; H, 5.82; N, 4.04. Found: C, 62.39; H, 5.87; N, 4.04.
calcd for C_{18}H_{20}ON_{7.9}Br 345.0729, found 345.0724. Anal. Calcd for C_{18}H_{20}ON_{7.9}Br: C, 62.44; H, 5.82; N, 4.04. Found: C, 62.35; H, 5.89; N, 4.01.

(Z)-6-Ph: colorless solid; mp 130–132 °C; δ_{H} 1.75–2.05 (m, 8 H), 1.96 (bs, 2 H), 2.18–2.28 (m, 3 H), 3.21 (s, 1 H), 7.39–7.42 (m, 3 H), 7.65–7.69 (m, 2 H); MS (EI, m/z) 343 (M^{+}, 100), 326 (44), 155 (25), 117 (32), 91 (39), 77 (33); HRMS calcd for C_{24}H_{25}ON 343.1938, found 343.1928. Anal. Calcd for C_{24}H_{25}ON: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.96; H, 7.34; N, 4.07.

(Z)-6-Ph: colorless solid; mp 125.5–127 °C; δ_{H} 1.52–1.56 (m, 6 H), 1.96 (bs, 2 H), 2.18–2.28 (m, 3 H), 3.21 (s, 1 H), 7.39–7.42 (m, 3 H), 7.65–7.69 (m, 2 H); MS (EI, m/z) 343 (M^{+}, 100), 326 (40), 155 (18), 117 (18), 91 (28), 77 (27); HRMS calcd for C_{24}H_{25}ON 343.1938, found 343.1938. Anal. Calcd for C_{24}H_{25}ON: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.84; H, 7.31; N, 4.08.

X-ray Structure Analysis of (Z)-5-F. A colorless prism crystal of C_{17}H_{18}ONSF was crystallized from 30% methylene chloride in hexanes. Its structure was determined by means of single-crystal X-ray analysis on a Rigaku AFC6S diffractometer with graphite-monochromated MoKα (λ = 0.710 70 Å) radiation at 296 ± 1 K, with an ω-2θ type scan at 16°/min (in ω). The crystals are C-centered monoclinic, with space group C2/c (15) and unit cell dimensions a = 19.454(4) Å, b = 6.635(5) Å, c = 24.956(4) Å, β = 111.30(2)°, V = 3001(1) Å³, Z = 8, μ_{calcd} = 1.343 g cm⁻³, crystal size (mm) 0.33 × 0.41 × 0.46, μ(MoKα) = 2.24 cm⁻¹, F(000) = 1280.00, 2554 reflections, 2467 unique reflections, 1403 with I > 3.0σ(I) and with 190 variable parameters. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The model was finally refined by the full-matrix least-squares methods with weight ω = 1/[σ^2(Fo)] to final R values of 0.048 and Rw = 0.037 (for details, see the Supporting Information).^{13}

Acknowledgment. We thank Professor T.-J. Lu for valuable suggestions. This work was supported at NCTU by the National Science Council of the Republic of China (Grant NSC-86-2113-M-002-004).

J O9703717

(13) The author has deposited atomic coordinates for (Z)-5-F with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.