1,3-Dipolar Cycloadditions of 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide to Phenoxy-Substituted Allenes

Gaetano Zecchi

Istituto di Chimica Industriale dell'Università, Centro del C.N.R. per la Sintesi e Stereochimica di Speciali Sistemi Organici, 20133 Milano, Italy

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Cycloaddition reactions of 1,3-dipoles to allenes are interesting since they involve both peri- and regioselectivity phenomena. With nitrile oxides, reports are available concerning unsubstituted as well as variously substituted allenes as dipolarophiles.[1-6] However, the observed product distribution is far from being thorougly rationalized and general rules on the behavior of allenes toward nitrile oxides cannot be stated at the present. Therefore, more experimental data seem to be desirable. In this context, we now wish to describe the reactions of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (1) with the phenoxy-substituted allenes **2a,b**.

Results and Discussion

Nitrile oxide 1 was made to react with equimolecular amounts of **2a,b** in boiling carbon tetrachloride; the reaction times, deduced by periodic TLC and IR analyses, were 8 and 20 h for **2a** and **2b**, respectively. In the case of **2a**, the reaction gave the isomeric monoadducts **3a** and **4a** in 36 and 15% yield and the spirobis(2-isoxazoline) diadduct **5** in 19% yield with respect to the starting moles of **2a**. In the case of **2b**, the products were **6a** (24%), **4b** (21%), **7** (6%), and **3b** (5%); in addition, side products arising from dimerization and/or isomerization of **1** were obtained in an overall quantity corresponding to ca. 10% of the starting nitrile oxide.[7]

The product structures are consistent with elemental analyses and NMR, IR, and mass spectral data; both ^1H and ^{13}C NMR spectra are available for diadduct **5** (see Experimental Section). Diadduct **7** was also obtained in an independent manner, i.e., by reacting **1** with 2-phenoxy-1,3-butadiene (**8**). For compound **6a**, the choice between this isoxazolic formula and the isomeric one having inverted substituents in the 4 and 5 positions is unequivocal on the basis of the following evidence. The mass spectrum of **6a** shows intense peaks at m/e 332 (100%) and 43 (85%) due to the loss of the acetyl fragment from the molecular ion. In the light of the well-studied mass-spectral properties of substituted isoxazoles,[8-12] this finding is only consistent with the methyl group located in the 5 position of the heterocyclic ring. The same fragmentation pattern is given by the methyl ether **6b**, which derived from phenol **6a** on reaction with methyl iodide under basic conditions.

The stereochemistry of **3a,b** and **4a,b** comes from their ^1H NMR spectra (see Experimental Section). In fact, as the molecular models indicate, the aryl ring in the 3 position exerts a shielding effect on the methyl group in compound **3b** and on the phenoxy group in compound **4a**, thus accounting for the observed δ values which are lower than those found for the corresponding isomers **3a** and **4b**, respectively. Interestingly, transoid (homo)allylic coupling constants are larger than cisoid ones, which is precedented in the case of exocyclic double bonds.[13]

A control experiment showed that **2b** isomerizes to the corresponding conjugated diene **8** on heating in carbon tetrachloride.[14] Thus, the formation of **7** in the reaction of **1** with **2b** is clearly due to a preliminary isomerization of the allene followed by cycloaddition of two molecules of 1 to 8. As to the formation of diadduct **5**, the primary monoadduct **9a** is a reasonable intermediate since *exo*-methylene cyclocompounds usually behave as good dipolarophiles.[15-18] The alternative route involving the

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(14) This isomerization was also observed when **2b** was left at room temperature for a few days.
(15) N. Barbulescu, P. Grünanger, M. R. Langella, and A. Quilico, *Tetrahedron Lett.*, 89 (1961).
(16) G. Lo Vecchio, G. Cum, and G. Stagno d'Alcontres, *Gazz. Chim. Ital.*, **95**, 206 (1965).
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(18) In particular, it has been shown[4] that 3-(3,5-dichloro-2,4,6-trimethylphenyl)-5,5-diphenyl-4-methylene-2-isoxazoline reacts with nitrile oxide 1 giving a spirobis(2-isoxazoline) similar to **5**.

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primary monoadduct **10** is to be discarded because such an intermediate should have little or no reactivity toward nitrile oxide **1**; an indirect support to this view is given by the fact that the isolated monoadducts **3a** and **4a** are not capable of adding a further molecule of **1** in boiling carbon tetrachloride.

The formation of **6a** represents an unprecedented feature of the reaction between allenes and nitrile oxides. It can be rationalized in terms of a Claisen-type rearrangement of the first-formed monoadduct **9b**, which structurally relates to the allylic ethers of phenol. To account for the different behavior of the similar species **9a** and **9b**, one may invoke in the case of **9b** stereochemical constraints favoring on entropic grounds the six-membered cyclic transition state involved in the Claisen rearrangement. As a consequence, the latter reaction would prevent the formation of conceivable diadducts.

On the basis of the above points, the conclusion can be drawn that the cumulated double bonds of **2a,b** are both reactive toward nitrile oxide **1**. However, while the reactivity ratio between α,β and β,γ double bond is ca. 30:70 for **2a**, no periselectivity is practically operating in the case of **2b**.[19] On considering that the ether function activates the olefinic bond toward the 1,3-dipoles,[20] a preference for the α,β double bond could be expected when allenyl ethers are used as dipolarophiles. Such a preference has been really observed in the reaction of picryl azide with aryloxyallenes,[21] while benzonitrile and 4-chlorobenzonitrile oxides have been recently shown[6] to add preferably to the β,γ double bond of **2a**.

Turning now to the regiochemistry of the above cycloadditions, it is to be stressed that all of them take place in a regiospecific fashion (within the experimental limits of detection) with the carbon of the 1,3-dipole always bonding to the sp hybridized carbon of the allenic function.[22] This is an interesting point since a lower regioselectivity has been found for benzonitrile and 4-chlorobenzonitrile oxides.[6] Finally, a brief comment is due to the syn/anti selectivity of the β,γ cycloadditions. The observed distribution of the isomers corresponds to a preferred attack of **1** to the less encumbered side of the β,γ double bond.

Experimental Section

Melting points were taken on a Buchi apparatus and are uncorrected. NMR spectra were obtained on Varian HA-100 and XL-100 instruments for the ^1H and ^{13}C nucleus, respectively; chemical shifts are reported in ppm from internal Me_4Si and refer to deuteriochloroform solutions. Infrared spectra were recorded on a Perkin-Elmer 377 spectrophotometer. Mass spectra were determined on a Varian MAT 112 spectrometer at 70 eV (direct insertion).

Compounds **1**[23] and **2a**[21] were prepared according to the literature methods.

Reaction of 1 with 2a. A solution of **1** (6.25 g) and **2a** (3.6 g) in carbon tetrachloride (270 mL) was refluxed for 8 h. The solvent was removed, and the residue was chromatographed on a silica gel column (900 g) with benzene as the eluent. First fractions gave 3,3′-bis(3,5-dichloro-2,4,6-trimethylphenyl)-5-phenoxy-4,5′-spirobis(2-isoxazoline) (**5**) (3.06 g): mp 199–200 °C (from *n*-hexane–chloroform); NMR δ 1.88 (6 H, s), 2.22 (3 H, s), 2.47, 2.52, 2.58 (9 H, three singlets), 2.95, 3.90 (2 H, AB type, J = 19 Hz),[24] 6.17 (1 H, s), 7.0–7.5 (5 H, m);[13]C NMR δ 17.5–19.4 (set of quartets), 40.3 (t), 100.0 (s), 103.0 (d), 116.7 (d), 123.6 (d), 124.8 (s), 126.7 (s), 129.8 (d), 132.7–136.6 (set of singlets), 155.4 (s), 157.3 (s), 157.6 (s).[28] Anal. Calcd for $C_{29}H_{26}Cl_4N_2O_3$: C, 58.80; H, 4.39; N, 4.72. Found: C, 58.58; H, 4.40; N, 4.64.

Subsequent fractions gave (*Z*)-3-(3,5-dichloro-2,4,6-trimethylphenyl)-4-phenoxymethylene-2-isoxazoline (**3a**) (3.55 g): mp 140 °C (from cyclohexane); NMR δ 2.30 (6 H, s), 2.52 (3 H, s), 5.32 (2 H, d, J = 3.8 Hz), 6.48 (1 H, t, J = 3.8 Hz), 6.8–7.4 (5 H, m); MS m/e (rel intensity) 361 (37), 332 (7), 302 (6), 268 (100). Anal. Calcd for $C_{19}H_{17}Cl_2NO_2$: C, 63.00; H, 4.73; N, 3.86. Found: C, 63.21; H, 4.81; N, 3.74.

Further elution provided **4a** (1.48 g): mp 102 °C (from diisopropyl ether); NMR δ 2.28 (6 H, s), 2.50 (3 H, s), 5.26 (2 H, d, J = 2.9 Hz), 6.4–6.7 (3 H, overlapping signals), 6.9–7.4 (3 H, m); MS m/e (rel intensity) 361 (21), 332 (5), 302 (6), 268 (100). Anal. Calcd for $C_{19}H_{17}Cl_2NO_2$: C, 63.00; H, 4.73; N, 3.86. Found: C, 63.10; H, 4.60; N, 3.79.

3-Phenoxy-1,2-butadiene (2b). A solution of 3-phenoxy-1-butyne (1.6 g) and potassium *tert*-butoxide (1.2 g) in *tert*-butyl alcohol (100 mL) was refluxed for 4 h. After it was cooled, the mixture was poured into water and extracted with pentane. The organic solution was washed several times with water, dried over sodium sulfate, and evaporated under reduced pressure to give essentially pure **2b** as a viscous oil (1.2 g): IR (film) 1960 cm^{-1}; NMR δ 1.98 (3 H, t, J = 3 Hz), 5.03 (2 H, q, J = 3 Hz), 6.7–7.2 (5 H, m). Attempted distillation of the product caused decomposition.

Isomerization of 2b. A solution of **2b** (0.30 g) in carbon tetrachloride (20 mL) was refluxed for 24 h. Evaporation of the solvent under reduced pressure gave a viscous oil (0.28 g) containing **8** in 90–95% purity: NMR δ 4.2–4.6 (2 H, complex), 5.10 (1 H, d with further splitting, J = 10.5 Hz), 5.50 (1 H, d with further splitting, J = 16.5 Hz), 6.16 (1 H, dd, J = 16.5 and 10.5 Hz), 6.7–7.4 (5 H, m). Attempted distillation caused decomposition.

Reaction of 1 with 8. A solution of **1** (0.69 g) and **8** (0.22 g) in carbon tetrachloride (30 mL) was refluxed for 24 h. The solvent was removed, and the residue was adsorbed onto a silica gel column (80 g). Elution with benzene gave some uncharacterized material followed by compound **7** (0.38 g): mp 189–190 °C (from *n*-hexane–chloroform); NMR δ 1.92 (6 H, s), 2.30 (6 H, s), 2.46, 2.50 (6 H, two singlets), 3.2–3.8 [4 H, overlapping AB system (J = 19Hz) and AB part of ABX system (J_{AB} = 18 Hz)], 5.10 (1 H, dd, J = 11 and 7.5 Hz), 7.1–7.5 (5 H, m). Anal. Calcd for $C_{30}H_{28}Cl_4N_2O_3$: C, 59.51; H, 4.66; N, 4.63. Found: C, 59.50; H, 4.70; N, 4.40.

Reaction of 1 with 2b. A solution of **1** (6.3 g) and **2b** (4.0 g) in carbon tetrachloride (275 mL) was refluxed for 20 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (900 g) with benzene as the eluent. First fractions gave a solid product (0.4 g) whose NMR spectrum showed a set of singlets at δ 2.0–2.7. Subsequent fractions contained a mixture of two components (A, 1.6 g) which was worked up as described below. Further elution gave some solid material (0.2 g; NMR δ 1.8–2.5) followed by (*E*)-3-(3,5-dichloro-2,4,6-trimethylphenyl)-4-(α-phenoxyethylidene)-2-isoxazoline (**4b**) (2.16 g): mp 125 °C (from diisopropyl ether); NMR δ 1.90 (3 H, t, J = 2.5 Hz), 2.11 (6 H, s), 2.37 (3 H, s), 5.23 (2 H, q, J = 2.5 Hz), 6.25–6.45 (2 H, m), 6.75–7.25 (3 H, m). Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$: C, 63.83; H, 5.10; N, 3.72. Found: C, 63.68; H, 4.90; N, 3.55.

The last eluted product was 3-(3,5-dichloro-2,4,6-trimethylphenyl)-4-(2-hydroxybenzyl)-5-methylisoxazole (**6a**) (2.47 g): mp

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172 °C (from *n*-hexane–benzene); IR (Nujol) 3200 cm^{-1}; NMR δ 1.83 (6 H, s), 2.37 (3 H, s), 2.50 (3 H, s), 3.33 (2 H, s), 5.6 (1 H, broad s), 6.1–7.0 (4 H, m); MS *m/e* (rel intensity) 375 (46), 374 (15), 360 (32), 358 (14), 332 (100), 43 (85). Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$: C, 63.83; H, 5.10; N, 3.72. Found: C, 64.08; H, 5.15; N, 3.50.

The product mixture labeled A was chromatographed on a silica gel column (200 g) by elution with hexane–diisopropyl ether (4:1). First fractions gave **3b** (0.51 g): mp 170 °C (from *n*-hexane–chloroform); NMR δ 1.38 (3 H, t, J = 3.1 Hz), 2.30 (6 H, s), 2.51 (3 H, s), 5.20 (2 H, q, J = 3.1 Hz), 6.8–7.4 (5 H, m). Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$: C, 63.83; H, 5.10; N, 3.72. Found: C, 63.61; H, 5.18; N, 3.54. Subsequent fractions contained **7** (0.98 g).

3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4-(2-methoxybenzyl)-5-methylisoxazole [6b]. Compound **6a** (0.37 g) was dissolved in 0.05 M methanolic sodium methoxide (20 mL) and treated with methyliodide (2.1 g). After the solution was refluxed for 5 h, the solvent was removed under reduced pressure, and the residue was taken up with water and extracted with ether. The organic solution was dried over sodium sulfate and evaporated, and the residue was absorbed onto a silica gel column (30 g). Elution with benzene–ethyl acetate (9:1) gave **6b** (0.18 g): mp 115 °C (from diisopropyl ether); NMR δ 1.85 (6 H, s), 2.43 (3 H, s), 2.54 (3 H, s), 3.39 (2 H, s), 3.60 (3 H, s), 6.3–7.2 (4 H, m); MS *m/e* (rel intensity) 389 (27), 374 (22), 358 (42), 346 (46), 43 (100). Anal. Calcd for $C_{21}H_{21}Cl_2NO_2$: C, 64.62; H, 5.43; N, 3.59. Found: C, 64.67; H, 5.24; N, 3.54.

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Registry No. 1, 13456-86-5; **2a**, 1595-40-0; **2b**, 1595-41-1; **3a**, 70288-44-7; **3b**, 70288-45-8; **4a**, 70288-46-9; **4b**, 70288-47-0; **5**, 70288-48-1; **6a**, 70288-49-2; **6b**, 70288-50-5; **7**, 70288-51-6; **8**, 53960-28-4; 3-phenoxy-1-butyne, 1596-40-3.

Synthesis and Properties of Pyrrolin-2-ones

Josefina T. Baker[1] and Stylianos Sifniades*

Corporate Research Center, Allied Chemical Corp., Morristown, New Jersey 07960

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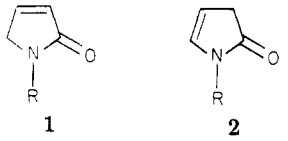
We were interested in the synthesis of Δ^3-pyrrolin-2-one (**1a**) as a potential monomer but were somewhat puzzled



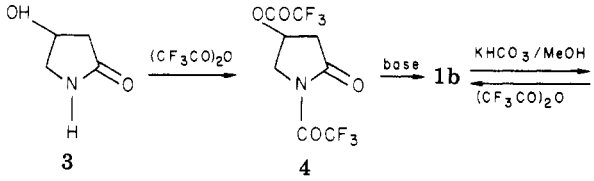
1 2

a, R = H
b, R = $COCF_3$
c, R = CH_3

by the conflicting properties attributed to this compound in the literature.

Langebeck and Boser[2] reported a preparation of **1a** that melted at 140 °C. This material was obtained from the hydrazinolysis of methyl 4-phthalimidocrotonate followed by the ring closure of the presumed methyl 4-aminocrotonate intermediate. Rapoport and Bordner[3] assigned structure **1a** for the material, mp 165 °C, obtained from the decarboethoxylation of *N*-(ethoxycarbonyl)-Δ^3-pyrrolin-2-one. The latter compound was hydrolyzed in dilute NaOH, acidified, and then sublimed. Bocchi et al.[4] synthesized a mixture of Δ^3- and Δ^4-pyrrolin-2-ones, **1a** and **2a**, respectively, by oxidation of pyrrole with aqueous hydrogen peroxide in 25–30% yield. The mixture consisted of nine parts **1a** and one part **2a** as analyzed by ^1H NMR. The isomeric mixture was a viscous, white, and hygroscopic liquid similar to the compound prepared by Grob and Ankli,[5] by hydrolysis and decarboxylation of 4-(ethoxycarbonyl)-Δ^4-pyrrolin-2-one, to which structure **2a** was assigned. We have repeated and confirmed the work of Bocchi's group. Furthermore, we were able to isolate pure **1a** from the mixture of isomers by preparative liquid chromatography and low-temperature crystallization. To a limited extent, we were able to follow the interconversion of the two isomers.

A new synthesis of **1a** and **2a** was carried out in 30–35% overall yield starting from methyl 4-bromocrotonate. Reaction of this material with potassium phthalimide gave methyl 4-phthalimidocrotonate,[6] which upon acid hydrolysis produced 4-amino-3-hydroxybutyric acid.[7] Cyclization of the amino acid yielded 4-hydroxypyrrolidin-2-one (**3**).[8] **3** was trifluoroacetylated completely to *N*,*O*-bis(trifluoroacetyl)-4-hydroxypyrrolidin-2-one (**4**). Base treatment of **4** readily gave *N*-(trifluoroacetyl)-Δ^3-pyrrolin-2-one (**1b**). This structure was assigned based on comparison with the ^1H NMR and ^{13}C NMR spectra of the unsubstituted pyrrolin-2-ones. Hydrolysis of **1b** with methanolic $KHCO_3$ gave the isomeric mixture of **1a** and **2a**. This mixture has properties similar to the pyrrolinones prepared from the peroxide oxidation of pyrrole.



3 4

1a + 2a

Δ^3-Pyrrolin-2-one (**1a**, 99.5% pure) is a very pale yellow material that melts at 23–27 °C. We were not successful in obtaining Δ^4-pyrrolin-2-one (**2a**) in purity greater than 84% because of fast isomerization. Neat samples were stored at −10 and 24 °C and analyzed quickly by ^1H NMR at 24 °C for isomer composition. **1a** (99.5%) remained essentially unchanged after storing for 27 days at −10 °C. Under these conditions enriched **2a** (74%) isomerized to nine parts **1a** and one part **2a**. **1a** was unstable at 24 °C. The isomer ratio was half-way to the equilibrium composition after 1 day. This point, a 9:1 mixture of **1a** and **2a**, was finally reached after 14 days at 24 °C.

The isomerization occurred via tautomerization to the enol as evidenced by the accelerated isomerization and concurrent deuterium–hydrogen exchange in positions 3 and 5 in CH_3OD solution in the presence of a base catalyst.

N-Methylpyrrolin-2-ones **1c** and **2c** were also prepared by the peroxide oxidation of *N*-methylpyrrole. Like the unsubstituted pyrrolin-2-ones an equilibrium isomer ratio of nine parts Δ^3 to one part Δ^4 was also obtained. As would be expected, the replacement of the amide hydrogen with an electron-donating methyl group decreased the acidity

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