Addition of Nitrile Oxides to Benzocyclobutene. Generation of 3-(*p*-Methoxyphenyl)benzo[3,4]cyclobuta[1,2-*d*]isoxazole, a Heterocyclic Analogue of Biphenylene

By **Thomas L. Gilchrist, Eric E. Nunn,** and **Charles W. Rees,*** The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

1,3-Dipolar cycloaddition to cyclobutadienes has been observed for the first time in the reaction of benzocyclobutene with benzonitrile oxides; the products, 3-aryl-3a,7b-dihydrobenzo[3,4]cyclobuta[1,2-*d*]isoxazoles (1), were isolated in good yields. Adducts were not obtained from cyclobutadiene or benzocyclobutene with several other 1,3-dipolar reagents; possible reasons for this are discussed. Monobromination of the 3-*p*-methoxyphenyl adduct (1c) followed by dehydrobromination with potassium t-butoxide gave 3-(*p*-methoxyphenyl)benzo[3,4]-cyclobuta[1,2-*d*]isoxazole (2) as a transient intermediate which rapidly formed the t-butyl alcohol 3a,7b-addition product (6).

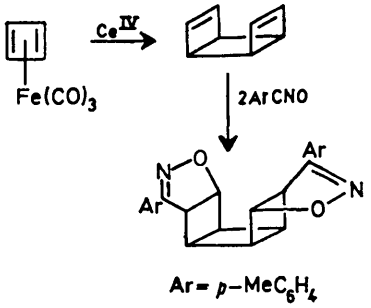
CYCLOBUTADIENE and benzocyclobutene, when generated by the oxidation of their iron tricarbonyl complexes,[1] can participate as the two-electron components in Diels–Alder reactions.[2] Corresponding reactions involving their cycloaddition to 1,3-dipoles have not been reported.

[1] (*a*) R. Pettit and J. Henery, *Org. Synth.*, 1970, **50**, 21; (*b*) G. F. Emerson, L. Watts, and R. Pettit, *J. Amer. Chem. Soc.*, 1965, **87**, 131.

[2] M. P. Cava and M. J. Mitchell, 'Cyclobutadiene and Related Compounds,' Academic Press, New York, 1967.

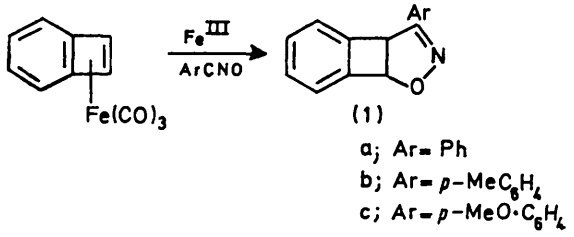
Since such reactions can in principle provide a route to new five- and seven-membered heterocyclic systems, an investigation of the potential of the dipolar additions was undertaken.

Cyclobutadiene was generated from its iron tricarbonyl complex by oxidation with cerium(IV) ammonium nitrate, in the presence of a range of 1,3-dipolar reagents. With benzyl azide, phenyl azide, and 3-methyl-2,4-diphenyl-1,3-oxazolium-5-olate, only the *syn*- and *anti*-dimers of cyclobutadiene were detected; these are also the products formed in the absence of an external reagent.[3] With *p*-toluonitrile oxide, an additional product was isolated (15%) which, from its analysis, mass spectrum, and other physical evidence, was adjudged to be a 2 : 2 adduct of the nitrile oxide with cyclobutadiene. This is probably formed from *syn*-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene, the major dimer of cyclobutadiene,[3] by cycloaddition of the nitrile oxide to both double bonds (Scheme 1). The direction of addition of the nitrile oxide units was not determined.



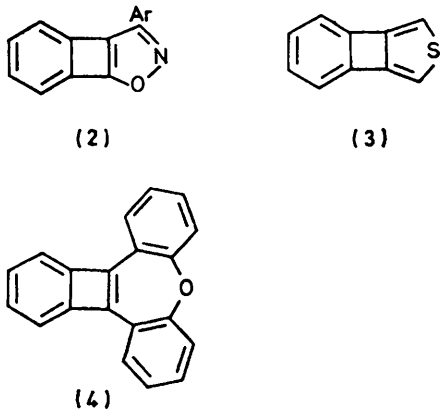
SCHEME 1

When corresponding reactions were performed with benzocyclobutene, 1 : 1 cycloadducts could be isolated in good yields. The structures (1) for the adducts (Scheme 2) were supported by analytical data and by the n.m.r. spectra, which showed the signals expected for the two methine protons as doublets (J 4·5 Hz). No adducts were detected, however, when benzocyclobutenetricarbonyliron was oxidised in the presence of phenyl azide, benzonitrile *N*-phenylimide, or α-(*p*-tolyl)benzylideneamine *N*-oxide.



SCHEME 2

The adducts (1) are dihydro derivatives of a heterocyclic analogue of biphenylene, the 3-arylbenzo[3,4]cyclobuta[1,2-*d*]isoxazole system (2). Such analogues are of theoretical interest because their stability should depend on the degree of cyclobutadienoid character in

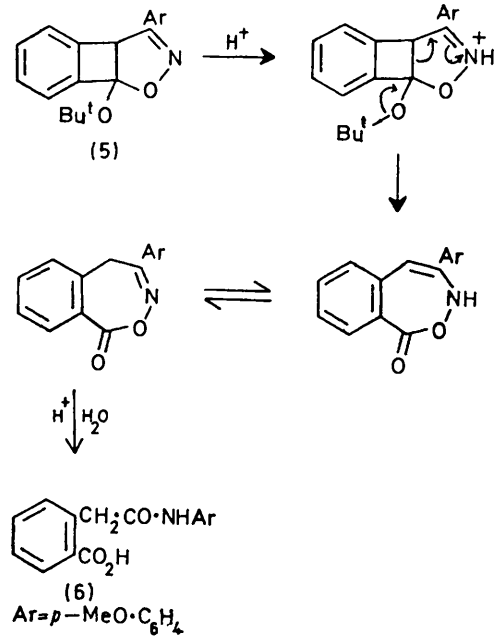


the central four-membered ring, as is the case with annulated biphenylenes.[2] Few such compounds are known; Garratt and Vollhardt have described the synthesis and properties of benzo[3,4]cyclobuta[1,2-*c*]-thiophen (3),[4] the stability of which contrasts with the instability of the oxahomobiphenylene derivative (4) generated by Cava and Buck.[5] Accordingly, a synthesis of a derivative of the benzocyclobuta[1,2-*d*]isoxazole system from the adduct (1c) was undertaken.

Bromination of the adduct (1c) with 2 mol. equiv. of *N*-bromosuccinimide gave the monobromo-derivative (7) as the major product; attempts to produce a dibromo-derivative by using a larger excess of *N*-bromosuccinimide or longer reaction times gave the same monobromo-derivative but in reduced yield. The structure (7) was assigned on the basis of its n.m.r. spectrum, which showed a singlet for the C-7b proton at τ 3·98 [*cf.* τ 3·92 for H-7b in (1c)]. The bromo-derivative (7) did not react with 1,5-diazabicyclo[4.3.0]non-5-ene and reacted only slowly with ethanolic sodium ethoxide. The poorly nucleophilic base lithium 2,2,6,6-tetramethylpiperidide [6] gave only polymeric material. With potassium t-butoxide in tetrahydrofuran a t-butoxy-derivative was isolated which showed a singlet in the n.m.r. spectrum at τ 5·03, corresponding to the C-3a proton signal of the parent system (1c) (τ 4·74). On this basis, and from its analytical data the t-butoxy-derivative was assigned the structure (5). This was further supported by its hydrolysis with trifluoroacetic acid to 2-(*p*-methoxyphenylcarbamoylmethyl)benzoic acid (6). An authentic specimen of the amide (6) was prepared from homophthalic anhydride and *p*-anisidine. The hydrolysis of the derivative (5) probably follows the course shown in Scheme 3, involving protonation at nitrogen, opening of the four-membered ring, and Beckmann rearrangement.

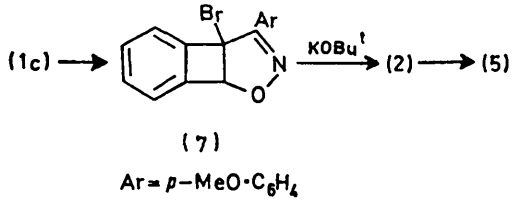
[3] E. K. G. Schmidt, L. Brener, and R. Pettit, *J. Amer. Chem. Soc.*, 1970, **92**, 3240.
[4] P. J. Garratt and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1972, **94**, 7087.
[5] M. P. Cava and K. T. Buck, *J. Amer. Chem. Soc.*, 1973, **95**, 5805.
[6] R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, 1973, **95**, 582.

The conversion of the 3a-bromo-derivative (7) into the 7b-t-butoxy-compound (5) can be rationalised if the benzo[3,4]cyclobuta[1,2-*d*]isoxazole (2; Ar = *p*-MeO·C_6H_4) is an intermediate (Scheme 4). Similar reactions



SCHEME 3

of bromodihydrobenzocyclobutenes with potassium t-butoxide have been observed before, and both benzocyclobutene derivatives [7] and carbenium ions [8] have been suggested as intermediates. The direction of addition of t-butyl alcohol observed in the present work rules out the second mechanism but is consistent with the first. The intermediate (2) could not be intercepted as a Diels–Alder adduct with cyclopentadiene or with 1,3-diphenylisobenzofuran.



SCHEME 4

The evident instability of the benzo[3,4]cyclobuta-[1,2-*d*]isoxazole system (2) is in accord with present understanding of factors affecting the stability of biphenylene analogues. In the stable benzo[3,4]cyclobuta[1,2-*c*]thiophen (3), bond localisation in the five-membered ring (as shown by reactions reflecting 'olefinic' character) results in minimal disruption of delocalisation in the fused benzene ring. In (2) and in the oxahomobiphenylene derivative (4), bond fixation in the heterocyclic ring inhibits delocalisation in the benzene ring, resulting in marked instability.

The failure of cyclobutadiene and benzocyclobutene to form cycloadducts with other 1,3-dipoles is clearly a limitation on the synthetic versatility of the reaction. Both compounds exist only as transient intermediates in solution and their reaction with external reagents must always compete with dimerisation. Many dienes are sufficiently reactive to compete effectively and to form Diels–Alder adducts. In contrast, the 1,3-dipoles appear to be either too unreactive or too short-lived to intercept the intermediates, nitrile oxides being the sole exception found so far.

Recently, perturbation molecular orbital theory has been used effectively to account for relative reactivities in Diels–Alder [9] and 1,3-dipolar [10] cycloadditions. Essentially, the theory emphasises the importance of the interactions of the frontier molecular orbitals of the reactants, the strength of the interactions depending on the energy separations of the HOMO of one component and the LUMO of the other. The smaller of these two energy separations determines which is the dominant interaction in the cycloaddition. Cyclobutadiene derivatives are unique among the two-electron components in having a high energy HOMO and a low energy LUMO. Among the isolable 1,3-dipoles, nitrile oxides have a relatively high energy HOMO (this being raised by aryl substitution) and a relatively low energy LUMO,[10] which must allow sufficiently strong interaction with the frontier orbitals of benzocyclobutene (but not of cyclobutadiene) to enable the cycloaddition to compete with dimerisation.

EXPERIMENTAL

I.r. spectra are recorded for Nujol mulls. Preparative layer chromatography was performed with Kieselgel G (Merck) as support.

Tricarbonylcyclobutadieneiron.—The complex was prepared from *cis*-3,4-dichlorocyclobutene and nonacarbonyldi-iron by the method of Pettit and Henery.[12a]

Benzocyclobutenetricarbonyliron.— Nonacarbonyldi-iron (120 g, 0·33 mol) was added in portions during 1 h to a solution of *trans*-1,2-dibromo-1,2-dihydrobenzocyclobutene (26·2, 0·1 mol) and bromoform (1 g) in pentane (500 ml) heated under nitrogen. The mixture was then filtered and the solvent removed from the filtrate. Pentacarbonyliron was removed by distillation at 25° and 0·02 mmHg. The residue was taken up in petroleum and was filtered through Florisil. Dodecarbonyltri-iron crystallised from the filtrate and was removed. The remainder was distilled and gave benzocyclobutenetricarbonyliron as a red oil (4·0 g, 17%), b.p. 63—64° at 0·02 mmHg (lit.,[12b] 73—78° at 0·1 mmHg), which rapidly crystallised on cooling.

Tricarbonylcyclobutadieneiron and p-*Toluonitrile Oxide.*— To tricarbonylcyclobutadieneiron (192 mg, 1 mmol) in acetone (15 ml) was added a solution of freshly prepared *p*-

[7] M. P. Cava and A.-F. C. Hsu, *J. Amer. Chem. Soc.*, 1972, **94**, 6441.
[8] E. Muller, H. Fettel, and M. Sauerbier, *Synthesis*, 1970, **2**, 82.
[9] R. Sustmann, *Tetrahedron Letters*, 1971, 2717, 2721.
[10] K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Amer. Chem. Soc.*, 1973, **95**, 7287; K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, p. 7301.

toluonitrile oxide [11] (655 mg, 5 mmol) in ether (15 ml). Cerium(IV) ammonium nitrate (3 g) was then added and the mixture was stirred at 0° until no more carbon monoxide was being evolved. Water (50 ml) was added and the mixture was shaken with chloroform (3 × 25 ml). The organic solution was washed with water, dried, and evaporated, and the residue was applied to a silica-coated plate (100 × 25 × 0·1 cm). Chromatography (benzene–ether, 10 : 1) gave, besides products derived solely from the nitrile oxide, a 2 : 2 *adduct* of unknown stereochemistry, m.p. 194—195° (Found: C, 77·2; H, 6·1; N, 7·4. $C_{24}H_{22}N_2O_2$ requires C, 77·8; H, 5·95; N, 7·6%); τ ($CDCl_3$) 7·63 (6H), 6·73 (4H, m), 5·24 (2H, d, *J* 6 Hz), 4·34 (2H, d, *J* 6 Hz), and 2·5—3·0 (8H, m); *m/e* 370 (M^+). Similar oxidations in the presence of benzyl azide, phenyl azide, and 3-methyl-2,4-diphenyl-1,3-oxazolium-5-olate, resulted in the recovery of these compounds. No adducts were detected.

Cycloadditions to Benzocyclobutene.—(a) 3a,7b-*Dihydro*-3-*phenylbenzo*[3,4]*cyclobuta*[1,2-d]*isoxazole* (1a). Benzocyclobutenetricarbonyliron (484 mg, 2 mmol) and triethylamine (303 mg, 3 mmol) were stirred in acetone (25 ml) at 0°. Benzohydroxamoyl chloride [12] (465 mg, 3 mmol) in ether (10 ml) was then added, followed by iron(III) nitrate heptahydrate (24 g). After 15 min the mixture, diluted with cold water (100 ml), was shaken with ether (3 × 25 ml). The ethereal solution was washed with water, dried, and evaporated. The product was purified by layer chromatography (silica; benzene) which gave the *adduct* (1a) (286 mg, 65%), m.p. 126—127° (prisms from ether–hexane) (Found: C, 81·6; H, 5·2; N, 6·4. $C_{15}H_{11}NO$ requires C, 81·4; H, 5·0; N, 6·3%); $\nu_{max.}$ 1356m, 884s, 738m, and 691m cm^{-1}; $\lambda_{max.}$ (EtOH) 263·5 (ε 10,800), 268·5 (11,250), and 275 nm (10,500); τ ($CDCl_3$) 4·73 (1H, d, *J* 4·5 Hz, H on C-3a), 3·90 (1H, d, *J* 4·5 Hz, H on C-7b), and 2·1—2·8 (9H, m); *m/e* 221 (M^+), 193 (M^+ — CO), 118 (base peak, M^+ — PhCN), and 102 (M^+ — PhCNO).

(b) 3a,7b-*Dihydro*-3-p-*tolylbenzo*[3,4]*cyclobuta*[1,2-d]*isoxazole* (1b). This was prepared by the procedure described in (a), from benzocyclobutenetricarbonyliron (242 mg, 1 mmol) and *p*-toluonitrile oxide (400 mg, 3 mmol). Crystallisation gave needles of the *product* (1b) (120 mg, 51%), m.p. 129—130° (from hexane) (Found: C, 81·5; H, 5·5; N, 5·8. $C_{16}H_{13}NO$ requires C, 81·7; H, 5·6; N, 5·95%); $\nu_{max.}$ 1376s, 880s, and 730s cm^{-1}; $\lambda_{max.}$ (EtOH) 263·5 (ε 13,200), 269 (14,500), and 275 nm (14,050); τ ($CDCl_3$) 7·65 (3H), 4·76 (1H, d, *J* 4·5 Hz, H on C-3a), 3·96 (1H, d, *J* 4·5 Hz, H on C-7b), and 2·2—2·9 (8H, m); *m/e* 235 (M^+), 207 (M^+ — CO), 118 (base peak, M^+ — C_7H_7CN), and 102 (M^+ — C_7H_7CNO).

(c) 3a,7b-*Dihydro*-3-p-*methoxyphenylbenzo*[3,4]*cyclobuta*[1,2-d]*isoxazole* (1c). This was prepared by the procedure described in (a) from benzocyclobutenetricarbonyliron (242 mg, 1 mmol) and *p*-methoxybenzonitrile oxide [13] (448 mg, 3 mmol). Crystallisation gave needles of the *product* (1c) (165 mg, 66%), m.p. 154·5—155·5° (Found: C, 76·6; H, 5·0; N, 5·5. $C_{16}H_{13}NO_2$ requires C, 76·5; H, 5·2; N, 5·6%), $\nu_{max.}$ 1516m, 1250s, 880s, 836s, and 732s cm^{-1}; $\lambda_{max.}$ (EtOH) 271 (ε 13,300) and 276 nm (14,500); τ ($CDCl_3$) 6·18 (3H), 4·73 (1H, d, *J* 4·5 Hz, H on C-3a), 3·92 (1H, d, *J* 4·5 Hz, H on C-7b), and 2·15—2·85 (8H, m); *m/e* 251 (M^+), 221, 118 (base peak), and 102.

3a-*Bromo*-3a,7b-*dihydro*-3-p-*methoxyphenylbenzo*[3,4]-*cyclobuta*[1,2-d]*isoxazole* (7).—The adduct (1c) (1·25 g, 5 mmol) and recrystallised *N*-bromosuccinimide (1·79 g, 10 mmol) were dissolved in tetrachloromethane (150 ml) and the solution was irradiated and heated under reflux for 1 h by means of a sunlamp (300 W). The mixture was then cooled and filtered, and the filtrate was evaporated to dryness. The residue was boiled with ether and the ether-soluble fraction applied to a chromatography column (silica). Elution with benzene gave the *bromo-derivative* (7) (0·60 g, 36%), m.p. 147—148° (from hexane) (Found: C, 58·4; H, 3·8; N, 4·3. $C_{16}H_{12}BrNO_2$ requires C, 58·2; H, 3·7; N, 4·2%); τ ($CDCl_3$) 6·17 (3H, *O*-Me), 3·98 (1H, H on C-7b), and 2·05—3·15 (8H, m); *m/e* 329 (M^+), 250 (M^+ — 79), 176, and 89 (base peak).

Reaction of the Bromo-compound (7) *with Potassium t-Butoxide.*—To the bromo-compound (7) (100 mg, 0·3 mmol) in tetrahydrofuran (5 ml) was added potassium t-butoxide (49 mg, 0·41 mmol) in tetrahydrofuran (10 ml) under nitrogen. After 1 h the mixture was poured into water (50 ml) and shaken with ether (3 × 20 ml). The organic fraction was applied to a preparative chromatography plate (Kieselgel G). Elution with benzene gave the bromo-compound (7) (58 mg, 58%) and also 3a,7b-*dihydro*-3-p-*methoxyphenyl*-7b-*t-butoxybenzo*[3,4]*cyclobuta*[1,2-d]*isoxazole* (5) (33 mg, 79% based on material consumed), m.p. 128° (Found: C, 73·8; H, 6·6; N, 4·3. $C_{20}H_{21}NO_3$ requires C, 74·3; H, 6·55; N, 4·3%); τ ($CDCl_3$) 8·52 (9H), 6·16 (3H), 5·04 (1H, H on C-3a), and 2·2—3·1 (8H, m); *m/e* 323 (M^+) and 267 (M^+ — C_4H_8, base peak).

A qualitative experiment using a large excess of potassium t-butoxide and a reaction time of 2 min resulted in complete conversion of the bromo-compound into the t-butoxy-derivative (5).

Hydrolysis of the t-Butoxy-compound (5).—The t-butoxy-derivative (30 mg) was dissolved in aqueous trifluoroacetic acid (90%; 5 ml) and the solution kept at room temperature for 5 min. It was then diluted with water and the precipitate was dried (19 mg). Crystallisation gave 2-(p-*methoxyphenylcarbamoylmethyl*)*benzoic acid* (6) (10 mg, 38%), m.p. 176° (from ethanol) (Found: C, 67·1; H, 5·3; N, 5·1. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3; N, 4·9%), $\nu_{max.}$ (Nujol) 3320 (NH), 1705, and 1663 (C=O) cm^{-1}; *m/e* 285 (M^+) and 123 ($C_7H_9NO^+$, base peak). A specimen of the compound prepared by the reaction of *p*-anisidine with homophthalic anhydride had m.p. and mixed m.p. 176°.

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[11] A. Dondoni and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna*, 1967, **25**, 155; C. Grundmann and P. Grunager, ' The Nitrile Oxides,' Springer-Verlag, Berlin, 1971, p. 17.

[12] A. Werner and H. Buss, *Ber.*, 1894, **27**, 2193.

[13] A. Dondoni,. A. Mangini, and S. Ghersetti, *Tetrahedron Letters*,1966, 4789; C. Grundmann and P. Grunager, ' The Nitrile Oxides,' Springer-Verlag, Berlin, 1971, p. 18.