

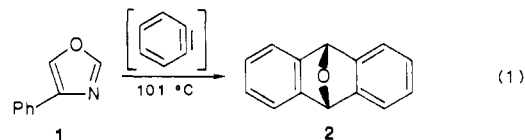
Acknowledgment. We thank the National Science Foundation and the Office of Naval Research for supporting this work.

Supplementary Material Available: Elemental analyses and spectroscopic data of hosts 1 and 2, experimental details of the temperature-dependent binding studies and of the crystal structure determination, and crystal data tables of atomic coordinates, equivalent isotropic thermal parameters, anisotropic thermal parameters, hydrogen positional parameters, and details of the molecular geometry for 1 as a diiodide (8 pages). Ordering information is given on any current masthead page.

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was carried out in refluxing dioxane (101 °C). At this temperature rapid retro-Diels–Alder loss of nitrile occurs, followed by addition of a second benzyne to the intermediate (isobenzofuran), to form the 2:1 adduct. This overall process appears to be relatively insensitive to substituents (H, alkyl, aryl) on the oxazole. For example, when subjected to the Reddy–Bhatt⁴ conditions (anthranilic acid + RONO, 101 °C), we find that 4-phenyloxazole⁵ (1) gives the 2:1 adduct 2⁶ in good yield (53% recrystallized).



Various limitations surface when low temperature formation of benzyne is addressed. The anthranilic acid method, because of thermal stability (in solution) of the intermediate diazonium carboxylate, requires a temperature well above ambient. Strong base induced methods are not suitable for 2-unsubstituted oxazoles.⁷ The 1-aminobenzotriazole (ABT)–Pb(OAc)₄ method developed by Campbell and Rees⁸ was especially attractive since it had been shown to produce benzyne rapidly even at –78 °C and, alone of the benzyne procedures considered, it gives high yields of biphenylene when carried out in the absence of other reactants.⁸ Biphenylene formation, even if diffusion controlled,^{9,10} requires that the (steady state) concentration of benzyne reach a level⁹ not attained, because of the intervention of various side reactions, in alternative procedures.

The Rees procedure⁸ calls for dropwise addition of ABT to a mixture of substrate and Pb(OAc)₄, and good yields of cycloadduct have been obtained by using this approach with very reactive dienes. The method is also satisfactory with less reactive dienes such as furan when these substrates can be employed in large excess (e.g. as solvent).¹¹

Slow (syringe pump) addition of a CH₂Cl₂ solution of ABT (ca. 1 molar equiv) to an equimolar mixture of 1 and Pb(OAc)₄ in the same solvent at 0 °C gave a crude product that contained (by NMR) substantial amounts of starting material and biphenylene. This disappointing result could be construed merely as signifying an unfavorable activation energy for the cycloaddition of benzyne with 1, but this would be an oversimplification. In fact 1 is highly competitive for reaction with benzyne when the process is given equal opportunity; problems arise instead because an alternative pathway for consumption of benzyne (dimeri-

Isolation of a 1:1 Oxazole–Benzyne Cycloadduct: An Improved Method for Generating Benzyne and a New Approach to Isobenzofuran¹

Summary: A dual syringe pump addition procedure for benzyne generation from 1-aminobenzotriazole with Pb(OAc)₄ is applied to 4-phenyloxazole at 0 °C, to give the isolable 1:1 benzyne/oxazole Diels–Alder adduct in essentially quantitative yield; mild solution thermolysis of this adduct gives isobenzofuran.

Sir: Reactions of acetylenic dienophiles with oxazoles form the basis of a useful synthesis of substituted furans.² With one curious exception,³ all such reactions involve facile loss of nitrile from the initially formed Diels–Alder adduct, precluding isolation of this species.

Benzyne is among the most reactive “acetylenic” dienophiles known, and we hoped that its use at low temperature might allow the isolation of such cycloadducts. The single report⁴ of reactions of benzyne with (trisubstituted) oxazoles is not informative on this point, since the reaction

(1) Part of this work was presented at the Third Chemical Congress of North America, Toronto, Canada, June 1988 (ORGN: 466).

(2) (a) Grigg, R.; Hayes, R.; Jackson, J. L. *Chem. Commun.* 1969, 1167. (b) Grigg, R.; Jackson, J. L. *J. Chem. Soc.* 1970, 552. (c) Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.* 1970, 92, 4340. (d) Kondrat'eva, G. Y.; Medvedskaya, L. B.; Ivanova, Z. N.; Shmelev, L. V. *Dokl. Akad. Nauk SSSR* 1971, 200, 1358 (Engl. transl. p 862). (e) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* 1978, 100, 7748. (f) Hutton, J.; Potts, B.; Southern, P. F. *Synth. Commun.* 1979, 9, 789. (g) Gorgues, A.; Le Coq, A. *Tetrahedron Lett.* 1979, 4829. (h) Ansell, M. F.; Caton, M. P. L.; North, P. C. *Tetrahedron Lett.* 1981, 22, 1727. (i) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* 1981, 46, 2065. (j) Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* 1983, 24, 2473.

(3) Crank, G.; Khan, J. R. *J. Heterocycl. Chem.* 1985, 22, 1281. This paper describes the exothermic reaction of various 2-aminooxazoles with DMAD to give 1:1 cycloadducts. NMR data that support the 2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene structures are reported. The isolation of these products is especially interesting given possible alternative reactions such as the (very rapid) Michael-type addition of amines to DMAD (see: George, M. V.; Khetan, S. K.; Gupta, R. K. *Adv. Heterocycl. Chem.* 1976, 19, 279) and recent evidence (see: Chung, Y. S.; Duerr, B. F.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* 1988, 53, 1336) that shows that bridgehead amino anthracene cycloadducts undergo retro-Diels–Alder reaction even more rapidly than their alkoxy analogues. The analogous 2- and 5-alkoxyoxazole 1:1 cycloadducts of acetylenic dienophiles have not been isolated and must expel nitriles rapidly at or below room temperature.^{1a,b} The only other mention of the 1:1 adduct ring system found in a CAS ONLINE partial structure search involves the claim of an intramolecular cycloaddition of a furan diene and nitrile dienophile (Tagmazyan, K. T.; Mkrtychyan, R. S.; Babayan, A. T. *Russ. J. Org. Chem.* 1974, 10, 1657); only IR, mp, and (marginal) N, H analytical data are given, and alternative structural possibilities were not ruled out.

(4) Reddy, G. S.; Bhatt, M. V. *Tetrahedron Lett.* 1980, 21, 3627; simultaneous addition of anthranilic acid and amyl nitrite was used to generate benzyne.

(5) 4-Phenyloxazole was prepared in 41% overall yield from phenacyl bromide and sodium formate, followed by heating with ammonium acetate in HOAc. The general procedure is that of Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* 1937, 2, 328.

(6) Compound 2 has been made previously, by treatment of preformed isobenzofuran with benzyne: Crump, S. L.; Netka, J.; Rickborn, B. *J. Org. Chem.* 1985, 50, 2746.

(7) Oxazoles that bear an H in the 2-position are very rapidly lithiated by RLi. To illustrate, treatment of a mixture 1 and *o*-dibromobenzene with *n*-BuLi followed by D₂O quench gave 2-deuterio-4-phenyloxazole; thus deprotonation occurs more rapidly than Br/Li exchange (compare the reactions of isobenzofuran⁶).

(8) Campbell, C. D.; Rees, C. W. *Proc. Chem. Soc.* 1964, 296; *J. Chem. Soc. C* 1969, 742.

(9) The (gas phase) dimerization of benzyne occurs at or near the diffusion-controlled limit;¹⁰ if a rate constant of $\leq 10^{10}$ mol⁻¹ s⁻¹ for reaction in solution is assumed, the steady state benzyne concentration must be $\geq 10^{-7}$ M to account for the rate (amount per L/time) of biphenylene formed in a typical reaction.

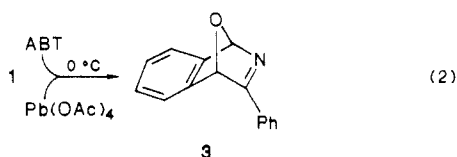
(10) Shafer, M. E.; Berry, R. S. *J. Am. Chem. Soc.* 1965, 87, 4497.

(11) For a novel application of furan and a bis-aminotriazole, see: Hart, H.; Ok, D. *J. Org. Chem.* 1986, 51, 979.

zation in this example) is *artificially* enhanced.

Very fast reactions may occur much more rapidly than bulk diffusion of reactants, even with good stirring, and this can lead to the localized formation of products in high nonequilibrium concentration. Although such mixing phenomena must be fairly common, we are aware of only a few documented instances in which the altered course of reaction can be attributed to this feature.^{12,13} It appeared that the visually very rapid ABT-Pb(OAc)₄ oxidation might exhibit such behavior. A modified procedure was therefore employed, involving the simultaneous¹⁴ introduction of both reagents via two syringes at opposite sides of a magnetically stirred three-neck flask. *This modification dramatically improves the outcome of the reaction with 1 and should be generally useful for benzyne applications.*¹⁶

Thus, CH₂Cl₂ solutions of ABT (ca. 0.3 M, 1.05 equiv) and Pb(OAc)₄ (ca. 0.3 M, 1.1 equiv) were simultaneously added over a period of ca. 0.5 h¹⁷ to an ice-bath cooled CH₂Cl₂ solution (initially 0.5 M) of 1 as shown in eq 2; the

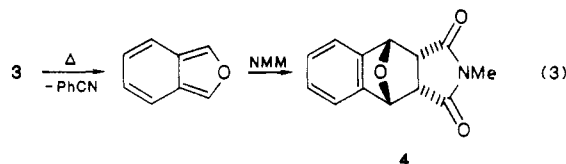


forked arrow signifies concurrent addition. The reaction mixture was promptly washed with base to remove HOAc and Pb(OAc)₂, and the solvent was removed in vacuo at room temperature to furnish a tan solid. This material, formed in essentially quantitative yield, proved to be the 1:1 cycloadduct 3.¹⁸

The (relative) thermal stability of 3 was a pleasant surprise in view of the usual reactivity of analogues noted previously.^{2,4} Solid 3 has been held at room temperature for several days without evidence of decomposition, and it may have a significant shelf life even without refrigeration; it does not seem to be especially sensitive to air.

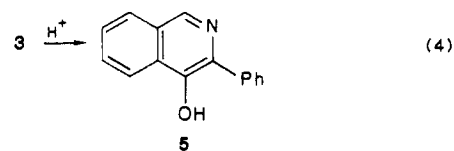
Retro-Diels-Alder reaction of 3 is observed in solution. Rate constants were determined for CDCl₃ solutions that

contained an equivalent of *N*-methylmaleimide (NMM)¹⁹ and Et₃N to prevent acid-catalyzed rearrangement of 3. The reaction of isobenzofuran with NMM is known to be very rapid, and at the temperatures employed gives the product 4 (endo/exo = 88/12), irreversibly.²⁰ The rate constants at 40.6, 61.3, and 69.4 °C are 1.92, 36.3, and 92.9 (all $\times 10^{-6} \text{ s}^{-1}$), respectively. The activation parameters are $\Delta H^\ddagger = 28.1 \text{ kcal}\cdot\text{mol}^{-1}$ and $\Delta S^\ddagger = 5 \text{ cal}\cdot\text{mol}^{-1}\cdot\text{deg}^{-1}$. The small activation entropy term is typical of many retro-Diels-Alder reactions and suggests that expulsion of a nitrile is not extraordinary.



The kinetic study shows that 3 is a convenient source of isobenzofuran used as a reactive intermediate. There is added value in procedures that allow the isolation (in solution) of this very reactive diene.²¹ This potential was tested by heating (80 °C) a 0.1 M benzene solution of 3 for 3 h, followed by cooling and treatment with a slight excess of NMM. The cycloadduct 4 was isolated by column chromatography in 78% yield, which corresponds to the minimum amount of free isobenzofuran present. Polymerization limits the concentration (as well as temperature and time) that can be employed for formation and subsequent use of isobenzofuran, a feature common to all procedures for isolation of this species.²¹ The good yield of solution-isolated isobenzofuran indicates that 3 will be a convenient source for this very reactive diene.

Attempts to purify 3 by silica gel chromatography gave only rearranged material, identified as 3-phenylisobenzofuran-4-ol (5) by comparison of mp and spectral features (IR, NMR) with those reported by Gilchrist et al.²² Slow, presumably acetic acid catalyzed, formation of 5 is also observed if the initially formed solution of 3 is not washed with base soon after formation (eq 2). The formation of 5 can be expedited in solution by the addition of a drop of stronger acid, e.g., trifluoroacetic acid.



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(12) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* 1984, 49, 1477.

(13) Beak, P.; Musick, T. J.; Chen, C. W. *J. Am. Chem. Soc.* 1988, 110, 3538.

(14) Simultaneous addition of anthranilic acid and RONO was first suggested by Friedman and Logullo¹⁵ as a way to limit the thermal decomposition of RONO in higher temperature reactions. Thus the experimental modification has precedent in benzyne generation, although the reasons are quite different than those involved in the present study.

(15) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* 1963, 85, 1549.

(16) The dual syringe pump ABT-Pb(OAc)₄ procedure in the absence of a reactive substrate gives phenyl acetate as the major product while, as expected, the amount of biphenylene is greatly reduced. Phenyl acetate is presumably formed by the addition of acetic acid to benzyne, and acetic acid accumulates as the oxidation proceeds. The prior addition of Et₃N (2 mol per mol of Pb(OAc)₄) prevents the formation of phenyl acetate, but in large part by reacting with benzyne itself (only a trace of cycloadduct of 1 is formed under these conditions). Different oxidants or more hindered bases may be useful in this context.

(17) Very slow addition is not needed and indeed is undesirable when the product is acid sensitive, because the oxidation of ABT with Pb(OAc)₄ is extremely rapid. The benefit of dual syringe pump addition arises from the controlled avoidance of concentration buildup of either reagent, which in turn prevents the development of local excess benzyne concentration.

(18) Compound 3 has the following properties: As obtained directly, it melts with decomposition at 105–110 °C. A light tan sample isolated by filtration followed by –78 °C precipitation from ether/hexane had mp 110–112 °C (open capillary, heating rate ca. 2 °C/min) and the melt had the odor of benzonitrile (tube crushed for this purpose): MS/CI (methane), *m/z* (relative intensity) 222 (P + H, 7.5), 221 (5.8), 120 (5.9), 119 (50.5), 118 (isobenzofuran, 100), 105 (7.4), 104 (77.6), 103 (PhCN, 36.4); NMR (500 MHz, CDCl₃) δ 6.26 (s, 1 H), 6.93 (s, 1 H), 7.05 (t, 1 H, *J* = 7.5 Hz), 7.08 (t, 1 H, *J* = 7.5 Hz), 7.42–7.52 (m, 5 H), and 7.84 ppm (d, 2 H, *J* = 7.5 Hz).

(19) The reaction of 3 with *in situ* NMM leads cleanly to 4, with no other significant products seen in the NMR spectrum. Rate constants were determined by integration of the upfield singlet of 3 and the combined downfield AA'BB' multiplet (endo) and singlet (exo) of 4. Good first-order behavior was observed for reactions followed over more than 3 half-lives.

(20) Tobia, D.; Rickborn, B. *J. Org. Chem.* 1987, 52, 2611.

(21) Rickborn, B. "Isobenzofurans", Chapter I in *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press Inc.: Greenwich, CT, in press.

(22) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* 1975, 1.

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