at 380 nm,[43] $V_{aq} = V_{org} = 50$ μL, and $[H_i^*]$ is the initial concentration of host (0.015 M in these experiments).

$$K_a = R_{CDCl_3}/[(1 - R_{CDCl_3})K_d\{[G_i^+]_{H_2O} - R_{CDCl_3}[H_i^*]_{CDCl_3}(V_{CDCl_3}/V_{H_2O})\}^2]$$

K_a[31] is the association constant corresponding to the equilibrium

$$host_{CDCl_3} + M^+ picrate^-_{CDCl_3} \rightleftarrows M^+ \cdot host \cdot picrate^-_{CDCl_3}$$

K_d is the distribution constant between $CDCl_3$ and water for potassium picrate ($K_d = 2.55 \times 10^{-3}$ M^{-1}) or sodium picrate ($K_d = 1.74 \times 10^{-3}$ M^{-1}).[43]

Acknowledgment. This research was supported by Public Health Service Research Grants GM24951 and GM27137 from the National Institute of General Medical Sciences. L. L. thanks the Central Laboratory of Chemistry, University of Pécs, Pécs Hungary, for a postdoctoral leave of absence.

Registry No. **9**, 112-60-7; **9** monobenzyl ether, 86259-87-2; **10**, 86259-55-4; **11**, 86259-56-5; **14**, 86259-57-6; **15**, 86259-58-7; **17**, 28765-36-8; **20**, 86259-59-8; **22**, 86259-60-1; **23**, 86259-61-2; **24**, 86259-62-3; **27**, 86259-63-4; **28**, 6931-10-8; **29**, 86259-64-5; **30**, 86259-65-6; **31**, 86259-66-7; **33**, 86259-67-8; **34**, 86259-68-9; **35**, 86259-69-0; **36**, 86259-70-3; **37**, 86259-71-4; **38**, 86259-72-5; **39**, 31255-26-2; **40**, 52559-90-7; **43**, 86259-73-6; **44** (R = H), 86259-74-7; **44** (R = CH_2OTHP), 86259-77-0; **45**, 86259-75-8; **46**, 86259-76-9; **48**, 86259-78-1; **49**, 86259-79-2; **51**, 23978-55-4; **52**, 81897-78-1; **53**, 69703-25-9; **54**, 86259-80-5; **55**, 86259-81-6; **56**, 86259-92-9; **59**, 86259-82-7; **60**, 86259-83-8; **61**, 86259-84-9; **61** benzyl derivative, 86259-85-0; **61**-ol benzyl derivative, 86259-86-1; $NaBPh_4$, 143-66-8; *o*-bromoanisole, 578-57-4; *o*-bromophenyl tetrahydropyranyl ether, 57999-46-9; 2-methyl-2-nitropentan-1-ol mesylate, 86259-88-3; *O*-tosyl-*O*-tetrahydropyranyltetraethylene glycol, 86259-89-4; 2-chloromethyl-4-methylanisole, 7048-41-1; 2-bromo-4-methyl-6-(bromomethyl)anisole, 86259-90-7; 2-bromo-4-methyl-6-(hydroxymethyl)anisole, 86259-91-8; bromoacetaldehyde diethyl acetal, 2032-35-1; vinyl bromide, 593-60-2; ethyl bromoacetate, 105-36-2; 2-bromo-4-methylanisole, 22002-45-5; 4-methylanisole, 104-93-8; sebacoyl chloride, 111-19-3; potassium picrate, 573-83-1; sodium picrate, 3324-58-1.

Potent Hydrophilic Dienophiles. Synthesis and Aqueous Stability of Several 4-Aryl- and Sulfonated 4-Aryl-1,2,4-triazoline-3,5-diones and Their Immobilization on Silica Gel

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Received January 25, 1983

The purpose of this investigation is the development of a series of sulfonated 4-aryl-1,2,4-triazoline-3,5-diones (TADs) useful as potent dienophiles for Diels–Alder reactions in aqueous solution and capable of providing a TAD moiety immobilized on an insoluble support. TADs **4**, **5**, **23**, **24**, and **29** were all prepared by oxidation of the corresponding urazoles with N_2O_4. The urazole precursors were prepared by chlorosulfonation of the appropriate 4-arylurazole, followed in some cases by hydrolysis and neutralization. While TAD sulfonic acids **5** and **29** were not stable toward isolation, the presence of the bulky isopropyl groups in **23** and **24** rendered these TADs isolable in pure form and sufficiently stable in water to allow Diels–Alder reactions to compete successfully with attack on the TAD moiety by the solvent (see following paper). Urazolesulfonyl chlorides **2**, **18**, and **19** reacted with aminopropylsilylated silica gel **31** to give the corresponding immobilized sulfonamides, which were readily oxidized to TAD silica gels **33** (red) and **34** (purple). TAD acid **23** and **31** gave silica gel **35** in which the TAD moiety was attached to the gel via an ionic bond. 1,3-Dienes were selectively and quantitatively removed from solution by these silica gels and could be recovered quantitatively therefrom.

1,2,4-Triazoline-3,5-diones (TADs) are among the most reactive dienophiles known for the Diels–Alder reaction.[1,2] Inert solvents such as benzene and CH_2Cl_2 are normally used, owing to the incompatibility of the TAD moiety with hydroxylic solvents. 4-Phenyl TAD, for example, decomposes rapidly in water[3] and alcohols,[4] the initial attack of the solvent postulated as being at one of the carbonyl groups of the TAD. In connection with the development[5] of a new class of 1,3-diene-containing detergents that can be modified by a Diels–Alder reaction under mild *aqueous* conditions,[6] we undertook to develop water soluble TADs that were sufficiently stable in water to allow a Diels–Alder reaction to compete successfully with decomposition. The new sulfonated 4-aryl TADs herein described not only fulfill this requirement but also permit for the first time the immobilization[7] of the TAD moiety on an insoluble matrix such as silica gel.[8] The resulting colorful TAD-

(1) Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. *Org. Synth.* **1971**, *51*, 121.
(2) Burrage, M. E.; Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1325.
(3) Wamhoff, H.; Wald, K. *Chem. Ber.* **1977**, *110*, 1699.
(4) Le Doe, H.; Mackay, D. *J. Chem. Soc., Chem. Commun.* **1976**, 326.
(5) Keana, J. F. W.; Guzikowski, A. P.; Morat, C.; Volwerk, J. J. *J. Org. Chem.* following paper in this issue.
(6) Few examples of Diels–Alder reactions in aqueous solution are available. Recently, Rideout and Breslow (Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816) have observed rate enhancements for certain Diels–Alder reactions run in aqueous solvent as compared with organic solvents.
(7) The immobilization of reagents or substrates on an insoluble inorganic (McKillop, A.; Young, D. W. *Synthesis* **1979**, 401 and 481) or organic (Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557) matrix is a widely exploited technique.
(8) Silica gel has served as a support, for example, for inductrially important catalysts (Yermakov, Yu. I.; Kuznetsov, B. N.; Zakharov, V. A. "Catalysis by Supported Complexes", Elsevier, New York, 1981), phase-transfer catalysis (Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1981**, *103* 856), and the automated synthesis of deoxyoligonucleotides (Matteucci, M. D.; Caruthers, M. H. *J. Am. Chem. Soc.* **1981**, *103*, 3185).

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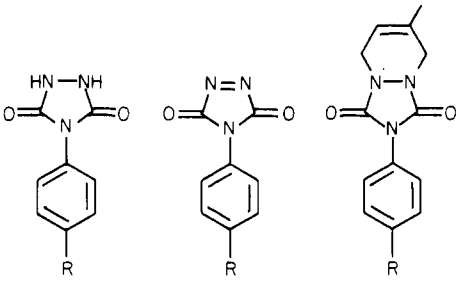
derivatized silica gels are shown to remove selectively 1,3-diene containing substrates quantitatively from solution, and the dienes may be recovered therefrom.

Results and Discussion

A. Synthesis of the Sulfonated 4-Aryl-1,2,4-triazoline-3,5-diones. Our first objective was the sulfonated[9] 4-phenyl TAD 5. Treatment of 4-phenylurazole (1) with

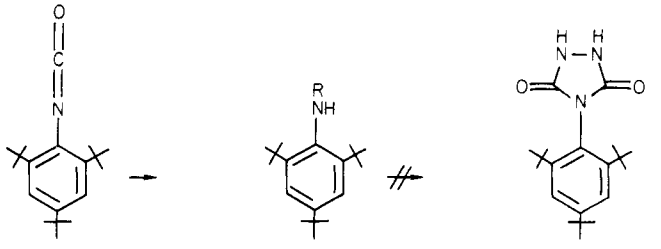


1, R = H
2, R = SO_2Cl
3, R = SO_3H
4, R = SO_2Cl
5, R = SO_3H
6, R = SO_2Cl
7, R = SO_3H

neat $ClSO_3H$ at 60 °C gave sulfonyl chloride 2 (68%). The sulfonic acid 3 (92%) was readily prepared from 2 by hydrolysis in water at 50 °C. Oxidation of 2 with N_2O_4 in CH_2Cl_2 gave TAD 4 (91%) as a bright red crystalline solid. Addition of isoprene to a CH_2Cl_2 solution of 4 at 0 °C instantly gave the adduct 6.

TAD sulfonic acid 5, however, proved more elusive. Exposure of a suspension of 3 in CH_2Cl_2 to N_2O_4 at 25 °C gave a red solid that quickly decomposed to a yellow gum. Treatment of a suspension of 3 in 1:1 THF–CH_2Cl_2 with N_2O_4 gave a deep red solution that instantly afforded adduct 7 upon addition of isoprene. Thus, 5 could be generated in dilute solution; however, concentration of the red solution to dryness led only to decomposition. In view of the known sensitivity (vida supra) of 4-phenyl TAD toward water, it was likely that water present with 3 or in the solvent was causing the decomposition of 5.

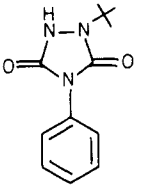
Reasoning that attack by water or other nucleophiles at the carbonyl groups of the TAD moiety should be impeded by the presence of bulky substituents at the 2- and 6-positions of the benzene ring, the synthesis of *tert*-butylated urazole 12 was pursued by adapting established urazole methodology. Thus, 2,4,6-tri-*tert*-butylaniline hydrochloride was converted[10] into isocyanate 8, mp 112–114 °C, in 95% yield. Interestingly, this highly hindered isocyanate was recovered unchanged after 3 days in ethanol at 25 °C. Refluxing the solution for 24 h, however, gave carbamate 10. Treatment of 8 with ethyl carbazate



8 9, R = $CONHNHCO_2C_2H_5$
10, R = $CO_2C_2H_5$
11, R = $CON(CH_3)_2$
12

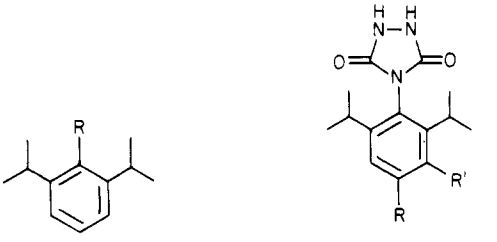
in refluxing benzene[11] gave semicarbazide 9 (66%). However, this substance failed to undergo cyclization to urazole 12 upon exposure to NaOEt in refluxing ethanol,[12] affording instead carbamate 10 (66%).[13] Also, heating 9 with NaH in DMF gave urea 11 in low yield as the only identifiable product.[14,15]

In a final attempt to prepare a *tert*-butyl-substituted phenylurazole, phenylurazole 1 was treated with isobutylene in nitrobenzene in the presence of H_2SO_4 at 100 °C. A crystalline material tentatively identified as N-*tert*-butylated urazole 13 was obtained in 61% yield.

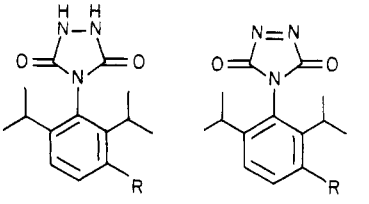


13

Success was achieved through use of isopropyl blocking groups. Thus, 2,6-diisopropylphenyl isocyanate (14) was



14, R = NCO
15, R = $NHCONHNHCO_2C_2H_5$
16, R = $NHCONHNH_2$
17, R = R′ = H
18, R = H; R′ = SO_2Cl
19, R = SO_2Cl; R′ = H



20, R = SO_3H
21, R = $SO_3^-Na^+$
22, R = H
23, R = SO_3H
24, R = $SO_3^-Na^+$

allowed to react with ethyl carbazate in refluxing benzene,[11] affording semicarbazide 15 (90%). Attempted cyclization to urazole 17 with KOH in hot water[11] gave instead the decarboxylated semicarbazide 16 (48%). However, the reaction of 15 with sodium ethoxide in ethanol[12] gave the desired urazole 17 in 74% yield. It was necessary to render the reaction mixture quite acidic (pH ~2) during workup since at pH ~7 the sodium salt of the urazole moiety was isolated. Oxidation of 17 with N_2O_4 in CH_2Cl_2 at 0 °C smoothly yielded the deep *purple* TAD 22 in 94% yield.

Treatment of 17 with neat $ClSO_3H$ at 95 °C gave a 9:1 mixture of isomeric sulfonyl chlorides 18 and 19 in which the meta isomer 18 predominated. Temperatures below 65 °C prolonged the reaction without significant change

(9) Suter, C. M.; Weston, A. W. *Org. React. (N.Y.)* **1956**, *3*, 141.
(10) This procedure is a modification of that of ref 12 and: Farlow, M. W. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 521.
(11) Arya, V. P.; Shenoy, S. J. *Ind. J. Chem.* **1976**, *14B*, 883.
(12) Paquette, L. A.; Doehner, R. F. *J. Org. Chem.* **1980**, *45*, 5105.
(13) Cyclization of 9 to 12 would presumably involve abstraction of the highly hindered proton on the nitrogen atom bearing the aryl group. Apparently, the EtO^- prefers instead to attack the adjacent carbonyl group, a process that leads to 10.
(14) DMF probably undergoes some decomposition to Me_2NH, which reacts with 9 to give 11 (cf. ref 13).
(15) Thermolysis[12] of 9 at 170 or 250 °C in an evacuated sealed tube afforded isocyanate 8 among the products. The product mixture did not give a characteristic red or purple color upon exposure to N_2O_4 in CH_2Cl_2, indicating that once again no 12 had been formed.

Table I. Decomposition of TADs 30, 28, 22, and 24 in Aqueous Solutions at 25 °C

TAD[e]	acetone, %	aq soln used	wavelength monitored, nm	time to total decay, min	$t_{1/2}$ min
30	90	water	524	7	~1
28	90	water	534	27	~4
22	90	water	541	46	~9
24	50	water	546	30	~4
24	50	pH 4.5 buffer[a]	546	25	~4
24	50	pH 7 buffer[b]	546	28	~4
24	50	pH 10 buffer[c]	546	4	<0.5
24	0	water	d	~1	

[a] 0.1 M NaOAc/HOAc. [b] 0.1 M Tris/HCl. [c] 0.1 M Tris/NaOH. [d] Monitored visually owing to vigorous gas evolution. [e] Initial concentration = 6.2×10^{-3} M.

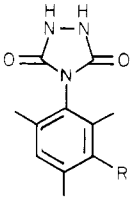
in the meta to para ratio. At 140 °C, the proportion of the para isomer increased (by NMR) such that **18** and **19** were produced in a ratio of 3:1. The pure meta isomer **18** could be isolated in 34% overall yield from the 9:1 mixture by repeated crystallization from EtOAc.

It is interesting to note that only the para isomer was isolated from the chlorosulfonation of phenylurazole **1**. Quite likely, the bulky isopropyl groups in **17** cause the urazole ring to be twisted out of the plane of the benzene ring, thus becoming a meta director.

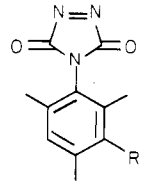
Hydrolysis of **18** in warm water gave sulfonic acid **20**, which was neutralized with Na_2CO_3 to give sodium salt **21**. Use of excess base resulted in formation of a disodium salt involving the urazole ring. Treatment of **20** and **21** with a large excess of N_2O_4 in CH_2Cl_2 led to the corresponding TADs **23** and **24** as *stable* (cf. **5**) purple crystalline solids in yields of >80%.

The preparation of pure **23** and **24** initially presented several difficulties. Whereas heretofore TADs were normally purified by sublimation, the highly polar nature of **23** and **24** prevented their ready sublimation under normal conditions. They were also not soluble in CH_2Cl_2; however, if solvents such as THF or EtOAc were added, the TADs dissolved but failed to crystallize. Precipitation by the addition of hexanes yielded impure compounds. The use of a large excess of N_2O_4 in CH_2Cl_2, however, gave a solvent system that readily dissolved **23** and **24**. Removal of most (but not all!) of the N_2O_4 with an N_2 purge followed by cooling of the resulting solution in the freezer for ~5 days, reproducibly gave crystalline **23** and **24**. Acid **23** is hygroscopic, gaining weight and becoming tacky when left on the bench top. Both **23** and **24** could be stored without noticeable decomposition for several weeks in the freezer.

In order to determine whether or not methyl groups would serve the same blocking function as the isopropyl groups, we applied the above sequence of reactions to 2,4,6-trimethylphenyl isocyanate. An added attraction in this series was the fact that only one isomer was possible from the $ClSO_3H$ reaction. Thus, urazole **25**, purple TAD



25, R = H
26, R = SO_2Cl
27, R = SO_3H



28, R = H
29, R = SO_3H

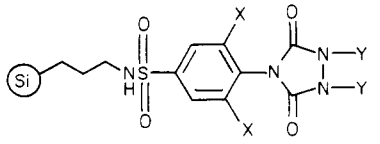
28, urazolesulfonyl chloride **26**, and urazolesulfonic acid **27** were prepared. Unfortunately, upon treatment with N_2O_4, **27** exhibited behavior more similar to that of **5** rather than the more stable **23**. One may conclude that methyl groups in the 2- and 6-positions of the benzene ring are not sufficiently bulky to allow convenient preparation of pure **29**.

B. Stability Studies of TADs 30, 28, 22, and 24, in Aqueous Solutions. The results of a qualitative study of the stability of phenyl TAD (**30**), 2,4,6-trimethylphenyl TAD (**28**), 2,6-diisopropylphenyl TAD (**22**), and TAD sodium salt **24** in various aqueous solutions are collected in Table I. Acetone was used as a cosolvent in order to slow the rates of decomposition for convenient measurement. Decomposition was monitored spectrophotometrically by observing the reduction in absorption over time at the wavelength of maximum visible absorption for each TAD.

The effect of the two ortho isopropyl groups is seen most clearly in the comparison between **30** and **22** in 9:1 acetone–water. Whereas **30** is totally consumed in ~7 min, under the same conditions **22** survives over 6 times longer (~46 min). Note also that the rate of decomposition of **24** in 50% aqueous acetone solutions is about the same ($t_{1/2}$ ~4 min) whether water or pH 4.5 or 7 buffer is used as the aqueous component. At pH 10, however, **24** is totally consumed after only 4 min. In one experiment acetone was omitted. Rapid gas evolution precluded use of the spectrophotometer; however, decomposition was complete after about 1 min.

Their rather rapid reaction with water notwithstanding, TADs **23** and **24** react even more rapidly with amphipathic 1,3-dienes in water, serving as highly useful dienophiles in Diels–Alder reactions in aqueous solution. These results are described in the accompanying paper.[5]

C. Preparation and Properties of TADs Immobilized on Silica Gel. With the various sulfonated TADs in hand, it was now straightforward to attach the TAD moiety to silica gel. The easily prepared 3-aminopropylsilylated Baker silica gel **31** (loading ~0.8 mmol NH_2 per gram) recently characterized by Waddel et al.[16] was treated with excess sulfonyl chloride **2** in EtOAc at 60 °C. Filtration, continuous extraction with EtOAc, and drying led to sulfonamidophenylurazole-derivatized silica gel **32** (loading ~0.7 mmol per g[17]). A suspension of **32** in



32, X = Y = H
33, X = H; Y, Y = double bond
34, X = $CH(CH_3)_2$; Y, Y = double bond
(contains some 3-sulfonyl isomer, see text)

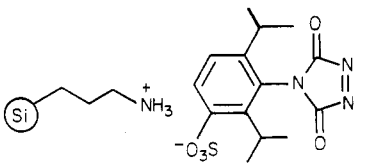
CH_2Cl_2 at 0 °C turned a brilliant red, characteristic of the TAD moiety, when treated with excess N_2O_4. Removal of the solvent gave the pink TAD-derivatized silica gel **33**.

(16) Waddell, T. G.; Leyden, D. E.; DeBello, M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5303.
(17) Loading is based on recovered substrate.

Titration of a toluene slurry with isoprene (pink → pale gold) indicated a loading of ~0.4 mmol of TAD per g. Silica gel **33** exhibited a gradual color change from pink to gold (unreactive toward isoprene) upon storage on the benchtop overnight. Quite likely, the longer term instability of **33** was due to attack by adventitious water or other nucleophile on one of the carbonyl groups of **33** (vida supra).

With the objective being a more stable TAD-derivatized silica gel, we next turned to the 2,6-diisopropyl series. Preliminary experiments demonstrated that the mixture of meta and para sulfonyl chloride isomers **18** and **19**[18] worked as well as pure **18** in the reaction with silica gel **31** and subsequent experiments. Oxidation with excess N_2O_4 gave the bright *purple* TAD-derivatized silica gel **34** (~0.3 mmol TAD per g). Silica gel **34** appeared to be stable for weeks on the benchtop. It is pertinent to note here that the TAD sulfonyl chlorides (e.g., **4**) do *not* afford the corresponding TAD-derivatized silica gels upon reaction with **31**. Apparently, the amino groups of **31** attack those substrates preferentially at the TAD moiety, affording unreactive (toward the Diels–Alder reaction) straw-colored silica gels.

Interestingly, when a purple EtOAc solution of TAD sulfonic acid **23** was added dropwise to a slurry of silica gel **31** in EtOAc, the silica gel rapidly acquired a purple color and the supernatent liquid became colorless. Thus, the free amino groups of **31** could be titrated with acid **23**. Filtration and a thorough rinse gave the stable, purple silica gel **35** in which the TAD moiety was held to the silica



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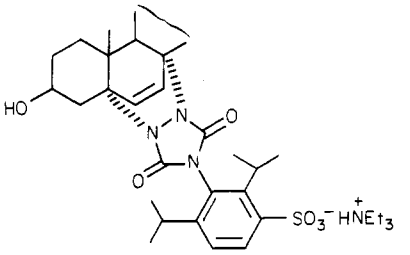
by ionic bonding (~0.5 mmol per g). Apparently, the acid–base neutralization reaction was sufficiently rapid that the TAD moiety was not attacked by the amino groups of **31** (cf. **4** results).

These TAD-functionalized silica gels may be used to remove selectively 1,3-diene-containing molecules from a mixture. For example, a mixture of ergosterol[19] and cholesterol in ether is easily separated by addition of dry TAD silica gel **34** to the swirled solution at 25 °C. After about 10 s no further bleaching of the purple color was observed. After filtration, evaporation of the filtrate, and recrystallization, pure cholesterol was recovered in near quantitative yield. Similar treatment of a mixture of ergosterol and pregnenolone acetate gave back the latter steroid in 96% yield. Silica gel **34** also removed 8(*E*),10(*E*)-dodecadienol rapidly and quantitatively from a THF solution. Similar results were observed with 1-chloro-, 2-chloro-, and 9-bromoanthracene, though much longer reaction times were required.

An interesting variation involved treatment of TAD–silica salt **35** with excess ergosterol in ether. In one experiment the silica gel phase was separated, dried, and shown to have removed 23.7 mg of ergosterol from the solution. Elution of this silica gel with an 18-fold excess of Et_3N in 20 mL of acetonitrile liberated the ergosterol–triazolinedione adduct **36**, mp 204.5–205 °C, in 98% yield. Treatment of **36** with refluxing THF containing



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excess $LiAlH_4$[19] afforded ergosterol in 76% yield. Alternatively, a sample of silica gel **34** known to have reacted with 130 mg of ergosterol was treated directly with $LiAlH_4$ in THF. The usual workup gave back 122 mg (94%) of recrystallized ergosterol.

These experiments demonstrate that a TAD moiety immobilized on silica gel[20] retains its dienophilicity. Quite likely, the rich and varied non-Diels-Alder chemistry exhibited by TADs[21] will be mirrored by the TAD-derivatized silica gels.

Experimental Section[22]

4-[4-(Chlorosulfonyl)phenyl]urazole (2). To 2.02 g (11.4 mmol) of 4-phenylurazole (Aldrich Co.) was added all at once 5.5 mL of $ClSO_3H$. The mixture was stirred under N_2 at 60 °C for 2 h, allowed to cool to 25 °C, and added dropwise to 40 mL of crushed ice. The resulting solid was collected on a coarse frit, washed with ice water, and dried at 70 °C (15 mm). The residue was dissolved in 50 mL of boiling EtOAc, filtered, concentrated to 25 mL, and 20 mL of hexane was added. After the solution was cooled to 25 °C, the resulting solid was collected and air-dried to yield 2.16 g (68%) of **2** as colorless needles, mp 203–204 °C. Further drying at 56 °C (0.005 mm) gave the analytical specimen: mp 218–219 °C; ^1H NMR (acetone-d_6) δ 8.11 (d, J = 10, 2 H), 8.22 (d, J = 10, 2 H). Anal. Calcd for $C_8H_6ClN_3O_4S$: C, 34.84; H, 2.19; N, 15.25. Found: C, 34.61; H, 2.31; N, 15.10.

4-(4-Sulfophenyl)urazole (3). A suspension of 210 mg (0.762 mmol) of **2** in 5 mL of water was stirred at 50 °C for 4 h. The solvent was removed from the resulting solution on a rotoevaporator, and the residue was dried at 80 °C (15 mm) to yield 196 mg (92%) of a colorless powdery solid: mp 279–280 °C; ^1H NMR (D_2O) δ 7.37 (d, J = 8, 2 H), 7.74 (d, J = 8, 2 H). Anal. Calcd for $C_8H_7N_3O_5S \cdot 1.2H_2O$: C, 34.46; H, 3.39; N, 15.06. Found: C, 34.41; H, 3.05; N, 14.72.

4-[4-(Chlorosulfonyl)phenyl]-1,2,4-triazoline-3,5-dione (4). To a stirred suspension of 292 mg (1.06 mmol) of **2** in 10 mL of CH_2Cl_2 at 0 °C was added 2.2 mL of a 0.5 M solution of N_2O_4 in CH_2Cl_2. A brilliant red solution formed over 5 min. Removal of the solvent followed by sublimation of the red residue at 100

(18) Para isomer **19** reacted with **31** faster than the meta isomer **18**, as shown by the enrichment of **18** in the NMR spectrum of recovered sulfonyl chloride mixture (excess used).

(19) The reaction of ergosterol with phenyl TAD and its regeneration from the [4 + 2] adduct by treatment with $LiAlH_4$ has been described. See: Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. D* **1970**, 939.

(20) Preliminary experiments indicate that the sulfonated TADs may be attached to aminomethyl polystyrene resin (Mitchell, A. R.; Kent, S. B. H.; Engelhard, M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845) by using methodology similar to that for silica gel.

(21) Other TAD reactions include the ene reaction (Gopalan, A.; Moerck, R.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1979**, 549. Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384), the oxidation of alcohols to aldehydes or ketones (Cookson, R. C.; Stevens, I. D. R.; Watts, C. T. *Chem. Commun.* **1966**, 744), and unusual modes of addition to strained substrates (for recent examples, see: Gassman, P. G.; Hoye, R. C. *J. Am. Chem. Soc.* **1981**, *103*, 2496. Adam, W.; De Lucchi, O.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Ibid.* **1982**, *104*, 161. Amey, R. L.; Smart, B. E. *J. Org. Chem.* **1981**, *46*, 4090.

(22) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on either a Varian XL-100 or Nicolet 360-MHz spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed in δ units with Me_4Si as an internal standard. J values are in hertz. Visible spectra were measured on a Cary 15 spectrophotometer. Elemental analyses were determined at the University of Oregon by Dr. R. Wielesek. All reactions were routinely run under a N_2 atmosphere. Solvents were routinely distilled.

°C (0.01 mm) gave 264 mg (91%) of a red solid: mp 107–108.5 °C; ^{1}H NMR δ 7.91 (d, J = 9, 2 H), 8.23 (d, J = 9, 2 H). Anal. Calcd for $C_8H_4ClN_3O_4S$: C, 35.12; H, 1.47; N, 15.35. Found: C, 35.03; H, 1.37; N, 14.95.

2-[4-(Chlorosulfonyl)phenyl]-5,8-dihydro-6-methyl-*s*-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (6). To a stirred suspension of 500 mg (1.81 mmol) of **2** in 10 mL of CH_2Cl_2 at 0 °C, was added 6.1 mL of a 0.3 M solution of N_2O_4 in CH_2Cl_2. After 5 min, the resulting deep red solution was partially concentrated to remove any unreacted N_2O_4. To the resulting solution was added dropwise at 0 °C 140 mg (2.12 mmol) of isoprene dissolved in 5 mL of CH_2Cl_2. After addition, the ice bath was removed and the mixture allowed to warm to 25 °C. The resulting cream colored precipitate dissolved on addition of 50 mL of CH_2Cl_2, and then EtOAc was added until the solution became cloudy. The solid that formed upon cooling was collected by filtration and dried at 56 °C (0.005 mm) to yield 276 mg (45%) of **6** as a colorless powder: mp 225–226 °C; ^{1}H NMR δ 1.91 (s, 3 H), 4.14 (m, 4 H), 5.66 (m, 1 H), 7.97 (d, J = 9, 2 H), 8.14 (d, J = 9, 2 H). Anal. Calcd for $C_{13}H_{12}ClN_3O_4S$: C, 45.68; H, 3.54; N, 12.29. Found: C, 45.54; H, 3.15; N, 12.29.

2-(4-Sulfophenyl)-5,8-dihydro-6-methyl-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (7). To a stirred suspension of 338 mg (1.30 mmol) of **3** in 10 mL of a 1:1 CH_2Cl_2–THF solution at 0 °C under N_2 was added 2.73 mL of a 0.5 M solution of N_2O_4 in CH_2Cl_2. A deep red solution containing TAD **5** formed over 5 min, which was partially concentrated to remove excess N_2O_4. To the resulting red solution of **5** was added dropwise at 0 °C 90 mg (1.3 mmol) of isoprene dissolved in 2.8 mL of CH_2Cl_2. The resulting mixture was allowed to warm to 25 °C and then was concentrated to 5 mL. Addition of 15 mL of EtOAc produced a solid that was collected and dried at 15 mm. This was recrystallized twice from 1:1 CH_2Cl_2–THF and dried at 56 °C (0.005 mm) to yield 130 mg (28%) of **7**, a colorless powder: mp 263–264 °C ^{1}H NMR (D_2O) δ 1.69 (s, 3 H), 3.96 (br s, 4 H), 5.72 (br s, 1 H), 7.52 (d, J = 8, 2 H), 7.88 (d, J = 8, 2 H). Anal. Calcd for $C_{13}H_{13}N_3O_6S{\cdot}1.4H_2O$: C, 44.80; H, 4.56; N, 12.05. Found: C, 44.79; H, 4.27; N, 12.09.

2,4,6-Tri-*tert*-butylphenyl Isocyanate (8). A mixture of 2.73 g (9.16 mmol) of 2,4,6-tri-*tert*-butylaniline hydrochloride [prepared by bubbling HCl through an ice-bath-cooled methanol solution of the free amine (Aldrich Co.) and removing the solvent] and 15 mL of a 12.5% phosgene in toluene solution (MCB) was placed in a Parr pressure reactor vessel. The sealed vessel was immersed in a 150 °C oil bath for 4 h and cooled to 25 °C. The resulting orange solution was purged with N_2 to remove the excess phosgene. Solvent removal then yielded 2.5 g (95%) of **8** as a brown solid that was suitable for subsequent steps: mp 101–106 °C; ^{1}H NMR δ 1.32 (s, 9 H), 1.47 (s, 18 H), 7.33 (s, 2 H). An analytical sample was prepared by sublimation at 50 °C (0.005 mm) to yield **8** as a colorless solid: mp 112–114 °C. Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.16; N, 4.87. Found: C, 79.29; H, 10.55; N, 4.86.

4-(2,4,6-Tri-*tert*-butylphenyl)-1-(ethoxycarbonyl)semicarbazide (9). A solution of 5.03 g (17.5 mmol) of **8** and 1.82 g (17.5 mmol) of ethyl carbazate in 50 mL of dry benzene was heated at reflux for 1 h under N_2 and then allowed to stir overnight at 25 °C. Removal of the solvent gave a colored solid, which was dissolved in boiling hexane, decolorized with activated charcoal, and filtered. Concentration gave a precipitate that failed to redissolve in boiling hexane. Enough EtOAc was added to dissolve the precipitate. The resulting solution was concentrated to 25 mL, diluted with 75 mL of hexane, and then cooled in a freezer with occasional violent agitation. The resulting precipitate was collected, washed with hexane, and dried at 25 °C (0.005 mm) to yield 4.52 g (66%) of **9**, a colorless powder: mp 160–161 °C; ^{1}H NMR δ 1.16–1.30 (30 H), 4.04–4.40 (overlapping q, 2 H), 7.43 and 7.44 (2 s, 2 H). In the 360-MHz NMR spectrum in acetone-d_6 at −80 °C, the methylene protons of the ethyl group appeared as three quartets of unequal relative intensity at δ 4.05, 3.97, and 3.88. At 40 °C the two larger quartets (δ 4.05 and 3.97) coalesced into a single quartet while the third quartet became broadened. In Me_2SO-d_6 at 25 °C only a single quartet was observed, while in $CDCl_3$ two equal quartets were observed at δ 4.23 and 4.12. Collectively, this behavior is indicative of hindered rotation caused by the bulky *tert*-butyl groups. An analytical sample was prepared by recrystallization from EtOAc–hexane followed by drying at 56 °C (0.005 mm): mp 162–164 °C. Anal. Calcd for $C_{22}H_{37}N_3O_3$: C, 67.48; H, 9.52; N, 10.73. Found: C, 67.35; H, 9.74; N, 10.57.

Ethyl (2,4,6-Tri-*tert*-butylphenyl)carbamate (10). A. From 9. A solution of 300 mg (0.766 mmol) of **9** in 5 mL of absolute EtOH was combined with a solution prepared by addition of 100 mg (4.8 mmol) of Na to 40 mL of absolute EtOH and heated at reflux under N_2 for 24 h, giving a cloudy colorless suspension. The pH of the cooled reaction mixture was adjusted to 2 by addition of a 1 M solution of HCl in absolute EtOH. Filtration and removal of the solvent gave a colorless solid that was sublimed at 125 °C (0.005 mm), yielding 162 mg (66%) of **10** as a colorless solid. The sublimate was recrystallized from EtOAc and dried at 25 °C (0.005 mm), yielding 64 mg (26%) of **10** as colorless prisms: mp 212–214 °C; ^{1}H NMR δ 1.04–1.48 (m, 30 H), 3.96–4.36 (2 overlapping unequal q, 2 H), 7.37 and 7.40 (2 unequal s, 2 H). The 360-MHz NMR spectral behavior was similar to that exhibited by **9**. Anal. Calcd for $C_{21}H_{35}NO_2{\cdot}^1/_5$EtOAc: C, 74.61; H, 10.51. Found: C, 74.83; H, 10.38.

B. From Isocyanate 8. To 15 mg of **8** was added 3 mL of absolute EtOH. After a 24-h reflux period, the solvent was removed, affording 18 mg (~100%) of **10**. After sublimation, the substance showed mp 213–214 °C and was identical with **10** obtained from **9** in the above experiment.

***N*-(2,4,6-Tri-*tert*-butylphenyl)-*N'*,*N'*-dimethylurea (11).** To 40 mg (1.7 mmol) of NaH in 15 mL of dry DMF was added 300 mg (0.766 mmol) of **9**. The reaction mixture evolved a gas and turned yellow. After a 24-h stir under N_2 at 100 °C, the mixture was cooled and acidified with 5 mL of 20% HCl. The mixture containing a light yellow precipitate was poured over 20 mL of crushed ice. The solid was collected and dried at 25 °C (0.005 mm), giving 166 mg of a yellow powder. This was dissolved in $CHCl_3$ and placed on a silica gel column that was eluted with 10% EtOAc in hexane. An initial bright yellow band was collected, giving 9 mg of an unidentified yellow solid: mp 134–135 °C; ^{1}H NMR δ 1.33 (s), 1.43 (s), 1.50 (s), 7.27 (s); MS, m/e 261.246 (calcd for $C_{18}H_{31}N$, 261.246, M^+). Further elution gave a colorless solid that was recrystallized from EtOAc and dried at 25 °C (0.005 mm), yielding 18 mg (7%) of **11** as colorless needles: mp 249–250 °C; ^{1}H NMR δ 1.32 (s, 9 H), 1.42 (s, 18 H), 3.08 (s, 6 H), 5.80 (br s, 1 H), 7.39 (s, 2 H); MS, m/e 332.286 (calcd for $C_{21}H_{36}N_2O$, 332.283, M^+).

1-*tert*-Butyl-4-phenylurazole (13). To a solution of 500 mg of 4-phenylurazole in 15 mL of nitrobenzene at 100 °C was added 5 drops of concentrated H_2SO_4, at which point the urazole started to precipitate. Isobutylene was bubbled through the mixture, and the mixture went homogeneous after a few minutes. Isobutylene addition and heating were continued for 23 h; then the solvent was removed by vacuum distillation (0.01 mm) at an oil-bath temperature of 60–70 °C. The residue was dissolved in EtOAc and filtered through a small column of silica gel to give a yellow solution. This was boiled with activated charcoal, filtered, and concentrated to dryness. The residue was washed with hexane, dried at 25 °C (0.005 mm), dissolved in 50 mL of boiling ether, filtered, diluted with 25 mL of hexane, and cooled to 25 °C. The resulting solid was collected, washed with 1:1 ether–hexane, and dried at 56 °C (0.005 mm) to yield 322 mg of **13** as colorless needles, mp 153–154 °C. The mother liquor was concentrated and cooled in an ice bath to yield another 84 mg (mp 153–154 °C) for a total yield of 61%: ^{1}H NMR (acetone-d_6) δ 1.54 (s, 9 H), 7.44 (m, 5 H). Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.01. Found: C, 61.70; H, 6.31; N, 17.87.

4-(2,6-Diisopropylphenyl)-1-(ethoxycarbonyl)semicarbazide (15). A solution of 13.12 g (64.5 mmol) of 2,6-diisopropylphenyl isocyanate (Trans World Chemicals) in 100 mL of dry benzene was poured into a stirred solution of 6.72 g (64.5 mmol) of ethyl carbazate in 100 mL of dry benzene and heated at reflux for 2.5 h under N_2. Removal of the solvent gave a colorless solid, that was dissolved in 100 mL of EtOAc, filtered, concentrated to 55 mL, and cooled in an ice bath. Hexane (120 mL) was added with rapid stirring until the solution became cloudy. This was stored overnight at 4 °C, and the resulting solid was collected, washed with ether, and then dried at 25 °C (0.005 mm) to yield 17.8 g (90%) of **15** as fine colorless crystals: mp 127–128 °C; ^{1}H NMR (acetone-d_6) δ 1.04–1.30 (complex m, 15 H), 3.34 (heptet, J = 7, 2 H), 4.16 (q, J = 7, 2 H), 7.00–7.22 (complex m, 3 H), 7.30 (br s, 1 H), 7.44 (br s, 1 H), 8.02 (br s, 1 H). Anal.

Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.50; H, 8.03; N, 13.75.

4-(2,6-Diisopropylphenyl)semicarbazide (16). A mixture of 3.0 g of **15** and 10 mL of 4 N aqueous KOH was heated on the steam bath for 20 min. The starting material went into solution, and then a white precipitate formed. The mixture was cooled and the pH was adjusted to 7–8 with 3 N HCl. The resulting precipitate was collected, washed with water, and air-dried to give 1.63 g of a white solid. Crystallization from EtOA–MeOH (5:1) gave 637 mg of **16** as colorless feathery needles, mp 231–232 °C. Drying at 56 °C (0.05 mm) gave the analytical sample: calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 65.93; H, 8.94; N, 17.76.

4-(2,6-Diisopropylphenyl)urazole (17). A solution of 11.5 g (37.4 mmol) of **15** in 100 mL of absolute EtOH was poured into a stirred solution prepared by addition of 4.30 g (187 mmol) of Na to 150 mL of absolute EtOH. The resulting orange solution was heated at reflux under N_2 for 15 h to give a colorless cloudy mixture that was allowed to cool to 25 °C. The pH was adjusted to 2 by addition of 1 M ethanolic HCl solution, and, after filtration, the solvent was removed. The resulting colorless solid was recrystallized from EtOAc, yielding 4.72 g of **17** as a colorless crystalline solid, mp 268–269 °C. Concentration of the mother liquor yielded another 2.56 g (mp 266–268 °C) for a total yield of 74%: ^{1}H NMR (acetone-d_6) δ 1.24 (d, J = 7, 12 H), 2.88 (heptet, J = 7, 2 H), 7.38 (complex m, 3 H). Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.77; H, 7.21; N, 16.21.

4-(2,6-Diisopropylphenyl)-1,2,4-triazoline-3,5-dione (22). To a stirred suspension of 300 mg (1.15 mmol) of **17** in 10 mL of CH_2Cl_2 at 0 °C was added 1.3 mL of a 0.9 M solution of N_2O_4 in CH_2Cl_2. The reaction mixture became homogeneous and turned deep purple over 5 min. Removal of the solvent gave a residue that was sublimed at 65 °C (0.003 mm) to yield 280 mg (94%) of **22** as a deep purple solid: mp 79–80 °C; ^{1}H NMR δ 1.18 (d, J = 7, 12 H), 2.34 (heptet, J = 7, 2 H), 7.38 (complex m, 3 H); visible λ_{max} 541 nm (log ϵ 2.16). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.65; H, 6.35; N, 16.26.

4-[3-(Chlorosulfonyl)-2,6-diisopropylphenyl]urazole (18) and 4-[4-(Chlorosulfonyl)-2,6-diisopropylphenyl]urazole (19). To 8.67 g of **17** was added 20 mL of $ClSO_3H$ all at once. The mixture was stirred for 5 h at 65 °C, and then the resulting solution was cooled and added dropwise to crushed ice. The resulting solid was collected, washed with ice water, and dried at 0.05 mm. Crystallization from EtOAc–hexane (activated charcoal used) yielded 9.83 g of a colorless crystalline 9:1 mixture of the 3- and 4-chlorosulfonyl isomers. This was combined with 11.60 g from another run and recrystallized from EtOAc. The crystals were dried at 140 °C (0.005 mm), yielding 8.35 g (34%) of pure 3-isomer **18** as fine colorless crystals: mp 253–254 °C; ^{1}H NMR (acetone-d_6) δ 1.26 (d, J = 7, 6 H), 1.42 (d, J = 7, 6 H), 2.91 (heptet, J = 7, 1 H), 4.44 (heptet, J = 7, 1 H), 7.79 (d, J = 8, 1 H), 8.32 (d, J = 8, 1 H). Anal. Calcd for $C_{14}H_{18}ClN_3O_4S$: C, 46.73; H, 5.04; N, 11.68. Found: C, 46.44; H, 4.74; N, 11.68.

4-(3-Sulfo-2,6-diisopropylphenyl)urazole (20). A suspension of 1.5 g (4.2 mmol) of **18** in 15 mL of H_2O was stirred at 55 °C for 14 h. The water was removed on a rotoevaporator, and the residue was dried at 140 °C (0.005 mm) to yield 1.5 g of **20** as a light brown powdery solid that was used without further purification: mp 289–290 °C; ^{1}H NMR (D_2O) δ 1.00 (d, J = 7, 6 H), 1.06 (d, J = 7, 6 H), 2.40 (heptet, J = 7, 1 H), 4.07 (heptet, J = 7, 1 H), 7.35 (d, J = 8, 1 H), 7.98 (d, J = 8, 1 H).

4-(3-Sulfo-2,6-diisopropylphenyl)urazole Sodium Salt (21). A suspension of 51 mg of **18** in 2 mL of water was stirred at 70 °C for 3 h, and then the solvent was removed under vacuum, leaving a residue that was dried at 80 °C (15 mm) for 1 h. The solid was dissolved in 2 mL of water and mixed with a solution of 8.7 mg of $Na_2CO_3 \cdot H_2O$ in 2 mL of water. The water was removed on a rotoevaporator, and the residue was dried at 140 °C (0.005 mm) to yield 50 mg (97%) of salt **21** as a grey powder that was used without further purification: mp >300 °C (preheated oil bath); ^{1}H NMR (D_2O) δ 1.10 (d, J = 7, 6 H), 1.15 (d, J = 7, 6 H), 2.48 (heptet, J = 7, 1 H), 4.17 (heptet, J = 7, 1 H), 7.46 (d, J = 8, 1 H), 8.08 (d, J = 8, 1 H).

4-(3-Sulfo-2,6-diisopropylphenyl)-1,2,4-triazoline-3,5-dione (23). Through a rapidly stirred suspension of 612 mg (1.79 mmol) of **20** in 80 mL of CH_2Cl_2 at 0 °C was bubbled a rapid stream of NO_2 for 15 min. The deep red mixture was allowed to warm to 25 °C over 20 min. The deep red cloudy suspension was purged of N_2O_4 with a stream of N_2. Gentle heating was provided to keep the mixture at about 25 °C. CH_2Cl_2 was added periodically to maintain a volume of 80–100 mL. When no more NO_2 was observed above the mixture, the mixture was filtered. The clear deep purple filtrate was stored in a freezer for 5 days. The cold mixture was filtered under N_2, and the collected solid was dried at 40 °C (0.005 mm) for 1 h to yield 405 mg (67%) of **23** as purple needles, mp 125–126 °C. Additional drying raised the melting point to 140 °C (preheated oil bath). The mother liquor was concentrated to 25 mL with a N_2 stream and gentle heating and then cooled in a freezer for 3 days to yield 192 mg (31%) of purple needles: mp 122–125 °C; ^{1}H NMR (acetone-d_6) δ 1.11 (d, J = 7, 6 H), 1.15 (d, J = 7, 6 H), 2.56 (heptet, J = 7, 1 H), 4.38 (m, 1 H), 7.65 (d, J = 8, 1 H), 8.28 (d, J = 8, 1 H); visible λ_{max} 546 nm (log ϵ 2.12). Anal. Calcd for $C_{14}H_{17}N_3O_5S \cdot 2H_2O$: C, 44.79; H, 5.64; N, 11.19. Found: C, 44.85; H, 5.52; N, 11.12.

4-(3-Sulfo-2,6-diisopropylphenyl)-1,2,4-triazoline-3,5-dione Sodium Salt (24). Through a stirred suspension of 43 mg (0.12 mmol) of **21** in 2 mL of CH_2Cl_2 at 0 °C was bubbled a gentle stream of NO_2 for 1 min. The vessel was then covered and removed from the ice bath, and the contents were stirred vigorously. A deep purple mixture formed over 10 min, which was filtered to give a clear crimson filtrate. This was diluted to 15 mL with CH_2CL_2, and N_2 was bubbled through the solution with gentle heating to maintain the solution at 25 °C until no more NO_2 was observed above the solution. The volume of the solution was maintained at 15 mL by the periodic addition of CH_2Cl_2. The solution was filtered, and the resulting clear purple filtrate was placed in a freezer for 19 h. Filtration (N_2) of the resulting *cold* mixture afforded, after drying at 25 °C (0.005 mm), 38 mg (89%) of **24** as fine purple needles: decomposes without melting, >130 °C; ^{1}H NMR (360 MHz, acetone-d_6) δ 1.06 (d, J = 7, 6 H), 1.12 (d, J = 7, 6 H), 2.51 (heptet, J = 7, 1 H), 4.70 (br m, 1 H), 7.39 (d, J = 8, 1 H), 8.35 (d, J = 8, 1 H); visible λ_{max} 546 nm (log ϵ 2.15). Anal. Calcd for $C_{14}H_{16}N_3NaO_5S \cdot 1.0H_2O$: C, 44.32; H, 4.78; N, 11.08. Found: C, 44.23; H, 4.92; N, 11.08.

4-(2,4,6-Trimethylphenyl)-1,2,4-triazoline-3,5-dione (28). Following the above procedures, 2,4,6-trimethylphenyl isocyanate was first converted into the corresponding semicarbazide, mp 219.5–220 °C (73%), which was cyclized to urazole **25**, mp 265–268 °C (86%), oxidation of which with N_2O_4 in CH_2Cl_2 gave pure TAD **28** (67%) after sublimation; mp 102–104 °C. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82, H, 5.10; N, 19.34. Found: C, 60.71; H, 4.79; N, 19.04.

4-(3-Sulfo-2,4,6-trimethylphenyl)urazole (27). Following the above procedure for the preparations of **18**, **19**, and **20**, urazole **25** was first converted into 3-chlorosulfonyl derivative **26** (65%, decomposes >240 °C without melting), which was then hydrolyzed quantitatively in water to give the title compound as a colorless crystalline solid, mp 234–236 °C. Anal. [after drying at 100 °C (0.005 mm)] Calcd for $C_{11}H_{13}N_2O_5S \cdot {}^1/_2H_2O$: C, 42.85; H, 4.58; N, 13.63. Found: C, 42.78; H, 4.62; N, 13.64.

Stability Studies of the TADs in Aqueous Solutions. The TAD was weighed out into a cuvette, and 2 mL of the appropriate solution was quickly added (initial concentration of the triazoline dione : 6.2×10^{-3} M). A timer was activated and the cuvette was given one quick shake, and then it was placed into the spectrophotometer. The decay of each triazolinedione was measured at its absorption maximum until there was no further reduction in absorption. One exception to the above procedure involved the decomposition of **24** in pure water (see Table I).

3-Aminopropylsilylated Silica Gel (31). The method of Waddell et al.[16] was adapted. To 4.94 g of dried (100 °C (0.05 mm), 4 h) silica gel (Baker 60–200 mesh) was added 30 mL of a 10% (v/v) solution of (3-aminopropyl)triethoxysilane in dry benzene. The slurry was stirred gently for 30 min, filtered through a Soxhlet thimble, and then continuously extracted with benzene for 2 h. The silica was then dried (100 °C (0.05 mm), 2 H), affording 5.51 g of **31**. This corresponds to a loading of 0.77 mmol per g of **31**. Loading varied somewhat from run to run.

4-(4-Sulfonamidophenyl)urazole-Derivatized Silica Gel 32. A slurry of 1.0 g of **31** in 10 mL of EtOAc containing 0.30 g (~2 equiv) of **2** was stirred at 60 °C for 3 h and then filtered. The silica gel was rinsed with EtOAc and dried (100 °C (0.05 mm),

1 h), affording 1.19 g of **32**. This was then extracted continuously with EtOAc in a Soxhlet apparatus for 4 h, affording 1.16 g of **32**. The total recovered urazole **2** was 0.14 g. Therefore, the loading of 2 on the basis of the increase in mass of the silica was 0.73 mmol per g of **32** (0.76 mmol per g of **32** based on recovered urazole).

4-(4-Sulfonamidophenyl)triazolinedione-Derivatized Silica Gel 33. A 1.16-g sample of **32** was dried (100 °C (0.05 mm), 14 h) and then slurried with 5 mL of 0.5 M N_2O_4 in CH_2Cl_2 at −20 °C for 30 min. The excess N_2O_4/CH_2Cl_2 was removed from the brilliant red suspension on a rotary evaporator (40 °C), and the residue was dried (25 °C (0.05 mm)). An aliquot was then slurried in 10 mL of toluene and titrated with a standard solution (0.11 M) of isoprene in toluene. A small portion of the silica was observed to remain red for several minutes even in the presence of 2–3 equiv of isoprene. Typical TAD values observed by this method were 0.34–0.40 mmol per gram of **33**.

4-(2,6-Diisopropyl-3(or 4)-sulfonamidophenyl)triazolinedione-Derivatized Silica Gel 34. An 11.35-g sample of Baker silica gel was treated with (3-aminopropyl)triethoxysilane as above and then slurried at 50 °C for 1 h with 50 mL of EtOAc containing 2.79 g of a 3.75:1 (by NMR) mixture of **18**:**19**. Workup was similar to that of **33**. Crystalline **18**, 0.29 g essentially free of the para isomer, was recovered by the washing procedure, indicating that the para isomer **19** reacts preferentially with **31**. There was obtained 14.42 g of urazole-derivatized silica gel. Oxidation with N_2O_4 as described for **31** afforded purple **34**. An isoprene titration showed a loading of 0.29 mmol of TAD per g of **34**.

Silica Gel 35. To a slurry of 0.50 g of silica gel **31** (loading 0.54 mmol NH_2 per g in 5 mL of EtOAc was added dropwise a solution (0.036 M) of TAD **23** in EtOAc until a faint purple color remained in the supernatant after swirling (7.0 mL added). During the addition, the silica phase acquired a deep purple color. The silica was isolated by centrifugation, rinsed with EtOAc, and dried (25 °C (0.05 mm), 15 min) (loading ~0.50 mmol TAD per g of **35**).

Separation of Ergosterol and Cholesterol Using Silica Gel 34. A mixture of cholesterol (0.0252 g) and ergosterol (0.0252 g, ~0.06 mmol) was dissolved in 10 mL of dry ether and added dropwise to a slurry containing 0.8 g of **34** (contained ~0.13 mmol of TAD) in 10 mL of ether. The reaction of the ergosterol with **34** appeared to be over in ~10 s (no further color fade). After 30 min, the purple mixture was filtered. The filtrate contained no ergosterol by NMR and afforded 0.025 g of cholesterol after recrystallization.

Ergosterol–TAD Adduct 36. To a slurry of 0.50 g of silica gel **35** (~0.25 mmol of TAD) in 10 mL of EtOAc was added 100 mg (0.25 mmol) of ergosterol dissolved in 10 mL of ether. After 10 s, the slurry (pale gold hue) was filtered and washed with ether. Evaporation of the filtrate gave 76.5 mg of recovered crystalline ergosterol. The silica phase containing the reacted ergosterol was slurried with a solution containing 50 μL of Et_3N (6-fold excess) dissolved in 10 mL of acetonitrile, allowed to stand for 15 min, and then filtered. The process was repeated twice. The combined filtrates were concentrated to dryness, affording 73.5 mg of a solid containing the adduct **36**. Recrystallization from EtOAc–hexane gave 50 mg (98%) of **36** as a white powder; mp 204.5–205 °C. Anal. Calcd for $C_{48}H_{76}NO_6S\cdot H_2O$: C, 67.41; H, 8.96; N, 6.55. Found: C, 67.06; H, 9.22; N, 6.86.

Adduct **36** was also prepared by using solution chemistry. To a deep purple solution of 0.10 g (0.42 mmol) of TAD acid **23** in 10 mL of EtOAc was added 0.17 g (0.42 mmol) of ergosterol dissolved in 20 mL of EtOAc. The resulting colorless solution was treated with 120 μL (0.84 mmol) of Et_3N. After several minutes a white precipitate formed. The mixture was concentrated to dryness, giving 0.31 g (100%) of faintly yellow adduct salt **36**. The NMR spectrum was identical to that of **36** obtained from the silica gel (see above).

Recovery of Ergosterol from Adduct 36. The method of Barton et al.[19] was adapted. To a solution of 0.311 g of adduct **36** in 25 mL of dry THF was added 3 mL of THF saturated with $LiAlH_4$. The mixture was refluxed for 16 h and quenched with EtOAc. The usual workup followed by preparative TLC over silica gel gave, after recrystallization from EtOH, 129 mg (76%) of ergosterol, mp 167–168 °C.

Recovery of Ergosterol from Ergosterol–Silica 34 Adduct. A 1.17-g sample of ergosterol–silica **34** adduct (known to have reacted with 130 mg of ergosterol) was slurried in 10 mL of THF and treated with 5 mL of saturated $LiAlH_4$–THF solution. After a 16-h reflux period, EtOAc was added and the mixture was filtered with the aid of a THF (5 mL) rinse. The usual workup gave 122 mg (94%) of ergosterol, mp 167–168 °C, after recrystallization from MeOH.

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