zano[3,4-*d*]pyrimidine (**6**) in 71% yield. Catalytic reduction of **6** in methanol led to smooth reductive cleavage of the furazan ring to give (presumably) the intermediate pyrimidine **7** which, without isolation, cyclized upon treatment with *p*-toluenesulfonic acid at room temperature to 2,4-diamino-7,8-dihydro-6(5*H*)-pteridinone (**8**). This latter compound proved to be too unstable for isolation, but treatment with iodine in aqueous base resulted in smooth dehydrogenation to 2,4-diamino-6(5*H*)-pteridinone (4-amino-4-deoxyxanthopterin) (**9**). Hydrolysis of **9** with refluxing 5% sodium hydroxide then gave xanthopterin (**10**) itself, identical in every respect with an authentic sample.[8]

In view of the remarkable effect on biological activity of replacement of the 4-"hydroxy" group in pterins by an amino substituent (cf. folic acid and aminopterin),[9] the biological (and antitumor) activity of **9** should be of particular interest.

Experimental Section

5,7-Bis(benzoylamino)furazano[3,4-*d*]pyrimidine (4). A flask containing 4.0 g of 5,7-diaminofurazano[3,4-*d*]pyrimidine and 40 g of solid benzoic anhydride was placed in an oil bath maintained at 200 °C. The resulting suspension was stirred for 1 h, during which time all solid material dissolved. The yellow solution was cooled to room temperature to give a solid yellow mass which was slurried in 100 mL of ether and stirred for 1 h. The pale yellow crystals were collected by filtration, washed with ether, and dried in vacuo, yield 8.6 g (91%). An analytical sample, mp 270–271 °C, was obtained by recrystallization from DMF: IR (KBr) ν_{max} 1660, 1620, 1585, 1445 cm^{-1}.

Anal. Calcd for $C_{18}H_{12}N_6O_3$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.93; H, 3.45; N, 23.51.

Salt of 5,7-Bis(benzoylamino)furazano[3,4-*d*]pyrimidine and Ethyl Glycinate (5). To a suspension of 1.8 g of 5,7-bis(benzoylamino)furazano[3,4-*d*]pyrimidine in 12 mL of THF was added 1 g of ethyl glycinate, and the resulting mixture was stirred vigorously until all solid material dissolved. The yellow solution was then allowed to stand at room temperature for 30 min. The colorless crystals which had separated were collected by filtration, washed with ethanol, and air-dried: yield 1.35 g (58%); mp 167–169 °C; NMR (CF_3COOH) δ 0.83 (t, 3 H), 3.6–4.1 (m, 4 H), 7.0–8.0 (m, 10 H); IR (KBr) ν_{max} 3450, 3400, 3320, 1725, 1640 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}N_7O_5$: C, 57.01; H, 4.57; N, 21.16. Found: C, 57.01; H, 4.78; N, 21.02.

5-Amino-7-(carbethoxymethylamino)furazano[3,4-*d*]pyrimidine (6). A flask containing a suspension of 3.6 g of 5,7-bis(benzoylamino)furazano[3,4-*d*]pyrimidine in 9 mL of ethyl glycinate was placed in an oil bath at 110 °C. After 1 min of stirring at this temperature, a red solution resulted which, within 5 min, solidified to a purple mass. The reaction mixture was cooled to room temperature and slurried in 25 mL of ethanol, and the purple solid was collected by filtration, washed free of color with cold ethanol, and dried: yield 1.69 g (71%); mp 245–246 °C dec (from dioxane); NMR (Me_2SO-d_6) δ 1.16 (t, 3 H), 4.13 (q, 2 H), 4.26 (s, 2 H), 7.19 (br s, 2 H); IR (KBr) ν_{max} 3450, 3360, 1735, 1660, 1600 cm^{-1}.

Anal. Calcd for $C_8H_{10}N_6O_3$: C, 40.33; H, 4.23; N, 35.28. Found: C, 40.52; H, 4.42; N, 35.29.

2,4-Diamino-7,8-dihydro-6(5*H*)-pteridinone (8). A suspension of 235 mg of 5-amino-7-(carbethoxymethylamino)furazano[3,4-*d*]-pyrimidine in 70 mL of methanol was stirred with 120 mg of 5% Pd–C under 1 atm of hydrogen until 3 mmol of hydrogen had been consumed (ca. 45 min). The catalyst was removed by filtration, and 5 mg of *p*-toluenesulfonic acid was added to the filtrate, which was then allowed to stand at room temperature for 3 h. During this period, colorless crystals started to separate from the solution, and this process was aided by refrigeration. The precipitate was collected by filtration, washed with ethanol and ether, and dried: yield 120 mg; mp >250 °C dec. Because of its instability, this material was not further purified and was used directly in the next reaction: NMR (Me_2SO-d_6) δ 3.80 (s, 2 H), 5.4 (br s, 2 H), 5.8 (br s, 2 H), 6.43 (br s, 1 H, N-8 H), 9.4 (br s, 1 H, N-5 H); IR (KBr) ν_{max} 3400, 3175, 1690, 1660, 1600 cm^{-1}.

2,4-Diaminopteridine-6(5*H*)-one (4-Amino-4-deoxyxanthopterin) (9). A solution of 100 mg of 2,4-diamino-7,8-dihydro-6(5*H*)-pteridinone in 8 mL of 0.5 N aqueous potassium hydroxide was cooled in an ice bath. To the stirred solution was added dropwise, over a period of 10 min, a solution of 200 mg of iodine in 2 mL of ethanol. After addition was complete, the reaction mixture was stirred at 0 °C for an additional 10 min and the product was then precipitated by addition of acetic acid to neutrality. The flocculent precipitate could be collected readily by filtration if the reaction flask was first warmed for several hours. An additional precipitation of this material from dilute potassium hydroxide with acetic acid gave 85 mg (74%): mp >350 °C; IR (KBr) ν_{max} 3340, 3150, 1650, 1515, 1410 cm^{-1}; UV (0.1 N HCl) λ_{max} (log ϵ) 245 (4.13), 275 (3.64), 354 (3.86), 367 (3.82) nm.

Anal. Calcd for $C_6H_6N_6O \cdot H_2O$: C, 36.73; H, 4.11; N, 42.84. Found: C, 37.00; H, 4.55; N, 43.24.

Xanthopterin (10). A solution of 100 mg of 2,4-diamino-6(5*H*)-pteridinone in 10 mL of 5% sodium hydroxide was stirred in a plastic flask for 24 h at 100 °C. The yellow solution was diluted with water to 20 mL and filtered, and the pH was adjusted to 2 with 6 N hydrochloric acid. The precipitate which had formed was collected by filtration and redissolved in 10 mL of 2% sodium hydroxide. Reprecipitation with acetic acid then gave 85 mg of pure xanthopterin, identical in all respects with authentic material.

Registry No.—**1** (R = NH_2), 30745-07-4; **4**, 68152-16-9; **5**, 68152-17-0; **6**, 68152-18-1; **8**, 26398-12-9; **9**, 1917-45-9; **10**, 119-44-8; ethyl glycinate, 459-73-4.

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Lithiation of *N,N*-Dimethyl-3-(phenylthio)-2-propenylamine

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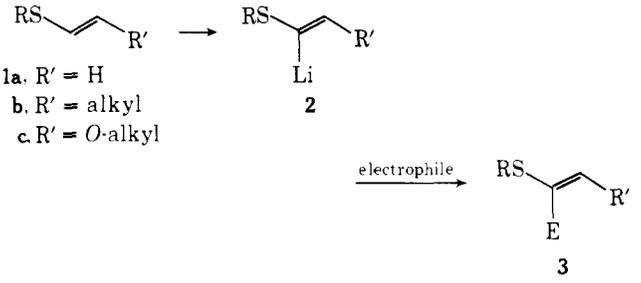
The α lithiation of vinyl sulfides (**1a,b**) is facile, and the resulting anions **2** constitute synthetic equivalents of acyl anions.[1] Possible side reactions are Michael-type additions of the metalating agent to the terminal of the olefinic bond, leading to saturated carbanions stabilized by the sp^3–d overlap.[2,3] α deprotonation, however, can be achieved exclusively by observing low temperatures and by the use of less nucleophilic metalating agents such as lithium diisopropylamide.[4,5]



1a, R′ = H
b, R′ = alkyl
c, R′ = *O*-alkyl

2

3

The latter fact is indicative of the considerable thermodynamic acidity of the α proton in such substrates ($pK_a \leq 30$).

In analyzing the directing influence of additional hetero-

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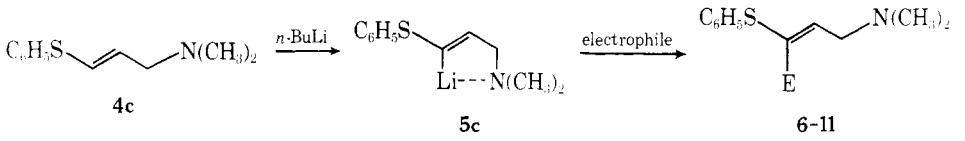
Table I. Reactions of *N,N*-Dimethyl-2-lithio-3-(phenylthio)-2-propenylamine with Electrophiles



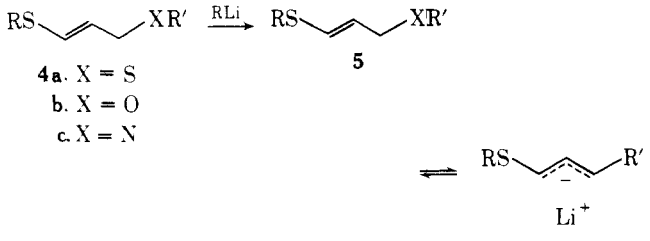
4c 5c 6-11

electrophile	registry no.	E	compd	registry no.	yield, %
D_2O	7789-20-0	D	6	68200-50-0	100
$(CH_3S)_2$	624-92-0	SCH_3	7	68200-51-1	100
t-BuNCO	1609-80-0	CONH-Bu-*t*	8	68200-52-2	79[a]
CH_3CHO	75-07-0	$CH(OH)CH_3$	9	68200-53-3	38[a]
2-CH_3O-C_6H_4CHO	135-02-4	$CH(OH)C_6H_4$-2-OCH_3	10	68200-54-4	64[a]
4-F-C_6H_4NCO	1195-45-5	$CONHC_6H_4$-4-F	11	68200-55-5	47

[a] HCl salt.

atoms in vinyl sulfides, it was found[6] that an ether function in a 2 or β position (**1c**) has no effect on the regioselectivity of the metalation. The exclusive deprotonation of the carbon atom next to sulfur is presumably due to the greater thermodynamic acidity as well as the β-directing influence of the ether oxygen.

By analogy with the corresponding benzylic systems,[7-9] the allylic thioethers **4a,b** are metalated exclusively at the sp^3 carbon, leading to allylic carbanions (**5**). In particular, 1,3-bis(methylthio)allyllithium (**5a**, R = R′ = CH_3) was intro-



duced as a synthon for a β-formylvinyl anion,[10] and more recently 3-methoxy-1-(phenylthio)-1-propene (**4b**; R = C_6H_5, R′ = CH_3) was reported to metalate rapidly with LDA.[11] The resulting allylic anion reacts in a regioselective manner with electrophiles at the carbon atom next to sulfur.

Our investigations of the reactivity of **4c** [R = C_6H_5, R′ = $(CH_3)_2$] revealed that in contrast to the sulfur and oxygen congeners **4a** and **4b**, lithiation takes place exclusively at the sp^2 carbon next to sulfur. Thus, the less electronegative nitrogen atom facilitates α lithiation as observed with regular vinyl sulfides (**1a, 1b**). The lithiation is exceedingly clean and quantitative and can be carried out with *n*-butyllithium at ice bath temperature. Even under these conditions no Michael-type addition of the metalating agent is observed. It is assumed that the basic nitrogen atom in **4c** serves as a ligand to depolymerize and thus activate the lithiating agent. The nitrogen atom also exerts a β-directing effect and stabilizes the resulting lithiated species **5c** via internal chelation.

The reactivity of **5c** toward a variety of electrophiles is demonstrated by the isolation of products **6–11** (Table I). The synthetic potential of **5c** as well as of the interesting basic ketene-*S*-acetal **7** is currently being explored.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); IR spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 using Me_4Si as an internal standard. The following abbreviations are used: (br) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (t) triplet, (q) quartet, (m) multiplet.

***N,N*-Dimethyl-3-(phenylthio)-2-propenylamine (4c).** To an ice-cold solution of dimethylamine (400 mL) in 700 mL of THF was added dropwise a solution of 3-chloro-1-(phenylthio)-1-propene[12] (185 g, 1.0 mol) in 700 mL of THF. After 18 h at room temperature, the solvent and excess dimethylamine were removed in vacuo. The residue was partitioned between ether and ice-cold 2 N NaOH (twice each). The ether solution was extracted with cold 2 N HCl (twice). The combined acidic solution was basified with excess 50% NaOH and extracted with CH_2Cl_2. The oil from the organic layer was distilled to give 124.2 g (64.4%) of amine **4c**: bp 79–80 °C (0.1 mm); NMR ($CDCl_3$) δ 2.21 (s, 6 H), 2.91–3.01 (d, 2 H), 5.62–6.51 (m, 2 H), and 7.30 (s, 5 H); IR (film) 1610, 1579, 1475, 735, and 685 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NS$: C, 68.37; H, 7.81; N, 7.25. Found: C, 68.33; H, 8.14; N, 7.44.

***N,N*-Dimethyl-3-(methylthio)-3-(phenylthio)-2-propenylamine (7).** A hexane solution of 1.6 M *n*-BuLi (7.5 mL, 12 mmol) was added dropwise to a solution of **4c** (1.93 g, 10 mmol) in 20 mL of dry ether at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1 h, whereupon a precipitate formed. A sample of the reaction mixture equivalent to 1.0 mmol of substrate was treated with D_2O. This mixture was partitioned between ether and a cold dilute Na_2CO_3 solution. The ether layer was dried (Na_2SO_4) and evaporated to give the deuterated compound **6** as an oil: NMR ($CDCl_3$) δ 2.20 (s, 6 H), 2.9–3.0 (d, 2 H), 5.66–6.0 (t, 1 H), and 7.22 (s, 5 H).

To the remainder of the reaction mixture (9.0 mmol of substrate) was added methyl disulfide (1.41 g, 15.0 mmol) in one portion. The ice bath was removed and the reaction mixture stirred for 2.0 h at room temperature. The reaction mixture was partitioned between ether and an ice-cold dilute Na_2CO_3 solution. The ether solution was washed with basic (Na_2CO_3) brine, dried, and concentrated to give 2.15 g (100%) of compound **7** as an oil: NMR ($CDCl_3$) δ 2.21 (br s, 9 H), 2.14–2.24 (d, 2 H), 6.07–6.28 (t, 1 H), and 7.26 (br s, 5 H).

***N*-*tert*-Butyl-4-(dimethylamino)-2-(phenylthio)crotonamide (8).** A solution of **4c** (3.86 g, 20 mmol) in ether was lithiated as described above. After 1.2 h at 0 °C, *tert*-butyl isocyanate (2.47 g, 25 mmol) was added neat and in one portion. The bath was removed and the reaction stirred at room temperature. After 3 h the reaction mixture was partitioned between ether and an ice-cold dilute Na_2CO_3 solution. The ether layer was washed again with basic (Na_2CO_3) brine, dried, and concentrated to give 5.9 g of crude amide **8** as an oil: NMR ($CDCl_3$) δ 1.17 (s, 9 H), 2.22 (s, 6 H), 3.25–3.35 (d, 2 H), 6.15–6.36 (t, 1 H), 7.16 (br, 1 H, ex), and 7.26 (s, 5 H). This oil was dissolved in acetone and treated with 1 equiv of HCl to give 5.19 g (79%) of **8** as the hydrochloride salt: mp 168–170 °C dec; IR (Nujol) 3275, 1667, 1611, 1520, and 940 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2OS$·HCl: C, 58.43; H, 7.66; N, 8.52. Found: C, 57.94; H, 7.47; N, 8.24.

5-(Dimethylamino)-3-(phenylthio)-3-penten-2-ol (9). A solution of **4c** (5.79 g, 30 mmol) in ether was lithiated as described. After 1.25 h at 0 °C, acetaldehyde (1.67 g, 38 mmol) was added neat and in one portion. The bath was removed and the reaction mixture stirred at room temperature. After 3 h the mixture was partitioned between ether and an ice-cold dilute Na_2CO_3 solution. The ether layer was washed with basic (Na_2CO_3) brine, dried, and evaporated to give 6.6 g of essentially pure **9** as an oil: NMR ($CDCl_3$) δ 1.33–1.43 (d, 3 H), 2.20 (s, 6 H), 2.90–3.00 (d, 2 H), 4.31–4.70 (q, 1 H), 5.49–5.75 (t, 1 H), and 7.20–7.40 (m, 5 H). This oil was dissolved in acetone and treated with 1 equiv of HCl to give 3.1 g (37.8%) of **9** as the hydrochloride salt: mp 134–136 °C; IR (Nujol) 3355, 1617, 1580, 1370, 1360, and 750 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NOS$·HCl: C, 57.02; H, 7.36; N, 5.12. Found: C, 57.17; H, 7.37; N, 5.03.

4-(Dimethylamino)-1-(2-methoxyphenyl)-2-(phenylthio)-2-buten-1-ol (10). A solution of **4c** (3.86 g, 20 mmol) in ether was lithiated as described. After 1.25 h at 0 °C, *o*-anisaldehyde (3.26 g, 24 mmol) was added neat and in one portion. The bath was removed and

the reaction mixture stirred at room temperature. After 18 h the mixture was partitioned between ether and an ice-cold dilute Na_2CO_3 solution. The ether layer was washed with basic (Na_2CO_3) brine, dried, and evaporated to give crude **10** as an oil. This was dissolved in acetone and treated with 1 equiv of HCl to give 4.71 g (64.4%) of hydrochloride salt: mp 144–146 °C dec; IR (Nujol) 3270, 1620, 1595, 1582, 1040, and 745 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_2S$·HCl: C, 62.36; H, 6.61; N, 3.83. Found: C, 62.21; H, 6.88; N, 3.65.

4-(Dimethylamino)-2-(phenylthio)-*N*-(*p*-fluorophenyl)-crotonamide (11). A solution of **4c** (3.86 g, 20 mmol) in ether was lithiated as described. After 1.25 h at 0 °C, a solution of 4-fluorophenyl isocyanate (3.29 g, 24 mmol) in 5 mL of ether was added dropwise. The bath was removed and the reaction mixture stirred at room temperature. After 18 h the reaction mixture was partitioned between ether and an ice-cold dilute Na_2CO_3 solution. The ether layer was washed with basic (Na_2CO_3) brine, dried, and evaporated to give an oily residue. Crystallization from ether–hexane gave 3.12 g (47.3%) of anilide **11**: mp 76–79 °C; NMR ($CDCl_3$) δ 2.29 (s, 6 H), 3.15–3.26 (d, 2 H), 6.06–6.28 (t, 1 H), 6.80–7.68 (m, 9 H), and 10.41 (br, 1 H, ex); IR (CH_2Cl_2) 1663, 1620, 1570, and 1212 cm^{-1}. Anal. Calcd for $C_{18}H_{19}FN_2OS$: C, 65.43; H, 5.80; N, 8.48. Found: C, 65.64; H, 5.90; N, 8.54.

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Registry No.—**4c**, 63905-40-8; **8** HCl, 68213-00-3; **9** HCl, 68200-56-6; **10** HCl, 68200-57-7; dimethylamine, 124-40-3; 3-chloro-1-(phenylthio)-1-propene, 58749-54-5.

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Synthetic Applications of *N*-Sulfonylamines: Reactions with Activated Dienes to Form Heterocycles

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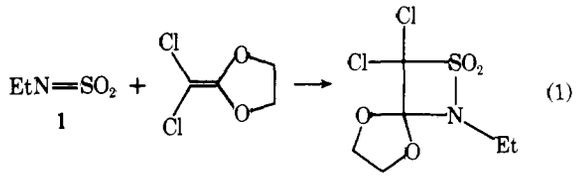
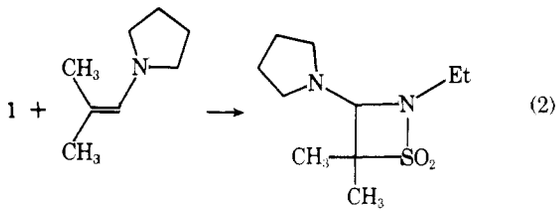
In 1967 Burgess reported the generation of a new class of heterocumulene, the *N*-sulfonylamines.[1] During the next few years he also described the generation and reactions of the related *N*-sulfonylamides[1,2] and *N*-sulfonylurethanes.[2,3] While the latter compounds were proven to be useful synthetically, the simple alkylsulfonylamines suffered from an overall lack of reactivity. Apart from interception by nucleophiles such as amines and anilines, the electrophilic reactivity of this species was limited to strongly nucleophilic olefins only. Thus Burgess was able to obtain 2 + 2 cycloadducts between *N*-ethylsulfonylamine (**1**)[4] and such reactive types as ketene acetals and enamines as shown (eq 1 and 2). Ethyl vinyl ether, however, failed to react.



(1)



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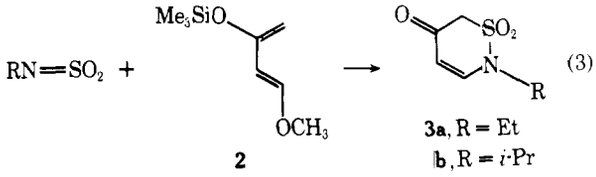
We now report that simple alkylsulfonylamines (e.g., **1**) react with certain activated dienes to form 1,2-thiazin-5(6*H*)-one 1,1-dioxides, a new heterocyclic ring system. This is an extension of the reactivity and synthetic utility of these unactivated heterocumulenes and represents the first example of their reaction with dienes in a formal 4 + 2 sense to afford six-membered heterocycles.

When a cold (−78 °C) solution of activated diene **2**[5] and a molar equivalent of triethylamine was treated with ethyl sulfamoyl chloride,[6] triethylamine hydrochloride immediately precipitated. Warming followed by filtration and concentration provided no characterizable products. However, when the reaction was worked up with aqueous acid, a single product, 2-ethyl-1,2-thiazin-5(6*H*)-one-1,1-dioxide (**3a**), was formed in 60% yield (eq 3). A similar experiment with *N*-isopropyl-

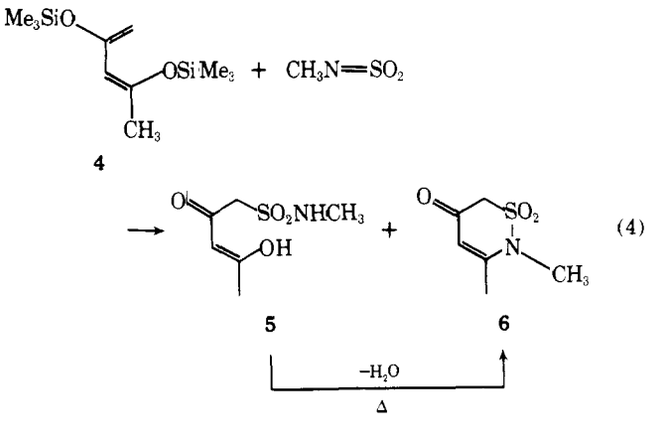


(3)

sulfonylamine gave the corresponding isopropyl derivative **3b**, in 71% yield. The assignment of these structures is based on spectral and analytical results, as well as analogy with Burgess' work.[1]

Although these products could arise from a concerted 4 + 2 cycloaddition, the failure to isolate products in the absence of an acidic workup certainly makes such an assumption suspect. Burgess investigated this question in the case of *N*-sulfonylurethanes and concluded that either a concerted or stepwise reaction was possible.[3b] To further probe this question, a second diene was examined.

When *N*-sulfonylmethylamine was generated in the presence of activated diene **4**,[7] two products arose after workup with aqueous acid[8] (eq 4).



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