Table I. Reaction of Lithiothioketene *S,S*-Acetal 2 with Various Electrophiles

entry	electrophile	reactn temp, °C	reactn time	yield, %
a	methyl iodide	−78–rt[a]	24 h	92
b	benzyl bromide	−40	3 h	78
c	benzoyl chloride	−78	4 h	82
d	benzaldehyde	−40	5 h	69
e	acetaldehyde	−78	14 h	60
f	acrolein	−78	3 h	75[b]
g	benzalacetophenone	−78	3 h	74[c]
h	methyl vinyl ketone	−78	3 h	36[c]
i	propene oxide	−20	1 week	80
j	1-butene oxide	−20	1 week	81
k	styrene oxide	−20	1 week	65
l	trimethylchlorosilane	−25	5 h	53
m	benzylideneaniline	−40	4 h	95
n	phenyl isocyanate	−78	3 h	82

[a] Room temperature. [b] Only 1,2-adduct was obtained. [c] 1,4-Adduct was obtained.

74.84 (d), 129.17 (d), 129.52 (d), 134.55 (d), 137.09 (s), 167.47 (s); high-resolution MS (*m/z*) found M^+ 240.0463, calcd for $C_{11}H_{12}O_4S$ M 240.0455. Anal. Found: C, 54.94; H, 5.04. Calcd for $C_{11}H_{12}O_4S$: C, 55.00; H, 5.04.

5-Phenyl-3-(phenylsulfonyl)tetrahydrofuran-2-one (6k). According to a procedure similar to that used for **6i**, from the alcohol **3k** (646 mg, 1.7 mmol) and *p*-TsOH (1.5 g, 6.8 mmol) in *t*-BuOH (30 mL) was obtained γ-lactone **6k** (503 mg, 98%) (cis:trans = 1:9): mp 134–135.5 °C (recrystallized from ethanol); IR ($CHCl_3$) 1780, 1450, 1330, 1150, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) trans isomer δ 2.64 (ddd, 1 H, *J* = 14.7, 9.8, and 9.0 Hz), 3.46 (ddd, 1 H, *J* = 14.7, 6.9, and 3.0 Hz), 4.18 (dd, 1 H, *J* = 9.8 and 3.0 Hz), 5.80 (dd, 1 H, *J* = 9.0 and 6.9 Hz), 7.58–8.02 (m, 10 H), cis isomer δ 2.87 (ddd, 1 H, *J* = 13.8, 10.8, and 9.5 Hz), 3.10 (ddd, 1 H, *J* = 13.8, 9.5, and 6.6 Hz), 4.41 (dd, 1 H, *J* = 10.8 and 9.5 Hz), 5.39 (dd, 1 H, *J* = 9.5 and 6.6 Hz), 7.58–8.02 (m, 10 H); ^{13}C NMR ($CDCl_3$) trans isomer 32.59 (t), 65.25 (d), 80.62 (d), 125.46 (d), 128.94 (d), 129.17 (d), 129.31 (d), 129.37 (d), 134.81 (d), 136.77 (s), 137.95 (s), 167.81 (s), cis isomer 32.16 (t), 64.33 (d), 78.72 (d), 125.86 (d), 128.94 (d), 129.17 (d), 129.23 (d), 129.63 (d), 134.61 (d), 136.92 (s), 137.55 (s), 167.10 (s); high-resolution MS (*m/z*) found M^+ 302.0612, calcd for $C_{16}H_{14}O_4S$ M 302.0612. Anal. Found: C, 63.64; H, 4.70. Calcd for $C_{16}H_{14}O_4S$: C, 63.57; H, 4.64.

5-Methyltetrahydrofuran-2-one (7i). Sulfone **6i** (4.69 g, 19.5 mmol) was dissolved in 10% aqueous THF (300 mL). Aluminum amalgam (0.195 g-atom, 5.0 g in 2% aqueous $HgCl_2$ solution) was added to the stirred solution. The resultant mixture was heated to reflux for 12 h. The resulting solid was then filtered and washed with THF. Most of the THF was removed from the filtrate, the residue was extracted with ether and dried ($MgSO_4$), the solvent was evaporated from the filtrate, and the residue was purified by silica gel column chromatography with benzene–ethyl acetate (20:1 v/v) as eluant to give **7i** as a colorless oil (0.642 g, 33% yield): bp 67–68 °C/5 mmHg; IR (neat) 2990, 1775, 1340, 1175, 940 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (d, 3 H), 1.45–2.70 (m, 4 H), 4.20–4.86 (m, 1 H).

5-Phenyltetrahydrofuran-2-one (7k). Lactone **7k** was obtained in 68% yield by the procedure described above: IR (neat) 1775, 1175, 1140, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14–2.25 (m, 1 H), 2.60–2.71 (m, 3 H), 5.49–5.54 (m, 1 H), 7.31–7.43 (m, 5 H); high-resolution MS (*m/z*) found M^+ 162.0672, calcd for $C_{10}H_{10}O_2$ M 162.0680.

Registry No. **1**, 41374-14-5; **3a**, 119336-15-1; **3b**, 119336-16-2; **3c**, 65019-70-7; **3d**, 119336-17-3; **3e**, 119336-18-4; **3f**, 119336-19-5; **3g**, 119336-20-8; **3h**, 119336-21-9; **3h** (alcohol analogue), 119336-28-6; **3i**, 119336-22-0; **3j**, 119336-23-1; **3k**, 119336-24-2; **3l**, 119336-25-3; **3m**, 119336-26-4; **3n**, 119336-27-5; **4h**, 119336-29-7; *cis*-**5h**, 119336-30-0; *trans*-**5h**, 119336-31-1; *cis*-**6i**, 119336-32-2; *trans*-**6i**, 119336-33-3; *cis*-**6k**, 72764-75-1; *trans*-**6k**, 72764-76-2; **7i**, 108-29-2; **7k**, 1008-76-0; benzyl bromide, 100-39-0; acetaldehyde, 75-07-0; acrolein, 107-02-8; benzalacetophenone, 94-41-7; methyl vinyl ketone, 78-94-4; propene oxide, 75-56-9; 1-butene oxide, 106-88-7; styrene oxide, 96-09-3; benzylideneaniline, 538-51-2; phenyl isocyanate, 103-71-9.

Reaction of 2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole with Hydrazine. The Synthesis of 4-Amino-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole

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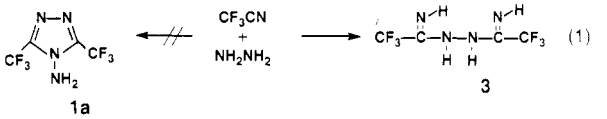
Introduction

Recently, we investigated the reaction of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole with primary amines to produce the corresponding 4-substituted 3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles.[2] In the course of this study, we had the occasion to make 4-amino-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole (**1a**). Examination of the literature revealed that the synthesis of **1a** had never been reported for the reaction of 3,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**2a**) with hydrazine, nor had its synthesis by any other method been correctly reported.

Brown and Pilipovich[3] reported in 1960 that trifluoroacetonitrile reacted with hydrazine to produce the 4-aminotriazole **1a**. Later, Brown and Wetzel[4] modified that claim and reported that the product was actually 1,2-bis(*N*-aminotrifluoroacetimidoyl)hydrazine (**3**), as shown in eq 1.



In 1966, Brown et al.[5] reported that the reaction of **2b–d** with hydrazine in methanol at 0 °C produced the corresponding 1-(*N*-aminoperfluoroalkylimidoyl)-2-(perfluoroacyl)hydrazines **4b–d**; these compounds were then treated with acetic acid at reflux to provide the corresponding 4-aminotriazoles **1b–d** in good yields (Scheme I). As means of structure proofs, **1b** and **1c** were deaminated with nitrous acid to the corresponding **5b** and **5c**, respectively, which had been made previously by the reaction of **2b** and **2c** with ammonia.[6] Haszeldine et al.[7] subsequently reported that **2a**, unlike **2b–d** previously reported by Brown et al., reacted with hydrazine in ethanol at 0 °C to afford the dihydrotetrazine **6a** in 30% yield. As means of a structure proof, **6a** (^{19}F δ = 8.4) was oxidized with $FeCl_3$ to the corresponding tetrazine **7a** (^{19}F δ = 10.5).[8] Surprisingly, we isolated **4a** in 76% yield when a methanolic solution of hydrazine at −42 °C was treated with **2a**. The isolation of **4a**, instead of the dihydrotetrazine **6a** as reported by Haszeldine et al., intrigued us so we examined the reaction more closely to determine if **6a** was a consequence of the reaction of **2a** with hydrazine at 0 °C or was

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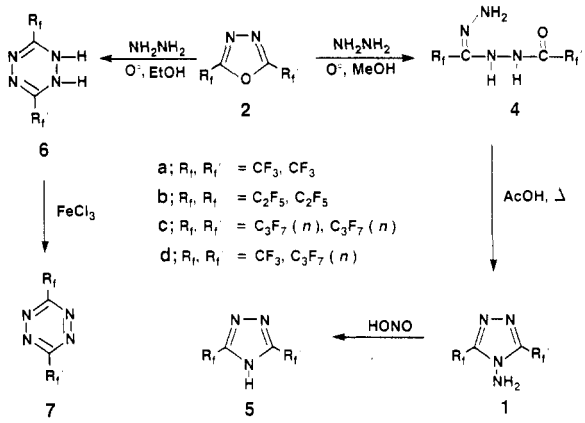
(8) Positive values to low field of external trifluoroacetic acid.

0022-3263/89/1954-1760$01.50/0

Scheme I



formed during the isolation procedure.

Results and Discussion

Fluorine nuclear magnetic resonance (^{19}F NMR) spectroscopy[9] proved very useful in monitoring the reaction of **2a** with hydrazine. An aliquot of the reaction mixture, prior to the addition of acid, revealed that all of **2a** (^{19}F δ = −67.1) had been consumed after 30 min at 0 °C and that the major product (>99%) observed was **4a** (^{19}F δ = −72.9, −72.6, −68.3, and −67.4) along with <1% of the triazole **1a** (^{19}F δ = 63.0). To ensure that **6a** was not formed under reaction conditions, authentic **6a** was added to the NMR sample. The product peaks were clearly different from the peak due to the added **6a** (^{19}F δ = −69.9). Moreover, addition of authentic **4a** only increased the intensity of the peaks already present. Thus, we concluded that **6a** must be a consequence of the isolation procedure employed.

Indeed, this is the case. Following Haszeldine's isolation procedure, concentrated hydrochloric acid was added to the ethanolic hydrazine solution at 0 °C; this reaction, as one might suspect, is very exothermic, and the reaction temperature can rise substantially if sufficient cooling is not provided. When the reaction temperature (as monitored by an internal thermometer) was maintained between −5 and 0 °C, the only product isolated was **4a** in 72% yield. The two possible products, **4a** and **6a**, are easily discernible; **4a** is a colorless solid that has no obvious odor while **6a** is a fairly volatile yellowish solid, which has a noticeable odor.

Treatment of **4a** with acetic acid at reflux produced the *N*-aminotriazole **1a** in 85% yield, similar to what was reported for **4b–d** by Brown et al. To ensure that the compound isolated was actually **1a**, an X-ray structure determination was obtained. The ORTEP representation for **1a** is shown in Figure 1.

Since **4b–d** and **6c** have been reported[5] to give **1b–d** on treatment with acid, the possibility exists that **6** might lie on the energetic pathway to **1**, i.e., it is an intermediate. It is also conceivable that **6** and **1** might actually be in equilibrium when **4** is treated with acetic acid at reflux, as shown in eq 2.

The reaction of **4a** with acetic acid at reflux is very fast. For example, a NMR sample of **4a** dissolved in DMSO-d_6 showed a noticeable exotherm when acetic acid was added

(9) The chemical shifts proved to be very sensitive to pH and to a lesser extent to the solvent used. For this reason, the addition of authentic material to the NMR sample proved to be the only way to positively identify the spectral peaks. Chemical shifts are reported relative to an external standard of fluorotrichloromethane; under these conditions, trifluoroacetic acid has a chemical shift of −76.2 ppm.

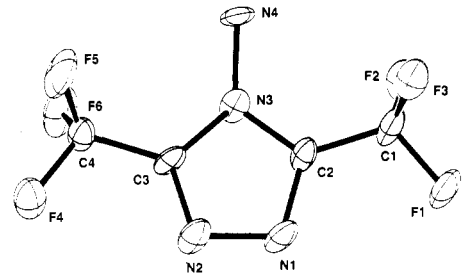
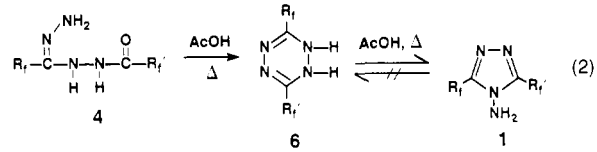


Figure 1. X-ray structure of **1a**.



a; Rf, Rf' = CF_3, CF_3
b; Rf, Rf = C_2F_5, C_2F_5
c; Rf, Rf' = C_3F_7 (n), C_3F_7 (n)
d; Rf, Rf' = CF_3, C_3F_7 (n)

at ambient temperature and was quantitatively converted to **1a** in the time it took to obtain a NMR spectrum (~5 min). On the other hand, only 49% of **6a** was converted to **1a** after 6 h in acetic acid at reflux (118 °C). This experiment convincingly demonstrates that **6a** cannot be an intermediate in the conversion of **4a** to **1a**. Furthermore, an acetic acid solution of **1a** at reflux gave no observable indication of **6a** by ^{19}F NMR after 5 days. Thus, if **1a** and **6a** are in equilibrium, the equilibrium position lies entirely on the side of **1a** in acetic acid at reflux.

Conclusion

The reaction of **2a** with hydrazine in alcoholic solutions at temperatures of 0 °C or below produced **4a**. When the pH of the reaction mixture was carefully adjusted to 6 while maintaining these temperatures, **4a** was isolated as the only product; however, when the pH was adjusted rapidly, the dihydrotetrazine **6a** was the sole product isolated, as previously reported.[7] The dihydrotetrazine **6a** was shown not to be an intermediate in the conversion of **4a** to **1a** in acetic acid at reflux. An X-ray structure determination for **1a** was obtained.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points, taken from distillations, are likewise uncorrected. Infrared spectra were obtained on a Nicolet 170 SK FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra for both ^{19}F and ^{13}C were obtained on a Varian XL-300 (300 MHz) spectrometer, and chemical shifts are reported in δ (ppm) relative to an external standard of $CFCl_3$ and an internal standard of tetramethylsilane (TMS), respectively. Mass spectra were obtained on a Finnigan TXQ46 spectrometer. Elemental analyses were obtained from Galbraith Laboratories, Inc. of Knoxville, TN. The X-ray crystal structure was solved by Molecular Structure Corporation of College Station, TX.

Materials. All solvents and starting materials from commercial sources were used without any further purification.

4-Amino-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole (1a). A solution of 5.0 g (21.0 mmol) of **4a** in 20 mL of acetic acid was stirred at reflux for 60 min, and the solvent was removed in vacuo. The residue was dissolved in 35 mL of hot toluene and filtered. Cooling in a freezer (−10 °C) overnight gave 3.94 g (85%) of **1a** as colorless needles: mp 76–77 °C; ^{19}F NMR (CD_3OD) δ −65.1 (s); ^{13}C NMR (CD_3OD) δ 115.7 (CNN), 119.2 (CF_3); IR (KBr) 3320, 3210, 1535, 1390, 1305, 1215, 1200, 1160, 990, 770 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 220 (70), 200 (23), 96 (45), 69 (100). Anal.

Calcd for $C_4H_2F_6N_4$: C, 21.83; H, 0.92; F, 51.79; N, 25.46. Found: C, 21.81; H, 0.93; F, 51.86; N, 25.48.

2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole (2a). By the procedure that we reported elsewhere,[2] **2a** was produced in 86% overall yield from ethyl trifluoroacetate and anhydrous hydrazine: bp 65 °C (lit.[10] bp 65 °C); ^{19}F NMR (CD_3OD) δ -67.1 (s). Anal. Calcd for $C_4F_6N_2O$: C, 23.32; F, 55.32; N, 13.60. Found: C, 23.17; F, 55.14; N, 13.57.

N^2-(α-Hydrazonotrifluoromethyl)-N^1-(trifluoroacetyl)-hydrazine (4a). A solution of 25 g (750 mmol) of anhydrous hydrazine in 125 mL of absolute methanol was cooled to -42 °C (CH_3CN/CO_2 bath), and 25.0 g (121 mmol) of **2a** was added dropwise (neat) over a 30-min period. After the addition was complete, the reaction was stirred for an additional 60 min. The reaction was cooled to -78 °C (acetone/CO_2 bath), and 250 mL of 2.5 M HCl was added at such a rate that the internal temperature was maintained below -40 °C. The bath was removed, and the ice was allowed to melt as the reaction warmed to -10 °C where the pH was carefully adjusted to 6 with additional 2.5 M HCl. After being allowed to stand in the freezer (-10 °C) overnight, the product was filtered, giving 22.1 g (76%) of colorless **4a**: mp 127-128 °C dec; ^{19}F NMR (CD_3OD) δ -77.5 (s, anti $COCF_3$), -76.7 (s, syn $COCF_3$), -71.3 (s, anti $CNCF_3$), -69.3 (s, syn $CNCF_3$). Anal. Calcd for $C_4H_4F_6N_4O$: C, 20.18; H, 1.69; F, 47.88; N, 23.53. Found: C, 20.04; H, 1.75; F, 47.78; N, 23.44.

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Registry No. **1a**, 103797-41-7; **2a**, 1868-48-0; **4a**, 118950-25-7; **6a**, 67096-88-2.

Supplementary Material Available: Crystallographic data and table of atomic coordinates for **1a** (13 pages). Ordering information is given on any current masthead page.

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A Short Route to 2,3-Bis(methylene)-7-oxabenzonorbornenes

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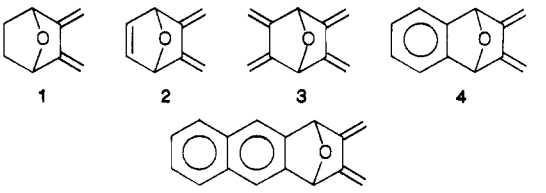
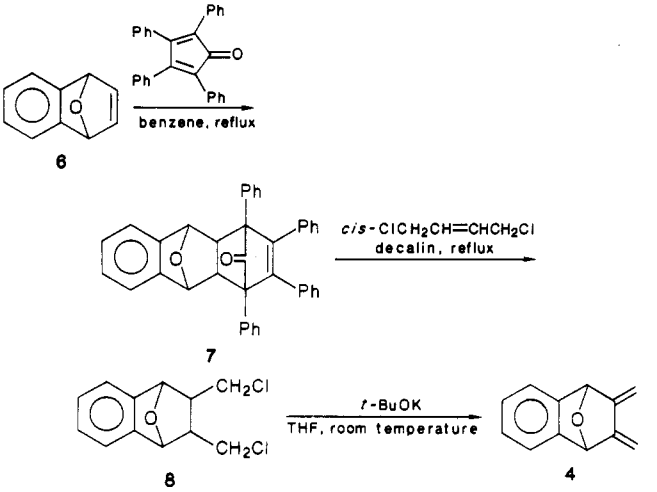
Bis(methylene)-7-oxanorbornenes **1**,[1] **2**,[2] and **3**[3] are dienes with theoretical interest[4] and synthetic[5] utility. Surprisingly, the benzo analogue **4** does not seem to have been prepared previously, although several naphtho analogues including **5** have been obtained as intermediates or byproducts in anthracycline syntheses from **3**.[5a,b,d,6]



We report here a short general route to the title compounds, including the first synthesis of **4** and an improved synthesis of **5**. The methodology is illustrated by the synthesis of **4** from naphthalene 1,4-endoxide **6**. Treatment of **6** with tetraphenylcyclopentadienone (TPCPD) gave adduct **7**, a known precursor of isobenzofuran (IBF).[7] On heating **7** in decalin with *cis*-1,4-dichloro-2-butene (DCB), the IBF-DCB adduct **8** was obtained as a mixture of endo/exo isomers (89:11). This mixture was then



dehydrohalogenated to give the desired **4**, mp 73-74 °C. The overall yield of **4** from **6** for the three steps was 65%; the only step that is not essentially quantitative is the isobenzofuran trapping (**7** → **8**). DCB has been used before as a dienophile with cyclopentadiene[1] and anthracene,[8] but does not react with furan or 1,3-cyclohexadiene;[1] as shown here, it is fairly effective toward isobenzofurans.

Tables I-III summarize our results. The only previously known final product is **5**[5b] (Table III), which was prepared by dehydrogenation of the benzyne monoadduct of **3** (18% yield, two steps, compared with 73% here for three steps).

The structures for all products are based on their method of synthesis and their spectral properties. Typical procedures and all physical constants for new compounds are given in the Experimental Section.

In summary, we describe here a general three-step synthesis of 2,3-bis(methylene)-7-oxabenzonorbornenes in 50-75% overall yield. The key step is the trapping of an isobenzofuran intermediate with 1,4-dichloro-2-butene. The product dienes should prove to be useful in linear acene synthesis and in other respects.

Experimental Section

General Procedures. NMR spectra (^1H and ^{13}C) were recorded on a Bruker WM 250-MHz spectrometer with $CDCl_3$ as solvent and $(CH_3)_4Si$ as the internal reference. Mass spectra were measured at 70 eV with a Finnigan 4000 spectrometer with the INCOS data system. Melting points (uncorrected) were determined on an electrothermal melting point apparatus (Fisher

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