Experimental Section

Isolation and Crystallization of Cyanobacterin. Batch cultures of *Scytonema hofmanni* (University of Texas Collection, 2349) were grown as described[1] and harvested after 4–5 weeks. Cyanobacterin was prepared by extraction of sonicated cells with *tert*-butyl methyl ether. Purification was completed by preparative TLC and HPLC. Presence of highly purified cyanobacterin was confirmed from NMR spectra. Details of purification and spectral data can be found in the previous publication.[3] Biological activity of the final product was determined by monitoring the inhibition of oxygenic photosynthetic electron transport in the cyanobacterium *Synechococcus* sp.[2] Highly purified cyanobacterin was crystallized by dissolving the compound in ethyl ether and adding a layer of hexane. The mixture was placed in a loosely stoppered vial and crystals grew in the hexane layer as the ether evaporated.

X-ray analysis: $C_{23}H_{23}O_6Cl$, crystal size ($0.25 \times 0.25 \times 0.30$ mm); orthorhombic; space group $P2_12_12_1$; $a = 7.707$ (1) Å, $b = 15.616$ (3) Å, $c = 17.420$ (3) Å, $z = 4$, $d_{calcd} = 1.37$ gm cm^{-3}, $\mu = 19.5$ cm^{-1}. Measurements were obtained with a Nicolet R3M automatic diffractometer using Cu Kα radiation ($\lambda = 1.54178$ Å) with a graphite monochromator in the incident beam, 3393 reflections were measured (including Friedel equivalents for absolute configuration calculations) at room temperature using the θ–2θ scan technique with a variable scan rate out to a $2\theta_{max} = 116°$. Data were corrected for Lorentz, polarization, and absorption effects (minimum and maximum transmission factors were 0.60 and 0.64, respectively). The structure was solved by direct methods.[7] Refinement was by full matrix least squares (non-H atoms anisotropic, H atoms coordinates only) using the 2837 reflections for which $|F_o| > 3\sigma|F_o|$ to a final R factor of 0.069, $R_w = 0.095$. The function minimized was $\sum\omega(|F_o| - |F_c|)^2$ where $\omega = 1/[\sigma^2(|F_o|) + g(F_o)^2]$ and $g = 0.0003$. The goodness of fit parameter was 4.7 which was acceptable when considering the marginal quality of the crystals available. Hamilton's test indicates that the probability that the configuration assignment is incorrect is less than 0.005.[8] The final difference map, except for diffraction ripples in the vicinity of the Cl atoms, was featureless. All calculations were carried out with the Shelxtl system of programs.[9]

Acknowledgment. This work has been funded by a grant to F.K.G. from the Minnesota Sea Grant College Program DOC/NA8 3AA-D-00056 R/NP-1. We thank D. Britton, University of Minnesota, for advice and helpful discussions.

Registry No. 1, 80902-00-7.

Supplementary Material Available: Tables of X-ray data for natural cyanobacterin: atomic coordinates and temperature factors, bond lengths, bond angles, anisotropic temperature factors, and hydrogen coordinates (5 pages). Ordering information is given on any current masthead page.

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An Unusual Cleavage of 2,5-Difluorobenzophenone

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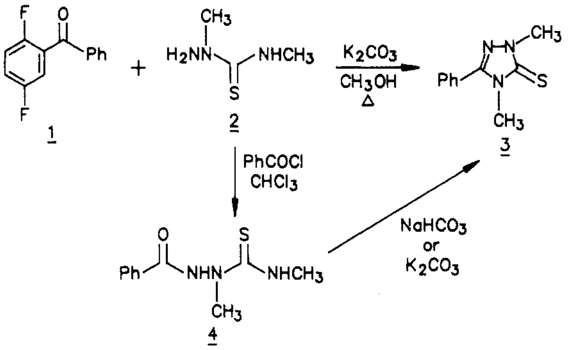
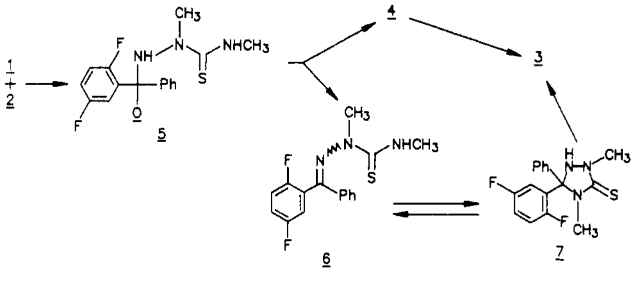
Received December 12, 1985

The alkaline cleavage of nonenolizable ketones has been the focus of considerable mechanistic[1-5] and synthetic[6-11] study. We have recently investigated the reactions of halo ketones and substituted thiosemicarbazides as routes to potential therapeutic agents.[12,13] During the course of our studies we observed an unusual reaction which resulted in both the facile cleavage of a diaryl ketone and the formation of a derivative of the 1,2,4-triazole ring system.

When 2,5-difluorobenzophenone (**1**),[13] 2,4-dimethylthiosemicarbazide (**2**),[14] and potassium carbonate were refluxed in methanol for 72 h, 2,4-dimethyl-5-phenyl-3*H*-1,2,4-triazole-3-thione (**3**)[15] was isolated in 73% yield. The structure of **3** was initially based upon its ^1H NMR spectrum and was later confirmed by an alternate synthesis[15] via 1-benzoyl-2,4-dimethylthiosemicarbazide (**4**). In order to form **3**, it is apparent that at some time during the course of the reaction, the difluorophenyl moiety must be cleaved. The relatively mild conditions under which this cleavage occurred and the good yield of **3** which was isolated prompted us to investigate this reaction more closely.



Mechanistically, formation of **3** might be rationalized in two ways.[16] Condensation of **1** and **2** presumably involves the formation of a tetrahedral intermediate **5**. Cleavage of the aryl group at this stage is reminiscent of the classical Haller–Bauer[10] reaction and would be expected to yield benzylthiosemicarbazide **4**. Cyclization of **4** under the alkaline reaction conditions should then



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(16) We briefly considered that the action of K_2CO_3 in refluxing methanol might cleave **1** directly. This was found not to be the case.

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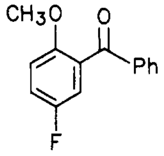
yield **3**. Indeed, refluxing **4** and potassium carbonate in methanol for 4 h afforded **3** in 91% yield. Alternatively, protonation and loss of water from **5** might yield thiosemicarbazone **6** which could then cyclize to triazolidine **7**. Elimination of the aryl moiety at this point would again yield **3**.

When the reaction was stopped after refluxing only 24 h, a complex mixture was obtained which was separated by flash chromatography,[17] affording six components. Two of these proved to be starting materials. Other components of this mixture were triazole **3**, isolated in 27% yield, and 5-fluoro-2-methoxybenzophenone (**8**),[18] isolated in 3% yield. Benzophenone **8** presumably resulted from the displacement of the activated 2-fluoro substituent of **1** by methanol. The remaining two components of the mixture were identified as thiosemicarbazone **6**, isolated in 5% yield, and the isomeric 1,2,4-triazolidine **7**, isolated in 15% yield. The structural assignments for these two isomers were based primarily upon their ^{13}C NMR spectra. Thus, thiosemicarbazone **6** exhibited an imine resonance at 152.3 ppm, while triazolidine **7** exhibited a quaternary carbon resonance at 84.1 ppm. The latter chemical shift was in good agreement with the chemical shift observed for the quaternary carbon of **9**[19] which occurred at 89.1 ppm. It is interesting to note that the protons and the carbon of the 4-methyl substituent of **7** are coupled to fluorine since their signals appear as doublets. This presumably is due to through-space coupling, a phenomenon which has ample precedent.[20] While a few 5,5-dialkyl- and 5-alkyl-5-aryl-1,2,4-triazolidine-3-thiones have been reported,[21] to the best of our knowledge **7** represents the first example of a 5,5-diaryl derivative of this ring system.



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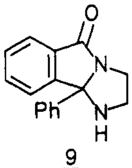

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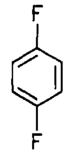
Although not isolated, two additional components of the reaction mixture were detected by GC/MS, those being 1,4-difluorobenzene (**10**) and 4-fluoro-anisole (**11**). The formation of both **10** and **11** was consistent with the hypothesis that the difluorophenyl moiety was ejected as an aryl anion which either was protonated yielding **10** or eliminated fluorine affording a benzyne which added methanol giving **11**.[22,23] Similar results have been observed by both Bunnett[1] and Hodge[3] for the cleavages of 2-halobenzophenones by either potassium amide or potassium *tert*-butoxide. Finally, it should be noted that at no time were we able to detect benzoylthiosemicarbazide **4** in the reaction of **1** and **2**.



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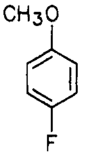

11

In order to confirm that **6** and **7** could be transformed to **3**, each compound was resubjected to the original reaction conditions. Thus refluxing thiosemicarbazone **6** and potassium carbonate in methanol gave triazole **3** in 75% yield, while under identical conditions, triazolidine **7** afforded **3** in 72% yield. In each reaction, the presence of the other isomer was detectable by both TLC and GC. Also detectable in both reactions was the presence of small amounts of benzophenone **1**. In fact after refluxing 24 h both **6** and **7** established essentially the same reaction mixtures as judged by GC. The cleavage of substituents from the 5-position of a triazolidinethione has previously been noted by Jochims[24,25] who observed the cleavage of alkyl groups from certain 5-alkyl-5-aryl-1,2,4-triazolidine-3-thiones.

In summary, this study demonstrates that the reaction of benzophenone **1** and thiosemicarbazide **2** in the presence of potassium carbonate results in the facile formation of triazole **3**. While we have evidence suggesting that thiosemicarbazone **6** and triazolidine **7** may be intermediates in this reaction, we cannot exclude the possibility that the reaction may be proceeding via formation of benzoylthiosemicarbazide **4** which undergoes ring closure too rapidly for its observation. In either case, the reaction is in a state of equilibrium which undoubtedly is shifted to the observed product **3** by the irreversible cleavage of the difluorophenyl moiety.

Experimental Section

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 180 spectrometer. NMR spectra were obtained on Varian EM390 and FT80A spectrometers. Chemical shifts are expressed in δ values with Me_4Si as an internal standard. MS data were determined with a Finnigan MAT 4600 system. GC data were obtained with a Hewlett-Packard 5890A system. Criteria used to establish identity were superimposable IR and NMR spectra, mixture mp determination, and idetical R_f values in two solvent systems.

2,4-Dimethyl-5-phenyl-3*H*-1,2,4-triazole-3-thione (3). Benzophenone **1** (0.44 g, 2.0 mmol), thiosemicarbazide **2** (0.24 g, 2.0 mmol), and K_2CO_3 (0.28 g, 2.0 mmol) were refluxed in CH_3OH (10 mL) for 72 h. The solvent was evaporated, and the resulting yellow residue was treated with H_2O. The aqueous mixture was extracted with CH_2Cl_2, and the combined CH_2Cl_2 extracts were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was evaporated to a pale yellow solid, which was purified by flash chromatography using 5% $EtOAc/CH_2Cl_2$. Crystallization from $i\text{-}C_3H_7OH$ gave colorless plates: 0.30 g (73%); mp 133–135 °C (lit.[15] mp 135.5–136 °C); identical with an authentic sample.[15]

Reaction of 4 and K_2CO_3. Benzoylthiosemicarbazide **4** (0.75 g, 3.4 mmol) and K_2CO_3 (0.47 g, 3.4 mmol) were refluxed in CH_3OH (17 mL) for 4 h. The reaction was then worked up as described above giving **3** as a colorless solid, which crystallized from $i\text{-}C_3H_7OH$ as colorless plates: 0.63 g (91%); mp 133–135 °C; identical with an authentic sample.[15]

Reaction of Benzophenone 1 and Thiosemicarbazide 2 for 24 h. Benzophenone **1** (13.1 g, 60.0 mmol), thiosemicarbazide **2** (7.15 g, 60 mmol), and K_2CO_3 (8.30 g, 60.0 mmol) were refluxed in CH_3OH (300 mL) for 24 h. The reaction was worked up as previously described affording a yellow oil, which was purified by flash chromatography using the step-gradient 20% hexane/CH_2Cl_2, 2% $EtOAc/CH_2Cl_2$, and 30% $EtOAc/CH_2Cl_2$. This

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(22) We were not able to detect any 3-fluoroanisole in this reaction by GC/MS.

(23) We considered that 11 may have resulted from cleavage of benzophenone 8. This was found not to be the case.

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resulted in the isolation of six compounds which are presented in order of their elution. **2,5-Difluorobenzophenone (1)**, after distillation at reduced pressure, was isolated as a clear, colorless oil: 5.1 g (39% recovery); bp 120–125 °C (0.35 mm) [lit.[13] bp 120–123 °C (0.35 mm)]. **5-Fluoro-2-methoxybenzophenone (8)**, after crystallization from hexane, was isolated as beige prisms: 0.38 g (3%); mp 78–80 °C (lit.[18] mp 80 °C); ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3, CH_3), 6.8–7.9 (m, 8, Ar); EIMS, m/z (relative intensity) 230 (34, M^+). **2,5-Difluorobenzophenone 2,4-dimethylthiosemicarbazone (6)** was flash chromatographed a second time using 10% EtOAc/hexane affording **6** as a yellow foam:[26] 0.96 g (5%); IR ($CHCl_3$) 1550 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.16 (d, 3, CH_3, J_{HH} = 5 Hz), 3.27 (s, 3, CH_3), 6.7–7.8 (m, 9, Ar, NH); ^{13}C NMR ($CDCl_3$) 32.1 (CH_3), 40.9 (CH_3), 115–120 (overlapping m), 127.6, 128.2, 130.6, 136.3, 152.3 (C=N), 155.1 (d, J_{CF} = 248.3 Hz), 158.2 (d, J_{CF} = 247.7 Hz), 182.1 (C=S); EIMS, m/z (relative intensity) 319 (50, M^+). **5-(2,5-Difluorophenyl)-2,4-dimethyl-5-phenyl-1,2,4-triazolidine-3-thione (7)**, after crystallization from CCl_4, was isolated as yellow prisms: 2.94 g (15%); mp 166–168 °C; IR (KBr) 3180 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.07 (d, 3, 4-CH_3, J_{HF} = 4 hz), 3.37 (s, 3, 2-CH_3), 4.46 (s, 1, NH), 6.9–7.6 (m, 8, Ar); ^{13}C NMR 31.9 (d, 4-CH_3, J_{CF} = 7.4 Hz), 35.4 (2-CH_3), 84.1 (C_5), 115–119 (overlapping m), 126.4, 128.8, 129.4, 137.1, 155.0 (d, J_{CF} = 244.2 Hz), 158.7 (d, J_{CF} = 243.7 Hz), 179.4 (C=S); EIMS, m/z (relative intensity) 319 (100, M^+). Anal. Calcd for $C_{16}H_{15}F_2N_3S$: C, 60.17; H, 4.73; N, 13.16. Found: C, 59.92; H, 4.70; N, 13.20. **2,4-Dimethyl-5-phenyl-3*H*-1,2,4-triazole-3-thione (3)**, after crystallization from i-C_3H_7OH, was isolated as colorless plates: 3.3 g (27%); mp 133–135 °C; identical with an authentic sample.[15] **2,4-Dimethylthiosemicarbazide (2)**, after crystallization from i-C_3H_7OH, was isolated as colorless needles: 2.2 g (31% recovery); mp 135–137 °C (lit.[14] mp 137–138 °C).

Reaction of 6 and K_2CO_3. Thiosemicarbazone **6** (0.37 g, 1.2 mmol) and K_2CO_3 (0.16 g, 1.2 mmol) were refluxed in CH_3OH (5.5 mL) for 17 h. The reaction was then worked up as previously described affording a pale yellow solid. Purification by preparative-layer chromatography using 20% EtOAc/hexane and crystallization from i-C_3H_7OH gave **3** as colorless plates: 0.18 g (75%); mp 133–135 °C; identical with an authentic sample.[15]

Reaction of 7 and K_2CO_3. Triazolidine **7** (2.00 g, 6.26 mmol) and K_2CO_3 (0.87 g, 6.3 mmol) were refluxed in CH_3OH (30 mL) for 24 h. The reaction was then worked up as previously described giving a pale yellow solid. Purification by flash chromatography using 2% $EtOAc/CH_2Cl_2$ and crystallization from i-C_3H_7OH afforded **3** as colorless plates: 0.92 g (72%); mp 133–135 °C; identical with an authentic sample.[15]

Registry No. 1, 85068-36-6; 2, 79-19-6; 3, 7112-00-7; 4, 7112-01-8; 6, 100994-58-9; 7, 100994-59-0; 8, 342-59-6.

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(26) A satisfactory elemental analysis could not be obtained for **6**.

Delocalized Carbanions: 3,3′,5,5′-Tetramethylenebiphenyl Tetraanion, a New Tetraanion

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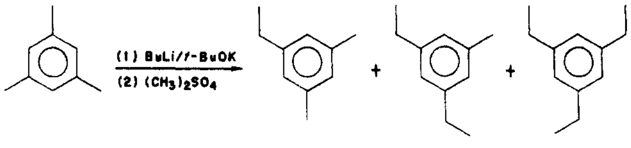
Received August 6, 1985

There have been many studies on delocalized carbanions in the past several years.(1–5) Indeed, carbanions can be very useful synthetically in a number of ways. Presently, we are studying new routes to anionic initiators to prepare linear and star polymers from delocalized carbanions where one arm of the star forms for each charge on the carbanion. In a previous paper we reported the use of the allyl anion (**1**), 2-methylenepropylenyl dianion (**2**), and the cycloheptatrienyl trianion (**3**) as anionic initiators.[5]

Table I. Quench Products of the Mesitylene Anions



4 **5a** **5b** **5c**

metalating system[a]	solvent/reactn temp (°C)	av[b] charge	prod. ratios **4:5a:5b:5c**
6	pentane/25	1.3	3:46:16:1
3.3	pentane/25	2.0	1:7:20:7
3.3	cyclohexane/78	2.4	1:1:2.7:3
4	hexane/69	2.7	1:1.5:7.5:37
6	hexane/69	2.6	1:1:5:14.5
4	heptane/90	1.9	1:1:3:9

[a] Equivalents of both n-BuLi and t-BuOK; all reactions were carried out for 24 h except for the first which was 2.5 h. [b] Determined from quench products by GC.

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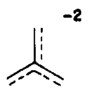

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3

The progression of mono-, di-, and trianion would naturally lead to a tetraanion. In the quest for precursors for a tetraanion, both benzylic and allylic precursors were initially investigated. Under the more rigorous conditions used, the benzylic precursors were shown not to undergo butyl addition side reactions. We report the preparation of 3,3′,5,5′-tetramethylenebiphenyl tetraanion (**9**) prepared from 3,3′,5,5′-tetramethylbiphenyl (TMBP) (**8**). A thallium(I) bromide/Grignard coupling procedure was utilized to couple two molecules of 5-bromomagnesio-m-xylene (**7**) (the Grignard of 5-bromo-m-xylene (**6**)) to prepare **8**.[6]

In the past, researchers have used n-butyllithium/tetramethylethylenediamine as a metalating reagent.[7,8] Lochmanns' base, n-butyllithium/potassium *tert*-butoxide, has been found to be a faster, less nucleophilic, metalating reagent for the preparation of delocalized carbanions.[4] For these reasons, Lochmann' base was used as the metalating reagent for **8**.

Mesitylene was used as a model system to obtain optimum metalating conditions. The amount of base, the solvent, and the reaction temperature were all varied. The carbanions prepared were quenched with dimethyl sulfate and characterized via ^{1}H NMR and GC. The results of several reactions are summarized in Table I.

The increase of reaction temperature from room temperature to that of refluxing solvent has a remarkable effect on the metalating power of the base (from an average charge of 1.3 at room temperature to 2.7 at reflux). Metalation of allylic moieties at elevated temperatures produce side reactions from butyl addition which are not

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