Adducts 21. The ^1H NMR spectrum (80 MHz) of the crude adduct mixture showed four separated doublets in the 9–10-ppm region from the aldehyde resonances of the four isomers. The meta adduct doublets (1:1) were found at 9.15 (endo) and 9.76 ppm (exo). The crude mixture was chromatographed on silica gel (230–440 mesh) in ethyl acetate–hexane (3:5) and two fractions containing pure *exo*-**21** and mainly *endo*-**21** were collected but neither fraction yielded any crystals.

***exo*-21**: ^1H NMR (80 MHz) δ 1.75 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 8.3, J_{gem} = 12.0), 2.3–2.9 (complex m, 2 H, H-2 and H-3β), 5.51 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.6), 6.02 (q, 2 H, OCH_2O, J_{AB} = 1.3), 6.8, 6.95 (2 × s, 1 H each, Ar H), 9.85 (d, 1 H, CHO, J = 2.9); IR ($CHCl_3$) 2780, 2740 (w), 1727 cm^{-1}; MS, 243 (15), 187 (100), 159 (15), 101 (9).

***endo*-21**: ^1H NMR (80 MHz) δ 1.82 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 3.9, J_{gem} = 11.7), 2.5 (complex m, 1 H, H-3β), 3.53 (m, 1 H, H-2, $J_{2,CHO}$ = 1.47, $J_{2,3\alpha}$ = 3.9, $J_{2,3\beta}$ = 10.1), 5.47 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.6), 6.0 (q, 2 H, OCH_2O, J_{AB} = 1.0), 6.8, 6.92 (2 × s, 1 H each, Ar H), 9.30 (d, 1 H, CHO, $J_{2,CHO}$ = 1.47).

Adducts 22. Crystallization of the crude endo–exo mixture from ether yielded the endo isomer of **22**: mp 144 °C; ^1H NMR (250 MHz) δ 1.83 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 4.05, J_{gem} = 11.3), 2.09 (s, 3 H, $COCH_3$), 2.40 (ddd, 1 H, H-3β, $J_{3\beta,4}$ = 4.9, $J_{2,3\beta}$ = 9.7, J_{gem} = 11.3), 3.61 (dd, 1 H, H-2, $J_{2,3\alpha}$ = 4.05, $J_{2,3\beta}$ = 9.7), 3.95 (s, 3 H, OMe), 5.39 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.9), 5.96 (q, 2 H, OCH_2O, J_{AB} = 1.05), 6.77, 6.98 (s, 2 × Ar H); MS, 290 (23), 220 (100), 189 (40), 162 (29), 133 (11); IR ($CHCl_3$) 1746, 1712 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.06; H, 4.82. Found: C, 62.06; H, 4.95.

Adducts 23. The crude mixture of adducts was chromatographed on a silica gel column in ethyl acetate/ligroin (1:1) and the pure endo isomer crystallized from ether–methanol: mp 175 °C; ^1H NMR (80 MHz) δ 1.73 (dd, 1 H, H-3α, J_{gem} = 11.2 Hz, $J_{2,3\alpha}$ = 3.9), 2.7 (ddd, 1 H, H-3β, J_{gem} = 11.2, $J_{2,3\beta}$ = 10.6, $J_{3\beta,4}$ = 4.7), 3.34 (dd, 1 H, H-2, $J_{2,3\alpha}$ = 3.9, $J_{2,3\beta}$ = 10.6), 4.02 (s, 3 H, OMe), 5.5 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.7), 6.05 (q, 2 H, OCH_2O, J = 1.5), 6.8, 7.15 (s, 2 × Ar H); IR (KBr) 2325, 1770 cm^{-1}; MS, 273 (8), 220 (100), 189 (20), 162 (16), 133 (8). Anal. Calcd for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.03; N, 5.13. Found: C, 61.57; H, 4.09; N, 4.90.

Adducts 24. The endo–exo mixture of ortho adducts could not be separated by chromatography or crystallization: MS (mixture), 306 (12), 275 (6), 220 (100), 189 (30), 162 (19), 133 (6).

Adducts 25. The mixture of ortho and meta adducts (6.3:1) was chromatographed on a silica gel column in ethyl acetate–hexane (7:3) and the ortho,endo isomer crystallized from ether–methylene chloride: mp 129 °C; ^1H NMR (80 MHz) δ 1.8 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 4.0, J_{gem} = 12.0), 2.42 (ddd, 1 H, H-3β, $J_{3\beta,4}$ = 4.8, J_{gem} = 12.0, $J_{2,3\beta}$ = 10.1), 3.28 (m, 1 H, H-2), 4.0 (s, 3 H, OMe), 5.45 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.8), 5.95 (q, 2 H, OCH_2O), 6.8, 6.92 (s, 2 × Ar H), 9.3 (d, 1 H, C*H*O, J = 2.5); MS, 276 (14), 220 (100), 189 (32), 162 (21), 133 (10). Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.35. Found: C, 60.78, H, 4.36.

Acknowledgment. We thank the National Sciences and Engineering Research Council of Canada for support of this work.

Registry No. **2**, 104172-43-2; **3**, 104172-48-7; **4**, 74879-22-4; **5**, 87850-43-9; **6**, 104172-44-3; **7**, 104172-40-9; **8**, 104172-45-4; *cis*-**10**, 104172-41-0; *trans*-**10**, 104172-42-1; *cis*-**11**, 104172-46-5; *trans*-**11**, 104172-47-6; **18** (isomer 1), 104172-49-8; **18** (isomer 2), 104264-05-3; **19** (isomer 1), 104172-50-1; **19** (isomer 2), 104264-06-4; **20** (isomer 1), 104172-51-2; **20** (isomer 2), 104264-07-5; **20** (isomer 3), 104172-56-7; **20** (isomer 4), 104264-13-3; **21** (isomer 1), 104172-52-3; **21** (isomer 2), 104264-08-6; **21** (isomer 3), 104172-57-8; **21** (isomer 4), 104264-14-4; **22** (isomer 1), 91758-99-5; **22** (isomer 2), 104264-09-7; **23** (isomer 1), 104172-53-4; **23** (isomer 2), 104264-10-0; **24** (isomer 1), 104172-54-5; **24** (isomer 2), 104264-11-1; **25** (isomer 1), 104172-55-6; **25** (isomer 2), 104264-12-2; **25** (isomer 3), 104172-58-9; **25** (isomer 4), 104264-15-5.

Supplementary Material Available: Tables S1–S4 and X-ray crystallographic data for **2** (4 pages). Ordering information is given on any current masthead page.

New Derivatizing Agents for Amino Acids and Peptides. 1. Facile Synthesis of N-Substituted 1-Cyanobenz[*f*]isoindoles and Their Spectroscopic Properties

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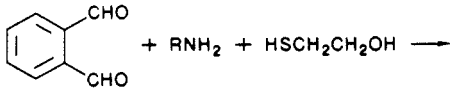
2,3-Naphthalenedicarboxaldehyde (NDA) is shown to be a very useful reagent for the derivatization of primary amines, amino acids, and small peptides. The reaction of these amino compounds with NDA and cyanide ion produces highly fluorescent 2-substituted 1-cyanobenz[*f*]isoindoles that are relatively stable. The physical and fluorescent properties of a variety of 1,2-disubstituted benz[*f*]isoindoles are presented.

The reaction of the fluorogenic reagent, *o*-phthalaldehyde (OPA, 1), with a primary amine function and a nucleophile such as 2-mercaptoethanol to produce a highly fluorescent N-substituted isoindole has become a standard method for the very low-level analysis of amines and amino acids.[1] Despite the widespread analytical application of this reagent, a number of drawbacks make it less than an ideal method. For example, the isoindoles **2** produced in the derivatization are relatively unstable and decompose to nonfluorescent products.[2a] Furthermore, it has been reported that OPA fails to give fluorescent products with small peptides,[2b] thus limiting the applications to simple amino acids.



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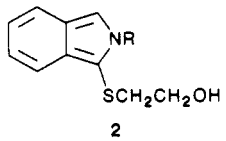


2

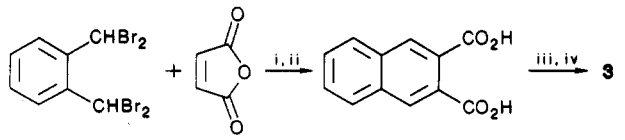
At the onset of this work, it was our goal to develop new derivatizing reagents that would retain the desirable

(1) (a) Roth, M. *Anal. Chem.* **1971**, *43*, 880. (b) Simons, S. S., Jr.; Johnson, D. F. *J. Am. Chem. Soc.* **1976**, *98*, 7098. (c) Simons, S. S., Jr.; Johnson, D. F. *J. Chem. Soc., Chem. Commun.* **1978**, 374. (d) Simons, S. S., Jr.; Johnson, D. F. *J. Org. Chem.* **1978**, *43*, 2886. (e) Lee, K. S.; Drescher, D. G. *Int. J. Biochem.* **1978**, *9*, 457.

(2) (a) For leading references see: Stobaugh, J. F.; Repta, A. J.; Sternson, L. A. *J. Org. Chem.* **1984**, *49*, 4306. (b) For leading references see: de Montigny, P.; Sternson, L. A. *Anal. Lett.* **1984**, *17*, 1893.

0022-3263/86/1951-3978$01.50/0

Scheme I[a]



[a] Key: (i) NaI, DMF; (ii) NaOH, H_2O, H_3O^+; (iii) $LiAlH_4$, Et_2O; (iv) oxalyl chloride, Me_2SO, CH_2Cl_2.

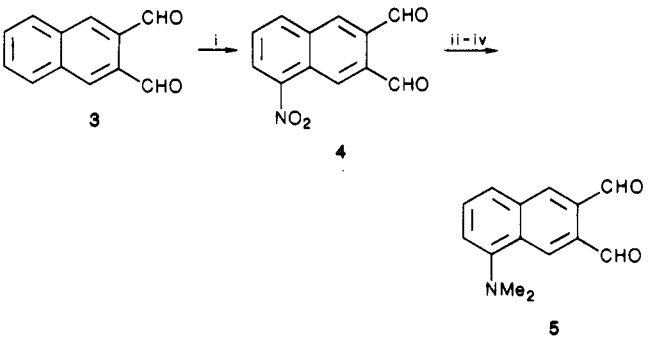
fluorogenic properties of OPA while at the same time adding certain new features such as greater solution stability and higher fluorescence efficiency of the product isoindole, derivatization of small peptides, and greater efficiency in the isoindole formation reactions. On the basis of recent work on benz[*f*]isoindoles by Rettig and Wirz,[3] 2,3-naphthalenedicarboxaldehyde (NDA, **3**) was thought to be an excellent candidate for such a derivatizing agent. In addition, 5-(*N*,*N*-dimethylamino)-2,3-naphthalenedicarboxaldehyde (DMA-NDA, **5**) was also selected as a candidate because (1) it was anticipated that it would have greater aqueous solubility—an important consideration in the low-level analysis of amino acids and peptides by RP-HPLC—and (2) the benz[*f*]isoindoles derived from it could conceivably exhibit enhanced fluorescence efficiency. In this paper we present our results on the synthesis of a variety of 1,2-disubstituted benz[*f*]-isoindoles and their physical and fluorescence properties.

Results

Synthesis of NDA and DMA-NDA. Initially, NDA was synthesized from 2,3-dimethylnaphthalene by the method of Ried.[4] Because 2,3-dimethylnaphthalene is no longer commercially available and is not readily available by synthesis, we have developed an attractive, efficient route to NDA is outlined in Scheme I[5] and detailed in the Experimental Section. The construction of the carbon skeleton is based on the generation of a dibromo-*o*-quinomethide from $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene by iodide and its subsequent Diels–Alder reaction with maleic anhydride. Conversion of this diacid to NDA was accomplished by the standard reduction–partial oxidation sequence as outlined in Scheme I.

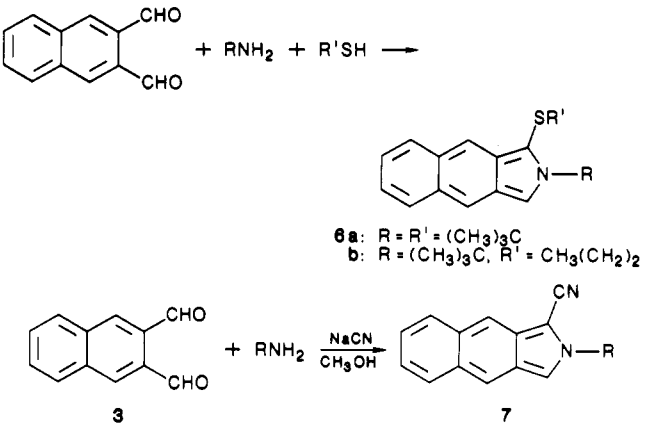
5-(*N*,*N*-Dimethylamino)-2,3-naphthalenedicarboxaldehyde (**5**) was prepared from NDA employing the sequence in Scheme II. That the nitration of NDA occurred at the 5-position was established by the ^1H NMR spectrum of **4** in which C1 and C4 protons appear as singlets at δ 8.59 and 9.15, respectively. The protons on C6 and C8 appear as doublets at δ 8.51 (J = 8 Hz) and 8.35 (J = 8 Hz) whereas the C7 proton appears as an overlapping doublet of doublets at δ 7.85 (J = 8, 8 Hz). The nitro dialdehyde **4** was first converted to the cyclic diethyl acetal and then hydrogenated (Pd/C) in the presence of formaldehyde to give the dimethylamino group. Hydrolysis of the diethyl acetal gave **5**. The aldehydic protons in the ^1H NMR of **5** appear as singlets at δ 10.71 and 10.58, the methyl groups attached to nitrogen also appear as a singlet at δ 2.96 and the splitting pattern of the aromatic protons was again consistent with a dimethylamino substituent located at C5.

Scheme II[a]



[a] Key: (i) HNO_3, $(CH_3CO)_2O$, 0 °C; (ii) EtOH, TsOH; (iii) H_2, CH_2O, Pd/C; (iv) H_3O^+.

Reactions of NDA and DMA-NDA with Primary Amines and Thiols. NDA reacted rapidly with *tert*-butylamine and *tert*-butyl mercaptan in ethanol to form benz[*f*]isoindole **6a**, which crystallized directly from the



reaction mixture as yellow-orange needles. The benz[*f*]-isoindole **6a** was moderately stable and could be stored in the refrigerator for several months without notable decomposition. Substitution of propylamine for *tert*-butylamine led to rapid formation of the benz[*f*]isoindole **6b** (by NMR analysis) which, however, proved to be very unstable and decomposed rapidly on exposure to air. Consequently, this derivative appears to provide no significant advantage over the traditional OPA method.[1]

Reaction of NDA/CN and DMA-NDA/CN with Primary Amines. Because electron-withdrawing groups are reported to stabilize benz[*f*]isoindoles,[6] we were encouraged to examine the reactions of NDA using cyanide ion as the nucleophile[7] for the derivatization of amines and amino acids. When NDA, sodium cyanide, and a primary amine were mixed in methanol at room temperature, the reaction mixture became highly fluorescent and the 1-cyano 2-substituted benz[*f*]isoindoles **7** were formed rapidly and in good yield. They were found to be much more stable than the benz[*f*]isoindoles **6** and could be isolated easily and stored in the refrigerator for several months without significant decomposition. Their structures are fully supported by their spectral properties (see the Experimental Section). A possible mechanism accounting for the formation of the benz[*f*]isoindoles **7** is shown in Scheme III.[8]

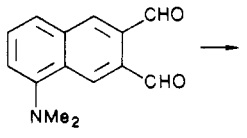
(3) Rettig, W.; Wirz, J. *Helv. Chim. Acta* **1976**, *59*, 1054.
(4) Ried, W.; Bodem, H. *Chem. Ber.* **1956**, *89*, 708.
(5) (a) Step (i) was a modification of the procedure of: Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1959**, *81*, 6458. (b) The reduction of naphthalene-2,3-dicarboxylic acid has been reported previously: Birkofer, L.; Gruner, W.; Stuhl, O. *J. Organomet. Chem.* **1980**, *194*, 159.
(6) For a recent review see: Bonnett, R.; North, S. A. *Adv. Heterocycl. Chem.* **1981**, *29*, 341.
(7) D'Amico, J. J.; Stults, B. R.; Ruminski, P. G.; Wood, K. V. *J. Heterocycl. Chem.* **1983**, *20*, 1283.
(8) For a recent study of the mechanism of the reaction of primary amines with OPA and thiols, see: Wong, O. S.; Sternson, L. A.; Schowen, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 6421.

Table I. Yields, MS (EI), and Fluorescence Quantum Yield Data for Benz[f]isoindoles 7

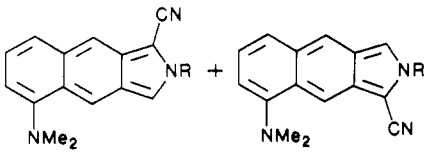
isoindole	R	% yield	MS (EI) m/e (rel intens)	ϕ_f[c]
7a	$CH_2CH_2CH_3$	58	234 (71, M^+), 206 (18), 192 (100)	0.41
7b	$CH_2CH_2CH_2CH_3$	68	248 (84, M^+), 206 (100), 192 (85)	0.38
7c	$C(CH_3)_3$	72	248 (18, M^+), 192 (100)	0.26
7d	CH_2CO_2Na	80	250 (15, M^+), 206 (68), 191 (43)[a]	0.66
7f	$CH(CH_3)CO_2Na$	99	264 (6, M^+), 220 (20), 192 (19), 191 (13)[a]	0.57
7h	$CH_2CONHCH_2CO_2Na$	82	308 (67, M^+), 192 (27)[a,b]	0.49
7i	$CH(CH_3)CONHCH(CH_3)CO_2Na$	67	335 (4, M^+), 192 (9)[a]	0.50

[a] MS recorded on carboxylic acid. [b] CI spectrum. [c] Phosphate buffer (0.05 M), pH 7.0/CH_3CN (40/60).

We had anticipated that the interaction of the electron-donating dimethylamino group with the aldehyde groups would provide the needed differentiation between the aldehyde groups to give only a single isomeric adduct in the reaction of **5** with primary amines and sodium cyanide. Unfortunately, the reaction of **5** with *tert*-butylamine or glycine and sodium cyanide produced two isomeric benz[*f*]isoindoles **8** and **9** in essentially a 1:1 ratio. We were able to obtain one of the isomeric benz[*f*]isoindoles (**8a** or **9a**) in pure form, but it was not possible to make an unambiguous structural assignment.



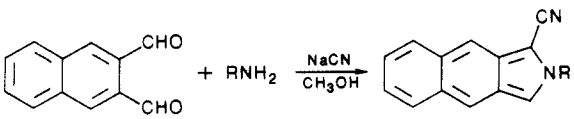
5



8a, R = $(CH_3)_3C$
b, R = CH_2CO_2H

9a, R = $(CH_3)_3C$
b, R = CH_2CO_2H

Reaction of NDA/CN with Amino Acids and Dipeptides. The reaction of NDA with glycine and *d,l*-alanine in the presence of sodium cyanide instantaneously gave a highly fluorescent reaction mixture from which the benz[*f*]isoindoles **7d** and **7f** were obtained. By way of



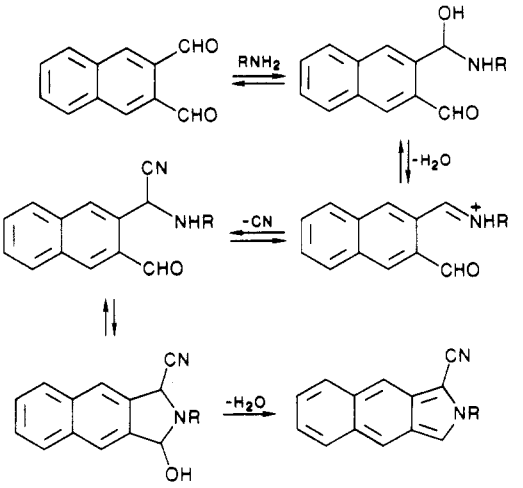
3

7a, R = $CH_3(CH_2)_2$
b, R = $CH_3(CH_2)_3$
c, R = $(CH_3)_3C$
d, R = CH_2CO_2Na
e, R = CH_2CO_2H
f, R = $CH(CH_3)CO_2Na$
g, R = $CH(CH_3)CO_2H$
h, R = $CH_2CONHCH_2CO_2Na$
i, R = $CH_2CONHCH_2CO_2H$
j, R = $CH(CH_3)CONHCH(CH_3)CO_2Na$
k, R = $CH(CH_3)CONHCH(CH_3)CO_2H$

comparison, the reaction was also performed with the dipeptides glycylglycine and D-alanyl-D-alanine, both of which required a somewhat longer period to reach completion. Once again, the products were highly fluorescent and sufficiently stable to allow isolation and complete characterization. These also proved to be stable upon storage for several months.

Fluorescent Properties of the Cyanobenz[*f*]isoindoles. The fluorescence emission spectra of a number of the benz[*f*]isoindoles **7** were determined in 40% 0.05 M aqueous phosphate buffer with excitation at 366 nm and the emission monitored at 485 nm, near the maximum for all of the stable benz[*f*]isoindoles studied. The absolute fluorescence quantum efficiencies were determined relative

Scheme III



to quinine bisulfate standard and were corrected for instrumental spectral response. The values, which are given in Table I, range from 0.26 for the *tert*-butyl derivative to 0.66 for the sodium salt of glycine, i.e. **7d**.

Conclusions. The cyanobenz[*f*]isoindoles produced by the reaction of NDA, a primary amine, and cyanide ion are superior derivatives for the very low-level analysis of primary amines and amino acids. They exhibit excellent fluorescent properties and good stability. A separate report describes the use of this system for the quantitative analysis of amino acids and small peptides.[9]

Experimental Section

General Procedures. Melting points were determined on a Fisher-Johns hot-stage apparatus and are uncorrected. Infrared spectra (IR) were determined on a Beckman Acculab 3 grating spectrophotometer or an IBM IR/32 FTIR. ^1H nuclear magnetic resonance spectra were recorded on the following instruments: 60 MHz, Varian EM360; 80 MHz, Varian FT-80A; 90 MHz, Perkin-Elmer R32; 300 MHz, Varian XL300. ^{13}C nuclear magnetic resonance spectra were recorded on a Brucker WP-80 or Varian XL300 instrument. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.00) as an internal standard. Mass spectra were acquired on a Ribermag quadropole R-10-10, Varian MAT CH-5, or a VG-ZAB high-resolution mass spectrometer. UV–vis absorption spectra were recorded on a Cary 14 or Hewlett-Packard 8450A diode array spectrophotometer. TLC analyses were carried out on Analtech silica gel plates (250-μm thickness) with fluorescent indicator. Unless otherwise stated, magnesium sulfate was used as a drying agent. 2,3-Naphthalenedicarboxaldehyde was prepared from 2,3-dimethylnaphthalene[4] or by the sequence given below.

2,3-Naphthalenedicarboxylic Acid.[10] The procedure of Cava[5a] was employed with minor modifications. A mixture of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (4.22 g, 0.01 mol), sodium iodide

(9) de Montigny, P.; Stobaugh, J. H.; Givens, R. S.; Carlson, R. G.; Sternson, L. A.; Higuchi, T.; Srinivasachar, K, submitted for publication in *Anal. Chem.*

(10) This is a modification of the Swern oxidation: Mancuso, A. J.; Huang, S.-H.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(10.0 g, 0.067 mol), maleic anhydride (3.0 g, 0.03 mol), and dry DMF (35 mL) was heated on a steam bath under aspirator vacuum for 4 h. The reaction mixture was poured into water (350 mL) containing sodium bisulfite (5.0 g). The pale yellow solid obtained on filtration was dissolved in dilute NaOH and the solution decolorized with charcoal. Charcoal was removed by filtration and the filtrate cooled in an ice bath. Acidification with concentrated H_2SO_4 gave a white precipitate that was filtered, washed with cold water, and dried for 12 h in a vacuum desiccator over P_2O_5. The yield of 2,3-naphthalenedicarboxylic acid was 1.30 g (60%). This sample was used in the next step without purification.

2,3-Bis(hydroxymethyl)naphthalene. A suspension of $LiAlH_4$ (0.76 g, 0.02 mol) in 40 mL of dry ether was stirred under N_2, and a solution of 2,3-naphthalenedicarboxylic acid (1.0 g, 0.005 mol) in 25 mL of dry THF was added dropwise at a rate that maintained a gentle reflux of the solvent. After the addition was complete, the reaction mixture was heated under reflux overnight. Excess $LiAlH_4$ was destroyed by the dropwise addition of ethyl acetate. Dilute aqueous HCl was added, the clear solution was carefully decanted, and more ether was added to the residual gray precipitate. The supernatant liquid was again removed by decantation. Water was added to the residue and the mixture extracted with ether. The ether extracts were combined and washed once with brine. After drying, the solvent was removed under reduced pressure to give a white solid that was filtered and washed with a mixture of ether–hexane (1:2). After drying, 670 mg (71%) of the diol was obtained; mp 158–160 °C (lit.[5b] mp 160 °C).

2,3-Naphthalenedicarboxaldehyde (3). Dry dimethyl sulfoxide (7.44 mL, 0.1 mol) in CH_2Cl_2 (22.5 mL) was added dropwise to a cold (−78 °C) solution of oxalyl chloride (4.5 mL, 0.05 mol) in CH_2Cl_2 (75 mL). After 5 min a solution of the diol (3.4 g, 0.018 mol) in a mixture of 25 mL of THF and 2 mL of dimethyl sulfoxide was added dropwise. The resulting white slurry was vigorously stirred for 1 h, triethylamine (28.2 mL, 0.2 mol) was added, and the reaction mixture was allowed to warm to room temperature. After 1.5 h, the reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with water and dried. Evaporation of the solvent gave a pale yellow solid that was recrystallized from ethyl acetate to yield 2.5 g (75%) of 2,3-naphthalenedicarboxaldehyde, mp 131–132 °C (lit.[4] mp 129–132 °C).

Preparation of 5-Nitro-2,3-naphthalenedicarboxaldehyde (4). A solution of 2,3-naphthalenedicarboxaldehyde (70 mg, 0.38 mmol) in 2 mL of acetic anhydride was cooled in an ice bath. A mixture of 0.5 mL of concentrated HNO_3 and 1.5 mL of glacial acetic acid was added dropwise with stirring. After 40 h at room temperature the yellow reaction mixture was cooled in an ice bath and treated dropwise with 20% aqueous HCl until a precipitate formed. The mixture was stored in the refrigerator to complete precipitation. The precipitate was isolated by filtration, washed with H_2O, and dried to afford 35 mg (40%) of 4. An analytical sample was obtained by crystallization from EtOAc: mp 180–182 °C; IR (KBr) 1680, 1520, 1330, 1180 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 10.70 (s, 1 H), 10.45 (s, 1 H), 9.15 (s, 1 H), 8.59 (s, 1 H), 8.51 (d, 1 H, J = 8 Hz), 8.35 (d, 1 H), 7.85 (overlapping dd, 1 H, J = 8, 8 Hz) (m, 1 H); mass spectrum, m/e (%) M^+ 229 (44), 155 (26), 154 (22), 127 (56), 126 (72), 115 (100). Calcd for $C_{12}H_7NO_4$: 229.03745. Found: 229.03674.

Preparation of 5-(*N*,*N*-Dimethylamino)-2,3-naphthalenedicarboxaldehyde (5). A suspension of 4 (1.0 g, 4.37 mmol) in 50 mL of absolute EtOH was converted into the acetal by treating it with a few crystals of *p*-toluenesulfonic acid. After the reaction mixture become homogeneous, the solvent was removed under reduced pressure. The residue was dissolved in EtOH and another crystal of *p*-toluenesulfonic acid added. After a few min the solvent was again removed on a rotary evaporator. The oily residue was dissolved in ether and extracted with saturated aqueous $NaHCO_3$. The organic phase was separated and dried over Na_2SO_4. Removal of the solvent yielded the acetal as a pale yellow oil that was used without further purification. To a solution of the acetal in 140 mL of ethanol was added 10 mL of aqueous formaldehyde (37%) and 400 mg of 10% Pd/C catalyst. The mixture was hydrogenated until uptake of hydrogen ceased. The catalyst was removed by filtration through Celite, and the filtrate was evaporated under reduced pressure. The residue was taken up in ether and extracted with aqueous 1 N NaOH solution. The organic phase was separated, washed with brine, and dried over K_2CO_3, and the solvent was removed under reduced pressure to give an oily residue. Hydrolysis of the acetal was accomplished by stirring it with 4 mL of 5% aqueous HCl in 20 mL of acetone overnight at room temperature. After evaporation of the solvent the residue was made basic with 2 N aqueous KOH and extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to yield a dark brown residue that was filtered through a short column of silica gel with methylene chloride for elution. The initial yellow fractions were collected and combined. After the solvent was removed, the residue was crystallized from methylene chloride–hexane to afford 390 mg (39%) of yellow needles. An analytical sample of **5** was prepared by recrystallization from ether–hexane: mp 85 °C; IR (KBr) 1685, 1450, 1355, 1185, 1170, 920, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.71 (s, 1 H), 10.58 (s, 1 H), 8.83 (s, 1 H), 8.41 (s, 1 H), 7.65 (m, 2 H), 7.26 (m, 1 H), 2.96 (s, 6 H); mass spectrum, m/e (%) M^+ 227 (95), 199 (24), 198 (82), 182 (18), 170 (77), 169 (80), 168 (89), 167 (18), 156 (26), 155 (63), 154 (88), 141 (20), 139 (19), 129 (45), 128 (69), 127 (100), 126 (52). Calcd for $C_{14}H_{13}NO_2$: 227.09455. Found: 227.09400.

General Procedure for the Reaction of 3 with NaCN and Amines. To a stirred suspension of 3 (184 mg, 1.0 mmol) in MeOH (20 mL) was added NaCN (50 mg, 1.0 mmol) at room temperature. The reaction mixture became homogeneous and turned pale yellow. Within 1 min, the amine (1.0 mmol) was introduced via syringe. The fluorescent reaction mixture (room light excitation) was stirred for an additional 30 min and then evaporated to dryness under reduced pressure. The residue was filtered through a short column of silica gel with methylene chloride as eluant. The initial bright yellow fraction afforded the crystalline adducts **7a–c**. These were further purified by recrystallization from methylene chloride–hexane.

7a: mp 111–113 °C; yield 58%; IR (KBr) 2205, 870, 750 cm^{-1}; UV–vis (EtOH) λ_{max} (ϵ) 441 (7521), 417 (7778), 400 sh (4744) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (br s, 2 H), 7.78 (t, J = 7.8 Hz, 2 H), 7.52 (s, 1 H), 7.24 (m, 2 H), 4.37 (t, J = 7.2 Hz, 2 H), 2.04 (sextet, J = 7.2 Hz, 2 H), 0.95 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.05, 130.84, 130.33, 128.86, 128.46, 125.32, 124.46, 124.13, 119.15, 118.59, 115.56, 115.33, 52.92, 24.82, 11.23; mass spectrum, m/e (%) M^+ 234 (71), 206 (18), 192 (100), 165 (30), 164 (31). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.69; H, 5.68; N, 12.10.

7b: mp 132–133 °C; yield 68.5%; IR (KBr) 2200, 870, 750 cm^{-1}; UV–vis (MeOH) λ_{max} (ϵ) 439 (5687), 416 (5974), 400 sh (3644) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (br s, 2 H), 7.81 (t, 2 H), 7.56 (s, 1 H), 7.26 (m, 2 H), 4.44 (t, J = 7.0 Hz, 2 H), 2.01 (q, 2 H), 1.37 (sextet, 2 H), 0.97 (t, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.15, 130.94, 130.46, 28.92, 128.55, 125.37, 124.61, 124.20, 119.16, 118.49, 115.54, 115.45, 51.22, 33.51, 20.04, 13.7; mass spectrum, m/e (%) M^+ 248 (84), 206 (100), 192 (85), 181 (16), 179 (16), 165 (31), 164 (25). Calcd for $C_{17}H_{16}N_2$: 248.13126. Found: 248.13156.

7c: mp 134–135 °C; yield 72%; IR (KBr) 2185, 1220, 860, 740 cm^{-1}; UV–vis (EtOH) λ_{max} (ϵ) 446 (4906), 423 (5304), 405 sh (3481) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1 H), 8.19 (s, 1 H), 7.80 (t, J = 9.0 Hz, 2 H), 7.73 (s, 1 H), 7.24 (m, 2 H), 1.91 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.02, 132.11, 130.22, 129.53, 128.78, 128.41, 125.20, 123.85, 123.11, 119.32, 117.17, 116.15, 114.86, 60.53, 30.28; mass spectrum, m/e (%) M^+ 248 (18), 192 (100), 165 (15), 164 (18), 57 (28). Calcd for $C_{17}H_{16}N_2$: 248.13126. Found: 248.13121.

Reaction of 3 with NaCN and Glycine. To a stirred suspension of 3 (92 mg, 0.5 mmol) in 25 mL of MeOH was added NaCN (25 mg, 0.5 mmol) at room temperature. The reaction mixture became homogeneous and turned pale yellow. Within 1 min, glycine (37.5 mg, 0.5 mmol) dissolved in 1 mL of H_2O was introduced via syringe. After the intensely fluorescent reaction mixture was stirred for a few minutes, a yellow solid precipitated. After the reaction flask was cooled in the refrigerator for 2 h, the product was filtered and dried to yield 70 mg of a shiny yellow solid. Concentration of the mother liquor and trituration with methylene chloride afforded a further 40 mg (80% combined yield) of the sodium salt **7d**: IR (KBr) 2200, 1600, 1380, 845, 725 cm^{-1}; UV–vis (MeOH) λ_{max} (ϵ) 442 (4732), 418 (5004), 400 sh (3140), 252 (46 342); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 8.41 (s, 1 H), 8.18

(s, 1 H), 8.03 (s, 1 H), 7.92 (t, J = 8.4 Hz, 2 H), 7.27 (m, 2 H), 4.79 (s, 2 H). Treatment of **7d** with aqueous trifluoroacetic acid and extraction with ether gave the acid **7e**: mass spectrum, m/e (%) M^+ 250 (15), 206 (68), 191 (43), 164 (22). Calcd for $C_{15}H_{10}N_2O_2$: 250.07416. Found: 250.07327.

Reaction of 3 with NaCN and *d,l*-Alanine. To a stirred suspension of **3** (92 mg, 0.5 mmol) in 15 mL of MeOH was added NaCN (25 mg, 0.5 mmol) at room temperature. A solution of alanine (22.5 mg, 0.25 mmol) in 1 mL of H_2O was quickly introduced into the homogeneous reaction mixture. An intense green fluorescence developed instantly. After ca. 15 min a pale yellow solid precipitated. Stirring was continued for an additional 45 min, and the reaction mixture was filtered to remove a side product (15 mg). The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in a small amount of MeOH to which methylene chloride was added dropwise to induce crystallization. After it was stored in the refrigerator overnight, the contents of the reaction flask were filtered and dried to give the sodium salt **7f** as a yellow crystalline solid in 98.6% yield: IR (KBr) 2200, 1615, 865, 745 cm^{-1}; UV–vis (MeOH) λ_{max} (ϵ) 442 (6484), 420 (7007), 400 sh (4394), 252 (64 186); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 8.39 (s, 1 H), 8.20 (s, 1 H), 8.15 (s, 1 H), 7.89 (t, J = 10 Hz, 2 H), 7.24 (m, 2 H), 5.01 (q, J = 7.2 Hz, 1 H), 1.81 (d, J = 7.2 Hz, 3 H). Treatment of **7f** with aqueous HCl and extraction with ether afforded the acid **7g**: mp 144–145 °C; mass spectrum, m/e (%) M^+ 264 (6), 220 (20), 192 (19), 191 (13), 165 (9), 164 (9). Calcd for $C_{16}H_{12}N_2O_2$: 264.08980. Found: 264.09003.

Reaction of 3 with NaCN and Glycylglycine. To a stirred suspension of **3** (92 mg, 0.5 mmol) in 15 mL of MeOH was added NaCN (25 mg, 0.5 mmol) at room temperature. A solution of glycylglycine (66 mg, 0.5 mmol) in 1 mL of H_2O was quickly introduced into the homogeneous reaction mixture. After the mixture was stirred for an additional 15 min, the solvent was removed under reduced pressure and the residue triturated with ether. The yellow precipitate was filtered and dried to yield 75 mg of product. Concentration of the filtrate afforded a second crop of 60 mg of the sodium salt **7h** 82.5% combined yield. **7h** was further purified by precipitation from a concentrated MeOH solution by the dropwise addition of methylene chloride: IR (KBr) 2200, 1650, 1600 br, 860, 735 cm^{-1}; UV–vis (MeOH) λ_{max} (ϵ) 442 (6089), 418 (6561), 400 sh (4167), 251 (61 115); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 8.43 (s, 1 H), 8.21 (s, 1 H), 8.16 (s, 1 H), 7.90 (q, 2 H), 7.28 (m, 2 H), 5.36 (s, 2 H), 3.51 (s, 2 H). The acid **7i** was prepared by acidifying an aqueous solution of **7h** with trifluoroacetic acid and extraction with ether: mass spectrum, CI, m/e (%) M^+ 308 (67), 206 (12), 205 (9), 192 (27). Calcd for $C_{17}H_{13}N_3O_3$: 307.09560. Found: 307.0975.

Reaction of 3 with NaCN and D-Alanyl-D-alanine. To a stirred suspension of **3** (184 mg, 1 mmol) in 30 mL of MeOH was added NaCN (50 mg, 1 mmol) at room temperature. A solution of D-alanyl-D-alanine (80 mg, 0.5 mmol) in 2 mL of H_2O was quickly introduced into the homogeneous reaction mixture. Stirring was continued overnight. The pale yellow side product that precipitated was separated by filtration and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in a small volume of MeOH, and CH_2Cl_2 was added dropwise to precipitate the yellow sodium salt. After filtration and drying, the yield of **7j** was 120 mg (67%): IR (KBr) 2200, 1660, 1610, 1410, 865, 740 cm^{-1}; UV–vis (H_2O) λ_{max} (ϵ) 444 (6012), 420 (6768), 400 sh (4256); ^1H NMR (300 MHz, Me_2SO-d_6) δ 8.47 (s, 1 H), 8.33 (s, 1 H), 8.20 (s, 1 H), 7.92 (t, J = 7.5 Hz, 2 H), 7.28 (m, 2 H), 5.67 (q, J = 7.2 Hz, 1 H), 3.80 (m, 1 H), 1.87 (d, J = 7.2 Hz, 3 H), 1.19 (d, J = 7.2 Hz, 3 H); mass spectrum (FAB), m/e, M^+ 357. Treatment of **7j** with aqueous trifluoroacetic acid and extraction with ether afforded the acid **7k**: mass spectrum, m/e (%) M^+ 335 (4), 192 (9), 165 (4). Found for $C_{19}H_{17}N_3O_3$: 335.12688. Found: 335.12611.

Reaction of 5 with NaCN and *tert*-Butylamine. To a stirred solution of **5** (46 mg, 0.2 mmol) in 20 mL of MeOH was added NaCN (10 mg, 0.2 mmol) at room temperature. After 1 min, *tert*-butylamine (0.02 mL, 0.2 mol) was introduced into the reaction mixture and stirring continued for an additional 0.5 h. The solvent was evaporated and the residue partitioned between methylene chloride and brine. The organic phase was dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, a yellow solid was obtained in 50-mg (86%) yield. The ^1H NMR of this product indicated the presence of two isomers in approximately equal amounts. Separation of these isomers was effected on a short silica gel column with methylene chloride as eluant. The initial yellow fractions were combined to yield 15 mg of pure **8a** or **9a** after crystallization from hexane: mp 154–155 °C dec; IR (KBr) 2200, 1615, 1385, 1300 cm^{-1}; UV–vis (EtOH) λ_{max} (ϵ) 453 (11 470), 430 (12 518), 410 (7860) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.63 (s, 1 H), 8.17 (s, 1 H), 7.76 (s, 1 H), 7.52 (d, J = 8.4 Hz, 1 H), 7.20 (dd, J = 8.4, 7.5 Hz, 1 H), 6.78 (d, J = 7.5 Hz, 1 H), 2.91 (s, 6 H), 1.98 (s, 9 H); mass spectrum, m/e (%) M^+ 291 (32), 236 (19), 235 (100), 234 (39), 192 (18), 164 (9), 57 (35). Calcd for $C_{19}H_{21}N_3$: 291.17343. Found: 291.17312. Later fractions were enriched in the other isomer. Attempts to crystallize it were not successful, and it was not further characterized.

Reaction of 5 with NaCN and Glycine. To a stirred solution of **5** (45.4 mg, 0.2 mmol) in 15 mL of MeOH was added NaCN (10 mg, 0.2 mmol). A solution of glycine (15 mg, 0.2 mmol) in 1 mL of H_2O was introduced into the reaction mixture. The deep yellow solution was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, the residue was dissolved in a small volume of MeOH and ether was added dropwise until a yellow precipitate formed. Precipitation was completed in the refrigerator. Filtration and drying afforded 60 mg (95%) of a yellow powder that was a mixture of two isomers by ^1H NMR (Me_2SO-d_6, 300 MHz). The IR spectrum (KBr) showed strong bands at 2200 and 1620 cm^{-1}. Separation of the two isomers was not attempted.

Reaction of 3 with *tert*-Butyl Mercaptan and *n*-Propylamine. A stirred suspension of **3** (110 mg, 0.6 mmol) in 2 mL of 95% EtOH was cooled in an ice bath and *tert*-butyl mercaptan (0.07 mL, 0.6 mmol) added. After a minute *n*-propylamine (0.05 mL, 0.6 mmol) was introduced into the reaction mixture. In ca. 15 min yellow crystals were deposited from the red-brown mixture. Crystallization was allowed to proceed in the refrigerator for 1 h. The crystals, collected by filtration under argon, were dried under vacuum to give 95 mg (53%) of **7a**: mp ~50 °C dec; ^1H NMR ($CDCl_3$, 80 MHz) δ 8.25 (s, 1 H), 8.08 (s, 1 H), 7.75 (m, 2 H), 7.65 (br s, 1 H), 7.10 (m, 2 H), 4.50 (t, J = 8.0 Hz, 2 H), 1.95 (m, 2 H), 1.28 (s, 9 H), 0.95 (t, J = 7.0 Hz, 3 H); **7a** decomposed rapidly and a satisfactory mass spectrum could not be obtained.

Reaction of 1 with *tert*-Butyl Mercaptan and *tert*-Butylamine. A stirred suspension of **1** (112 mg, 0.6 mmol) in 2 mL of 95% EtOH was cooled in an ice bath and *tert*-butyl mercaptan (0.07 mL, 0.6 mmol) added. Within 1 min *tert*-butylamine (0.06 mL, 0.6 mmol) was introduced into the reaction mixture. The initial greenish yellow reaction mixture turned orange in a few minutes. Crystals were deposited upon standing at room temperature for 20 min. Crystallization was completed in the refrigerator. Filtration and drying afforded 120 mg (64%) of **7b**. An analytical sample of **7b** was prepared by recrystallization from EtOH: yellow-orange needles; mp 103–105 °C; IR (KBr) 1490, 1440, 1365, 1310, 1210, 1160, 1145, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 8.20 (s, 1 H), 8.00 (s, 1 H), 7.75–7.55 (m, 2 H), 7.15–6.97 (m, 2 H), 1.92 (s, 9 H), 1.33 (s, 9 H); mass spectrum, m/e (%) M^+ 311 (20), 255 (24), 199 (84), 198 (55), 182 (30), 154 (35), 57 (72). Calcd for $C_{20}H_{25}NS$: 311.17064. Found: 311.17003.

Relative Fluorescence Quantum Yields. Fluorescence emission spectra were determined in a 1-cm quartz cell with an Aminco-Bowman spectrofluorimeter using the IP 28 photomultiplier with an excitation wavelength of 366 nm. Quantum yields were obtained by comparison with quinine sulfate (5.39×10^{-5} M in 0.1 N H_2SO_4) as a standard (Φ_f 0.55).[11] Fluorescence emission was monitored at 455 nm for the standard and 485 nm for the benz[*f*]isoindoles. One-millimeter monochromator slit widths were employed in all measurements. Before the fluorescence emission was recorded, the UV–vis spectra of the samples were taken on a Hewlett-Packard 8450A diode array spectrophotometer. For fluorescence efficiency measurements the concentrations of quinine sulfate, as a standard, and of the benz[*f*]isoindoles were adjusted so that the absorptions of the systems were practically the same at 366 nm. The quantum yields of fluorescence of the benz[*f*]isoindoles were determined by

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comparison of the areas under their emission curves with those of the standard.

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Registry No. **3**, 7149-49-7; **3** (2,3-diacid), 2169-87-1; **3** (2,3-dialcohol), 31554-15-1; **4**, 103836-27-7; **4** (bis(diethyl acetal)), 103836-43-7; **5**, 103836-28-8; **5** (bis(diethyl acetal)), 103836-44-8; **6a**, 103851-02-1; **6b**, 103851-03-2; **7a**, 103836-29-9; **7b**, 103836-30-2; **7c**, 103836-31-3; **7d**, 103836-32-4; **7e**, 103836-33-5; (±)-**7f**, 103851-04-3; (±)-**7g**, 103836-34-6; **7h**, 103836-35-7; **7i**, 103836-36-8; D,D-**7j**, 103836-37-9; D,D-**7k**, 103836-38-0; **8a**, 103836-39-1; **8b**, 103836-40-4; **9a**, 103836-41-5; **9b**, 103836-42-6; 2-$Br_2CHC_6H_4CHBr_2$, 13209-15-9; $(H_3C)_3CNH_2$, 75-64-9; $(H_3C)_3CSH$, 75-66-1; $H_3C(CH_2)_2NH_2$, 107-10-8; EtOH, 64-17-5; CH_2O, 50-00-0; $H_3C(CH_2)_3NH_2$, 109-73-9; maleic anhydride, 108-31-6; glycine, 56-40-6; DL-alanine, 302-72-7; glycylglycine, 556-50-3; D-alanyl-D-alanine, 923-16-0; 1-cyano-2H-benz[*f*]isoindole, 103836-45-9.

A Comparison of the Reactions of [(Phenylthio)(trimethylsilyl)methyl]lithium with α,β-Unsaturated Ketones and Those of Other Acyl Anion Equivalents Containing Sulfur[1]

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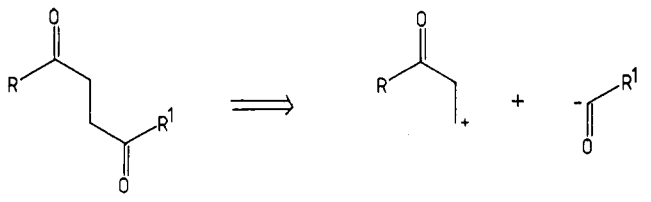
The factors influencing the site of attack of [(phenylthio)(trimethylsilyl)methyl]lithium (1) with enones were investigated. Cyclohexenone (2) was chosen as a model compound, and conjugate addition occurred in THF–HMPA or DME; this mode of addition was also promoted by a potassium counterion. When the reaction was carried out with other enones, conjugate addition in THF–HMPA or DME was only observed if the β-position or the α,β-unsaturated ketone was not disubstituted. 1,4-Addition of 1 could be accomplished by preparation of the cuprate. The use of this approach was illustrated by a preparation of 4,4-dimethylcyclopent-2-en-1-one (**28**). For determination of the influence of DME on the regiochemical control of the addition of other sulfur-containing anions to enones, the study was extended to the anions derived from 1,3-dithian (**29**), bis(phenylthio)methane (**30**), bis(phenylthio)(trimethylsilyl)methane (**35**), and bis(trimethylsilyl)(phenylthio)methane (**36**). With these anions, DME did not promote conjugate addition to any significant extent.

α-Silyl sulfides have been used as formyl anion equivalents for the preparation of aldehydes.[2] The utility of these α-silyl sulfides has been expanded to the synthesis of alkenes[3] and ketones.[4] The observation that [(phenylthio)(trimethylsilyl)methyl]lithium (1) added in a 1,4-manner to cyclohexenone (2), when 1,2-dimethoxyethane (DME) was used as the solvent,[5] prompted us to investigate the general application of these reaction conditions. Indeed, the conjugate addition of formyl and acyl anion equivalents to α,β-unsaturated carbonyl compounds (Scheme I) has been the subject of many investigations as the products,[6-8] 1,4-dicarbonyl compounds, are extremely useful synthetic intermediates.

Scheme I



In addition to defining the scope and limitations of DME

Table I. Reactions of [(Phenylthio)(trimethylsilyl)methyl]lithium (1) with Cyclohexenone (2) in Various Solvents with Temperature Variations

			yields,[a] %		
entry	solv	temp, °C	recovered (3)	1,2-addn (6)	1,4-addn (7)
1	THF	rt[b]	10	90	0[c]
2		0	10	90	0
3		−23	15	75	10
4		−78	10	80	10
5	DME	rt[b]	28	0	72
6		0	26	0	74
7		−23	30	0	70
8		−78	36	0	64
9	Et_2O	rt[b]	65	35	0
10		0	55	45	0
11		−23	70	30	0
12		−78	56	44	0
13	hexane	0	100	0	0

[a] By NMR and confirmed by GLC.[12] [b] Room temperature. [c] None detected, i.e., <5%.

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