

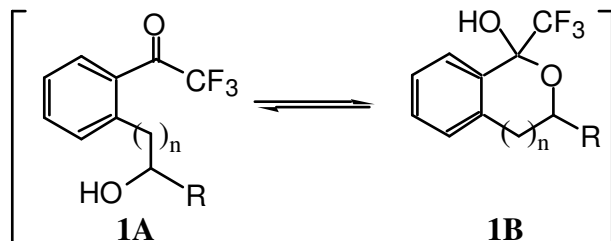
ONE-POT PREPARATION OF 1,3-DIHYDRO-1-(TRIFLUOROMETHYL)ISOBENZOFURAN-1-OL DERIVATIVES FROM 1,2-DIBROMOBENZENE

Daniel P. Becker,* Hui Li, and Daniel L. Flynn

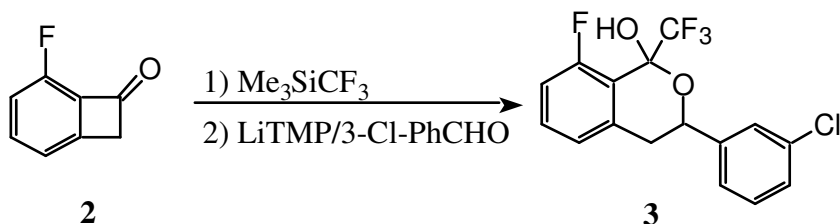
Department of Chemistry, Searle Research & Development,
4901 Searle Parkway, Skokie, IL 60077 USA

ABSTRACT: A one-pot method for the preparation of 1,3-dihydro-1-(trifluoromethyl)isobenzofuran-1-ol derivatives **5** from 1,2-dibromobenzene is described.

Trifluoromethyl ketones are of great pharmaceutical interest as transition-state esterase and protease inhibitors,¹ and aryl trifluoromethyl ketones are known to be extremely potent acetylcholinesterase inhibitors.² Our own research program led us to examine various aryl trifluoromethyl ketone derivatives **1A** which are internally bound as the trifluoromethyl lactol **1B**.³ Along these lines we have recently reported⁴ the conversion of benzocyclobutenones **2** to trifluoromethyl δ -lactols **3** via base-induced trifluoromethyl benzocyclobutenol fragmentation to a laterally-lithiated⁵ trifluoromethyl ketone intermediate.



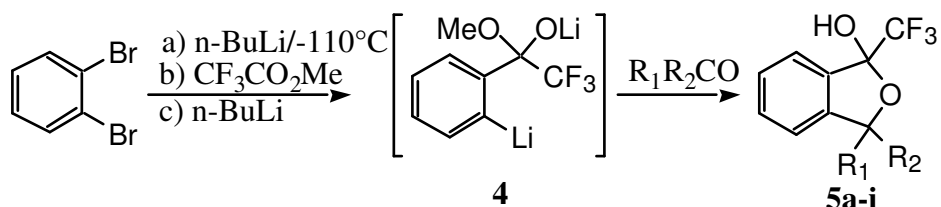
*To whom correspondence should be addressed



We also required a preparation of the corresponding 1,3-dihydro-1-(trifluoromethyl)isobenzofuran-1-ol derivatives **1B** ($n = 0$). Toward this end we envisioned the reaction of a synthon for an ortho-lithiated trifluoromethylketone with a carbonyl compound. Tamborski⁶ described the utilization of intermediate **4** which was quenched with either carbon dioxide and methyl trifluoroacetate to give compounds of type **5** ($\text{R}_1, \text{R}_2 = \text{O}$; and $\text{R}_1=\text{CF}_3, \text{R}_2=\text{OH}$, respectively.) Considering the great importance of trifluoromethylketones, it is surprising that this methodology has not been applied to the preparation of other functionalized aryl trifluoromethylketone derivatives. We now report that we have prepared the intermediate **4** and quenched with a variety of aldehydes and ketones giving rise to a series of 1,3-dihydro-1-(trifluoromethyl)isobenzofuran-1-ol derivatives **5** in one step from dibromobenzene.

The results are summarized in the Table. All four steps are performed at $-110\text{ }^\circ\text{C}$, which is critical if any product is to be obtained. After quenching with the selected carbonyl compound, the reaction is allowed to warm to room temperature before quenching. Products were purified by trituration with diethyl ether or by flash chromatography to afford analytically pure materials. Both electron-rich and electron-deficient aromatic aldehydes were examined. Heterocyclic aldehydes were employed, including N-methyl indole, thiophene, pyridine, and quinoline (entries c-f). Aromatic aldehydes lack an alpha-hydrogen which could be problematic due to competing deprotonation, however desired products were obtained from 3-phenylpropionaldehyde (entry g) and isobutyraldehyde (entry h). The ketone 4-phenyl-2-butanone also gave the desired trifluoromethyl lactol, albeit in only 8.5% yield (entry i). The best yield represented overall was obtained utilizing 3-(4-chlorophenoxy)benzaldehyde which gave the desired lactol **5b** in

44% yield. All compounds isolated were diastereomeric mixtures as judged by NMR (^1H , ^{13}C and



Entry	$\text{R}_1\text{R}_2\text{CO}$	Product	Yield (% isol.)	Diast. ratio
a		5a	28	3:2
b		5b	44	3:2
c		5c	33	3:2
d		5d	16	3:2
e		5e	30	2:1
f		5f	17	6:1
g		5g	19	2:1
h		5h	10	1:1
i		5i	8.5	3:2

^{19}F). The estimated diastereomeric ratios are shown in the Table and range from 1:1 (entry h) to 6:1 (entry f). The most surprising aspect of the diastereomeric ratios is the difference between **5e** (2:1) and **5f** (6:1). However, compound **5e** was

chromatographed on silica gel, and **5f** was only triturated with ether to effect purification, suggesting that epimerization may take place via the trifluoromethylketone (**1A**) on silica gel. No attempt was made to separate the diastereomers.

In summary, a variety of 1,3-dihydro-1-(trifluoromethyl)isobenzofuran-1-ol derivatives of type **1** have been prepared utilizing Tamborski's⁶ ortho-lithiated trifluoromethylketone synthon **4** and quenching with both aldehydes and ketones. These compounds exist as the cyclic hemiketal forms (**1B**) of the corresponding trifluoromethylketones (**1A**) based on the ¹H and ¹³C NMR data. In all cases the yields are modest, however this is offset by the fact that these compounds are available in one pot from cheap and readily-available 1,2-dibromobenzene.

Experimental Section

All reactions were performed under an atmosphere of argon. Chemicals were purchased from Aldrich Chemical Co. and used without further purification. THF was distilled from sodium benzophenone ketyl immediately prior to use. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Merck Kieselgel 60 F254 DC-Fertigplatten (0.25 mm, Art. 5719) were used for TLC. ¹H NMR spectra were recorded at 300 MHz or 400 MHz with TMS as an internal reference. Noise-decoupled and APT ¹³C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer or at 125 MHz on a VXR-500, and apparent diastereomeric pairs of peaks are listed together joined by "and". ¹⁹F NMR spectra were recorded at 188 MHz on a VXR-200 spectrometer. IR spectra were recorded on a Perkin Elmer 685 spectrophotometer. DSC refers to differential scanning calorimetry. MIR refers to multiple internal reflectance infrared spectroscopy of solid-state sample. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument.

General Procedure:

Reactions were performed starting with 2.0 g of dibromobenzene unless otherwise noted. Thus, to a stirred solution of o-dibromobenzene (2.0 g, 8.4 mmol) in a

mixture of Et₂O-THF (6.5/40 mL) at -110 °C was added n-BuLi (3.5 mL of 2.4M in hexane, 8.4 mmol) over a period of 25 min. After stirring for 20 min at -110 °C, methyl trifluoroacetate (0.93 mL, 1.18 g, 9.2 mmol) was added dropwise over 10 min and the reaction mixture was stirred at -110 °C for an additional 45 min. A second portion of n-BuLi (4.2 mL of 2.4 M solution in hexane, 10.1 mmol) was then added over 25 min while maintaining the temperature at -110°C. The reaction mixture was stirred for additional 2 h during which time a white solid appeared. The appropriate aldehyde or ketone (9.2 mmol) was slowly added into the reaction solution over a period of 20 min and the reaction solution was stirred at -110° C for 4 h. Then the reaction was allowed to warm to rt overnight and was then hydrolyzed by pouring into a 1.5M HCl ice-water mixture followed by work-up via Method A or B.

Workup Method A: The organic layer was separated and the aqueous layer was extracted three times with Et₂O. The combined organic layer was dried over MgSO₄ and evaporation of solvent gave the crude product which was purified by flash chromatography.

Workup Method B: The aqueous layer was separated and neutralized with K₂CO₃. Then it was extracted with Et₂O three times and the combined Et₂O layers were dried over MgSO₄. Evaporation of the solvent gave a residue which was triturated with ether or was purified by flash column chromatography to give the desired compound.

1,3-Dihydro-3-(4-methoxyphenyl)-1-trifluoromethyl)isobenzofuran-1-ol (5a)

Quenching with m-anisaldehyde and workup via method A gave a residue which was purified by flash chromatography eluting with 10/90 EtOAc/hex to give **5a** (0.733 g, 27.7%) as a ca. 3:2 diastereomer mixture. ¹H NMR (400 MHz, CDCl₃) δ 7.50-7.40 (2H, m), 7.30-7.35 (1H, m), 7.12-7.08 (1H, m), 6.95-6.80 (3H, m), 6.35 (0.4H, s) and 6.25 (0.6H, s), 3.95 (1h, br, s), 3.75 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 159.8, 143.4 and 143.1, 141.6 and 140.5, 134.4 and 133.9, 131.1 and 131.0, 129.9 and 129.7, 128.9 and 128.8, 123.0 and 122.6 (q, J=287 Hz), 123.6 and 123.2, 122.4, 119.8 and 119.5, 114.6 and 114.1, 112.9 and 112.7, 104.1 and 103.9 (q, J=34 Hz), 86.6 and 86.0, 55.2 and 55.1; ¹⁹F NMR (188 MHz, CDCl₃) δ -82.1, -83.7; exact mass calcd for C₁₆H₁₃O₃F₃ 310.0816, found

310.0823 (EI). Anal. calcd for C₁₆H₁₃O₃F₃. 0.25 H₂O: C, 61.05; H, 4.32. Found: C, 61.14; H, 4.42.

3-[3-(4-Chlorophenoxy)phenyl]-1,3-dihydro-1-(trifluoromethyl)iso-benzofuran-1-ol (5b)

Quenching with 3-(4-chlorophenoxy)-benzaldehyde followed by workup according to method A and chromatography on silica gel eluting with 5/95 EtOAc/hex gave **5b** (1.5 g, 43.6%) as a 3:2 diastereomer mixture. DSC (10 deg/min.) 110.8 °C; IR (MIR) 3595, 1604, 1583, 1483, 1448, 1242, 1176, 764, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60-6.90 (12H, m), 6.40 (0.4H, s) and 6.25 (0.6H, s), 3.54 (0.6H, br, s) and 3.40 (0.6H, br, s); ¹³C NMR (125 MHz, CDCl₃) δ 157.30 and 157.27, 155.6 and 155.5, 143.1 and 142.7, 142.2 and 141.0, 134.3 and 137.7, 131.24 and 131.16, 130.3 and 130.2, 129.80, 129.75 and 129.71, 128.5 and 128.3, 122.8 and 122.4 (q, J=286 Hz), 122.5 and 122.3, 122.4 and 122.2, 120.2, 120.1, 119.0 and 118.8, 117.74 and 117.65, 104.0 (q, J=35 Hz), 86.5 and 85.8; ¹⁹F NMR (188 MHz, CDCl₃) δ -82.3, -83.8; exact mass calcd for C₂₁H₁₄ClO₃F₃ 406.0583, found 406.0576. Anal. calcd for C₂₁H₁₄ClO₃F₃.0.1 CH₂Cl₂: C, 61.03; H, 3.45; Cl, 10.24. Found: C, 60.85; H, 3.68; Cl, 10.19.

1,3-Dihydro-3-(1-methyl-1H-indol-3-yl)-1-(trifluoromethyl)iso-benzofuran-1-ol (5c)

Quenching with N-methylindole-3-carboxyaldehyde and workup according to method B gave a residue which was purified on silica gel eluting with 20/80 EtOAc/hex to afford **5c** (0.923 g, 32.5%) as a 3:2 diastereomer mixture. DSC (10 deg/min.) 237.6 °C; IR (MIR) 3446, 3050, 1706, 1551, 1474, 1463, 1251, 1167, 1131, 1119, 1034, 1014, 970, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.00 (9H, m), 6.80 (0.4H, s) and 6.60(0.6H, s), 3.75 (1.8H, s) and 3.72(1.2H, s), 3.40 (0.6H, s) and 3.38 (0.4H, s); ¹³C NMR (125 MHz, CDCl₃) δ 143.0 and 142.9, 137.7 and 137.4, 134.9 and 134.7, 131.0 and 130.9, 129.1 and 128.7, 126.6 and 126.1, 123.7 and 123.3, 122.9 and 122.5 (q, J=287 Hz), 122.7 and 122.6, 122.5 and 122.1, 119.9 and 119.7, 119.4, 113.3 and 112.1, 109.6 and 109.5, 103.18 and 103.13 (q, J=34 Hz), 81.0 and 80.1, 32.9 and 32.8; ¹⁹F NMR (188 MHz, CDCl₃) δ -82.5, -83.8; exact mass calcd for C₁₈H₁₄NO₂F₃ 333.0977, found 333.0980. Anal. calcd for C₁₈H₁₄NO₂F₃: C, 64.86; H, 4.23; N, 4.20. Found: C, 65.17; H, 4.89; N, 3.86.

1,3-Dihydro-3-(2-thienyl)-1-(trifluoromethyl)isobenzofuran-1-ol (5d)

Starting with 4.0 g dibromobenzene (16.8 mmol) and quenching with thiophene-2-carboxaldehyde followed by workup according to method A and chromatography on silica gel eluting with 10/90 EtOAc/hex afforded **5d** (0.80 g, 16.4%) as a 3:2 diastereomer mixture. DSC (10 deg/min.) 243.6 °C; IR (MIR) 3513, 3390, 1462, 1306, 1237, 1169, 1118, 1070, 1033, 1016, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.00 (7H, m), 6.70 (0.4H, s) and 6.52(0.6H, s); ¹³C NMR (125 MHz, CDCl₃) δ 143.5, 142.5 and 142.4, 134.1, 131.24 and 131.19, 129.30 and 129.28, 127.3 and 127.1, 127.0 and 126.7, 126.94 and 126.91, 123.7 and 123.4, 122.7 and 122.6, 122.67 and 122.60 (q, J=287 Hz), 103.72 and 103.68 (q, J=35 Hz), 81.8 and 81.7; exact mass calcd for C₁₃H₉O₂SF₃ 286.0275, found 286.0293. Anal. calcd for C₁₃H₉O₂SF₃: C, 54.54; H, 3.17; S, 11.20. Found: C, 54.24; H, 3.12; S, 11.58.

1,3-Dihydro-3-(2-pyridinyl)-1-(trifluoromethyl)isobenzofuran-1-ol (5e)

Quenching with pyridine-2-carboxaldehyde and work-up according to method B afforded a residue which was triturated with ether to afford **5e** (0.71 g, 29.7%) as a 2:1 diastereomer mixture. DSC (10 deg/min.) 181.0 °C. IR (MIR) 3064, 3.25, 2686, 1598, 1174, 1134, 1090, 1036, 1003, 764 cm⁻¹; ¹H NMR (400 MHz, CD₃SOCD₃) δ 8.30-8.10 (2H, m), 7.90-7.80 (1H, m), 7.60-7.30 (6H, m), 6.21(1H, s); ¹³C NMR (125 MHz, CD₃SOCD₃) δ 159.5 and 158.8, 149.1 and 148.9, 141.7 and 141.1, 137.4 and 137.2, 134.5 and 134.1, 130.9 and 130.7, 128.9 and 128.7, 123.6, 123.1 and 123.0, 123.1 and 122.8 (q, J=287 Hz), 122.6 and 122.4, 104.09 and 103.9 (q, J=34 Hz), 85.0 and 84.3; ¹⁹F NMR (188 MHz, CD₃SOCD₃) δ -81.30, -81.39; MS calcd for C₁₄H₁₀NO₂F₃ 281, found 281 (NH₃-PCI). Anal. calcd for C₁₄H₁₀NO₂F₃: C, 59.79; H, 3.58; N, 4.98. Found: C, 59.45; H, 3.76; N, 4.92.

1,3-Dihydro-3-(2-quinolinyl)-1-(trifluoromethyl)isobenzofuran-1-ol (5f)

Quenching with quinoline-2-carboxaldehyde and workup according to method B afforded a residue which was triturated with dry ether to give **5f** (0.245, 17 %) as a 6:1 diastereomer mixture. DSC (10 deg/min) 188.2 °C; IR (MIR) 3105, 3068, 2966, 1599, 1507, 1462, 1173, 1125, 1090. 1041, 992, 833, 752 cm⁻¹; ¹H NMR

(400 MHz, CD₃SOCD₃) δ 8.70 (1H, br, s), 8.45 (1H, d, J=8 Hz), 8.15 (1H, d, J=8 Hz), 8.0 (1H, d, J=8 Hz), 7.83 (1H, t, J=8 Hz), 7.70-7.35 (6H, m), 6.70 (0.2H, s) and 6.40 (0.8H, s); ¹³C NMR (125 MHz, CD₃SOCD₃) δ 159.2 and 158.6, 145.6 and 145.0, 141.4 and 141.1, 139.1 and 138.8, 134.9 and 134.1, 131.0, 130.8 and 130.6, 129.1, 128.1, 128.0 and 127.6, 127.3 and 127.1, 123.7 and 123.0, 123.0 and 122.6 (q, J=286 Hz), 122.6 and 122.5, 104.6 and 104.3 (q, J=33 Hz), 84.7 and 84.3; ¹⁹F NMR (188 MHz, CD₃SOCD₃) δ -79.6, -81.3; MS calcd for C₁₈H₁₂NO₂F₃ 331, found 331 (NH₃-PCI). Anal. calcd for C₁₈H₁₂NO₂F₃.H₂O: C, 61.89; H, 4.04; N, 4.01. Found: C, 61.95; H, 3.72; N, 3.78.

1,3-Dihydro-3-(2-phenylethyl)-1-(trifluoromethyl)isobenzofuran-1-ol (5g)

Starting with 6.0 g of dibromobenzene (25.2 mmol) and quenching with 3-phenylpropionaldehyde and workup according to method A gave a residue which was purified by chromatography on silica gel eluting with 10/90 EtOAc/hex to afford **5g** (1.52 g, 19.4%) as a 2:1 diastereomer mixture. DSC (10 deg/min.) 266.2 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.00 (9H, m), 5.42 (0.33H, dd, J=18, 8 Hz) and 5.36(0.66H, dd, J=9, 8 Hz), 3.92 (0.33H, br, s) and 3.88(0.66H, br, s), 2.90-2.70 (2H, m), 2.30-2.00 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 143.0 and 143.1, 141.4 and 141.3, 131.0 and 130.9, 128.71 and 128.66, 128.52 and 128.47, 126.03 and 126.01, 123.8 and 123.6, 122.8 and 122.4 (q, J=287 Hz), 121.24 and 121.16, 103.7 and 103.58 (q, J=34 Hz), 83.2 and 83.7, 38.0 and 37.7, 31.6 and 31.1; ¹⁹F NMR (188 MHz, CDCl₃) δ -83.1, -83.9; MS calcd for C₁₇H₁₅O₂F₃ 308, found 308 (NH₃-PCI). Anal. calcd for C₁₇H₁₅O₂F₃.0.25 H₂O: C, 65.28; H, 4.99. Found: C, 65.17; H, 4.88.

1,3-Dihydro-3-(1-methylethyl)-1-(trifluoromethyl)isobenzofuran-1-ol (5h)

Quenching with isobutyraldehyde and workup according to method A afforded a residue which was chromatographed on silica gel eluting with 5/95 EtOAc/hex to afford **5h** (0.2 g, 10 %) as a 1:1 diastereomer mixture. DSC (10 deg/min.) 267.4 °C; IR (MIR) 3443, 3409, 2966, 2934, 2877, 1464, 1169, 1122, 1073, 1044, 1021, 970, 764, 732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.20 (4H, m), 5.31 (0.5H, d, J=6 Hz) and 5.28 (0.5H, d, J=3 Hz), 3.30 (1H, s), 2.25 (1H, m), 1.14

(1.5H, d, J=7.2 Hz) and 1.11 (1.5H, d, J=7.2 Hz), 0.9 (1.5H, d, J=7.2 Hz) and 0.82 (1.5H, d, J=7.2 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 142.44 and 142.37, 135.1 and 134.7, 130.8 and 130.6, 128.6 and 128.5, 123.7 and 123.4, 122.8 and 122.5 (q, J=287 Hz), 121.8 and 121.6, 103.3 and 103.1 (q, J=33.7 Hz), 89.8 and 89.1, 32.9 and 32.6, 18.9 and 18.8, 16.7 and 16.0; MS calcd for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{F}_3$ 246, found 228 (APCI) for 246-18 (H_2O). Anal. calcd for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{F}_3 \cdot 0.15$ hex: C, 59.79; H, 5.87. Found: C, 59.89; H, 5.45.

1,3-Dihydro-3-methyl-(2-phenylethyl)-1-(trifluoromethyl)isobenzo-furan-1-ol (5i)

Starting with 6.0 g of dibromobenzene (25.2 mmol) and quenching with 4-phenyl-2-butanone followed by workup according to method A and chromatography on silica gel eluting with 5/95 EtOAc/hex gave **5i** (0.7 g, 8.5%) as a 3:2 diastereomer mixture. DSC (10 deg/min.) 256.2 and 315.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.50-7.00 (9H, m), 3.9 (0.6H, s) and 3.8 (0.4H, s), 2.80-2.40 (2H, s), 2.30-2.10 (2H, s), 1.65 (0.4H, s) and 1.60 (0.6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 147.5, 147.3, 146.6, 142.6, 142.2, 141.9, 141.6, 134.0, 133.9, 131.2, 131.0, 128.68, 128.66, 128.4, 128.3, 126.7, 125.9, 125.8, 125.7, 124.8, 124.7, 120.8, 122.55 and 122.53 (q, J=287 Hz), 102.9 (q, J=36 Hz), 91.0 and 90.4, 45.9, 43.65, 42.9, 41.8, 30.62, 30.5, 28.8, 27.5, 26.9; ^{19}F NMR (188 MHz, CDCl_3) δ -82.6, -83.5; MS calcd for $\text{C}_{18}\text{H}_{17}\text{O}_2\text{F}_3$ 322, found 322 (EI).

References and Notes

- 1) a) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123. b) Begue, J.-P.; Delpon, D. B. *Tetrahedron* **1991**, *47*, 3207.
- 2) Nair, H. K.; Lee, K.; Quinn, D. M.; *J. Am. Chem. Soc.* **1993**, *115*, 9939-41
- 3) The strong electron-withdrawing nature of the trifluoromethyl group forces the equilibrium to lie on the side of the cyclic 1,3-dihydro-1-(trifluoromethyl)isobenzofuran-1-ol. The equilibrium is also under the influence of other structural features, such as lactol ring size.
- 4) Becker, D. P.; Flynn, D. L. *SynLett*, **1996**, 57-59.
- 5) For a comprehensive review of lateral lithiation see Clark, R.D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.

6) Prabhu, U. D. G.; Eapen, K. C.; Tamborski, C., *J. Org. Chem.* **1984**, *49*, 2792.