Notes

An Efficient Synthesis of 1-Substituted Acenaphthylenes and Acenaphthenes, Synthesis of Acenaphthene-1-carboxylic Acid

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Several 1-substituted acenaphthenes have been shown to exhibit biological activity. For instance, 1-(aminomethyl)acenaphthene (**1a**) (Figure 1) is a hypotensive agent,[1] acenaphthene-1-carboxylic acid (**1b**) is a plant-growth controlling substance,[2] and its amide derivative with *N*-methyl-2-pyrrolidinocyclohexylamine (**1c**) shows very high k-Opioid receptor affinity and selectivity,[3] it is 100 times more potent than morphine. Moreover, the acenaphthene skeleton is an important precursor in the construction of polycyclic aromatic hydrocarbons which are air pollutants and potent carcinogens.[4] Several synthetic approaches to acenaphthenes have been presented in the literature; for instance, nucleophilic substitution of some nucleophiles such as sodium malonates[2a] or lithiated tris(methylthio)methane[2b] on 1-bromoacenaphthenes, reductive alkylation of acenaphthylene,[2c] and hydroformylation of acenaphthylene.[2d] In spite of the interest in 1-substituted acenaphthenes as products or starting materials for products possessing biological properties, only recently have Consiglio[5] et al. reported some success (48% ee on 35% conversion) in the first enantioselective hydroformylation of acenaphthylene. Though these approaches serve some purposes, neither of them is highly enantioselective, and the adaptation of synthetic work of the preparation of closely related substituted systems often necessitates an independent sequence.

We report herein a simple and general synthesis of 1-substituted acenaphthylenes and their conversion to the corresponding acenaphthenes. Our work provides a convenient synthesis of racemic acid **5c** in good yield.

Results and Discussion

The title method is based on the formation of 1-lithioacenaphthylene (**3**), followed by subsequent addition to an electrophile. The desired anion **3** was easily prepared upon treatment of 1-bromoacenaphthylene[6] with *n*-butyllithium at low temperature (−78 °C), facilitated by the presence of TMEDA (Scheme 1). Treatment of **3** with D_2O at −78 °C afforded a deuterated single product in 88% yield. The significant decrease in the intensity of the singlet peak at 7.08 ppm to one proton clearly indicates that the deuterium is introduced at position C-1 to give 1-deuterioacenaphthylene (**4a**). A similar result at −40 °C indicates the stability of the intermediate **3** at that temperature. When the temperature of the anion **3** (prepared at −78 °C) was allowed to reach 0 °C, a mixture of undefined products was obtained.

Various electrophiles were used in order to examine the generality of the sequence; the results are summarized in Table 1. Treatment of **3** with dimethylformamide[7] (DMF) afforded the corresponding aldehyde **4b** in 90% yield; this aldehyde was recently prepared[8] in 16%

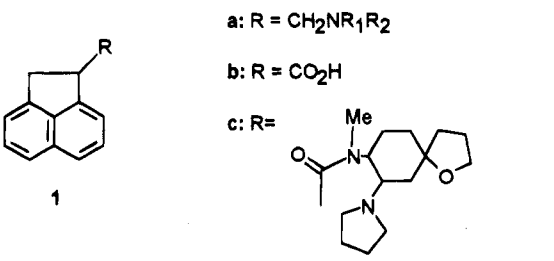
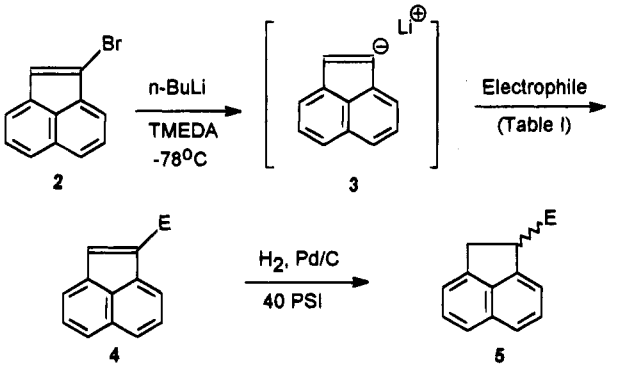


Figure 1.

Scheme 1



a: E=D; **b**: E=CHO; **c**: E=CO_2H; **d**: E=CH_2CH_2OH
e: E=CH_2-CH=CH_2; **f**: E=$(CH_2)_3$-CH=CH_2; **g**: CH_2OH; **h**: CH_2Br

Table 1. Addition of 3 to Electrophiles

entry	electrophile	product	% yield[a]
1	D_2O	**4a**	88
2	DMF	**4b**	90
3	CO_2	**4c**	83
4	ethylene oxide	**4d**	54
5	allyl bromide	**4e**	75
6	5-bromo-1-pentene	**4f**	60
7	HCHO	**4g**	35

[a] Isolated yield.

(1) 1-(Aminomethyl)acenaphthenes as hypotensive agents: Himmek, W.; Siegel, H.; Amann, A.; Giertz, H. Ger. Offen. 2 252 945, 1974; *Chem. Abstr.* **1974**, *81*, 37429v.
(2) (a) Fredga, A.; Svensson, T. *Ark. Kemi.* **1966**, *25*, 81. (b) Halfpenny, P.; Horwell, D.; Rees, D. *Synthesis* **1990**, 517 and references cited therein. (c) Canceill, J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1973**, 2727. (d) Raffaelli, A.; Rosini, C.; Dini, M.; Salvadori, P. *Synthesis* **1988**, 893.
(3) Horwell, D.; Rees, D. U. S. Patent, 4 906 655, 1990; *Chem. Abstr.* **1990**, *113*, 231204n.
(4) (a) Yang, C.; Harvey, R. G. *Polycyclic Aromatic Hydrocarbon Compounds* **1992**, *2*, 229. (b) Harvey, R. G.; Pataki, J.; Cortez, C.; Di Raddo, P.; Yang, C. *J. Org. Chem.* **1991**, *56*, 1210.
(5) Consiglio, G.; Nefkens, S. C. A. *Tetrahedron Asymm.* **1990**, *1*, 417.
(6) Baciocchi, E.; Ruzziconi, R.; Sebastiani, G. V. *J. Org. Chem.* **1982**, *47*, 3237.
(7) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.
(8) Adeney, M.; Brown, R.; Coulson, K.; Eastwood, F.; James, W. *Austr. J. Chem.* **1991**, *44*, 967.

0022-3263/94/1959-6090$04.50/0

yield by formylation of acenaphthylene with phosphoryl chloride and DMF and converted into the corresponding 1-ethynylacenaphthylene. With carbon dioxide[9] acenaphthylene-1-carboxylic acid (**4c**) was obtained in 83% yield. This acid was previously prepared[10] in 35% yield from **2** *via* the corresponding cyanide which then hydrolyzed to the carboxylic acid. Furthermore the intermediate **3** reacted with ethylene oxide[11] at −78 °C to produce the corresponding alcohol **4d** in moderate yield. High yield alkylation was achieved upon treatment of **3** with different alkenyl bromides (Table 1, entries 5 and 6); the functionality of the corresponding products might be of interest for further transformations. When anion **3** was treated with formaldehyde,[12] the corresponding alcohol **4g** was obtained in 35% yield; alternatively **4g** was obtained in 85% yield upon reduction of the unsaturated aldehyde **4b** with $NaBH_4$.

Subsequent catalytic hydrogenation of substituted acenaphthylenes affords the corresponding acenaphthenes in a two-step sequence. Catalytic hydrogenation of the unsaturated acid **4c** over 10% Pd/C under 40 psi pressure of hydrogen at room temperature afforded acenaphthene-1-carboxylic acid (**5c**) in 76% over all yield. Catalytic hydrogenation of **4c**, **4d**, and **4g** under these conditions afforded **5c**, acenaphthene-1-ethanol (**5d**), and acenaphthene-1-methanol (**5g**)[13] in 92, 83, and 85% yields, respectively. **5d** is an important precursor for synthesis of cyclopenta[*def*]phenanthrene.[4a] Transformation of **5g** into 1-(bromomethyl)acenaphthene (**5h**), an important precursor for the synthesis of cyclopenta[*def*]-chrysene,[4b] was accomplished *via* the corresponding mesylate and then treatment with LiBr, in 90% yield[14] and 59% total yield from **2** following the sequence **2** → **4b** → **4g** → **5b** → **5h**.

Experimental Section

Materials and Methods. THF was distilled from the potassium benzophenone ketyl, DMF was distilled over CaH_2, and TMEDA was distilled and stored over KOH. Silica gel 60 (230−400-mesh ASTM) for column chromatography was used.

All melting points are uncorrected. Infrared absorption spectra were recorded on a Perkin-Elmer 298 spectrophotometer with $CHCl_3$ as a solvent. Nuclear magnetic resonance spectra were obtained on Bruker AM-400 MHz and AM-200 MHz NMR instruments. High-resolution MS were measured on a Varian MAT-711 mass spectrometer. Ultraviolet spectra were taken on a Hewlett Packard 8452A spectrometer.

General Procedure for the Preparation of 1-Lithioacenaphthylene (3). To a cooled solution (−78 °C) of **2** (3 g, 13 mmol) in THF (50 mL) and TMEDA (1.95 mL, 13 mmol) under N_2 was added *n*-BuLi (6.5 mL, 15.6 mmol, 2.5 M solution in cyclohexane) over a 10-min period. The orange solution was stirred for 30 min at the same temperature to ensure complete formation of the anion **3**. The additions and reactions of **3** with electrophiles were all carried out at −78 °C.

1-Deuterioacenaphthylene[15] (4a). D_2O (1 mL) was added to **3** (prepared from 0.5 g of **2**, 2.2 mmol) at −78 °C. Water (10 mL) and ether (25 mL) were added. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic extracts were washed with cold 10% hydrochloric acid and brine, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification by column chromatography using hexane as eluent yielded 0.29 g (88%) of a yellow solid: mp 89−91 °C. The NMR spectrum closely matched that of acenaphthylene except for the decrease of the singlet peak at 7.08 (98% deuterium purity); HRMS calcd for $C_{12}H_7D$ *m/z* 153.0665, found *m/z* 153.0677.

Acenaphthylene-1-carboxaldehyde[8] (4b). DMF (1 mL) was added to anion **3** (prepared as above from **2**; 4 g, 17.3 mmol) at −78 °C. After additional stirring for 45 min at this temperature, water (30 mL) and ether (50 mL) were added. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic extracts were washed with cold 10% hydrochloric acid and brine, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification by chromatography on silica gel (4:1 CH_2Cl_2:hexane mixtureas eluent) afforded 2.8 g (90%) of **4b**: mp 40−41 °C; IR ($CHCl_3$) 1695 cm^{-1} (CHO); NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.34 (d, 1H), 7.99 (d, 1H), 7.91 (d, 1H), 7.87 (d, 1H), 7.78 (s, 1H), 7.66−7.57 (m, 2H, Ar); UV λ_{max} (EtOH) (log ϵ) 412 (3), 362 (3.82), 332 (4.09), 320 (3.94), 270 (3.91), 236 (4.1), 216 (4.00); HRMS calcd for $C_{13}H_8O$ *m/z* 180.0575, found *m/z* 180.0579.

Acenaphthylene-1-carboxylic Acid (4c). Anion **3** (prepared as above from 3 g, 13 mmol of **2**) was cannulated under N_2 to a flask containing dry ice and allowed to stand until complete evaporation of the solid CO_2 occurred. Then 30 mL of 10% HCl and 50 mL of ether were added. The water layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with a 10% NaOH solution (2 × 20 mL). The aqueous layers were washed with ether (30 mL) and then acidified with 10% HCl. The produced yellow solid was filtered by suction, dried, and recrystallized from toluene to give 2.11 g of **4c** (83%) as yellow leaves: mp 235−236 °C (lit.[10] mp 234 °C); IR ($CHCl_3$) 3450 (OH), 1750 cm^{-1} (CO); NMR (DMSO-d_6) δ 12.80 (s, 1H), 8.19 (d, 1H), 8.09 (d, 1H), 8.02 (d, 1 H), 7.99 (d, 1H), 7.86 (s, 1H), 7.72−7.63 (m, 2H); UV λ_{max} (EtOH) (log ϵ) 356 (3.79), 330 (4.10), 316 (3.91), 264 (3.60), 236 (4.23); HRMS calcd for $C_{13}H_8O_2$ *m/z* 196.0524, found *m/z* 196.0530.

Acenaphthylene-1-ethanol (4c) was prepared from anion **3** (2 g of **2**, 8.65 mmol, as describe above) and ethylene oxide (0.5 mL) following the procedure described for **4b**. Similar workup afforded 0.92 g of **3d** (54%): mp 38−39 °C; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 7.80 (d, 1H), 7.73 (d, 1H), 7.67 (d, 1H), 7.57−7.48 (m, 3H), 6.84 (s, 1H), 4.00 (bd, 2H), 3.09 (t, 2H), 1.59 (s, 1H); UV λ_{max} (EtOH) (log ϵ) 340 (3.6), 322 (3.97), 312 (3.91), 278 (3.52), 268 (3.55), 260 (3.47), 234 (4.07), 214 (3.95); HRMS calcd for $C_{14}H_{12}O$ *m/z* 196.0892, found *m/z* 196.0890.

1-Allylacenaphthylene (4e) was preared from anion **3** (1 g of **2**, 4.3 mmol, as described above) and allyl bromide (0.62 g, 5.1 mmol) following the procedure described for **4b**. Similar workup afforded 0.62 g (75%) of **4e** as a yellow oil: IR ($CHCl_3$) 3095 (=CH), 1630 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.77 (d, 1H), 7.70 (d, 1H), 7.66 (d, 1H), 7.54−7.45 (m, 3H), 6.75 (s, 1H), 6.16−6.10 (m, 1H), 5.25 (d, 1H), 5.15 (d, 1H), 3.58 (d, 2H); UV λ_{max} (EtOH) (log ϵ) 340 (3.74), 334 (3.79), 322 (4.06), 312 (4.02), 276 (3.80), 266 (3.81), 234 (4.21), 216 (4.09); HRMS calcd for $C_{15}H_{12}$ *m/z* 192.0939, found *m/z* 192.0924.

1-(4-Pentenyl)acenaphthylene (4f) was prepared from anion **3** (2 g of **2**, 8.65 mmol, as described above) and 5-bromopentene (0.89 g, 6 mmol) following the procedure described above for **4b**. Similar workup afforded 0.8 g (60%) of **4f** as a yellow oil: IR ($CHCl_3$) 3090 (=CH), 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.77 (d, 1H), 7.69 (d, 1H), 7.64 (d, 1H), 7.54−7.45 (m, 3H), 6.72 (s, 1H), 5.95−5.80 (m, 1H), 5.07 (d, 1H), 5.01 (d, 1H), 2.83 (t, 2H), 2.22 (q, 2H), 1.89 (p, 2H); UV λ_{max} (EtOH) (log ϵ) 322 (3.81), 310 (3.81), 270 (3.36), 230 (4.39), 204 (4.25); HRMS calcd for $C_{17}H_{16}$ *m/z* 220.1252, found *m/z* 220.1252.

Acenaphthylene-1-methanol (4g). Method A. Formaldehyde (13 mmol, from 400 mg of paraformaldehyde heated over 200 °C) was bubbled through a solution of anion **3** (from 1.5 g of **2**, 6.5 mmol). The mixture was stirred for 2 h at −78 °C. The usual workup (described for **4a**) and then purification by column chromatography (1:1 ether:hexane mixture as eluent) afforded 413 mg of **4g** (35%): mp 49−50 °C; IR ($CHCl_3$) 3450 cm^{-1} (OH); NMR ($CDCl_3$) δ 7.80 (d, 1H), 7.76 (d, 2H), 7.61 (d, 1H), 7.56−7.51 (m, 3H), 6.94 (s, 1H), 4.93 (s, 2H), 1.74 (s, 1H); UV λ_{max}

(9) Gilman, H.; Kirby, R. *Organic Syntheses*; Wiley: New York, 1932; Collect. Vol. I, p 353. Bowen, M. *Org. Synth.* 1955; Collect. Vol. III, p 553.

(10) Castellan, A.; Dumartin, E.; Galanate, H.; Laurent, H. *Bull. Soc. Chem. Fr.* **1976**, 217.

(11) For nucleophilic ring opening of oxiranes, see: Rosowsky, A. In *Heterocyclic Compounds with Three- and Four Membered Rings*, Part I; Weissberger, A., Ed., Interscience: New York, 1964; pp 386−417. Parker, R.; Issacs, N. *Chem. Rev.* **1959**, *59*, 779.

(12) Gilman, H.; Catlin, W. *Organic Syntheses*; Wiley: New York, 1932; Collect. Vol. I, p 182.

(13) Himmele, W.; Aquila, W. Ger. Offen. 2 064 279, 1972; *Chem. Abstr.* **1972**, *77*, 114126r.

(14) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

(15) Gerson, F.; Weidman, B. *Helv. Chim. Acta* **1966**, *49*, 1837.

(EtOH) (log ϵ) 340 (3.74), 334 (3.79), 322 (4.06), 312 (4.02), 276 (3.80), 266 (3.81), 234 (4.21), 216 (4.09); HRMS calcd for $C_{13}H_{10}O$ *m/z* 182.0731, found *m/z* 182.0732.

Method B. The aldehyde **4b** (0.8 g, 4.4 mmol) in 10 mL of methanol was added dropwise to a precooled (0 °C) solution of sodium borohydride (0.33 g, 8.6 mmol) in ethanol (30 mL). The mixture was stirred for an additional 30 min and then concentrated under reduced pressure; the resulting residue was dissolved in ether, recooled to 0 °C, and cautiously decomposed by the addition of cold 10% HCl. The aqueous layer was extracted with ether, and the combined organic extracts were washed with $NaHCO_3$ and then brine solutions, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by chromatography (as above) afforded 0.68 g of **4g** (85%).

Acenaphthene Derivatives (General Procedure). The general procedure is illustrated by the following hydrogenation procedure of **5c**.

Racemic Acenaphthene-1-carboxylic Acid (5c). A solution of the unsaturated acid **4c** (200 mg, 1 mmol) in 30 mL of absolute ethanol was hydrogenated over 10% Pd/C (30 mg) at 40 psi pressure and room temperature. The reaction was completed after 3 h. Filtration of the catalyst and concentration of the filtrate under reduced pressure afforded the crude product **5c** which was recrystallized from toluene to give 185 mg (92%) as off-white crystals: mp 160–161 °C (lit.[2b] mp 164 °C); NMR ($CDCl_3$) δ 11.72 (br s, 1H), 7.67 (d, 1H), 7.62 (d, 1H), 7.55–7.29 (m, 4H), 4.59 (dd, 1H), 3.95 (dd, 1H), 3.63 (dd, 1H).

Acenaphthene-1-ethanol[4a] (5d): yield 83%; IR ($CHCl_3$) 3480 cm^{-1} (OH); NMR ($CDCl_3$) δ 7.60 (d, 2H), 7.45 (dt, 2H), 7.26 (d, 2H), 3.87 (t, 3H), 3.60 (dd, 1H), 3.09 (dd, 1H), 2.22 (m, 1H), 1.95 (m, 1H), 1.39 (s, 1H).

Acenaphthene-1-methanol[14] (5g): yield 85%; IR ($CDCl_3$) 3480 cm^{-1} (OH); NMR ($CDCl_3$) δ 7.64 (2 d overlapping, 4H), 7.32 (t, 2H), 3.88 (s + dd overlapping, 3H), 3.52 (dd, 1H), 3.22 (dd, 1H), 1.60 (s, 1H); HRMS calcd for $C_{13}H_{12}O$ *m/z* 184.0888, found *m/z* 184.0889.

1-(Bromomethyl)acenaphthene (5H) was prepared from alcohol **5g** (300 mg, 1.63 mmol) *via* the corresponding mesylate, following a reported procedure for similar transformation;[14] 363 mg of **5h** was obtained in 90% yield: NMR ($CDCl_3$) δ 7.68 (d, 1H), 7.63 (d, 1H), 7.52–7.29 (m, 4H), 4.11 (m, 1H), 3.85 (dd, 1H), 3.70 (dd, 1H), 3.55 (dd, 1H), 3.34 (dd, 1H).

Supplementary Material Available: Copies of ^1H NMR (400 MHz) spectra and peak assignment of compounds **4d–g** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.