ramide (caution: this step is exothermic), the solvent was evaporated, and the residue was dissolved in hexane, washed with water three times, and chromatographed on TLC alumina (15 g), eluting with hexane and then 10% ethyl acetate/hexane to yield morpholinyl *tert*-butyl sulfide (1.55 g, 97%); mp ca. 20–22 °C, d_{21} = 0.953; ^{1}H NMR (60 MHz) δ 3.63 (4 H, m), 2.93 (4 H, m), 1.25 (9 H, s); MS *m/z* rel intensity) 175 M^+, 149, 119 (100), 91, 75, 57. Anal. Calcd for $C_8H_{17}NOS$: C, 54.81; H, 4.78; N, 7.99; S, 18.29. Found: C, 55.00; H, 4.85; N, 8.18; S, 18.28.

4-Morpholinyl 2-Pyridyl Sulfide. The chloramide solution was prepared by adding 2 equiv of morpholine to excess sodium hypochlorite solution and extracting with chloroform. Ten further equivalents of morpholine were added and then, after cooling, the thiol was stirred in. The reaction was worked up as above with sulfite. Washing the hexane solution with water and then acetonitrile left the sulfenamide (ca. 40% after recrystallization from Et_2O/hexane): mp 62–65 °C; NMR δ 6.5–8.1 (4 H, m), 3.77 (4 H, m), 3.27 (4 H, m); MS *m/z* 196 M^+ and 197. Anal. Calcd for $C_9H_8N_2OS$: C, 55.07; H, 6.16; N, 14.27; S, 16.34. Found: C, 55.05; H, 6.30; N, 14.35; S, 16.09.

4-Morpholinyl benzyl sulfide[14] and **cyclohexylamino benzyl sulfide**[15] were prepared as above in 96% and 84% yields, respectively.

4-Morpholinyl cholesteryl sulfide (3b) was prepared as above (95%): mp 97–101 °C (after recrystallization from $CHCl_3$/acetonitrile, mp 99–103 °C); $[\alpha]_D$ = −18° (*c* = 1.3, $CHCl_3$); NMR δ 5.37 (1 H, s, H-6), 3.63 (4 H, m), 3.00 (4 H, m). Anal. Calcd for $C_{31}H_{53}NOS$: C, 76.32; H, 10.95; N, 2.87; S, 6.57. Found: C, 76.09; H, 10.97; N, 2.71; S, 6.57.

Registry No. **3a**, 1249-81-6; **3b**, 136263-01-9; *t*-BuSH, 75-66-1; $PhCH_2SH$, 100-53-8; 2-pyridinethiol, 2637-34-5; 4-morpholinyl *tert*-butyl sulfide, 7257-74-1; 4-morpholinyl 2-pyridyl sulfide, 2244-48-6; 4-morpholinyl benzyl sulfide, 7257-55-8; cyclohexylamino benzyl sulfide, 35242-69-4; morpholine, 110-91-8; cyclohexanamine, 108-91-8; 4-chloromorpholine, 23328-69-0; *N*-chlorocyclohexanamine, 52185-81-6.

(14) Dunbar, J. E.; Rogers, J. H. *J. Org. Chem.* **1966**, *31*, 2842.
(15) Harpp, D. N.; Back, T. G. *Tetrahedron. Lett.* **1971**, *52*, 4953.

Regioselectivity in the Acid-Catalyzed Isomerization of 2-Substituted 1,4-Dihydro-1,4-epoxynaphthalenes

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Received April 30, 1991

In the course of examining the structure–activity relationships of a series of 5-lipoxygenase-inhibitory 2-(arylmethyl)-1-naphthols,[1] we wanted to prepare 8-substituted analogues, hoping that greater metabolic stability would result from steric hinderance near the hydroxyl group. Synthetic approaches involving elaboration of preexisting 2- or 8-substituted naphthols were excluded because of potential difficulties arising from peri interactions, which can induce unusual reactivities in both the rings and substituents.[2-4] Instead, we chose the more convergent Diels–Alder reaction of substituted furans with substituted benzynes, followed by acid-catalyzed rearrangement of the intermediate 1,4-dihydro-1,4-epoxynaphthalenes.[5] Although four isomeric naphthols are possible in this two-step sequence, a surprising regioselectivity in the epoxy ring-opening reaction, giving only two of the expected isomers, was discovered.

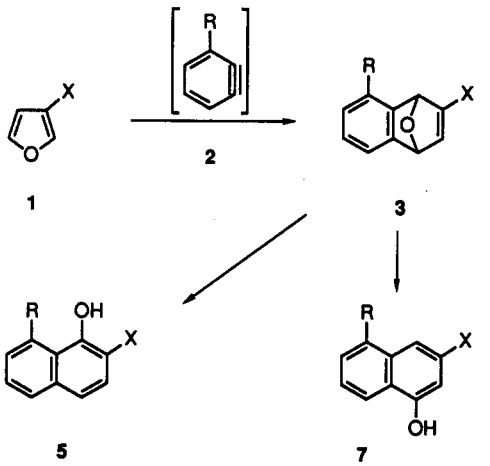
(1) Batt, D. G.; Maynard, G. D.; Petraitis, J. J.; Shaw, J. E.; Galbraith, W.; Harris, R. R. *J. Med. Chem.* **1990**, *33*, 360.
(2) Balasubramaniyan, V. *Chem. Rev.* **1966**, *66*, 567.
(3) Kirby, A. J.; Percy, J. M. *Tetrahedron* **1988**, *44*, 6903.
(4) Kirby, A. J.; Percy, J. M. *Tetrahedron* **1988**, *44*, 6911.
(5) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.

Table I. Preparation of Disubstituted Naphthols

entry	R	yield[a] (%) of 3 + 4 (ratio)[b]	yield[c] (%) of 5 + 6 (ratio)[b]
a	Me	75 (1:1)	88 (1:1)
b	Ph	88 (1:1)	63 (1:1)
c	COOMe	72 (1:1)	49 (2:1)

[a] Purified yield of combined isomers after chromatography. [b] By NMR integration. [c] Combined yield after chromatographic separation.

Table II. Preparation of Monosubstituted Naphthols



entry	R	X	yield[a] (%) of 3	yield[b] (%) of 5 + 7 (ratio)[c]
d	Me	H	64	87 (1:3)
e	Ph	H	29	50 (1:1)
f	Br	H	7	66 (9:1)
g	H	CH_2Ph	55	100 (98:2)
h	H	4-MeO-$C_6H_4CH_2$	56	97 (96:4)
i	H	4-tBu-$C_6H_4CH_2$	98	85 (98:2)
j	H	4-CF_3-$C_6H_4CH_2$	70	91 (98:2)
k	H	Me	52	85 (>99:1)
l	H	tBu	75	100 (>99:1)
m	H	Ph	*d*	
n	H	Br	40	75 (>99:1)
o	H	COOEt	45	15 (>98:2)

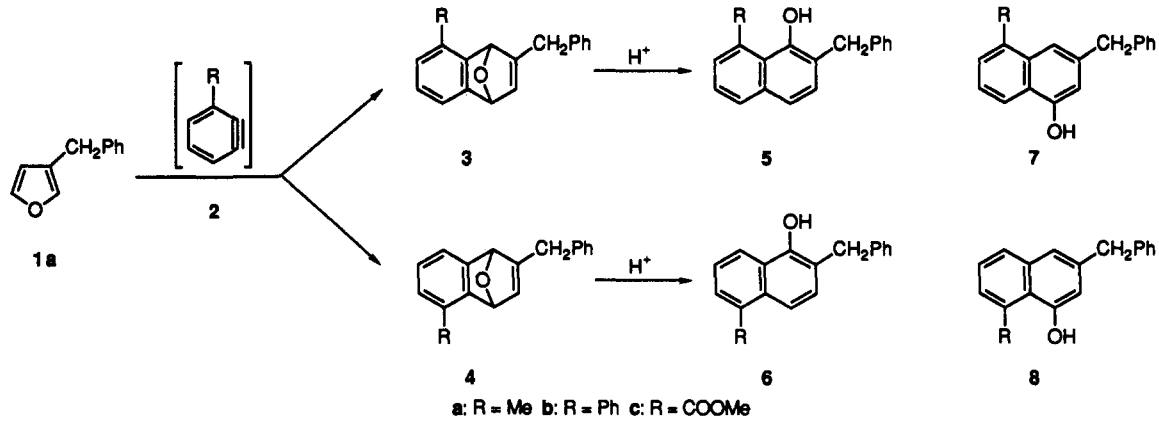
[a] Yield of purified material. [b] Combined yield of purified products. [c] Ratio by GC analysis of crude reaction product. [d] No product obtained.

Treatment of a mixture of 3-benzylfuran (**1a**) and isoamyl nitrite with 2-amino-3-methylbenzoic acid gave (via the intermediate 3-methylbenzyne **2a**) a 1:1 mixture of the isomeric cycloadducts **3a** and **4a** (Scheme I). This mixture, inseparable by TLC, was treated with concentrated HCl in methanol. Of the four possible naphthols only the 2-substituted isomers (**5a** and **6a**), which were easily separated by flash chromatography, were present by NMR. No 3-substituted-1-naphthols **7a** or **8a** could be detected. The same result was obtained for other 8-substituents (Table I).

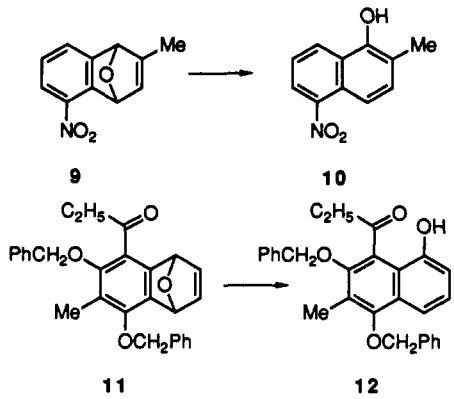
Only one example of such regioselectivity has been reported previously for a 1,4-dihydro-1,4-epoxynaphthalene with this substitution pattern. Nishiyama and Kameoka reported that **9** rearranged to **10** in 89% yield on treatment with sulfuric acid in ethanol.[6] A directing effect of the nitro group was invoked to explain the observed result. However, in another report, **11** (lacking the substituent on the dihydro ring) opened in the opposite direction with respect to the electron-withdrawing substituent, providing only **12** in 79% yield.[7] Our example **3c** + **4c** also indicated that the directing effect of the benzyl group outweighed any effect of the electron-withdrawing ester.

(6) Nishiyama, T.; Kameoka, H. *Chem. Exp.* **1988**, *3*, 41.
(7) Nakata, M.; Wada, S.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1801.

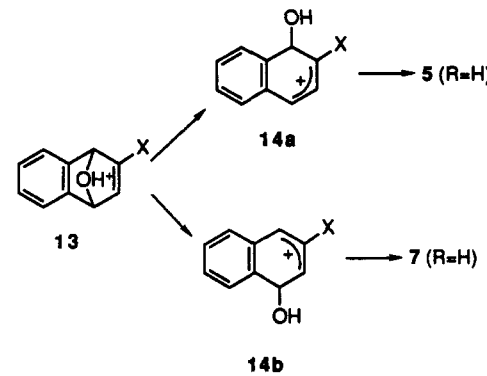
Scheme I



Scheme II



Scheme III



To further explore this effect we examined additional examples unsubstituted at either C2 or C5 (C8) (Table II). The cycloadducts **3** were prepared as described above, except for the bromo case **3f** where the benzyne was generated by treatment of 1,3-dibromobenzene with lithium piperidide.[8] Isomerization in methanol was catalyzed by a small amount of concentrated HCl or H_2SO_4. Ratios of the products were determined by NMR integration (**d–f**) or GC analysis (**g–o**) of the crude reaction mixtures, with authentic characterized samples of each product as GC references.

Regioisomer identification rests on comparison with authentic samples prepared by different routes and on characteristic NMR spectral features. Compounds **6** and **7**, which lack an 8-substituent, show a downfield signal for the 8-proton (δ 8.0–8.4), deshielded by the peri-related hydroxyl group; in 8-substituted analogues **5** (R $\neq$ H) this signal is missing. (In the cases of the esters **5c** and **6c** and the bromo derivatives **5f** and **7f**, the protons near the electron-withdrawing substituents are also deshielded, but the assignments are obvious when the spectra for pairs of compounds are compared.) In the case of 2- vs 3-substituents, the 3-substituted cases **7** (X $\neq$ H) display a characteristic singlet in the region δ 6.6–6.8 due to the 2-proton. Additionally, the 2- and 8-substituted compounds, with more hindered hydroxyl groups, are without exception chromatographically more mobile than the corresponding 3- or 5-substituted analogues.

The cycloadducts of furan and three 3-substituted benzynes (**3d–f**) all gave mixtures after isomerization. The methyl case (**d**) gave the same result reported previously by Gavina et al.,[9] although those workers reported a 1:6 product ratio. In agreement with Kinoshita and coworkers,[7] some indication of an electronic effect by the 5-substituent is evident, since methyl gave somewhat more 1,5-isomer while the 1,8-isomer was favored in the bromo case (**f**). However, the selectivity in these three cases was much less dramatic than that observed in cases **a–c**.

In all cases bearing a 2-substituent but lacking the 5-substituent (**g–o**), the 2-substituted naphthol was strongly favored (>20:1). The electronic nature of the benzyl substituent had no effect on the outcome (entries **h–j**), and simple alkyl groups (**k** and **l**) gave the same effect. Except for the bromo case (**n**), nonaliphatic substituents on furan were much less synthetically useful. The ester **3o** gave a very low yield of naphthols from the isomerization step, although the products identified still greatly favored the 1,2-isomer **5o**. 3-Phenylfuran **1m** gave no isolable cycloadduct with benzyne.

The mechanism of this acid-catalyzed ring opening has been studied by Vernon and co-workers,[10] who found support for a rate-determining ring-opening of the protonated oxygen-bridged species **13** (X = H) to give an allylic cation **14a** (≡**14b**) (X = H), followed by a proton rearrangement to give the naphthol product (Scheme III). In the case where X $\neq$ H, **14a** would lead to the observed major product (**5g–o**), while **14b** would give the minor product (**7g–o**). If the ring opening is rate determining, the stability of the cation **14** should affect the outcome of the reaction. Ab initio[11] and semiempirical[12] calculations have indicated that a methyl substituent on the terminal carbon of an allyl cation stabilizes this species much more than a methyl on the central carbon. By analogy, **14a** would be predicted to be more stable than **14b**. Our own semiempirical calculations support this explanation, giving enthalpies of formation favoring **14a** (X = Me) by about

(8) Huisgen, R.; Mack, W.; Herbig, K.; Ott, N.; Anneser, E. *Chem. Ber.* **1960**, *93*, 412.

(9) Gavina, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Gil, P. *Tetrahedron Lett.* **1986**, *42*, 5641.

(10) Cooke, M. D.; Dransfield, T. A.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1377.

(11) Mayr, H.; Forner, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1979**, *101*, 6032.

(12) Jarjis, H. M.; Khalil, S. M. *Z. Naturforsch.* **1987**, *42a*, 174.

3.4 kcal/mol. Interestingly, geometry optimization of **13** (X = Me) led directly to the optimized geometry and ΔH_f of **14a**. This ring opening did not occur in the similar calculation on the unsubstituted case **13** (X = H).

When X is an electron-withdrawing substituent, such stabilization would not be expected. Indeed, the ester case (**o**) gave very little product (15%), although this product was still almost entirely the 2-substituted isomer. Selectivity cannot be assumed in this case, however, since most of the starting material reacted by alternative, unknown pathways to give uncharacterizable products. The bromo substituent (**n**) behaved like an electron-donating group; presumably resonance stabilization outweighed inductive effects, favoring **14a** in this case.

In summary, we have found interesting regioselectivity in the acid-catalyzed isomerization of 2-alkyl-substituted 1,4-dihydro-1,4-epoxynaphthalenes, giving almost exclusively the 2-substituted 1-naphthols in synthetically useful yields and purity. This effect may be due to the stabilization of the allylic cation, which results from the rate-determining ring opening of the oxygen-protonated starting material.

Experimental Section

Reactions were conducted under N_2. Following aqueous workups, all organic phases were dried over anhydrous $MgSO_4$ or Na_2SO_4 and concentrated on a rotary evaporator at aspirator pressure. Column chromatography was done using the medium-pressure flash method.[13] Gas chromatography was done on a 30-m DB-17 capillary column, using H_2 carrier gas and flame ionization detection. Melting points are uncorrected. NMR spectra were recorded at 300 MHz in $CDCl_3$ using Me_4Si as the internal standard. IR spectra were obtained as KBr pellets (solids) or neat films (oils), unless otherwise indicated. Low-resolution mass spectra were obtained using methane chemical ionization. Microanalysis results were within 0.4% of the calculated values. (Where not tabulated, spectral and analytical data are available as supplementary material.) Semiempirical molecular orbital calculations were carried out with full geometry optimization using the AM1 method[14] in the MOPAC program (Version 5.0) on a Tektronix CAChe workstation.

3-Benzylfuran (1a). 3-Furaldehyde (27.87 g, 0.29 mol) in ether (175 mL) was treated at 0 °C with PhMgBr (3.0 M in ether; 100 mL, 0.30 mol) over 30 min. After 1.5 h at rt, 1 N HCl was added dropwise. The resulting emulsion was filtered through Celite and extracted with ether. The organic phase was dried and concentrated to give α-phenyl-3-furanmethanol (43.4 g, 86%): mp 65–67 °C (hexane/BuCl)(lit.[15] mp 65–65.5 °C); NMR δ 7.4–7.25 (7 H), 6.32 (s, 1 H), 5.75 (s, 1 H), 2.21 (br s, 1 H); MS *m/z* 175 (100). $LiAlH_4$ (1.0 M in ether; 50 mL, 50 mmol) was treated at rt with $AlCl_3$ (6.67 g, 50 mmol) in ether (35 mL) over 2 min. The carbinol (8.71 g, 50 mmol) in ether (50 mL) was added at a rate that resulted in gentle refluxing (ca. 20 min). After 1 h at rt, the mixture was cooled on ice and treated with H_2SO_4 (8 mL in 30 mL water) by VERY SLOW dropwise addition. Water (50 mL) was then added, and the mixture was stirred until the solids dissolved. The aqueous phase was extracted with ether, and the combined extracts were dried and concentrated. The residue was distilled (Kugelrohr; 100 °C (0.5 Torr)), providing **1a** (5.53 g, 70%): mp ca. 24 °C (lit.[16] oil); NMR δ 7.35 (s, 1 H), 7.3–7.2 (6 H) 6.24 (s, 1 H), 3.77 (s, 2 H); MS *m/z* 159 (100).

3-[(4-Methoxyphenyl)methyl]furan (1h). 4-Bromoanisole (19.45 g, 0.104 mol) in ether (100 mL) was stirred at −78 °C and treated with BuLi (1.6 M in hexane; 71.5 mL, 0.114 mol) over 30 min. After 60 min more, 3-furaldehyde (10.00 g, 0.104 mol) in ether (100 mL) was added over 15 min. The mixture was warmed to rt and stirred for 2 h. Saturated aqueous NH_4Cl (50 mL) was added, and the aqueous phase was extracted with ether. The combined extracts were dried and concentrated. The residue was chromatographed (toluene/ethyl acetate (95:5)) to give α-(4-methoxyphenyl)-3-furanmethanol (18.20 g, 86%): oil; NMR; IR; MS; Anal. This material was reduced as described for **1a** to provide **1h** (83%): oil; NMR; MS; Anal.

3-[(4-*tert*-Butylphenyl)methyl]furan (1i). α-(4-*tert*-Butylphenyl)-3-furanmethanol was prepared by the same method as the 4-methoxyphenyl derivative (84%): mp 89–89.5 °C (cyclohexane/petroleum ether); NMR; IR; MS; Anal. Reduction by the method used for **1a** gave **1i** (49%): oil; NMR; MS; Anal.

3-[[4-(Trifluoromethyl)phenyl]methyl]furan (1j). α-[4-(Trifluoromethyl)phenyl]-3-furanmethanol was prepared by the same method as the 4-methoxyphenyl derivative (97%): oil; NMR; IR; MS; Anal. Reduction by the method used for **1a** gave **1j** (51%): oil; NMR; HRMS.

2-Amino-3-phenylbenzoic Acid. Using the method of Marvel and Hiers,[17] 2-aminobiphenyl was converted to α-oximino-2-phenylacetanilide (42%): mp 125–126 °C (CCl_4); NMR δ 9.18 (br s, 1 H), 8.52 (br s, 1 H), 8.32 (d, *J* = 9 Hz, 1 H), 7.5–7.2 (8 H); IR 3366, 1664 cm^{-1}; MS *m/z* 241 (100). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.70; H, 4.77; N, 11.39. This (6.00 g, 25 mmol) was added portionwise over 30 min to concd H_2SO_4 (20 mL) at 0 °C. The mixture was warmed to rt and stirred for 4 h and then was poured into cold water. The orange precipitate was dissolved in CH_2Cl_2/methanol (95:5) and filtered through a plug of silica gel. The effluent was concentrated to provide 7-phenylisatin (4.90 g, 88%) as orange crystals: mp 184–184.5 °C; NMR δ 7.82 (br s, 1 H), 7.7–7.4 (7 H), 7.22 (t, *J* = 9 Hz, 1 H); IR 3274, 1752, 1742 cm^{-1}; MS *m/z* 224 (100). Anal. Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 74.93; H, 3.83; N, 6.14. By use of the procedure of Baker et al.,[18] this was converted into 2-amino-3-phenylbenzoic acid (49%): mp 148–149 °C (lit.[19] mp 209–212 °C); NMR δ 7.98 (d, *J* = 9 Hz, 1 H), 7.5–7.3 (5 H), 7.24 (d, *J* = 9 Hz, 1 H), 6.73 (t, *J* = 9 Hz, 1 H); IR 3490, 3368, 3000–2500, 1664 cm^{-1}; MS *m/z* 214 (100), 196 (61). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.98; H, 5.23; N, 6.49.

2-(and 3-)Benzyl-8-methyl-1,4-dihydro-1,4-epoxynaphthalene (3a + 4a). A solution of isoamyl nitrite (0.67 mL, 5.0 mmol) and **1a** (0.63 g, 4.0 mmol) in CH_2Cl_2 (5 mL) was heated at reflux and treated dropwise with a solution of 2-amino-3-methylbenzoic acid (0.60 g, 4.0 mmol) in THF (5 mL). Following addition, the mixture was heated for 90 min, cooled to rt, and poured into water. Extraction with ethyl acetate, drying, and concentration gave a crude product that was chromatographed (hexane/ethyl acetate (3:1)) to provide **3a + 4a** (0.79 g, 75%) as an inseparable mixture of isomers (1:1), which was used without further purification: oil; NMR δ 7.3–6.7 (8 H), 6.51 and 6.45 (2 br s, 0.5 H each), 5.77 and 5.66 (2s, 0.5 H each), 5.44 and 5.34 (2s, 0.5 H each), 3.59 and 3.57 (2s, 1 H each), 2.28 and 1.98 (2s, 1.5 H each); HRMS calcd for $C_{18}H_{16}O$ 248.1201, found 248.1207.

Using the same procedure, the following compounds were also prepared.

From 2-amino-3-phenylbenzoic acid, **2-(and 3-)benzyl-8-phenyl-1,4-dihydro-1,4-epoxynaphthalene (3b + 4b)** (88%) as an inseparable mixture of isomers (65:35), which was used without further purification: oil; NMR; MS.

From 2-(methoxycarbonyl)-6-aminobenzoic acid,[20] **2-(and 3-)benzyl-8-carbomethoxy-1,4-dihydro-1,4-epoxynaphthalene (3c + 4c)** (72%) as an inseparable mixture of isomers (1:1), which was used without further purification: oil; NMR; MS.

From 2-amino-3-methylbenzoic acid and furan, **5-methyl-1,4-dihydro-1,4-epoxynaphthalene (3d)**[9] (71%): oil (lit.[21] mp 21 °C); NMR; MS.

From 2-amino-3-phenylbenzoic acid and furan, **5-phenyl-1,4-dihydro-1,4-epoxynaphthalene (3e)** (29%): mp 64–65 °C

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(14) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(15) Tsuge, O.; Oe, K.; Tashiro, M. *Tetrahedron* **1973**, *29*, 41.
(16) Inomata, K.; Aoyama, S.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 930.
(17) Marvel, C. S.; Hiers, G. S. *Organic Syntheses*; Wiley: New York, 1932; *Collect. Vol. 1*, p 327.
(18) Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 141.
(19) Troshchenko, A. T.; Lobanova, T. P. *J. Org. Chem. USSR (Engl. Transl.)* **1967**, *3*, 480; *Zh. Org. Khim.* **1967**, *3*, 501.
(20) Rogers, M. E.; Averill, B. A. *J. Org. Chem.* **1986**, *51*, 3308.
(21) Harrison, R.; Heaney, H.; Lees, P. *Tetrahedron* **1968**, *24*, 4589.

(hexane/BuCl); NMR; MS; Anal.

From anthranilic acid and **1a**, **2-benzyl-1,4-dihydro-1,4-epoxynaphthalene (3g)** (55%): oil; NMR; MS; Anal.

From anthranilic acid and **1h**, **2-[(4-methoxyphenyl)methyl]-1,4-dihydro-1,4-epoxynaphthalene (3h)** (56%): mp 82–82.5 °C (petroleum ether/methylcyclohexane); NMR; MS; Anal.

From anthranilic acid and **1i**, **2-[(4-*tert*-butylphenyl)methyl]-1,4-dihydro-1,4-epoxynaphthalene (3i)** (98%): oil; NMR; MS; Anal.

From anthranilic acid and **1j**, **2-[[4-(trifluoromethyl)phenyl]methyl]-1,4-dihydro-1,4-epoxynaphthalene (3j)** (70%): mp 82–82.5 °C (petroleum ether/cyclohexane); NMR; MS; Anal.

From anthranilic acid and 3-methylfuran,[22] **2-methyl-1,4-dihydro-1,4-epoxynaphthalene (3k)** (52%): oil; NMR.

From anthranilic acid and 3-*tert*-butylfuran[23] (prepared by the procedure of Liotta et al.[24]), **2-*tert*-butyl-1,4-dihydro-1,4-epoxynaphthalene (3l)** (75%): oil; NMR; MS; Anal.

From anthranilic acid and 3-bromofuran, **2-bromo-1,4-dihydro-1,4-epoxynaphthalene (3n)** as an oil (40%), still impure after chromatography, which was used without further purification due to instability: NMR.

From anthranilic acid and ethyl 3-furoate, **2-(ethoxycarbonyl)-1,4-dihydro-1,4-epoxynaphthalene (3o)** as a yellow oil (45%), still impure after chromatography, which was used without further purification due to instability: NMR.

Attempts to prepare **2-phenyl-1,4-dihydro-1,4-epoxynaphthalene (3m)** by this method from anthranilic acid and 3-phenylfuran[25] were unsuccessful, providing only a very impure product that decomposed on attempted purification.

5-Bromo-1,4-dihydro-1,4-epoxynaphthalene (3f). Piperidine (9.23 mL, 93.3 mmol) in ether (200 mL) was treated at 0 °C with BuLi over 30 min. After 10 min at rt the solution was added over 1 h to furan (61.7 mL, 848 mmol) and 1,3-dibromobenzene (10.2 mL, 84.8 mmol) in ether (200 mL) at 0 °C. After 1.5 h more, the reaction was quenched with water and extracted with ether. the organic phase was dried and concentrated, and the residue was chromatographed (hexane/ethyl acetate (95:5)) to provide **3f** (1.31 g, 7%): oil; NMR; MS; Anal.

Isomerization of 2-(and 3-)Benzyl-8-methyl-1,4-dihydro-1,4-epoxynaphthalene (3a + 4a). A solution of the epoxide mixture (0.79 g, 3.0 mmol) in methanol (20 mL) and concd HCl (2 mL) was heated at reflux for 16 h and then cooled to room temperature. The mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was dried and concentrated to provide an essentially pure mixture of two compounds (1:1 by NMR). Chromatography (hexane/ethyl acetate (9:1)) provided **2-benzyl-8-methyl-1-naphthol (5a)** (0.35 g, 44%): mp 53–54 °C (hexane/BuCl); NMR δ 7.63 (d, *J* = 7 Hz, 1 H), 7.5–7.2 (9 H), 5.16 (s, 1 H), 4.15 (s, 2 H), 2.92 (s, 3 H); IR; MS; Anal. Also obtained was **2-benzyl-5-methyl-1-naphthol (6a)** (0.35 g, 44%): mp 44–47 °C; NMR δ 7.98 (d, *J* = 7 Hz, 1 H), 7.59 (d, *J* = 7 Hz, 1 H), 7.4–7.2 (8 H), 5.13 (s, 1 H), 4.20 (s, 2 H), 2.66 (s, 3 H); IR; HRMS; Anal.

Using the same procedure, the following compounds were also prepared.

From **3b + 4b** after chromatography (hexane/ethyl acetate (9:1)), **2-benzyl-8-phenyl-1-naphthol (5b)** (22%): mp 108–108.5 °C (petroleum ether); NMR δ 7.82 (d, *J* = 7 Hz, 1 H), 7.5–7.1 (14 H), 5.60 (s, 1 H), 4.07 (s, 2 H); IR; MS; Anal. Also **2-benzyl-5-phenyl-1-naphthol (6b)** (41%): mp 87–87.5 °C (petroleum ether/methylcyclohexane); NMR δ 8.16 (d, *J* = 7 Hz, 1 H), 7.6–7.2 (14 H), 5.15 (s, 1 H), 4.17 (s, 2 H); IR; MS; Anal.

From **3c + 4c** after chromatography (toluene/ethyl acetate (98:2)), **2-benzyl-8-carbomethoxy-1-naphthol (5c)** (34%): mp 71–72 °C (petroleum ether/ether); NMR δ 10.44 (s, 1 H), 8.23 (d, *J* = 9 Hz, 1 H), 7.99 (d, *J* = 9 Hz, 1 H), 7.4–7.1 (8 H), 4.22 (s, 2 H), 4.04 (s, 3 H); IR; MS; Anal. Also **2-benzyl-5-carbomethoxy-1-naphthol (6c)** (24%): mp 60.5–62 °C; NMR δ 8.46 (d, *J* = 9 Hz, 1 H), 8.39 (d, *J* = 9 Hz, 1 H), 8.13 (d, *J* = 9 Hz, 1 H), 7.5–7.1 (6 H), 5.17 (s, 1 H), 4.17 (s, 2 H), 3.98 (s, 3 H); IR; MS; Anal.

From **3d** after chromatography (toluene/ethyl acetate (95:5)) **8-methyl-1-naphthol (5d)** (29%): mp 63–64 °C (hexane) (lit.[26] mp 56–57 °C); NMR δ 7.62 (d, *J* = 7 Hz, 1 H), 7.38 (d, *J* = 7 Hz, 1 H), 7.3–7.1 (3 H), 6.70 (d, *J* = 7 Hz, 1 H), 5.28 (s, 1 H), 2.92 (s, 3 H). Also **5-methyl-1-naphthol (7d)** (58%): mp 97–99 °C (hexane) (lit.[9] mp 98 °C); NMR δ 8.06 (d, *J* = 7 Hz, 1 H), 7.58 (d, *J* = 7 Hz, 1 H), 7.4–7.1 (3 H), 6.83 (d, *J* = 7 Hz, 1 H), 5.35 (br s, 1 H), 2.70 (s, 3 H); GC (crude product) **5d:7d** = 27:73 (t_R 3.87 min and 4.09 min, respectively, at 180 °C).

From **3e** after chromatography (toluene/ethyl acetate (98:2)), **8-phenyl-1-naphthol (5e)** (30%): oil; NMR δ 7.87 (d, 1 H), 7.5–7.3 (8 H), 7.21 (d, 1 H), 6.92 (d, 1 H), 5.41 (s, 1 H); IR; MS; Anal. Also **5-phenyl-1-naphthol (7e)** (20%): mp 90–91 °C (hexane) (lit.[27] mp 93–94 °C); NMR δ 8.23 (d, 1 H), 7.6–7.4 (8 H), 7.25 (d, 1 H), 6.84 (d, 1 H), 5.30 (br s, 1 H); GC (crude product) **5e:7e** = 39:43 (t_R 3.22 min and 4.95 min, respectively, at 240 °C).

From **3f** after chromatography (hexane/ethyl acetate (95:5)), **8-bromo-1-naphthol (5f)** (58%): mp 54–55 °C (lit.[28] mp 56 °C); NMR δ 8.05 (s, 1 H), 7.75 (d, *J* = 8 Hz, 1 H), 7.60 (d, *J* = 8 Hz, 1 H), 7.40 (m, 2 H), 7.18 (t, *J* = 8 Hz, 1 H), 7.05 (d, *J* = 8 Hz, 1 H). Also **5-bromo-1-naphthol (7f)** (8%): mp 139–140 °C (lit.[27] mp 136–137 °C); NMR δ 8.20 (d, *J* = 8 Hz, 1 H), 7.80 (m, 2 H), 7.40 (t, *J* = 8 Hz, 1 H), 7.30 (t, *J* = 8 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 1 H), 5.35 (br s, 1 H); GC (crude product) **5f:7f** = 9:1 (t_R 2.90 min and 4.94 min, respectively, at 200 °C).

From **3g**: The residue (100%) was essentially pure **2-benzyl-1-naphthol (5g)**, contaminated with a small amount of **3-benzyl-1-naphthol (7g)**: GC (crude product) **5g:7g** = 98:2 (t_R 2.39 and 2.80 min, respectively, at 280 °C). The identities were confirmed by comparison with authentic materials prepared by other routes.[1]

From **3h** after chromatography (toluene), **2-[(4-methoxyphenyl)methyl]-1-naphthol (5h)** (95%): mp 81.0–81.3 °C (petroleum ether/methylcyclohexane) (lit.[1] mp 80–81 °C); NMR δ 8.09 (m, 1 H), 7.78 (m, 1 H), 7.43 (m, 3 H), 7.26 (m, 1 H), 7.15 (d, *J* = 8 Hz, 2 H), 6.83 (d, *J* = 8 Hz, 2 H), 5.19 (s, 1 H), 4.09 (s, 2 H), 3.76 (s, 3 H). Also, **3-[(4-methoxyphenyl)methyl]-1-naphthol (7h)** (2%): gum, NMR δ 8.10 (m, 1 H), 7.73 (m, 1 H), 7.44 (m, 2 H), 7.25 (m, 1 H), 7.14 (d, *J* = 9 Hz, 2 H), 6.84 (d, *J* = 9 Hz, 2 H), 6.61 (s, 1 H), 5.23 (s, 1 H), 4.00 (s, 2 H), 3.79 (s, 3 H); IR; HRMS; GC (crude product) **5h:7h** = 96:4 (t_R 3.92 min and 4.80 min, respectively, at 280 °C).

From **3i** after chromatography (toluene), **2-[(4-*tert*-butylphenyl)methyl]-1-naphthol (5i)** (83%): mp 71–73 °C (petroleum ether/ether); NMR δ 8.11 (m, 1 H), 7.78 (m, 1 H), 7.44 (m, 3 H), 7.3 (m, 3 H), 7.17 (d, *J* = 7 Hz, 2 H), 5.14 (s, 1 H), 4.12 (s, 2 H), 1.29 (s, 9 H); IR; MS; Anal. Also **3-[(4-*tert*-butylphenyl)methyl]-1-naphthol (7i)** (1.4%): oil; NMR δ 8.10 (m, 1 H), 7.74 (m, 1 H), 7.43 (m, 2 H), 7.30 (m, 3 H), 7.15 (d, *J* = 7 Hz, 2 H), 6.63 (s, 1 H), 4.04 (s, 2 H), 1.28 (s, 9 H); IR; HRMS; GC (crude product) **5i:7i** = 98:2 (t_R 3.80 min and 4.70 min, respectively, at 280 °C).

From **3j** after chromatography (toluene), **2-[[4-(trifluoromethyl)phenyl]methyl]-1-naphthol (5j)** (89%): mp 83.5–84 °C (petroleum ether/methylcyclohexane); NMR δ 8.03 (m, 1 H), 7.81 (m, 1 H), 7.2 (8 H), 5.15 (s, 1 H), 4.11 (s, 2 H); IR; MS; Anal. Also **3-[[4-(trifluoromethyl)phenyl]methyl]-1-naphthol (7j)** (1.7%): gum; NMR δ 8.10 (m, 1 H), 7.74 (m, 1 H), 7.5–7.2 (7 H), 6.66 (s, 1 H), 5.25 (br s, 1 H), 4.08 (s, 2 H); IR; HRMS; GC (crude product): **5j:7j** = 98:2 (t_R 2.03 min and 2.29 min, respectively, at 280 °C).

From **3k**. The residue (85%) was mostly (>95%) **2-methyl-1-naphthol (5k)**, identified by comparison with an authentic sample. This material was mostly pure by GC, with minor traces of several other materials. **3-Methyl-1-naphthol (7k)** was less

(22) Kutney, J. P.; Cable, J.; Gladstone, W. A. F.; Hanssen, H. W.; Vijay Nair, G.; Torupka, E. J.; Warnock, W. D. C. *Can. J. Chem.* **1975**, *53*, 1796.

(23) Schmit, C.; Sahraoui-Taleb, S.; Differding E.; Dehasse-De Lombert, C. G.; Ghosez, L. *Tetrahedron Lett.* **1984**, *25*, 5043.

(24) Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* **1983**, *24*, 2473.

(25) Pridgen, L. N.; Jones, S. S. *J. Org. Chem.* **1982**, *47*, 1590.

(26) Lacy, P. H.; Smith, D. C. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 419.

(27) Ishii, H.; Hanaoka, T.; Asaka, T.; Harada, Y.; Ikeda, N. *Tetrahedron* **1976**, *32*, 2693.

(28) Hellwinkel, D.; Krapp, W. *Chem. Ber.* **1977**, *110*, 693.

than 2% of the mixture, by coinjection with an authentic sample;[29] also, no trace of an aromatic singlet below δ 6.8 was detected by NMR.

From **3l**. The residue (99%) was essentially pure **2-*tert*-butyl-1-naphthol (5l)**, identified by comparison with an authentic sample.[30] This material was ≥99% pure by GC, and no trace of a singlet below δ 6.8 was detected by NMR.

From (impure) **3n**. The residue (75%) was essentially pure **2-bromo-1-naphthol (5n)**, identified by comparison with an authentic sample.[31] This material was ≥98% pure by GC (t_R 5.69 min at 280 °C), and no trace of a singlet below δ 6.8 was detected by NMR.

From (impure) **3o** after chromatography, **2-(ethoxycarbonyl)-1-naphthol (5o)** (15%). The presence of this material as well as a small amount of **3-(ethoxycarbonyl)-1-naphthol (7o)** was detected in the crude product by GC (**5o**:**7o** = 98:2, t_R 2.82 and 6.26 min, respectively, at 240 °C) by comparison with authentic materials.[1]

Acknowledgment. We are grateful to P. E. Crawford, R. A. Quas de Penno, D. Timby, and K. F. Blom for their assistance in obtaining spectral data. We also thank D. C. Spellmeyer for helpful discussions on the semiempirical molecular orbital calculations.

Registry No. **1a**, 62495-31-2; **1h**, 136131-34-5; **1i**, 136131-35-6; **1j**, 136131-36-7; **3a**, 136131-37-8; **3b**, 136131-38-9; **3c**, 136131-39-0; **3d**, 19061-32-6; **3e**, 136131-40-3; **3f**, 136131-50-5; **3g**, 136131-41-4; **3h**, 136131-42-5; **3i**, 136131-43-6; **3j**, 136131-44-7; **3k**, 136131-45-8; **3l**, 136131-46-9; **3m**, 136131-49-2; **3n**, 136131-47-0; **3o**, 136131-48-1; **4a**, 136131-51-6; **4b**, 136131-52-7; **4c**, 136131-53-8; **5a**, 136131-54-9; **5b**, 136131-55-0; **5c**, 136131-56-1; **5d**, 32849-41-5; **5e**, 129957-20-6; **5f**, 62456-32-0; **5g**, 36441-32-4; **5h**, 109380-82-7; **5i**, 136131-57-2; **5j**, 136131-58-3; **5k**, 7469-77-4; **5l**, 27286-81-3; **5n**, 771-15-3; **5o**, 33950-71-9; **6a**, 136131-59-4; **6b**, 136131-60-7; **6c**, 136131-61-8; **7d**, 51149-87-2; **7e**, 136131-62-9; **7f**, 52927-23-8; **8g**, 123239-69-0; **7h**, 136131-63-0; **7i**, 136131-64-1; **7j**, 136131-65-2; **7k**, 13615-40-2; **7o**, 91307-39-0; 3-furancarboxaldehyde, 498-60-2; 4-bromoanisole, 104-92-7; α-(4-methoxyphenyl)-3-furanmethanol, 136131-66-3; 1-bromo-4-(1,1-dimethylethyl)benzene, 3972-65-4; 1-bromo-4-(trifluoromethyl)benzene, 402-43-7; 2-amino-1,1'-(biphenyl), 90-41-5; α-oximino-2-phenylacetanilide, 136131-67-4; 2-amino-3-methylbenzoic acid, 4389-45-1; 2-amino-3-phenylbenzoic acid, 4445-39-0; 6-amino-2-(methoxycarbonyl)benzoic acid, 103259-06-9; anthranilic acid, 118-92-3; 3-methylfuran, 930-27-8; 3-(1,1-dimethylethyl)furan, 7040-42-8; 3-bromofuran, 22037-28-1; ethyl 3-furancarboxylate, 614-98-2; 3-phenylfuran, 13679-41-9.

Supplementary Material Available: Tabulated spectral data and analytical results for **1h-j**, **3b-o**, **5a-j**, and **7a-j** (6 pages). Ordering information is given on any current masthead page.

(29) Tishler, M.; Fieser, L. F.; Wendler, N. L. *J. Am. Chem. Soc.* **1940**, *62*, 2866.
(30) Hirashima, T.; Miyata, T. *Yuki Gosei Kagaku Kyokai Shi* **1976**, *34*, 433; *Chem. Abstr.* **1977**, *86*, 171123x.
(31) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.

Reaction of Enol Silyl Ethers and Enol Acetates with Copper(II) Nitrate-Iodine: Synthesis of α-Iodo Ketones

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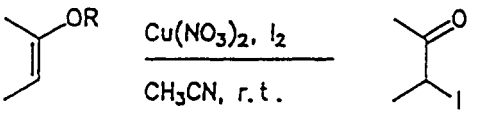
Received April 25, 1991

During the last few years a number of methods for the preparation of α-iodo ketones[1] from ketones, enol acetates, and enol silyl ethers have been reported. Although some of them represent a significant advance in this field,[2,3] there are still some disadvantages due, for instance, to the use of highly toxic reagents, such as thallium(I) acetate,[4] or to some substrate limitations.[5,6] At present, the most general method available consists of the sequential treatment of enol silyl ethers with silver acetate-iodine, followed by triethylammonium fluoride.[7] However, new efficient and cheaper methods for the preparation of these compounds are still desirable, in view of the extensive use of α-iodo carbonyl compounds in the synthesis of electrophilic α-oxo alkyl radicals.[8]

This paper reports a new and convenient procedure for the preparation of α-iodo ketones from the corresponding enol silyl ether or enol acetate with I_2 and copper(II) nitrate under mild reaction conditions, according to the following equation:



1 2

R = $SiMe_3$, Ac

Treatment of the enol derivative **1** with 1 molar equiv of copper(II) nitrate and 1 molar equiv of iodine in CH_3CN at rt for a few minutes affords the corresponding α-iodo ketone in very good yield. The results, displayed in Table I, clearly show the general applicability of the procedure. Under the same conditions, i.e., copper(II) nitrate and I_2, anisole gives iodoanisole in 64% yield after 24 h, while no ring iodination occurs by this procedure during the short time needed to obtain the corresponding α-iodo ketone in the case of compounds **1d** and **1h**. Moreover, the direct treatment of the enol silyl ether of cyclohexanone with molecular iodine without the copper salt does not afford any detectable trace of iodo ketone after 4 h. From these observations we can probably say that copper(II) nitrate plays a dual role in this reaction. First of all, it promotes the iodination process acting as a Lewis acid catalyst, and then it reoxidizes iodide ions back to iodine, analogous to a scheme that has been already proposed by Baird et al.[9] for the synthesis of aryl iodides. Although it is known that both copper(I) and copper(II) salts show Lewis acid properties capable of polarizing the iodo group and facilitating cleavage of the silyl group,[10] copper(II) is also a good oxidant. For this reason an alternative hypothesis has to be considered, in which the species involved in the process is I^+, which is generated from I_2 by oxidation with copper nitrate, as postulated in the synthesis of α-iodo ketones by electrochemical procedures[11] or by use of the *m*-chloroperoxybenzoic acid/sodium iodide reagent.[3]

In conclusion, iodination of trimethylsilyl enol ethers and enol acetates with copper(II) nitrate and I_2 represents a

(1) For general references, see: De Kimpe, N.; Verhé, R. *The Chemistry of α-Halo ketones, α-Halo aldehydes and α-Halo imines*; Patai, S., Rappoport, Z., Eds.; Interscience: New York, 1988; p 50.
(2) Motohashi, S. M.; Satomi, M. *Synthesis* **1982**, 1021.
(3) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919.
(4) Cambie, R. C.; Hayward, R. C.; Yurlina, J. L.; Rutledge, P. S.; Woodgate, J. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 126.
(5) Cardillo, G.; Shimizu, M. *J. Org. Chem.* **1977**, *42*, 4268.
(6) D'Auria, M.; D'Onofrio, F.; Piancatelli, G.; Scettri, A. *Synth. Commun.* **1982**, *12*, 1127.
(7) Rubottom, G. M.; Mott, R. C. *J. Org. Chem.* **1974**, *44*, 1731.
(8) Curran, D. P. *Synthesis* **1988**, 417, 489; Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, 3745.
(9) Baird, W. C., Jr.; Surridge, J. H. *J. Org. Chem.* **1970**, *35*, 3436.
(10) Dalla Cort, A. *Synth. Commun.* **1990**, *20*, 757.

0022-3263/91/1956-6708$02.50/0