added, giving a yellow color and a precipitate that came down slowly. The crude product was chromatographed (TLC, 20% EtOAc/$CHCl_3$) to yield **24** (119 mg, 54%), which was crystallized from MeOH to give: mp 138–140 °C (solidifying and remelting at 147–148 °C); $[\alpha]_D$ −17° (*c* 1.085, $CHCl_3$); NMR δ 5.26 (s, H-6), 2.45 (s, H-α to carbonyl), 1.12 (s, 2 Me's). Anal. Calcd for $C_{35}H_{56}O_2S$: C, 77.72; H, 10.44; S, 5.93. Found: C, 77.92; H, 10.64; S, 5.95.

Reaction of 4c with Iodide To Give 15. The sulfenylating agent **4c** (252 mg, 0.373 mmol) and Bu_4NI (209 mg, 0.569 mmol) were dissolved in CH_2Cl_2 (3 mL). Iodine was removed by washing with aqueous sodium thiosulfate. The solution was dried and chromatographed (TLC, CH_2Cl_2 eluant) to yield the disulfide **15** (127 mg, 88%), mp 140–143 °C, and thioamide **5** (40 mg, 85%) (by NMR). The ethylated sulfenylating agent **4b** gave 80% of **15**, mp 145–147 °C.

Reaction of 4c with Aqueous Sodium Bicarbonate To Give 16. The sulfenylating agent **4c** (100 mg, 0.148 mmol) was dissolved in DMF (2 mL), and $NaHCO_3$ (29 mg, 0.35 mmol) was added with stirring. No obvious reaction occurred (no color change). Water (5 mL) was added, and the precipitate that formed was filtered off, washed with water, and dried to yield crude **16** (60 mg). Preparative TLC (CH_2Cl_2 as eluant) yielded **16**, 50 mg (82%). Recrystallization ($CHCl_3$/MeCN) yielded 20 mg **16**: mp 170–173 °C, which was identical by mixed mp and spectral data with an authentic specimen (prisms) prepared as follows.

Unambiguous Preparation of 16. Dicholest-5-en-3β-yl disulfide (374 mg, 0.466 mmol) was dissolved in CH_2Cl_2 (5 mL), and *m*-chloroperbenzoic acid (94 mg, 0.55 mmol) was added. Purification of the product by TLC yielded **16** (283 mg, 74%). Recrystallization from $CHCl_3$/MeCN yielded 219 mg comprising two crystalline modifications, needles and prisms. These were separated manually to give 25 mg of needles and 194 mg of prisms. The IR spectra of the two forms were almost identical except for the SO stretch. Needles: mp 188–195 °C; $[\alpha]_D$ 21° (*c* 1.32, $CHCl_3$); IR ν_{max} 1080 s, 1070 s cm^{-1}. Prisms: mp 170–173 °C; $[\alpha]_D$ 3.8° (*c* 1.32, $CHCl_3$); IR 1080 s cm^{-1}. Both: NMR δ 5.43 (1 H, s, H-6); UV λ_{max} (EtOH) 260 nm (2500). Anal. (Prisms, mp 170–173 °C) Calcd for $C_{54}H_{90}OS_2$: C, 79.15; H, 11.07; S, 7.83. Found: C, 78.85; H, 11.33; S, 7.44.

Reaction of 4a with Tetrahydroisoquinoline To Give 23. A solution of the steroidal sulfenylating agent **4a** (200 mg, 0.320 mmol) was dissolved in DMF (3 mL) and stirred with powdered 4A molecular sieves. Tetrahydroisoquinoline (0.040 mL, 43 mg, 0.32 mmol) was added, followed by diisopropylethylamine (0.060 mL, 45 mg, 0.34 mmol). After 1 min, water (6 mL) was added and the precipitate that formed was filtered off, washed with water, and dried. The crude product was dissolved in $CHCl_3$, the sieves were filtered off, and the filtrate was crystallized from MeCN/$CHCl_3$ to yield **23** (130 mg, 2 crops, 76%): mp 116–125 °C; $[\alpha]_D$ −5° (*c* 1.05, $CHCl_3$); NMR δ 7.17 (4 H, br s, arom), 5.37 (1 H, br s, H-6), 4.23 (2 H, br s, H-1), 3.32 (t) and 2.92 (t) (H-3′ and H-4′); MS 533 (M^+) 402. Anal. Calcd for $C_{36}H_{55}NS$: C, 80.99; H, 10.38; N, 2.62; S, 6.01. Found: C, 80.74; H, 10.22; N, 2.40; S, 6.21. Compound **23** decomposed giving a mixture of compounds on attempted chromatography (silica TLC).

Reaction of 4c with Morpholine To Give 11. Morpholine (0.200 mL, excess) was added to a solution of the sulfenylating agent **4c** (255 mg, 0.277 mmol) in CH_2Cl_2. The product was isolated by preparative T.L.C. to afford **11** (68 mg, 37%) (some decomposition took place on the plate). A sample of **11** crystallized from $CHCl_3$/CH_3CN had: 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), 3.0 (4 H, m). Anal. Calcd for $C_{31}H_{33}NOS$: 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.

Reaction of 4a with Propranolol To Give 22b: Propranolol (**22a**; 33 mg, 320 μmol) was added to a solution of the sulfenylating agent **4a** (200 mg) dissolved in DMF (1.5 mL) and the mixture stirred until solution was complete. Diisopropylethylamine (56 μL, 41 mg, 320 μmol) was added and the solvent removed in vacuo. The residue was dissolved in toluene and the solvent removed in vacuo. This was repeated several times. Chromatography afforded pure **22b** (160 mg, 76%) as an oil: NMR δ (7 H, aromatic), 5.3 (1 H, br s, H-6). Anal. Calcd for $C_{43}H_{65}NO_2S$: C, 78.24; H, 9.93; S, 4.86. Found: C, 78.10; H, 9.74; S, 4.95.

Notes

A "One-Pot" Synthesis of Sulfenamides[1]

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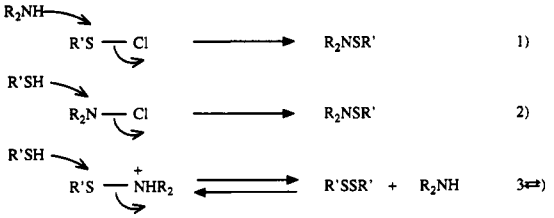
While sulfenamides are stable and reactive sulfenylating agents,[2] they are not commonly employed for this purpose, due largely to the fact that they are typically prepared through reaction of another sulfenylating agent (e.g. sulfenyl chloride) with an amine[2] (eq 1). Although sulfenyl chlorides are generally useful reagents, their application is limited by their very reactivity. For example, the double bond in cholestenethiol (**3a**) would be incompatible with a sulfenyl chloride functionality in the same molecule.

In principle, sulfenamides can be formed through an umpolung of eq 1, i.e., reaction of a thiol with a halamide (eq 2) (Scheme I). This method serves for the synthesis of certain heterocyclic sulfenamides (e.g., **1** and **2**), used as vulcanization accelerators in the rubber industry,[4] typically using aqueous or two-phase conditions. However, this reaction is by no means general, and in fact aliphatic and simple aromatic thiols are reported to lead exclusively to disulfides[5] rather than sulfenamides.

Scheme I



The difference in behavior between the aforementioned heterocyclic thiols (which yield sulfenamides) and ordinary thiols (which yield disulfides) can be rationalized using the following mechanistic scheme.

† Present address: Ciba-Geigy AG, 4002 Basel, Switzerland.

(1) Taken in part from the Ph.D. Thesis of A. C. O'Sullivan, University of London, 1981.

(2) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulfenic Acids and Their Derivatives*; Patai S., Ed.; Wiley: Chichester, UK, 1990; pp 403–516. Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689. We have found that sulfenamides are particularly useful for the synthesis of unsymmetrical disulfides, when treated with a thiol in the presence of acetic acid.[3]

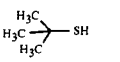
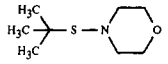
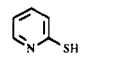
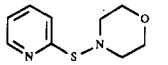
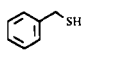
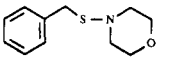
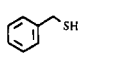
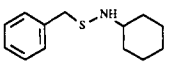
(3) Hesse R. H.; O'Sullivan, A. C. *J. Org. Chem.* In press.

(4) See, for instance: Hurley, T. J.; Robinson, M. A. *J. Med. Chem.* **1965**, *8*, 888. Carr, E. L.; Smith, G. E. P.; Alliger, G. *J. Org. Chem.* **1949**, *14*, 921. Greenbaum, S. B. *J. Am. Chem. Soc.* **1954**, *76*, 6052. Baltrop, J. A.; Morgan, K. J. *J. Chem. Soc.* **1957**, 3072.

(5) Sisler, H. H.; Kotia, N. K.; Highsmith, R. E. *J. Org. Chem.* **1970**, *35*, 1742.

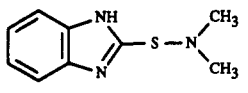
0022-3263/91/1956-6702$02.50/0

Table I

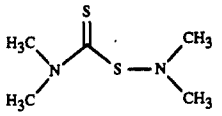
thiol	amine	sulfenamide	isolated yield
			97%
			40%
			96%
			84%
3a		3b	95%

It is probable that the disulfide formation observed in the aliphatic series (eq 3→) also intrudes when starting from 2-mercaptobenzimidazole and analogues, but these electrophilic disulfides then react further with amine to form the desired sulfenamide (eq 3←), building an equilibrium (eq 3⇌), which is driven to the left by conversion of the thiol according to eq 2, and disulfide does not accumulate as a byproduct. Indeed, disulfide can be substituted for thiol as starting material with this method,[6] in which case the reaction becomes simply one example of the more general and well-understood reaction of these electrophilic disulfides with amines, in which the thiol generated by eq 3← is recycled to disulfide by any one of a number of oxidizing agents.[7] On the other hand, aliphatic or simple aromatic disulfides are much less electrophilic, and once formed according to eq 3→, are slow to react further with amines[8] (eq 3←). Consequently disulfides accumulate and are often the only product isolated.[5] Thus in order to expand the range of utility of the reaction to aliphatic and simple aromatic disulfides, it is imperative to suppress the disulfide formation shown in eq 3→.

In mechanistic studies of the synthesis of the vulcanization accelerators 1 and 2, Ignatov et al.[9] have shown that



1

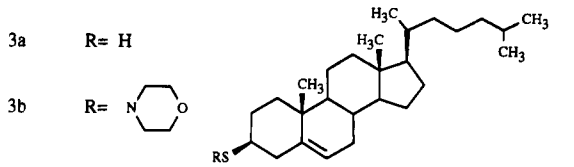


2

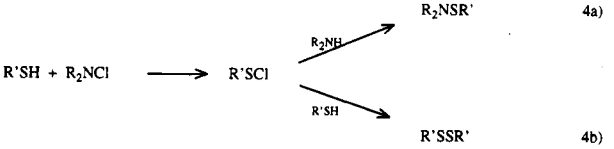
under aprotic conditions, 2-mercaptobenzimidazole attacks chloramides in an SN_2 reaction to afford sulfenamides according to eq 2. They also found the attack of thiol upon sulfenamide (eq 3→) to form the undesired disulfide to be acid catalyzed. This second observation suggests that disulfide formation from more typical thiols could be controlled through maintainance of high pH and use of a nonpolar aprotic solvent, thus generalizing this inherently useful reaction from a few special cases to a range of aliphatic and aryl sulfenamides.

We now report that under basic conditions a variety of thiols react with chloramides (formed in situ) in a nonpolar medium to afford sulfenamides in good yield. $CHCl_3$ was used throughout as solvent and the basic conditions were assured by simply using an excess of amine. The sulfenamides can be purified by distillation in vacuo, chromatography on alumina or Florisil (silica gel chromatography results in considerable loss), or crystallization. As 4-morpholinyl 2-pyridyl sulfide (Table I) was required as a starting material for another purpose,[3] a number of experiments had been performed using typical aqueous or two-phase conditions before the conditions described here were implemented. In these cases a mixture of the desired sulfenamide and dipyridyl disulfide was always obtained. By contrast, the present procedure afforded the sulfenamide free of disulfide.

One might consider mechanisms for this reaction other than the SN_2 reaction expressed in eq 2. For instance, sulfenylation of amine by disulfide according to reaction 3←. However we have shown that the disulfide of 3β-mercapto-5-cholestene (**3a**) is recovered unchanged fol-



lowing exposure to a mixture of morpholine and *N*-chloromorpholine. This observation also precludes involvement of the most attractive mechanistic alternative to eq 2, i.e., chlorination of the thiol to afford a sulfenyl chloride, which then reacts with amine to produce the sulfenamide (eq 4a). Typical sulfenylating agents are



4a)

4b)

reported to react 10^7–10^8 times more rapidly with thiols than with amines.[10] Thus sulfenyl chloride, if formed as in eq 4, would be expected to combine with unreacted thiol[11] to afford disulfide (eq 4b), which we have observed to be inert to the reaction conditions. A radical mechanism can also be excluded, as the amination reaction of **3a** with morpholine affords compound **3b** in good yield even in the presence of a large excess of styrene.[12]

We thus presume that the synthesis of sulfenamides we describe here proceeds through an SN_2 attack of thiol on the chloramide as proposed by Ignatov et al.[9] The reaction is extremely convenient and particularly valuable for the preparation of sulfenamides from thiols which cannot be converted into sulfenyl chlorides.

Experimental Section[13]

4-Morpholinyl *tert*-Butyl Sulfide. Morpholine (10.0 mL, 10.0 g; 115 mmol) was added to aqueous sodium hypochloride (42 mL, 465 mmol) and the mixture extracted with chloroform (10 mL). More morpholine (10.0 mL, 10.0 g, 115 mmol) was added to the chloroform extract, which was cooled to 0 °C, and the thiol (820 mg, 9.11 mmol) added with stirring. After 5 min, the solution was washed with aqueous sodium sulfite to destroy excess chlo-

(6) D'Amico, J. J.; Morita, E. *Rubber Chem. Technol.* **1971**, *44*, 891.
(7) Torii, S., Tanaka, H.; Ukida, M. *J. Org. Chem.* **1978**, *43*, 3223. Torii, S.; Tanaka, H.; Ukida, M. *J. Org. Chem.* **1979**, *44*, 1554.
(8) Simple aliphatic disulfides will react with amines when activated with Ag or Hg salts. Davies, F. A.; Friedman, A. J.; Kluger, E. W.; Skibo, E. B.; Fretz, E. R.; Milicia, A. P.; LeMasters, W. C.; Bentley, M. D., Lacadie, J. A.; Douglass, I. B. *J. Org. Chem.* **1977**, *42*, 976. An iodide-catalyzed reaction of morpholine with diphenyl disulfide with concomitant electrolytic oxidation has been described. Torii, S.; Tanaka, H.; Ukida, M. *J. Org. Chem.* **1979**, *44*, 1554.
(9) Ignatov, V. A.; Akchurina, R. A.; Volkov, I. V.; Pinogov, P. A. *Zh. Obsch. Khim.* **1977**, *47*, 1096 (Engl. 1004). Ignatov, V. A.; Val'kov, P. G.; Sukhanov, S. V.; Lazovenko, A. N. *Ibid.* **1979**, *49*, 841 (Engl. 731). Ignatov, V. A.; Pirogov, P. A. *Khim. Geterotsikl. Soedin.* **1970**, 89 (Engl. 85).
(10) Kice, J. L.; Liu, C. C. A. *J. Org. Chem.* **1979**, *44*, 1918. Wilson, J. M.; Bayer, R. J.; Hupe, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 7922. Al-Rawc, H.; Stacey, K. A.; Weatherhead, R. H.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 663.
(11) This presupposes that the reaction of thiol with chloramide is not notably faster than reaction of thiol with sulfenyl chloride. This may be reasonably inferred from refs 9 and 10.
(12) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1982**, *104*, 1701.
(13) General procedures were as reported in: Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819.

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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Inflammatory Diseases Research, The Du Pont Merck Pharmaceutical Co., Wilmington, Delaware 19880-0353

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.

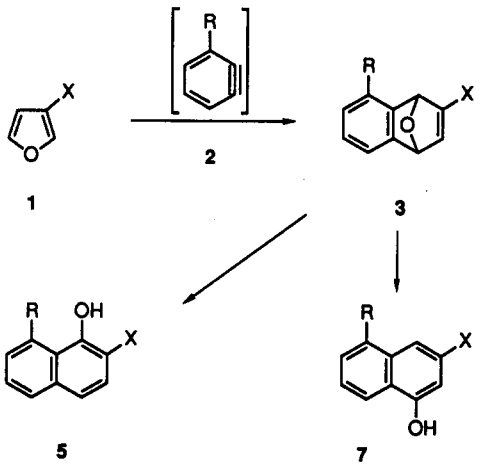
(1) Batt, D. G.; Maynard, G. D.; Petraitis, J. J.; Shaw, J. E.; Galbraith, W.; Harris, R. R. *J. Med. Chem.* **1990**, *33*, 360.
(2) Balasubramaniyan, V. *Chem. Rev.* **1966**, *66*, 567.
(3) Kirby, A. J.; Percy, J. M. *Tetrahedron* **1988**, *44*, 6903.
(4) Kirby, A. J.; Percy, J. M. *Tetrahedron*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