and then methyl iodide (0.168 mL, 2.7 mmol) was added all at once via syringe. The solution was warmed to ambient temperature, and then the solvent was removed at reduced pressure. The residue was partitioned between ether (75 mL) and water (25 mL) followed by workup as usual to leave 0.34 g of a pale yellow oil. Chromatography on silica gel (50 g) proceeded as follows: 10% ether–hexane, 100 mL, nil; 125 mL, 0.14 g, 46% of **9** as a colorless oil. Elution continued as follows: 10% ether–hexane, 125 mL, nil; 20% ether–hexane, 70 mL, nil; 175 mL, 0.13 (31%) of colorless oil, **10**, identical with an authentic sample in NMR and IR spectral properties; mass spectrum, *m/e* 175.

**Acknowledgment.** I thank Thomas Miller for technical assistance.

**Registry No.** **1**, 86064-95-1; **2**, 86064-96-2; **3**, 30093-99-3; **4**, 86064-97-3; **5**, 86064-98-4; **6**, 86064-99-5; **7**, 86065-00-1; **8**, 86065-01-2; **10**, 19312-06-2; **11**, 86065-02-3; *n*-BuLi, 109-72-8; PhLi, 591-51-5; *t*-BuLi, 594-19-4; LDA, 4111-54-0; diphenyl disulfide, 882-33-7; di-*p*-tolyl disulfide, 103-19-5; di-*p*-chlorophenyl disulfide, 1142-19-4; di-3,4-dichlorophenyl disulfide, 4235-78-3; di-*O*-bromophenyl disulfide, 71112-91-9; di-4-chloro-2-methylphenyl disulfide, 86065-03-4; 2-amino-2-methylpropanol, 124-68-5; thiophenyl chloroformate, 13464-19-2; lithium, 7439-93-2.

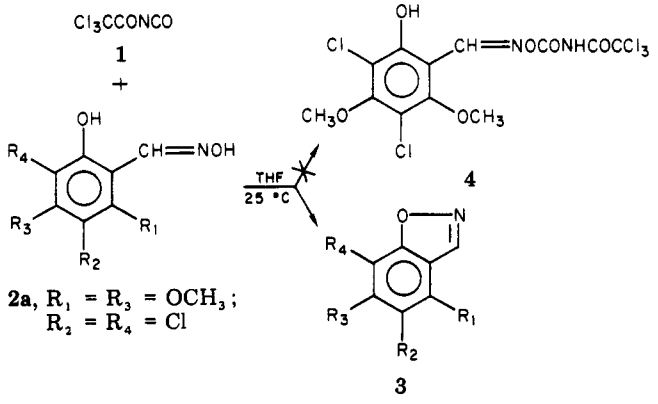
## Preparation of 1,2-Benzisoxazoles from Salicylaldoximes via Trichloroacetyl Isocyanate

Gerald Stokker

*Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486*

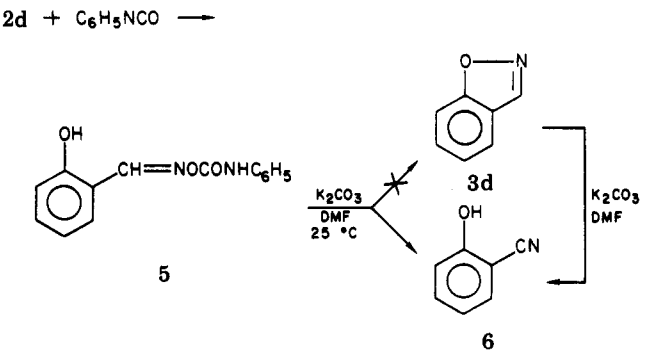
*Received November 17, 1982*

Trichloroacetyl isocyanate (**1**)[1,2] has been used since 1965[1] as a derivatization reagent for the classification of alcohols. In this regard, we recently attempted to identify unequivocally the phenolic proton and the hydroxylimine proton in the $^1H$ NMR spectrum of **2a** (br s at $\delta$ 11.6 and 11.8) by treatment with **1**. Instead of the expected carbamoylaldoxime **4**, the only product obtained was the 1,2-benzisoxazole **3a** in 81% yield. A limited study was initiated in order to assess the scope and generality of this reaction as a means for preparation of 1,2-benzisoxazoles.



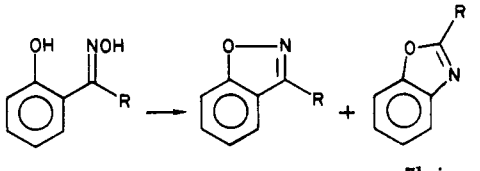

Compound **2a** was the only oxime in this study (see Tables I and II), which, on treatment with **1** in THF, spontaneously cyclized in greater than trace amouts without the addition of a base ($K_2CO_3$).[3] Replacement of THF by $Et_2O$ or MeCN resulted in lower yield, while substitution by DMF resulted in a violent exothermic reaction.

Chlorosulfonyl isocyanate, recently demonstrated by Olah to be a mild and effective dehydrating agent for aldoximes,[4] provided a slightly lower yield than **1** in this reaction. Only a trace (TLC) of **3a** was observed with the use of *n*-propyl, *n*-butyl, or *tert*-butyl isocyanates or 4-nitrophenyl isothiocyanate in THF with or without the addition of $K_2CO_3$. Substitution of phenyl isocyanate for **1** resulted in a lower yield (56%) of **3a**, although this could be increased to 76% by the addition of 1 equiv of $K_2CO_3$. Upon treatment of **2d** with phenyl isocyanate, intermediate **5** precipitated before the base was added.[5] When **5** was subsequently dissolved in DMF and treated with $K_2CO_3$, and exothermic reaction ensued to yield **6** in 66% yield instead on the expected **3d**. 2-Hydroxy nitrile **6** was also obtained from **3d** when it was reacted similarly with $K_2CO_3$ in DMF at 25 °C.




On standing several months at ambient temperature in the dark, **3e** was found to have undergone ring opening and concomitant prototropic rearrangement, even in the solid state, to provide the corresponding 2-hydroxy nitrile.[6] The only other 1,2-benzisoxazoles in this study to display this tendency, albeit to a much lesser extent, were **3c** and **3f**, as judged by the emergence of the CN peak (2220–2230 $cm^{-1}$) in the IR and slight broadening of the melting point.

Two 2-hydroxy ketoximes (**2h–i**) were also studied, and in each case the yields of the expected isoxazoles were lower than from the aldoximes and were accompanied by formation of the corresponding oxazole resulting from a Beckmann rearrangement of the intermediate carbamoyl oxime[7] and subsequent ring closure.



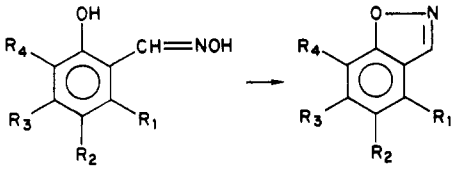

2h, R = $CH_3$

i, R = 


(1) Goodlett, V. W. *Anal. Chem.* **1965**, *37*, 431.
(2) Meyer zur Heyde, M. *Fresenius Z. Anal. Chem.* **1979**, *295* (*2/3*), 125.
(3) The explanation for the ability of **2a** to spontaneously form **3a** without the addition of a base was originally thought to be a functon of its $pK_a$ (7.65 in 30% EtOH). However, the reason must be more complex than the mere acidity of the salicylaldoximes for **2g** is more acidic ($pK_a$ = 6.8), while **2c** is of equivalent acidity ($pK_a$ = 7.60) and the remaining salicylaldoximes are less acidic ($pK_a$ values, 8.95–9.70).
(4) Olah, G. A.; Vankar, Y. D.; Garcia-Luna, A. *Synthesis* **1979**, 227.
(5) Collected by cooling to −20 °C, 50% yield, mp 148–149 °C dec; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 6.8–8.0 (9 H, m), 8.8 (H, s, CH=N), 9.9 (H, s), 10.3 (H, s).
(6) Mp 86–86.5 °C from hexane; $^1H$ NMR ($CDCl_3$), $\delta$ 1.30 (9 H, s), 7.46 (H, d, $J$ = 3 Hz), 7.56 (H, d, $J$ = 3 Hz); IR (Nujol) 3500–3050 (OH), 2220 (C≡N) $cm^{-1}$; Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 62.88; H, 5.93; N, 6.41.
(7) Kuhara has previously demonstrated that benzenesulfonyl esters of diaryl oximes rearranged spontaneously at 20 °C and further that the rate of rearrangement was proportional to the strength of the esterifying acid as cited by Smith, P. A. S. In "Molecular Rearrangements"; deMayo, P., Ed.; Interscience: New York, 1963; pp 488–489.

0022-3263/83/1948-2613$01.50/0 

Table I. Conversion of Salicylaldoximes[a] to 1,2-Benzisoxazoles

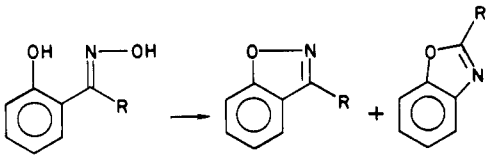


2 3

| compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | yield,[b] % | mp °C (lit.) | recryst solvent | formula[c,d] |
|---|---|---|---|---|---|---|---|---|
| 3a | $OCH_3$ | Cl | $OCH_3$ | Cl | 81 | 138-139 | EtOH | $C_9H_7Cl_2NO_3$ (ref 14) |
| 3b | $OCH_3$ | | $OCH_3$ | | 72 | 100-101 | $MeOH/H_2O$ | $C_9H_9NO_3$ (ref 14) |
| 3c | | Cl | | Cl | 82 | 101-103 (107)[10] | | $C_7H_3Cl_2NO$ |
| 3d | | | | | 67 | 90-93 (15 mm) (84 (11 mm))[10] | | $C_7H_5NO$ |
| 3e | | $t$-$C_4H_9$ | | Cl | 90 | 46-48 | petroleum ether | $C_{11}H_{12}ClNO$ (ref 14) |
| 3f | | $t$-$C_4H_9$ | | I | 46 | 106-109 | $MeOH/H_2O$ | $C_{11}H_{12}INO$ (ref 14) |
| 3g | | $NO_2$ | | | 61 | 126-128 (126)[10] | $EtOH/H_2O$ | $C_7H_4N_2O_5$ |

[a] Oximes **2a,c-d,g** have been described,[9] as have 1,2-benzisoxazoles **3c-d,g**.[10] [b] Unoptimized isolated yields of pure product. [c] Elemental analysis for C, H, N were performed on all new compounds and are within ±0.4% of the theoretical values. [d] NMR spectra of all compounds are consistent with the assigned structures.

Table II. Reaction of 2-Hydroxy Ketoximes[a]



2 3 7

| compd | R | yield,[b] % | mp °C (lit.) | recryst solvent | formula[c,d] |
|---|---|---|---|---|---|
| 3h | $CH_3$ | 34[e] | 100-102 (14 mm) (92.5 (11 mm))[10] | | $C_8H_7NO$ |
| 7h | $CH_3$ | 15[e] | 80-85 (15 mm) (200-201)[11] | | |
| 3i | 2-$OHC_6H_4$ | 33[f] | 94-95 | $MeOH/H_2O$ | $C_{13}H_9NO_2$ (ref 14) |
| 7i | 2-$OHC_6H_4$ | 26[f] | 122-124 (120-121)[11] | MeOH | |

[a] Oximes **2h,i** have been described,[9] as have 1,2-benzisoxazole **3h** and 1,3-benzoxazoles **7**.[11] [b-d] See corresponding footnotes to Table I. [e] The isomers were separated by chromatography on silica gel, eluting with $CHCl_3$: **3h**, $R_f$ 0.51; **7h**, $R_f$ 0.19. [f] The isomers were separated by chromatography on silica gel, eluting with $CCl_4$: **3i**, $R_f$ 0.09; **7i**, $R_f$ 0.27.

We have thus demonstrated the synthetic utility of trichloroacetyl isocyanate as an effective reagent in the preparation of 1,2-benzisoxazoles from salicylaldoximes. This procedure also represents an alternative to that of Kalkore and Goswami[8] ($SOCl_2$ in dry $Et_2O$ at 0 °C, yields of **3a, 3b, 3e** were 75% (80% with THF), 56% and 79%, respectively). In the instances where the products are solids, the present procedure represents an improvement in ease of isolation.

## Experimetnal Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. $^1H$ NMR spectra were recorded in $Me_2SO$-$d_6$, unless otherwise noted, on either a Varian T-60 or Nicolet NT-360 spectrometer. Chemical shifts are reported in parts per million relative to $Me_4Si$ as the internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory. Infrared spectra were determined on a Perkin-Elmer Model 297 infrared spectrophotometer. All starting materials were commercially available unless so indicated.

**Synthesis of Salicylaldoximes.** A solution of sodium acetate trihydrate (40 mmol in 10 mL of $H_2O$) was added to a warm solution of the salicylaldehyde (20 mmol) and the hydroxylamine hydrochloride (40 mmol) in 80% aqueous ethanol (50 mL). After refluing for 3 h, the reaction mixture was diluted with hot $H_2O$ (10 mL) and then cooled to -10 °C. The solid obtained was filtered off, washed with $H_2O$, and recrystallized from aqueous alcohol.

**2b**: 96% from aldehyde; mp 119–120 °C; $^1H$ NMR ($CDCl_3$) δ 3.8 (6 H, s), 6.0 (H, d, $J$ = 3 Hz), 6.15 (H, d, $J$ = 3 Hz), 7.4 (H, s), 8.6 (H, s), 10.55 (H, s). Anal. ($C_9H_{11}NO_4$) C, H, N.

**2e**: 99% from aldehyde;[12] mp 167–168.5 °C; $^1H$ NMR δ 1.25 (9 H, s), 7.395 (H, d, $J$ = 2.3 Hz), 7.452 (H, d, $J$ = 2.3 Hz), 8.42

(8) Kalkote, U. R.; Goswami, D. D. *Aust. J. Chem.* **1977**, *30*, 1847.

(9) **2a**: Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Ludden, C. T.; Russo, H. F.; Scriabine, A.; Sweet, C. S.; Watson, L. S. *J. Med. Chem.* **1980**, *23*, 1414. **2c**: Biltz, H.; Stept, K. *Chem. Ber.* **1904**, *37*, 4022. **2d**: Holly, F. W.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1875. **2g**: Eastman Organic Chemicals. **2h**: Dunsten, W. R.; Henry , T. A. *J. Chem. Soc.* **1899**, *75*, 66. **2i**: v. Auwers, K.; Jordan, O. *Chem. Ber.* **1925**, *58*, 26.

(10) **3c**: Caronna, G.; Palazzo, S. *Gazz. Chim. Ital.* **1959**, *89*, 1009; *Chem. Abstr.* **1960**, *54*, 22571g. **3d**: v. Auwers, K. *Chem. Ber.* **1924**, *57*, 461. **3g,h**: Lindemann, H.; Thiele, H. *Justus Liebigs Ann. Chem.* **1926**, *449*. 63.

(11) **7h**: Ladenburg, A. *Chem. Ber.* **1876**, *9*, 1524. **7i**: see ref 8, **21**.

(12) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Russo, H. F.; Watson, L. S. *J. Med. Chem.* **1981**, *24*, 1063.

(H, s), 10.9 (H, s), 11.7 (H, s). Anal. ($C_{11}H_{14}ClNO_2$) C, H, N.

**2f**: 86% from aldehyde;[13] mp 156–157.5 °C; $^1$H NMR $\delta$ 1.25 (9 H, s), 7.486 (H, d, $J$ = 2.3 Hz), 7.694 (H, d, $J$ = 2.3 Hz), 8.37 (H, s), 10.8 (H, br s), 11.25 (H, br s). Anal. ($C_{11}H_{14}INO_2$) C, H, N.

**Synthesis of 1,2-Benzisoxazoles.** To a solution of **2** (10 mmol) in dry THF (10 mL) was added **1** (10.5 mmol) in dry THF (5 mL) at room temperature (very slight exotherm). After 10 min $K_2CO_3$ (11 mmol) was added and the mixture was stirred for an additional 30 min before it was poured into $H_2O$ (400 mL) with vigorous stirring. The solid products were treated as indicated in Table I, while the liquids (**3d,h, 7h**) were extracted into $Et_2O$, washed with $H_2O$ and staturated brine, dried ($MgSO_4$), and distilled.

**Acknowledgment.** We extend our thanks to K. B. Streeter and his staff for elemental analysis, to Y. C. Lee for p$K_a$ determinations, to Dr. D. W. Cochran for helpful discussions on the NMR data, and to Kevin Stokker and Mary Zook for assistance in manuscript preparation.

**Registry No.** 1, 3019-71-4; **2a**, 38730-67-5; **2b**, 71253-52-6; **2b** (aldehyde), 708-76-9; **2c**, 5331-93-1; **2d**, 94-67-7; **2e**, 71064-05-6; **2e** (aldehyde), 71730-43-3; **2f**, 71064-04-5; **2f** (aldehyde), 71064-03-4; **2g**, 1595-15-9; **2h**, 1196-29-8; **2i**, 54758-73-5; **3a**, 71064-06-7; **3b**, 71064-07-8; **3c**, 86013-72-1; **3d**, 271-95-4; **3e**, 86013-73-2; **3f**, 71097-36-4; **3g**, 39835-28-4; **3h**, 4825-75-6; **3i**, 86013-74-3; **7h**, 95-21-6; **7i**, 835-64-3; **5**, 86013-75-4; **6**, 611-20-1; $C_6H_5NCO$, 103-71-9.

(13) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Russo, H. F.; Watson, L. S. *J. Med. Chem.* **1982**, *25*, 735.

(14) **3a**: $^1$H NMR ($CDCl_3$) $\delta$ 4.0 (3 H, s), 4.2 (3 H, s), 8.8 (H, s). **3b**: $^1$H NMR ($CDCl_3$) $\delta$ 3.8 (3 H, s), 3.83 (3 H, s), 6.23 (H, d, $J$ = 1 Hz), 6.62 (H, d, $J$ = 1 Hz), 8.6 (H, s). **3e**: $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (9 H, s), 7.55 (2 H, s), 8.72 (H, s). **3f**: $^1$H NMR ($CDCl_3$) $\delta$ 1.4 (9 H, s), 7.7 (H, d, $J$ = 1 Hz), 8.0 (H, d, $J$ = 1 Hz), 8.85 (H, s). **3i**: $^1$H NMR ($CDCl_3$) $\delta$ 6.93–8.27 (8 H, m), 9.73 (H, s).

## Identification of the Reactive Electronic Excited State in the Photocycloaddition of Alkenes to Cyclic Enones[1,2]

David I. Schuster,* Marc M. Greenberg, Ivan M. Nuñez, and Philip C. Tucker

*Department of Chemistry, New York University, New York, New York 10003*

*Received July 28, 1982*

Photocycloaddition of alkenes to cyclic enones has become an important tool in the arsenal of synthetic organic chemists,[3] stimulated by the pioneering studies of Corey nearly 20 years ago.[4] Various aspects of the mechanism of this reaction are understood,[3,5] although a fully precise mechanistic description has yet to be presented. Corey[4] suggested that the reaction involves a triplet excited state of the enone, which forms an "oriented $\pi$ complex" with the alkene. This species, an exciplex in modern parlance,[6,7] is thought to proceed to give a 1,4-diradical on formation of a covalent bond between C-3 of the enone and one of the olefinic carbons. This biradical was subsequently[5,6] suggested to be a relatively long-lived triplet species. Closure to a four-membered ring completes the sequence, in competion with H transfer and reversion to ground states of the starting materials.[6] The exciplex and diradical are needed to account for the regioselectivity of the reaction and the failure to preserve the stereochemistry of the olefinic moiety in the cycloadduct.[3-5] It has also been observed that the major adduct formed from electron-rich alkenes and 2-cyclohexenones usually has a trans fusion of the four- and six-membered rings.[3-5]

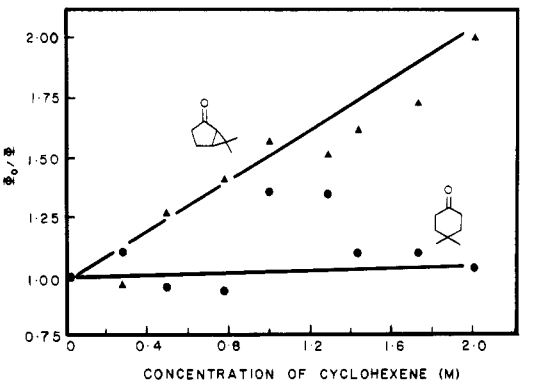



**Figure 1.** Quenching by cyclohexene of the formation of photoproducts **2** and **4** on irradiation of enone **1** in IPA (run I).

The enone excited state responsible for this reaction has not been precisely identified. Corey[3] implicitly assumed that the reactive state in the case of cyclohexenone was a triplet n,$\pi^*$ state, although there was no direct evidence to support that proposal. In his studies of photocycloaddition of 1,1-dimethoxyethylene to 4,4-dimethylcyclohex-2-en-1-one (**1**), Chapman[8] concluded that trans-fused cycloadducts and oxetanes arose from n,$\pi^*$ triplet excited states of the enone while cis-fused adducts arose from $\pi,\pi^*$ triplets. McCullough[9] later concluded that cycloaddition of cyclopentene to enone **1** involved the same excited state (which was not explicitly identified) as that responsible for photorearrangement of **1**,[10] on the basis of the observation that the ratio of adducts to rearrangement products (**2** and **3**) was unchanged in the presence of 0.05 M naphthalene, a well-known triplet quencher. He also argued cogently that it was likely that the reactive enone excited state was twisted about the C=C bond, in order to account for the high yield of trans-fused cycloadducts. A mechanism (see Scheme I) was presented involving initial complexation of the olefin and a twisted enone triplet, leading to a twisted 1,4-diradical in which formation of trans-fused adducts by ring closure was competitive with relaxation of the diradical to a more stable geometry, which in turn afforded only cis-fused products on ring closure.[9]

Taking advantage of our knowledge of the detailed mechanisms of photorearrangement and photoreduction of **1** in isopropyl alcohol (IPA) to give **2**, **3**, and **4**[11-13] and

(1) Photochemistry of Ketones in Solution. 70. Part 69: Brisimitzakis, A. C.; Schuster, D. I., submitted for publication in *Tetrahedron Lett.*

(2) Taken in part from the B.S. Honors Thesis of M.M.G. and the Ph.D. Dissertation of I.M.N., 1982.

(3) For a review, see: Baldwin, S. W. *Org. Photochem.* **1981**, *5*, 123.

(4) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

(5) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41.

(6) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559.

(7) Caldwell, R. A.; Creed, D. *Acc. Chem. Res.* **1980**, *13*, 45.

(8) Chapman, O. L.; Koch, T. H.; Klein, F.; Nelson, P. J.; Brown, E. L. *J. Am. Chem. Soc.* **1968**, *90*, 1657.

(9) Bowman, R. M.; Calvo, C.; McCullough, J. J.; Rasmussen, P. W.; Snyder, F. F. *J. Org. Chem.* **1972**, *37*, 2084.

(10) For a recent review of the literature on photorearrangement of enones, see: Schuster, D. I. In "Rearrangements of Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3.

(11) Schuster, D. I.; Brown, R. H.; Resnick, B. M. *J. Am. Chem. Soc.* **1978**, *100*, 4505.

(12) Schuster, D. I.; Nuñez, I. M.; Chan, C. B. *Tetrahedron Lett.* **1981**, *22*, 1187.

0022-3263/83/1948-2615$01.50/0 