STUDY OF THE REACTION OF SEVERAL KETONE ENOLATES WITH 3-IODOBENZO[b]THIOPHENE UNDER THERMALLY INITIATED $S_{RN}1$ REACTION CONDITIONS

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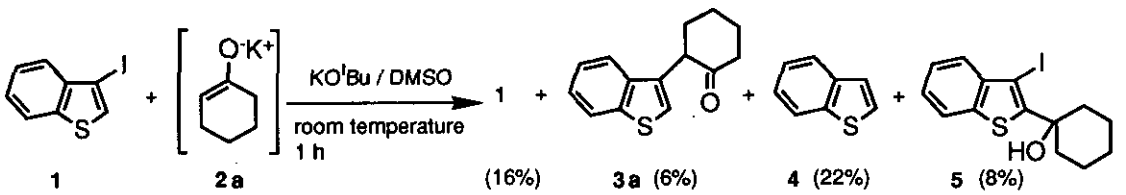
Abstract- The reaction of 3-iodobenzo[b]thiophene (1) with the potassium enolates of cyclohexanone (**2a**), acetone (**2b**), and acetophenone (**2c**) in DMSO for 1 h at room temperature in the dark, gave the desired α-hetaryl ketones (**3a-c**) in low yield. The thermally activated $S_{RN}1$ reaction with the ion enolate (**2a**) was studied in more detail and it was found that the radical chain $S_{RN}1$ mechanism could compete with one of ionic character.

In connection with a research program directed toward the preparation of α-benzo[b]thenyl ketones we focused our attention on the radical chain $S_{RN}1$ mechanism of aromatic nucleophilic substitution, which was first recognized in 1970.[1] It is well known that this type of reaction allows the substitution of appropriate leaving groups on aromatic and heteroaromatic substrates for various nucleophiles, such as ketone enolates.[2] Most aromatic and heteroaromatic $S_{RN}1$ reactions require stimulation by photons, solvated electrons, or electrons from a cathode. However, the initial examples of aryl iodides reacting with KNH_2 involved no intentional stimulation.[1] More recently, it was observed that enolate ions of ketones react spontaneously with iodobenzene in dimethyl sulfoxide (DMSO) in the dark,[3] and with halogenated quinolines,[4] pyrimidines,[2c] pyridazines,[2c] and pyrazines[2c] in liquid ammonia (also in the dark), to give the corresponding α-aryl and α-hetaryl ketones. In spite of this, there are still relatively few examples of this type of reaction in the area of heteroaromatic nucleophilic substitution.

In the present study, we consider the reactions of 3-iodobenzo[b]thiophene (**1**) with potassium enolates of cyclohexanone (**2a**), acetone (**2b**) and acetophenone (**2c**).

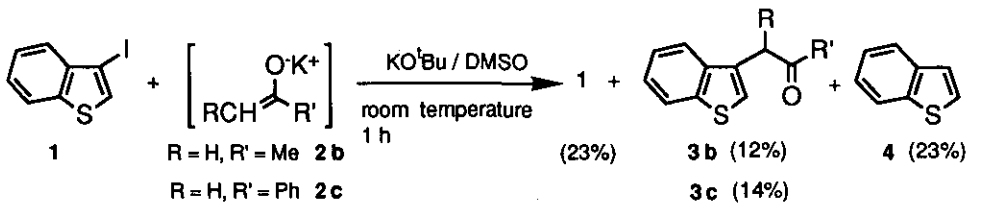
Scamehorn *et al.*[5] have described a remarkable reaction between the enolate ions of acetone, pinacolone, cyclohexanone, 2-butanone, and 3-pentanone and iodobenzene in DMSO. This aromatic nucleophilic substitution reaction, which proceeds rapidly in the dark, has the characteristics of a free radical chain reaction, and is thought to occur by the $S_{RN}1$ mechanism.

Following the method of Scamehorn *et al.* we studied the reaction of the potassium enolate of cyclohexanone (**2a**) with 3-iodobenzo[b]thiophene (**1**) in DMSO for 1 h in the dark at room temperature. This reaction gave the desired substitution product 2-(3-benzo[b]thienyl)cyclohexanone (**3a**) in 6% yield. In addition, benzo[b]-thiophene (**4**) and 1-(3-iodo-2-benzo[b]thienyl)cyclohexanol (**5**) were produced in yields of 22 and 8% respectively, while unaltered **1** was recovered in 16% yield (Scheme 1).



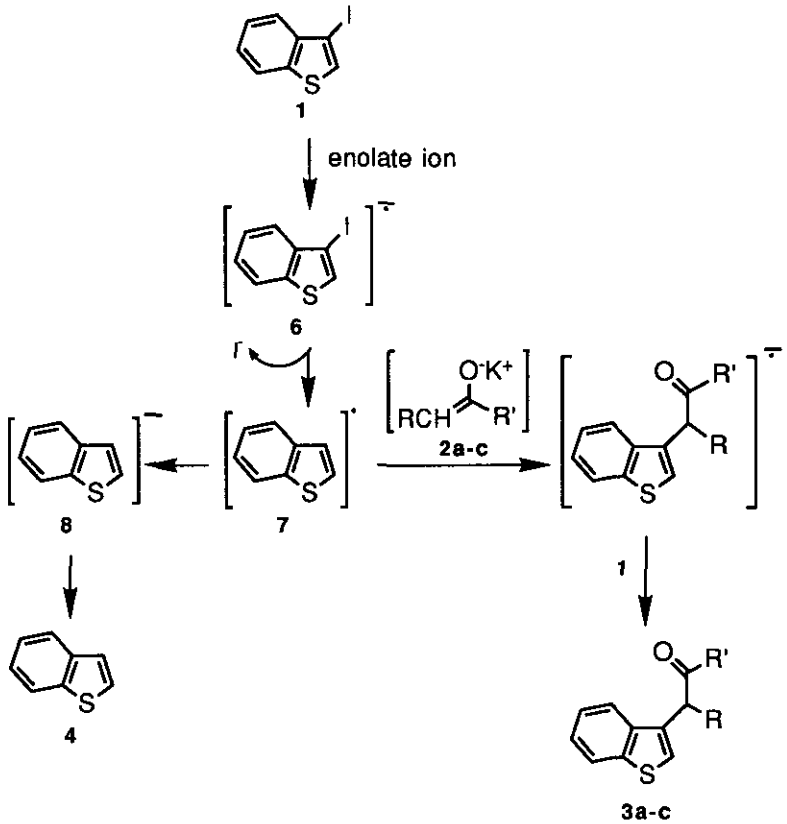
Scheme 1

When the potassium enolates of acetone (**2b**) and acetophenone (**2c**) were treated with 3-iodobenzo[b]thiophene (**1**) in the same reaction conditions, the corresponding α-hetaryl ketones, 3-benzo[b]thienylacetone (**3b**) and 2-(3-benzo[b]thienyl)-1-phenylethanone (**3c**) were obtained in yields of 12 and 14% respectively (Scheme 2). In these reactions, the substrate (**1**) and the benzo[b]thiophene (**4**) were isolated in 23% yield. Repetition of these reactions in the presence of 10 mol % of the inhibitor p-dinitrobenzene (DNB)[6] afforded 65% of starting material (**1**), but did not give detectable amounts of the substitution products (**3b-c**) nor of the dehalogenated substrate (**4**).



Scheme 2

These results suggest that benzo[b]thiophene (**4**) and the α-hetaryl ketones (**3a-c**) could be formed through an $S_{RN}1$ process as indicated in Scheme 3, but a not well defined ionic mechanism leading to alcohol (**5**) may occur in competition with this radical chain mechanism in the reaction between the substrate (**1**) and the ketone enolate (**2a**). In the $S_{RN}1$ mechanism shown in Scheme 3, the initiation probably involves electron transfer from the enolate ion[7] to produce the radical anion (**6**), which could be fragmented to produce radical (**7**).[8] The generation of benzo[b]thiophene (**4**) from radical (**7**) would involve the capture of a hydrogen atom from the solvent[9] (this fact is unlikely when DMSO is used as a solvent because of its low reactivity as a hydrogen atom donor toward aryl radicals[10]) or an electron transfer from the anionic species present in the reaction mixture followed by protonation of anion (**8**) by the solvent.[9] Finally, if radical (**7**) goes into the propagation cycle of the $S_{RN}1$ reaction, the desired α-hetaryl ketones (**3a-c**) would be produced. Formation of benzo[b]thiophene (**4**) indicates that reduction of radical (**7**) to anion (**8**) and subsequent protonation by the solvent strongly competes with the desired combination of radical (**7**) with the enolate ions (**2a-c**).



Scheme 3

Thus, the reaction between the enolate ion (**2a**) and substrate (**1**) in DMSO was studied in more detail. The progress of the reaction between the cyclohexanone enolate (**2a**) and 3-iodobenzo[b]thiophene (**1**) at room temperature in KO^{t}Bu/DMSO was followed by high-performance liquid chromatography (hplc), the substitution product (**3a**) being formed maximally after 60 minutes. Interestingly, the main product after 10 minutes was the iodinated alcohol (**5**), which was isolated in 38% yield when the reaction was stopped after 10 minutes. On the other hand, when the 1-(3-iodo-2-benzo[b]thienyl)cyclohexanol (**5**) was treated with the cyclohexanone enolate (**2a**) at room temperature for 1 h in the dark, and the crude product was analyzed by combined gas chromatography-mass spectrometry (gc-ms), compounds (**1**, **3a**, **4**, **5**) and 1-(2-benzo[b]thienyl)cyclohexanol (**9**) were detected. The presence of these products could be justified if there is a reversible ionic reaction between the 3-iodobenzo[b]thiophene (**1**) and the enolate ion (**2a**) that would afforded the isolated compound (**5**).
Several experiments were performed to improve the yield of 2-(3-benzo[b]thienyl)cyclohexanone (**3a**) following the procedure of Moon and Wolfe,[11] who found that the use of potassium hydride in tetrahydrofuran (KH/THF) or in dimethyl sulfoxide (KH/DMSO) is a valid alternative to the use of the potassium tert-butoxide in dimethyl sulfoxide (KO^{t}Bu/DMSO), in the thermally induced $S_{RN}1$ reaction between the 2-chloroquinoline and the potassium enolate of the acetone (**2b**). Unfortunately, the reaction between the enolate ion (**2a**) and the substrate (**1**) at room temperature was sluggish in KH/THF and also in KO^{t}Bu/THF, as observed when the progress of the reaction was followed by hplc. The crude material consisted mainly of starting material (**1**), and compounds (**4**) and (**5**) were detected only in trace amounts. When the reaction was carried out in KH/DMSO at room temperature for 10 minutes, only the dehalogenated substrate (**4**) was formed in 70% yield. In no case was the desired α-hetaryl ketone (**3a**) produced.
Although the yields in substitution product are low, there are many reactions of ketone enolates and other carbanions with halogenated heteroaromatics characterized by low yields and poor material balances.[12] Hence, this work presents a contribution to the study of the thermally induced $S_{RN}1$ reactions in heterocyclic substrates. It is believed that the radical chain $S_{RN}1$ mechanism is initiated by an electron transfer from the enolate ions (**2a-c**) to the substrate (**1**), and the reduction of radical (**7**) to anion (**8**) and subsequent protonation by the solvent strongly competes with the desired $S_{RN}1$ reaction.

EXPERIMENTAL SECTION

General. All reactions were performed in flame- or oven-dried glassware under a positive pressure of prepurified nitrogen. Sensitive liquids and solutions were transferred by syringe and were introduced into reaction flasks through rubber septa. Melting points were determined on a Büchi apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a Varian XL-200 spectrometer and on a Perkin-Elmer R-24B (60 MHz)

spectrometer. Chemical shifts are reported in ppm relative to Me_4Si and coupling constants are in hertz. Ir spectra were recorded on a Perkin-Elmer 681 Infrared spectrophotometer. Ms spectra were obtained on a Hewlett-Packard 5988-A spectrometer. Elemental analyses were performed by the C.S.I.C. (Barcelona) Micro-Analysis Laboratory. Flash column chromatography refers to the method of Still et al.[13] Hplc analyses of crude materials were carried out on a Waters Associates (Milford, MA, U.S.A.) instrument equipped with high-pressure pumps (Model M-45 and M-6000A), a Model 450 variable-wavelength detector, a Model 660 solvent programmer and a data integrator module. The injector was a Rheodyne 7125.

Materials. The DMSO was purified by drying for two days over molecular sieves followed by vacuum distillation through a Vigreux column (<45 °C). After a second distillation from calcium hydride, the DMSO was stored under nitrogen. THF was dried by distillation from sodium benzophenone ketyl. Potassium tert-butoxide was freshly sublimed. 3-Iodobenzo[b]thiophene (**1**) was prepared by iodination of benzo[b]thiophene (**4**) following a method described by Gaertner.[14] 1-(2-Benzo[b]thienyl)cyclohexanol (**9**) was prepared from benzo[b]thiophene (**4**) and cyclohexanone following a procedure described in the literature.[15] The ketones (analytical grade) and KH were supplied by Fluka (Buchs, Switzerland) and were used as received.

Dark Reactions in DMSO/KO^{t}Bu. General Procedure. The ketone (16 mmol) was added dropwise at room temperature, to a solution of KO^{t}Bu (16 mmol) in anhydrous DMSO (40 ml). After stirring the mixture for 5 min, the flask was wrapped in several layers of black cloth, the room lights were turned off, and then the 3-iodobenzo[b]thiophene (**1**) (4 mmol) was added dropwise. After 1 h, 3 N sulfuric acid was added until neutral pH. The solution was diluted with water and extracted with CH_2Cl_2. The combined organic extract was washed with water, dried ($MgSO_4$), and concentrated. For each ketone studied, the product was isolated by flash column chromatography on silica gel with CH_2Cl_2 as eluant.

Dark Reaction of 3-iodobenzo[b]thiophene (1) with the enolate ion of the cyclohexanone (2a). The reaction between the substrate (**1**) (0.63 g, 2.42 mmol) and the enolate ion (**2a**) (9.68 mmol) prepared from cyclohexanone (0.95 g, 9.68 mmol) and KO^{t}Bu (1.09 g, 9.71 mmol) under the conditions described above, after the usual workup and purification, gave 100 mg (16%) of starting material (**1**), 70 mg (22%) of benzo[b]thiophene (**4**), 33 mg (6%) of the desired 2-(3-benzo[b]thienyl)cyclohexanone (**3a**) as a colorless oil, and 70 mg (8%) of 1-(3-iodo-2-benzo[b]thienyl)cyclohexanol (**5**) as a white solid.

2-(3-Benzo[b]thienyl)cyclohexanone (**3a**). ^{1}H-Nmr ($CDCl_3$) δ: 7.85 (1 H, m, H_{arom}), 7.71 (1 H, m, H_{arom}), 7.29 (3 H, m, H_{arom}), 3.98 (1 H, dd, J = 10.9 Hz, J = 5.5 Hz, CHCO), 2.65-2.35 (2 H, m, CH_2), 2.30-1.75 (6 H, m, CH_2); ir (film) ν: 3060, 2940, 1715 cm^{-1}; ms, m/z (relative intensity): 230 (M^+, 30), 172 (56), 42 (100). Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 72.80; H, 6.17; S, 13.70.

1-(3-Iodo-2-benzo[b]thienyl)cyclohexanol (**5**). mp 120-122 °C (CH_2Cl_2-hexane); ^{1}H-nmr ($CDCl_3$) δ: 7.77 (2 H, m, H_{arom}), 7.38 (2 H, m, H_{arom}), 2.42 (3 H, m, CH_2), 1.96 (3 H, m, CH_2), 1.75 (5 H, m, CH_2 +

OH); ir (KBr) ν: 3410, 3080, 2950, 1440 cm^{-1}; ms, m/z (relative intensity): 358 (M^+, 8), 357 (52), 187 (87), 55 (100). Anal. Calcd for $C_{14}H_{15}OIS$: C, 46.94, H, 4.22; S, 8.95. Found: C, 46.74; H, 4.28; S, 8.80.

This reaction was repeated using 1 mmol scale on substrate and its evolution was followed by hplc. Thus, every 5 min, a 2-ml aliquot was removed from the reaction mixture and the usual workup gave a crude material that was dissolved in MeOH and analyzed by hplc.

The reaction was repeated using 0.50 g (1.92 mmol) of the substrate (**1**), 0.75 g (7.64 mmol) of cyclohexanone, and 0.86 g (7.66 mmol) of KO^tBu. After stirring for 10 min, the usual workup and purification gave 0.26 g (38%) of 1-(3-iodo-2-benzo[b]thienyl)cyclohexanol (**5**).

Dark reaction of substrate (1) with the enolate ion of the acetone (2b). The reaction between the substrate (**1**) (1.36 g, 5.23 mmol) and the enolate ion (**2b**) (21.01 mmol) generated from acetone (1.22 g, 21.01 mmol) and KO^tBu (2.36 g, 21.03 mmol) under the usual conditions, gave, after the usual workup and purification, 310 mg (23%) of starting material (**1**), 160 mg (23%) of dehalogenated compound (**4**), and 115 mg (12%) of the desired 3-benzo[b]thienylacetone (**3b**) as a oil[16]: ^{1}H-Nmr ($CDCl_3$) δ: 8.00-7.30 (5 H, m, H_{arom}), 3.90 (2 H, s, CH_2), 2.20 (3 H, s, CH_3); ir (film) ν: 3080, 2940, 1720 cm^{-1}; ms, m/z (relative intensity): 190 (M^+, 14), 147 (61), 43 (100).

Dark reaction of substrate (1) with the enolate ion of the acetophenone (2c). The reaction between the substrate (**1**) (1.00 g, 3.84 mmol) and the enolate ion (**2c**) (15.40 mmol) generated from acetophenone (1.85 g, 15.40 mmol) and KO^tBu (1.73 g, 15.42 mmol) gave under the usual conditions a crude product which, after purification, afforded 230 mg (23%) of starting material (**1**), 120 mg (23%) of dehalogenated compound (**4**), and 130 mg (14%) of the desired 2-(3-benzo[b]thienyl)-1-phenylethanone (**3c**) as a white solid: mp 66-67 °C; ^{1}H-nmr ($CDCl_3$) δ: 8.00 (4 H, m, H_{arom}), 7.50 (6 H, m, H_{arom}), 3.10 (2 H, s, CH_2); ir (KBr) ν: 3080, 2950, 1685 cm^{-1}; ms, m/z (relative intensity): 252 (M^+, 2), 105 (100), 77 (68). Anal. Calcd for $C_{16}H_{12}OS$: C, 76.16; H, 4.79; S, 12.71. Found: C, 75.90; H, 4.85; S, 12.91.

Dark reaction of substrate (1) with the enolate ion of the acetone (2b) in the presence of DNB. To a solution of the enolate ion (**2b**) (21.01 mmol), prepared from acetone (1.22 g, 21.01 mmol) and KO^tBu (2.36 g, 21.03 mmol) in DMSO, 87 mg (0.52 mmol) of DNB was added. After stirring for 5 min the mixture, the flask was wrapped in several layers of black cloth, the room lights were turned off, and then the 3-iodobenzo[b]thiophene (**1**) (1.36 g, 5.23 mmol) was added dropwise. After 1 h, 3 N sulfuric acid was added until neutral pH and then processed in the normal manner. Chromatography of the reaction product on silica gel with CH_2Cl_2 as eluant, afforded 0.88 g (65%) of the starting material (**1**).

Dark reaction of the substrate (1) with the cyclohexanone in KO^tBu/THF. The reaction between the substrate (**1**) (0.25 g, 0.96 mmol) and the enolate ion (**2a**) (7.44 mmol) generated from the cyclohexanone (0.73 g, 7.44 mmol) and KO^tBu (0.84 g, 7.49 mmol) in anhydrous THF (20 ml) under the usual reaction conditions (see the same reaction in DMSO), was followed by hplc. Thus, every 5 min, a 2-ml aliquot was

removed from the reaction mixture. The usual workup gave a crude material that was dissolved in MeOH and analyzed by hplc.

Dark reaction of the substrate (1) with the cyclohexanone in KH/DMSO. To a 20% dispersion of KH (0.72 g, 3.59 mmol) in mineral oil previously washed with hexane in anhydrous DMSO (14 ml), was added dropwise at room temperature the cyclohexanone (0.35 g, 3.57 mmol). After stirring the mixture for 10 min, the flask was wrapped in several layers of black cloth, the room lights were turned off, and then the substrate (**1**) (0.25 g, 0.96 mmol) was added dropwise. After stirring the mixture for 10 min at room temperature, the reaction mixture was diluted with water. The aqueous layer was extracted with ether several times, the organic solution was dried ($MgSO_4$), and concentrated. Purification of the crude material by flash column chromatography on silica gel with CH_2Cl_2 as eluant, gave 90 mg (70%) of dehalogenated substrate (**4**).

Dark reaction of the substrate (1) with the cyclohexanone in KH/THF. The reaction between the substrate (**1**) (0.25 g, 0.96 mmol) and the enolate ion (**2a**) (3.57 mmol) generated from the cyclohexanone (0.35 g, 3.57 mmol) and a 20% dispersion of KH (0.72 g, 3.59 mmol) in mineral oil washed with hexane in anhydrous THF (15 ml) under the usual reaction conditions (see above), was followed by hplc. Thus, every 5 min, a 2-ml aliquot was removed from the reaction mixture. The usual workup (see above) gave a crude material that was dissolved in MeOH and analyzed by hplc.

Treatment of the 1-(3-iodo-2-benzo[b]thienyl)cyclohexanol (5) with the cyclohexanone in KO^{t}Bu/DMSO. Treatment of the compound (**5**) (88 mg, 0.25 mmol) with cyclohexanone (97 mg, 0.99 mmol) and KO^{t}Bu (112 mg, 1.00 mmol) in DMSO (10 ml) under the usual reaction conditions (1 h, room temperature, in the dark), gave a crude product which was analyzed by gcms, the following compounds being detected: 9 mg (14%) of 3-iodobenzo[b]thiophene (**1**), 7.5 mg (13%) of 2-(3-benzo[b]thienyl)cyclohexanone (**3a**), 1.5 mg (4%) of benzo[b]thiophene (**4**), 5.7 mg (6%) of 1-(3-iodo-2-benzo[b]thienyl)cyclohexanol (**5**), and 6.3 mg (11%) of 1-(2-benzo[b]thienyl)cyclohexanol (**9**).

REFERENCES

1. J. K. Kim and J. F. Bunnett, J. Am. Chem. Soc., 1970, **92**, 7463.
2. (a) J. F. Bunnett, Acc. Chem. Res., 1978, **11**, 413; (b) J. F. Wolfe and D. R. Carver, Org. Prep. Proced. Int., 1978, **10**, 225 and references therein; (c) D. R. Carver, A. P. Komin, J. S. Hubbard, and J. F. Wolfe, J. Org. Chem., 1981, **46**, 294; (d) R. Beugelmans and G. Roussi, Tetrahedron, 1981, **37**, 393; (e) C. Galli and J. F. Bunnett, J. Org. Chem., 1984, **49**, 3041; (f) V. Nair, S. D. Chamberlain, J. Am. Chem. Soc., 1985, **107**, 2183; (g) L. Estel, F. Marsais, and G. Quéguiner, J. Org. Chem., 1988, **53**, 2740.

3. R. G. Scamehorn and J. F. Bunnett, J. Org. Chem., 1977, **42**, 1449.
4. J. V. Hay, T. Hudlicky, and J. F. Wolfe, J. Am. Chem. Soc., 1975, **97**, 374.
5. R. G. Scamehorn, J. M. Hardacre, J. M. Lukanich, and L. R. Sharpe, J. Org. Chem., 1984, **49**, 4881.
6. (a) R. C. Kerber, G. W. Urry, and N. Kornblum, J. Am. Chem. Soc., 1964, **86**, 3904; (b) R. C. Kerber, G. W. Urry, and N. Kornblum, J. Am. Chem. Soc., 1965, **87**, 4520.
7. (a) J. E. Swartz and J. F. Bunnett, J. Org. Chem., 1979, **44**, 340; (b) M. A. Fox, J. Younathan, and G. E. Fryxell, J. Org. Chem., 1983, **48**, 3109.
8. M. Chanon and M. L. Tobe, Angew. Chem., Int. Ed. Engl., 1982, **21**, 1.
9. C. Amatore, J. Pinson, J. M. Sáveant, and A. Thiébault, J. Am. Chem. Soc., 1982, **104**, 817.
10. J. F. Bunnett, R. G. Scamehorn, and R. P. Traber, J. Org. Chem., 1976, **41**, 3677.
11. M. P. Moon and J. F. Wolfe, J. Org. Chem., 1979, **44**, 4081.
12. (a) R. Levine and W. W. Leake, Science, 1955, **121**, 780; (b) H. Boer and H. J. den Hertog, Tetrahedron Lett., 1969, 1943; (c) T. Higashino and E. Hayashi, Chem. Pharm. Bull., 1970, **18**, 1457.
13. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1978, **43**, 2923.
14. R. Gaertner, J. Am. Chem. Soc., 1952, **74**, 4950.
15. (a) A. W. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan, and R. J. Ferlauto, J. Med. Chem., 1966, **9**, 551; (b) B. Iddon, C. K. Thadani, B. J. Northover, and R. G. Sommerville, Chim. Ther., 1970, **5**, 149.
16. N. B. Chapman, R. M. Scrowston, and R. Westwood, J. Chem. Soc. (C), 1969, 1855.

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