A New Synthetic Approach to the C-D Ring Portion of Streptonigrin Analogues

John J. Kilama*, Bhashyam S. Iyengar and William A. Remers*

Department of Pharmaceutical Sciences, University of Arizona, Tucson, Arizona 85721

Eugene A. Mash

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received February 22, 1990

Development of an efficient synthesis of the C-D ring portion of streptonigrin is a key operation in the synthesis of this antibiotic and its analogues. A new method for the synthesis of 3-cyano-5,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-2-pyridone (**14**), a compound having the requisite functionality for conversion into a streptonigrin analogue, has been established. It involves treatment of 3,4,5-trimethoxybenzonitrile with ethylmagnesium bromide and malononitrile to give propylenemalononitrile derivative **7**, which is condensed with trimethyl orthoacetate to give a mixture of **9** and pyridine derivative **12**. Demethylation of **12** then affords **14**. The overall yield for this route was 50%, allowing for conversion of **9** to **12**.

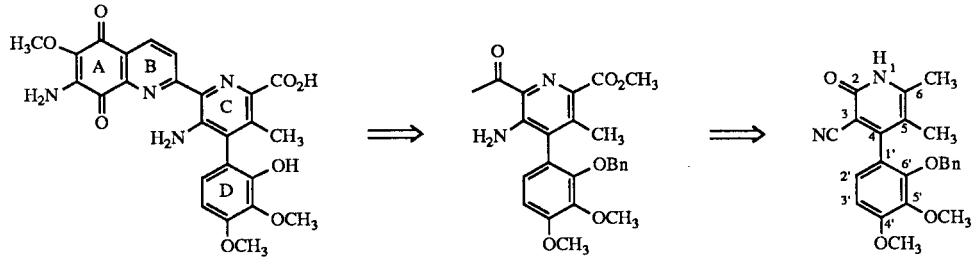
J. Heterocyclic Chem., **27**, 1437 (1990).

Streptonigrin (**1**) is an antitumor antibiotic produced by *Streptomyces flocculus* [1]. It has an unusual structure that is based on a 2'-pyridyl-2-quinoline system in which the quinoline moiety is functionalized as a quinone and the highly substituted pyridyl ring bears a trisubstituted phenyl ring [2]. Its high activity against experimental lymphomas led to clinical trials, but severe toxicity to the hematopoietic system prevented acceptance into human medicine [3]. Many studies on the synthesis of streptonigrin and analogues have been undertaken in the hope that they might provide compounds with improved therapeutic properties. This research has resulted in three elegant total syntheses [4] (one actual and two formal) plus a variety of interesting partial syntheses [5].

The main challenge in a streptonigrin synthesis is construction of the C and D rings with proper substituents and functionalization appropriate for addition of the A and B rings. Among the approaches to C and D ring synthesis, we became interested in those that involve intermediates related to **3**. This compound has been synthesized in two different laboratories [6], and it has functional groups that have been converted into those found in streptonigrin. Thus, the 6-methyl group of a related compound was transformed into a carbomethoxy group by sequential oxidation with selenium dioxide and sodium chlorite followed by methylation [4b], the carbonyl group of a related compound was converted into an acetyl group by the sequence phosphoryl chloride, sodium cyanide, methylmagnesium bromide [4b], and the cyano group of a related compound was changed to an amino group by the Yamada modification of the Curtuis degradation [4a]. A compound such as **2**, containing all of these transformations, would be ideally suited for the addition of rings A and B as accomplished in a simpler analogue by Hibino and Weinreb [7].

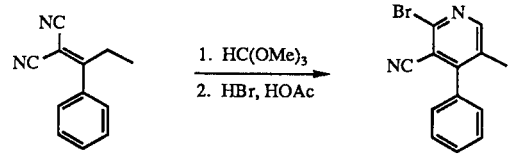
Although the previous syntheses of **3** were worthwhile, it appeared that an alternative route based on chemistry developed by Baldwin, *et al* [8] would be advantageous for certain analogues. This chemistry involved condensation of triethyl orthoformate with alkylidene malononitriles, followed by treatment with hydrogen bromide in acetic acid, to 4,5-disubstituted-2-bromo-3-cyanopyridines. For example, **4** was converted into **5** in 42% yield. A more fully elaborated analogue would represent streptonigrin intermediate **3** carried one step closer to **2**.

Our initial target compound was **14**, a closely related analogue of **3**. It was chosen because the starting material 3,4,5-trimethoxybenzonitrile **6** was inexpensive and suitable for development of the required chemistry. Treatment of **6** with ethylmagnesium bromide in THF followed



by 2 equivalents of malononitrile [9] gave 1-(3,4,5-trimethoxy)propylenemalonitrile **7** in 91% yield (Scheme II). Attempted condensation of **7** with triethyl orthoacetate in the presence of acetic anhydride and zinc chloride was unsuccessful. However, when acetic anhydride was omitted and excess triethyl orthoacetate was used as the solvent, a mixture of the desired product **8** (55% yield) and substituted 2-ethoxypyridine **11** (30% yield) was obtained. When methyl orthoacetate was used instead of ethyl orthoacetate, analogous products **9** (60% yield) and **12** (35% yield) were obtained. An increased combined yield for the methyl orthoacetate reaction suggests that steric hindrance may be a factor in the condensation. The corresponding reaction in methyl orthoformate gave products **10** (40% yield) and **13** (45% yield). In this case, the total yield was not increased, but the pyridine ring was formed to a greater extent. Attempts to convert **8** or **11** into 2-bromopyridine derivative **15** with hydrogen bromide [8] or hydrogen chloride in acetic acid were unsuccessful. None of this compound could be detected. This problem led us to examine ways to increase the yield of 2-alkoxypyridines in the orthoacetate condensations and explore their cleavage to the corresponding 2-pyridones. We focussed on the formation of **12** because it appeared that a methyl ether would be easier to cleave than an ethyl ether. Although no improvement in the ratio of **12** to **9** could be obtained in the condensation, it was possible to convert **9** into **12** in 51% yield by treating it again with zinc chloride in trimethyl orthoacetate. Thus, a single recycling of **9** would be expected to afford a combined yield of 66% for **12**. Cleavage of the methyl ether group of **12** by Olah's method (iodotrimethylsilane) [10] provided the desired 2-pyridone **14** in 85% yield.

Scheme I



4 5

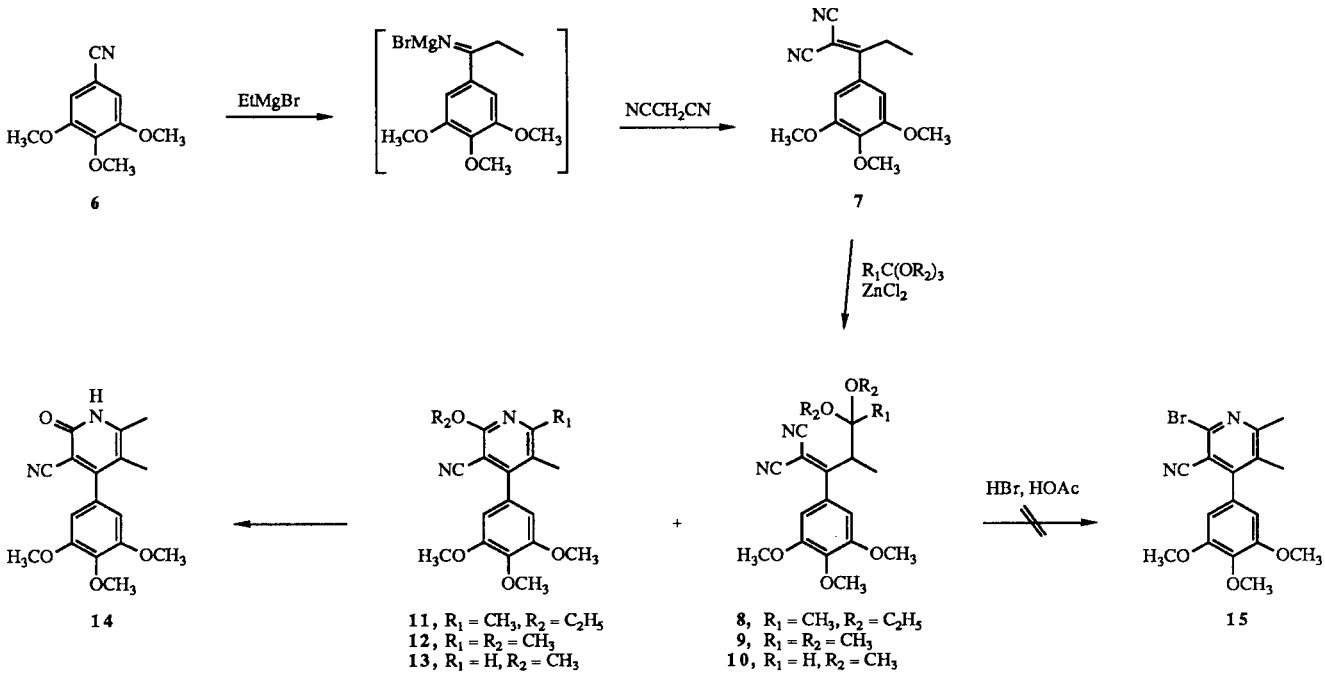
In summary, the route to 3-cyano-2-pyridone **14**, outlined in Scheme II, could provide a valuable entry into the synthesis of certain streptonigrin analogues. A 51% overall yield of **14** from 3,4,5-trimethoxyibenzonitrile could be realized, assuming the recycling of intermediate **9**.

EXPERIMENTAL

Reactions were monitored by thin layer chromatography (tlc) on commercial 250 micron silica gel GF plates from Analtech. Merck silica gel 60 (70-230 mesh) was used for column chromatography. Tetrahydrofuran (THF) and diethyl ether (ether) were freshly dried over LAH and distilled under nitrogen.

Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. The ir spectra were taken on a Beckman IR-33 spectrometer with samples prepared as potassium bromide pellets or as a film on sodium chloride

Scheme II



plates. Absorptions are reported in cm^{-1}. The ^1H nmr spectra were acquired on a Jeol FXQ 90 MHz spectrometer unless indicated otherwise. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Carbon-13 magnetic resonance spectra were recorded on a Jeol FXQ 90 MHz or a Bruker WM-250 MHz spectrometer. Absorptions are reported in ppm from the center line of the chloroform-d_1 triplet (77.00 ppm).

Mass spectral data were resolved *via* electron impact (EI) or chemical ionization (CI) on a Varian Mat 90 spectrometer at the Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, Az. Molecular ions and intense ions are reported. The elemental analyses were performed by Desert Analytics, Tucson, Arizona.

1-(3,4,5-Trimethoxyphenyl)propylenemalononitrile (**7**).

A solution of ethylmagnesium bromide (20 ml, 0.06 mole) was added dropwise to a dry 3-neck round bottom flask equipped with rubber septum, condenser with drying tube, dry nitrogen inlet and containing a solution of 3,4,5-trimethoxybenzonitrile (10.5 g, 0.05 mole) in THF (100 ml).

After stirring for 1.5 hours, the reaction mixture was cooled to 0° and then quenched by rapidly adding a solution of malononitrile (7.19 g, 0.11 mole) in THF (20 ml). A vigorous reaction gave a yellowish gummy solid which was dissolved by addition of 50 ml of dilute hydrochloric acid. Anhydrous ether (100 ml) was added and the solution was washed several times with water.

The combined ether layer was dried over magnesium sulfate and concentrated *in vacuo* to yield a dark oil which solidified after a few hours. Recrystallization from methanol gave 12.3 g (91%) of pure colorless compound **7**, mp 82-84°; pmr (deuteriochloroform): δ 6.84 (s, 2H), 4.02 (s, 3H, OCH_3), 3.9 (s, 6H, OCH_3), 3.01 (q, 2H, CH_2), 1.23 (t, 3H, CH_3); cmr (deuteriochloroform): δ 180.94 (C), 153.42 (C), 141.50 (CH), 129.37 (C), 113.22 (CN), 112.68 (CN), 105.53 (CH), 83.10 (C), 60.89 (OCH_3), 56.45 (OCH_3), 30.88 (CH_2), 13.00 (CH_3); ir (neat): 1580, 2120, 3080 cm^{-1}; ms: M^+ = 272.3.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.12; H, 5.8; N, 10.28. Found: C, 66.18; H, 5.87; N, 10.16.

3,3-Diethoxy-2-methyl-1-(3,4,5-trimethoxypenyl)butylenemalonitrile (**8**).

A mixture of **7** (3.03 g, 0.01 mole), triethyl orthoacetate (2.75 ml, 0.02 mole) and zinc chloride (50 mg) was heated overnight at 100°. After 18 hours, the volatiles were removed by distillation at atmospheric pressure. When tlc still showed the presence of starting material, an additional 2 ml of triethyl orthoacetate and 10 mg of zinc chloride were added and heated at 110°. After 10 hours the solution was cooled and concentrated *in vacuo* to one third the volume. It was purified by chromatography on silica gel (90:10 hexane-ethyl acetate). The light yellow front moving band was collected and the solvent was removed at reduced pressure to give pure compound **11**. The deep yellow slow moving band was also collected and the solvent was evaporated *in vacuo* to give pure **8** (2.14 g, 55%) as a light yellow compound, mp 117-119°; pmr (deuteriochloroform): 6.75 (s, 2H), 6.00 (q, 1H, CH), 4.35 (q, 2H, OCH_2), 3.95 (m, 11H, OCH_2, OCH_3, OCH_3), 2.3 (s, 3H, CH_3), 1.85 (d, CH_3), 1.45 (t, 3H, CH_3), 1.21 (t, 3H, CH_3); cmr (deuteriochloroform): 165.88, 153.53, 137.71; 132.51, 127.74, 105.64, 104.88, 84.83, 67.6, 65.00, 64.03, 63.71, 61.00, 60.78, 56.34, 29.47, 19.6, 18.41, 16.14, 15.06, 14.4, 14.08; ir 2195, 1650, 1590 cm^{-1}; ms: m/e (relative intensity, %) 388.2 (11.13), 359.2 (39.55), 289.1 (100).

Anal. Calcd. for $C_{21}H_{28}O_5N_2$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.85; H, 7.21; N, 7.20.

3-Cyano-5,6-dimethyl-2-ethoxy-4-(3,4,5-trimethoxyphenyl)pyridine (**11**).

Compound **11** was isolated as a light yellow band from the above reaction. Evaporation of the solvent *in vacuo* left a white solid which was recrystallized from 5% ethyl acetate in hexane to give pure product (1.03 g, 30%), mp 141-143°; pmr (deuteriochloroform): δ 6.43 (s, 2H), 4.54 (q, 2H, OCH_2), 3.90 (s, OCH_3), 3.8 (s, 6H, OCH_3), 2.5 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.34 (t, 3H, CH_3); cmr (deuteriochloroform): δ 162.24 (C), 155.81 (C), 153.63 (C), 138.68 (C), 131.86 (C), 122.43 (C), 115.61 (C), 105.95 (CH), 94.01 (C), 62.69 (OCH_3), 60.97 (OCH_3), 56.30 (OCH_3), 23.69 (CH_3), 15.57 (CH_3), 14.49 (CH_3); ms: m/e (relative intensity, %) 342.2 (100), 327 (32), 299 (8.6).

Anal. Calcd. for $C_{19}H_{22}O_4N_2$: C, 66.66; H, 6.48; N, 8.18. Found: C, 66.61; H, 6.67; N, 8.16.

3,3-Dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)butylenemalononitrile (**9**).

To a solution of **7** (3.00 g, 0.011 mole) in trimethyl orthoacetate (50 ml), zinc chloride (100 mg) was added. The mixture was heated at reflux for 18 hours using a steam jacketed column for continuous removal of methanol. The solution was cooled and most of the orthoacetate was removed *in vacuo*. The residue was purified by chromatography on silica gel (10% ethyl acetate in hexane) to yield compounds **9** and **12**. Recrystallization of the light yellow solid from 5% ethyl acetate gave 2.48 g (63%) of **9** as a white crystalline solid, mp 111-113°; ir: 2100, 1650, 1590 cm^{-1}; pmr (deuteriochloroform): δ 6.62 (s, 2H, aromatic), 6.05 (q, 1H, CH), 3.58-3.85 (m,12H, OCH_3), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 1.86 (d, 3H, CH_3); cmr (deuteriochloroform): δ 166.65, 152.99, 136.95, 131.97, 127.96, 120.05, 103.91, 60.79, 56.12, 55.15, 54.82, 29.69, 17.99, 15.93; ms: m/e (relative intensity, %) 360 (16), 345 (100), 303 (96), 273 (20).

Anal. Calcd. for $C_{19}H_{24}O_5N_2$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.29; H, 6.61; N, 7.73.

3-Cyano-5,6-dimethyl-2-methoxy-4-(3,4,5-trimethoxyphenyl)pyridine (**12**).

Compound **12** was obtained as a white solid which upon recrystallization from 5% ethyl acetate in hexane gave 33% of colorless crystals, mp 153-155°; ir: 2200, 1590 cm^{-1}; pmr (deuteriochloroform): δ 6.45 (2, 2H), 4.1 (s, 3H, OCH_3), 3.85-3.95 (m, 9H, OCH_3), 2.50 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); cmr (acetone-d_6): δ 162.95; 161.05, 157.00, 154.90, 139.87, 133.97, 124.61, 115.50, 107.86, 94.95, 60.90, 57.00, 54.50, 23.99, 16.00; strong blue fluorescence under long wavelength uv light.

Anal. Calcd. for $C_{18}H_{20}O_4N_2$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.92; H, 6.19; N, 8.5.

Conversion of **9** into **12**.

A mixture of **9** (3.00 mg), zinc chloride (10 mg, excess) and trimethyl orthoacetate (5 ml) was heated at reflux for 20 hours, cooled to room temperature, and diluted with ethyl acetate (20 ml). The resulting solution was washed with water (2 x 5 ml), dried (sodium sulfate), filtered, and concentrated under reduced pressure. Tlc on silica gel with ethyl acetate-hexane (2:8 v/v) showed

no starting material, a major spot corresponding in R_f to **12** (strong blue fluorescence under long wavelength uv) and two faster moving spots. The concentrate was purified by preparative tlc on a silica gel plate (5 cm x 10 cm x 250 μ) with ethyl acetate-hexane (2:8 v/v) as solvent. The zone corresponding to **12** was scraped off and extracted with ethyl acetate. This extract was filtered and evaporated under reduced pressure to give 1.48 mg (51%) of **12**.

3,3-Dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)propylenemalononitrile (**10**).

A mixture of **7** (2.5 g, 7.2 mmoles), acetic anhydride (5 ml), trimethyl orthoformate (1.01 g, 9.02 mmoles), and zinc chloride (50 mg) was refluxed overnight. After 15 hours the solution was cooled and added to saturated sodium carbonate solution. The aqueous solution cooled and added to saturated sodium carbonate solution. The aqueous solution was extracted with chloroform (3 x 25 ml). The combined organic layer was dried over sodium sulfate, filtered, and concentrated to dryness. The residue was purified by chromatography on silca gel (5% ethyl acetate in hexane) to give 1.05 g (40%) of **10**, mp 78-80°; pmr (deuteriochloroform): δ 6.51 (s, 2H, aromatic), 4.35 (d, 1H, CH), 3.90 (m, 10H), 3.39 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 1.29 (d, 3H, CH_3); cmr (deuteriochloroform): 179.82, 152.74, 151.98, 138.66, 129.45, 110.80, 105.17, 103.76, 103.22, 86.64, 59.56, 55.08, 55.05, 51.54, 43.31, 13.19; ms: m/e (relative intensity, %) 346.38 (96.94), 331.2 (22), 283.2 (12.49), 75 (100).

Anal. Calcd. for $C_{18}H_{22}O_5N_2$: C, 62.42; H, 6.40; N, 8.08. Found: C, 62.80; H, 6.55; N, 7.84.

3-Cyano-2-methoxy-5-methyl-4-(3,4,5-trimethoxyphenyl)pyridine (**13**).

Trimethyl orthoformate (30 ml), zinc chloride (50 mg), and compound **7** (3.45 g, 0.01 mole) were heated at reflux for 16 hours. The reaction mixture was allowed to cool, and 10 ml of trimethyl orthoformate and 10 mg of zinc chloride were added and heated for an additional 7 hours. The solution was cooled and most of the excess orthoformate was removed *in vacuo*. The residue was purified by chromatography on silca gel (5% ethyl acetate in hexane) to give **10** (1.09 g, 40%) and **13** (1.23 g, 45%). Compound **13** had mp 95-97°; ir: 2215, 1600, cm^{-1}; pmr (deuteriochloroform): δ 8.23 (s, 1H, pyridine), 6.52 (s, 2H, benzyl), 4.10 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 2.15 (s, 2H, CH_3); cmr (deuteriochloroform): 163.61, 156.13, 153.63, 151.15, 130.67, 105.97, 61.00, 56.45, 54.50, 16.47; ms: m/e (relative intensity, %) 314 (100), 299 (38.5).

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.75; H, 5.67; N, 8.87. Found: C, 64.96; H, 5.77; N, 8.91.

3-Cyano-5,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-2-pyridone (**14**).

A two-neck 25 ml flask was fitted with a water condenser and a solution of sodium iodide (1.05 mmoles) and compound **12** (325 mg, 1.05 mmoles) in acetonitrile was added. The flask was continuously flushed with dry nitrogen. To the solution was added chlorotrimethylsilane (1.05 mmoles) slowly with continuous stirring. The reaction mixture was stirred at room temperature for 30 minutes and then quenched with water (10 ml). A light yellow solid which precipitated was filtered and dried *in vacuo* to give **14** (87%); ir: 2200, 1650, 1590 cm^{-1}; pmr (deuteriochloroform): δ 6.55 (s, 2H), 3.92 (s, 3H), 385 (s, 6H), 2.50 (s, 3H), 2.02 (s, 3H); cmr (deuteriochloroform): δ 166.56, 162.85, 153.92, 148.97, 138.55, 130.00, 114.45, 104.58, 60.05, 55.08, 18.56, 14.92; ms: m/z (relative intensity, %), 314 (100), 299 (48), 77 (49); hrms: M^+ 314.1248; mw Calcd: 314.1267.

REFERENCES AND NOTES

[1] K. V. Rao and W. P. Cullen, *Antibiot. Ann.*, 950 (1959-1960).

[2a] K. V. Rao, K. Biemann and R. B. Woodward, *J. Am. Chem. Soc.*, **85**, 2532 (1963); [b] Y.-Y. K. Chiu and W. N. Lipscomb, *J. Am. Chem. Soc.*, **97**, 2525 (1975).

[3] E. W. Humphrey and F. S. Dietrich, *Cancer Chemother. Rep.*, **33**, 21 (1963).

[4a] F. Z. Basha, S. Hibino, D. Kim, W. E. Pye, T.-T. Wu and S. M. Weinreb, *J. Am. Chem. Soc.*, **102**, 3962 (1980); [b] A. S. Kende, D. P. Lorah and R. J. Boatman, *J. Am. Chem. Soc.*, **103**, 1271 (1981); [c] D. L. Boger and J. S. Panek, *J. Org. Chem.*, **48**, 121 (1983).

[5] For a review of streptonigrin partial syntheses see W. A. Remers, The Chemistry of Antitumor Antibiotics, Vol **2**, Wiley, New York, 1988, pp 243-262.

[6a] T. Kametani, A. Kozuka and S. Tanaka, *Yakugahu Zasshi*, **90**, 1574 (1970); [b] T. K. Liao, W. H. Nyberg and C. C. Cheng, *J. Heterocyclic Chem.*, **13**, 1063 (1976).

[7] S. Hibino and S. M. Weinreb, *J. Org. Chem.*, **42**, 232 (1977).

[8] J. J. Baldwin, A. W. Raab and G. S. Ponticello, *J. Org. Chem.*, **43**, 2529 (1978).

[9] E. Campaigne, D. Mais and E. M. Yokley, *Synth. Commun.*, **4**, 379 (1974).

[10] G. A. Olah, S. C. Narang, G. B. Gupta and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979).