of **9** (210 mg, 0.545 mmol) in 10 mL of methanol was stirred under nitrogen with 1 mL 37% formalin at room temperature for 30 min. Sodium borohydride (400 mg) was added and the solution was stirred for an additional 1 h. The solvent was removed under vacuum, water was added, and the mixture was extracted with dichloromethane. The organic extract was dried (Na_2SO_4) and then evaporated to give a residue gum (190 mg), which was purified by preparative TLC ($CHCl_3$:EtOAc, 3:1) to give 65 mg (30%) of pure **10** as a gum: ^1H NMR ($CDCl_3$) δ 6.76, 6.58 (2 d, J = 8.4 Hz, 2 H, 2 Ar H); 5.97 (s, 1 H, Ar H), 5.83, 5.82 (2 s, 2 H, OCH_2O), 3.99, 3.87, 3.84 (3 s, 12 H, 4 OCH_3), 2.44 (s, 3 H, NCH_3). This material was used directly for the coupling reaction without additional characterization.

Leucoxylonine (1). A solution of **10** (40 mg, 0.10 mmol) in 1.5 mL of CCl_4 and 0.5 mL of BF_3·Et_2O was added all at once to a cooled (0 °C) solution of thallium(III) trifluoroacetate (TTFA) (75 mg, 0.14 mmol) in CH_3CN (10 mL) and CCl_4 (1.5 mL) under nitrogen. The reaction mixture was allowed to warm to room temperature and then stirred for a further 2 h. Solvent was removed under reduced pressure, water was added, and the aqueous solution was extracted with CH_2Cl_2 after the solution had been adjusted to pH 9 with NH_4OH. The organic extract was dried (Na_2SO_4) and then evaporated under vacuum to give a dark gum (26 mg). Purification by preparative TLC ($CHCl_3$:$CH_3COOC_2H_5$, 3:1) gave synthetic leucoxylonine as a gum (R_f 0.13–0.2, 10 mg. 20%). The spectral data for the synthetic leucoxylonine were identical with those reported for the natural product:[2] ^1H NMR δ ($CDCl_3$) 7.42 (s, 1 H, Ar H), 6.07, 5.91 (2 d, J = 13 Hz, OCH_2O), 4.01, 3.91, 3.90, 3.86 (4 s, 12 H, 4 OCH_3), 2.56 (s, 3 H, NCH_3); HRMS, m/e 399.1720 (M^+); calcd for $C_{22}H_{25}NO_6$ 399.1717.

Acknowledgment. We thank the University of Ibadan, Nigeria, for a research leave to A.A.A.

Registry No. (±)-1, 91199-16-5; 2, 5779-99-7; 4, 58343-44-5; 5, 91129-06-5; 6, 2220-19-1; 6·oxalate, 91129-10-1; 7, 22480-91-7; 8, 91129-07-6; 9, 91129-08-7; (±)-10, 91129-09-8; piperonal, 120-57-0.

3-Alkoxypyrroles by Reduction of Alkoxypyrrolinones[1]

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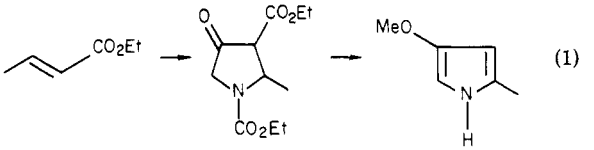
Received July 5, 1983

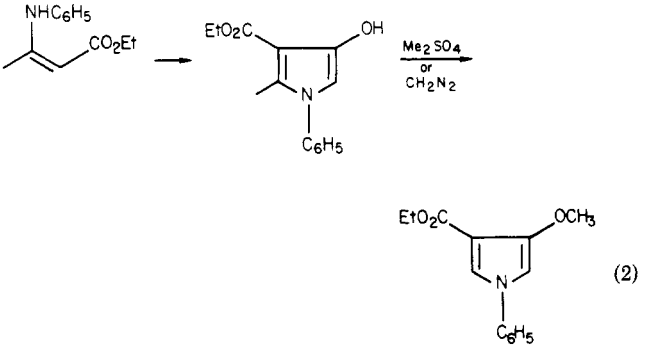
There has been tremendous interest in the chemistry of pyrroles for many years.[2] The isolation of the natural product prodigiosin, a pigment having antibiotic activity, stimulated work in 3-alkoxypyrrole synthesis and resulted in the successful preparation of this compound and various analogues.[3]

Basically, there are four methods for the generation of 3-alkoxypyrroles. Rapoport's elegant synthesis of prodigiosin[3b] used chemistry of Kuhn and Osswald.[3a,4] An initial conjugate addition to an unsaturated ester followed by Dieckmann condensation, hydrolysis, ketal formation, and dehydrogenation gives the 3-methoxypyrrole (eq 1).



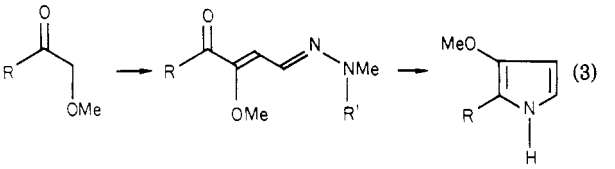
(1)

Campaigne[3d] used a similar sequence to prepare 3-alkoxy-5-arylpyrroles. A second method uses enamino esters derived from ethyl acetoacetate which are acylated with chloroacetyl chloride followed by a Dieckmann ring closure to give 3-hydroxypyrroles which can be O-methylated (eq 2).[5] Similarly, Bauer[3c] formed enamino esters from β-keto



(2)

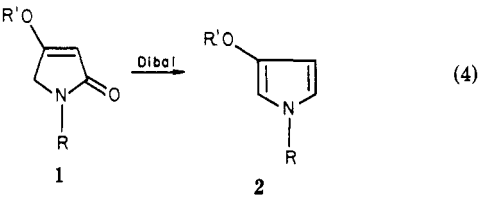
esters and ethyl glycinate and then obtained 3-alkoxypyrroles after a Dieckmann step and O-alkylation.[6] The approach of Severin[7] involves the condensation of α-methoxy ketones with glyoxalmonohydrazones followed by reduction with sodium dithionite to give 3-methoxypyrroles (eq 3). One last preparation of limited scope uses the



(3)

base-catalyzed addition of methanol to 3,4-dinitropyrroles as a key step followed by elimination of methanol.[8]

We report a new and efficient method for the preparation of 3-alkoxypyrroles (eq 4). Thus, the 4-alkoxy-Δ^3-



(4)

1 2

pyrrolin-2-ones **1**,[9] readily available from β-keto esters (see Experimental Section), are simply allowed to react with

(1) Presented in part at the 17th Middle Atlantic Regional Meeting of the American Chemical Society, April 6-8, 1983, White Haven, PA, Abstract No. 332.

(2) For example, see: "The Chemistry of Pyrroles"; Jones, R. A., Bean, G. P., Eds.; Academic Press: New York, 1977.

(3) (a) Rapoport, H.; Willson, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 630. (b) Rapoport, H.; Holden, H. G. *Ibid.* **1962**, *84*, 635. (c) Bauer, H. *Liebigs Ann. Chem.* **1970**, *736*, 1. (d) Campaigne, E.; Shutske, G. M. *J. Heterocycl. Chem.* **1976**, *13*, 497.

(4) Kuhn, R.; Osswald, G. *Chem. Ber.* **1956**, *89*, 1423.

(5) (a) Benary, E.; Silberman, B. *Chem. Ber.* **1913**, *46*, 1363. (b) Benary, E.; Konrad, R. *Ibid.* **1923**, *56*, 44.

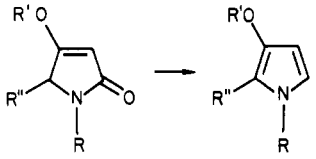
(6) Other workers had performed the same sequence of reactions but had postulated that the initial step formed an imino ester: Triebs, A., Ohorodnik, A. *Liebigs Ann. Chem.* **1958**, *611*, 139, 149.

(7) Severin, T.; Poehlmann, H. *Chem. Ber.* **1977**, *110*, 491. Severin, T.; Supp, W.; Manninger, G. *Ibid.* **1979**, *112*, 3013.

(8) Bonaccina, L.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1979**, *44*, 4420.

(9) These compounds are readily available from β-keto esters. Kochhar, K. S.; Carson, H. J.; Clouser, K. A.; Elling, J. W.; Gramens, L. A.; Parry, J. L.; Sherman, H. L.; Braat, K.; Pinnick, H. W. *Tetrahedron Lett.*, in press (see Experimental Section). Elaboration of ethyl acetoacetate via the monoanion or the dianion leads to a wide variety of the unsaturated lactams **1**.

Table I. 3-Alkoxypyrroles[a]

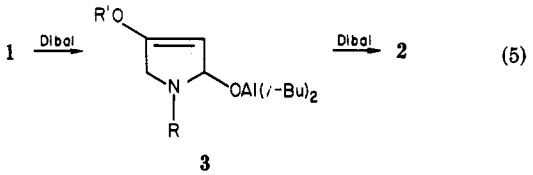


R	R′	R″	bp, °C (mm)	yield, %	^{1}H NMR[12] H-2	H-4	H-5
CH_3	CH_3	H	50–55 (0.5)	45	6.18	5.80	6.35
CH_3	C_2H_5	H	135–145 (1.8)	62	6.15	5.78	6.32
C_2H_5	CH_3	H	60–65 (0.5)	52	6.23	5.80	6.42
C_2H_5	C_2H_5	H	93–98 (0.5)	55	6.23	5.78	6.41
$C_6H_5CH_2$	CH_3	H	130–135 (0.5)	75	6.20	5.84	6.44
$C_6H_5CH_2$	C_2H_5	H	130–140 (0.5)	83	6.21	5.85	6.45
CH_3	C_2H_5	C_2H_5	110–120 (0.5)[b]	65[b]		5.71	6.28
C_2H_5	C_2H_5	C_2H_5	76–83 (0.1)	63[13]		5.83	6.34

[a] Yields of isolated products except as noted. [b] Yield based on GC/MS and ^{1}H NMR; product contained 20% starting material.

excess diisobutylaluminum hydride (Dibal) followed by workup with aqueous sodium hydroxide. A wide range of 3-alkoxypyrroles **2** can be prepared by this method (see Table I). For example, 1-methyl-3-ethoxypyrrole (**2**, R = methyl, R′ = ethyl) can be obtained in 62% yield. The reaction gives satisfactory yields on scales from a few milligrams to several grams. Consequently, this method avoids the deficiencies of earlier preparations (limited substitution patterns, lengthy sequences, and the use of starting materials which are not readily available).

The reaction mechanism almost certainly involves initial reduction to an aluminum carbinolamine species **3** which then suffers elimination of the aluminum alkoxide (eq 5).



(5)

3

This is supported by the observation that unsaturated lactams with a hydrogen on the nitrogen atom (**1**, R = H) do not undergo this reaction. Instead, they apparently first lose a proton and this effectively protects the lactam from reduction. The analogous reduction of α,β-unsaturated butyrolactones with Dibal leads to furans.[10]

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on Varian EM-360 and JEOL FX-90Q spectrometers, respectively. IR spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer using the 1601-cm^{-1} polystyrene peak for calibration. GC/MS data were obtained on a Finnigan 4021-C instrument. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. All reactions were run under a nitrogen atmosphere in flame-dried apparatus, and tetrahydrofuran was freshly distilled from benzophenone potassium.

Preparation of 1. General Procedure. 1-Methyl-4-ethoxy-Δ^3-pyrrolin-2-one. Ethyl acetoacetate (52.0 g, 0.40 mol) and triethyl orthoformate (59.2 g, 0.40 mol) were mixed with 12 drops of concentrated sulfuric acid and stirred for 12 h. Quinoline (20 drops) was added, and the product was distilled to give 59.8 g (95%) of ethyl 3-ethoxy-2-butenoate as a clear liquid that solidified on standing: bp 86–88 °C (14 mm) [lit.[14] bp 90–92 °C (14 mm)], mp 30 °C (lit.[14] mp 30 °C).

A mixture of this compound (7.0 g, 44.3 mmol), *N*-bromosuccinimide (8.28 g, 46.5 mmol), and benzoyl peroxide (0.1 g) in 50 mL of CCl_4 was refluxed for 3 h under nitrogen. After cooling and filtration, the filtrate was dried over $MgSO_4$, concentrated, and distilled to give 9.4 g (90%) of ethyl 4-bromo-3-ethoxy-2-butenoate as a light-yellow liquid: bp 94–97 °C (0.2 mm) [lit.[15] bp 79–84 °C (0.05–0.15 mm)].

The bromo ester (2.0 g, 8.43 mmol) was added to 15 mL of 40% aqueous methylamine over 2–3 min, and the mixture was stirred at room temperature for 12 h. The aqueous layer was extracted with two 30-mL portions of $CHCl_3$ and two 30-mL portions of ether. The combined extracts were dried over $MgSO_4$ and concentrated, and the residue was distilled to give 0.83 g (70%) of clear liquid 1-methyl-4-ethoxy-Δ^3-pyrrolin-2-one, which solidified on standing. A sample was purified by sublimation at 50 °C (0.5 mm): bp 105–110 °C (0.5–0.6 mm); mp 62–64.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3 H), 2.94 (s, 3 H), 3.84 (s, 2 H), 4.00 (q, J = 7 Hz, 2 H), 5.00 (s, 1 H); GC/MS, m/z (relative intensity) 141 (M^+, 72), 112 (M^+ – 29, 56); IR (NaCl, Nujol) 1670, 1615, 1225 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.52; H, 7.86; N, 9.88.

The other 1-alkyl- and 1-benzyl-4-alkoxy-Δ^3-pyrrolin-2-ones were prepared by the same route.[9]

Preparation of 2. General Procedure. 1-Benzyl-3-ethoxypyrrole. To a stirred solution of 150 mg (0.69 mmol) of 1-benzyl-4-ethoxy-Δ^3-pyrrolin-2-one in 15 mL of THF at 0 °C was added a solution of 290 mg (2 mmol, 3 equiv) of Dibal in hexane dropwise over 2 min. The mixture was allowed to warm slowly to room temperature and was stirred for 12 h. It was then poured into 30 mL of cold 1 N aqueous NaOH and was extracted with three 30-mL portions of ether. The combined extract was dried over $MgSO_4$ and concentrated, and the residue was distilled to give 116 mg (83%) of colorless liquid;[11] bp 130–140 °C (0.5 mm). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.60; H, 7.51; N, 6.96. Found: C, 77.35; H, 7.57; N, 6.92.

The procedure was repeated on a larger scale, starting with 3.10 g (14.3 mmol) of the unsaturated lactam to give 2.15 g of the pyrrole (75% yield from the lactam, or 45% overall from ethyl acetoacetate).

Table I lists the yields, boiling ranges, and ^{1}H NMR signals of the pyrrole hydrogens[12] of pyrroles prepared by this procedure on a scale of 0.5–2.1 mmol. All the pyrroles had ^{1}H NMR peaks

(10) (a) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 377. (b) Minato, H.; Nagasaki, T. *Ibid.* **1968**, 621. (c) Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542. (d) McMurry, J. E.; Donovan, S. F. *Tetrahedron Lett.* **1977**, 2869. (e) Tsuboi, S.; Shimozuma, K.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 1517. (f) Tius, M. A.; Takaki, K. S. *Ibid.* **1982**, *47*, 3166.

(11) All of the pyrroles are colorless liquids after distillation which darken upon standing unless stored under nitrogen in a freezer.

(12) In general, the pyrrole hydrogens are insufficiently resolved even at 90 MHz to show the expected fine structure and thus are described as multiplets.

(13) This reaction did not go to completion after the usual treatment with Dibal so the crude reaction product was exposed to Dibal a second time and this reaction showed that all of the starting material was consumed.

(14) Smissman, E. E.; Voldeng, A. *J. Org. Chem.* **1964**, *29*, 3161.

(15) Piantadosi, C.; Skulason, V. G. *J. Pharm. Sci.* **1964**, *53*, 902.

characteristic of the hydrocarbon substituents and characteristic IR peaks at 1570, 1325, and 1040 cm^{-1}. Mass spectra all showed the M^+ peak and, except for the *N*-benzyl derivatives, a principal second peak representing loss of the *O*-alkyl group.

Acknowledgment. This work was supported in part by a grant from the Research Corporation, to whom we are grateful. We also appreciate the assistance of Robert Zimmermann with all NMR spectra run on the JEOL FX-90 Q and of Jim Spriggle with GC–mass spectra.

Registry No. 1 (R = R′ = CH_3), 90968-33-5; 1 (R = CH_3, R′ = C_2H_5), 90968-34-6; 1 (R = C_2H_5, R′ = CH_3), 90968-35-7; 1 (R = R′ = C_2H_5), 90968-36-8; 1 (R = $C_6H_5CH_2$, R′ = CH_3), 90968-37-9; 1 (R = $C_6H_5CH_2$, R′ = C_2H_5), 90968-38-0; 2 (R = R′ = CH_3), 90968-41-5; 2 (R = CH_3, R′ = C_2H_5), 90968-42-6; 2 (R = C_2H_5, R′ = CH_3), 90968-43-7; 2 (R = R′ = C_2H_5), 90968-44-8; 2 (R = $C_6H_5CH_2$, R′ = CH_3), 90968-45-9; 2 (R = $C_6H_5CH_2$, R′ = C_2H_5), 90968-46-0; Dibal, 1191-15-7; 1,5-dihydro-4-ethoxy-5-ethyl-1-methyl-2*H*-pyrrol-2-one, 90968-39-1; 1,5-dihydro-4-ethoxy-1,5-diethyl-2*H*-pyrrol-2-one, 90968-40-4; 3-ethoxy-2-ethyl-1-methylpyrrole, 90968-47-1; 3-ethoxy-1,2-diethylpyrrole, 90968-48-2; ethyl acetoacetate, 141-97-9; triethyl orthoformate, 122-51-0; ethyl 3-ethoxy-2-butenoate, 998-91-4; ethyl 4-bromo-3-ethoxy-2-butenoate, 1116-50-3.

Supplementary Material Available: ^1H NMR, ^{13}C NMR, IR, and mass spectral data of all 2 and of 1 (R = CH_3, R′ = C_2H_5) (5 pages). Ordering information is given on any current masthead page.

Stereochemistry of Ethyl 2,6-Dimethyl-4-oxocyclohex-2-enecarboxylate (6-Methyl Hagemann's Ester) and Its Products of Conjugate Addition by Vinylmagnesium Bromide/Copper(I) Iodide

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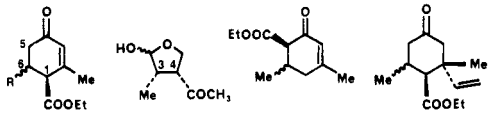
Received September 7, 1983

Given the ready availability and widespread use of 6-alkyl Hagemann's esters as building blocks for organic synthesis, it is remarkable (if not disconcerting) that no one has reported the fact that the 6-methyl derivative (ethyl 2,6-dimethyl-4-oxocyclohex-2-enecarboxylate, 1)

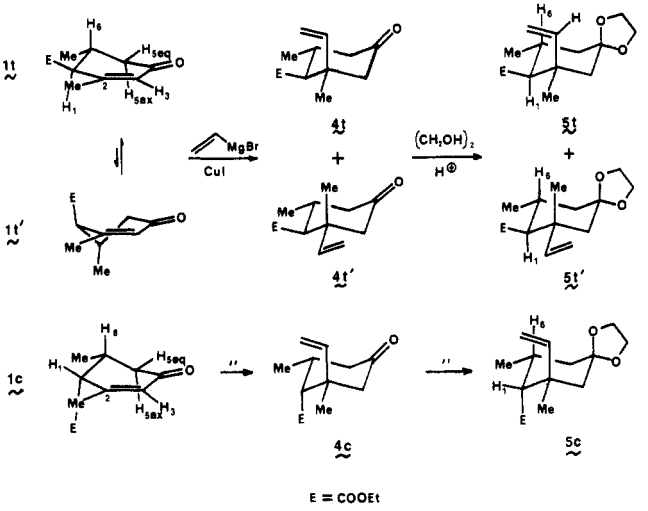


1 R=Me 2 3 4

exists as a readily interconverted pair of diastereomers. This is all the more true in the specific instance in which 1 was assumed to be of trans stereochemistry and then used as the starting material in a synthesis of botryodiplodin (2), thus "proving" the 3,4-cis relationship in the antibiotic.[1] In another study[2] it was recognized that the preparation of 1 gave a mixture of two isomers (which were characterized and separated as their 2,4-DNP derivatives), but these were assigned, incorrectly, as the regioisomers 1 and 3 and the stereochemical issue was again ignored. On the other hand, Kingsbury has demonstrated[3] that the 6-phenyl derivative 1, R = Ph (except as the methyl ester), has the trans configuration on the basis of the vicinal couplings: $J_{H(1),H(6)}$ = 9.1 Hz, $J_{H(5ax),H(6)}$ = 12.4 Hz, and $J_{H(5eq),H(6)}$ = 3.7 Hz. Having a need for the vinylated derivatives 4, we employed the Kametani method of copper(I)-mediated addition of vinylmagnesium bromide to 1 and describe the results here.

The McCurry procedure[5] for the piperidine-catalyzed condensation of ethyl acetoacetate (2 equiv) with acetaldehyde was reproduced, but the 80-MHz ^1H NMR spectrum of the distilled product indicated the presence of two isomers. Separation by HPLC provided a 3:2 ratio of the trans and cis isomers **1t** and **1c**. Either could be readily converted to the same 3:2 mixture by brief exposure to DBU in $CDCl_3$ at room temperature. Stereochemistry was assigned on the basis of high-field ^1H NMR data which suggested that (i) H(1) is pseudoaxial in the major isomer **1t** (since $J_{H(1),C(2)CH_3}$ = 1.2 Hz and $J_{H(1),H(3)}$ = 1.5 Hz) whereas it is pseudoequatorial in **1c** (since no nonvicinal coupling is observed), (ii) H(6) is axial in both **1t** and **1c** (since $J_{H(6),H(5ax)}$ = 11 Hz and 13 Hz and $J_{H(6),H(5eq)}$ = 4.4 Hz and 4.0 Hz, respectively), (iii) H(1) and H(6) are trans in **1t** (since $J_{H(1),H(6)}$ = 7.7 Hz) and cis in **1c** (since $J_{H(1),H(6)}$ = 5.0 Hz). It is interesting that a 0.7-Hz long-range coupling between H(3) and $H(5_{eq})$ is observed in **1c** but is nonexistent in **1t**. Model analysis suggests a distortion of the ring which reduces the allylic ($A_{1,2}$) strain[6] between the ethoxycarbonyl and C(2)-methyl groups in **1t** also precludes $H(5_{eq})$–CCC–H(3) planarity and results in a H(6)–CC–H(1) dihedral angle of ~150°.

The stereochemical assignments of **1c** and **1t** are supported by the reactions of the two isomers with vinyl cuprate. The cis isomer **1c** reacts to give a single product



assigned as **4c**, as does Hagemann's ester itself.[4] However, the trans isomer **1t** gives a 4:1 mixture of adducts **4t** and **4t′**, which we could not separate but whose stereochemistries were assigned after conversion to the ketals **5t** and **5t′**. If one assumes exclusive axial approach of the vinyl group in the conjugate addition, then the products **4t** and **4t′** arise from competitive addition to conformers **1t** and **1t′** via processes which involve a 1,2-interaction between the entering vinyl and the pseudoequatorial ethoxycarbonyl group vs. a (slightly less favorable) 1,3-diaxial

(1) McCurry, P. M., Jr.; Ahe, K. *J. Am. Chem. Soc.* **1973**, *95*, 5824.
(2) Binns, T. D.; Brettle, R. *J. Chem. Soc. C* **1966**, 336.
(3) Kingsbury, C. A.; Egan, R. S.; Perun, T. J. *J. Org. Chem.* **1970**, *35*, 2913.
(4) Kametani, T.; Tsubuki, M.; Nemoto, H. *J. Org. Chem.* **1980**, *45*, 4391.
(5) McCurry, P. M., Jr.; Singh, R. K. *Synth. Commun.* **1976**, *6*, 75.
(6) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

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