strument (silica gel, elution with 2% ethyl acetate in petroleum ether). There was isolated 1.36 g (27%) of **9** and 2.13 g (50% based on recovered starting material) of **10** as a colorless oil: IR (CCl_4) 2940, 2890, 1735, 1460, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 3 H), 2.22 (s, 2 H), 2.05–1.6 (m, 3 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.10 (s, 3 H), 0.86 (s, 3 H); mass spectrum, *m/e* calcd 196.1463, obsd 196.1458.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.20; H, 10.24. Found: C, 72.85; H, 10.12.

Cyclization of 10. A solution containing **10** (2.13 g, 11 mmol), 8.5 mL of concentrated hydrochloric acid, 25 mL of methanol, and 4 mL of water was heated at the reflux temperature for 8 h. After the solution cooled, most of the methanol was removed under reduced pressure and the residue was partitioned between ether (75 mL) and water (50 mL). The aqueous phase was extracted with ether (2 × 75 mL), and the combined organic layers were washed with saturated sodium bicarbonate and brine solutions prior to drying and solvent evaporation. There was obtained 1.62 g (82%) of **11** as a brown oil which was purified by silica gel high-pressure liquid chromatography (elution with 6% ethyl acetate in petroleum ether). The pure lactone was a colorless crystalline solid: mp 42–43 °C; IR (CCl_4) 2950, 2860, 1770, 1450, 1190, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (m, 1 H), 2.75 (m, 1 H), 1.85 (m, 2 H), 1.6 (s, 2 H), 1.5 (s, 3 H), 1.4 (s, 3 H), 1.15 (s, 3 H), 1.0 (s, 3 H); mass spectrum, *m/e* calcd ($M^+ - CH_3$) 167.1072, obsd 167.1066.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.32; H, 9.95.

Selenation–Oxidation of 11. A solution of **11** (200 mg, 1.10 mmol) in dry tetrahydrofuran (4 mL) was added to a cold (−78 °C) lithium diisopropylamide solution [prepared from diisopropylamine (0.32 mL, 2.6 mmol) and *n*-butyllithium (0.86 mL of 1.55 m in hexane, 1.30 mmol) by stirring for 10 min at −20 °C] and the mixture was stirred for 30 min. Phenylselenyl bromide (300 mg, 1.10 mmol) dissolved in tetrahydrofuran (6 mL) was added and the mixture was stirred at −78 °C for 2 h before being poured into ice-cold dilute hydrochloric acid. The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic layers were washed with saturated sodium bicarbonate and brine solutions prior to drying. Solvent evaporation left an oil (220 mg) from which the selenide was obtained by preparative TLC on silica gel plates. In addition to the product (90 mg, 25%) there was recovered 25 mg of **11**: IR (CCl_4) 3300, 2960, 2280, 1730, 1580, 1390, 1260, 1160, 1140, 1020, 950, 900, 680 cm^1; ^1H NMR ($CDCl_3$) δ 7.75–7.15 (m, 5 H), 2.75 (t, J = 8 Hz, 1 H), 2.0 (s, 2 H), 1.64 (s, 3 H), 1.62–1.5 (m, 2 H), 1.32 (s, 3 H), 1.05 (s, 3 H), 0.98 (s, 3 H); mass spectrum, *m/e* calcd 338.0785, obsd 338.0777.

To a solution of the phenylseleno lactone (34.1 mg, 0.10 mmol) in carbon tetrachloride (15 mL) was added a 4:1:4 mixture of water/acetic acid/30% hydrogen peroxide (v/v/v, 4.5 mL). The biphasic mixture was heated at reflux for 7.5 h and poured into saturated sodium bicarbonate solution (25 mL) admixed with dichloromethane (25 mL). The layers were separated, and the organic phase was washed with 25-mL portions of water, dilute hydrochloric acid, water and brine. Following drying and solvent evaporation, there was obtained 10.5 mg (60%) of **12** as a colorless crystalline solid: mp 65–69 °C; IR (CCl_4) 2960, 1770, 1290, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 4 H), 1.46 (s, 6 H), 1.25 (s, 6 H); mass spectrum, *m/e* calcd 180.1150, obsd 180.1157.

Bromination of 11. To a cold (−78 °C) solution of the lithium enolate of **11** (300 mg, prepared as above) was added 3 mL of 1,2-dibromoethane. The reaction mixture was stirred at room temperature for 2 h, evaporated under reduced pressure, and treated with water. The aqueous mixture was extracted with ether (3 × 50 mL). The usual workup gave an orange oil (550 mg) which was purified by preparative TLC chromatography on silica gel (elution with 20:1 petroleum ether/ethyl acetate). There was obtained 260 mg (61%) of **13** as an off-white solid: mp 71–75 °C; IR (CCl_4) 2960, 2860, 1760, 1460, 1385, 1370, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15 (dd, J = 12 and 6 Hz, 1 H), 2.35 (m, 2 H), 1.7 (s, 3 H), 1.55 (s, 2 H), 1.35 (s, 3 H), 1.20 (s, 3 H), 1.05 (s, 3 H); mass spectrum, *m/e* calcd 245.0178, obsd 245.0186.

4,7,7-Trimethyl-*cis*-bicyclo[3.3.0]oct-3-en-2-one (3). Into a solution of phosphorus pentoxide (4.5 g) in methanesulfonic acid (57 g), prepared by heating with stirring at 80 °C under nitrogen, was added lactone **11** (400 mg, 2.2 mmol) in small portions. The dark reaction mixture was heated at 50 °C for 48 h and added dropwise to water (150 mL). The resulting aqueous suspension was extracted with dichloromethane (6 × 25 mL), and the combined organic layers were washed successively with sodium bicarbonate solution (30 mL), water (30 mL), and brine (30 mL). Drying and solvent evaporation left a brown oil (298 mg) which was filtered through a silica gel plug (6.3% ethyl acetate in petroleum ether) to give 238 mg (70%) of **3**. The analytical sample was obtained by VPC (2 ft × 0.25 in. 5% SE-30 on Chromosorb G, 150 °C): IR (CCl_4) 2950, 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.5 (s, 1 H), 3.4–2.8 (m, 2 H), 2.02 (s, 3 H), 2.0–1.1 (m, 4 H), 1.03 (s, 6 H); mass spectrum, *m/e* calcd 164.1201, obsd 164.1199.

Acknowledgment. We are indebted to the National Institutes of Health (Grant GM-28468) and Eli Lilly Co. for financial support of this research.

Registry No. **3**, 53874-09-2; **6**, 4255-62-3; **7**, 50388-51-7; **7** (ethylene ketal ester), 79618-60-3; **8**, 79618-61-4; **9**, 79618-62-5; **10**, 79618-63-6; **11**, 79618-64-7; **11** (phenylseleno lactone), 79618-65-8; **12**, 79618-66-9; **13**, 79618-67-0; methyl iodide, 74-88-4.

Preparation of Bicyclo[3.3.0]oct-1-en-3-one and Bicyclo[4.3.0]non-1(9)-en-8-one via Intramolecular Cyclization of α,ω-Enynes

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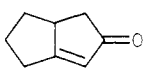
The presence of the bicyclo[3.3.0]octane ring system in a variety of biologically active natural products has generated considerable interest in the synthesis of its functionalized derivatives. In particular, two recent reports have described syntheses of enone **1**, a compound whose



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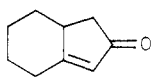
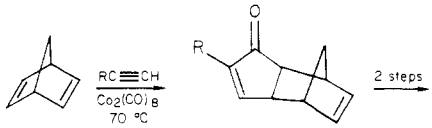


2

preparation has proved to be unexpectedly challenging.[1,2] We report here exceptionally simple syntheses of both **1** and its homologue **2**, syntheses that are unique in that they allow the preparation of these ketones *directly from acyclic starting materials*, without the need for prior formation of monocyclic intermediates.

The syntheses make use of the cobalt carbonyl promoted cocyclization of alkynes, alkenes, and carbon monoxide, a reaction first reported by Pauson and co-workers in 1973. The reaction utilizing norbornadiene[3,4] as the alkene provides good yields of products which, we have shown, are readily converted into simple cyclopentenone derivatives (eq 1).[5] Unfortunately, unstrained alkenes are consider-



50–60% 60–90% (1)

(1) Smith, Amos, III; Toder, B.; Branca, S.; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 1996.
(2) Klipa, D. K.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815 and references therein.
(3) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.
(4) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 30.

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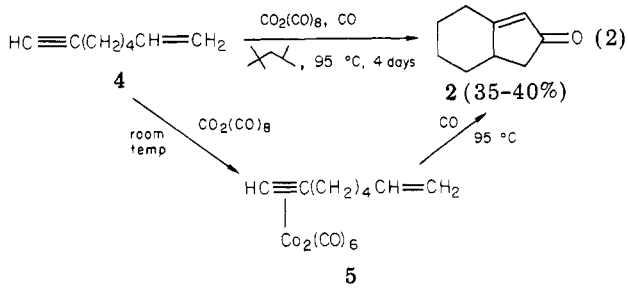
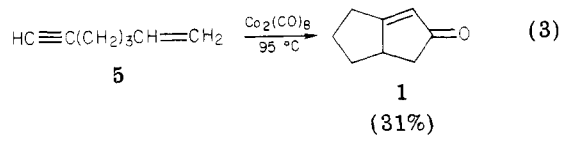
ably less reactive in this cyclization process, thus severely limiting its generality: simple olefins react only under forcing conditions, and the yields of cyclopentenones obtained vary greatly.[6] We suspected, however, that the intramolecular disposition of the functional groups in α,ω-enynes might enhance the desired mode of reactivity. We therefore prepared enynes **4** and **5** and submitted them to the cyclization conditions as follows. Reaction of **4** with $Co_2(CO)_8$ in pentane at room temperature (eq 2) affords



a good yield of the hexacarbonyldicobalt derivative (**5**), containing, as expected, complexed alkyne and free alkene moieties. Heating of **5** in 2,2,4-trimethylpentane or direct reaction of **4** with ca. 0.5 equiv of $Co_2(CO)_8$ at 85–95 °C gives rise to a 35–40% yield of cyclopentenone **2**[7] *under considerably milder conditions* than are required for the corresponding intermolecular reactions of simple alkenes.

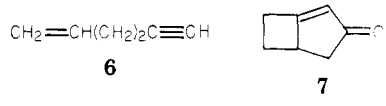
Reaction with the related substrate hept-1-en-6-yne (**5**) similarly generates cyclopentenone **1**[8] in 31% yield (eq 3).



(3)

In both cases preliminary purification of the product is achieved by Florisil chromatography to remove nonpolar materials. In the case of **2**, pure ketone is then isolable by distillation. Ketone **1** is best isolated by derivatization with Girard reagent "T", extraction, and liberation in order to separate it from small amounts of a nonketonic polar side product.[9]

Attempted cyclization of hex-1-en-5-yne (**6**), which would give rise to bicyclo[3.2.0]hept-1-en-3-one (**7**), instead



6 7

exclusively produces a mixture of products of trimerization of the alkyne functionality. Although four-membered-ring formation occurs readily in the $C_5H_5Co(CO)_2$-catalyzed cyclotrimerization of 1,5-hexadiyne,[10] we find no trace of four membered ring containing products in the enyne system.

Although ketone **2** has been available via conventional condensation chemistry for some time,[2] this route now provides the most direct synthesis of **1** from readily available starting materials.

Experimental Section

Trimethylpentane (Phillips) was dried over 4A molecular sieves before use. Dimethyl sulfoxide (Mallinkrodt) was distilled from calcium hydride at reduced pressure and stored over 4A molecular sieves. Lithium acetylide–ethylenediamine complex (Alfa), 5-chloro-1-pentene (ICN), 6-chloro-1-hexene (ICN), and Girard reagent "T" (Fisher) were obtained commercially and used as received.

1-Hepten-6-yne (5). A mixture of 3.00 g (28.0 mmol) of lithium acetylide–ethylenediamine in 15 mL of dimethyl sulfoxide was cooled to 15 °C under Ar, and 2.91 g (27.8 mmol) of 5-chloro-1-pentene was then added, dropwise, to the stirred mixture over a period of several minutes.[11] The mixture was warmed to room temperature and stirred for 15 h. The reaction was quenched with 10 mL of 6 N HCl, and poured into 30 mL water, and the product was extracted into 30 mL of ether. The ether was washed with 15 mL of water and 10 mL of brine and dried ($CaSO_4$). Removal of ether (spinning-band distillation) left a liquid from which 1.75 g (74% yield) of **5** was isolated by room temperature distillation at high vacuum into a −196 °C trap and was stored at 0 °C. This represents a slight improvement in yield over the literature procedure[12] which utilizes sodium acetylide and 5-bromo-1-pentene: IR (film) 1640, 3310 cm^{-1}; NMR (neat, 90 MHz) δ 1.55 (m, 2 H), 1.95 (t, J = 2 Hz, 1 H), 2.10 (m, 4 H), 4.92 (dd, J = 2, 10 Hz, 1 H), 4.98 (dd, J = 2, 17 Hz, 1 H), 5.76 (ddt, J = 10, 17, 7 Hz, 1 H).

4,5,6,6a-Tetrahydro-2(1*H*)-pentalenone (Bicyclo[3.3.0]-oct-1-en-3-one, 1).[1,2,8] A stirred mixture of 3.05 g (32.5 mmol) of **5** and 11.00 g (32.5 mmol) of octacarbonyl dicobalt[13] in 50 mL of CO-purged trimethylpentane was heated to 95 °C under a CO atmosphere for 4 days. After cooling, the entire reaction mixture was loaded onto a Florisil column, and both trimethylpentane and a small quantity of nonpolar organometallic material (mostly the unreacted hexacarbonyldicobalt complex of **5**) were removed by hexane elution. This fraction also contained 0.38 g of a material possessing both vinyl and aromatic NMR signals which was not characterized further but was presumed to be a mixture of isomers of tris(4-pentenyl)benzene. Crude **1** was obtained by ether elution, and the yield of impure material was 1.66 g. Purification of **1** was achieved as follows. To a mixture of 1.04 g Girard reagent "T", 1.2 mL of acetic acid, and 15 mL of 95% ethanol was added 1.00 g of crude ketone. The mixture was refluxed for 30 min, cooled, poured into 150 mL saturated aqueous NaCl, and extracted with ether (4 × 75 mL). The aqueous layer was acidified with 30 mL of concentrated HCl and heated to boiling, whereupon it became heterogeneous. After the mixture cooled, the liberated ketone was extracted with ether (3 × 75 mL) which was dried (K_2CO_3) and stripped, leaving 0.75 g ketone **1** which was ≥97% pure by NMR (31% yield). Analytically pure material was obtained by GC (10 ft × 0.25 in. column, 3% Carbowax 20M on Chromasorb W at 150 °C): IR (film) 1627, 1696 cm^{-1}; NMR (CCl_4 + $CDCl_3$, 360 MHz) δ 1.17 (ddt, J = 7, 7, 14 Hz, 1 H), 2.04 (m, 3 H), 2.18 (ddt, J = 4, 7, 7 Hz, 1 H), 2.60 (m, 3 H), 2.88 (m, 1 H), 5.86 (m, 1 H); mass spectrum calcd for $C_8H_{10}O$, m/e 122.0732, found m/e 122.0735.

1-Octen-7-yne (4) was prepared in 60% yield via a procedure identical with that used for **5**. This material has previously been prepared in 70% yield from sodium acetylide and 6-iodo-1-hexene.[14]

3,3a,4,5,6,7-Hexahydro-2(2*H*)-indenone (bicyclo[4.3.0]-non-1(9)-en-8-one, 2)[7] was prepared in 35–40% yield by a procedure similar to that used for **1**. The ketone was obtained directly

(5) Schore, N. E. *Synth. Commun.* **1979**, *9*, 41.
(6) E.g., 1-octene + phenylacetylene at 160 °C in 18% total yield (2 products): Khand, I. U.; Pauson, P. L. *J. Chem. Res., Miniprint* **1977**, 0168. Review: Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2.
(7) 3,3a,4,5,6,7-Hexahydro-2(2*H*)-indenone: Wada, E.; Nakai, T.; Okawara, M. *Chem. Lett.* **1976**, 1025. Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* **1952**, 4086.
(8) 4,5,6,6a-Tetrahydro-2(1*H*)-pentalenone first reported in: Poulton, G. A.; Wiesner, K. *Symp. Pap.—IUPAC Int. Symp. Chem. Nat. Prod. 11th* **1978**, *3*, 115.
(9) A small amount of 5-methoxy-3-methyl-1-pentanol, the origin of which is unclear, has been isolated and spectroscopically characterized.
(10) Vollhardt, K. P. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4996. Aalbersberg, W. G. L.; Barkovich, A. J.; Funk, R. L.; Hilliard, R. L., III; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1975**, *97*, 5600.
(11) General method of: Gibson, T. W.; Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 4771.
(12) Rienaecker, R.; Schwengers, D. *Justus Liebigs Ann. Chem.* **1977**, 1633.
(13) In somewhat smaller scale runs we have found that reduction of the quantity of octacarbonyldicobalt to ca. 50 mol % has little effect on the yield of **1**.
(14) Black, H. K.; Weedon, B. C. L. *Chem. Ind. (London)* **1953**, 40.

by distillation of the dichloromethane fraction from Florisil chromatography of the crude reaction mixture; bp 70 °C (1 mmHg). Pure **2** could be isolated by GC (10 ft × 0.25 in. column, 5% DEGS on Chromasorb P, 135 °C).

Acknowledgment. We are grateful to Professor R. G. Bergman for advice and encouragement. This research was supported by a grant from the National Institutes of Health (PHS GM26294).

Registry No. 1, 72200-41-0; 2, 39163-29-6; 4, 65909-92-4; 5, 65939-59-5; 6, 14548-31-3; lithiumacetylide-ethylenediamine complex, 39990-99-3; 5-chloro-1-pentene, 928-50-7; 6-chloro-1-hexene, 928-89-2.

N-Methylation of *O*-Benzyl N^{α}-(Alkoxycarbonyl) α-Amino Acid Hydroxamate Derivatives

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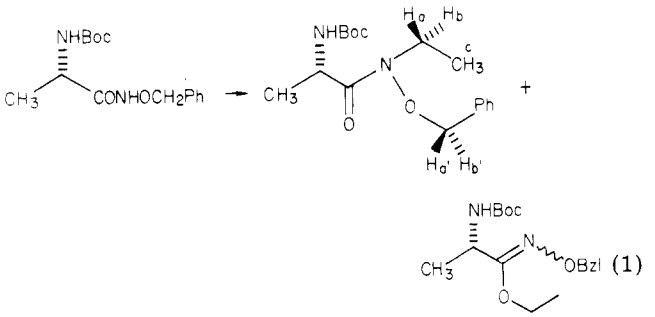
The hydroxamate group is an important functionality in several natural products and is especially prevalent in certain siderophores such as ferrichrome, where it plays a key role in the complexation of ferric ion by these substances.[1] Our interest in the synthesis of siderophore analogues made it desirable to be able to cleanly effect intermolecular N-alkylation of the hydroxamate function of α-amino acid hydroxamate derivatives.

Because of the enhanced acidity (pK_a = 6–10)[2-4] of the hydroxamate NH as compared to an amide or urethane NH group ($pK_a \approx 15$), it would be anticipated that selective N-alkylation should readily occur. The intermolecular N-alkylation by alkyl halides of hydroxamates of simple carboxylic acids has been reported,[5-7] though in some instances O-alkylation also has been observed. Intermolecular alkylation of hydroxamates with alcohols mediated by diethyl azodicarboxylate–triphenylphosphine gives mainly or entirely the O-alkylated product.[6,7b] Clean intramolecular alkylation on nitrogen has been reported[7] in the preparation of β-lactams from β-chloroalanine or serine and threonine hydroxamate derivatives.

The *O*-benzyl N^{α}-(alkoxycarbonyl) α-amino acid hydroxamates (**1**) used in this study were prepared by carbodiimide-mediated condensation of the appropriate N-protected α-amino acids with *O*-benzylhydroxylamine (Table I).[3]

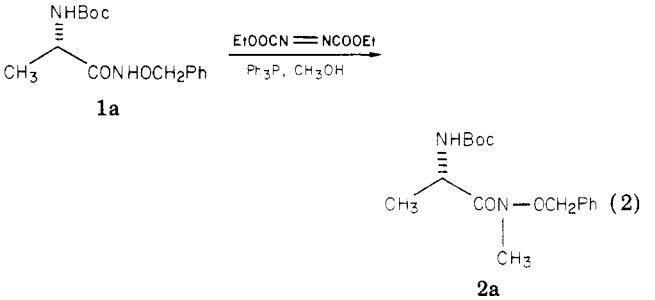
We have observed that *O*-benzyl N^{α}-(alkoxycarbonyl) α-amino acid hydroxamates (**1**) undergo N-methylation on the hydroxamate function with sodium hydride–methyl iodide in dimethylformamide–methylene chloride at 50 °C to form the desired product **2** (Table II). The reaction, if carried out at room temperature, was not complete after 20 h. Analysis of the ^{1}H NMR spectra of the crude reaction products did not show the presence of any O-alkylated product nor of any product resulting from N-methylation of the urethane nitrogen. The *O*-methyl peak would be expected[5,6] to occur at about δ 4.0, while that of the hydroxamate *N*-methyl resonance occurs in the region of δ 3.25 and the urethane N-methyl at about δ 2.8, as described below. We likewise did not observe, upon purification of the *N*-methylhydroxamates by preparative medium-pressure liquid chromatography, other O- or N-methylated products. It appears, therefore, that these products are not formed in the methylation reaction to any significant extent.

Clean N-alkylation of the hydroxamate function apparently is unique for methyl iodide as an alkylation agent. Alkylation of Boc-Ala-NHOBzl (**1a**) with ethyl iodide or benzyl bromide furnished a mixture of products in each case, from which we were able to isolate the *N*- and *O*-alkyl products. For the reaction with ethyl iodide (eq 1), the



N-ethyl and *O*-ethyl products were formed in an approximate ratio of 4:1. The 360-MHz ^{1}H NMR spectrum of the *N*-ethyl product was interesting in that each of the *O*-benzyl protons and the methylene protons of the *N*-ethyl group were nonequivalent. The benzylic protons occurred as an AB quartet centered at δ 4.9, while the *N*-ethyl methylene protons appeared as multiplets at δ 3.4 and 3.95. Decoupling of each of these multiplets caused, in turn, the triplet at δ 1.08 due to the ethyl CH_3 group to collapse to a doublet ($J_{ac} = J_{bc}$ = 7 Hz).

Reaction of **1a** with diethyl azodicarboxylate–triphenylphosphine and methanol provided the N-alkylated hydroxamate **2a** (eq 2) but in only 39% yield. It appears,



1a

2a

therefore, that alkylation with methyl iodide in dimethylformamide–methylene chloride is the method of choice for preparation of these *N*-methylhydroxamate derivatives.

Methylation of **1a**, when carried out in tetrahydrofuran as the solvent and with 1 equiv of sodium hydride and methyl iodide, gave a low yield of alkylated product accompanied by recovered reactant. Use of 2 equiv each of base and methyl iodide gave an equal mixture of the N^{α}-methyl derivative **3** and N,N^{α}-dimethyl derivative **4** (eq 3). The ^{1}H NMR spectrum of **3** had an *N*-methyl peak at δ 2.83, while **4** had two *N*-methyl peaks at δ 2.93 and 3.23. The monoalkylated product in this case resulted from

(1) Emery, T. "Metal Ions in Biological Systems"; Sigel, H., Ed.; Marcel Dekker: New York, 1978; Vol. 7, p 77.
(2) Exner, D.; Simon, W. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4078.
(3) Miller, M. J.; DeBons, F. E.; Loudon, G. M. *J. Org. Chem.* **1977**, *42*, 1750.
(4) Stolberg, M. A.; Tweit, R. C.; Steinberg, G. M.; Wagner-Jauregg, T. *J. Am. Chem. Soc.* **1955**, *77*, 765.
(5) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284.
(6) Maurer, P. J.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 2835.
(7) (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *Ibid.* **1981**, *103*, 2909.

0022-3263/81/1946-5438$01.25/0