triguing possibility is in progress and will be reported separately.

Leo A. Paquette
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210
Received June 25, 1970

A New β-Keto Ester Synthesis. The Triethyloxonium Ion Catalyzed Homologation of Ketones with Diazoacetic Esters

Sir:

We have discovered a novel technique for the one-carbon homologation of ketones, which should have broad synthetic utility in view of its experimental simplicity and generally high yields. The new reaction involves the insertion of a carbalkoxymethylene group from an alkyl diazoacetate into a carbonyl–alkyl or –aryl bond under the catalytic influence of triethyloxonium fluoroborate.[1]

Cyclohexanone does not react with ethyl diazoacetate in methylene chloride solution in the absence of Lewis acid catalysts. Furthermore, we have found that there is no discernible reaction between these individual components and triethyloxonium fluoroborate in this solvent (at 0°). However, when these three substances are combined in methylene chloride at 0–25°, rapid evolution of nitrogen is noted, and after its cessation a high yield of 2-carbethoxycycloheptanone may be obtained by quenching with aqueous bicarbonate solution followed by simple extraction. Generally, the only identifiable by-product (0–5%) is the glycidic ester derived from the ketone and the diazoacetate.

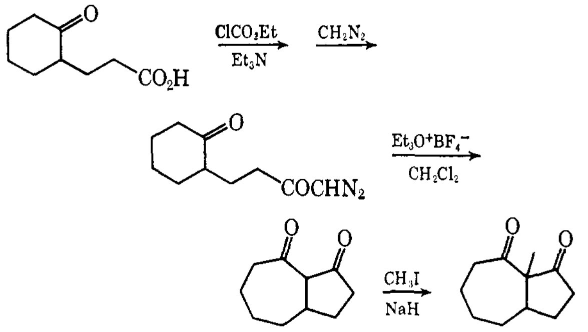
A model experimental procedure for the reaction is appended to this report. With respect to the scope of this technique the following points are pertinent. (1) Yields are uniformly high (Table I). (2) Since the rate-determining step has been shown to involve alkylation of the ketone, selectivity may be anticipated depending upon the environment of the carbonyl group. (3) Since the triethyloxonium fluoroborate is a true catalyst (and does not otherwise enter into the reaction), massive amounts may be used to force unfavorable cases. (4) Further control may be exercised by manipulation of temperature; the reaction has been observed to proceed at as low as −20° and in refluxing methylene chloride (40°). (5) The homologation stops after the introduction of one carbethoxy group; no biscarbethoxy ketone is formed. (6) The carbethoxy group may be removed by hydrolysis and decarboxylation; in view of the high yields, it is feasible to build large size rings by sequential expansion from more readily accessible medium ring ketones. (7) The β-keto ester product is highly suitable for further functionalization (*e.g.*, alkylation) prior to removal of the carbethoxy group. (8) Examination of migratory aptitudes in the homologation step is at a preliminary stage; however, there does not appear to be great discrimination between possible products in unsymmetrical ketones. (9) The technique appears to be extendible to other diazo compounds; we have prepared 2-cyanocycloheptanone in 58% yield from cyclohexanone and diazoacetonitrile.

Table I. Ketone Homologations with Ethyl Diazoacetate and Triethyloxonium Fluoroborate[a]

Cyclohexanone → 2-carbethoxycycloheptanone	90%[b]
Cycloheptanone → 2-carbethoxycyclooctanone	81%
Cyclooctanone → 2-carbethoxycyclononanone	73%[c]
Acetone → ethyl 2-methylacetylacetate	78%
3-Pentanone → ethyl 2-ethylpropionylacetate	86%
Acetophenone → ethyl 2-phenylacetylacetate	74%
+ ethyl 2-methylbenzoylacetate	6%

[a] Standard procedure similar to that found optimal for cyclohexanone. [b] Typical yield of distilled material may contain 0–5% of glycidic ester and diethyl diglycolate; however, it has independently been established that there was an 8% loss of product upon distillation—yields of this and the other equally unstable keto esters may be adjusted upwards accordingly. [c] Contaminated with unknown by-products.

Whereas analogous expansion does not seem to occur in satisfactory fashion with simple diazo ketones (diazoacetone in place of ethyl diazoacetate), we have found that the intramolecular counterpart constitutes an especially promising synthetic route to polycyclic diketones. Conversion of (2-oxocyclohexane)propionic acid to the corresponding diazo ketone,[2] followed by treatment with triethyloxonium fluoroborate, gave apparently complete conversion to the novel diketone[3] shown (eq 1). The product was characterized by methylation (to give a diketone[3] clearly containing five- and seven-membered ring carbonyls, λ_{max} 5.72 and 5.91 μ, respectively) and by basic cleavage to (3-oxocycloheptane)propionic acid.[4] Clearly this method, which combines annelation with ring expansion and produces an intermediate highly suitable for further manipulation, has great potential in organic synthesis for the construction of elaborate polycyclic ring systems.



(1)

2-Carbethoxycycloheptanone. A solution of 4.9 g (0.05 mol) of cyclohexanone in 150 ml of methylene

---

[1] In fact, our procedure is a variant of that reported by W. T. Tai and E. W. Warnhoff (*Can. J. Chem.*, **42**, 1333 (1964)), in which the same reaction is catalyzed by boron trifluoride etherate. The new technique is superior from the point of view of yield (Warnhoff's procedure, which we have found unsuccessful in some cases, was reported as giving 38% conversion of cyclohexanone to 2-carbethoxycycloheptanone *vs.* our >90% yield with complete conversion) and other experimental factors as subsequently discussed.

[2] It appears to be necessary to use the mixed anhydride method: D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957); T. L. Burkoth, *Tetrahedron Lett.*, 5049 (1969); D. Hodson, G. Holt, and D. K. Wall, *J. Chem. Soc. C*, 971 (1970).

[3] Carbon and hydrogen analyses within 0.3% of theoretical values have been obtained.

[4] This represents an otherwise not readily accessible type of keto acid. It was characterized by Wolff–Kishner reduction to cycloheptanepropionic acid, to which comparison was made with authentic material (amide, mp and mmp 81.5–82.5°). Similarly, it was shown that (3-oxocyclopentane)valeric acid was absent (<0.5%) in the hydrolysate of the diketone.

chloride was cooled to 0° under an inert atmosphere. To the magnetically stirred solution, 16.7 g (0.088 mol) of triethyloxonium fluoroborate was added, followed by dropwise addition of 10.0 g (0.088 mol) of ethyl diazoacetate. The reaction mixture was maintained at 0° for 3 hr, during which time nitrogen evolved, and then was quenched with 150 ml of saturated sodium bicarbonate solution. After stirring for 0.5 hr at room temperature, the methylene chloride was separated and dried, and the solvent was removed. Distillation of the residue at reduced pressure gave 8.2 g (90%) of 2-carbethoxycycloheptanone, bp 80–82° (0.05 mm).

* To whom correspondence should be addressed.

William L. Mock,* Marvis E. Hartman
Department of Chemistry, Carnegie-Mellon University
Pittsburgh, Pennsylvania 15213
Received May 23, 1970

Apical Interaction in the Copper(II) Complex of L-Alaninamide with Diethylenetriamine

Sir:

In the previous paper,[1] we reported studies on the poly-L-lysine–copper(II) complex whose circular dichroism (CD) in the ligand-field region was not observed until the peptide amide nitrogen coordinated to the copper(II) ion. In order to clarify the structure of the poly-L-lysine–copper(II) complex, it was necessary to examine amplitudes and wavelengths at CD extrema for the copper(II) complex, in which an amide nitrogen coordinates to the copper(II) ion in the planar or the apical position.

In this communication, we wish to report experimental results which demonstrate that the copper(II) complex of L-alaninamide with diethylenetriamine (dien) has the amide nitrogen coordinated to the copper(II) ion in the apical position, whereas the copper(II) complex of L-alaninamide with ethylenediamine (en) has the amide nitrogen in the planar position.

Wellman, *et al.*,[2] reported detection of apical interaction in copper(II) complexes of potential tridentate α-amino acids by optical rotatory dispersion, and that an α-amino acid substituted with a heteroatom X (*e.g.*, $HOOCCHNH_2(CH_2)_nX$), capable of coordinating with the apical position, might disturb the ring conformational equilibrium ($\lambda \rightleftharpoons \delta$) in favor of an increased λ population with a concomitant shift in the observed Cotton-effect amplitude toward more positive values. However, no study has been reported in relation to the vicinal effects of an asymmetric carbon in a ligand coordinated apically to a copper(II) ion.

The L-alaninamide (L-alaamide) used here as a ligand was derived from L-alanine by a method similar to that described in the literature,[3] which had mp 79–81° (lit.[4] 83–84°) and $[\alpha]_D$ +16.3° (*c* 2.35, H_2O) (lit.[4] +11.1°). All other materials were guaranteed reagents and purified in the usual manner. The pH titrations were carried out by the use of a Hiranuma Model RAT-101 recording pH apparatus. dien and en were protonated by adding HCl in preparing the stock solution. During titration, the solutions were protected from CO_2 by a stream of nitrogen. Both absorption and CD spectra were obtained by a Jasco Model ORD/UV-5 spectrophotometer with a CD attachment. The infrared absorption spectra were recorded on a Hitachi Model G_2 grating infrared spectrophotometer with small bags made of polyethylene films held between NaCl plates.

Potentiometric titrations with base of 1:1:1 molar ratio of copper(II):L-alaninamide:dien or en were performed. The titration curves show a definite inflection at $\alpha = 3$ or 2 in the case of dien or en, respectively, where α is the number of moles of base added per mole of ligand (L-alaninamide). From the stability constant[5] of dien or en with copper(II) ion, the first 2 or 3 equiv of protons titrated are thought to be due to the ammonium protons in dien or en, respectively.

In the infrared (ir) spectra of the copper(II) complex of L-alaninamide with dien in an aqueous (D_2O) solution, a band around 1633 cm^{-1} is seen at pD below 8.5, which is assigned to an amide carbonyl band. At pD 9.45 a weak band at 1565 cm^{-1} was observed together with the strong band at 1633 cm^{-1}. As the pD value increases over 9.5, the band at 1633 cm^{-1} is replaced by a strong band around 1565 cm^{-1}, which is considered to be due to the carbonyl group of the amide coordinated to the copper(II) ion with displacement of proton.[6] On the other hand, in the case of the copper(II) complex of L-alaninamide with en, the band of the amide carbonyl group coordinating to the copper(II) ion was observed at 1615 cm^{-1} at pD 5.4. At pD 6.60 the weak band around 1565 cm^{-1} appeared beside a strong band at 1615 cm^{-1}. The band at 1565 cm^{-1} became stronger as the acidity of the solution was decreased, whereas the band at 1615 cm^{-1} became weaker. At pD 7.88, the band at 1565 cm^{-1} became stronger than that at 1615 cm^{-1}. As pD increases further, the band at 1615 cm^{-1} is replaced by a strong band at 1565 cm^{-1}.

Table I shows the absorption and CD spectral data of the copper(II) complexes.

Table I. Absorption (AB) and Circular Dichroism (CD) Spectra Data of Copper(II) Complexes

Complex	pH	AB Log ϵ ($\tilde{\nu}_{max}$, 10^3 cm^{-1})	CD $\Delta\epsilon^a$ ($\tilde{\nu}_{max}$, 10^3 cm^{-1})
Cu(dien)(L-alaamide)	4.8	1.95 (16.3)	
	7.8	1.99 (16.5)	−0.013 (18.1)
	9.4	1.99 (16.5)	−0.016 (18.2)
	11.8	1.99 (16.5)	−0.019 (18.3)
Cu(en)(L-alaamide)	5.0	1.42 (15.0)	
	6.5	1.68 (16.8)	−0.033 (16.6)
	7.6	1.77 (17.8)	−0.065 (17.7)
	11.7	1.81 (18.5)	−0.108 (18.2)
Cu(dien)(L-alanine)	6.2	1.98 (16.3)	−0.010 (16.5)
	9.3	2.06 (16.2)	−0.032 (17.6)
	11.7	2.00 (16.4)	−0.005 (17.3)

[a] The magnitudes of the deflections observed in comparison to the noise level were less than ±5%.

---

(1) M. Hatano, T. Nozawa, and M. Yoneyama, *Bull. Chem. Soc. Jap.*, 43, 295 (1970), and references cited there.

(2) K. M. Wellman, T. G. Mecca, W. Mungall, and C. R. Hare, *J. Amer. Chem. Soc.*, 90, 805 (1968).

(3) P. S. Yang and M. M. Rising, *ibid.*, 53, 3183 (1931); G. Hillmann, *Z. Naturforsch.*, 1, 682 (1946).

(4) T. Komorita, J. Hidaka, and Y. Shimura, *Bull. Chem. Soc. Jap.*, 42, 168 (1969).

(5) G. Sillen and A. E. Martell, "Stability Constants of Metal-Ion Complexes," Special Publication No. 17, The Chemical Society, London, 1964, pp 370 and 472.

(6) K. Nakamoto in "Spectroscopy and Structure of Metal Chelate Compounds," K. Nakamoto and P. J. McCarthy, Ed., Wiley, New York, N. Y., 1968, p 279.