Reactions of Carbethoxycarbene with Enaminones. Formation of Unexpected Pyrroles

Rodinei Augusti, Marcos N. Eberlin and Concetta Kascheres*

State University of Campinas-Unicamp, Institute of Chemistry, CP 6154, Campinas, SP 13083-970, Brazil

Received February 24, 1995
Revised May 10, 1995

The reactions of carbethoxycarbene (:CH_2-CO_2Et, **2**) with several acyclic enaminones (RCOCH=CR^1NHR^2, **3**) lead to the unexpected formation of 2-Me, 3-CO_2Et, 4-H, 5-R^1-pyrroles **4**. Structural variations of the enaminones show that the structural fragments C(3)-CO_2Et and C(2)-Me are provided by **2** and that the fragment C(5)-R^1NHR^2 originates from the enaminones **3**, while the RCO group from **3** is eliminated during the course of reaction. Reactions with cyclic and nitrogen-hindered enaminones do not lead to pyrrole formation but occur by simple insertion of **2** to the Cα-H bond.

J. Heterocyclic Chem., **32**, 1355 (1995).

Introduction.

Stabilized ketocarbenes, often generated from catalyzed decomposition of α-diazocarbonyl compounds are of great synthetic utility [1]. These reactive species have been extensively used in cyclization processes where they act as key intermediates by promoting a series of intramolecular and intermolecular electrophilic attacks. These processes lead to the net result of ketocarbene insertion to several X-H bonds (X = C,N,S,O) and important compounds, mostly heterocyclics, have been synthesized by this approach [2].

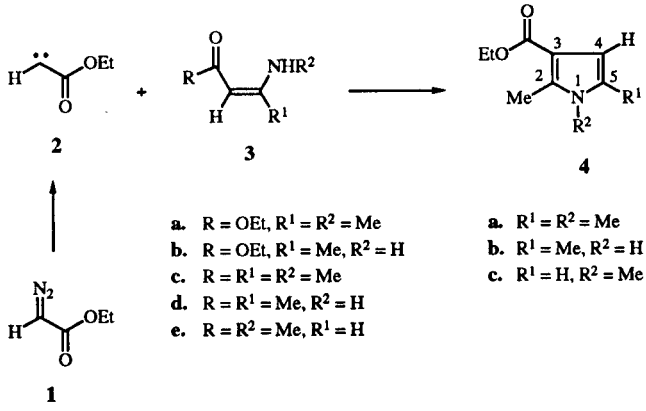
Enaminones also display a diverse and rich chemistry, being versatile compounds in synthesis [3]. These multifunctional reagents contain several centers subject to either nucleophilic or electrophilic attack, and their site selectivity is often controlled by the different configurations they can adopt, which is regulated mostly by the presence or not of intramolecular hydrogen bonds [4].

We have reported a new method of pyrrole synthesis by cupric acetylacetonate catalyzed reactions of several α-diazoketones with primary and secondary enaminones [5]. In view of these results, a study of the behavior in these reactions of the easily accessible carbethoxycarbene **2** has been carried out. If a similar mechanism were to take place in this case, these reactions would consist in an interesting synthetic pathway to 2-alkoxy or 2,3-dihydropyrroles.

Results and Discussion.

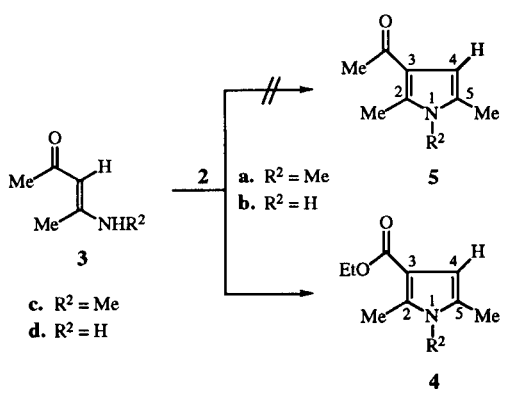
The reaction of **2**, produced by cupric acetyacetonate catalyzed decomposition [6] of ethyl diazoacetate (**1**), with the enaminoester **3a** leads to formation of a white solid product easily separated by column chromatography from the reaction mixture, which consisted mainly of polar, unidentified compounds. From the spectral data of the isolated compound, the unexpected formation of pyrrole **4a** was revealed (Scheme 1). In addition, reaction of enaminoester **3b** with **2** under similar conditions leads to formation of pyrrole **4b**.

Scheme 1



The results displayed in Scheme 1 show that the task of establishing a mechanism for this reaction is not simple. A preliminary look at the pyrrole structure suggests that the fragment EtOCO-C(3)-C(2)Me-NR_2 originates from the enaminoesters **3a-b**, while the origin of the C(4)H-C(5)Me fragment is more difficult to rationalize. The car-

Scheme 2



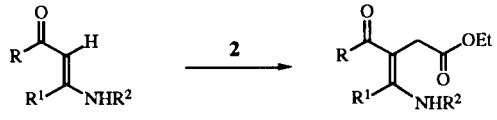
bene **2** might be considered as being involved in the formation of the C(4)H-C(5)-Me fragment. If the above assumptions about the origin of the structural fragments of these pyrroles are correct, reactions of **2** and the enaminoketones **3c-d** would lead to formation of pyrroles **5a-b**, as shown in Scheme 2.

However, when these reactions were carried out under similar conditions, the formation of the same pyrroles **4a** and **4b** was observed, respectively (Scheme 2).

These results give a clear indication that in these pyrroles the C(3)-CO_2Et structural fragment comes in fact from **2**, and not from the enaminones **3** as initially postulated, and that the fragment originating from the enaminones is, in fact, C(4)H-C(5)-R^1NR^2. The position of the C(3)-CO_2Et fragment in the pyrrole structure indicates that the initial step of the reaction mechanism occurs through an electrophilic attack of the carbene **2** at the α-carbon of the enaminones, leading to the net result of Cα-H insertion. This is the expected result since previous works show that the α-carbon is the preferred site for electrophilic attack of ketenes [4a] and ketocarbenes [5] to these enaminones, which are predominantly in the *Z-s-Z* form [4b]. To investigate the origin of the C(2)Me fragment, the reaction of **1** and the enaminoketone **3e** (no substituent at both α and β carbons) was performed. Work-up of the reaction mixture revealed pyrrole **4c** (Scheme 1) as the only product which could be isolated and identified. This result indicates that the C(2)-Me fragment originated from a second molecule of **2** and also confirms that the C(4)H-C(5)R^1NR^2 fragment of the pyrrole structure indeed comes from the enaminones **3**.

These results so far obtained show that the COR groups from **3** (Schemes 1 and 2) are eliminated during the course of reaction. If this is the case, a similar reaction for the cyclic enaminoketone **6** (Scheme 3) could, in principle, elucidate how this COR elimination occurs. This is so because the COR group should be retained in the product structure given the cyclic nature of **6**. However, compound **7** was the only product isolated and identified from the reaction mixture, a product formed by insertion of **2** to the Cα-H bond of **6**.

Scheme 3



6. R, $R^1 = CH_2C(Me)_2CH_2$; R^2 = H
3f. R = R^1 = Me; R^2 = ^{t}Bu

7. R, $R^1 = CH_2C(Me)_2CH_2$; R^2 = H
8. R = R^1 = Me; R^2 = ^{t}Bu

Similarly, the Cα-H insertion product **8** was the only compound isolated from the reaction mixture of the *N*-^{t}Bu substituted enaminoketone **3f** with **2** (Scheme 3). Ring formation in this case would require participation of the crowded *tert*-butylamine nitrogen in an intramolecular nucleophilic attack and therefore its low nucleophilicity appears to be keeping the reaction from proceeding to pyrrole formation. Both of these results are additional evidence suggesting that the first reaction step that leads to pyrrole formation for **3a-d** is indeed the insertion of **2** to the Cα-H bond of the enaminones.

Other examples of enigmatic mechanisms of pyrrole formation are described in the literature. Biellman and Callot [7], for instance, observed the thermal decomposition of dihydropyrimidic acids leads to formation of a pyrrole occurring by loss of $CHCO_2$ and CO_2Et (or CO_2 and $CHCO_2$Et) groups in a so-called obscure mechanism. Other processes leading to pyrrole formation by loss of COR groups are described in the literature and the driving force for those are always considered to be the formation of the stable, aromatic pyrrole ring [8].

Conclusion.

The reactions of carbethoxycarbene **2** with the acyclic enaminones **3** lead to the unexpected formation of pyrroles **4** through a sequence of reaction steps which is initiated by insertion of **2** to Cα-H bond, followed by a cyclization process that involves further reaction with **2**, and a final decarboxylation step which generates the aromatic pyrrole ring. The determination of the origin of all the fragments of the pyrrole structure could be achieved by changing the substituents in some specific positions of the enaminone structure, and from this information the reaction sequence just described could be proposed.

EXPERIMENTAL

The column chromatography was carried out with neutral alumina using mixtures of hexane, methylene chloride and methanol as eluents. The polarity of the starting eluent mixture (hexane/methylene chloride 10:1) was successively increased to a maximum of methylene chloride/methanol 10:1. Under these conditions the cupric acetylacetonate catalyst did not elute. The infrared spectra were obtained with a Perkin-Elmer 399B instrument, the band at 1601 cm^{-1} of a polystyrene film being used as the internal reference. The ^1H nmr spectra were obtained on a Bruker AW-80 or Varian XL-100 instruments using deuteriochloroform or carbon tetrachloride as the solvent and tetramethyl silane as the internal reference. The mass spectra were acquired using a Varian 311-A spectrometer at 70 eV ionization energy. The enaminones **3** and **6** [3] and ethyl diazoacetate (**1**) [9] were prepared according to reported procedures. Cupric acetylacetonate was purchased from Aldrich, dried at 110° for several hours and used without further purification.

General Procedure for the Reaction of Ethyl Diazoacetate **1** with Enaminones **3, 6**.

Ethyl diazoacetate (**1**, 171 mg, 1.5 mmoles), cupric acetylacetonate (100 mg) and the enaminone **3** or **6** (1.0 mmole) were dissolved in 25 ml of methylene chloride free of ethanol and this solution was sealed in a flask and heated up to 55-60° for 3 days, when infrared spectrum of the reaction mixture indicated total consumption of **1** (absence of the characteristic band at 2100 cm^{-1}). After evaporation of the solvent, the reaction mixture was submitted to column chromatography. The physical properties and spectral data of the identified reaction products are described below, together with the eluent mixture used when the corresponding product eluted from the chromatography column.

3-Carboethoxy-1,2,5-trimethylpyrrole (**4a**).

The compound was obtained as a colorless solid (25 mg and 50 mg, in the reaction with **3a** and **3c**, respectively), eluent, hexane/methylene chloride 7:3, mp 48-49° (lit [7] 48°); ir (potassium bromide): 1705, 1435, 1225, 1190, 1065, 775 cm^{-1}; ^1H nmr (deuteriochloroform): [7] δ 1.32 (3H, t, J = 7 Hz), 2.17 (3H, s), 2.48 (3H, s), 3.37 (3H, s), 4.23 (2H, q, J = 7 Hz), 6.23 (1H, s); ms: m/z (relative abundance) 181 (71), 152 (100), 136 (56), 108 (13), 107 (11), 67.5 (5), 67 (11), 65 (5), 56 (21).

3-Carboethoxy-2,5-dimethylpyrrole (**4b**).

The compound was obtained as a colorless solid (36 mg and 25 mg in the reaction with **3b** and **3d**, respectively), eluent, methylene chloride/hexane 1:1, mp 118-119° (lit [7] 118-119°); ir (potassium bromide): 3300, 1695, 1620, 1440, 1225, 1085, 805, 780 cm^{-1}; ^1H nmr (deuteriochloroform): [7] δ 1.32 (3H, t, J = 7 Hz), 2.17 (3H, s), 2.48 (3H, s), 4.25 (2H, q, J = 7 Hz), 6.20 (1H, m), 8.4 (1H, b); ms: m/z (relative abundance) 167 (82), 138 (100), 122 (76), 121 (7), 120 (9), 94 (14), 93 (12), 67 (10), 53 (6), 52 (5).

3-Carboethoxy-1,2-dimethylpyrrole (**4c**).

The compound (a colorless oil) eluted from the chromatography column (eluent, methylene chloride/hexane 5:1) together with ethyl maleate and fumarate (adducts of carbethoxycarbene **2**). They were eliminated by hydrolysis (reflux for 3 hours in 10% ethanolic solution of potassium hydroxide) followed by extraction of **4c** (25 mg) with methylene chloride; ir (neat): 1695, 1530, 1420, 1250, 1255, 1065 cm^{-1}; ^1H nmr (carbon tetrachloride): [10] δ 1.35 (3H, t, J = 7 Hz), 2.50 (3H, s), 3.53 (3H, s), 4.25 (2H, q, J = 7 Hz), 6.50 (2H, m); ms: m/z (relative abundance) 167 (65), 152 (6), 139 (10), 138 (80), 123 (9), 122 (100), 91 (14), 90 (11).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.52; H, 7.95; N, 8.19.

Ethyl 2-(2'-Amino-4'-dimethyl-6'-oxo-1'-cyclohexen-1'-yl)-ethanoate (**7**).

This compound was obtained as a colorless solid (18 mg), eluent, methylene chloride/methanol 99:1, mp 116-117°; ir (potassium bromide): 3400, 3235, 1720, 1655, 1560, 1545, 1425 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.04 (6H, s), 2.02 (3H, t, J = 7 Hz), 2.00 (2H, s), 2.04 (2H, s), 3.35 (2H, s), 4.08 (2H, q, J = 7 Hz), 5.05 (2H, b); ms: m/z (relative abundance) 225 (27), 180 (19), 179 (100), 153 (7), 152 (7), 123 (10), 96 (30), 69 (5), 68 (16), 67 (7).

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.12; H, 8.41; N, 6.01.

Ethyl 3-Acetyl-4-(*tert*-butylamino)-3-pentenoate (**8**).

This compound was obtained as a colorless oil in 15% yield, eluent, methylene chloride; ir (neat): 1730, 1590, 1365, 1285, 1235, 1190, 1155, 1025, 850 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.23 (3H, t, J = 7 Hz), 1.43 (9H, s), 2.03 (3H, s), 2.08 (3H, s), 3.13 (2H, s), 4.12 (2H, q, J = 7 Hz), 12.55 (1H, b); ms: m/z (relative abundance) 241 (16), 169 (5), 168 (40), 114 (5), 113 (7), 112 (100), 98 (6), 69 (9), 57 (18), 43 (18).

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.59; H, 9.53; N, 5.69.

Acknowledgments.

The authors thank the Research Support Foundation of the State of São Paulo (FAPESP) and the Brazilian National Research Council (CNPq) for financial support.

REFERENCES AND NOTES

[1] A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, **91**, 263 (1991).

[2a] A. Padwa, K. E. Krumpe, Y. Gareau and U. Chiachio, *J. Org. Chem.*, **56**, 2523 (1991); [b] D. F. Taber, M. J. Henessy and J. P. Louey, *J. Org. Chem.*, **57**, 436 (1992); [c] G. Maas, *Top. Curr. Chem.*, **137**, 77 (1987).

[3a] J. V. Greenhill, *Chem. Soc. Rev.*, **6**, 277 (1977); [b] V. G. Granik, *Russ. Chem. Rev. (Engl. Transl.)*, **53**, 383 (1984).

[4a] M. N. Eberlin, Y. Takahata and C. Kascheres, *J. Org. Chem.*, **55**, 5150 (1990); [b] M. N. Eberlin, Y. Takahata and C. Kascheres, *J. Mol. Struc. (Theochem)*, **207**, 143 (1990).

[5] M. N. Eberlin and C. Kascheres, *J. Org. Chem.*, **53**, 2084 (1988).

[6] Cupric acetylacetonate was added to lower the nitrogen loss decomposition temperature of ethyl diazoacetate (**1**). Formation of the carbene **2** is also evident in non-catalyzed, refluxing toluene conditions. In fact, the reaction of enaminoketone **3c** with **1**, in refluxing toluene (3 days), furnished the same pyrrole **4a** together with toluene insertion products (detected by gc/ms). This result shows that the presence of the catalyst does not affect the nature of the pyrroles obtained.

[7] J. F. Biellman and H. J. Callot, *Tetrahedron*, **26**, 4809 (1970). The pyrroles **4a** and **4b** display similar ^1H nmr spectra to those reported in this reference.

[8a] J. B. Paine III and D. Dolphin, *J. Org. Chem.*, **50**, 5598 (1985); [b] J. B. Paine III, J. R. Brough, K. K. Buller and E. E. Erickson, *J. Org. Chem.*, **52**, 3986 (1987).

[9] R. Adams and W. D. Langley, *Org. Synth. Coll. Vol.*, **1**, 355 (1941).

[10] A. R. Mattocks, *J. Chem. Soc., Perkin Trans. 1*, 896 (1978). The pyrrole **4c** displays similar ^1H nmr spectrum to that reported in this reference.