

$\beta$ -Substitution of Simple Pyrroles in Metal-assisted  
Reactions with Ethyl Diazoacetate

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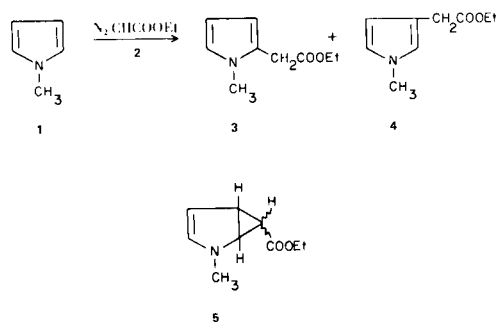
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The reaction of *N*-methylpyrrole with ethyl diazoacetate, assisted by copper bronze or copper powder, as described previously by a number of researchers, produces not only ethyl *N*-methylpyrrole-2-acetate (**3**), but also heretofore unrecognized ethyl *N*-methylpyrrole-3-acetate (**4**); the ratio of **3/4** was *ca.* 84/16. Promotion of this reaction with other transition metal catalysts furnished differing proportions of **3** and **4**, indicating that the metal is intimately involved in the substitution process. Certain agents, notably cupric fluoborate, cupric trifluoromethylsulfonate, palladous acetate, and  $(\pi\text{-C}_3\text{H}_5\text{PdCl})_2$ , were particularly active in this reaction and gave  $\beta$ -substitution to the extent of *ca.* 35-45%. Other pyrrole compounds, namely 1,2-dimethylpyrrole, 1,3-dimethylpyrrole, **3**, and pyrrole, were also found (in preliminary work) to undergo  $\beta$ -substitution in their reaction with copper carbenoids.

*J. Heterocyclic Chem.*, **14**, 177 (1977).

Sir:

The reaction of pyrrole derivatives with diazo compounds has been reported as a useful synthetic approach for functionalizing the  $\alpha$ -position of the pyrrole nucleus (1,2). In one of the more studied cases, the reaction of *N*-methylpyrrole (**1**) with ethyl diazoacetate (**2**) under elemental copper catalysis, ethyl *N*-methylpyrrole-2-acetate (**3**) has been recognized as the sole product (1a,1b). We wish to report, rather, that this process produces an isomeric by-product, identified as  $\beta$ -substituted ester **4**, and that this operation is capable of generating a considerable amount of **4** under the influence of appropriate transition metal catalysts.



Neat **2** (1 molar equivalent) was added drop by drop to a heated (100°) mixture of **1** and copper bronze (0.1

molar equivalent) with stirring. Heating was continued for a brief period and excess **1** was recovered by distillation *in vacuo*. The product was isolated by kugelrohr distillation (80° pot temperature/0.2 torr) and a viscous, dark residue remained. Analysis of the pale yellow distillate (*ca.* 40% yield based on **2**) by glc (6 ft x 1/8 in, 1.35% OV-17 on Chromosorb W AW/DMS column) revealed mainly two substances (84/16), which had essentially identical mass spectra: *m/e* (relative abundance) 168 (5), 167 (35), 95 (8), 94 (100), 93 (5), 53 (3), 42 (3) [major glc peak]. A similar product was obtained using copper powder or no added catalyst, but yields were slightly reduced (see Table). Other agents were tried in this reaction and the results are given the the Table.

A small quantity of the minor component was isolated from the cupric sulfate-promoted reaction by preparative glc and its <sup>1</sup>H nmr spectrum was recorded (carbon tetrachloride):  $\delta$  1.20 (t, 3H), 3.25 (s, 2H), 3.52 (s, 3H), 4.03 (q, 2H), 5.85 (narrow m, 1H, 4-*H*), 6.35 (m, 2H, 2- and 5-*H*). Comparison with the <sup>1</sup>H nmr spectral data for pure **3** (3), (carbon tetrachloride):  $\delta$  1.22 (t, 3H), 3.45 (s, 2H), 3.54 (s, 3H), 4.07 (q, 2H), 5.83 (narrow m, 2H, 3- and 4-*H*), 6.38 (narrow m, 1H, 5-*H*), clearly indicates that the by-product should be assigned structure **4**, alternative azabicyclo[3.1.0]hexane structure **5** being excluded (4). Hitherto, the only reported instances of  $\beta$ -substitution of

Table I

Results for the Reaction of **1** and **2** Using Various Promoting Agents (a)

Agent	Molar % Copper	Temperature	% <b>3</b> + <b>4</b> (b)	<b>3/4</b>
Copper bronze	10	100°	41 (c)	86/14 (c,d)
Copper powder	10	110°	31	81/19
		reflux	37	79/21
Cuprous chloride	2.5	80°	45	78/22
Cupric sulfate	2.5	80°	58	65/35
Cuprous oxide	2.5	100°	45	80/20
( $\pi$ -C <sub>3</sub> H <sub>5</sub> PdCl) <sub>2</sub>	1.5	35°	42	67/33
Palladous acetate	1.5	30°	35	65/35
Cupric trifluoromethylsulfonate	1.5	40°	61	59/41
Cupric fluoroborate	1.5	40°	63	57/43

(a) All experiments were performed with a 200% excess of **1**. (b) The yield is based on **2**. (c) Average of two experiments. (d) Glc analysis of the product mixture before workup showed the same isomer ratio.

pyrroles by means of diazo compounds were those (involving **2**) in which both  $\alpha$ -positions of the substrate were blocked by substituents (6).

The variation of the product distribution with the type of catalyst employed suggests that the reactive, electrophilic species in the copper-promoted reaction is a copper complex of **2** or of carbethoxycarbene. This adds to the body of other work which has provided evidence for the intermediacy of carbene-metal complexes in metal-assisted decompositions of diazo compounds (7). It should be noted that ( $\pi$ -C<sub>3</sub>H<sub>5</sub>PdCl)<sub>2</sub>, palladous acetate, cupric trifluoromethylsulfonate, and cupric fluoborate were extremely active promoting agents, functioning at comparatively low temperatures and with essentially no latency period (8). The increased amounts of  $\beta$ -substitution obtained with these salts (and with cupric sulfate) reflects the lack of discrimination intrinsic to the more reactive, intermediate carbenoids derived therefrom.

In preliminary work with 1,2-dimethylpyrrole, 1,3-dimethylpyrrole, pyrrole, and **3** as substrates, we have also observed significant amounts of  $\beta$ -substitution. We are currently pursuing an investigation of the effect of transition metal compounds on the reaction of diazo compounds with pyrrole derivatives in order to define the scope of this process and gain insight into the nature of the reactive intermediate.

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(2) Reactions of pyrroles with diazo compounds, in general, have been discussed briefly: see A. Gossauer, "Die Chemie der Pyrrole," Springer-Verlag, Berlin, 1974, pp. 126-128. These examples dealt primarily with elemental copper as a catalyst.

(3) The author wishes to thank Mr. J. Hortenstine for a sample of **3**, prepared from *N*-methylpyrrole-2-acetonitrile [W. Orth, L. Rappen and G. Busse, U. S. Patent 3,523,952 (1970); U. S. Patent 3,544,589 (1970)].

(4) Compounds of this type have been synthesized by the reaction of diazomethane and **2** with *N*-carbalkoxy-pyrroles (5).

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(8) Latency periods of 30 seconds to 3 minutes are typically observed in transition metal-promoted carbenoid reactions (see, e.g., reference 7b).