$C_{19}H_{14}N$, 256.1126), 255.1054 (22; $C_{19}H_{13}N$, 255.1048), 254.1008 (19; $C_{19}H_{12}N$, 254.0970).

Registry No. 10a, 78-93-3; **10b**, 96-22-0; **10c**, 108-10-1; **10d**, 120-92-3; **10e**, 103-79-7; **10f**, 590-50-1; **11**, 110-16-7; **12a**, 71700-53-3; **12b**, 71700-54-4; **12c**, 71700-55-5; **12d**, 71700-56-6; **12e**, 71700-57-7; **12f**, 71700-58-8; **13a**, 71700-59-9; **13b**, 71700-60-2; **13c**, 71700-61-3; **13d**, 71700-62-4; **13d′**, 71700-63-5; **13e**, 71700-64-6; **14a**, 71700-65-7; **14b**, 71700-66-8; **14c**, 71700-67-9; **14d**, 71700-68-0; **14e**, 71700-69-1; **21**, 71700-70-4; indole, 120-72-9; 3-methyl-2-butanone, 563-80-4.

Supplementary Material Available: Detailed mass spectral fragmentations of the compounds (14 pages). Ordering information is given on any current masthead page.

Carbenoid Chemistry. Reaction of Pyrrole Derivatives with Ethyl Diazoacetate[1]

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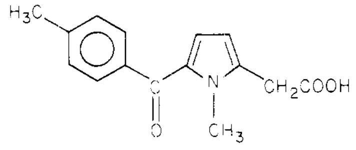
Reaction of *N*-methylpyrrole (NMP) with ethyl diazoacetate (EDA) produced monoacetate adducts **2** and **4**, with a wide range of copper promoting agents. Minor amounts of diacetate adducts (**20a–c**) were also formed (about one-tenth the amount of monoacetates). The relative amounts of **2** and **4** varied according to promoting agent (**2**/**4** ratio ranged from 16/1 to 3/2). The regiochemistry of the reactions served to characterize the relative reactivity of the metal–carbenoid reagents. The least discriminant agents were $Cu(OTf)_2$ and $Cu(BF_4)_2$, and the most discriminant ones (for α substitution) were certain copper(II) 1,3-diketone, salicylaldehyde, and salicylaldimine chelates (**5a**, **5c**, **6c**, **6g**, and **6h**). Certain copper(II) chelates of these classes also furnished optimal yields of **2** (**5g**, **6b**, **6d**, **6e**, **6g–i**, and **8**). Other pyrrolic compounds were also studied with a limited number of promoting agents [generally $Cu(acac)_2$, copper bronze, and/or $Cu(OTf)_2$]. Pyrrole gave 2- and 3-acetates (**13** and **14**), with no N-H insertion product **15**. *N*-Isopropylpyrrole gave 2- and 3-acetates, but *N-tert*-butylpyrrole gave only 3-acetate. With a specific promoting agent, the N-substituted pyrroles showed an increasing proportion of β substitution with increasing steric bulk of the N group (*tert*-butyl > isopropyl > methyl > hydrogen). Reaction of 1,2- and 1,3-dimethylpyrroles with EDA afforded mixtures of three isomeric monoacetates; the *C*-methyl substituent exhibited an ortho-directing influence. In the reaction of NMP with EDA, employing certain copper(I) and copper(II) halides, a carbethoxycarbene trimer, triethyl (*E*)-aconitate, was identified; this represents a "propene" trimerization pathway for $:CHCO_2C_2H_5$ as opposed to the more common "cyclopropane" pathway. On the basis of the variation of α/β isomer ratio with promoting agent and the substituent effects, the mechanism of the reaction of *N*-H and *N*-alkyl pyrroles with EDA is depicted as an electrophilic substitution (rather than insertion) process leading directly to acetate adducts (i.e., not involving distinct homopyrrole intermediates).

In connection with a search for new synthetic processes leading efficiently to tolmetin (**1**),[2] an important nonsteroidal antiinflammatory agent for the treatment of arthritis, we initiated a study of the reaction of *N*-methylpyrrole (NMP) with ethyl diazoacetate (EDA). This reaction, with copper metal as a promoting agent,[3] had been reported to afford **2** as the sole monoadduct.[4] However, a significant amount of another isomer, first suspected to be a product of double-bond insertion (viz., **3**) but later identified as acetic ester **4**, forms as well.[4] This outcome underscores a chemical dichotomy that exists in the reaction of π-excessive heterocycles with carbene entities. For instance, furan and thiophene undergo double-bond insertion to produce cyclopropane species,[5] whereas pyrrole undergoes C–H insertion[4-7] to give products formally derived by electrophilic substitution.



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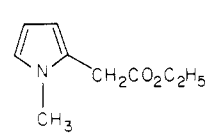

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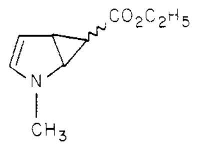

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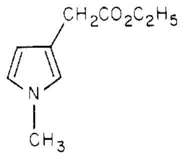

4

We have examined the reactions of simple pyrrole derivatives with EDA in the presence of transition metal promoting agents. Of particular interest in this work is the effect of metal agent and pyrrole substituents on the regiochemistry of the substitution reactions. In the course of this study, we hoped to find a means of optimizing the **2**/**4** ratio and total yield of **2** in the reaction of NMP and EDA.

Results

***N*-Methylpyrrole.** The reaction of NMP and EDA with the assistance of copper bronze or copper powder, as described by several research groups, produced acetic esters **2** and **4** in ratios (**2**/**4**) ranging from 84/16 to 79/21.[4] Promotion with different transition-metal agents afforded

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[1] Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, California, Aug 1976.

[2] J. R. Carson, D. N. McKinstry, and S. Wong, *J. Med. Chem.*, 14, 646 (1971). Tolmetin sodium dihydrate is sold by McNeil Laboratories under the registered tradename Tolectin.

[3] The term "promoting agent" is used to mean a material which effectuates or facilitates a chemical reaction even when employed in a much less than stoichiometric amount. The agent functions as a catalyst but may be chemically altered in the course of the reaction, whereas a true catalyst remains unchanged by the reaction that it induces.

[4] B. E. Maryanoff, *J. Heterocycl. Chem.*, 14, 177 (1977); U.S. Patent 4136097 (1979).

[5] V. Dave and E. W. Warnhoff, *Org. React.*, 18, 217 (1970).

[6] E. g., A. Gossauer, "Die Chemie der Pyrrole", Springer-Verlag, West Berlin, 1974, pp 126–8.

[7] Double bond insertion was reported for *N*-carbalkoxypyrrole, but this substrate is electronically perturbed, being more like a diene than a pyrrole (see Discussion).[8]

[8] (a) S. R. Tanny, J. Grossman, and F. W. Fowler, *J. Am. Chem. Soc.*, 94, 6495 (1972); (b) J. F. Biellman and M. P. Goeldner, *Tetrahedron*, 27, 2957 (1971).

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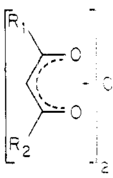
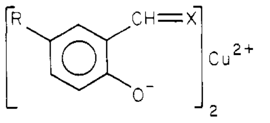
differing yields of total monoadduct and differing proportions of **2** and **4** (see Table I[9]), indicating an intimate involvement of the metal in the substitution process. Promoting agents $CuSO_4$, $Cu(BF_4)_2$, $Cu(OSO_2CF_3)_2$, $Pd[OC(O)CH_3]_2$, and $(\pi\text{-}C_3H_5PdCl)_2$, some capable of functioning around 25 °C, gave *β* substitution to the extent of 35–45%.

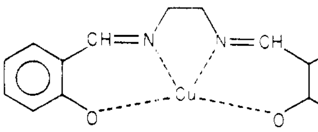
Salicylaldehyde, "salicylaldimine", and 1,3-diketone complexes of copper(II) (see **5–9**) were explored (Table II[9]). Some of these complexes gave especially favorable results either in increased purity of *α* isomer (**2**) or in overall yield of *α* isomer. Agents **5a**, **5c**, **6e**, and **6g–i** gave less than 10% *β* isomer contaminant; agents **5d**, **5g**, **6a–g**, **6i**, and **8** gave 50% or more total monoester (**2** and **4**). As classes, 1,3-diketonates and salicylaldimines tended to provide higher purity **2**, and salicylaldehydates afforded high yields of monoadduct mixtures. Mixed chelates **8** and **9** gave isomer ratios which are a compromise between the corresponding homogeneous copper agents (cf. **8** with **5a** and entry 12 of Table I; **9** with **5a** and entry 22 of Table I). Highest yields of **2** (total yield corrected for purity by GLC) were achieved with **5g** (44%), **6b** (48%), **6d** (47%), **6e** (46%), **6g** (47%), **6h** (44%), **6i** (47%), and **8** (48%) (see Table II).



5a, $R_1 = R_2 = CH_3$
b, $R_1 = R_2 = t\text{-}C_4H_9$
c, $R_1 = CH_3$; $R_2 = C_6H_5$
d, $R_1 = CH_3$; $R_2 = CF_3$
e, $R_1 = CH_3$; $R_2 = OC_2H_5$
f, $R_1 = R_2 = C_6H_5$
g, $R_1 = R_2 = CF_3$
h, $R_1 = CF_3$; R_2 = 2-thienyl



6a, R = H; X = O
b, R = Cl; X = O
c, $R = OCH_3$; X = O
d, $R = NO_2$; X = O
e, R = H; X = NH
f, R = H; X = NOH
g, R = H; $X = N\text{-}i\text{-}C_3H_7$
h, R = H; $X = NCH_2C_6H_5$
i, R = H; $X = N\text{-}4\text{-}ClC_6H_4$
j, $R = NO_2$; X = NH



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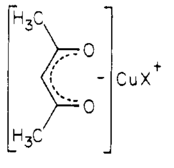
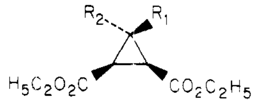
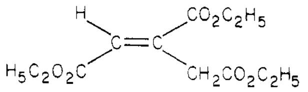


8, $X = OSO_2CF_3$
9, $X = OCH_3$



10, $R_1 = H$; $R_2 = CO_2C_2H_5$
11, $R_1 = CO_2C_2H_5$; $R_2 = H$



12

Salicylaldehydate and salicylaldimine complexes of copper(II) generally are square planar and possess a trans geometry.[10] Complex **6g** is an exception, having distorted (local) tetrahedral symmetry,[11] a factor which does not appear to affect the reaction outcome. Imposition of a cis-planar geometry, as in **7**, results in a decreased yield but no change in isomer ratio.

Table I. Reaction of NMP with EDA by Using Various Promoting Agents[a]

entry	agent	mol % agent	bath temp, °C	total yield, %	2/4 ratio
1	none		125	37	3.8
2	Cu powder	10	110	31	4.3
3[b]	Cu bronze	10	100	40	5.2
4	Cu bronze	2	100	30	4.6
5[c]	Cu bronze	10	105	38	3.8
6	Cu_2O	2.5	100	45	4.0
7	$CuSO_4$	2.5	80	58	1.9
8	$Cu(OAc)_2$	1.5	80	45	4.3
9	$Cu(NO_3)_2$	1.5	55	54	2.5
10	CuCN	2.5	70	43	3.2
11	$Cu(BF_4)_2$	1.5	50	66	1.2
12	$Cu(OSO_2CF_3)_2$	1.5	40	63	1.4
13	CuCl	1.5	75	48	4.0
14	$CuCl\cdot(EtO)_3P$	1.5	60	51	4.3
15	CuBr	1.5	60	27[d]	4.0
16	$CuBr\cdot(EtO)_3P$	1.5	65	34[d]	4.6
17	CuI	1.5	75	34[d]	4.3
18	$CuI\cdot(EtO)_3P$	1.5	65	27[d]	5.2
19	CuF_2	1.5	80	43	5.7
20	$CuCl_2$	1.5	75	42	4.6
21	$CuBr_2$	1.5	60	33[d]	4.3
22	$Cu(OCH_3)_2$	1.5	60	45	4.9
23	$Pd(OAc)_2$	1.5	30	35	1.9
24	$(\pi\text{-}C_3H_5PdCl)_2$	1.5	35	42	2.0
25	$DiphosNiCl_2$	1.0	90	13	2.0
26	ZnI_2	1.5	110	~3	
27	$LiClO_4$	2.5	110	15	
28	$[Rh(OAc)_2]_2$	1.5	80	e	
29	$[(C_6H_5)_3P]_3$-RhCl	1.0	80	0	
30	$AgBF_4$	1.5	100	0[f]	

[a] All reactions were performed in the same manner (scale, addition time, workup) unless otherwise noted. See Experimental Section for general procedure. [b] Two runs gave virtually the same results. [c] Exact repetition of literature: same reaction scale and addition time as reported by Rapoport; see ref 37a and H. Rapoport, C. G. Christian, and G. Spencer, *J. Org. Chem.*, 19, 840 (1954). [d] Amount of pyrrole adducts obtained by subtracting estimated amount of byproduct **12**. [e] Multitude of products by GLC; little of desired adducts. [f] No nitrogen evolved.

A series of halides was studied (Table I, entries 12–21). In contrast to copper(II) fluoride and chloride, $CuBr_2$ afforded triester **12**, a trimer of carbethoxycarbene,[12] which comprised about 20% of the distilled product. With copper(I), CuCl was normal, but CuBr and CuI afforded **12**, comprising 30–36% and 25% of the distilled product, respectively. Since the difference in results may have arisen from solid-state effects of the heterogeneous catalyst, homogeneous experiments were performed. Solubilization of CuCl, CuBr, and CuI with triethyl phosphite hardly altered the overall results of total yield, isomer ratio, or amount of byproduct. Structure **12**, rather than **10** or **11**,[12] was supported by GLC/MS, ^1H NMR, and ^{13}C NMR data and comparison with an authentic sample (esterification of (*E*)-aconitic acid[14]).

Considering all of the data, the reaction of NMP with EDA is insensitive to reaction temperature[15] and small

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(9) See supplementary material.

(10) (a) R. H. Holm, G. W. Everett, Jr., and A. Chakravorty, *Prog. Inorg. Chem.*, 7, 83 (1966); (b) for **6f**: M. A. Jarski and E. C. Lingafelter, *Acta Crystallogr.*, 17, 1109 (1964); (c) R. H. Holm and M. J. O'Connor, *Prog. Inorg. Chem.*, 14, 241 (1974).

(11) L. Sacconi and M. Ciampolini, *J. Chem. Soc.*, 276 (1964); H. Yokoi and A. W. Addison, *Inorg. Chem.*, 16, 1344 (1977). *α*-Branched *N*-alkyl groups generally induce a change in structure from square planar to nearly tetrahedral: see ref 10c. The *N*-cyclohexyl analogue of **6g** is, however, planar: H. Tamura, K. Ogawa, A. Takeuchi, and S. Yamada, *Chem. Lett.*, 889 (1977).

(12) The trimer was first suspected to be **10** or **11**. Treatment of it with ethanolic $NaOC_2H_5$ caused no change, excluding **11**. An authentic sample of **10**[9,13] ruled out this possibility.

(13) (a) G. B. Payne, *J. Org. Chem.*, 32, 3351 (1967); A. W. Johnson and R. T. Anell, *ibid.*, 33, 1240 (1968). (b) Samples of **10** from the reaction[13a] of $(CH_3)_2S{=}CHCOOC_2H_5$ and diethyl fumarate or maleate are contaminated by **12** (10–15%), a fact heretofore unnoticed.[9]

(14) "The Merck Index", M. Windholz, Ed., Merck and Co., Rahway, NJ, 1976, p 113.

Table II. Reaction of NMP with EDA by Using 1,3-Diketone and Salicylaldehyde Complexes of Copper(II)

agent	mol % agent	bath temp, °C	total yield, %	2/4 ratio
5a[a]	1.5	50	36	10.6
5a	0.5	50	34	14.2
5a[b]	1.5	55	42	11.5
5c	1.5	55	44	9.0
5c[b]	1.5	55	45	10.5
5d	1.5	55	54	3.8
5g	1.5	55	57	3.5
5g[b]	1.5	55	57	4.1
6a	1.5	55	54	4.9
6b	1.5	55	60	4.0
6c	1.5	55	51	4.9
6d	1.5	55	63	2.8
6e	1.5	80[c]	50	11.0
6f	1.5	70[c]	51	4.5
6g	1.5	50[d]	50	16.9
6h	1.5	55[e]	47	15.7
6i	1.5	60[d]	52	10.1
6j	1.5	60	44	5.7
7	1.5	100	42	8.1
8	0.5	60	58	4.3
9	1.5	55	37	9.0

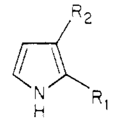
[a] Average of two identical experiments. [b] Catalyst purified by sublimation. [c] Reaction would not initiate at 60 °C. [d] Five-second delay before nitrogen evolution. [e] Three-minute delay before nitrogen evolution.

Table III. Reactivity Scale for $CuX_n \cdot N_2CHCOOC_2H_5$ Based on 2/4 Isomer Ratios

class of reactivity	class of promoting agent
1	fluoborate, triflate
2	sulfate
3	nitrate, cyanide, 5-nitrosalicylaldehydate
4	acetate, halides, Cu(0), fluorinated 1,3-diketonates, alkoxide, mercaptide, acetylide, oxide, salicylaldehydates, 5-nitrosalicylaldimine
5	1,3-diketonates, salicylaldimines

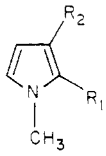
changes in the amount of promoting agent. However, the reaction is very sensitive to the type of agent used, the absence of which (entry 1, Table I) leads to a very sluggish reaction. Several metals other than copper or palladium (nickel, rhodium, zinc, silver, and lithium) were ineffective in promoting this reaction (Table I). The variation in α/β isomer ratio permits establishment of a casual relative reactivity scale (Table III), which will be discussed later.

Pyrrole. The reaction of pyrrole with EDA using copper bronze has been reported by several groups to give only α substitution (see **13**).[16] We studied this reaction with three agents representing the range of reactivity obtained with NMP: $Cu(acac)_2$ (**5a**), copper bronze, and copper(II) triflate (Table IV). Two isomeric monoadducts were detected in each reaction distillate by GLC/MS. ^1H NMR integration of the pyrrole vinyl proton resonances was consistent with the GLC isomer ratios if the isomers were **13** and **14**, N-H insertion product **15** being excluded. ^1H NMR chemical shifts for the CH_2 signals of the two isomers in the copper triflate reaction product agreed with this assignment, and no peak corresponding to the CH_2 signal of authentic **15** was evident. Further confirmation



13, $R_1 = CH_2CO_2C_2H_5$; $R_2 = H$
14, $R_1 = H$; $R_2 = CH_2CO_2C_2H_5$

15, R = $CH_2CO_2C_2H_5$
16a, R = isopropyl
b, R = *tert*-butyl
c, R = phenyl



17a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = 4\text{-}ClC_6H_4C(O)$; $R_2 = H$

of **13** and **14** was provided by a lanthanide-induced shift (LIS) study with $Eu(fod)_3$[17] on the ca. 3:1 mixture from the $Cu(OTf)_2$ reaction. Thus, N-H insertion is negligible.

Table IV. Reaction of Pyrrole with EDA

agent	total yield,[a] %	13/14 ratio	NMP 2/4 ratio
$Cu(acac)_2$	53	~17	11-14
copper bronze	42	~11	4-5
$Cu(OSO_2CF_3)_2$	52	2.7	1.4

[a] Corrected for the presence of byproducts.

Table V. Reaction of N-Substituted Pyrroles with EDA[a]

pyrrole	agent	total yield of monoacetates, %	α/β ratio
16a	$Cu(acac)_2$	30	1.5
16a	$Cu(OTf)_2$	20	0.85
16b	$Cu(acac)_2$	34	<0.02
16c	$CuCl \cdot (EtO)_3P$	less than 2	
16c	$Cu(OTf)_2$	~5	0.5[b,c]
16c	copper bronze	trace of adduct[c]	
16c	$Cu(acac)_2$	trace	

[a] Reactions with $Cu(acac)_2$ at 60-65 °C and with $Cu(OTf)_2$ at 35-40 °C. [b] A ratio of 2-/3-isomer (isomers confirmed by GLC/MS) of 0.6 was indicated by GLC (column B). The ratio of 0.5 was determined by integration of the CH_2CO resonances in $Eu(fod)_3$-shifted ^1H NMR spectra, which also served to identify the two isomers (the CH_2CO resonance of the 3-isomer undergoes a greater relative shift; see ref 53). The CH_2CO chemical shifts without added $Eu(fod)_3$: 2-isomer, δ 3.57; 3-isomer δ 3.60. [c] Monoacetates were detected by mass spectroscopy of the product mixture.

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(15) Many reactions exhibited various induction periods (from 5 s to 3 min) depending on the promoting agent and the initial temperature. In certain instances, the temperature was elevated initially above the reaction temperature shown in order to reduce the induction time and then returned to the reaction temperature after nitrogen evolution was first witnessed. Occasionally, small variations in isomer ratio for a particular reaction were observed for different scales (e.g., 10 mmol vs. 0.5 mol), which may be related to temperature control.

(16) (a) C. D. Nenitzescu and E. Solomonica, *Chem. Ber.*, **64**, 1924 (1931); (b) W. Kutscher and O. Klamerth, *Z. Physiol. Chem.*, **289**, 229 (1952); G. M. Badger, J. A. Felix, and G. E. Lewis, *Aust. J. Chem.*, **20**, 1777 (1967); L. Mandell and E. C. Roberts, *J. Heterocycl. Chem.*, **2**, 479 (1965); J. Schnekenburger and E. Breit, *Arch. Pharm. (Weinheim, Ger.)*, **310**, 153 (1977); T. R. Govindachari, T. G. Rajagopalan, and N. Viswanathan, *J. Chem. Soc., Perkin Trans. 1*, 1161 (1974).

(17) R. E. Sievers, Ed., "NMR Shift Reagents", Academic Press, New York, 1973.

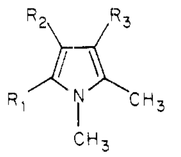
Methylation of a mixture of 13 and 14 with KH/CH_3I produced a mixture of 2 and 4.

The α/β isomer ratios for the pyrrole reactions and for the NMP reactions show the same trend. The relatively larger amounts of α isomer in the pyrrole cases may be due to diminished steric hindrance to α attack by having hydrogen on the ring nitrogen atom in lieu of a methyl group.

Other N-Substituted Pyrroles. To probe the steric effects of the nitrogen substituent further, *N*-isopropyl- and *N*-*tert*-butylpyrroles **16a** and **16b** were subjected to the EDA reaction (see Table V). The large increase in β vs. α substitution for **16a**, and more so for **16b**, clearly illustrates the sensitivity of the carbenoid reaction to steric factors. This steric influence may militate against initial formation of a fleeting cyclopropyl intermediate (cf. 3) followed by ring opening to acetic esters in favor of an electrophilic substitution mechanism (see Discussion). A similar trend in α/β isomer ratios was reported for the Vilsmeier–Haack formylation of N-substituted pyrroles, an electrophilic substitution process.[18]

N-Phenyl derivative **16c** did not readily undergo the EDA reaction. Unreacted starting material was recovered, and the yield of acetic esters was less than 5%. The acetic esters were identified by GLC/MS and the α/β isomer ratio was estimated (see Table V). No evidence for an azabicyclo[3.1.0]hexane compound[8a] was found by ^1H NMR. The EDA reaction appears to be very sensitive to electronic deactivation of the pyrrole nucleus, compared to, for example, Vilsmeier–Haack formylation,[18] possibly because of side reactions of the short-lived carbenoid species.

C-Substituted Pyrroles. Pyrroles substituted by methyl groups, **17a** and **17b**, were examined in the EDA reaction to determine the effect on the regiochemistry of carbenoid substitution (Table VI). From the isomer distributions for **17a** and **17b** (q.v. **18** (**a**/**b**/**c**) and **19** (**a**/**b**/**c**) in Table VI), it is evident that the carbenoid substitution is directed to positions α to the *C*-methyl groups. For **17a** this ortho effect enhances β substitution relative to NMP, but **18a** still predominates.[19a] For **17b** the ortho effect overcomes the steric hindrance involved with substitution at the 2-position (q.v. **19b**). Electrophilic substitution of pyrroles is normally directed to positions α to alkyl substituents on the carbon framework.[6,19b]



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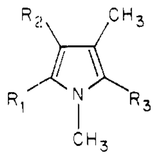

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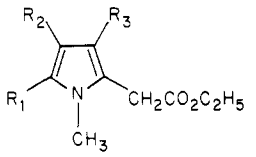

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a, $R_1 = CH_2CO_2C_2H_5$; $R_2 = R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = CH_2CO_2C_2H_5$
c, $R_1 = R_3 = H$; $R_2 = CH_2CO_2C_2H_5$

The reaction of **17c** with EDA was investigated since this process (with methyl instead chloro) represents a potentially useful route to tolmetin (1). A negligible amount of adduct was formed with CuCl·$(C_2H_5O)_3P$. With $Cu(OTf)_2$ a small amount (ca. 5%) of adducts was produced, but the major isomer in the mixture was ethyl *N*-methyl-5-(*p*-chlorobenzoyl)pyrrole-3-acetate, rather than the desired 2-acetate, related to tolmetin (1) (Table VI).

Table VI. Reaction of C-Substituted Pyrroles with EDA

pyrrole	agent	total yield of monoacetates, %	product (ratio, a/b/c)
17a	$Cu(acac)_2$	34	18 (25/6/1)
17a	$Cu(OTf)_2$	64	18 (2/1/1)
17b	$Cu(acac)_2$	65	19 (4/2/1)
17b	$Cu(OTf)_2$	74	19 (1.3/1/1)
17c	CuCl·$(EtO)_3P$	trace	
17c	$Cu(OTf)_2$	~5	[a]
2	$Cu(acac)_2$	60	20 (16/3/1)[b]
2	$Cu(OTf)_2$	56	20 (2.6/1/1)[b]

[a] The product was a mixture of three isomers: ethyl 1-methyl-5-(*p*-chlorobenzoyl)pyrrole-2-acetate (4 molar equiv), -3-acetate (8 molar equiv), and -4-acetate (1 molar equiv) [GLC; GLC/MS; TLC and ^1H NMR comparison with authentic samples of 2-acetate[2] and 3-acetate (J. A. Meschino and W. A. Szabo, unpublished work)]. ^1H NMR (mixture) δ 3.47 (s, CH_2CO, 3-acetate), 3.73 (s, CH_2CO, 2-acetate), 4.00 (s, NCH_3), 4.18 (q, OCH_2, 3-acetate), 4.23 (q, OCH_2, 2-acetate), 6.17 (d, J = 4 Hz, 3-H of 2-acetate), 6.67 (d, J = ~2 Hz, 3-acetate), 6.70 (d, J = 4 Hz, 4-H of 2-acetate), 6.97 (d, J = 1.5 Hz, 3-acetate); ^1H NMR (authentic 2-acetate) δ 3.68 (s, 2), 3.94 (s, 3), 4.20 (q, 2), 6.10 (d, 1, J = 4 Hz), 6.63 (d, 1, J = 4 Hz); ^1H NMR (authentic 3-acetate) δ 3.40 (s, 2), 4.02 (s, 3), 4.21 (q, 2), 6.68 (d, 1, J = 1–2 Hz), 6.97 (d, 1, J = 1–2 Hz).

[b] Ratio corresponds to 2,5-diacetate/2,3-diacetate/2,4-diacetate; the 2,3- and 2,4-diacetates were tentatively assigned by an ^1H NMR LIS study with $Eu(fod)_3$.[9]

Reactions of **2** with EDA were performed by using $Cu(acac)_2$ and $Cu(OTf)_2$ (Table VI). The predominant product was 2,5-diacetate **20a** (vinyl proton singlet at δ 5.98).[16a,20] The α/β proton ratios for the $Cu(acac)_2$ and $Cu(OTf)_2$ reactions, from integration of ^1H NMR spectra of product mixtures, were consistent with the composition from GLC analysis (Table VI). The isomer ratios (**20a**/**20b**/**20c**) in the reaction of **2** with EDA are analogous to ratios (**18a**/**18b**/**18c**) obtained in the reaction of **17a** with EDA. Thus, a polar alkyl substituent has only a minor effect on the regiochemistry of substitution. In two reports[16a,20b] on the reaction of **2** with EDA using copper bronze, the product (alleged to be **20a**) probably contained isomeric contaminants **20b** and **20c**.

In the reactions of NMP and EDA, monoacetate products **2** and **4** can react further with EDA to give diacetates. This side reaction is generally minor (5–10% based on EDA; amount of diacetates <0.1 of the amount of monoacetates) but, at times, constitutes as much as 15% (e.g., see Large-Scale Preparation of **4** in the Experimental Section). If the reactivities of **2** and **4** with EDA were substantially different, then a significant amount of side reaction could have an influence on the **2**/**4** isomer ratios. Since a large difference in reactivity could make the measured **2**/**4** isomer ratios (Tables I and II[9]) an inaccurate gauge of regiochemistry in the direct substitution of NMP, we evaluated the relative reactivities of **2** and **4** with EDA in competition experiments. A mixture of **2** and **4** (2 mol equiv; **2**/**4** ratio = 2.0) was reacted with EDA (1 mol equiv) by using $Cu(acac)_2$, and also by using $Cu(OTf)_2$. The reaction mixtures were analyzed by GLC, before workup, to determine the relative amounts of recovered (unreacted) **2** and **4**. The $Cu(OTf)_2$ experiment showed a final **2**/**4** ratio of 1.7, and the $Cu(acac)_2$ experiment showed a ratio of 1.9.

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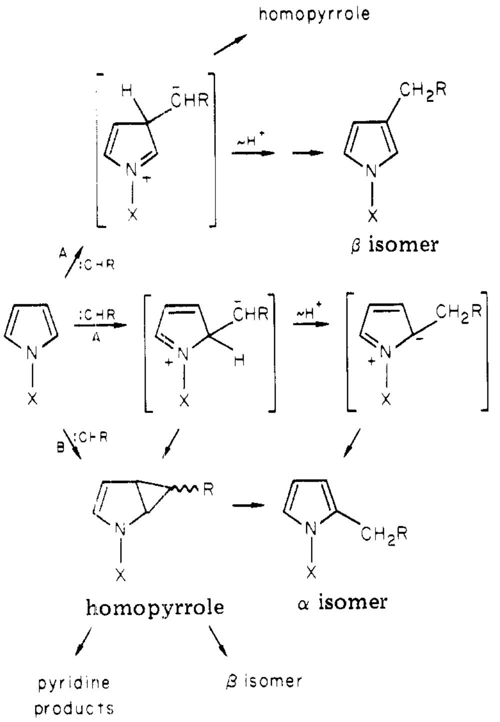
Scheme I



Pathway A, substitution; pathway B, addition

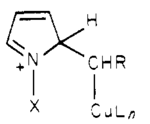
Thus, the reactivities of 2 and 4 with EDA are not different enough under usual reaction conditions, employing two copper(II) promoting agents, to cause the isomer ratios in Tables I and II to depart from those of direct substitution.

Discussion

The reaction of diazoacetic esters with π electronic systems has received a great deal of attention.[5,21] In the case of benzenoid compounds, norcaradiene derivatives are first formed and subsequently suffer valence tautomerism to cycloheptatriene carboxylates. In contrast, polynuclear aromatic compounds give stable double-bond-insertion products, cyclopropane carboxylates. In general, additions to benzenoid systems require highly reactive, and indiscriminant, thermally or photochemically generated carbenes,[5,21] whereas additions to polynuclear systems can also occur under conditions of metal "catalysis".

π-Excessive heteroaromatic compounds react readily with diazoacetic esters (and other carbenic species under copper catalysis). Heterocycles containing oxygen and sulfur generally give cyclopropanes (by *addition*),[5,21] which may undergo subsequent fragmentation (especially for oxygen compounds).[22] On the contrary, heterocycles containing nitrogen, which are not perturbed electronically into behaving like dienes by strong electron withdrawing groups on nitrogen,[8,22d] give alkylated derivatives (by *substitution*).[4-6] Cyclopropane derivatives have never been observed or implicated in carbenic reactions of pyrroles and indoles lacking nitrogen substitution that depletes their (hetero) aromaticity.[4-6,22d] We thus address the question of reaction mechanism.

Mechanistic Aspects. Scheme I depicts the two possible routes, "substitution" and "addition", leading to α and β pyrrole acetic esters.[23] The intermediate zwitterionic species may be associated with the metal of the promoting agent, as in **21**. An analogous, organomercurial



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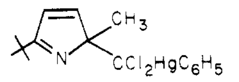

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adduct, **22**, is formed in the reaction of phenyl(trichloromethyl)mercury(II)/NaI, a dichlorocarbenoid source, with 2-methyl-5-*tert*-butylpyrrole.[24]

When X = acyl,[8] stable homopyrroles are formed, but when X = H or alkyl, only alkylpyrroles are formed. In the latter instance, the addition route would proceed through a thermally unstable homopyrrole, and the substitution route would not. Since cyclopropanation with *N*-acylpyrroles does not require that cyclopropanes also serve as intermediates with *N*-H and *N*-alkyl compounds, one may ask: Are unobserved homopyrroles actually involved in the carbenoid reactions of *N*-H and *N*-alkylpyrroles?

For homopyrroles to be intermediates, they must be able to rearrange to alkylpyrroles. However, thermal fragmentation of homopyrroles (X = acyl, $T > 250$ °C) affords *dihydropyridine* products.[8] On the other hand, copper(I) can induce thermal conversion of a homopyrrole (X = acyl, $T = 150$ °C for 8 h) to an α-alkylpyrrole.[8a] Thus, the mechanistic question remains unanswered by reference to the chemical literature. Our results favor an electrophilic substitution process.

If **3** were an unstable intermediate in the reaction of NMP and EDA, then it would have to fragment in two different ways, giving **2** and **4**; the observed regiochemistry would be a consequence of this fragmentation. The variation of isomer distribution with metal promoting agent (Tables I and II) works against the intermediacy of **3**; the influence of promoting agent on regiochemistry is more compatible with an electrophilic substitution process in which the reactivity of the electrophile is modified by coordination (or interaction) with the metal species. The reactivity index (Table III; see next subsection) shows a trend whereby the more reactive, less discriminant, copper carbenoids have anions derived from stronger acids (e.g., $BF_4 \approx OSO_2CF_3 > SO_4 > NO_3 >$ halide $\gg$ acac), which are more weakly coordinating ligands. The copper carbenoid reagent may constitute, at least in part, a species such as $X^-(Cu)^+CHCO_2C_2H_5$, wherein the anion (X) modulates the electrophilicity of the acetate carbon.

The steric effect of the nitrogen substituent on regiochemistry ($H < CH_3 < i\text{-}C_3H_7 < t\text{-}C_4H_9$) reinforces this point of view. It is unlikely that fragmentation of an *N*-H homopyrrole analogous to **3** would give >90% α isomer, while fragmentation of an *N*-*tert*-butyl homopyrrole would give >95% β isomer. However, a bimolecular electrophilic substitution reaction would show steric effects of this kind (cf. formylation results[18] and other reactions of *N*-R pyrroles with electrophiles[19b]).

Reactivity Index for Copper Carbenoids. The isomer distribution data obtained in the reaction of NMP with EDA using copper agents permits the organization of a relative reactivity scale for the copper–carbenoid reagents

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(Table III). Product-"catalyst" dependencies in transition metal promoted reactions of diazo compounds have been reported by other researchers,[25] and in some cases reactivity patterns can be perceived.

Simple pyrroles generally are much more reactive toward electrophiles at the α position because the intermediate heteroarenium ion from α attack is more stable than that from β attack.[6,19b] A more reactive carbenoid electrophile will generally be less discriminant and so furnish more β substitution (Hammond postulate).[26] Five categories of reactivity are represented in Table III. At the ends of the spectrum, class 1 gave an α/β ratio of ca. 3/2 and class 5 gave a ratio of 15/1 to 7/1. The results suggest that the reactive carbenic species is intimately involved with the copper and the anionic ligands in a coordination complex.

The reactivity behavior of the metal agents in the NMP/EDA reaction could be extrapolated to other, nonpyrrolic substrates. This is valid for the work of Salomon and Kochi with olefins where $Cu(OTf)_2$ and $Cu(BF_4)_2$, compared to $(CH_3O)_3PCuCl$, $Cu(acac)_2$, and $CuSO_4$, generated much more reactive copper carbenoids.[25c] However, the reactivity of the diverse copper (metal) carbenoids in the NMP/EDA reaction will not necessarily correspond to reactivity with other types of substrates. Caution in making the extrapolation is indicated since many examples exist where a promoting agent gives a certain result with one type of substrate but a different result with another.[5,25] Similar reactivity properties for copper carbethoxy carbenoids were observed with the various pyrrolic substrates in our study.

Carbenoid Intermediate. Diazoalkanes decompose in the presence of metal halides and other Lewis acids (e.g., $CuCl$, $FeCl_2$, BF_3, $HgCl_2$, $PdCl_2$) evolving nitrogen (eq 1).

$$R\bar{C}H\text{-}N_2^+ \xrightarrow{MX_n} RCXH\text{-}MX_{n-1} + N_2 \qquad (1)$$

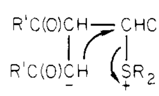
When a metal is involved, an organometallic species is generated, which in certain cases (e.g., $ZnCl_2$) is an α-haloalkyl derivative (eq 1). Depending on the metal, the organometallic intermediate may or may not exhibit carbenoid reactivity.[27]

Copper, in its zerovalent, monovalent, and divalent oxidation states,[28] has been especially effective in promoting the decomposition of diazoalkanes and in providing species which possess carbenoid reactivity. Although organocopper intermediates have never been directly observed, a vast body of evidence supports their existence.[21,26c,27,29] But the fact that there is direct interaction between the carbenic precursor and the copper entity in the product-forming step offers no information about the structural characteristics of the carbenoid complex. The intermediate involved in product determination may be a copper-diazoalkane complex (nitrogen intact), examples of which have been reported for transition metals other than copper,[30] or a copper-carbene complex (nitrogen evolved), many of which have been reported for transition metals other than copper.[27b,31]

The influence of the counterion on the copper-promoted reaction of NMP with EDA may reflect on the carbenoid intermediate. Since anions derived from stronger acids seem to afford more reactive (more electrophilic) carbenoids, a structure with accentuated carbocationic properties may play an important role (the electron-deficient carbon would be directly modulated by the properties of the anion).

Formation of Triethyl Aconitate (12). The formation of triethyl (*E*)-aconitate (**12**) in the reaction of NMP with EDA specifically occurred with CuBr, $CuBr_2$ and CuI; no normal dimeric products[32] (maleate and fumarate) were present (GLC). Diethyl maleate and fumarate were produced when NMP was replaced by an inert solvent in the CuBr/EDA reaction. This suggests that NMP participates in the mechanism producing **12**: NMP may be π coordinated or covalently bound to the copper carbenoid or diazoacetate complex.

Trimerizations of diazo compounds during their decomposition have been reported, but cyclopropane derivatives are generally produced.[22d,25e,25k,33] Decomposition of diazo ketones with copper agents in the presence of organic sulfides generates triacylcyclopropanes (trimers),[33] by a process involving intermediate sulfur ylides.[34] Only small amounts of dimeric olefins were observed, while the yields of cyclopropanes were relatively high, in analogy to our observations. These results were explained on the basis of intermediate **23**, which collapses by intramolecular S_N2 displacement of R_2S. Perhaps, a related zwitterionic intermediate containing NMP, such as **24**, is involved in the formation of **12**, wherein intramolecular proton transfer



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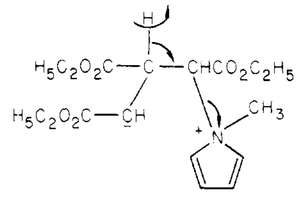

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is succeeded by Hofmann elimination.[35] Triethyl (*E*)-aconitate is produced in the CuCl-induced decomposition of EDA in the presence of alcohols, along with diethyl maleate and fumarate.[36]

The formation of "propene" trimers in the decomposition of diazoacetic esters[5,21] (and other diazo compounds[27b,32b]) has not received recognition in the chemical literature. This viable reaction pathway may be associated with interaction of a metal carbenoid and a hard Lewis base (ether oxygen,[36] amine nitrogen) to give an onium species and with special properties of the metal promoting agent. Interaction of a metal carbenoid with a soft Lewis base (sulfide sulfur) to give an onium species directs the course of trimerization toward cyclopropanes.

Conclusions

In contrast to the belief expressed in the chemical literature that the reactions of *N*-methylpyrrole (NMP) and pyrrole with ethyl diazoacetate (EDA) using copper(0) give only 2-acetic ester, we have found that these reactions also produce 3-acetic ester.[4] Study of a wide variety of promoting agents in the reaction of NMP with EDA revealed that the 3-acetic ester isomer is always generated, in some cases to the extent of 40%.

The relative amounts of 2- and 3-acetic esters were dependent on the promoting agent. Maximum β substitution occurred with $Cu(BF_4)_2$ and $Cu(OTf)_2$, and minimum β substitution occurred with $Cu(acac)_2$ and certain Cu(II) salicylaldimine complexes. The observed regioselectivity should be a manifestation of the relative reactivity of the carbenoid reagents, and so was used to organize a rough reactivity index.

The mechanism of reaction of NMP (and other *N*-H and *N*-alkyl pyrroles) with EDA is suggested to not involve distinct homopyrrole intermediates. The results are rationalized adequately by a direct electrophilic substitution process.

The discovery of triethyl (*E*)-aconitate (**12**), a trimer of carbethoxycarbene, in certain reactions of NMP and EDA leads to the recognition of a "propene" trimerization pathway, which has received little attention in the chemical literature.

Finally, the reaction of NMP with EDA is a viable process for preparation of **2**, en route to tolmetin (**1**), providing that special copper(II) chelates are employed as promoting agents. The preferred agents for highest yield of **2** are **5g**, **6b**, **6d**, **6e**, **6g**–**i**, and 8, and those for minimum production of byproduct 4 are **5a**, **5c**, **6c**, **6g**, and **6h**.

Experimental Section[9]

General. Infrared (IR) spectra were recorded on Perkin-Elmer 727B, 521, or 283 spectrophotometers (s = strong, m = medium, and w = weak). Proton nuclear magnetic resonance (^1H NMR) spectra were determined on Perkin-Elmer EM-360 (60 MHz) or R32 (90 MHz) spectrometers using $CDCl_3$ as solvent, unless otherwise noted, and tetramethylsilane (Me_4Si) as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, brs = broadened singlet, m = multiplet). Mass spectra (electron impact) were obtained on a Hitachi Perkin-Elmer RMU-6E or a Finnigan GC-MS-DS Model 9500-3300-6100 instrument at an ionizing voltage of 70 eV, unless otherwise noted. Exact mass determinations (electron impact) were performed at 70 eV on an AEI MS-902 double-focusing, high-resolution mass spectrometer equipped with a Digital Equipment Corp. PDP 8/I computer (at The Pennsylvania State University) with appropriate mass markers for references. Carbon-13 NMR spectra were recorded on a JEOL FX60Q spectrometer system (15.00 MHz) or on a JEOL JNM-PS-100 high-resolution spectrometer (25.035 MHz) equipped with a Nicolet Instrument Corp. computer (at The Pennsylvania State University) in $CDCl_3$; chemical shifts are reported in ppm downfield from Me_4Si. Both proton noise decoupled and off-resonance decoupled ^{13}C spectra were determined; only noise-decoupled data are reported. GLC analyses were performed on a Perkin-Elmer 3920B instrument with a flame-ionization detector, equipped with a Hewlett-Packard Model 3352B data system and Hewlett-Packard 18652 A A/D converter. The following glass columns were employed: column A, 6 ft × $^1/_8$ in., 1.35% OV-17 on Chromosorb W AW/DMS (100/120 mesh); column B, 6 ft × $^1/_4$ in., 1.35% OV-17 on Chromosorb W AW/DMS (80/100); column C, 6 ft × $^1/_8$ in., 3% OV-225 on Chromosorb W HP (100/120); column D, 8 ft × $^1/_8$ in., 1% Carbowax 20 M on Chromosorb W AW/DMS (100/120); column E, 6 ft × $^1/_8$ in., 3% SE-30 on Chromosorb Q (100/120); column F, 6-ft version of column D; column G, 6 ft × $^1/_4$ in., 3% OV-17 on Chromosorb Q (100/120). Boiling and melting points are uncorrected. All experiments involving the reaction of EDA and pyrroles were conducted under a dry nitrogen atmosphere.

Materials. *N*-Methylpyrrole (Aldrich Chemical Co.) was distilled from CaH_2, and the constant-boiling center cut was collected and stored under nitrogen at 5 °C. Commercial pyrrole was distilled, and the constant-boiling center cut was collected and stored under nitrogen at −20 °C. 1,2-Dimethylpyrrole (**17a**) was prepared from *N*-methylpyrrole-2-acetic acid.[37] *N*-Isopropyl- (**16a**)[18] and *N*-*tert*-butylpyrrole (**16b**)[18] were prepared from 2,5-dimethoxytetrahydrofuran.[18,38] Ethyl diazoacetate (EDA) was prepared by nitrosation of ethyl glycinate hydrochloride,[25l] and the crude yellow product was distilled (**Caution**: explosion hazard) at 20 torr (ca. 45 °C) to furnish purified yellow liquid (73% yield, excellent ^1H NMR spectrum). For large-scale experiments, EDA purchased from Aldrich Chemical Co. (containing 5.5 mol % methylene chloride by ^1H NMR) was used. Many of the metal promoting agents were obtained from commercial sources (mainly Alfa Inorganics), whereupon the highest grade materials were employed. Copper bronze was bought from Gallard Schlesinger Chemical Mfg. Trifluoromethanesulfonic acid (triflic acid, TfOH) was purchased from 3M Co. Copper(II) *meso*-tetraphenylporphine, rhodium(II) acetate dimer, and ethylenebis(salicylimine) were obtained from Strem Chemicals, Inc. Copper(II) phthalocyanine, acetylacetonate (acac), trifluoroacetylacetonate [tf(acac)], hexafluoroacetylacetonate [hf(acac)], and ethylacetoacetate were purchased from Research Organic/Inorganic Chemical Co. Copper(I) phenylacetylide was obtained from Parish Chemical Corp. Copper(II) fluoborate hydrate (Alfa) was dried at 100 °C under high vacuum for 5 h to give a pale bluish white powder. Nickel(II) chloride bis(diphenylphosphino)ethane (diphos) complex was prepared according Broth and Chatt.[39] Copper(I) phenylmercaptide was prepared from thiophenol and copper(I) oxide.[40] Copper(I) chloride[41] and bromide,[41] zinc iodide,[42] and copper(II) triflate[43] were prepared by known procedures. Copper(I) iodide was purified by dissolution in hot saturated KI solution, decolorization of the hot solution with activated carbon, and reprecipitation of CuI by cooling and addition of deionized water; the colorless powder was dried in vacuo. Commercial copper(II) nitrate trihydrate and sulfate pentahydrate were dried in vacuo at 100 °C. Europium(III) tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione], $Eu(fod)_3$, was purchased from Norell Chemical Co., Inc.

Determinations of the Ratio of 2 and 4. Mixtures of 2 and

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(35) Although a pyrazoline trimer could be a precursor to **12** [H. Werner and J. H. Richards, *J. Am. Chem. Soc.*, **90**, 4976 (1968)], thermal decomposition thereof was reported rather to afford cyclopropane **10** in excellent yield [A. D. Forbes and J. Wood, *J. Chem. Soc. B*, 646 (1971)].

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(39) G. Broth and J. Chatt, *J. Chem. Soc.*, 3238 (1965).

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(41) A. I. Vogel, "Practical Organic Chemistry", 3rd ed., Longmans Green, and Co., London, 1957, pp 190–1.

(42) G. Brauer, Ed., "Handbook of Preparative Inorganic Chemistry", Vol. II, 2nd ed., Academic Press, New York, 1965, pp 1073–4.

(43) P. G. Moniotte, A. J. Hubert, and P. Teyssie, *J. Organomet. Chem.*, **88**, 115 (1975).

4 were analyzed by GLC predominantly on columns A and B. The relative amounts are reported by assuming a detector response factor of 1.0 for the isomers. On one occasion the 1.0 response ratio was confirmed by using 10:90, 50:50, and 90:10 mixtures prepared from the separate isomers. ^{1}H NMR integral ratios for α and β pyrrolic protons on several product mixtures were in excellent agreement with GLC-derived isomer ratios.

Preparation of 1,3-Diketone and Salicylaldehyde Complexes 5b, 5c, 5f, 5h, and 6a–d. A solution of $Cu(NO_3)_2 \cdot 3H_2O$ (1.61 g, 6.65 mmol) and sodium acetate (1.25 g, 15.2 mmol) in 25 mL of deionized water was treated with a solution of 1,3-diketone or salicylaldehyde (13.3 mmol) in 25 mL of 95% ethanol. The mixture was stirred, warmed gently, and cooled. The solid was collected, rinsed with deionized water, and dried in vacuo. The copper(II) chelates are generally known compounds.[44]

Preparation of Salicylaldimine Complexes 6e–j and 7.[10a] These compounds were prepared by reaction of the appropriate salicylaldehyde chelate with ammonia[45] or by preformation of the salicylaldimine followed by reaction with copper(II), as for the salicylaldehyde chelates.[10a]

Preparation of Mixed Acac Complexes 8 and 9. $[Cu(acac)OCH_3]_2$ (**9**) was prepared as reported.[46]

Cu(acac)OTf (**8**) was prepared as follows. $Cu(acac)_2$ (1.31 g, 5 mmol) was suspended in 15 mL of dry ether and CF_3SO_3H (0.75 g, 5 mmol) was added slowly with stirring. After 10 min, the mixture was filtered, and the light green solid was dried (1.60 g). A portion (0.50 g) of the solid was dissolved in 5 mL of warm ethyl acetate; the solution was filtered, rewarmed, and diluted with hexane. Green crystals were collected and dried in vacuo (0.30 g): mp 147–150 °C (darkened); IR (KBr) ν_{max} 2940/2870 (CH stretch), 1590–1530 (β-diketonate), 1410 (aliphatic), 1275 (CF_3), 1170–1050 (SO_2O), 650 (CF_3) cm^{-1}; mol wt (osmometry in acetone) 340, calcd for $C_6H_7CuF_3O_5S$ 311.7. Anal. Calcd for $C_6H_7CuF_3O_5S$: C, 23.12; H, 2.26; Cu, 20.28; S, 10.29. Found: C, 25.61; H, 3.78; Cu, 18.72; S, 8.41. (Ethyl acetate and water may be present.)

Ethyl *N*-Methylpyrrole-2-acetate (2). Independent Synthesis.[47] *N*-Methylpyrole-2-acetonitrile[47a,48] was hydrolyzed with aqueous NaOH (25% w/w) at 100 °C for 1.5 h, and the solution was acidified to afford the 2-acetic acid (91%; precipitated from aqueous solution), mp 108–110 °C (lit.[37a] mp 110–112 °C, recrystallized). Dry *N*-methylpyrrole-2-acetic acid (390 g, 2.8 mol) was added to a slurry of anhydrous K_2CO_3 (773 g, 5.6 mol) in 2 L of dry dimethylformamide. The mixture was stirred for 1 h and treated slowly with dimethyl sulfate (431.7 g, 2.8 mol) over 1 h. After 20 h, the mixture was diluted with 6 L of water and extracted twice with 6 L of ether. The ethereal extracts were washed with water (2 × 4 L) and concentrated to a brown oil, which was distilled to yield 405 g (87%) of product: bp 70–73 °C (0.10 torr) [lit.[47b] bp 70–75 °C (0.15 torr)], identical by GLC (columns A, B, G) with major isomer **2**; IR (neat) ν_{max} 2982, 2935, 1735 (CO), 1494, 1298, 1236, 1176, 1028, 709 cm^{-1}; ^{1}H NMR δ 1.24 (t, 3), 3.55, 3.58 (2 s, 5, NCH_3 and CH_2CO, respectively), 4.14 (q, 2), 6.01 (m, 2, β-pyrrole H), 6.54 (t, 1, J = 2.5 Hz, α-H); ^{1}H NMR (CCl_4);[4] ^{13}C NMR δ 14.6 (CH_3), 32.9 (CH_2), 34.0 (NCH_3), 61.2 (OCH_2), 107.3 (C_3), 109.0 (C_4), 122.8 (C_5), 125.5 (C_2), 170.8 (CO).

Representative Reactions of NMP and EDA. (1) No Catalyst. *N*-Methylpyrrole (3.24 g, 40 mol) in a nitrogen-flushed flasked (equipped with condenser, magnetic stirrer, and needle valve controlled addition funnel) was heated in an oil bath at 125–130 °C. Ethyl diazoacetate (2.28 g, 20 mmol) and NMP (1.62 g, 20 mmol) were combined and added drop by drop to the hot reaction, at a rate affording smooth gas evolution (10 min). After being heated for an additional 50 min, the mixture was distilled at 20 torr to remove unreacted NMP (dry ice cooled receiver; yield 3.05 g). The residue was distilled by Kugelrohr methods (100 °C pot temperature, 1 torr) to give 1.25 g (37%) of yellow oil. GLC (columns A and B) and ^{1}H NMR analysis indicated an isomer ratio (**2**/**4**) of 3.8:1.

(2) Copper Bronze. NMP (4.86 g, 60 mmol) and copper bronze (0.13 g, 2.0 mmol) were stirred at 100 °C. A couple of drops of EDA (2.28 g, 20 mmol) were added, and, after a 5-s induction time for nitrogen evolution, the remainder was added over 10 min. After being heated for 50 min more, the reaction was worked up by distillation as before. The recovered NMP weighed 2.45 g, and the product (100 °C pot temperature, 0.5 torr), having an isomer ratio (**2**/**4**) of 5.2:1, weighed 1.35 g (40.5%). The tarry pot residue accounted for 1.5 g. GLC/MS (column A) identified isomers **2** and **4**.[4]

(3) Cuprous Chloride–Triethyl Phosphite Reaction. A homogeneous solution of NMP (4.86 g, 60 mmol), CuCl (30 mg, 0.3 mmol), and triethyl phosphite (52 mg, 0.3 mmol) at 55–60 °C was treated with EDA (2.28 g, 20 mmol) in the usual way. Workup of the solution, now containing a dark precipitate, gave 3.80 g of NMP and 1.70 g (51%) of product with an isomer ratio (**2**/**4**) of 4.3:1.

(4) Cupric Sulfate. GLC Isolation of 4. NMP (4.86 g, 60 mmol) and anhydrous $CuSO_4$ (85 mg, 0.5 mmol) were treated with EDA (2.28 g, 20 mmol) over 10 min as usual (1-min induction time with first couple of drops added). Workup gave 3.80 g of recovered NMP and 1.95 g (58%) of product with an isomer ratio (**2**/**4**) of 1.9:1. Samples of the product were repetitively separated by GLC (column G), and the minor peak (**4**) was collected: ^{1}H NMR (CCl_4) δ 1.21 (t, 3, J = 7 Hz, CH_3C), 3.26 (s, 2, CH_2CO), 3.54 (s, 3, NCH_3), 4.03 (q, 2, OCH_2), 5.86 (m, 1, β-pyrrole H), 6.35 (m, 2, α-H).

Large-Scale Preparation of Ethyl *N*-Methylpyrrole-3-acetate (4). NMP (145.8 g, 1.8 mol) and $Cu(BF_4)_2$ (1.4 g, 6 mmol; pale blue powder) were warmed at 50 °C with stirring. EDA (72.4 g, 0.6 mol; Aldrich) was added over a period of 1.5 h, while a reaction temperature of 50–55 °C was maintained by countering the heat evolved with a water bath. After being stirred 30 min longer at 50 °C, the NMP was distilled at 20 torr into a dry ice cooled receiver (113 g, 32.5% unreacted NMP + 2 mol excess). Distillation of the residue by Kugelrohr methods (80–90 °C pot temperature, 0.5 torr) afforded 58.7 g (58.6%) of yellow liquid with a **2**/**4** ratio of 65:35. Further distillation of the residue (150–180 °C pot temperature, 0.5 torr) gave 12.2 g of orange oil, which was largely a mixture of isomeric diacetates (16% based on EDA): GLC/MS (column G) m/e (rel intensity) 253 (30, molecular ion), 207 (25), 180 (100, M − $CO_2C_2H_5$), 179 (25), 108 (40); ^{1}H NMR (90 MHz) δ 1.23 (t, 6, CH_3), 3.4–3.7 (m, 7, NCH_3 and CH_2CO), 4.16 (q, 4, OCH_2), 5.9–6.1 [m, 1.3, β-pyrrole H; 5.96 (s, 2,5-isomer), 6.03 (d, 2,3- and 2,4-isomer, J = 3 Hz)], 6.5–6.6 [m, 0.8, α-H; 6.51 (d, 2,3- and 2,4-isomer, J = 3 Hz)].[20a] The measured β/α integral ratio of 1.6 corresponds to nearly a 3:1 ratio of 2,3- and 2,4-diacetate to 2,5-diacetate; only minor amounts of 3,4-diacetate could be present.[49] The monoacetate mixture (53.4 g) was distilled on a spinning-band column (Nester-Faust, ca. 40 cm, Teflon band) to furnish 17.4 g of **2** (>99% isomeric purity, 50% recovery), bp 78–79 °C (1.0 torr), and 4.3 g of **4** (>99% isomeric purity, 23% recovery), bp 82–83 °C (1.0 torr). For **4**: IR (neat) ν_{max} 2981 (m), 2935 (m), 1733 (s), 1508 (w), 1367 (w), 1241 (m), 1164 (m), 1030 (m), 760 (m), 703 (w) cm^{-1}; ^{1}H NMR δ 1.24 (t, 3), 3.43 (s, 2), 3.57 (s, 3) 4.13 (q, 2), 6.03 (t, 1, J = 2 Hz), 6.51 (m, 2); ^{13}C NMR δ 14.6 (CH_3), 33.5 (CH_2), 36.4 (NCH_3), 60.8 (OCH_2), 109.3 (C_4), 115.6 (C_3), 120.8 (C_2), 122.1 (C_5), 172.8 (CO).

Reaction of NMP and EDA Using CuBr. Isolation of 12. To NMP (4.86 g, 60 mmol) and CuBr (43 mg, 0.3 mmol) at 30 °C was added a few drops of EDA (2.28 g, 20 mmol). Reaction began immediately, and the rest of the EDA was added drop by drop over 10 min. After the mixture was heated for 50 min at 45 °C, normal workup afforded 4.30 g of recovered NMP and 1.60 g of product, which contained a higher boiling component (60% of mixture) by GLC (column B), in addition to **2** and **4** in a ratio

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[44] G. S. Hammond, D. C. Nonhebel, and C.-H. S. Wu, *Inorg. Chem.*, **2**, 73 (1963); E. W. Berg and J. T. Truemper, *J. Phys. Chem.*, **64**, 487 (1960); H. A. Kuska and M. T. Rogers, *J. Chem. Phys.*, **43**, 1744 (1965); K. Clarke, R. A. Cowen, G. W. Gray, and E. M. Osborne, *J. Chem. Soc.*, 245 (1963).

[45] S. V. Sheat and T. N. Waters, *Inorg. Nucl. Chem.*, **26**, 1221 (1965).

[46] J. A. Bertrand and R. I. Kaplan, *Inorg. Chem.*, **4**, 1657 (1965).

[47] (a) W. Orth, L. Rappen, and G. Busse, U.S. Patent 3 523 952 (1970); (b) U.S. Patent 3 544 589 (1970).

[48] J. R. Carson, J. T. Hortenstine, B. E. Maryanoff, and A. J. Molinari, *J. Org. Chem.*, **42**, 1096 (1977).

[49] The 2,3-diacetate probably predominated over the 2,4-diacetate, given the vicinal coupling constant of 3 Hz ($J_{2,3}$, not $J_{2,4}$)[50] and the regiochemistry observed for EDA additions to **2** (and to 1,2- and 1,3-dimethylpyrroles).

[50] L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969, p 306.

of 4.7:1 (ca. 0.6 g of **2** and **4** for a yield of 18%). GLC/MS of new material (17 eV, column A) *m/e* (rel intensity) 213 (23), 212 (100), 184 (27), 167 (15), 156 (19), 140 (19); (70 eV, column D) *m/e* (rel intensity) 258 (trace), 213 (35), 212 (50), 185 (24), 184 (16), 167 (26), 157 (16), 156 (53), 140 (21), 139 (42), 138 (100), 128 (18), 112 (49), 111 (17), 94 (12), 84 (26), 45 (38), 44 (36), 40 (46), 39 (20); compared favorably with authentic **12** (vide infra).

The CuBr product (3.0 g) was distilled at 0.1 torr by using a 9-cm Vigreux column. The following fractions were collected: (1) 49–51 °C (800 mg), (2) 51–86 °C (180 mg), (3) 86–89 °C (270 mg), (4) 90--93 °C (620 mg). The fourth fraction was homogeneous by GLC (columns A, D, E) and corresponded to the new, higher boiling substance: MS *m/e* (rel intensity) 258 (5), 213 (46), 212 (51), 185 (19), 184 (21), 167 (37), 157 (19), 156 (23), 140 (37), 139 (58), 138 (33), 112 (100), 84 (42); exact mass *m/e* 213.0762 (found for $C_{10}H_{13}O_5$, 213.0762), 185.0797 (found for $C_9H_{13}O_4$, 185.0813), 167.0339 (found for $C_8H_7O_4$, 167.0343);[9] ^{1}H NMR δ 1.1–1.5 (m, 9, t centered at δ 1.22 for CH_3 and at 1.30 for 2 CH_3), 3.94 (brs, 2, CH_2CO, J = ca. 0.5 Hz), 4.0–4.5 (m, 6, OCH_2, q centered at δ 4.14, 4.23, and 4.37), 6.93 (brs, 1, vinyl H); IR (neat) compared favorably with authentic **12** (vide infra); ^{13}C NMR.[9]

Reaction of EDA with CuBr. EDA (1.14 g, 10 mmol) in 2 mL of 1,2-dichloroethane was added slowly to a stirred suspension of CuBr (36 mg, 0.25 mmol) in 2 mL of 1,2-dichloroethane at 60–65 °C. GLC analysis (columns B and E) revealed a mixture of only diethyl fumarate (DEF) and diethyl maleate (no trimers evident), in a ratio (column F) of 1.7:1.

Triethyl (*E*)-Aconitate (12). Fisher esterification of aconitic acid with ethanol and methanesulfonic acid provided crude **12** (yellow oil; ^{1}H NMR, GLC, and mass spectra comparable to those of the high-boiling substance from reaction of NMP, EDA, and CuBr). Distillation by Kugelrohr methods (120 °C pot temperature, 0.5 torr) yielded a colorless liquid, which corresponded by GLC coinjection (column F) to the high-boiling substance of the CuBr reaction: GLC/MS (column D) *m/e* (rel intensity) 213 (15), 212 (27), 185 (8), 184 (21), 167 (19), 157 (8), 156 (50), 140 (19), 139 (38), 138 (100), 128 (17), 112 (5), 111 (19), 94 (16), 84 (35); MS *m/e* (rel intensity) 213 (39), 212 (40), 185 (16), 184 (18), 167 (30), 157 (24), 156 (21), 140 (34), 139 (52), 138 (24), 115 (76), 112 (100); ^{1}H NMR (60 MHz) δ 1.1–1.5 (m, CH_3), 3.97 (brs, CH_2CO), 4.1–4.6 (m, OCH_2), 7.00 (brs, vinyl H); ^{13}C NMR.[9]

1,3-Dimethylpyrrole (17b).[51,52] *N*-Methylpyrrole-2-carboxaldehyde (80 g, 0.73 mol) in 600 mL of chloroform was added slowly to a mixture of 500 mL of chloroform and 500 mL of triflic acid. After 30 h at reflux, the red solution was cooled in an ice bath, poured carefully into a cold solution of sodium acetate trihydrate (1360 g) in 3 L of water, and stirred for 30 min. The organic phase was separated, washed (Na_2CO_3 solution), dried (K_2CO_3), treated with activated charcoal, and concentrated to a pale red oil (52 g, 65%). The oil, a mixture of 2- and 3-carboxaldehydes in a ratio of 3:7 (GLC on column E), was distilled through a 6-in. silvered column packed with berel saddles. After a low-boiling fraction [bp 25–27 °C (0.1 torr)], the product was collected: bp 70–72 °C (0.1 torr); 28 g (35%); ^{1}H NMR δ 3.72 (s, 3, CH_3), 6.63 (m, 2, α protons), 7.27 (t, 1, β protons), 9.78 (s, 1, CHO).

N-Methylpyrrole-3-carboxaldehyde[52] (5.45 g, 0.18 mol) was combined under nitrogen with 30 mL of diethylene glycol, 5 mL of 85% hydrazine hydrate, and pulverized KOH (6.7 g, 0.14 mol, 85% assay) in a flask equipped with a reflux condenser, thermometer, and magnetic stirrer. The mixture was refluxed for 1 h, the condenser was replaced by a distillation head, and water was removed until the pot temperature reached 200 °C. After 3 h at 200 °C, more water (10 mL) was added to the reaction, and it was removed by distillation. The distillate (two layers) was diluted with 25 mL of *n*-pentane and separated. The organic solution was dried (Na_2SO_4) and evaporated at normal pressure to give a pale yellow liquid: ^{1}H NMR δ 2.10 (brs, 3), 3.73 (s, 3), 6.13 (t, 1 J = ca. 2 Hz, H_4), 6.56 and 6.67 (m, 2, brs for H_2 and sharp t for H_5, respectively). Distillation gave 2.95 g of **17b**, bp 128–135 °C (major portion 134–135 °C), in 97% purity by GLC (column G).

Reaction of Pyrrole and EDA. Pyrrole (2.01 g, 30 mmol) and $Cu(acac)_2$ (40 mg, 0.15 mmol) were reacted with EDA (1.14 g, 10 mmol) at 55 °C in the usual manner (2-min lag time observed). Workup gave 0.8 g of unreacted pyrrole and 0.95 g of product (62%). GLC analysis (column A) and GLC/MS indicated the following composition (in order of elution): **13** (82%), *C*-methyl-**13** (5%), *C*-methyl-**13** (3%), **14** (5%), *C*-methyl diacetic ester (2%). The ratio of **13**/**14** is ca. 17:1. ^{1}H NMR integration of the pyrrole α and β protons indicated that the ratio of **13**/**14** was greater than 15:1.

The reaction was conducted by using copper bronze (0.07 g) at 100 °C. Workup gave 1.1 g of unreacted pyrrole and 0.75 g (49%) of product. GLC analysis (column A) showed that **13** made up ca. 80% of the mixture and that the ratio of **13**/**14** was ca. 11:1; ^{1}H NMR allowed an isomer ratio of ca. 10:1.

The reaction was conducted with $Cu(OTf)_2$ (54 mg, 0.15 mmol) at 40 °C. Workup gave a pale yellow product (0.80 g, 52%) with a **13**/**14** ratio of 2.7:1 by GLC (column A). A ^{1}H NMR LIS study on this mixture with $Eu(fod)_3$ supported this ratio by establishment of peak assignments.[9,53] Integration of $Eu(fod)_3$-shifted spectra furnished a **13**/**14** isomer ratio of 2.6:1. The shift behavior observed for the pyrrolic *C* protons in the LIS study was not consistent with the presence of N-H insertion product **15**, since the two α protons were shifted more than the two β protons.[9]

An authentic sample of **15**[54] confirmed the GLC data and the ^{1}H NMR interpretations: ^{1}H NMR (**15**) δ 1.26 (t, 3), 4.23 (q, 2), 4.60 (s, 2), 6.20 (t, 2, 3,4-H), 6.67 (t, 2, 2,5-H); IR[54a] (neat) ν_{max} 1750 (C=O), 1295, 1195 (C—O), 715 cm^{-1}. In the above reaction product mixtures, GLC showed no **15**, and ^{1}H NMR showed no peaks at δ 4.60 (CH_2CO of **15**).

A sample of product mixture (**13** and **14**) from the $Cu(OTf)_2$ reaction (765 mg, 5.0 mmol) in 2 mL of dry THF was added slowly to a slurry of ether-rinsed KH (210 mg, 5.2 mmol) in 2 mL of dry THF at 0 °C (under nitrogen). The reaction was stirred for 15 min, treated with a solution of methyl iodide (1.42 g, 10 mmol) in 2 mL of THF, and quenched with water after 1 h at 20 °C. GLC analysis (column A) revealed the presence of **2** and **4** (coinjection with authentic specimens) in a ratio of ca. 2.5:1. The reaction was diluted with ether. The organic layer was separated, rinsed (water), dried (Na_2SO_4), and evaporated. ^{1}H NMR examination of the crude oil verified the presence of **2** and **4**.

Reaction of 1,2-Dimethylpyrrole with EDA. 1,2-Dimethylpyrrole (2.28 g, 24 mmol) was reacted at 55 °C with EDA (912 mg, 8 mmol) by using $Cu(acac)_2$ (31 mg, 0.12 mmol). GLC analysis (column F) indicated three possible isomers, confirmed by GLC/MS (column D), in a ratio of 76:18:3 (in order of increasing retention time). Usual workup gave 1.6 g of recovered **17a** and 0.49 g (34%) of oily product mixture. ^{1}H NMR revealed a pyrrole α/β proton ratio of 1:8, which corresponds to the ratio of 1:8.6 derived from GLC analysis. The major component is therefore **18a**. Since the α-proton signal showed a splitting of 2.5 Hz, consonant with $J_{2,3}$ and not $J_{2,4}$, the next populous isomer is **18b**. A ^{1}H NMR LIS study on the isomeric mixture with $Eu(fod)_3$ supported this assignment.[9] For **18a**, **18b**, and **18c**, one would predict the following relative shifts[53] respectively: $H_2 > H_3 > NCH_3 > CH_3$; $H_3 > H_4$, $CH_3 > NCH_3$; $H_2 \approx H_4$, $CH_3 \approx NCH_3$. Integration of $Eu(fod_3)$-shifted spectra gave an isomer ratio for **18a**/**18b** of 4:1.

Reaction of 1,3-Dimethylpyrrole with EDA. 1,3-Dimethylpyrrole (885 mg, 9 mmol) in 0.5 mL of 1,2-dichloroethane (DCE) was reacted at 40 °C with EDA (342 mg, 3 mmol) in 0.3 mL of DCE by using $Cu(OTf)_2$ (16 mg, 0.045 mmol) in the usual manner. Distillation (Kugelrohr) gave 400 mg (74%) of product, which was composed of three major substances (confirmed as isomers by GLC/MS) in a ratio of 1.3:1.1:1 (GLC, column A, order of increasing retention).

This reaction was also performed by using $Cu(acac)_2$ (12 mg, 0.045 mmol) at 50 °C. GLC analysis of the product mixture (350

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(51) (a) Several different trials to prepare **17b** by pyrolysis of *N*-methylpyrrole-3-acetic acid[51b] were unsuccessful. (b) The acid, from saponification of **4**, had mp 37–38 °C.

(52) The method used here for preparing *N*-methylpyrrole-3-carboxaldehyde has been reported: J. R. Carson, U.S. Patent 4 002 643 (1975).

(53) ^{1}H NMR LIS experiments were performed on **2** and **4** in order to establish model proton-shifting trends.[9]

(54) (a) R. A. Jones, *Aust. J. Chem.*, **19**, 289 (1966); (b) I. Gloede, K. Poduska, H. Gross, and J. Rudinger, *Collect. Czech. Chem. Commun.*, **33**, 1307 (1968).

mg, 65%) disclosed three isomeric monoadducts (GLC/MS) in a ratio of 3.8:1.8:1 (order of increasing retention). A ^{1}H NMR LIS study on this mixture with Eu(fod)$_3$ showed that the isomeric ratio corresponds to **19b**/**19a**/**19c**, respectively.[9,53] An authentic sample of **19a**[55] confirmed the GLC and ^{1}H NMR assignments for it.[9]

Reaction of *N*-Isopropylpyrrole with EDA. *N*-Isopropylpyrrole (1.31 g, 12 mmol) was reacted with EDA (456 mg, 40 mmol) by using Cu(acac)$_2$ (15.6 mg) at 60 °C as usual. Workup afforded 0.27 g of product (34%), which was analyzed by GLC. Two major peaks comprising 88% of the product in a ratio of 1.3/1 (column B) or 92% in a ratio of 1.4/1 (column F) were observed (order of increasing retention time; corrected yield ca. 30%): GLC/MS (3% OV-17, 100/120 mesh, 4-ft column) (1) major isomer, *m/e* (rel intensity) 195 (13, molecular ion), 123 (11), 122 (88), 121 (12), 80 (100), 79 (18), 53 (22), 52 (15), 43 (14), 41 (22), 39 (21); (2) minor isomer, *m/e* (rel intensity) 195 (11, molecular ion), 123 (12), 122 (96), 121 (15), 80 (100), 79 (17), 53 (30), 52 (22), 51 (10), 43 (22), 41 (27), 39 (19); ^{1}H NMR δ 3.53 (s, CH$_2$CO, minor isomer, 38%), 3.69 (s, CH$_2$CO, major isomer, 62%); a Eu(fod)$_3$ LIS study supported the assignment of δ 3.53 and 3.69 peaks to the 2- and 3-isomers, respectively (the 3-isomer experienced a greater downfield shift per unit of Eu(fod)$_3$[53]); the 62/38 isomer ratio (2-isomer/3-isomer) was verified by the integral ratio for the α and β pyrrolic protons (α/β: found, 1.22; calcd 1.17).

Reaction of **16a** (1.31 g) with EDA (450 mg) at 35 °C using Cu(OTf)$_2$ (22 mg) gave two product fractions on workup. The first fraction (0.16 g, 20.5%) from Kugelrohr distillation at a 120–130 °C pot temperature (0.5 torr) was 98% pure monoadducts with an α/β substitution ratio of 0.85:1 (GLC on column B). The second fraction (0.16 g) from Kugelrohr distillation at a 130–180 °C pot temperature (0.5 torr) was a complex mixture.

Reaction of *N*-*tert*-Butylpyrrole with EDA. *N*-*tert*-Butylpyrrole (1.48 g, 12 mmol) was reacted with EDA (456 mg, 4 mmol) by using Cu(acac)$_2$ (15.6 mg) at 60 °C as usual. Workup gave 0.31 g of product (40%), which was analyzed by GLC. Only one major peak, accounting for 86% of the mixture (ca. 10% starting material was present), was observed (column F): corrected yield 34%; GLC/MS (3% OV-17, 100/120 mesh, 4-ft column) *m/e* (rel intensity) 209 (2, molecular ion), 194 (17), 120 (16), 80 (65), 79 (21), 65 (16), 57 (83), 56 (10), 53 (24), 52 (27), 51 (17), 42 (24), 41 (100), 40 (13), 39 (58); ^{1}H NMR δ 3.54 (s, CH$_2$CO), 6.23 (m, 1, β-H), 6.88 (m, 2, α-H); the α/β proton ratio of 2.1 verified the sole presence of the 3-isomer; the Eu(fod)$_3$-shifted spectra showed no doubling of the CH$_2$CO resonance.

Reaction of Ethyl *N*-Methylpyrrole-2-acetate (2) with EDA. Acetate **2** (5.01 g, 30 mmol) was reacted with EDA (1.14 g, 10 mmol) in the usual manner by using Cu(OTf)$_2$ (32 mg, 1 mol %) at 30–35 °C. Kugelrohr distillation at a 90–110 °C pot temperature (0.15 torr) furnished 3.6 g of recovered starting material and at a 130–150 °C pot temperature (0.15 torr) furnished a second fraction, 1.5 g (59%), as a mixture of diacetates. GLC/MS (column A) identified three isomeric diacetates, which were present in a ratio of 1/2.6/1 (GLC on column A; order of increasing retention). Since the product contained 4% of **2**, the corrected yield is about 56%. ^{1}H NMR (mixture) δ 1.25 (t, 6), 3.4–3.6 (m, 7), 4.16 (q, 4), 5.98 and 6.0–6.1 (s and m, 1.55), 6.35–6.55 (m, 0.45) (β/α pyrrolic proton ratio observed = 3.4; GLC composition gives a theoretical β/α ratio of 3.6). A ^{1}H NMR LIS study on the product mixture with Eu(fod)$_3$ characterized the pyrrolic protons of the three isomers.[9]

The same reaction was conducted by using Cu(acac)$_2$ (39 mg, 1.5 mol %) at 60 °C. Analogous workup gave 3.6 g of starting material and 1.6 g (63%) of product mixture. GLC analysis (column A) showed three isomeric diacetates in a ratio of 3/16/1 (order of increasing retention). Since the product contained 4% of **2**, the corrected yield is 60%. ^{1}H NMR (mixture) δ 3.48 and 3.62 (2 s, 7), 5.98 and 6.0–6.1 (s and m, 1.75), 6.35–6.55 (m, 0.25) (β/α ratio = 7; GLC gave a β/α ratio of 8.5). A ^{1}H NMR LIS study with Eu(fod)$_3$ supported the isomer assignments **20a**/**20b**/**20c** = 16/3/1.[9]

Competition Experiment. Reaction of a Mixture of 2 and 4 with EDA. A mixture of **2** (1.67 g, 10 mmol) and **4** (0.80 g, 5 mmol) was reacted with EDA (0.86 g, 7.5 mmol) in the usual way. One reaction was performed with Cu(acac)$_2$ (39 mg, 2 mol %) at 60 °C and another was performed with Cu(OTf)$_2$ (27 mg, 1 mol %) at 30–35 °C. The reaction mixtures were analyzed directly (no workup) by GLC (column A), and the GLC ratios of **2**/**4** in the reactions were compared with the GLC ratio of **2** and **4** in the starting material. Thus, the comparison (**2**/**4** initial)/(**2**/**4** final) for Cu(acac)$_2$ was 1.04 and for Cu(OTf)$_2$ was 1.16. Of course, if **2** and **4** had reacted at the same rate, the comparative ratio would have been 1.00. The comparison values do not differ enough from 1.0 to seriously alter the reported **2**/**4** isomer ratios (Tables I and II), especially when one considers that the diacetates only comprise 5–15% (based on EDA) of the product mixtures from reaction of NMP and EDA [ca. 5% for Cu(acac)$_2$ and 15% for Cu(OTf)$_2$].

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Supplementary Material Available: Tables of the following: ^{1}H NMR LIS data for mixtures of **2** and **4** (Table I), **18a–c**, (Table II), **19a–c** (Table III), **13** and **14** (Table IV), **20a–c** (Table VII), and for **15** (Table VI); high-resolution mass spectral data for **12** from the CuBr reaction (Table V); expanded versions of Tables I and II in the paper with data for additional promoting agents; ^{1}H NMR data for **19a**; ^{13}C NMR data for authentic **12**, **12** from the CuBr reaction, and **10** (with **12** as a minor contaminant) (Table VIII); experimental description and spectral data for **10** (15 pages). Ordering information is given on any current masthead page.

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(55) J. R. Carson and S. Wong, *J. Med. Chem.*, 16, 172 (1973).