Unusual Reactions between Some 1-Aroyl-4,5-dihydro-4,4-dimethyl-5-methylene-1*H*-pyrazoles and Ketenes

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5-Methylene-4,5-dihydropyrazoles **1a-d** react with diphenylketene (DPK), affording the pyrazolyl-3,3-diphenyl-2-propenyl benzoates **2a-d**, very likely via the corresponding pyrazolyl-enol esters **7** as intermediates. By acid hydrolysis of **2** the (diphenyloxopropyl)pyrazole derivative **3** in its enol form is isolated, whereas by cycloaddition with 4-methylbenzonitrile oxide the spiro compound **4** is obtained. 5-Methylene-4,5-dihydropyrazoles **1a-c** and **1g** also react with dichloroketene (DCK) to give the corresponding 5-hydroxypyrazolines **5**. The structure of **2b** has also been confirmed by X-ray crystallography.

The [2 + 2], thermally induced, cycloadditions of ketenes with methylenecycloalkanes are well-known.[2] On the other hand there is considerable interest for both synthetic and mechanistic reasons in [2 + 2] cycloadditions across the C=N bond of various thiazoline,[3] benzothiazine,[4] and benzoxazine[5] derivatives, leading to the formation of the compounds of interest due to their biological activity, fused β-lactam derivatives. In addition the chemistry of pyrazoles and especially of N-acetylated pyrazoles continues to attract interest[6] because of their presence in numerous biologically active compounds both natural and synthetic.

In relation to our interest in the chemistry of pyrazoles,[7,8] we describe in this paper the reaction of 5-methylene-4,5-dihydro-1*H*-pyrazoles containing an exomethylenic double bond as well as a C=N double bond, with ketenes.

Fused four-membered rings were not obtained; instead the reactions afforded unexpected 1:2 pyrazole-ketene adducts.

Results and Discussion

The 3-methyl-5-methylene-4,5-dihydropyrazoles **1a-c** and the 3-ethyl-5-methylene derivative **1d** on treatment with an excess of diphenylketene (generated in situ by the dehydrochlorination of the corresponding acyl chloride by the use of triethylamine) in refluxing methylene chloride afforded good yields (~60%) of the pyrazolyl-3,3-diphenyl-2-propenyl benzoates **2a-d**, whereas the 3-methyl-5-ethylidene derivative **1e**, the unsubstituted in the 3-position compound **1f**, and the 3-phenyl-5-methylene derivative **1g** were inert (Scheme I). The pyrazolyl benzoates **2** are stable crystalline compounds. In the ^{1}H NMR spectra, taken in $CDCl_3$, the methylene protons resonate at δ ~3.50, the COC*H*Ph_2 proton at δ ~6.05, and the C=CH_2 protons at δ ~4.50 and δ ~6.00, whereas in the case of the 5-ethylidenepyrazolyl derivative **2d**, a doublet at δ 1.76 and a quartet at δ 6.91 are observed for the C=CHMe protons. On acid hydrolysis, performed on **2a** and **2b**, the (diphenyloxopropyl)pyrazole derivative **3** in its enol form was isolated (Scheme I). The enol form is probably stabilized due to hydrogen bond formation as is also supported by the spectral data. The existence of the exocyclic double bond in compounds **2** was also proved by a cycloaddition reaction of **2b** with 4-methylbenzonitrile oxide, leading to the formation of the spiro compound **4** (Scheme I).

An X-ray crystallographic analysis on **2b** was performed (Figure 1) to ascertain unambigously the structure of **2**.

Scheme II provides an interpretation for the formation of the pyrazolyl benzoates **2**. The reaction pathway involves the formation of the 1,4-dipole **6**, which leads to the intermediate **7** by aroyl migration. Quaternization of the former N-2 of the pyrazole ring by a second molecule of ketene leads to the zwitterion **8**, which by removal of a hydrogen of the former C-3 substituent evolves toward **2**. This is consistent with the fact that the reaction was observed only when the C-3 substituent of the pyrazole ring was methyl or ethyl and no reaction took place when this substituent was hydrogen or phenyl. In favor of the proposed mechanism was the isolation, from the reaction of **1d** with DPK, of the 5-ethylidenepyrazolyl benzoate **2d** and not of the isomeric 5-methylenepyrazolyl benzoate. The above mechanism is also consistent with both the well-known electron acceptor properties and charge distribution of ketenes[9] and also with the results of the charge density distribution calculated by the MINDO method[10] for **1a** (Figure 2), which indicates that the largest negative charge is observed on the N-1 atom of the pyrazole ring.

The 4,5-dihydropyrazoles **1** were unreactive with dimethylketene. With dichloroketene the reaction was followed by TLC and almost complete disappearance of the dihydropyrazoles **1** was observed after 6 h. However, addition products analogous to the pyrazolyl benzoates **2** were not obtained, but from dihydropyrazoles **1a-c** and **1g** the 5-hydroxypyrazolines **5a-c** and **5g** were isolated, respectively, whereas in the case of the dihydropyrazoles **1d-f** only unidentified decomposition products were formed. The 5-hydroxypyrazolines **5a-c** were identified by comparison with authentic samples, whereas the iden-

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(2) Brady, W. T. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley-Interscience: New York, 1980; pp 279-308.
(3) Christjohannes, J.; Prewo, R.; Bieri, J. H.; Heimgartner, H. *Helv. Chim. Acta* **1986**, *69*, 1424.
(4) Sohár, P.; Fodor, L.; Szabó, J.; Bernáth, G. *Tetrahedron* **1984**, *40*, 4387.
(5) Sohár, P.; Stájer, G.; Pelczer, I.; Szabó, A. E.; Szúnyog, J.; Bernáth, G. *Tetrahedron* **1985**, *41*, 1721.
(6) (a) Scharma, R. S.; Pathak, R. B.; Bahel, S. C. *J. Indian Chem. Soc.* **1985**, *62*, 625. (b) Carlsohn, H.; Hipler, U. C.; Breuer, A.; Schuetz, A.; Schuetz, H.; Hartmann, M. *Pharmazie* **1983**, *38*, 823.
(7) Papadopoulos, S.; Stephanidou-Stephanatou, J. *J. Chem. Res., Synop.* **1986**, 368; *J. Chem. Res., Miniprint* **1986**, 3084.
(8) Stephanidou-Stephanatou, J. *J. Heterocycl. Chem.* **1983**, *20*, 845.
(9) Chosez, L.; O'Donnel, M. J. In *Pericyclic Reactions*; Marchand, A. P.; Lehr, R. E., Ed.; Academic Press: New York, 1977; Vol. 2, p 79.
(10) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

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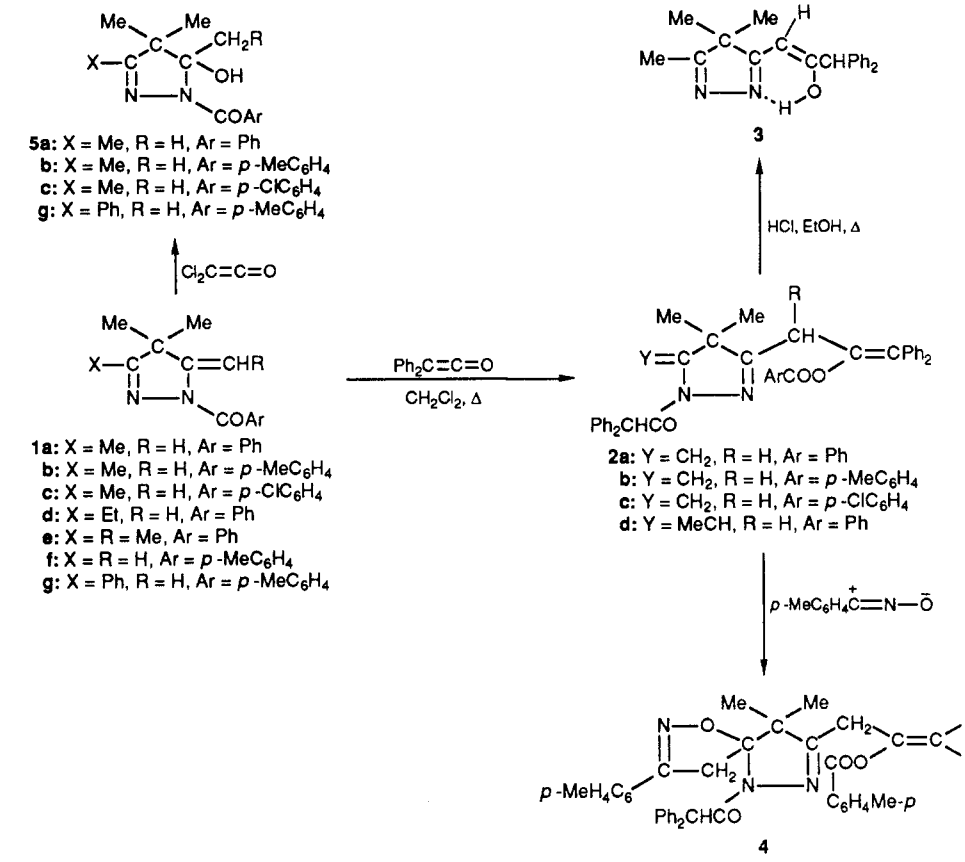
Scheme I



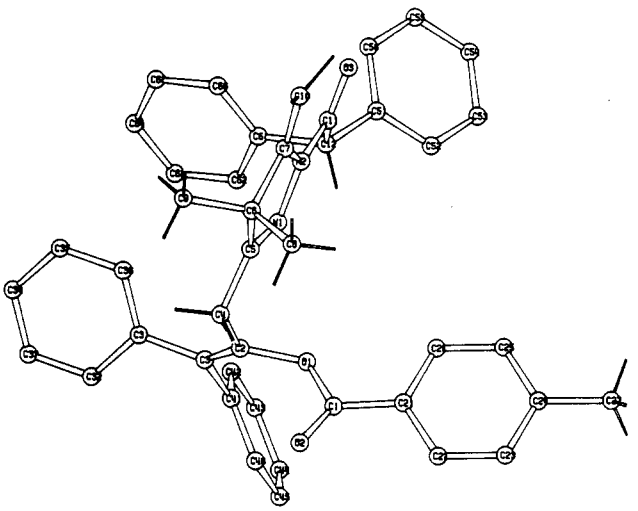


Figure 1. X-ray crystal structure of **2b**.

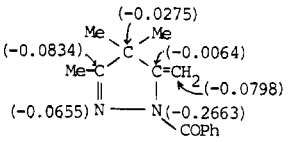
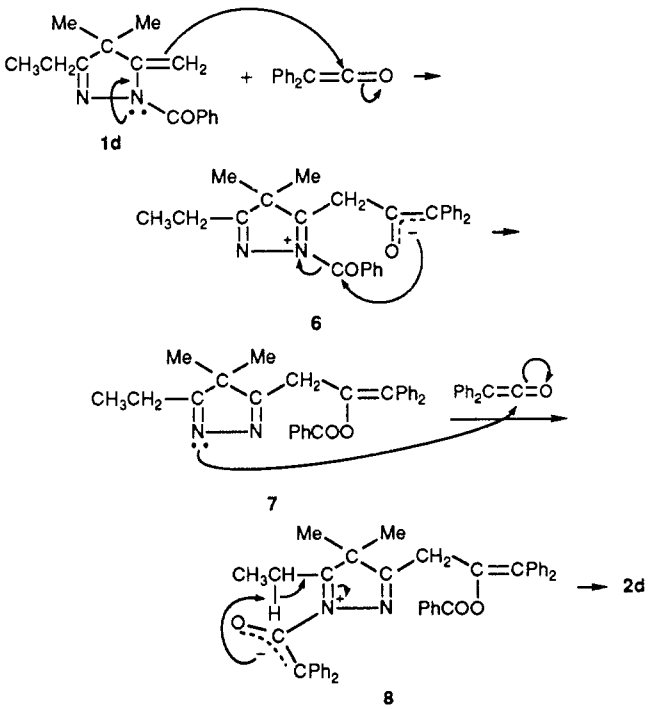


Figure 2. Calculated net charges (in parentheses) for compound **1a**.

tification of **1g** was based on its ^{13}C NMR spectrum where the 5-Me carbon, attached to an sp^3 carbon, appeared as a quartet at δ 19.71 (see Experimental Section) compared with the isomeric 4,5-dihydro-5-hydroxy-3,4,4-trimethyl-5-phenyl-1-(*p*-toluoyl)-1*H*-pyrazole, where the 3-Me carbon, attached to an sp^2 carbon, appeared as a quartet at δ 12.33 in agreement with previous results[11] and therefore our previous assignment[7] should be reconsidered.

Scheme II



The possibility of formation of the 5-hydroxypyrazolines **5** by hydration of **1** by traces of water in the reaction

(11) (a) Rees, R. G.; Green, M. J. *J. Chem. Soc. B* **1968**, 387. (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, p 191.

mixture was also examined. However, the methylenepyrazoles 1 remained unchanged after being stirred in dry dichloromethane containing some triethylamine at 25 °C for 2 days.

Experimental Section

All melting points are uncorrected. NMR spectra (in $CDCl_3$) were obtained on a JEOL JNM-GX 270 (270.05 MHz) spectrometer. Chemical shifts are given in parts per million from Me_4Si. Mass spectra were recorded at 70 eV on a Hitachi-Perkin-Elmer RMU-6L spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 297 spectrometer. Analyses were performed with a Perkin-Elmer Model 240B CHN Analyzer.

Diphenylketene (DPK), dichloroketene (DCK), and dimethylketene (DMK) were generated in situ by dehydrochlorination of the corresponding acid chlorides[12] with triethylamine.

1-Aroyl-4,5-dihydro-3,4,4-trimethyl-5-methylene-1*H*-pyrazoles **1a–c** and 4,5-dihydro-4,4-dimethyl-5-methylene-3-phenyl-1-(*p*-toluoyl)-1*H*-pyrazole (**1g**) were prepared as described.[8,13]

4,5-Dihydro-4,4-dimethyl-5-methylene-1-(*p*-toluoyl)-1*H*-pyrazole (**1f**) was prepared by condensation of α-acetylisobutyraldehyde with *p*-toluohydrazide and thermolysis of the appropriate hydroxy derivative:[14] mp 101–103 °C (from ether–hexane); IR (Nujol) 1665 (C=O) cm^{-1}; ^1H NMR δ 1.26 (s, 6 H, CMe_2), 2.37 (s, 3 H, *p*-Me), 4.70 and 6.12 (two s, 2 H, C=CH_2), 7.20 (d, 2 H, Ar H, J = 10.0 Hz), 7.65 (d, 2 H, Ar H, J = 10.0 Hz); mass spectrum, m/z (rel intensity) 228 (M^+, 8), 119 (100). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.66; H, 6.92, N, 12.41.

Preparation of 1-Benzoyl-3-ethyl-4,5-dihydro-4,4-dimethyl-5-methylene-1*H*-pyrazole (1d) and 1-Benzoyl-5-ethylidene-4,5-dihydro-3,4,4-trimethyl-1*H*-pyrazole (1e). To a solution of 3,3-dimethyl-2,4-hexanedione (1.42 g, 1.0 mmol) in toluene (50 mL) was added benzoic hydrazide (1.50 g, 1.1 mmol), and the mixture was refluxed for 6 h. The solvent was removed and the mixture chromatographed (silica gel, hexane/ethyl acetate) to give the dihydropyrazole **1d** (0.7 g, 29%), the dihydropyrazole **1e** (0.84 g, 35%), and 1-benzoyl-3-ethyl-4,5-dihydro-5-hydroxy-4,4,5-trimethyl-1*H*-pyrazole (0.42 g, 16%).

Dihydropyrazole **1d**: oil; IR (film) 1660 (C=O) cm^{-1}; ^1H NMR δ 1.16 (t, 3 H, CH_2CH_3, J = 7.0 Hz), 1.28 (s, 6 H, CMe_2), 2.32 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 4.67 and 6.15 (two s, 2 H, C=CH_2), 7.35–7.47 (m, 3 H, Ar H), 7.83–7.87 (m, 2 H, Ar H); mass spectrum, m/z (rel intensity) 242 (M^+, 11), 105 (100). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.21; H, 7.59; N, 11.60.

Dihydropyrazole 1e: mp 107–108 °C (from hexane); IR (Nujol) 1645 (C=O) cm^{-1}; ^1H NMR δ 1.45 (s, 6 H, CMe_2), 1.91 (s, 3 H, MeC=N), 1.93 (d, 3 H, C=CH*Me*, J = 7.0 Hz), 7.02 (q, 1 H, C=C*H*Me, J = 7.0 Hz), 7.37–7.42 (m, 3 H, Ar H), 7.68–7.72 (m, 2 H, Ar H); mass spectrum, m/z (rel intensity) 242 (M^+, 8), 202 (7), 105 (100). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.11; H, 7.30; N, 11.43.

1-Benzoyl-3-ethyl-4,5-dihydro-5-hydroxy-4,4,5-trimethyl-1*H*-pyrazole: mp 84–86 °C (from ethanol–water); IR (Nujol) 3430 (OH), 1645 (C=O) cm^{-1}; ^1H NMR δ 1.10 (t, 3 H, CH_2CH_3, J = 7.0 Hz), 1.17 (s, 6 H, CMe_2), 2.28 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 3.60 (br s, 1 H, OH), 7.30–7.51 (m, 3 H, Ar H), 7.74–8.04 (m, 2 H, Ar H); mass spectrum, m/z (rel intensity) 260 (M^+, 5), 245 (2), 243 (1), 105 (100). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.38; H, 7.88; N, 10.81.

Reaction of 1-Benzoyl-4,5-dihydro-3,4,4-trimethyl-5-methylene-1*H*-pyrazole (1a) with DPK. To a stirred solution of **1a** (342 mg, 1.5 mmol) and Et_3N (202 mg, 2.0 mmol) in dry dichloromethane (45 mL) was added dropwise a solution of diphenylacetyl chloride (414 mg, 1.8 mmol) in the same solvent (10 mL) in about 2 h. The reaction mixture was refluxed for 24 h, then a second amount of Et_3N (202 mg, 2.0 mmol) was added, followed by the dropwise addition of a solution of diphenylacetyl chloride (414 mg, 1.8 mmol) in dry dichloromethane (10 mL) in about 2 h. The reaction mixture was refluxed for another 24 h and then was washed with water, the organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. Column chromatography of the reaction mixture (silica gel, 15:1 *n*-hexane/ethyl acetate) gave the enol ester **2a** (638 mg, 69%): mp 122–123 °C (from ethanol); IR (Nujol) 1715 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR δ 0.93 (s, 6 H, CMe_2), 3.39 (s, 2 H, CH_2), 4.39 (d, 1 H, C=CH_2, J = 1.0 Hz), 5.89 (d, 1 H, C=CH_2, J = 1.0 Hz), 5.97 (s, 1 H, C*H*Ph_2), 7.04–7.27 (m, 22 H, Ar H), 7.40–7.45 (m, 1 H, Ar H), 7.68–7.71 (m, 2 H, Ar H); mass spectrum, m/z (rel intensity) 616 (M^+, 3), 511 (0.5), 422 (2), 194 (4), 152 (100), 135 (84). Anal. Calcd for $C_{42}H_{36}N_2O_3$: C, 81.79; H, 5.88; N, 4.54. Found: C, 81.64; H, 5.88; N, 4.53.

Reaction of 4,5-Dihydro-3,4,4-trimethyl-5-methylene-1-(*p*-toluoyl)-1*H*-pyrazole (1b) with DPK. The reaction was carried out as described above for **1a**. The enol ester **2b** was isolated in 58% yield: mp 122–123 °C (from ethanol); IR (Nujol) 1720 (C=O), 1680 (C=O) cm^{-1}; ^1H NMR δ 1.03 (s, 6 H, CMe_2), 2.37 (s, 3 H, *p*-Me), 3.49 (s, 2 H, CH_2), 4.50 (d, 1 H, C=CH_2, J = 1.0 Hz), 6.0 (d, 1 H, C=CH_2, J = 1.0 Hz), 6.04 (s, 1 H, C*H*Ph_2), 7.13–7.31 (m, 22 H, Ar H), 7.70 (d, 2 H, Ar H, J = 8.5 Hz); mass spectrum, m/z (rel intensity) 630 (M^+, 4), 511 (0.5), 436 (7), 194 (39), 119 (100). Anal. Calcd for $C_{43}H_{38}N_2O_3$: C, 81.88; H, 6.07; N, 4.44. Found: C, 81.96; H, 6.09; N, 4.39.

Reaction of 1-(*p*-Chlorobenzoyl)-4,5-dihydro-3,4,4-trimethyl-5-methylene-1*H*-pyrazole (1c) with DPK. The reaction was carried out as described above for **1a**. The enol ester **2c** was isolated in 59% yield: mp 131–132 °C (from ethanol); IR (Nujol) 1720 (C=O), 1680 (C=O) cm^{-1}; ^1H NMR δ 1.04 (s, 6 H, CMe_2), 3.49 (s, 3 H, CH_2), 4.51 (d, 1 H, C=CH_2, J = 1.0 Hz), 6.01 (d, 1 H, C=CH_2, J = 1.0 Hz), 6.05 (s, 1 H, C*H*Ph_2), 7.16–7.31 (m, 22 H, Ar H), 7.68 (d, 2 H, Ar H, J = 9.0 Hz); mass spectrum, m/z (rel intensity) 652/650 (M^+, 6), 511 (0.5), 458/456 (8), 194 (50), 152 (45), 77 (100). Anal. Calcd for $C_{42}H_{35}ClN_2O_3$: C, 77.47; H, 5.42; N, 4.30. Found: C, 77.28; H, 5.31; N, 4.23.

Reaction of 1-Benzoyl-3-ethyl-4,5-dihydro-4,4-dimethyl-5-methylene-1*H*-pyrazole (1d) with DPK. The reaction was carried out as described above for **1a**. The enol ester **2d** was isolated in 47% yield: mp 129–130 °C (from ethanol); IR (Nujol) 1725 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR δ 1.19 (s, 6 H, CMe_2), 1.76 (d, 3 H, CH*Me*, J = 8 Hz), 3.47 (s, 2 H, CH_2), 6.12 (s, 1 H, C*H*Ph_2), 6.91 (q, 1 H, C=C*H*Me, J = 8 Hz), 7.20–7.30 (m, 22 H, Ar H), 7.51–7.57 (m, 1 H, Ar H), 7.78–7.81 (m, 2 H, Ar H); mass spectrum, m/z (rel intensity) 630 (M^+, 4), 525 (1), 436 (4), 194 (28), 165 (100), 105 (54). Anal. Calcd for $C_{43}H_{38}N_2O_3$: C, 81.88; H, 6.07; N, 4.44. Found: C, 81.98; H, 6.02; N, 4.31.

Hydrolysis of 2a. To a solution of **2a** (197 mg, 0.32 mmol) in ethanol (10 mL) was added hydrochloric acid (2 mL), and the mixture was refluxed for 4 h. The reaction mixture was then made alkaline by addition of aqueous NaOH (10%), the ethanol was evaporated under vacuum, and the remainder was extracted with chloroform (2 × 25 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under vacuum, and the residue was chromatographed (silica gel, 7:1 *n*-hexane/ethyl acetate) to give in elution order ethyl benzoate (22 mg, 46%), ethyl diphenylacetate (39 mg, 51%), and 3-(2-hydroxy-3,3-diphenyl-1-propenyl)-4,4,5-trimethyl-4*H*-pyrazole (**3**) (78 mg, 77%): mp 136–138 °C (from ether); IR (Nujol) 3290 (OH) cm^{-1}; ^1H NMR δ 1.18 (s, 6 H, CMe_2), 2.03 (s, 3 H, MeC=N), 5.09 and 5.20 (two s, 2 × 1 H, C*H*Ph_2 and CH), 7.30–7.45 (m, 10 H, Ar H); mass spectrum, m/z (rel intensity) 318 (M^+, 14), 304 (0.5), 151 (100), 123 (40). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 78.98; H, 6.84; N, 8.66. By acidification of the aqueous layer, a mixture of benzoic acid and diphenylacetic acid precipitated.

Hydrolysis of 2b. The hydrolysis was carried out as described above to give again compound **3** in 56% yield.

Reaction of 2b with 4-Methylbenzonitrile Oxide. A stirred solution of **2b** (630 mg, 1.0 mmol) in dry dichloromethane (30 mL) was treated with an equivalent of 4-methylbenzonitrile oxide (from 4-methylbenzohydroxamoyl chloride and triethylamine) for 12 h at 20 °C. The mixture was washed with water and $NaHCO_3$ solution (10%), the organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The crude mixture was chromatographed (silica gel, 10:1 *n*-hexane/ethyl acetate) to give the spiro derivative **4** (542 mg, 71%), mp 108–110

(12) McDonald, R. N.; Cousins, R. C. *J. Org. Chem.* **1980**, *45*, 2976.
(13) (a) Elguero, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1966**, 2832. (b) Völker, E. J.; Moore, J. A. *J. Org. Chem.* **1969**, *34*, 3639.
(14) Mitkidou, S.; Stephanidou-Stephanatou, J. Unpublished results.

°C (ethanol): IR (Nujol) 1715 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR δ 0.90 (s, 3 H, CMe_2), 0.99 (s, 3 H, CMe_2), 2.33 (s, 3 H, *p*-Me), 2.39 (s, 3 H, *p*-Me), 3.26 (d, 2 H, CH_2, J = 17 Hz), 3.43 (d, 2 H, $Ph_2C{=}CCH_2$, J = 17 Hz), 3.53 (d, 2 H, $Ph_2C{=}CCH_2$, J = 17 Hz), 4.04 (d, 2 H, CH_2, J = 17 Hz), 5.89 (s, 1 H, $COCHPh_2$), 7.02–7.30 (m, 24 H, Ar H), 7.53 (d, 2 H, Ar H, J = 7 Hz), 7.77 (d, 2 H, Ar H, J = 7 Hz); mass spectrum, m/z (rel intensity) 569 (M^+ – $Ph_2C{=}C{=}O$, 2), 433 (5), 375 (4), 194 (31), 165 (60), 119 (100). Anal. Calcd for $C_{51}H_{45}N_3O_4$: C, 80.49; H, 5.93; N, 5.50. Found: C, 80.28, H, 6.07; N, 5.44.

Reaction of 1a with DCK. To a stirred solution of **1a** (342 mg, 1.5 mmol) and Et_3N (202 mg, 2.0 mmol) in dry dichloromethane (45 mL) was added dropwise a solution of dichloroacetyl chloride (266 mg, 1.8 mmol) in the same solvent (10 mL) in about 2 h. The reaction mixture was stirred at room temperature for 24 h, then a second amount of Et_3N (202 mg, 2.0 mmol) was added, followed by the dropwise addition of a solution of dichloroacetyl chloride (266 mg, 1.8 mmol) in dichloromethane (10 mL) in about 2 h. The reaction mixture was stirred for another 24 h and then was washed with water, the organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. Chromatography of the reaction mixture (silica gel, 10:1 *n*-hexane/ethyl acetate) gave the hydroxypyrazoline **5a** (250 mg, 69%), mp 158–161 °C (lit.[8] mp 158–161 °C).

Reaction of 1b with DCK. The reaction was carried out as described above to give the hydroxypyrazoline **5b** in 67% yield, mp 159–161 °C (lit.[8] mp 159–161 °C).

Reaction of 1c with DCK. The reaction was carried out as described above to give the hydroxypyrazoline **5c** in 59% yield, mp 142–144 °C (lit.[8] mp 142–144 °C).

Reaction of 1g with DCK. The reaction was carried out as described above to give the hydroxypyrazoline **5g** in 56% yield: mp 117–119 °C (ethanol); IR (Nujol) 3420 (OH), 1645 (C=O) cm^{-1}; ^1H NMR δ 1.31 (s, 3 H, CMe_2), 1.43 (s, 3 H, CMe_2), 1.76 (s, 3 H, 5-Me), 2.36 (s, 3 H, *p*-Me), 5.11 (br s, 1 H, OH), 7.16–7.41 (m, 5 H, Ar H), 7.56–7.91 (m, 4 H, Ar H); ^{13}C NMR δ 19.71 (q, J = 128 Hz, 5-Me), 21.35 (m, 4,4-Me), 21.52 (q, J = 128 Hz, *p*-Me), 53.16, 96.61, 127.59, 128.36, 128.44, 129.71, 130.25, 131.30, 131.40, 141.80, 162.06, 170.03; mass spectrum, m/z (rel intensity) 322 (M^+, 4), 119 (100).

X-ray Crystallographic Analysis of 2b. The compound **2b**, $C_{43}H_{38}N_2O_3$, M_r = 630.73, crystallizes as triclinic crystals in space group $P\bar{1}$, a = 12.072 (4), b = 11.664 (3), and c = 14.061 (4) Å, α = 112.22 (2)°, β = 76.84 (2)°, γ = 109.13 (2)°, V = 1785.5 (6) Å^3, Z = 2, D_m = 1.15 g cm^{-3}, D_c = 1.173 g cm^{-3}, μ = 0.4 cm^{-1}. Data were collected by using a crystal of ca. 0.29 × 0.32 × 0.42 mm dimensions, mounted on a Nicolet $P2_1$ diffractometer, $\omega/2\theta$ mode, Mo K$\bar{\alpha}$ Zr-filtered radiation (λ = 0.71069 Å), with scan width 1.8° (2θ) plus α_1–α_2 divergence, scan speed 2–18° 2θ°/min, $2\theta_{max}$ = 44°. Out of 3577 collected reflections 3359 were unique and 2315 were considered observed with I_0 $2.1\sigma(I_0)$. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using SHELXS-86[15] and refined by full matrix least squares using SHELX-76[16] with all non-H atoms refined anisotropically. Although most hydrogens were located from difference Fourier maps, they were all placed in calculated positions at 0.98 Å from their respective C-atoms. Methyl groups and phenyl rings (C–C = 1.4 Å) were refined as rigid groups. Final R/R_w = 0.0611/0.0565 for observed data using unit weights. $\Delta\rho_{max}/\Delta\rho_{min}$ = 0.28/–0.17 e Å^{-3}.

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Registry No. **1a**, 87885-78-7; **1b**, 87885-80-1; **1c**, 98669-81-9; **1d**, 127519-02-2; **1e**, 127519-03-3; **1f**, 127519-04-4; **1f** hydroxy derivative, 127519-05-5; **1g**, 109072-63-1; **2a**, 127519-06-6; **2b**, 127519-07-7; **2c**, 127519-08-8; **2d**, 127519-09-9; **3**, 127519-10-2; **4**, 127519-11-3; **5a**, 87885-62-9; **5b**, 87885-63-0; **5c**, 87885-65-2; **5g**, 109072-62-0; α-acetylisobutyraldehyde, 1750-73-8; *p*-toluohydrazide, 3619-22-5; 3,3-dimethyl-2,4-hexanedione, 6303-70-4; benzoic hydrazide, 613-94-5; 1-benzoyl-3-ethyl-4,5-dihydro-5-hydroxy-4,4,5-trimethyl-1*H*-pyrazole, 127519-12-4; diphenylacetyl chloride, 1871-76-7; ethyl benzoate, 93-89-0; ethyl diphenylacetate, 3468-99-3; 4-methylbenzonitrile oxide, 13820-14-9; 4-methylbenzohydroxamoyl chloride, 36288-37-6; dichloroacetyl chloride, 79-36-7.

Supplementary Material Available: Tables of X-ray data for **2b** (4 pages). Ordering information is given on any current masthead page.

(15) Sheldrick, G. M. SHELXS-86 program for solution of crystal structure; Göttingen, FRG, 1986.
(16) Sheldrick, G. M. SHELX-76 program for crystal structure determination, Univ. of Cambridge, England, 1976.

Application of 2-Substituted Vinamidinium Salts to the Synthesis of 2,4-Disubstituted Pyrroles

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A variety of 2-substituted vinamidinium salts react with α-amino acid esters under basic conditions to produce 2-carbethoxy-4-substituted-pyrroles in good yield. The overall process represents a short and efficient synthesis of highly functionalized pyrroles from α-substituted acetic acid precursors. Such reactions may involve the intermediacy of azomethine ylids or "pentadienyl like" anions.

The synthesis of pyrrole derivatives[1] and related compounds has been actively pursued in recent years due in part to the pharmacological properties of certain members of this class of substances. For example pyrrolnitrin (1)[2] is a naturally occurring 4-arylpyrrole, and a number of related compounds possess antidiabetic,[3] fungicidal,[4] muscle relaxant,[5] and antibacterial[6] properties.

(1) For the synthesis of 3-substituted pyrroles, see: Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353. For the synthesis of pyrrolidine derivatives, see: Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkataramanan, M. K.; Wong, G. S. *J. Org. Chem.* **1989**, *54*, 644 and references therein.

(2) Herbert, R. B. In *The Alkaloids*; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. 12.
(3) Holland, G. F. U.S. Patent 4,282,242, 1981; *Chem. Abstr.* **1981**, *95*, 187068e.
(4) Nippon Soda Co. Ltd. Japanese Patent 8,179,672, 1981; *Chem. Abstr.* **1981**, *95*, 187069f.

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