A Synthetic Route to Bicyclic Pyrazolenines via 3-Chloropyrazolines and the Ring Opening of Pyrazolenines to Diazoalkenes

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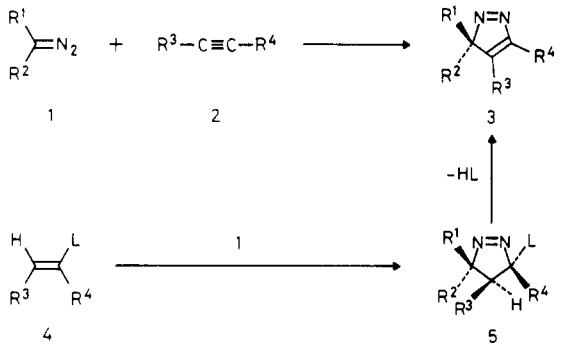
Treatment of 5,5-disubstituted 3-chloro-1-pyrazolines, derived from the reaction between disubstituted diazomethanes and dimethyl chlorofumarate, with triethylamine gives the corresponding 3,3-disubstituted 3*H*-pyrazoles in good yield. This method was applied to the synthesis of bicyclic pyrazolenines. The system fused to a five-membered imide ring did not afford 3*H*-pyrazoles but the diazoalkenes (**20b–e**), formed by thermal ring opening of the 3*H*-pyrazoles. In contrast, in a six-membered ring fused system, the 3*H*-pyrazoles (**14a–d**) were isolated. The isolation of diazoalkenes from the five-membered ring fused system is explained by destabilization of the 3*H*-pyrazoles due to strain arising from fusion of two five-membered rings.

Introduction

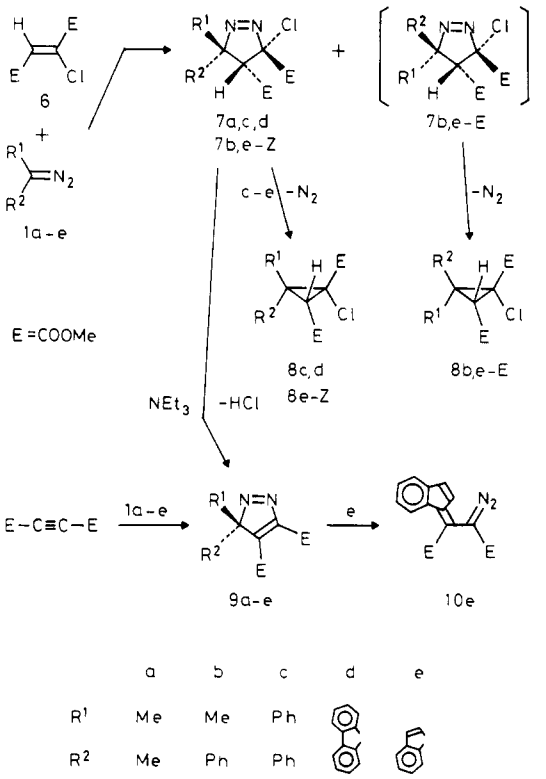
Most known 3*H*-pyrazoles (pyrazolenines) have been synthesized by 1,3-dipolar cycloaddition of diazoalkanes (**1**) to alkynes (**2**).[1] It is known that 3*H*-pyrazoles (**3**) undergo thermal [1,5]-sigmatropic rearrangement (the van Alphen–Hüttel rearrangement[2]) to give 1*H*- and/or 4*H*-pyrazoles and also photochemical ring opening to diazoalkenes followed by decomposition to vinyl carbenes,[1] whereas a few examples of thermal ring opening to diazoalkenes have been reported.[3,4] However, few bicyclic pyrazolenines have been reported because of poor availability of cycloalkynic compounds, except for cyclooctyne and benzyne.

We studied thermal decomposition of 5,5-disubstituted pyrazolines (**5**), which were prepared by the reaction of disubstituted diazomethanes (**1**) with 1-chloro-1,2-diacylethylene derivatives (**4**).[5] The pyrazolines **5** bearing a chlorine at C-3 as a suitable leaving group could in principle undergo dehydrochlorination by treatment with base to give the corresponding 3*H*-pyrazole derivatives (**3**).



We have studied here the synthesis of 3*H*-pyrazoles (**3**) by elimination of hydrogen chloride from pyrazolines (**5**) and have extended it to the synthesis of ring-fused systems which cannot be obtained by traditional alkyne–diazoalkane cycloaddition. We also find that 3*H*-pyrazoles fused to a five-membered imide ring undergo facile thermal ring-opening to vinyldiazoalkanes.

Scheme I



Results and Discussion

Treatment of 3,4-bis(methoxycarbonyl)-3-chloro-5,5-dimethyl-1-pyrazoline (**7a**), prepared from dimethyl chlorofumarate (**6**) and 2-diazopropane (**1a**),[5] with an equimolar amount of triethylamine gave the corresponding 3*H*-pyrazole **9a** in high yield (Scheme I). Similarly, dehydrochlorination of 3-chloropyrazoline **7b-Z** bearing a methyl and a phenyl group at C-5, which was isolated in the reaction of 1-phenyldiazoethane (**1b**) with **6**,[5] also gave the 3*H*-pyrazole **9b** in high yield. However, as the reactions of **6** with diphenyldiazomethane (**1c**), 9-diazofluorene (**1d**), and diazoindene (**1e**), did not afford pyrazolines but the corresponding cyclopropanes (**8c**, **8d**,[5] **8e-Z**, and **8e-E**[6]), the reactions of **6** with diaryldiazomethanes

(1) (a) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. Synthetic Application of Diazoalkanes. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; Part 2, p 884. (b) Sammes, M. P.; Katritzky, A. R. The 3*H*-pyrazoles. In *Advances in Heterocyclic Chemistry*; Academic Press, Inc.: New York, 1983; Vol. 34, p 1. (c) Regitz, M.; Heydt, H. Diazoalkanes. In *1,3-Dipolar Cycloaddition Chemistry General Heterocyclic Chemistry Series*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 502.

(2) (a) van Alphen, J. *Recl. Trav. Chim. Pays-Bas* **1943**, *62*, 485. (b) van Alphen, J. *Ibid.* **1943**, *62*, 491. (c) Hüttel, R.; Franke, K.; Martin, H.; Riedl, J. *Chem. Ber.* **1960**, *93*, 1433.

(3) (a) Mataka, S.; Takahashi, K.; Tashiro, M. *Chem. Lett.* **1979**, 1033. (b) Mataka, S.; Ohshima, T.; Tashiro, M. *J. Org. Chem.* **1981**, *46*, 3960.

(4) Padwa, A.; Goldstein, S. *Can. J. Chem.* **1984**, *62*, 2506.

(5) Nakano, Y.; Hamaguchi, M.; Nagai, T. *J. Org. Chem.* **1989**, *54*, 1135. Reaction of 1-phenyldiazoethane with dimethyl chlorofumarate (**6**) and 2-chloro-1,4-naphthoquinone (**11**) gave the corresponding pyrazolines **7b-Z** and **12b-Z** and cyclopropanes **8b-E** and **13b-E**, respectively.

(6) Nakano, Y.; Hamaguchi, M.; Nagai, T., unpublished results.

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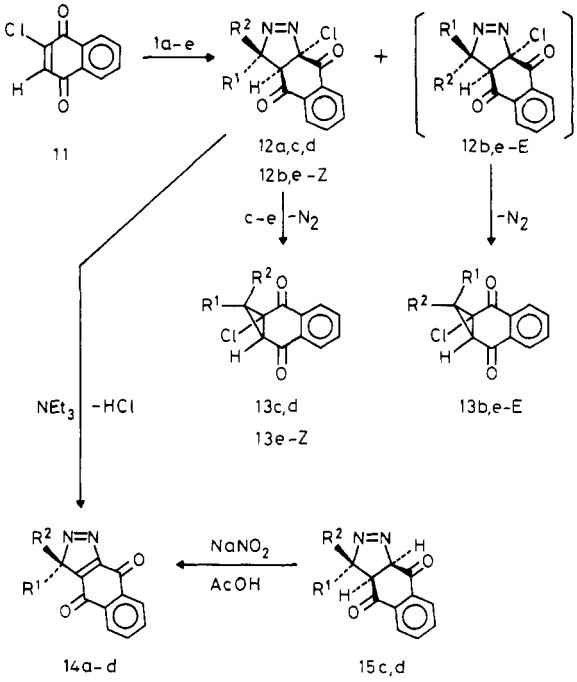
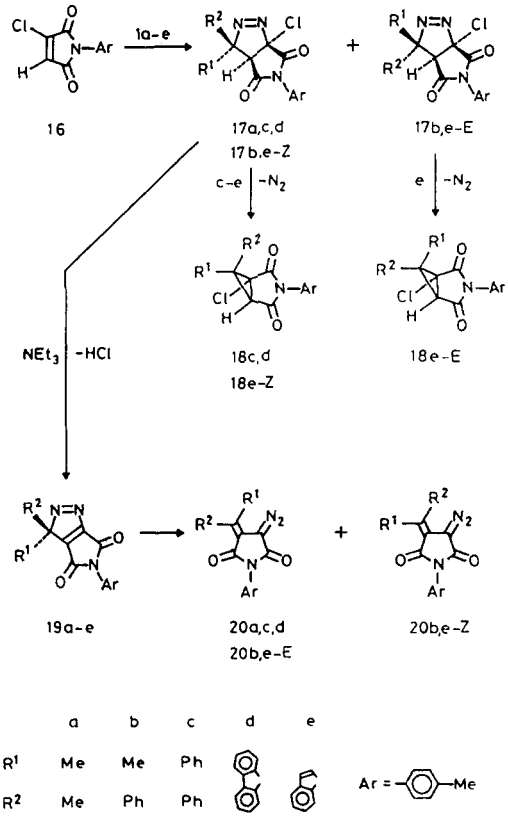
Scheme II



Scheme III



(**1c**, **1d**, and **1e**) were carried out in the presence of triethylamine in order to obtain 3*H*-pyrazoles from unstable intermediary pyrazolines (**7c**, **7d**, **7e-E**, and **7e-Z**). The reaction in the presence of an equimolar amount of triethylamine resulted in formation of the corresponding cyclopropanes (**8c**, **8d**, and **8e-Z** and **8e-E**) as major products, accompanied with small amounts of 3*H*-pyrazoles **9c** and **9d**, respectively, indicating that the elimination of hydrogen chloride from the 3-chloropyrazolines under this condition competed less effectively with the cyclopropanation. Whereas with triethylamine as solvent the reaction of **1c** with **6** gave the 3*H*-pyrazole **9c** in 82% yield with a trace amount of **8c**, the reaction of **1d** with **6** in triethylamine gave the 3*H*-pyrazole **9d** and the cyclopropane **8d** in a ratio of 1:2.26. The reaction of **1e** with **6** in triethylamine did not afford the 3*H*-pyrazole **9e** but the cyclopropanes **8e-Z** (2%) and **8e-E** (28%) along with a small amount of the diazoalkene **10e** (9%), the IR of which showed a characteristic diazo band at 2096 cm^{-1}. Formation of **10e** can be explained by thermal ring opening of the 3*H*-pyrazole **9e**, arising from the elimination reaction of the pyrazoline **7e-Z** (or **7e-E**). Padwa et al. reported that the 3*H*-pyrazole **9e** underwent the ring opening to **10e** in the reaction of **1e** with dimethyl acetylenedicarboxylate.[4] Obviously, the yield of 3*H*-pyrazoles is dependent on the relative rates of dehydrochlorination and cyclopropanation of the pyrazolines. These 3*H*-pyrazoles proved identical with authentic samples, which were prepared by 1,3-dipolar cycloaddition between diazoalkanes **1a–d** and dimethyl acetylenedicarboxylate.[2,6,7]

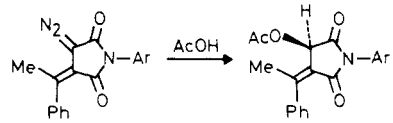
Furthermore, we extended the present synthetic procedure to the synthesis of bicyclic 3*H*-pyrazoles, which could not be prepared by conventional 1,3-dipolar cycloaddition between diazo compounds and alkynes. Bicyclic pyrazolines **12a** and **12b-Z**, prepared from reaction of 2-chloro-1,4-naphthoquinone (**11**) with the diazoalkanes **1a** and **1b**,[5] were treated with triethylamine at room temperature to give the corresponding 3*H*-pyrazoles **14a** and **14b** in high yield. As pyrazolines **12c**, **12d**, **12e-Z**, and **12e-E** were too unstable to be isolated and decomposed to the cyclopropanes **13c**, **13d**, **13e-Z**, and **13e-E**,[5,6] the reactions of chloronaphthoquinone (**11**) with **1c** and **1d** were carried out in the presence of a large excess of triethylamine to give the 3*H*-pyrazoles **14c** (75%) and **14d** (83%), respectively, which were identical in all properties with authentic samples synthesized by oxidation of **15c** and **15d**[8] (Scheme II). But the reaction of **1e** with **11** in the presence of triethylamine did not afford any characterizable products. Thus, this method proved useful in the synthesis of some bicyclic 3*H*-pyrazoles.

Next, the pyrazoline **17a**, which was prepared by the 1,3-dipolar cycloaddition between **1a** and *N*-tolylchloromaleimide (**16**),[5] was treated with an equimolar amount of triethylamine to give the 3*H*-pyrazole **19a** in 95% yield (Scheme III). However, when the pyrazolines **17b-Z** and **17b-E**, isolated from the reaction of 1-phenyldiazoethane (**1b**) with **16**,[5] were treated with triethylamine, two kinds of orange solids were isolated in a ratio of 2:1. Elemental analysis of these solids indicated that they were isomers of the corresponding 3*H*-pyrazole **19b**. The IR spectra of the major (A) and the minor product (B) exhibited characteristic diazo bands at 2085 and 2107 cm^{-1} with carbonyl bands at 1749, 1701 cm^{-1} and 1745, 1705 cm^{-1}, respectively, indicating isomeric ring-opened vinyldiazo compounds **20b-E** and **20b-Z**. A methyl singlet of B (δ 2.71) appeared at lower field than that of A (δ 2.31) in their ^1H NMR spectra. ^{13}C NMR spectra of A and B showed two carbonyl carbons at δ 166.37, 161.77 and δ 166.15, 163.67, respectively. High-field carbonyl carbon of B showed long-range coupling with methyl protons ($^4J_{CH}$ = 1.1 Hz), whereas other carbonyl carbons appeared as singlets. Because the anisotropy effect of diazo group is ambiguous and ^4J(C,H) coupling have been observed in trans and cis configuration,[9] the stereochemistry of A and B are ambiguous from

(7) Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett.* **1969**, 15.

(8) (a) Fieser, L. F.; Peters, M. A. *J. Am. Chem. Soc.* **1931**, *53*, 4080. (b) Horner, V. L; Lingnan, E. *Justus Liebigs Ann. Chem.* **1955**, *591*, 21.

the spectral data described above. In order to obtain additional information for structural assignment, decomposition of A and B in acetic acid was carried out, giving the corresponding acetate **21b-E** and **21b-Z**, respectively. The structures of **21b-E** and **21b-Z** were assigned on the basis of their NMR spectra. The acetate **21b-E** showed two singlets at δ 2.17 (3 H) and 2.29 (3 H), a doublet at 2.24 (3 H, J = 1.1 Hz), a quartet at 5.92 (1 H, J = 1.1 Hz), and aromatic protons at 7.13 (5 H) and 7.26 (4 H). The acetate **21b-Z** showed two singlets at δ 1.60 (3 H) and 2.35 (3 H), a doublet at 2.67 (3 H, J = 1.5 Hz), a quartet at 6.02 (1 H, J = 1.5 Hz), and aromatic protons at 7.07–7.42 (9 H). In both products, the hydrogen attached to the carbon bearing an acetoxy group exhibited homoallylic long-range coupling across five bonds with methyl protons. Cis configuration of phenyl group toward acetoxy group in **21b-Z** can be rationalized in terms of appearance of acetoxy methyl protons of **21b-Z** (δ 1.60) at high field, due to the shielding effect of cis phenyl group, in comparison with that of **21b-E** (δ 2.24). The results described above allowed the structures of A and B to be assigned **20b-E** and **20b-Z**, respectively.



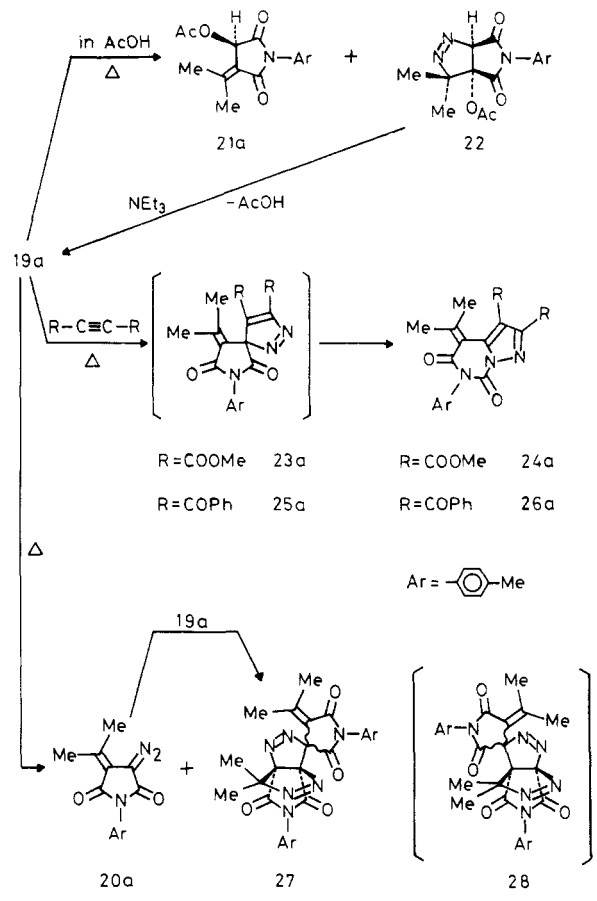
20b-E 21b-E

20b-Z 21b-Z

In the reaction of chloromaleimide **16** with **1c**, **1d**, and **1e** the initially formed pyrazolines **17c**, **17d**, **17e-Z**, and **17e-E** were not isolated, giving the corresponding cyclopropanes **18c**, **18d**,[5] **18e-Z**, and **18e-E**,[6] respectively. So, the reactions were carried out in the presence of a large amount of triethylamine, resulting in that not the corresponding 3*H*-pyrazoles **19c**, **19d**, and **19e** but the vinyldiazo compounds **20c** (77%), **20d** (71%), and **20e-E** (or **20e-Z**) (11%) were isolated with trace amounts of the corresponding cyclopropanes. The IR spectra of **20c**, **20d**, and **20e-E** (or **20e-Z**) exhibited characteristic diazo bands at 2109, 2093, and 2092 cm^{-1}, respectively. Formation of the vinyldiazo compounds **20b–e** can be rationalized in terms of the thermal ring-opening of 3*H*-pyrazoles (**19b–e**).

Among 3*H*-pyrazoles studied here, the system fused by a five-membered imide ring afforded the vinyldiazoalkane derivatives **20b–e**, whereas the system fused by a six-membered ring afforded the 3*H*-pyrazoles **14a–d**. Which product is preferentially formed, a 3*H*-pyrazole or a diazoalkene, should depend upon the relative stability between the 3*H*-pyrazole and the vinyldiazoalkane. In general 3*H*-pyrazoles are more stable than ring-opened derivatives,[10] though in some special cases vinyldiazoalkanes have been isolated as stable isomers.[3,4] It seems likely that, in the five-membered imide ring-fused 3*H*-pyrazole system,

Scheme IV



ring-opened derivatives **20** are more stable than the corresponding 3*H*-pyrazoles **19**. However, 3*H*-pyrazole **19a** was isolated as a stable compound without formation of the ring-opened product **20a**.

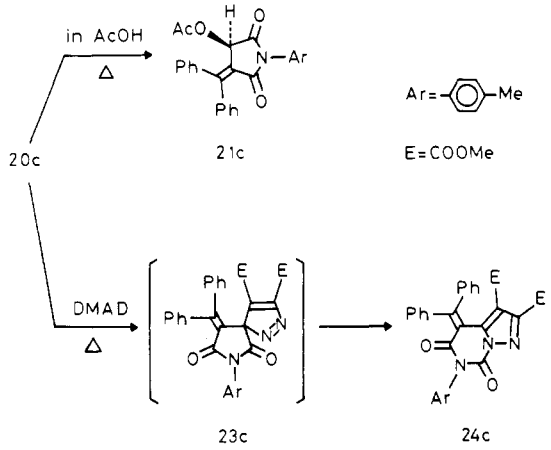
In order to check whether the 3*H*-pyrazole **19a** is kinetically or thermodynamically more stable than the diazoalkene **20a**, we heated **19a** under several conditions. The van Alphen–Hüttel rearrangement is known to be catalyzed by acetic acid as solvent,[2,11] so thermal decomposition of the 3*H*-pyrazole **19a** was carried out in acetic acid (Scheme IV). Column chromatography of the reaction mixture gave the acetate derivative **21a** (23%) and a white crystalline solid (46%). The NMR spectrum of **21a** showed homoallylic long-range coupling between the methine proton and the protons of either methyl group. Elemental analysis of the solid was in accord with an adduct of **19a** with acetic acid, the structure of which was assigned the bicyclic pyrazoline **22**. The structure **22** was supported by the fact that treatment of **22** with triethylamine gave the 3*H*-pyrazole **19a**. Formation of **21a** is expected to occur via two possible paths: (i) extrusion of nitrogen from **19a** to generate the carbene followed by insertion into the O–H bond of acetic acid; (ii) thermal ring opening of **19a** to the diazoalkene **20a** with subsequent acetic acid decomposition. Similar to the case of **20b-Z** and **20b-E**, decomposition of the diazo compound **20c** in refluxing acetic acid also gave the corresponding acetate **21c** in good yield, suggesting path (ii) in the above **19a** reaction (Scheme V). Appearance of the methyl protons of acetoxy group in **21c** at high field (δ 1.66) due to the shielding effect of the cis phenyl group provides additional

(9) Kalinowski, H.-O.; Berger, S.; Braun, S. ^{13}C–X Spin–Spin Coupling. In *Carbon-13 NMR Spectroscopy*; Wiley: New York, 1988; p 543.

(10) (a) Adamson, D. W.; Kenner, J. *J. Chem. Soc.* **1935**, 286. (b) Hurd, C. D.; Lui, S. C. *J. Am. Chem. Soc.* **1935**, *57*, 2656. (c) Ledwith, A.; Parry, D. *J. Chem. Soc. B* **1967**, 41. (d) Brewbaker, J. L.; Hart, H. *J. Am. Chem. Soc.* **1969**, *91*, 711. (e) Pincock, J. A.; Murray, K. P. *Can. J. Chem.* **1979**, *57*, 1043. (f) Pincock, J. A.; Mathur, N. C. *J. Org. Chem.* **1982**, *47*, 3699.

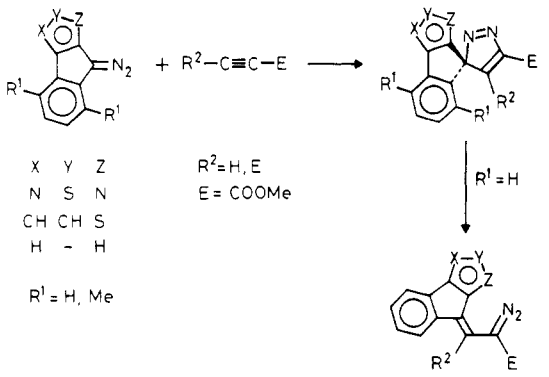
(11) Baumes, R.; Elguero, J.; Jacquier, R.; Tarrago, G. *Tetrahedron Lett.* **1973**, 3781.

Scheme V



support for the structural assignment of **21b-Z** and **21b-E**. We attempted to trap **20a** by dimethyl acetylenedicarboxylate (DMAD) and dibenzoylacetylene (DBA). When **19a** was heated in the presence of DMAD or DBA for 10 min in toluene, a 1:1 adduct of **19a** with DMAD or DBA was isolated in good yield, indicating the ring opening of **19a** to **20a**. The structures of the 1:1 adducts were not assigned the 1,3-dipolar cycloadducts **23a** and **25a** of **20a** with DMAD and DBA, but the bicyclic 1*H*-pyrazoles **24a** and **26a**, on the basis of the following results. IR spectra of **24a** and **26a** exhibited two cyclic imide absorption bands with comparable intensity at 1770, 1704 cm^{-1} (with additional ester absorption at 1729 cm^{-1}) and 1762, 1705 cm^{-1} (with additional carbonyl absorption at 1654 cm^{-1}), respectively. Twin five-membered cyclic imide bands of **17a**, **19a**, **21a**, and **21c** appeared at 1774–1791 cm^{-1} (weak absorption) and 1710–1735 cm^{-1} (strong absorption). The absorption at lower frequency than those of five-membered ring imides of **17a**, **19a**, **21a**, and **21c** and the comparable intensity of twin imide bands for the obtained adducts can exclude the structures **23a** and **25a**, which should exhibit a characteristic absorption of a five-membered cyclic imides. UV spectra of the adducts **24a** and **26a** showed absorptions in the wavelength region different from that of β-methylcrototoluide,[12] which would be contained in **23a** and **25a** as a chromophore. Thermal stability of the adducts in refluxing toluene and acetic acid supports the structures of **24a** and **26a** on the basis of the facts that many 3-acylpyrazolenines have been reported to be unstable and to easily undergo [1,5]-sigmatropic acyl rearrangement to 1-acylpyrazoles.[13] Reaction of the isolated vinyldiazoalkane **20c** with DMAD also gave a yellow 1:1 adduct **24c**, which showed a very similar IR spectrum (1763, 1730, 1710 cm^{-1}) to that of **24a**. These results allow these adducts to be assigned the structures **24a,c** and **26a**. After heating the 3*H*-pyrazole **19a** for 10 min in toluene, treatment of the reaction mixture with column chromatography gave a white solid and a fraction containing the diazoalkene **20a** contaminated with the solid. The IR spectrum of **20a** exhibited a diazo band at 2089 cm^{-1}, and the ^1H NMR spectrum showed three methyl singlets at δ 2.05, 2.36, and 2.46. The high-field singlet (δ 2.05) and the low-field singlet (δ 2.46) were assigned to the protons of methyl group cis to diazo group and the protons of trans

Scheme VI



methyl group, respectively, on the basis of ^1H NMR spectra of **20b-E** and **20b-Z**. These results indicate the shielding effect of the diazo group toward the *Z*-methyl group in this type of diazo compounds. Elemental analysis and the ^1H NMR spectrum of the white solid indicate a dimer of the 3*H*-pyrazole **19a**. The NMR spectrum of the dimer showed five methyl singlets at δ 1.56, 1.71, 1.76, 2.38 (2 Me), and 2.46 and absorptions of two nonequivalent tolyl groups. We presumed that the structure of the dimer was 1,3-dipolar adduct **27** or **28** between **19a** and **20a** on the basis of the fact that some 3*H*-pyrazoles undergo 1,3-dipolar cycloaddition with diazoalkanes.[14] However, adducts bearing a carbon substituted by two geminal azo groups are known to be unstable,[14] so the structure **28** can be excluded. Furthermore, to prevent dimerization a very dilute toluene solution of **19a** was refluxed for 10 min and gave **20a** (59%) as a major product and the dimer **27** as a minor product (5%). The structure of the dimer **27** was confirmed by allowing **20a** to react with **19a** at room temperature for 14 days, giving **27** in 88% yield, though **19a** was stable under the same condition without **20a**. These results indicate that 3*H*-pyrazole **19a** isomerizes to the corresponding vinyldiazoalkane **20a** on heating. We concluded that **20a** is thermodynamically more stable than **19a** and that **19a** has a high activation energy for the ring opening to **20a** compared with **19b–e**, allowing the isolation of **19a** as a stable product at room temperature.

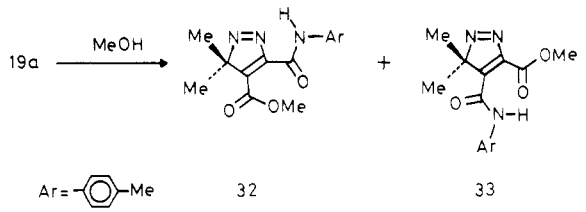
In the system **9a–d** bearing two ester groups and the system **14a–d** fused by a six-membered ring, the 3*H*-pyrazoles were isolated without formation of the diazoalkenes. In careful inspection of IR spectra of the reaction mixture of the thermal decomposition product of 3*H*-pyrazoles **14**, the diazo absorption was not observed. These results suggest that the relative stability between 3*H*-pyrazoles and vinyldiazoalkanes in the maleimide fused system is opposite to that in other systems. Several examples in which ring-opened derivatives are more stable than the 3*H*-pyrazoles are known. Padwa et al. found that the reactions of diazoindene (**1e**) with acetylenic esters gave diazoalkenes.[4] Mataka et al. reported that the reactions of five-membered heterocyclic ring-fused diazoindenes with acetylenic esters gave diazoalkenes, while the corresponding 3*H*-pyrazoles were isolated when a steric interaction between the ester and a 5-methyl group of the indenothiazole ring was present[3] (Scheme VI). We also found that elimination of hydrogen halide from 4-halopyrazolines bearing two electron-withdrawing groups at C-3 gave diazoalkenes.[6] These results suggest that the relative stability between 3*H*-pyrazoles and diazoalkenes

(12) UV spectrum of β-methylcrototoluid: λ_{max} (MeOH) 210.2 nm (ε 20 200), 271.4 nm (ε 16 100).

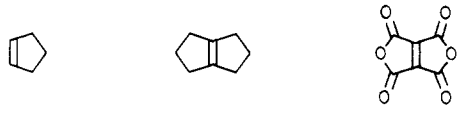
(13) (a) Yamazaki, J.; Shechter, H. *Tetrahedron Lett.* **1973**, 1417. (b) Yamazaki, J.; Shechter, H. *Ibid.* **1972**, 4533. (c) Elzinga, J.; Hogeveen, H.; Schudde, E. P. *J. Org. Chem.* **1980**, *45*, 4337. (d) Franck-Neumann, M.; Dietrich-Buchecker, C. *Angew. Chem.* **1973**, *85*, 259.

(14) (a) Franck-Neumann, M.; Martina, D.; Dietrich-Buchecker, C. *Tetrahedron Lett.* **1975**, 763. (b) Franck-Neumann, M.; Martina, D. *Ibid.* **1975**, 1767. (c) Dietrich-Buchecker, C.; Franck-Neumann, M. *Tetrahedron.* **1977**, *33*, 745.

Scheme VII



might depend on the substituents at C-3. Electron-withdrawing groups including the indene system at C-3 may cause the ring-opened systems to be more stable than the ring-closed systems. However, in spite of various substituents at C-3, all maleimide-fused systems described here gave the diazoalkenes as the more stable isomers, suggesting that the instability of the maleimide-fused system is not connected to the substituent at C-3 but to the five-membered imide ring. The 3*H*-pyrazoles **19a–e** corresponding to the diazoalkenes **20a–e** are composed of two five-membered ring fused bicyclic system. Although two five-membered ring fused ethylene derivatives have been known as stable compounds,[15] ethylenetetracarboxylic acid anhydride (**31**), one of them, easily undergoes hydrolysis,[15b] indicating that it is due to the strain of the molecule. Our MM2[16] calculation for $\Delta^{1,5}$-bicyclo[3.3.0]-octene (**30**) showed that the strain energy is 17.60 kcal/mol greater than that of cyclopentene (**29**).[17] Similarly, 3*H*-



pyrazoles **19a–e** are expected to have greater strain energy than those of monocyclic 3*H*-pyrazoles **9a–e** and six-membered ring fused 3*H*-pyrazoles **14a–e** and also the diazoalkenes **20a–e**. This strain energy causes destabilization of the ring-closed systems, resulting in isolation of the ring-opened systems as stable compounds. MNDO[18] calculation showed that the difference in the heat of formation between the parent imide ring fused system of **19a–e** and the corresponding diazoalkene is ca. 20 kcal/mol less than the difference between the parent 3*H*-pyrazole and vinyldiazomethane, indicating destabilization due to the fused imide ring.[19] As strained imides are known to undergo hydrolysis,[20] methanolysis of **19a** was carried out in order to obtain chemical evidence of the bicyclic ring strain for the 3*H*-pyrazoles **19**. The 3*H*-pyrazole **19a** was treated with four molar amounts of methanol in the presence of triethylamine in dichloromethane to give two isomeric products (**32** and **33**) (Scheme VII), arising from the methanolysis of imide ring in **19a**, but *N*-tolylmaleimide was stable under the same condition. The structure of **32** and **33** were assigned on the basis of the following data. NMR spectra of **32** and **33** showed very similar patterns. The major isomer **32** has a broad singlet (N–H) at δ 11.38 and carbonyl absorptions at 1697 and 1664 cm^{-1} and the minor isomer **33** exhibited an N–H proton at δ 9.41.

These results support the premise that isolation of the diazoalkenes **20a–e** is no doubt mainly connected to the ring strain of the $\Delta^{1,5}$-bicyclo[3.3.0]octene system of **19a–e**.

Experimental Section

The ^{1}H NMR and ^{13}C NMR spectra were obtained with a Varian EM-390 (90 MHz) and a JEOL JNM-GX500 instrument, respectively, with tetramethylsilane as the internal standard. The IR spectra were recorded on Perkin-Elmer 983G infrared spectrophotometer. All melting points were uncorrected.[21]

The pyrazolines (**7a**, **7b-Z**, **12a**, **12b-Z**, **17a**, **17b-Z**, and **17b-E**) were synthesized by the methods reported in the previous paper.[5]

Treatment of Disubstituted 3,4-Bis(methoxycarbonyl)-3-chloropyrazolines (7) with Triethylamine. Reaction of *trans*-3,4-Bis(methoxycarbonyl)-3-chloro-5,5-dimethyl-1-pyrazoline (7a) with an Equimolar Amount of Triethylamine. A solution of **7a** (2.00 mmol) and triethylamine (2.00 mmol) in benzene (4 mL) was allowed to stand at room temperature for 3 days. The reaction mixture was dissolved in CH_2Cl_2, and the solution was washed with water and then dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed over silica gel with benzene as eluent. The main fraction gave 4,5-bis(methoxycarbonyl)-3,3-dimethyl-3*H*-pyrazole (**9a**) as a yellow oil (84%): NMR δ 1.58 (s, 6 H), 3.89 (s, 3 H), 3.97 (s, 3 H); IR (film) 1730, 1636 cm^{-1}. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.61; H, 5.96; N, 12.95.

Reaction of 3-Chloro-*r*-3,*t*-4-bis(methoxycarbonyl)-*c*-5-methyl-*t*-5-phenyl-1-pyrazoline (7b-Z) with an Equimolar Amount of Triethylamine. By using a similar procedure to that described above (reaction time 8 days), 4,5-bis(methoxycarbonyl)-3-methyl-3-phenyl-3*H*-pyrazole (**9b**) (93%) was obtained from **7b-Z** (2.00 mmol) and triethylamine (2.04 mmol) in benzene (2.5 mL). Recrystallization from benzene gave yellow prisms: mp 68 °C; NMR δ 1.95 (s, 3 H), 3.72 (s, 3 H), 3.95 (s, 3 H), 7.03–7.39 (m, 5 H); IR (KBr) 1747, 1721 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.39; H, 5.16; N, 10.19.

Reaction of Diphenyldiazomethane (1c) with Dimethyl Chlorofumarate (6) in the Presence of an Equimolar Amount of Triethylamine. To **6** (2.40 mmol) was added a solution of **1c** (2.00 mmol) and triethylamine (2.00 mmol) in benzene (5 mL), and the mixture was allowed to stand at room temperature for 2 days. The reaction mixture was dissolved in CH_2Cl_2, and the solution was washed with water and then dried with anhydrous magnesium sulfate. Removal of the solvent left an oil, which was chromatographed over silica gel using benzene as eluent. Elution gave *trans*-1,3-bis(methoxycarbonyl)-1-chloro-2,2-diphenylcyclopropane (**8c**) (73%). Recrystallization of **8c** from CH_2Cl_2/pentane gave white prisms: mp 138–139 °C; NMR δ 3.47 (s, 3 H), 3.72 (s, 4 H), 7.06–7.47 (m, 10 H); IR (KBr) 1735 cm^{-1}. Anal. Calcd for $C_{19}H_{17}O_4Cl$: C, 66.19; H, 4.97. Found: C, 66.39; H, 4.97. Further elution gave 4,5-bis(methoxycarbonyl)-3,3-diphenyl-3*H*-pyrazole (**9c**) (11%). Recrystallization of **5c** from CH_2Cl_2/pentane gave yellow prisms: mp 87.5–88.5 °C; NMR δ 3.73 (s, 3 H), 4.01 (s, 3 H), 7.12–7.37 (m, 10 H); IR (KBr) 1735, 1637 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.74; H, 4.84; N, 8.11.

Reaction of 9-Diazofluorene (1d) with Dimethyl Chlorofumarate (6) in the Presence of an Equimolar Amount of Triethylamine. By using a similar procedure to that described above (reaction time 26 h), *trans*-2,3-bis(methoxycarbonyl)-2-chlorospiro[cyclopropane-1,9′-fluorene] (**8d**) (76%) and a trace amount of 4,5-bis(methoxycarbonyl)spiro[3*H*-pyrazole-3,9′-

(15) (a) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311. (b) Sauer, J.; Schroder, B.; Wiemer, R. *Chem. Ber.* **1967**, *100*, 306. (c) Vogel, E. *Chem. Ber.* **1952**, *85*, 25. (d) Ripoll, J.-L. *Tetrahedron Lett.* **1974**, 1665.

(16) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Allinger, N. L.; Yuh, Y. H.; Chong, D. P. *QCMP 004. QCPE Bull.* **1984**, *4*, 113. (c) Allinger, N. L.; Yuh, Y. H. *QCPE* **1984**, *12*, 395.

(17) Heats of formation of cyclopentene (**29**) and $\Delta^{1,5}$-bicyclo[3.3.0]-octene (**30**) were calculated to be 2.11 and 5.14 kcal/mol, respectively. Strain energies of **29** and **30** were calculated to be 0.89 and 18.49 kcal/mol, respectively.

(18) (a) Beppu, Y.; Ninomiya, I. *QCPE* **1981**, *14*, 409. (b) Thiel, W. *QCPE* **1978**, *11*, 353. (c) Sasaki, Y.; Takagi, T.; Tanaka, A.; Tokura, T. *Bulletin of Computation Center Osaka University* **1985**, *14*, 103.

(19) Nakano, Y.; Hamaguchi, M.; Nagai, T., unpublished results. Heats of formation of the parent 3*H*-pyrazole and the corresponding vinyldiazoalkane were calculated to be 50.51 and 77.34 kcal/mol, respectively. Heats of formation of 4,6-dihydro-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-c]pyrazole (the parent system of **19a–e**) and the corresponding vinyldiazoalkane (3,4-dihydro-3-diazo-4-isopropylidene-1-tolylpyrrole-2,5-dione) were calculated to be −2.87 and 1.87 kcal/mol, respectively.

(20) Hargreaves, M. K.; Pritchaed, J. G.; Dave, H. R. *Chem. Rev.* **1970**, *70*, 440.

(21) All of obtained compounds did not show any thermal hazards.

fluorene] (**9d**) was obtained from **1d** (2.01 mmol), triethylamine (2.01 mmol), and **6** (2.40 mmol); **8d** was recrystallized from CH_2Cl_2/pentane as colorless prisms: mp 132.5–134 °C; NMR δ 3.64 (s, 3 H), 3.74 (s, 3 H), 6.97–7.52 (m, 5 H), 7.66–7.83 (m, 3 H); IR (KBr) 1743 cm^{-1}. Anal. Calcd for $C_{19}H_{15}O_4Cl$: C, 66.42; H, 4.41. Found: C, 66.42; H, 4.39.

Reaction of Diazoindene (1e) with Dimethyl Chlorofumarate in the Presence of an Equimolar Amount of Triethylamine. A solution of **1e** (2.01 mmol), triethylamine (2.03 mmol), and **6** (2.40 mmol) in benzene (1.0 mL) was allowed to stand at room temperature for 14 days. The reaction mixture was dissolved in CH_2Cl_2, and the solution was washed with water and then dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed over silica gel using benzene/hexane (4:1) as eluent. Elution gave *trans*-2,3-bis(methoxycarbonyl)-2-chlorospiro[cyclopropane-1,1′-*endo*-indene] (**8e-Z**) (7%) as a colorless oil: NMR δ 3.69 (s, 3 H), 3.73 (s, 4 H), 3.76 (s, 1 H), 6.92 (s, 2 H), 6.97–7.33 (m, 4 H); IR (KBr) 1734 cm^{-1}. Anal. Calcd for $C_{15}H_{13}O_4Cl$: C, 61.55; H, 4.58. Found: C, 61.21; H, 4.51. Further elution gave *trans*-2,3-bis(methoxycarbonyl)-2-chlorospiro[cyclopropane-1,1′-*exo*-indene] (**8e-E**) (40%) as a colorless oil: NMR δ 3.66 (s, 3 H), 3.77 (s, 4 H), 3.81 (s, 1 H), 6.09 (d, 1 H, J = 5.5 Hz), 6.83 (d, 1 H, J = 5.5 Hz), 7.04–7.34 (m, 3 H), 7.58–7.76 (m, 1 H); IR (KBr) 1735 cm^{-1}. Anal. Calcd for $C_{15}H_{13}O_4Cl$: C, 61.55; H, 4.58. Found: C, 61.16; H, 4.44.

Reaction of Diphenyldiazomethane (1c) with Dimethyl Chlorofumarate (6) in Triethylamine. A solution of **1c** (4.02 mmol) and **2** (4.78 mmol) in triethylamine (10 mL) was stirred for 7 days. The reaction mixture was chromatographed over silica gel using benzene as eluent. The main fraction gave **9c** (82%) and a trace amount of **8c**.

Reaction of 9-Diazofluorene (1d) with Dimethyl Chlorofumarate (6) in Triethylamine. A solution of **1d** (3.99 mmol) and **6** (4.82 mmol) in triethylamine was stirred for 4 days. After the solution was treated by the procedure described above, chromatography of the residue gave **8d** (61%). Further elution gave 4,5-bis(methoxycarbony)spiro[3*H*-pyrazole-3,9′-fluorene] (**9d**) (27%). Recrystallization of **9d** from CH_2Cl_2/pentane yielded yellow prisms: mp 114.5–117 °C; NMR δ 3.25 (s, 3 H), 6.74–6.83 (m, 2 H), 7.11–7.52 (m, 4 H), 7.22–7.82 (m, 2 H); IR (KBr) 1750, 1735, 1717, 1628 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_2O_4$: C, 68.25; H, 4.22; N, 8.38. Found: C, 68.31; H, 4.24; N, 8.26.

Reaction of Diazoindene (1e) with Dimethyl Chlorofumarate (6) in Triethylamine. A solution of **1e** (2.02 mmol) and **6** (2.37 mmol) in triethylamine (1.5 mL) was stirred for 10 days at room temperature. After the solution was treated by the procedure described above, chromatography of the residue gave **1e** (11%) and a mixture of cyclopropanes **8e-Z** (2%) and **8e-E** (28%). Further elution gave dimethyl (*Z*)-diazo-1*H*-inden-1-ylidenebutanedioate (**10e**) (9%): NMR δ 3.79 (s, 3 H), 3.86 (s, 3 H), 6.83 (d, 1 H, J = 6.0 Hz), 6.90 (d, 1 H, J = 6.0 Hz), 7.00–7.34 (m, 4 H); IR (KBr) 2096, 1707 cm^{-1}.

Treatment of 3a,4,9,9a-Tetrahydro-9a-chloro-4,9-dioxo-3*H*-benz[*f*]indazole (12) with Triethylamine. Treatment of 3a,4,9,9a-Tetrahydro-9a-chloro-3,3-dimethyl-4,9-dioxo-3*H*-benz[*f*]indazole (12a) with an Equimolar Amount of Triethylamine. To a solution of **12a** (1.51 mmol) in CH_2Cl_2 (3 mL) was added a solution of triethylamine (1.51 mmol) in CH_2Cl_2 (3 mL), and the solution was stirred at room temperature. After 1 day, the solution was diluted with CH_2Cl_2 (100 mL), washed with water, and then dried over anhydrous magnesium sulfate. Chromatography of the reaction mixture gave 4,9-dihydro-3,3-dimethyl-4,9-dioxo-3*H*-benz[*f*]indazole (**14a**) as yellow plates (97%): mp 176.5–177.5 °C; NMR δ 1.73 (s, 6 H), 7.69–7.90 (m, 2 H), 8.02–8.35 (m, 2 H); IR (KBr) 1678, 1658, 1618, 1593 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.09; H, 4.32; N, 12.38.

Treatment of 3a,4,9,9a-Tetrahydro-9a-chloro-*exo*-3-methyl-*endo*-3-phenyl-4,9-dioxo-3*H*-benz[*f*]indazole (12b) with an Equimolar Amount of Triethylamine. A solution of **12b** (1.03 mmol) and triethylamine (1.04 mmol) in CH_2Cl_2 (15 mL) was stirred for 2 days at room temperature. The solution was treated by the procedure described above. The main fraction gave 4,9-dihydro-3-methyl-3-phenyl-4,9-dioxo-3*H*-benz[*f*]indazole (**14b**) as green yellow plates (90%): mp 136–137 °C; NMR δ 2.07 (s, 3 H), 7.22–7.38 (m, 5 H), 7.86–7.87 (m, 2 H), 7.98–8.30 (m, 2 H); IR (KBr) 1684, 1664 cm^{-1}. Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.72; H, 4.29; N, 9.60.

Reaction of Diphenyldiazomethane (1c) with 1,4-Chloronaphthoquinone (11) in the Presence of Triethylamine. To a benzene (3 mL) solution of **11** (2.40 mmol) was added a solution of **1c** (2.03 mmol) in triethylamine (2 mL), and the mixture was stirred for 4 days. The precipitate was filtered and washed with water to give 4,9-dihydro-3,3-diphenyl-4,9-dioxo-3*H*-benz[*f*]indazole (**14c**) (48%), which was recrystallized from CH_2Cl_2/pentane as orange-yellow needles: mp 158 °C dec; NMR δ 7.21–7.38 (m, 10 H), 7.59–7.87 (m, 2 H), 8.02–8.33 (m, 2 H); IR (KBr) 1678, 1664 cm^{-1}. Anal. Calcd for $C_{23}H_{14}N_2O_2$: C, 78.84; H, 4.03; N, 8.00. Found: C, 78.51; H, 4.07; N, 8.01. The filtrate was diluted with CH_2Cl_2 (100 mL), washed with water, and then dried with anhydrous magnesium sulfate. After removal of the solvent the residue was chromatographed over silica gel using benzene as eluent. The main fraction gave **14c** (27%, total 75%).

Reaction of 9-Diazofluorene (1d) with 1,4-Chloronaphthoquinone (11) in the Presence of Triethylamine. To a benzene solution (3 mL) of **11** (2.41 mmol) was added a solution of **1d** (2.02 mmol) in triethylamine (3 mL), and the mixture was stirred for 4 days at room temperature. After the solution was treated by the procedure described above, chromatography of the reaction mixture gave 4,9-dihydro-4,9-dioxospiro[3*H*-benz[*f*]-indazole-3,9′-fluorene] (**14d**) (83%). Recrystallization of **14d** from CH_2Cl_2/pentane yielded a red powder: mp 140 °C dec; NMR δ 6.67 (d, 2 H, J = 7.5 Hz), 7.18 (td, 2 H, J = 7.5, 1.2 Hz), 7.48 (td, 2 H, J = 7.5, 1.2 Hz), 7.88 (d, 2 H, J = 7.5 Hz), 7.66–7.89 (m, 3 H), 8.23–8.38 (m, 1 H); IR (KBr) 1673, 1610 cm^{-1}. Anal. Calcd for $C_{23}H_{12}N_2O_2$: C, 79.30; H, 3.47; N, 8.04. Found: C, 79.04; H, 3.74; N, 8.06.

Treatment of 3a,4,6,6a-Tetrahydro-6a-chloro-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (17) with Triethylamine. Reaction of 3a,4,6,6a-Tetrahydro-6a-chloro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (17a) with Triethylamine. A solution of **17a** (4.00 mmol) and triethylamine (4.03 mmol) in CH_2Cl_2 (10 mL) was stirred for 2 days at room temperature. The solution was washed with water and then dried with anhydrous magnesium sulfate. Evaporation of the solvent gave 4,6-dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (**19a**) (95%). Recrystallization of **19a** from ether gave yellow needles: mp 126–128 °C; NMR δ 1.72 (s, 6 H), 2.38 (s, 3 H), 7.09–7.31 (m, 4 H); IR (KBr) 1780, 1735 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.69; H, 5.12; N, 16.17.

Reaction of 3a,4,6,6a-Tetrahydro-6a-chloro-4,6-dioxo-*exo*-3-methyl-*endo*-3-phenyl-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (17b-Z) with Triethylamine. To a suspension of **17b-Z** (2.00 mmol) in CH_2Cl_2 (6 mL) was added a dichloromethane solution (4 mL) of triethylamine (2.05 mmol), and the solution was stirred for 1 day at room temperature. The procedure described above gave 3-diazo-3,4-dihydro-4-((*E*)-1-phenethylidene)-1-tolylpyrrole-2,5-dione (**20b-Z**) (22%). Recrystallization of **20b-Z** from CH_2Cl_2/pentane yielded orange thin plates: mp 132.5–134 °C dec; ^1H NMR δ 2.37 (s, 3 H), 2.73 (s, 3 H), 7.24 (s, 5 H), 7.25–7.38 (m, 4 H); ^{13}C NMR δ 21.19, 21.74, 60.91, 113.59, 126.58, 127.43, 128.37, 129.14, 129.34, 129.71, 138.39, 140.66, 145.47, 163.67, 166.15, IR (KBr) 2107, 1745, 1705, 1684, 1630, 1388 cm^{-1}. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.95; H, 4.92; N, 13.20. Further elution gave 3-diazo-3,4-dihydro-4-((*Z*)-1-phenethylidene)-1-tolylpyrrole-2,5-dione (**20b-*E***) (44%). Recrystallization of **20b-E** from CH_2Cl_2/pentane yielded orange needles: mp 147–149.5 °C dec; ^1H NMR δ 2.31 (s, 6 H), 7.15 (s, 5 H), 7.29 (s, 4 H); ^{13}C NMR δ 21.14, 23.19, 60.37, 112.93, 126.52, 127.58, 128.09, 128.43, 129.25, 129.53, 138.29, 140.63, 144.35, 161.77, 166.37; IR (KBr) 2085, 1749, 1701, 1690, 1637, 1375 cm^{-1}. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.62; H, 4.90; N, 13.07.

Reaction of 3a,4,6,6a-Tetrahydro-6a-chloro-4,6-dioxo-*endo*-3-methyl-*exo*-3-phenyl-5-tolyl-3*H*-pyrrolo[3,4-*c*]-pyrazole (17b-E) with Triethylamine. Reaction of **17b-E** (2.00 mmol) with triethylamine (2.01 mmol) in CH_2Cl_2 (10 mL) similarly gave **20b-Z** (29%) and **20b-E** (44%).

Reaction of Diaryldiazomethanes (1c–e) with *N*-Tolylchloromaleimide (16) in the Presence of a Large Excess of Triethylamine. General procedure: A dichloromethane solution

(6 mL) of **1c–e** (2.00 mmol) and **16** (2.40 mmol) was stirred at room temperature for 1 day except the reaction of **1e** with **16** (14 days). The reaction mixture was dissolved in CH_2Cl_2, washed with water, and then dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed over silica gel using benzene as eluent.

Reaction of Diphenyldiazomethane 1c with *N*-Tolylchloromaleimide (16). Reaction of **1c** with **16** gave 2-diazo-3,4-dihydro-3-(diphenylmethylene)-1-tolylpyrrole-2,5-dione (**20c**) (75%) and a trace amount of 3a,4a-dihydro-3a-chloro-4,4-diphenyl-2-tolyl-4*H*-cyclopropa[*c*]pyrrole-1,3-dione (**18c**). Recrystallization of **20c** from CH_2Cl_2/pentane gave orange columns: mp 129–131 °C dec; NMR δ 2.30 (s, 3 H), 7.06–7.35 (m, 14 H); IR (KBr) 2109, 1748, 1704, 1688, 1591 cm^{-1}. Anal. Calcd for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.08. Found: C, 75.90; H, 4.55; N, 11.02.

Reaction of 9-Diazofluorene (1d) with *N*-Tolylchloromaleimide (16). Reaction of **1d** with **16** gave 3-diazo-3,4-dihydro-4-fluorenylidene-1-tolylpyrrole-2,5-dione (**20d**) (71%) and a trace amount of 3a,4a-dihydro-3a-chloro-2-tolylspiro[4*H*-cyclopropra[*c*]pyrrole-4,9′-fluorene]-1,3-dione (**18d**). Recrystallization of **20d** from ether/pentane yielded orange prisms: melting point could not be determined because the orange crystals gradually changed to brown tar; ^1H NMR δ 2.40 (s, 3 H), 7.00–7.38 (m, 9 H), 7.55–7.65 (m, 2 H), 8.92–9.01 (m, 1 H); IR (KBr) 2090, 1749, 1710, 1697, 1610, 1376 cm^{-1}. Anal. Calcd for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.14. Found: C, 76.27; H, 4.28; N, 11.07.

Reaction of Diazoindene (1e) with *N*-Tolylchloromaleimide (16). Chromatography of the reaction mixture of **1e** with **16** gave 3,4-dihydro-3-diazo-4-indenylidene-1-tolylpyrrole-2,5-dione **20e-E** (or **20e-Z**) (11%) and a trace amount of 3a,4a-dihydro-3a-chloro-2-tolylspiro[4*H*-cyclopropa[*c*]pyrrole-4,*exo*-1′-indene]-1,3-dione (**18b-E**) with **1e** (57%); **20e-E** (or **20e-Z**) was recrystallized from CH_2Cl_2/pentane as deep red prisms: mp 122 °C dec; NMR δ 2.73 (s, 3 H), 6.82 (d, 1 H, J = 5.7 Hz), 7.02–7.30 (m, 8 H), 7.73 (d, 1 H, J = 5.7 Hz); IR (KBr) 2092, 1752, 1703 cm^{-1}. Anal. Calcd for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84. Found: C, 73.09; H, 4.11; N, 12.46.

Thermolysis of 3-Diazo-3,4-dihydro-4-((*Z*)-1-phenethylidene)-1-tolylpyrrole-2,5-dione (20b-E) in Acetic Acid. A solution of **20b-E** (1.00 mmol) in acetic acid (10 mL) was refluxed for 5 min. Removal of the solvent left an oil, which was chromatographed over silica gel. Elution with benzene gave 3,4-dihydro-((*Z*)-1-phenethylidene)-4-acetoxy-1-tolylpyrrole-2,5-dione **21b-E** (55.6%). Recrystallization of **21b-E** from ether/pentane yielded a white crystalline solid: mp 74.0–77.0 °C; NMR δ 2.17 (s, 3 H), 2.24 (d, 3 H, J = 1.1 Hz), 2.29 (s, 3 H), 5.92 (q, 1 H, J = 1.1 Hz), 7.13 (s, 5 H), 7.26 (s, 4 H); IR (KBr) 1780, 1748, 1719, 1646 cm^{-1}. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.84; H, 5.56; N, 4.02.

Thermolysis of 3-Diazo-3,4-dihydro-4-((*E*)-1-phenethylidene)-1-tolylpyrrole-2,5-dione (20b-Z) in Acetic Acid. A solution of **20b-Z** (1.00 mmol) in acetic acid (10 mL) was refluxed for 5 min. Removal of the solvent left an oil, which was chromatographed over silica gel. Elution with benzene gave 3,4-dihydro-((*E*)-1-phenethylidene)-4-acetoxy-1-tolylpyrrole-2,5-dione **21b-Z** (71.0%), which was recrystallized from ether/pentane as white prisms: mp 160.5–162.0 °C; NMR δ 1.60 (s, 3 H), 2.35 (s, 3 H), 2.67 (d, 3 H, J = 1.5 Hz), 6.02 (q, 1 H, J = 1.5 Hz), 7.07–7.42 (m, 9 H); IR (KBr) 1773, 1745, 1710, 1638 cm^{-1}. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.07; H, 5.59; N, 4.07.

Thermolysis of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a) in Acetic Acid. A solution of **19a** (1.00 mmol) in acetic acid (10 mL) was refluxed for 2 h. Removal of the solvent left an oil, which was chromatographed over silica gel. Elution with CH_2Cl_2 gave 3,4-dihydro-3-isopropylidene-4-acetoxy-1-tolylpyrrole-2,5-dione (**21a**) (23%). Recrystallization of **21a** from ether/pentane yielded white powders: mp 123.0–124.0 °C; NMR δ 2.00 (s, 3 H), 2.14 (s, 3 H), 2.36 (s, 3 H), 2.41 (d, 3 H, J = 1.4 Hz), 5.82 (br s, 1 H), 7.19 (AB q, 2 H, J = 9.6 Hz), 7.21 (AB q, 2 H, J = 9.6 Hz); IR (KBr) 1774, 1746, 1710 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.72; H, 6.03; N, 4.87. Further elution gave 3a,4,6,6a-tetrahydro-3a-acetoxy-4,6-dioxo-3,3-dimethyl-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (**22**) (46%), which was recrystallized from ether as white prisms: mp 162 °C dec; NMR δ 1.51 (s, 3 H), 1.70 (s, 3 H), 2.18 (s, 3 H), 2.37 (s, 3 H), 5.98 (s, 1 H), 7.05 (d, 2 H, J = 8.6 Hz), 7.23 (d, 2 H, J = 8.6 Hz); IR (KBr) 1789, 1724 cm^{-1}. Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.32. Found: C, 60.97; H, 5.48; N, 13.26.

Reaction of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a) with Dimethyl Acetylenedicarboxylate (DMAD). A solution of **19a** (1.00 mmol) and DMAD (10 mmol) in toluene (10 mL) was refluxed for 10 min and cooled. A white precipitate, 4,5,6,7-tetrahydro-2,3-bis(methoxycarbonyl)-4-isopropylidene-5,7-dioxo-6-tolylpyrazolo[1,5-*c*]pyrimidine (**24a**) (70%), was separated from the solution: mp 208.0–209.5 °C; NMR δ 2.12 (s, 3 H), 2.43 (s, 3 H), 3.88 (s, 3 H), 3.94 (s, 3 H), 7.09 (d, 2 H, J = 8.4 Hz), 7.27 (d, 2 H, J = 8.4 Hz); IR (KBr) 1770, 1729, 1704 cm^{-1}; UV λ_{max} (MeOH) 241.4 (ε 18 000), 328 (shoulder, ε 1020). Anal. Calcd for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.58. Found: C, 60.61; H, 4.87; N, 10.45.

Reaction of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a) with Dibenzoylacetylene (DBA). A solution of **15a** (1.00 mmol) and DBA (1.00 mmol) in toluene (10 mL) was refluxed for 10 min. After removal of the solvent, the reaction mixture was recrystallized from CH_2Cl_2/pentane to give 4,5,6,7-tetrahydro-2,3-dibenzoyl-4-isopropylidene-5,7-dioxo-6-tolylpyrazolo[1,5-*c*]pyrimidine (**26a**) as white powders (57%): mp 186.0–188.0 °C; NMR δ 1.93 (s, 3 H), 2.34 (s, 3 H), 2.42 (s, 3 H), 7.07–7.55 (m, 10 H), 7.72–7.88 (m, 2 H), 7.95–8.12 (m, 2 H); IR (KBr) 1762, 1705, 1654, 1596, 1547 cm^{-1}; UV λ_{max} (MeOH) 257.8 (ε 35 500), 319 (shoulder, ε 5900). Anal. Calcd for $C_{30}H_{23}N_3O_4$: C, 73.60; H, 4.74; N, 8.58. Found: C, 73.40; H, 4.87; N, 8.37.

Thermolysis of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a). A solution of **19a** (1.00 mmol) in toluene (10 mL) was refluxed for 10 min. Removal of the solvent left an oil, which was chromatographed over silica gel. Elution with benzene gave a mixture of dimer **27** (59%) and 3,4-dihydro-3-diazo-4-isopropylidene-1-tolylpyrrole-2,5-dione **20a** (7%). Recrystallization of the mixture from ether/pentane yielded **27** as white prisms: mp 149.5 °C dec; ^1H NMR δ 1.56 (s, 3 H), 1.71 (s, 3 H), 1.76 (s, 3 H), 2.38 (s, 3 H), 2.46 (s, 3 H), 7.04 (d, 2 H, J = 8.9 Hz), 7.23 (d, 2 H, J = 8.9 Hz), 7.26 (s, 4 H); ^{13}C NMR δ 21.20, 21.23, 21.46, 22.96, 24.11, 24.22, 98.22, 100.85, 108.15, 108.30, 118.42, 125.08, 126.33, 127.51, 128.47, 129.86, 130.16, 139.28, 139.89, 158.73, 164.46, 164.93, 165.59, 165.97; IR (KBr) 1778, 1725, 1647 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_6O_4$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.07; H, 5.31; N, 16.32.

To refluxing toluene (980 mL) was added a solution of **19a** (2.00 mmol) in toluene (20 mL), and the solution was refluxed for 10 min. Removal of the solvent by rotary evaporator left an oil, which was chromatographed over silica gel. Elution with benzene gave the dimer **27** (5%) and **20a** (59%); **20a** was recrystallized from ether/pentane as orange prisms: mp 137.0–140.0 °C; ^1H NMR δ 2.05 (s, 3 H), 2.36 (s, 3 H), 2.46 (s, 3 H), 7.22 (s, 4 H); ^{13}C NMR δ 21.19, 22.30, 22.59, 59.63, 111.61, 126.62, 129.43, 129.69, 138.37, 145.23, 163.26, 166.70; IR (KBr) 2092, 1739, 1685, 1645, 1369 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.59; H, 5.27; N, 16.09.

Reaction of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a) with 3,4-Dihydro-3-isopropylidene-4-diazo-1-tolylpyrrole-2,5-dione (20a). A solution of **19a** (0.20 mmol) and **20a** (0.20 mmol) in benzene (1 mL) was stirred at room temperature for 14 days. Removal of the solvent left an oil, which was chromatographed over silica gel using benzene as eluent. The main fraction gave the dimer (**27**) (88%).

Thermolysis of 3,4-Dihydro-3-(diphenylmethylene)-4-diazo-1-tolylpyrrole-2,5-dione (20c) in Acetic Acid. A solution of **20c** (0.498 mmol) in acetic acid (5 mL) was refluxed for 2 h. Removal of the solvent by rotary evaporator left an oil. Treatment of the oil with CH_2Cl_2/pentane yielded 3,4-dihydro-4-acetoxy-3-(diphenylmethylene)-1-tolylpyrazole-2,5-dione (**21c**) as white prisms (70%): mp 198–199 °C; NMR δ 1.66 (s, 3 H), 2.34 (s, 3 H), 6.27 (s, 1 H), 7.09–7.43 (m, 14 H); IR (KBr) 1780, 1750, 1718, 1623 cm^{-1}. Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.89; H, 5.14; N, 3.40. Found: C, 75.73; H, 5.29; N, 3.36.

Reaction of 3,4-Dihydro-3-(diphenylmethylene)-4-diazo-1-tolylpyrrole-2,5-dione (20c) with Dimethyl Acetylenedicarboxylate (DMAD). A solution of **20c** (0.50 mmol) and

DMAD (0.60 mmol) in CH_2Cl_2 (4 mL) was refluxed for 4 h. Chromatography of the reaction mixture gave 4,5,6,7-tetrahydro-2,3-bis(methoxycarbonyl)-4-(diphenylmethylene)-5,7-dioxo-6-tolylpyrazolo[1,5-*c*]pyrimidine (**24c**) (100%). Recrystallization of **24c** from CH_2Cl_2/pentane yielded orange-yellow needles: mp 277.5–279.0 °C; NMR δ 2.33 (s, 3 H), 3.55 (s, 3 H), 3.88 (s, 3 H), 6.98–7.40 (m, 14 H); IR (KBr) 1763, 1730, 1710 cm^{-1}; UV λ_{max} (MeOH) 238 (shoulder, ε 27 900), 387.4 (ε 10 400). Anal. Calcd for $C_{30}H_{23}N_3O_6 \cdot CH_2Cl_2$: C, 61.39; H, 4.16; N, 6.92. Found: C, 61.77; H, 4.27; N, 6.99.

Reaction of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a) with Methanol. A solution of **19a** (1.00 mmol), methanol (4.00 mmol), and triethylamine (1.00 mmol) in CH_2Cl_2 (3 mL) was stirred for 1 day at room temperature. The reaction mixture was dissolved in CH_2Cl_2. The solution was washed with water and then dried over anhydrous magnesium sulfate. After evaporation of the solution, the residue was chromatographed over silica gel using benzene as eluent. Elution gave 3,3-dimethyl-4-(methoxycarbonyl)-5-(tolylcarbamoyl)-3*H*-pyrazole (**32**) (41%). Recrystallization of **32** from CH_2Cl_2/pentane yielded yellow needles: mp 171.5–172.5 °C; NMR δ 1.73 (s, 6 H), 2.32 (s, 3 H), 4.13 (s, 3 H), 7.13 (d, 2 H, J = 8.4 Hz), 7.55 (d, 2 H, J = 8.4 Hz), 11.38 (br s, 1 H); IR (KBr) 3261, 3123, 3077, 1697, 1664, 1620, 1591 cm^{-1}. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.60; H, 5.95; N, 14.54. Further elution gave 3,3-dimethyl-5-(methoxycarbonyl)-4-(tolylcarbamoyl)-3*H*-pyrazole (**33**) (18%) as a yellow oil: NMR δ 1.59 (s, 6 H), 2.33 (s, 3 H), 3.94 (s, 3 H), 7.12 (d, 2 H, J = 8.4 Hz), 7.55 (d, 2 H, J = 8.4 Hz), 9.41 (br s, 1 H); IR (KBr) 3307, 3127, 3031, 1728, 1676, 1631, 1610 cm^{-1}.

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Regiospecific Alkylation of 3-Substituted-2-cyclohexen-1-ones. Synthesis and Conformational Analysis of 6-(Carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones

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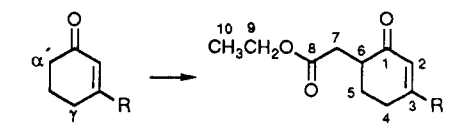
The reaction of 3-substituted-2-cyclohexen-1-ones **1–5** with lithium diisopropylamide in tetrahydrofuran, followed by ethyl bromoacetate, generated 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones **6–10** in a 55–88% yield, regardless of the stoichiometry of the base (LDA) and cyclohexenone used in the reaction, provided that the temperature of the reaction was maintained at or below −50 °C. The use of dipolar aprotic solvents (e.g., HMPA and DMPU) with THF afforded no additional advantage in the reaction; however, with diethyl ether as the solvent no reaction occurred. Alkylation reactions involving ethyl bromoacetate or ethyl iodoacetate gave similar yields, but no alkylation product was obtained when ethyl chloroacetate was used. The use of lithium diisopropylamide or lithium bis(trimethylsilyl)amide at low temperature resulted in alkylation of 3-substituted-2-cyclohexen-1-ones only at the 6-position. The use of 2D NMR has allowed the complete assignment of the ^1H and ^{13}C NMR data. As a result, the dominant solution conformation for derivatives **6–10** is that having the 6-alkyl substituent in the equatorial orientation.

The regiospecific α′-alkylation of 3-alkoxy-2-cyclohexen-1-one and substituted 2-cyclohexen-1-ones was independently reported in 1973 by Stork and Danheiser and Lee et al., respectively.[1] Although many synthetic intermediates have been synthesized by this methodology, very few comparative reaction data are available.[2] In 1981, Chen et al. found that deprotonation of 3-ethoxy-2-cyclohexen-1-one, with excess lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LBTSA) in tetrahydrofuran (THF) at −78 °C, led to the formation of the α′-dienolate;[3] however, under no conditions was the γ-dienolate formed. Selective formation of the α′- or γ-dienolate of 3-(dimethylamino)-2-cyclohexen-1-one[3] and 2-methyl-3-pyrrolidinyl-2-cyclohexen-1-one[4] was dependent on the exact experimental conditions and lithium amide base employed.

A need for a variety of 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-one derivatives (Scheme I) and a lack of comparative reaction data stimulated us to investigate the effect that variation in solvent, electrophile, stoichiometry, temperature, and lithium amide base have on the regiospecific alkylation of various 3-substituted-2-cyclohexen-1-ones. In this report we also describe a detailed NMR investigation and resulting conformational analysis of the 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones.

Scheme I



1, R = H
2, R = CH_3
3, R = $CH_2(CH_2)_2CH_3$
4, R = Ph
5, R = OCH_2CH_3

6, R = H
7, R = CH_3
8, R = $CH_2(CH_2)_2CH_3$
9, R = Ph
10, R = OCH_2CH_3

A procedure similar to that described in the literature[5] was used to examine the effect of solvent on this reaction. Briefly, this involved the slow addition of 2-cyclohexen-1-one (**1**) to excess lithium diisopropylamide (LDA) at low temperature, followed by the slow addition of ethyl iodo-

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