thiolate on the sulfilimine seems to be concerted with proton transfer. The last requirement to make the reaction *fully* concerted (S–N cleavage) is inferred since (by the pK_a argument presented earlier) general catalysis is not expected to be thermodynamically favorable unless S–N bond breaking is also occurring (general catalysis of sulfurane formation is "disallowed" because the sulfilimine–NH_2^+ in the transition state would be a stronger acid than the acetate catalyst). Hence the conclusion that the reaction is behaving *as if* it was fully concerted. The observed structure/reactivity cross-correlations (p_{xy} coefficients)[12] for this coupled reaction are generally very large and, for Hammett data, the direct p_x coefficient is $\neq 0$. The sensitivity of the transition state to changes in reactant structure strongly suggests that the intrinsic Marcus barrier,[13,17] $\Delta G_0^{\ddagger}$, is very small and that a significant work (w_r) term contributes to $\Delta G_{obsd}^{\ddagger}$. The visualization of a multidimensional surface such as that in Figure 2 is not trivial, and it is difficult to intuitively grasp the physical meaning of a saddle point when it is described in (at least) four dimensions. Predictions, such as those given above, can often be obtained by separately visualizing each face as a three-dimensional surface and assuming that the resultant movement of the transition state will be the vector sum of each of those movements. While this approximation will give generalized indications of the direction of transition-state movements in response to structural changes, it would be very naive to suppose that changes in energies in one "face" were not iterated into the energies of all of the potential intermediates, resulting in complex, coupled movements. The reaction cube in the figure is, however, a useful tool for visualizing and appreciating the complexity of a highly coupled reaction such as this and for allowing qualitative explanations and predictions to be made. It should be noted that general catalysis is rarely seen in concerted displacement reactions, probably because of the entropic requirements of such a highly coupled transition states. In the present case, the high polarizability of the sulfur d orbitals may allow the formation of "unusually tight" encounter complexes, in effect, making the general catalyzed reaction "pseudo second order" and reducing the entropic requirements to attainable levels.

(17) Albery, W. J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 227–264. Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891–899.

Acknowledgment. This work was supported by a grant from the National Science Foundation, CHE 8511865.

Registry No. *p*-$MeOC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-57-0; *p*-$MeC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-58-1; *m*-$MeC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-60-5; $C_6H_5S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 39149-52-5; *m*-$MeOC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-62-7; *p*-$FC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-64-9; *p*-$ClC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 80723-63-3; *p*-$BrC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-66-1; *m*-$ClC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 108297-68-3; *p*-$O_2NC_6H_4S(CH_3)NH_2^+ \cdot 2,4,6\text{-}Me_3C_6H_2SO_3^-$, 80723-54-2; *m*-$HSC_6H_4CO_2H$, 4869-59-4; D_2, 7782-39-0; MSH, 36016-40-7; *S*-methylthiophenol, 100-68-5; 2-nitro-4-thiobenzoic acid, 103840-07-9.

Nucleophilic Additions to Triazolinedione Ylides, Extremely Reactive Carbonyl Equivalents: A New Class of Condensation Reactions[1]

R. Marshall Wilson* and Alvan Hengge

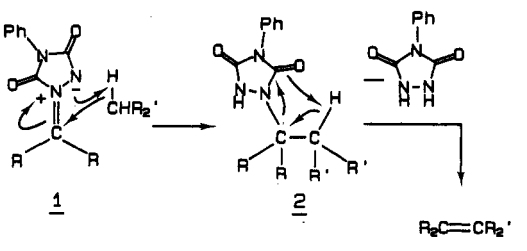
Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

Received October 7, 1986

The ylides of *N*-phenyltriazolinedione (**10** and **13**) are readily prepared when the ylide carbon atom is substituted by phenyl or 3-methylindol-2-yl groups. In fact the indole-substituted ylide **10** is sufficiently stabile to be isolated in good yield when it is formed by the oxidation of the corresponding urazole **9** with *tert*-butyl hypochlorite followed by dehydrohalogenation with triethylamine. These triazolinedione ylides both undergo facile addition of nucleophiles at the ylide carbon atoms. In the case of nucleophilic addition by enolate species, the initial adducts undergo subsequent elimination of *N*-phenylurazole to form olefinic condensation products, while nucleophilic addition of pyrrole or *n*-butanethiol results in bis adducts in which two molecules of the nucleophile become attached to what had been the ylide carbon atom. The in situ generation of these triazolinedione ylides and subsequent transformations are operationally extremely simple procedures that frequently afford high product yields and as such would seem to offer considerable promise as synthetic methods.

Carbonyl condensation reactions are among the most important reactions in organic chemistry. It occurred to us that certain azomethine imine ylides might function as highly polar carbonyl analogues in this same capacity as outlined in Scheme I. In particular, triazolinedione ylides (**1**) have been generated by several methods[2] and are readily available through simple oxidation of appropriately substituted urazoles (vide infra). These ylides might be expected to offer several advantages in condensation reactions over the parent carbonyl compounds. The ylide itself might serve as the base to generate the requisite nucleophile when dealing with relatively acidic systems (Scheme I). The resulting protonated ylide, and possibly even the ylide itself, should be a substantially better electrophile than the parent carbonyl group. Finally, the resulting substituted urazole adduct (**2**) would be expected

Scheme I

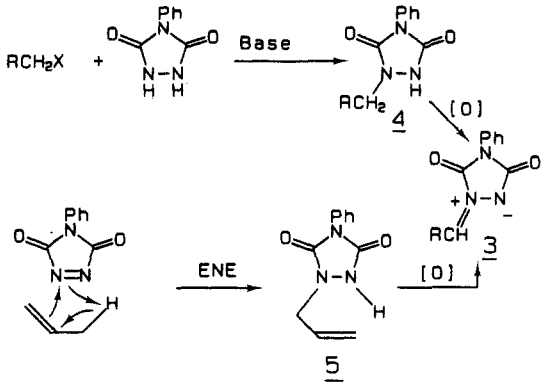


(1) For a preliminary communication of a portion of the work described here, see: Wilson, R. M., Hengge, A. *Tetrahedron Lett.* **1985**, *26*, 3673.

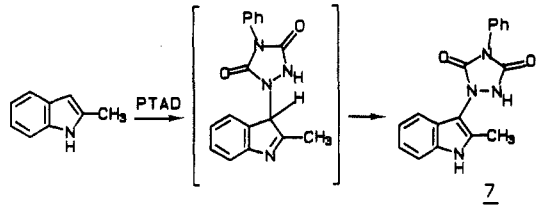
(2) (a) Cheng, C.-C.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2917. (b) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1982**, 766. (c) Bethäuser, W.; Regitz, M.; Theis, W. *Tetrahedron Lett.* **1981**, *22*, 2535. (d) Bettinetti, G. F.; Capretti, L. *Gazz. Chim. Ital.* **1965**, *95*, 33.

0022-3263/87/1952-2699$01.50/0

Scheme II



Scheme III



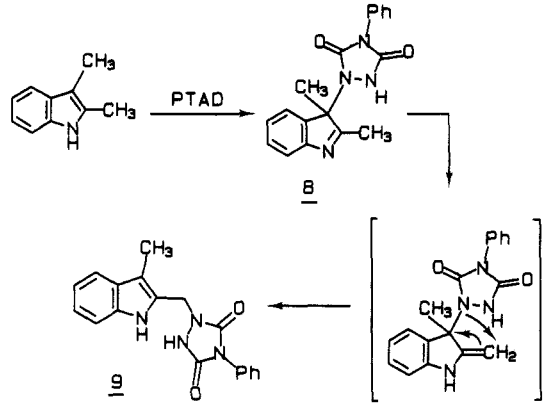
to eliminate *N*-phenylurazole with significantly greater ease than the elimination of water from the β-hydroxycarbonyl intermediates of conventional condensation reactions. Considerations such as these have led us to explore the feasibility of triazolinedione ylide condensation reactions. In this paper we report our initial results in this area.

Preparation of Triazolinedione Ylides

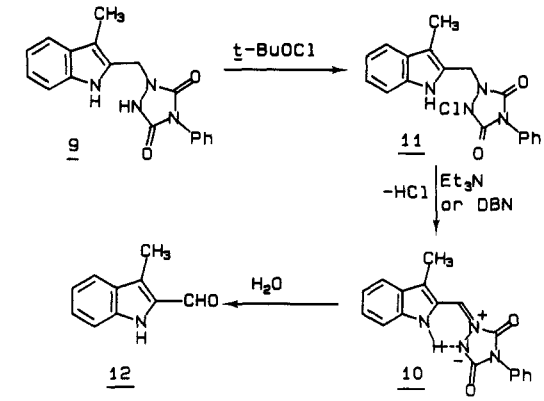
Triazolinedione ylides have been isolated from the reactions of triazolinediones with appropriately substituted diazoalkanes,[2c,d] isobenzofurans,[2b] and acetylenes.[2a] However, all of these entries to triazolinedione ylides are rather limited in scope and not of broad synthetic utility. Since N′-substituted *N*-phenylurazoles are readily available from simple nucleophilic substitution reactions and perhaps even more generally through the ubiquitous ene reaction of olefins with *N*-phenyltriazolinedione (PTAD) (Scheme II), the ideal synthetic route to triazolinedione ylides such as **3** would seem to be through the oxidation of substituted *N*-phenylurazoles such as **4** and **5**.

Examples of both of these approaches have been realized. Simple substitution of *N*-phenylurazole with benzyl bromide can be achieved in nearly quantitative yield based upon recovered starting material. The reactions of methylindoles provide a particularly interesting set of examples of the formation of substituted urazoles via the ene reaction. The reactions of PTAD with indole itself, as well as 2-methyl-, 3-methyl-, and 2,3-dimethylindole, have been examined. In all cases the indoles bleach the red color of the PTAD immediately. The reaction of PTAD with indole has been studied previously,[3] and in accord with these earlier observations, only polar, polymeric materials were found in this reaction. Also the reaction of 3-methylindole with PTAD afforded a complex reaction mixture from which no products could be isolated in pure form. In contrast, the reaction of 2-methylindole with PTAD at 0 °C cleanly yields a single product, which crystallizes from the reaction mixture in 76% yield (Scheme III). This substance proved to be the 3-substituted indole **7** (δ 2.31 (s, 3 H); λ_{max} (CH_3CN) 286 nm (ε 6400), 268 (8400), 218 (49 000)), rather than the desired isomer with the urazole substituted on the indole methyl. The reaction of 2,3-dimethylindole with PTAD under similar conditions (0 °C) afforded a single somewhat-unstable product, which could be isolated as a red oil. This material had δ 1.64 (s, 3 H) and 2.34 (s, 3 H) as well as λ_{max} (CH_3CN) 223 nm (ε 29 000), 216 (36 000), and 210 (35 000) and, therefore, has been assigned the indolenine structure **8** (Scheme IV). Upon heating or prolonged standing at room temperature, **8** undergoes rearrangement to the indole **9**: δ 2.36 (s, 3 H), 4.88 (s, 2 H); λ_{max} (CH_3CN) 274 nm (ε 7900), 226 (38 000). The formation of **9** is most conveniently performed in a single operation through the reaction of 2,3-dimethylindole with PTAD followed by heating at 60 °C for 24 h. Under these conditions **9** is obtained in 56%.

Scheme IV



Scheme V



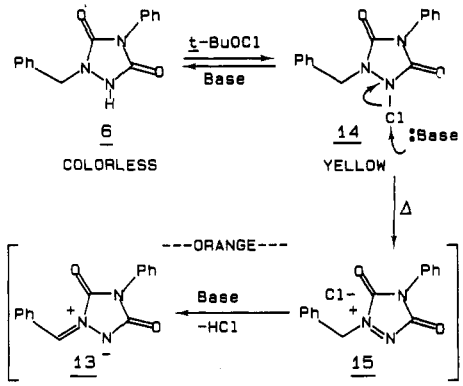
Oxidation of the urazole **9** to the triazolinedione ylide **10** is readily achieved with *tert*-butyl hypochlorite followed by treatment with base, as shown in Scheme V. Other oxidizing agents such as DDQ and *o*-chloranil also have been found to produce the ylide **10**, but these oxidizing agents provide lower yields and are less convenient. A thorough investigation of potential oxidizing agents has not been conducted. However, *tert*-butyl hypochlorite has been found to afford good to excellent results and has been used in all ylide-forming reactions described in this paper.

It is well-known that 2,3-disubstituted indoles are easily oxidized with *tert*-butyl hypochlorite to form 3-chloroindolenines.[4] However, when the indole **9** (Scheme V) is treated with *tert*-butyl hypochlorite, the disappearance of the urazole N–H signal at δ 9.53 in the ^1H NMR spectrum occurs within 30 s of mixing and no other alterations in the spectrum are evident. Consequently, N-chlorination appears to be a particularly facile reaction in these substituted-urazole systems. Treatment of the yellow-orange

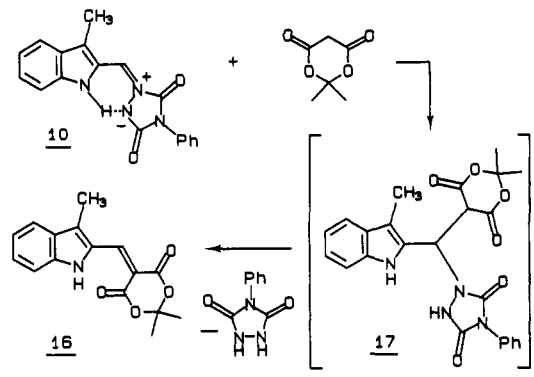
(3) Hall, J. H.; Kaler, L.; Herring, R. *J. Org. Chem.* **1984**, *49*, 2579.

(4) Ikeda, M.; Tamura, Y. *Heterocycles* **1980**, *14*, 867. Gassman, P. G.; Campbell, G. A.; Mehta, G. *Tetrahedron* **1972**, *28*, 2749.

Scheme VI



Scheme VII



solution of *N*-chlorourazole **11** with bases such as triethylamine or DBN causes an immediate generation of a deep red-orange color and rapidly leads to the formation of a suspension of the red-orange ylide **10**. This ylide (**10**) is easily isolated in 80% yield by simple filtration of the crude reaction mixture through a short column of Florisil and evaporation of the solvent from the filtrate.

The spectral properties of this red-orange solid are consistent with the proposed ylide structure. Particularly diagnostic is the ^{13}C NMR chemical shift of the ylide carbon, δ 141.2. This value is in good agreement with those of known triazolinedione ylides, which fall in the range of δ 150–138.[2a,b] The proton on the ylide carbon atom is deshielded by the electron-deficient iminium double bond, δ 8.37. The carbonyl groups are evident in both the ^{13}C NMR (δ 154.5 and 150.7) and the IR spectra (ν_{max} 1785 and 1700 cm^{-1}). Finally, the indole N–H proton is unusually deshielded (δ 11.38) relative to other indole N–H protons (ca. δ 8.0). These data suggest that **10** exists in the internally hydrogen bonded configuration shown in Scheme V.

The unusual stability of the ylide **10** is probably due in large part to the strongly electron donating indole substituent on the ylide carbon atom. In general, isolable triazolinedione ylides seem to require diaryl or electron-donating substitution on the ylide carbon atom.[2] In addition, the masking of the negative terminus of the dipolar system in **10** through internal hydrogen bonding probably contributes further to its stability. The stability of **10** is most evident in its complete lack of reactivity toward a variety of dipolarophiles. In distinct contrast, **10** displays a high degree of reactivity toward nucleophiles. For example, in the presence of traces of water, **10** rapidly undergoes quantitative hydrolysis to the known aldehyde **12**.[5,6] This oxidation–hydrolysis sequence (Scheme V) not only provides an excellent method for converting urazolyl compounds to aldehydes, but also, in the case of urazole **9**, unequivocally establishes the location of the urazole substituent as being on the 2-methyl group rather than on the 3-methyl group of the indole.

The *N*-benzylurazole **6** does not afford an isolable ylide upon treatment with *tert*-butyl hypochlorite and base, nor have room-temperature NMR studies led to the detection of this ylide (**13**). Nevertheless, ylide formation apparently does occur in good yield from **6**, since benzaldehyde is the major product observed by NMR when urazole **6** is oxidized in the presence of water. The conditions for the formation of the putative ylide **13** from urazole **6** may offer some insights into the mechanism for ylide formation (Scheme VI). In order to realize optimum ylide generation in this system, the *N*-chlorourazole **14** must be heated briefly to about 60 °C *before* the addition of the base. During this heating period, the yellow color of the *N*-chlorourazole **14** is replaced by an orange color, which becomes more intense upon the addition of base. This orange color is most probably due to the ylide **13** or its immediate precursor **15**. If base is added before the development of the orange color, the starting urazole **6** is recovered as the major constituent of the reaction mixture. These observations indicate that the loss of HCl or chloride ion from the *N*-chlorourazole **14** must occur prior to the addition of the base. This sequence of events can be easily rationalized by an initial heterolytic rupture of the N–Cl bond to form **15** or **13** as shown in Scheme VI. Under these conditions the base would function merely as a sponge for the liberated HCl. In contrast, at least in this benzyl system, base does not seem to dehydrohalogenate the *N*-chlorourazole, but rather to displace the heterocycle from the chlorine atom and regenerate the starting urazole **6** as shown in Scheme VI.

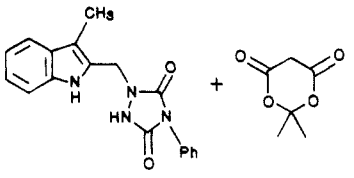
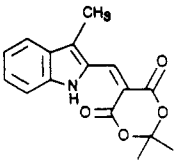
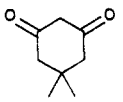
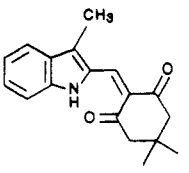
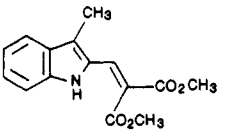
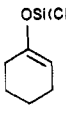
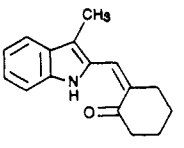
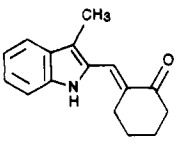
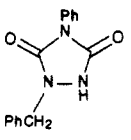
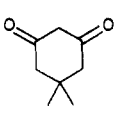
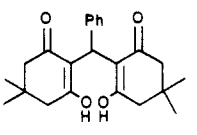
Finally it should be noted that the oxidative formation of triazolinedione ylides constitutes a new and perhaps the most versatile method for generating these most interesting ylide species. The most thoroughly investigated alternative method for the preparation of triazolinedione ylides is the reaction of PTAD with diazoalkanes.[2c,d] A unique example of a stable triazolinedione ylide has been observed in an "arrested" Diels–Alder reaction between PTAD and 1,3-dimesitylisobenzofuran.[2b] Finally, unusual bis 1,2-triazolinedione ylides result from the reactions of PTAD with electron-rich diarylacetylenes.[2a] However, in none of these previous studies were the reactions of the triazolinedione ylides with nucleophiles explored systematically.

Reactions of Triazolinedione Ylides with Nucleophiles

Reactions with Active Methylene Compounds. The isolable indole triazolinedione ylide **10** has provided definitive evidence that these ylide species are the pivotal intermediates in the condensation reactions to be described below. Thus, if **10** is treated with Meldrum's acid (Scheme VII), the red-orange color of **10** is bleached within 30 s, and after an additional 30 min at room temperature, the condensation product **16** can be isolated in quantitative yield. The overall rate of these condensation reactions is determined by the relatively slow elimination of the *N*-phenylurazole in the second step. In this particular reaction, the initial adduct **17** can be observed by ^1H NMR spectroscopy (δ 4.78 (d, J = 10 Hz) and 6.0 (d, J = 10 Hz), but attempts to isolate **17** have led to its decomposition with the formation of the elimination product **16**.

(5) (a) Taylor, W. I. *Helv. Chim. Acta* **1950**, *33*, 164. (b) Itahara, T.; Ouya, H.; Kozono, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3861.
(6) Akasaka, T.; Sonobe, H.; Sato, R.; Ando, W. *Tetrahedron Lett.* **1984**, *25*, 4757.

Table I. Conditions, Products, and Yields for Ylide Condensations with Enolate Species

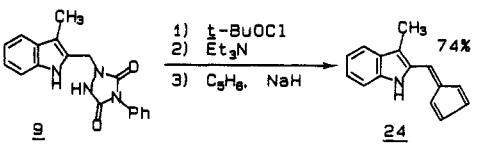
starting materials	base[a]	reaction conditions[b]	products	yields, %
 **9**	Et_3N	rt,[c] 30 min	 **16**	100
9 + 	Et_3N	rt, 30 min	 **18**	75
9 + $CH_2(COOCH_3)_2$	NaH	60 °C, 12 h	 **19**	99
9 + 	MeLi	60 °C, 16 h	 **20** +  **21**	14, 58[d]
 **6** + 	Et_3N	rt, 8 h	 **22**	75
6 + $CH_2(CO_2CH_3)_2$	NaH	60 °C, 18 h	$PhCH{=}C(CO_2CH_3)_2$ **23**	51

[a] Base used for the generation of the enolate species. [b] Conditions required for *N*-phenylurazole elimination. [c] Room temperature, rt. [d] Product ratio variable as **21** isomerizes to **20** under ambient conditions.

A number of other condensation products of **10** with enol and enolate species have been realized, and these are listed in Table I. Since the formation of ylide **10** via the aforementioned oxidation procedure and the subsequent condensation sequence both occur with such extreme facility, it is not necessary to isolate the intermediate ylide. Thus, the yields listed in Table I are based upon starting from the urazoles **6** and **9** with sequential formation of the ylides **13** and **10**, respectively, and their condensation products in a single plot. All subsequent ylide reactions described in this paper were also conducted via the generation of the ylides in situ.

With regard to the condensation reactions under consideration in this section, several points are worthy of emphasis. First, the condensations of Meldrum's acid, dimethyl malonate, and dimedone with ylide **10** all proceed in the absence of base. However, the addition of base or the prior formation of the appropriate enolate species does substantially accelerate the bleaching of the red-orange ylide color. Consequently it appears that in the case of the highly acidic carbonyl systems mentioned above, the ylide **10** is either sufficiently basic to generate the requisite enolates or sufficiently electrophilic to react with the enol forms of these carbonyl compounds. Furthermore, even though the bleaching of the red-orange ylide color is extremely rapid (<10 s) in all cases, the reaction times and temperatures required to produce the optimum yields of the final condensation products are highly variable. This variation in conditions is thought to reflect the ease with which *N*-phenylurazole is eliminated from the initial ylide adducts related to **17** in Scheme VII. Finally, in the condensations of the less stable phenyl ylide **13**, the yields of the condensation products are enhanced significantly through the application of an excess of the enolate species, which apparently increases the efficiency of trapping this transient ylide.

Scheme VIII

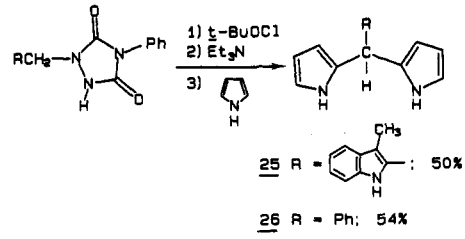


9 **24**

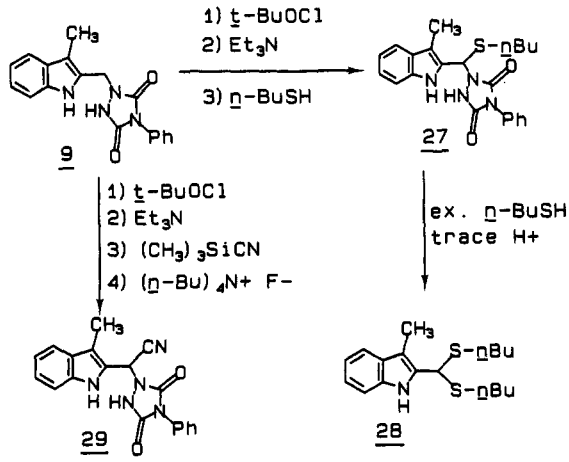
In addition to these enolate condensation reactions, the ylide **10** also undergoes a facile condensation with cyclopentadienide anion to afford good yields of the rather unstable fulvene **24** (Scheme VIII). While **24** could be characterized, it does decompose rapidly in solution and more slowly at 0 °C in the solid phase.

Reactions with Pyrrole. The electron-rich double bonds of pyrrole are also sufficiently nucleophilic to undergo extremely facile condensations with the ylides **10** and

Scheme IX



Scheme X



13 (Scheme IX). In these reactions, simple treatment of the ylides with pyrrole at room temperature results in the formation of substituted 2,2′-dipyrrylmethanes in moderate yields. These conditions are substantially milder than those required for the condensations of pyrroles with carbonyl compounds.[7] Thus, extremely electron rich 2,2′-dipyrrylmethanes such as **25** become readily available through this route. This substance is quite sensitive to air oxidation but may be stored for long periods under an inert atmosphere. The unusual bis(pyrroles) made available by this simple method cannot be obtained by conventional carbonyl condensation chemistry and should be useful intermediates in the synthesis of porphyrins with novel substituents.

Reaction with *n*-BuSH. The reaction of ylide **10** with *n*-BuSH leads to the rapid and quantitative formation of the adduct **27** under mildly basic conditions (Scheme X). This adduct can be easily isolated in high purity by simple removal of the suspended solids from the crude reaction mixture by filtration and evaporation of the solvent from the filtrate. However, upon standing in neutral solution, **27** slowly undergoes a thiol exchange to form the dithioacetal **28**, the ylide **10**, and *N*-phenylurazole. The dithioacetal **28** can be formed rapidly and in quantitative yield by treating the monoadduct **27** with excess *n*-BuSH and a catalytic amount of trifluoroacetic acid (Scheme X). In contrast, under the mildly basic conditions initially used to form the monoadduct **27**, no dithioacetal **28** is generated from **27** even in the presence of excess thiol, with prolonged reaction times, or at elevated temperatures.

Reaction with Cyanide. The treatment of ylide **10** with cyanide salts led to quite unsatisfactory results, since these salts could not be obtained in rigorously anhydrous form. Consequently, the expected cyanide adduct **29** (Scheme X) was always contaminated with the aldehyde **12**, which was formed from the hydrolysis of the ylide **10**. This problem can be easily overcome by generating cyanide ion in situ from trimethylsilyl cyanide with tetra-*n*-butylammonium fluoride. In this system the excess trimethylsilyl cyanide acts as a scavenger for any water introduced into the system with the fluoride salt. Even though the cyanide adduct **29** is quite unstable, it can be obtained in pure form by simply washing the crude reaction mixture with water and evaporating the solvent.

Discussion and Conclusions

Triazolinedione ylides are readily available through the *tert*-butyl hypochlorite oxidation of *N*′-benzyl and related N′-substituted *N*-phenylurazoles. In favorable cases, these ylides are remarkably stable and easily isolated. These intriguing species have been found to react with a wide variety of nucleophiles to form adducts and condensation products under surprisingly mild conditions. Even triazolinedione ylides that exhibit only transient existence can be effectively trapped when they are generated in the presence of suitable nucleophiles.

While the scope of this new condensation procedure remains to be determined, this type of procedure would seem to offer several distinct synthetic advantages. First of all, the overall procedure couples the preparation of the carbonyl moiety directly to the condensation step. Thus, not only does the triazolinedione ene–ylide formation and hydrolysis sequence provide an extremely mild route to carbonyl compounds that might not be so readily available by other means, but it also becomes unnecessary to apply the carbonyl compound itself in the condensation step when its precursor ylide can be a better condensation substrate. Furthermore, the condensation chemistry described here does parallel conventional condensation chemistry and might frequently be conducted more conveniently in the conventional fashion, as in the case of the benzaldehyde equivalent **13**. However, this is not always the case. Carbonyl systems such as the indole aldehyde **12**, where electron-donating substituents deactivate the carbonyl group toward attack by nucleophiles, can be reluctant condensation substrates. In these cases the triazolinedione ylide method offers a powerful alternative, since these ylides behave as highly polar carbonyl equivalents that undergo many of the reactions typical of the carbonyl group, but under much milder conditions. Consequently, these novel ylide intermediates can provide access to unusual condensation products, which in some cases would be most difficult if not impossible to obtain via traditional carbonyl condensation chemistry.

We are continuing to investigate the scope and applications of this chemistry, and further condensation reactions of other classes of triazolinedione ylides will be reported in the near future.[8]

Experimental Section

General Procedures. Melting points were determined with a Mettler FP2 melting point apparatus using a polarizing microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with either an IBM NR-80 80-MHz spectrometer or a Nicolet NT 300-MHz spectrometer. Spectra were recorded in $CDCl_3$ except where noted otherwise, and chemical shifts are reported in δ downfield from tetramethylsilane as an internal standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Infrared spectra were recorded on a Perkin-Elmer 599 infrared spectrometer and were calibrated with a polystyrene film. High-resolution mass spectra were obtained with a Kratos MS801-DS55 spectrometer. UV–vis spectra were recorded with a Perkin-Elmer Lambda 5 spectrometer.

(7) Paine, J. B. *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, 1978; Vol. I, Part A, p 163.

(8) Hengge, A.; Wilson, R. M. *Abstracts of Papers, American Chemical Society 18th Central Regional Meeting*; Abstract 337, June 1–5, 1986.

Analytical thin-layer chromatography was conducted by using E. Merck silica gel 60-F254 precoated plates. Compounds were visualized by UV light (254 nm) and by I_2 vapor. Preparative chromatographic separations were conducted with a Chromatotron using plates coated with E. Merck silica gel 60-PF254 or by column chromatography using Fisher neutral alumina, 80–200 mesh.

Solvents and reagents were used as received unless noted otherwise. Tetrahydrofuran was freshly distilled from benzophenone ketyl. Benzene was dried over sodium ribbon. All reactions were conducted under an atmosphere of either nitrogen or argon in oven-dried glassware.

PTAD was prepared by a modification of the standard *tert*-butyl hypochlorite method.[9] These modifications consisted of adding the *tert*-butyl hypochlorite to the 4-phenylurazole solution over about 1 h rather than 20 min and maintaining the reaction temperature at 5 °C rather than room temperature. If material obtained by this procedure was immediately and rapidly sublimed at 95 °C (10^{-3} mm), yields of pure material in excess of 98% were obtained routinely. This compares with the published PTAD yields, which are quoted in the range of 62–64%.[9]

Preparation of 1-Benzyl-4-phenylurazole (6). A solution of 2 g (11.2 mmol) of 4-phenylurazole and 285 mg (2.8 mmol) of triethylamine was stirred in 50 mL of dry THF at 40 °C for 20 min. To this solution was added 477 mg (2.8 mmol) of benzyl bromide, and the reaction mixture was stirred at 40 °C for 20 h. Upon cooling to room temperature, the reaction mixture was poured into NH_4Cl/brine and extracted with ethyl acetate (3×). The combined organic extracts were dried over $MgSO_4$, evaporated to dryness, and redissolved in methylene chloride. The insoluble 4-phenylurazole was removed by filtration and the filtrate chromatographed on silica gel eluting with ethyl acetate/methylene chloride (1:1) to afford 345 mg (1.29 mmol, 47%, ~100% yield based upon recovered starting material[10]) of the benzylurazole **6** as colorless crystals: mp 143.2–143.7 °C; IR ($CHCl_3$) 3010, 1775, 1720, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 2 H), 7.28 (s, 5 H), 7.42–7.46 (m, 5 H), 9.0 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.25 (t), 125.41 (d), 128.23 (d), 128.50 (d), 128.70 (d), 128.80 (d), 129.07 (d), 131.08 (s), 133.80 (s), 152.37 (s), 153.34 (s); UV (MeCN) λ_{max} 258 nm (ϵ 300); HRMS, m/z calcd for $C_{15}H_{13}N_3O_2$ (M^+) 267.1008, found 267.1013.

Preparation of 1-(2,3-Dimethyl-3*H*-indol-3-yl)-4-phenylurazole (8). To a solution of 2,3-dimethylindole (221 mg, 1.53 mmol) in 15 mL of benzene cooled in an ice bath was added dropwise over 1 min a solution of PTAD (270 mg, 1.54 mmol). The discharge of the red color of PTAD was immediate. A single product was formed, as judged by TLC. The resulting yellow reaction mixture was concentrated under reduced pressure to yield the indolenine **8** as an unstable reddish oil: IR ($CHCl_3$) 3500–2600, 1780, 1720, 1596, 1500, 1420 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.64 (s, 3 H), 2.34 (s, 3 H), 7.0–7.5 (m, 9 H), 8.69 (br s, 1 H); UV (MeCN) λ_{max} 210 (ϵ 35 000), 216 (36 000), 223 nm (29 000). When this material was dissolved in benzene and heated to 60 °C with stirring, crystals of the rearranged indole **9** began to precipitate within 30 min (see the following procedure for the preparation of **9**).

Preparation of 1-[(3-Methyl-2-indolyl)methyl]-4-phenylurazole (9). To a solution of 2,3-dimethylindole (2.00 g, 13.7 mmol) in 200 mL of dry benzene was added a solution of 2.10 g (12.0 mmol) of PTAD in 50 mL of benzene. After addition, the solution was heated to 60 °C and maintained at this temperature for 24 h. Upon cooling to room temperature, the product precipitated, was collected by filtration, and was washed with methylene chloride. Recrystallization from hot ethyl acetate afforded **9** (2.25 g, 7.03 mmol, 59%) as colorless crystals: mp 202.3–203.0 °C; IR (KBr) 3490, 1785, 1725, 1500 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3/Me_2SO$-d_6, 10:1) δ 2.36 (s, 3 H), 4.88 (s, 2 H), 7.07–7.53 (m, 10 H), 9.53 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3/Me_2SO$-d_6, 10:1) δ 8.42 (q), 41.43 (t), 110.46 (s), 111.04 (d), 118.77 (d), 118.87 (d), 122.11 (d), 125.40 (d), 127.63 (d), 127.78 (s), 128.25 (s), 128.89 (d), 131.49 (s), 135.92 (s), 152.57 (s), 152.84 (s); UV (MeCN) λ_{max} 226 (ϵ 38 000), 274 nm (7900); HRMS, m/z calcd for $C_{18}H_{16}N_4O_2$ (M^+) 320.1201, found 320.1237.

Preparation of 1-(2-Methyl-3-indolyl)-4-phenylurazole (7). To a solution of 2-methylindole (762 mg, 5.81 mmol) in 10 mL of chloroform at 0 °C was added dropwise over 10 min a solution of 120 mg (0.69 mmol) of PTAD in 20 mL of chloroform. The solution was allowed to warm to room temperature and stirred at this temperature for 1 h. The reaction mixture was concentrated to about one-half its original volume under reduced pressure and stored at −5 °C for 2 days. The resulting colorless crystals were collected by filtration to afford 160 mg (0.52 mmol, 76%) of the product: mp 170 °C dec; IR (KBr) 3460, 1780, 1740, 1500, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/Me_2SO$-d_6, 10:1) δ 2.31 (s, 3 H), 7.06–7.12 (m, 2 H), 7.22–7.25 (m, 1 H), 7.36–7.51 (m, 5 H), 7.63 (d, J = 8 Hz, 2 H), 10.24 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3/Me_2SO$-d_6, 10:1) δ 10.96 (q), 107.22 (s), 111.32 (d), 116.76 (d), 119.91 (d), 121.46 (d), 124.12 (s), 125.71 (d), 127.74 (d), 128.91 (d), 131.87 (s), 133.93 (s), 134.75 (s), 151.03 (s), 152.18 (s); UV (MeCN) λ_{max} 218 (ϵ 49 000), 268 (8400), 286 nm (6400); HRMS, m/z calcd for $C_{17}H_{14}N_4O_2$ (M^+) 306.1117, found 306.1128.

Preparation of the Triazolinedione Ylide 10. To a solution of the urazole **9** (53.3 mg, 0.166 mmol) in 15 mL of dry THF was added *tert*-butyl hypochlorite[11] (19.8 μL, 0.166 mmol) followed after 30 s by triethylamine (22.8 μL, 0.166 mmol). The resulting dark red-orange suspension was filtered through a 3 × 3 cm column of Florisil (60–100 mesh, Fisher), which had been dried at 110 °C overnight. The Florisil was washed with an additional 20 mL of dry THF, and the combined filtrates were evaporated to dryness to afford 42.4 mg (0.133 mmol, 80%) of the pure ylide **10**: mp 205 °C dec; IR ($CHCl_3$) 1785, 1700, 1595, 1490, 1380, 1335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 3 H), 7.35–7.80 (m, 9 H), 8.37 (s, 1 H), 11.38 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.95, 110.10, 113.21, 121.66, 121.85, 122.83, 124.91, 125.39, 128.12, 128.38, 129.31, 131.05, 131.48, 141.23, 150.75, 154.51; UV (MeCN) λ_{max} 220 (ϵ 15 500), 335 (3600), 470 nm (13 500); HRMS, m/z calcd for $C_{18}H_{14}N_4O_2$ (M^+) 318.1117, found 318.1125.

Preparation of 2-Formyl-3-methylindole (12). To a solution of the urazole **9** (21.5 mg, 0.067 mmol) in 6 mL of THF was added 8.0 μL (0.067 mmol) of *tert*-butyl hypochlorite.[11] The solution rapidly developed an orange color. After about 1 min, 9.3 μL (0.067 mmol) of triethylamine was added, giving rise to a dark red-orange color. Several drops of distilled water were added, and the reaction mixture was stirred at room temperature for 90 min. The resulting nearly colorless solution was poured into brine and extracted with ethyl acetate (2×). The organic layers were dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride/ethyl acetate (5:1) afforded 10.5 mg (0.066 mmol, 99%) of the known aldehyde **12** as pale yellow crystals: mp 138.0–138.5 °C (lit.[5a] 138–139 °C); IR ($CHCl_3$) 3460, 2920, 2840, 1650, 1550, 1360 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 2.64 (s, 3 H), 7.1–7.8 (m, 5 H), 10.04 (s, 1 H).

Preparation of 2-[(4,4-Dimethyl-2,6-dioxo-3,5-dioxanylidene)methyl]-3-methylindole (16). Meldrum's acid[12] (13.5 mg, 0.094 mmol) and triethylamine (9.5 mg, 0.094 mmol) in 5 mL of THF were stirred at room temperature for 10 min. In a separate flask, 30 mg (0.094 mmol) of the urazole **9** was dissolved in 10 mL of THF and 10.2 mg (0.094 mmol) of *tert*-butyl hypochlorite[11] added. An orange color developed rapidly. After about 1 min, 9.5 mg (0.094 mmol) of triethylamine was added, at which point the color intensified to a deep red-orange. The Meldrum's acid/triethylamine solution was added immediately and the reaction mixture stirred for 30 min. The resulting light orange solution was poured into NH_4Cl/brine and the mixture extracted with methylene chloride (2×). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with cyclohexane/methylene chloride (2:1) followed by recrystallization from cyclohexane afforded 27 mg (0.095 mmol, 100%) of **16** as yellow-orange crystals: mp 196.1–196.6 °C; IR ($CHCl_3$) 3300, 1765, 1690, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79

(9) Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. *Org. Synth.* **1971**, *51*, 121.

(10) It must be noted that if this reaction is taken much beyond about 50% conversion, a significant amount of the dibenzylated urazole results even when a larger excess of *N*-phenylurazole and only 1 equiv of base are employed. Apparently the monobenzylated urazole **6** is much more easily alkylated than the parent *N*-phenylurazole.

(11) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 184.

(12) Meldrum, A. N. *J. Chem. Soc.* **1908**, *93*, 598.

(s, 6 H), 2.64 (s, 3 H), 7.1–7.7 (m, 4 H), 8.56 (s, 1 H), 11.83 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.97 (q), 27.33 (q), 103.34 (s), 104.38 (s), 112.81 (d), 120.88 (d), 121.60 (d), 127.92 (s), 129.50 (s), 129.87 (d), 133.34 (s), 139.96 (s), 141.22 (d), 163.76 (s), 164.04 (s); UV (MeCN) λ_{max} 208 (ϵ 20800), 420 nm (29500); HRMS, m/z calcd for $C_{16}H_{15}NO_4$ (M^+) 285.1001, found 285.1026.

Preparation of 16 from the Isolated Ylide 10. To a solution of Meldrum's acid[11] (7.0 mg, 0.049 mmol) in 5 mL of THF was added 4.9 mg (0.049 mmol) of triethylamine, and the solution was stirred for 5 min. This solution was added to a stirred suspension of the ylide **10** (14.0 mg, 0.044 mmol) in 10 mL of THF, and the resulting mixture was stirred at room temperature for 20 min. Isolation and purification as described above afforded 12.6 mg (0.044 mmol, 100%) of **16**.

Preparation of 2-[(4,4-Dimethyl-2,6-dioxocyclohexylidene)methyl]-3-methylindole (18). To a solution of dimedone (5,5-dimethyl-1,3-cyclohexanedione) (13.8 mg, 0.098 mmol) in 5 mL of THF at 0 °C was added 9.3 mg (0.092 mmol) of triethylamine, and the solution was stirred for 15 min. In a separate flask, a solution of 29.6 mg (0.093 mmol) of the urazole **9** in 10 mL of THF was treated sequentially with 10.0 mg (0.093 mmol) of *tert*-butyl hypochlorite[11] followed by 9.3 mg (0.092 mmol) of triethylamine as described in the previous procedure. The dimedone solution was added to this dark red-orange solution and the resulting solution stirred at room temperature for 30 min. The reaction mixture was poured into NH_4Cl/brine and extracted with methylene chloride (2×). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride followed by recrystallization from methylene chloride/hexane afforded 19.0 mg (0.068 mmol, 75%) of **18** as orange crystals: mp 147.1–147.2 °C; IR ($CHCl_3$) 3230, 1630, 1620, 1520, 1480 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 2.58 (s, 2 H), 2.65 (s, 5 H), 7.07–7.65 (m, 4 H), 8.40 (s, 1 H), 12.40 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.02 (q), 28.50 (q), 30.06 (s), 51.99 (t), 53.91 (t), 112.79 (d), 120.44 (d), 121.22 (d), 123.33 (s), 128.49 (s), 129.09 (d), 130.85 (s), 132.19 (s), 137.14 (d), 138.68 (s), 197.80 (s), 199.61 (s); UV (MeCN) λ_{max} 206 (ϵ 29000), 252 (8000), 456 nm (36000); HRMS, m/z calcd for $C_{18}H_{19}NO_2$ (M^+) 281.1416, found 281.1387.

Preparation of 2-[2,2-Bis(methoxycarbonyl)vinyl]-3-methylindole (19). To a solution of 10.4 mg (0.079 mmol) of dimethyl malonate in 3 mL of dry THF at 0 °C was added 3.6 mg (0.075 mmol) of a 50% oil dispersion of sodium hydride. This mixture was stirred for 20 min at 0 °C. In a separate flask, 23.8 mg (0.074 mmol) of the urazole **9** in 8 mL of THF was treated successively with *tert*-butyl hypochlorite[11] and triethylamine as described above. About 1 min following the addition of the triethylamine, the aforementioned solution of the dimethyl malonate enolate was added to the ylide solution and the resulting mixture was heated to 60 °C for 12 h. Upon cooling to room temperature, the yellow reaction mixture was poured into NH_4Cl/brine and extracted with ethyl acetate (2×). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride afforded 20.0 mg (0.073 mmol, 99%) of **19** as yellow crystals. Following recrystallization from ether/pentane, **19** had the following: mp 95.6–96.4 °C; IR ($CHCl_3$) 3380, 1715, 1590, 1435 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 3.87 (s, 3 H), 3.94 (s, 3 H), 7.09–7.65 (m, 4 H), 7.96 (s, 1 H), 10.39 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.36 (q), 52.58 (q), 52.83 (q), 111.97 (d), 116.45 (s), 120.02 (d), 120.45 (d), 124.70 (s), 126.56 (d), 127.85 (s), 128.32 (s), 134.20 (d), 138.05 (s), 166.68 (s), 168.61 (s); UV (MeCN) λ_{max} 210 (ϵ 19500), 252 (5500), 362 nm (25000); HRMS, m/z calcd for $C_{15}H_{15}NO_4$ (M^+) 273.1001, found 273.1016.

Preparation of the *Z* and *E* Isomers of 3-Methyl-2-[(2-oxocyclohexylidene)methyl]indole (20 and 21, Respectively). To a solution of 75.8 mg (0.88 mmol) of the trimethylsilyl enol ether of cyclohexanone[13] in 10 mL of THF at 0 °C was added 21.5 mg (0.98 mmol) of methyllithium dropwise with stirring over 1 min, and the reaction mixture was stirred for an additional 40 min at 0 °C. In a separate flask, 197.7 mg (0.62 mmol) of the urazole **9** in 40 mL of THF at 0 °C was treated with 67.3 mg (0.62 mmol) of *tert*-butyl hypochlorite[11] followed after 4 min by 62.0 mg (0.62 mmol) of triethylamine. The aforementioned cyclohexanone enolate solution was added to the ylide solution via cannula 2 min later. After 5 min at room temperature, this mixture was heated to 60 °C and stirred at this temperature for 16 h. Upon cooling to room temperature, several drops of acetic anhydride were added and the reaction mixture was evaporated to dryness. Column chromatography using neutral alumina and eluting initially with methylene chloride/cyclohexane (1:1) followed by methylene chloride yielded 18.4 mg (0.076 mmol, 14%) of the less polar *Z* isomer **20** and 86 mg (0.36 mmol, 58%) of the more polar *E* isomer **21**.

The *Z* isomer **20** upon recrystallization from ether/methanol formed orange crystals: mp 114.9–115.5 °C; IR ($CHCl_3$) 3300, 2960, 1660, 1555 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84–1.95 (m, 4 H), 2.43 (s, 3 H), 2.56 (t, J = 6.7 Hz, 2 H), 2.74 (t, J = 6.0 Hz, 2 H), 6.72 (s, 1 H), 7.06–7.56 (m, 4 H), 11.44 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.11 (q), 23.40 (t), 24.19 (t), 36.41 (t), 41.66 (t), 111.73 (d), 117.94 (s), 119.23 (d), 119.37 (d), 124.58 (d), 126.56 (d), 128.29 (s), 129.72 (s), 130.54 (s), 135.82 (s), 203.86 (s); UV (hexane) λ_{max} 217 (ϵ 18500), 259 (5200), 390 nm (13200); HRMS, m/z calcd for $C_{16}H_{17}NO$ (M^+) 239.1310, found 239.1329.

The *E* isomer **21** upon recrystallization from ether/hexane formed yellow crystals: mp 139.7–140.1 °C; IR ($CHCl_3$) 3490, 2920, 1665, 1570 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–1.91 (m, 4 H), 2.41 (s, 3 H), 2.52 (t, J = 6.5 Hz, 2 H), 2.99 (m, 2 H), 7.12–7.59 (m, 4 H), 7.74 (s, 1 H), 8.26 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.30 (q), 22.86 (t), 23.51 (t), 28.55 (t), 39.81 (t), 111.08 (d), 119.71 (d), 119.98 (d), 120.15 (s), 124.63 (d), 124.89 (d), 128.32 (s), 130.53 (s), 130.97 (s), 137.52 (s), 200.23 (s); UV (MeCN) λ_{max} 215 (ϵ 20100) 258 (6100), 371 nm (17200); HRMS, m/z calcd for $C_{16}H_{17}NO$ (M^+) 239.1310, found 239.1315.

The relative yields of **20** and **21** are somewhat variable. It was noted that **21** is readily converted to **20** either upon standing in solution in the laboratory light or on silica gel.

Preparation of Bis(4,4-dimethyl-2-hydroxy-6-oxo-1-cyclohexen-1-yl)phenylmethane (22). To a solution of dimedone (5,5-dimethyl-1,3-cyclohexanedione) (43.4 mg, 0.31 mmol) in 6 mL of benzene was added 29.8 mg (0.30 mmol) of triethylamine, and the solution was stirred for 15 min. In a separate flask, a solution of the benzylurazole **6** (28.0 mg, 0.104 mmol) in 4 mL of benzene was warmed to 50 °C and treated with *tert*-butyl hypochlorite[11] (11.4 mg, 0.104 mmol). After about 1 min, the dimedone solution was added to this red-orange ylide solution and the resulting pale yellow solution stirred at room temperature for 8 h. The reaction mixture was poured into NH_4Cl/brine and extracted with ethyl acetate (2×). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride followed by recrystallization from methylene chloride/cyclohexane afforded 28.9 mg (0.079 mmol, 75%) of **22** as colorless crystals: mp 187.5–188.8 °C; IR ($CHCl_3$) 3000–2500, 1595, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 6 H), 1.24 (s, 6 H), 2.34–2.44 (m, 8 H), 5.54 (s, 1 H), 7.08–7.26 (m, 5 H), 11.09 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4 (q), 29.6 (q), 31.4 (s), 32.7 (d), 46.4 (t), 47.0 (t), 115.5 (s), 125.8 (d), 126.7 (d), 128.2 (d), 138.0 (s), 189.3 (s), 190.4 (s); UV (MeCN) λ_{max} 259 nm (ϵ 17500); HRMS, m/z calcd for $C_{23}H_{28}O_4$ (M^+) 368.1988, found 368.1994.

An authentic sample of **22** was prepared by the conventional base-catalyzed condensation between dimedone and benzaldehyde. This material was found to be identical with that prepared in the above ylide condensation as judged by comparison of TLC behavior, melting points, and NMR spectra.

Preparation of Dimethyl Benzylidenemalonate (23). To a solution of 31.2 mg (0.236 mmol) of dimethyl malonate in 10 mL of THF at 0 °C was added 11.9 mg (0.236 mmol) of a 50% oil dispersion of sodium hydride, and the mixture was stirred for 15 min. In a separate flask, a solution of 31.6 mg (0.118 mmol) of the benzylurazole **6** in 15 mL of THF was treated with 12.8 mg (0.12 mmol) of *tert*-butyl hypochlorite.[11] The solution became the characteristic yellow color of the *N*-chlorourazole within several seconds. Upon immersion of the reaction flask in an oil bath that had been preheated to 70 °C, the solution became orange after

(13) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

heating for 2 min. At this time the solution of the enolate of dimethyl malonate was added, and the resulting cloudy, colorless solution was heated with stirring at 60 °C for 18 h. Upon cooling, the reaction mixture was poured into brine and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Chromatography on a Chromatotron eluting with methylene chloride afforded 13 mg (0.059 mmol, 51%) of **23** as a clear oil: IR ($CHCl_3$) 1728, 1630, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.848 (s, 3 H), 3.852 (s, 3 H), 7.39–7.41 (m, 5 H), 7.78 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.67 (q), 125.44 (s), 128.89 (d), 129.37 (d), 130.70 (d), 132.72 (s), 142.94 (d), 164.48 (s), 167.16 (s); UV (MeCN) λ_{max} 216 (ϵ 9700), 277 nm (14 700); HRMS, m/z calcd for $C_{12}H_{12}O_4$ (M^+) 220.0735, found 220.0735. This material was identical with an authentic sample[14] as judged by comparison of TLC behavior and NMR spectra.

Preparation of 2-(2,4-Cyclopentadienylidenemethyl)-3-methylindole (24). To a solution of 24.3 mg (0.37 mmol) of freshly distilled cyclopentadiene[15] in 3 mL of THF at −78 °C was added 18 mg (0.37 mmol) of a 50% oil dispersion of sodium hydride with stirring. The mixture was allowed to warm to 0 °C over 30 min. In a separate flask, a solution of 29.8 mg (0.093 mmol) of the indole urazole **9** in 10 mL of THF was treated sequentially with *tert*-butyl hypochlorite[11] and triethylamine as described above. One-half of the aforementioned cyclopentadienide solution was added to the ylide solution, and the reaction mixture was stirred at room temperature for 12 h. The crude reaction mixture was filtered to remove particulate matter and the filtrate evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride afforded 14.3 mg (0.069 mmol, 74%) of the fulvene **24**. When freshly prepared, **24** is a yellow solid, but it decomposes slowly upon standing as the solid, and more rapidly in solution, into a brown polar material. When freshly prepared, **24** had the following: IR ($CHCl_3$) 1600, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 6.39–6.42 (m, 1 H), 6.48–6.50 (m, 1 H), 6.72–6.74 (m, 2 H), 7.10–7.15 (m, 1 H), 7.25–7.36 (m, 3 H), 7.57–7.61 (m, 1 H), 8.27 (br s, 1 H); UV (MeCN) λ_{max} 214 (ϵ 6075), 387 (8300), 407 nm (8600); HRMS, m/z calcd for $C_{15}H_{13}N$ (M^+) 207.1048, found 207.1046.

Preparation of 2,2′-Dipyrryl(3-methyl-2-indolyl)methane (25). Sequential treatment of a solution of 107.2 mg (0.34 mmol) of the indole urazole **9** in 20 mL of THF with *tert*-butyl hypochlorite[11] followed by triethylamine formed the triazolinedione ylide **10** as described above. Excess pyrrole (480 mg, 7.1 mmol) then was added to the ylide solution and the mixture stirred at room temperature for 22 h. The reaction mixture was poured into NH_4Cl/brine and extracted with ethyl acetate, and the combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride afforded 45.7 mg (0.166 mmol, 50%) of the dipyrrylmethane **25** as a colorless oil: IR ($CHCl_3$) 3420, 2995, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 5.73 (s, 1 H), 6.02–6.05 (m, 2 H), 6.17–6.20 (m, 2 H), 6.65–6.67 (m, 2 H), 7.09–7.18 (m, 3 H), 7.53–7.56 (m, 1 H), 7.62 (br s, 1 H), 7.89 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.41 (q), 35.66 (d), 107.09 (d), 108.22 (s), 108.78 (d), 110.78 (d), 117.38 (d), 118.50 (d), 119.35 (d), 121.78 (d), 129.30 (s), 130.13 (s), 133.11 (s), 135.18 (s); UV (hexane) λ_{max} 226 (ϵ 29 700), 284 nm (6400); HRMS, m/z calcd for $C_{18}H_{17}N_3$ (M^+) 275.1423, found 275.1438.

Preparation of 2,2′-Dipyrrylphenylmethane (26). Treatment of a solution of the phenyl urazole **6** (91.9 mg, 0.344 mmol) in 15 mL of benzene at 50 °C with *tert*-butyl hypochlorite[11] (41 μL, 0.344 mmol) gave an orange-colored solution after 60 s. To this was added a solution containing excess pyrrole (960 mg, 14 mmol) and DBN (43 μL, 0.35 mmol) in 5 mL of benzene. The resulting dark solution was stirred at room temperature for 12 h. The reaction mixture was passed through a 1.5 × 3.0 cm plug of flash silica gel eluting with methylene chloride to remove polar impurities. Evaporation of solvent was followed by removal of excess pyrrole under vacuum. Centrifugal chromatography using a Chromatotron and eluting with methylene chloride/hexane (3:1) afforded 41.5 mg (54%) of the dipyrrylmethane **26** as pale tan crystals: mp 100.2–101.1 °C; IR ($CHCl_3$) 3450, 3010, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 5.90 (br s, 2 H), 6.15 (dd, J = 5.7 and 2.4 Hz, 2 H), 6.65 (dd, J = 4.4 and 1.9 Hz, 2 H), 7.18–7.34 (m, 5 H), 7.87 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.85 (d), 107.13 (d), 108.31 (d), 117.17 (d), 126.88 (d), 128.30 (d), 128.56 (d), 132.44 (s), 142.02 (s); UV (hexane) λ_{max} 208 (ϵ 36 000), 306 nm (640); HRMS, m/z calcd for $C_{15}H_{14}N_2$ (M^+) 222.1139, found 222.1148.

Preparation of 1-[1-(3-Methyl-2-indolyl)-2-thiahexyl]-4-phenylurazole and 2-[Bis(butylthio)methyl]-3-methylindole (27 and 28, Respectively). Sequential treatment of a solution of 41.5 mg (0.13 mmol) of the indole urazole **9** in 12 mL of THF with *tert*-butyl hypochlorite[11] followed by triethylamine formed the triazolinedione ylide **10** as described above. To this ylide solution was added 12.9 mg (0.14 mmol) of *n*-butylthiol, and the resulting solution was stirred at room temperature for 2 h. The solvent was removed under reduced pressure at room temperature, the residue redissolved in ethyl acetate and filtered to remove the insoluble material, and the filtrate evaporated to dryness to afford 51.5 mg (0.126 mmol, 98%) of the monosulfide **27** as a pale yellow oil. Judging from the ^1H NMR spectrum, this substance was >95% pure: ^1H NMR (80 MHz, $CDCl_3$) δ 0.86 (t, J = 7 Hz, 3 H), 1.36 (tq, J = 7 and 7 Hz, 2 H), 1.53 (tt, J = 7 and 7 Hz, 2 H), 2.36 (s, 3 H), 2.50 (t, J = 7 Hz, 2 H), 6.67 (s, 1 H), 7.0–7.7 (m, 10 H), 8.94 (br s, 1 H). The monosulfide **27** was quite unstable and rapidly formed a mixture of the dithioacetal **28**, ylide **10**, monosulfide **27**, and phenylurazole upon standing neat or even more rapidly in solution.

This monosulfide **27** (51.5 mg, 0.126 mmol) was redissolved in 5 mL of methylene chloride and 160 mg (1.77 mmol) of *n*-butylthiol added followed by a catalytic amount of trifluoroacetic acid (2 μL, 2.96 mg, 0.026 mmol). After 1 h, the reaction mixture was filtered and the filtrate evaporated to dryness. The residue was purified by centrifugal chromatography using a Chromatotron and eluting with methylene chloride to afford 39.3 mg (0.122 mmol, 95%) of dithioacetal **28** as a colorless oil: IR ($CHCl_3$) 3445, 2990–2850, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6 H), 1.37 (tq, J = 7.4 and 7.4 Hz, 4 H), 1.54 (tt, J = 7.5 and 7.5 Hz, 4 H), 2.29 (s, 3 H), 2.51 (t, J = 7.5 Hz, 4 H), 5.23 (s, 1 H), 7.1–7.6 (m, 4 H), 8.32 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.54 (q), 13.58 (q), 21.88 (t), 31.31 (t), 32.35 (t), 43.11 (d), 109.61 (s), 110.79 (d), 118.70 (d), 119.21 (d), 122.29 (d), 128.64 (s), 131.36 (s), 135.63 (s); UV (MeCN) λ_{max} 226 (ϵ 41 300), 285 (16 500), 295 nm (13 500); HRMS, m/z calcd for $C_{18}H_{27}S_2N$ (M^+) 321.1584, found 321.1595.

Preparation of 1-[(3-Methyl-2-indolyl)cyanomethyl]-4-phenylurazole (29). To a solution of 28.6 mg (0.29 mmol) of trimethylsilyl cyanide in 5 mL of THF was added 90 μL (0.09 mmol) of a 1.0 M solution of tetra-*n*-butylammonium fluoride in THF, and the solution was stirred at room temperature for 20 min. In a separate flask, a solution of 61.4 mg (0.19 mmol) of the indole urazole **9** in 15 mL of THF was treated with *tert*-butyl hypochlorite[11] followed by triethylamine to form the triazolinedione ylide **10** as described above. The aforementioned trimethylsilyl cyanide solution was added to the ylide solution and the mixture stirred at room temperature for 1 h. The pale brown reaction mixture was poured into brine, several drops of dilute HCl were added, and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure, and the polar impurities were removed by filtration of the concentrate through a 1.5 × 3.0 cm plug of flash silica gel eluting with ethyl acetate. This operation must be conducted rapidly (<15 s) as the nitrile **29** decomposes rapidly on silica gel even at −40 °C. Evaporation of the filtrate to dryness under reduced pressure afforded 60.0 mg (0.17 mmol, 89%) of the nitrile **29** as orange crystals, which were ca. 95% pure as judged by ^1H NMR: mp 83 °C dec, IR ($CHCl_3$) 3350, 2200 (w), 1785, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 6.36 (s, 1 H), 7.08–7.12 (m, 3 H), 7.29–7.35 (m, 5 H), 7.47–7.50 (m, 2 H), 9.34 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.43 (q), 44.90 (d), 111.56 (d), 113.08 (s), 114.05 (s), 119.45 (d), 119.88 (d), 121.29 (s), 123.83 (d), 125.45 (d), 127.76 (s), 128.60 (d), 129.13 (d), 130.41 (s), 136.26 (s), 153.53 (s), 153.99 (s); UV (MeCN) λ_{max} 222 (ϵ 18 400), 285 (4400), 320 nm (3100); CIMS, parent peak 319 (M^+ − CN).

Acknowledgment. The financial support of the Na-

(14) Anschütz, R. *Annalen* **1907**, *354*, 117.
(15) Korach, M.; Nielsen, D. R.; Rideout, W. H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 414.

tional Science Foundation (CHE-8312691) and the University of Cincinnati for the award of a fellowship to A. H. is gratefully acknowledged. In addition we thank the National Science Foundation for grants used to purchase the NMR (CHE-8102974) and mass spectrometry (PCM-8219912) facilities used in this research.

Registry No. 6, 107798-93-6; 7, 107798-94-7; 8, 103865-84-5; 9, 103865-85-6; 10, 107798-95-8; 12, 5257-24-9; 16, 103865-88-9; 18, 103865-91-4; 19, 103865-92-5; 20, 103865-90-3; 21, 103865-89-0; 22, 7600-00-2; 23, 6626-84-2; 24, 107798-96-9; 25, 107798-97-0; 26, 107798-98-1; 27, 107798-99-2; 28, 107799-00-8; 29, 107799-01-9; PTAD, 4233-33-4; $MeO_2CCH_2CO_2Me$, 108-59-8; BuSH, 109-79-5; $PhCH_2Br$, 100-39-0; Me_3SiCN, 7677-24-9; 4-phenylurazole, 15988-11-1; 2,3-dimethylindole, 91-55-4; 2-methylindole, 95-20-5; Meldrum's acid, 2033-24-1; dimedone, 126-81-8; (1-cyclohexen-1-yloxy)trimethylsilane, 6651-36-1; pyrrole, 109-97-7; cyclopentadiene, 542-92-7.

Stereocontrolled Route to 2,3,5-Trisubstituted Tetrahydrofurans. Intermediates for the Total Synthesis of Polyether Antibiotics†

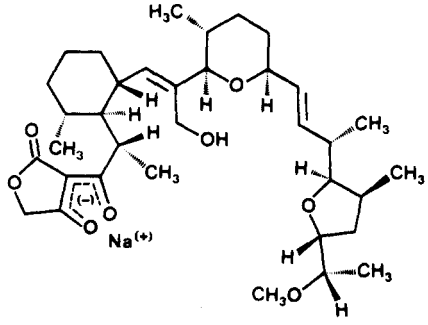
Herbert Frauenrath* and Jan Runsink

Institut für Organische Chemie der Technischen Hochschule Aachen, Professor-Pirlet-Str. 1, D 5100 Aachen, FRG

Received October 8, 1986

The stereoselective synthesis of diastereomers of 2,3,5-trisubstituted tetrahydrofurans has been accomplished by Lewis acid catalyzed vinyl acetal rearrangement. The reaction sequence starts with 4,7-dihydro-1,3-dioxepins **4**, which are isomerized to 4,5-dihydro-1,3-dioxepins **6**. The key step of the procedure is the stereocontrolled rearrangement of these mixed alkyl vinyl acetals **6**, followed by reduction. 2,3,5-Trisubstituted tetrahydrofurans are of general interest for the synthesis of polyether antibiotics.

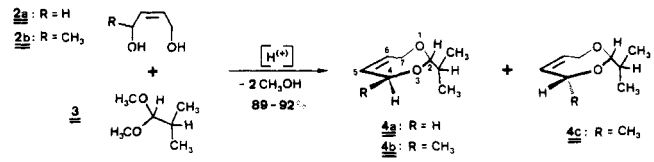
Several naturally occurring compounds, especially a wide variety of important polyether antibiotics, contain tetrahydrofuran rings with a diversity of substitution patterns and stereochemistry.[1] Tetrahydrofuran rings with 2,3-cis and 2,5-trans relationship are common features in this class of compounds, as demonstrated with polyether antibiotic ICI 139603 produced by streptomyces longisporoflavus (**1**).[1,2]



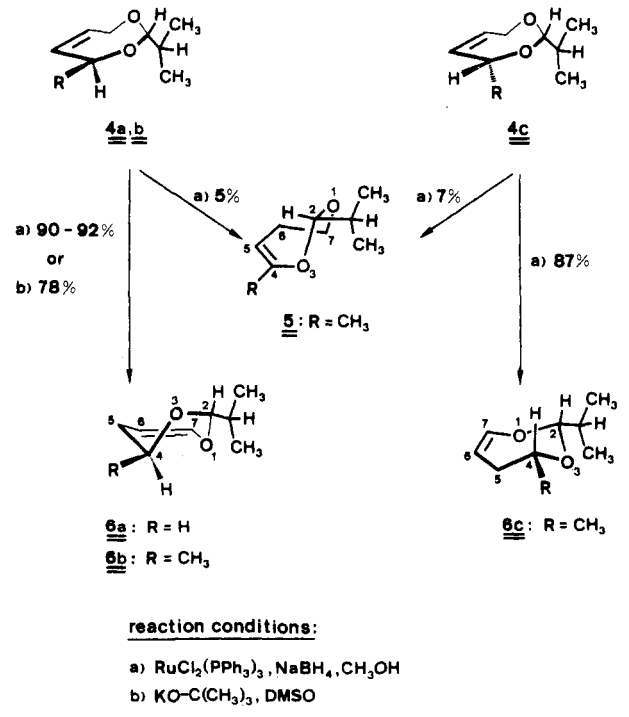
1

Although there are many routes to substituted tetrahydrofurans, only few proceed with high stereoselectivity.[3] Recently, we devised a new stereoselective preparation of 2,3-substituted tetrahydrofurans and 3,4-substituted 4-butanolides.[4] In this paper we now report the stereocontrolled synthesis of 2,3,5-substituted tetrahydrofurans starting with 2,4-substituted 4,7-dihydro-1,3-dioxepins. We used diastereomers of 2-isopropyl-4-methyl-4,7-dihydro-1,3-dioxepins **4b,c** as model compounds (Scheme I).[5] 2-Isopropyl-4,7-dihydro-1,3-dioxepin (**4a**) was used as starting material and transformed by the same reaction sequence for comparison and determination of the structures and conformations of the products.

Scheme I



Scheme II



4a,b **4c** **5**: R = CH_3 **6a**: R = H **6b**: R = CH_3 **6c**: R = CH_3

† Presented in part at the VI International Conference on Organic Synthesis, Moscow, USSR, August 10-15, 1986, as a poster.

0022-3263/87/1952-2707$01.50/0