

behavior in both polar THF and nonpolar C_6D_6 solvents lends further support to this interpretation. The fact that the relative rates of decomposition of the three alcohols qualitatively follow the release of steric strain, while the reactions proceed by two fundamentally different mechanisms may simply be fortuitous.

We can also now comment on the question of why alcohol **1a** can be synthesized with lithium metal but not with sodium. Treatment of a THF solution of **1a** with an excess of methyl lithium produced the lithium salt **2a** ($M = Li$). The solution was stable, giving back 85% of **1a** upon aqueous quenching after 24 h. However, when the solution of **2a** was treated with moist 12-crown-4 ether, it behaved as the potassium salt and quickly decomposed to give **5** and **3a** in high yields with no recovery of **1a**. A reasonable interpretation of this behavior is that a more covalent bond between lithium and oxygen compared to sodium or potassium and oxygen permits the lithium salt to persist during the synthesis until quenched during workup, whereas the sodium salt rapidly decomposes to **5** and **3a** by path (a).¹⁴ Such considerations are likely to be important in other syntheses as well.

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(14) Alternatively, the behavior could be discussed in terms of the different reactivity of tight ion pairs.

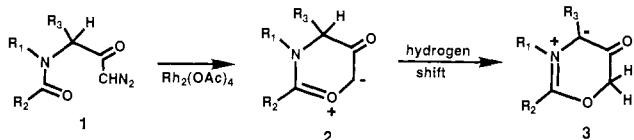
1,3-Dipole Cascade. A New Method for Azomethine Ylide Formation

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1,3-Dipoles have become extremely valuable intermediates in synthetic organic chemistry.¹ Their best known reaction corresponds to a 1,3-dipolar cycloaddition reaction.² The importance of this cycloaddition in organic synthesis derives in large part from its ability to generate five-membered heterocyclic rings containing several contiguous stereogenic centers in one synthetic operation.^{3,4} Less attention, however, has been placed upon the interconversion of one dipole into another.⁵ In this communication, we report the novel rearrangement of an α -diazo ketone (**1**) to an azomethine ylide (**3**), which proceeds via the intermediacy of a carbonyl ylide (**2**). We refer to the overall process as a *dipole cascade*.



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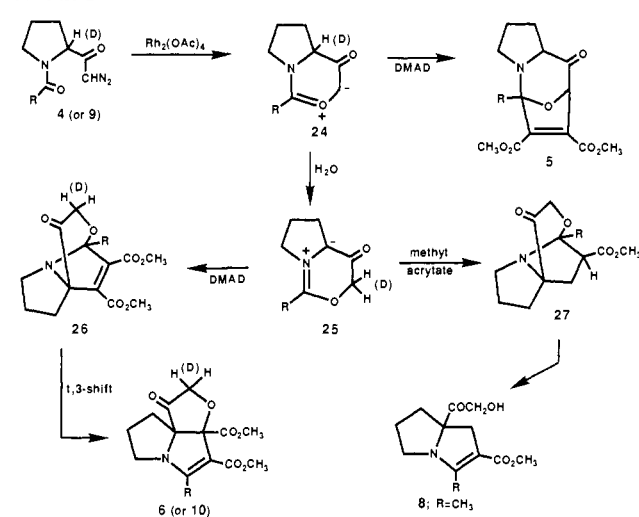
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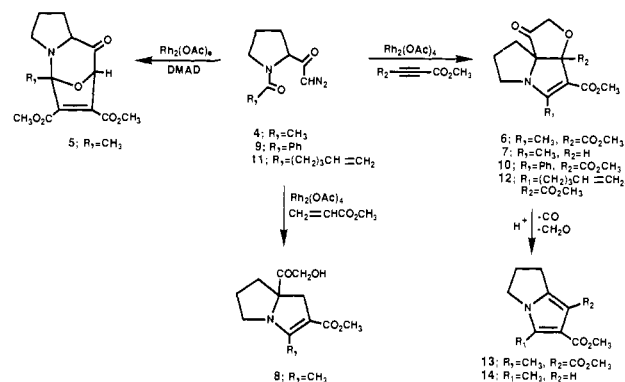
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Scheme 1



Recently, a tandem cyclization-cycloaddition reaction was developed in our laboratories as a method for synthesizing oxapolycyclic ring systems.⁶ It involves a rhodium(II) acetate induced diazo ketone cyclization onto a neighboring carbonyl group to generate a carbonyl ylide followed by 1,3-dipolar cycloaddition.^{7,8} The wealth of strategically located functionality that could result from the rhodium-catalyzed reaction of an α -diazo keto acyl amide of type **1** motivated us to focus on the possible utilization of this tandem cyclization-cycloaddition reaction for alkaloid synthesis. During the course of our studies, we uncovered the first example of the dipole cascade which involves three distinct classes of 1,3-dipoles.

Our initial endeavors focused on the behavior of (*S*)-1-acetyl-2-(1-diazoacetyl)pyrrolidine (**4**). Treatment of **4** with 1.5



equiv of dimethyl acetylenedicarboxylate (DMAD) in the presence of a catalytic quantity of $Rh_2(OAc)_4$ at 25 °C afforded very little (<10%) of the expected carbonyl ylide derived cycloadduct **5**.⁹ Instead, the major product obtained (90%) corresponded to structure **6**.⁹ Unequivocal proof of the proposed structure was obtained by an X-ray single-crystal structure analysis.¹⁰ In a similar manner, dihydropyrrolizines **7** and **8** were isolated in high

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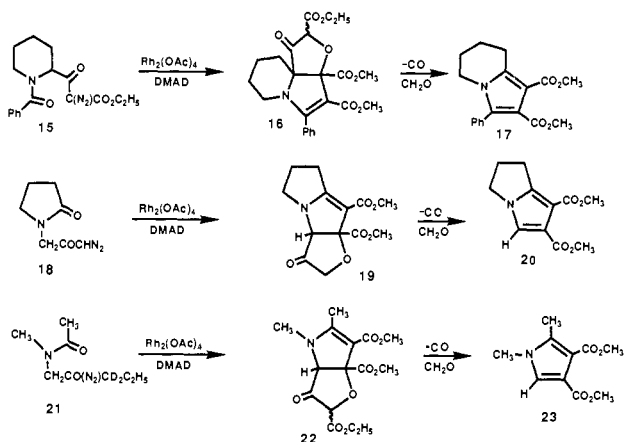
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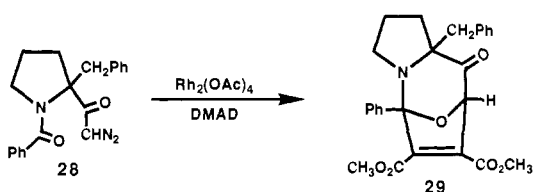
(9) Compound **5** ($R = CH_3$): NMR ($CDCl_3$, 300 MHz) δ 1.65–1.84 (m, 2 H), 1.70 (s, 3 H), 1.86–1.98 (m, 1 H), 2.14–2.26 (m, 1 H), 2.90–3.04 (m, 2 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 4.09 (td, 1 H, $J = 8.1, 1.5$ Hz), 4.95 (d, 1 H, $J = 1.5$ Hz). Compound **6**: δ 1.64–1.76 (m, 1 H), 1.91–2.04 (m, 2 H), 2.30 (s, 3 H), 2.30–2.35 (m, 1 H), 3.27 (ddd, 1 H, $J = 11.0, 7.9, 5.5$ Hz), 3.45 (dt, 1 H, $J = 11.0, 6.8$ Hz), 3.71 (s, 3 H), 3.80 (s, 3 H), 4.14 (d, 1 H, $J = 17.0$ Hz), 4.34 (d, 1 H, $J = 17.0$ Hz).

(10) Unit cell parameters were determined on a Syntex P2₁ automated diffractometer using Mo $K\alpha$ radiation. Details associated with the X-ray crystal structure are available as Supplementary Material.

yield (ca. 85%) when methyl propiolate or methyl acrylate was used as the trapping agent. Structures **6** and **7** were readily converted to the 5-methylpyrrolopyrroles **13** and **14** when treated with a trace of acid. Analogous cycloadditions were also encountered with the closely related benzoyl system **9** as well as with diazo amides **15**, **18**, and **21**.



A mechanism that rationalizes the formation of the products and that is consistent with all the data (vide infra) is outlined in Scheme I. The initial reaction involves generation of the expected carbonyl ylide dipole **24** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. Isomerization of **24** to the thermodynamically more stable azomethine ylide **25** (vide infra) occurs via proton exchange with the small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with DMAD provides cycloadduct **26**, which undergoes a subsequent 1,3-alkoxy shift to generate the tricyclic dihydropyrrolizine **6**.¹¹ The reaction was followed by NMR spectroscopy and the initially formed dipolar cycloadduct **26** (R = CH₃) could be readily detected [(benzene-*d*₆, 300 MHz) δ 1.20–1.45 (m, 2 H), 1.55–1.82 (m, 2 H), 1.51 (s, 3 H), 2.42–2.56 (m, 2 H), 3.21 (s, 3 H), 3.33 (s, 3 H), 4.24 (d, 1 H, *J* = 17.4 Hz), 4.33 (d, 1 H, *J* = 17.4 Hz)]. This material was quantitatively converted to **6** (or **10**) upon standing for 1 h in the NMR tube. In the case where methyl acrylate was used as the dipolarophile, cycloadduct **27** was not detected as it readily rearranged to **8**, presumably via an iminium ion intermediate. When **4-d** was used, cycloadduct **6** had incorporated a deuterium atom onto the α -carbon atom. It should also be noted that a significant quantity of cycloadduct **5** (ca. 45%) was produced starting from **4-d**. The slower rate of dipole conversion (i.e., **24** \rightarrow **25**) is consistent with the involvement of a deuterium isotope effect. When the α -position of the pyrrolidine ring was blocked by a benzyl group, the rhodium-catalyzed cycloaddition with DMAD led to the carbonyl ylide cycloadduct **29** in 95% yield.



The possibility of intramolecular trapping of either the carbonyl ylide or the azomethine ylide was explored by using the *N*-(5-hexenylcarboxy) analogue **11**. Exposure of **11** to Rh₂(OAc)₄ under standard conditions produced a complex mixture of products and none of the expected intramolecular cycloadducts. In contrast to this finding, addition of DMAD to the reaction mixture led cleanly to the azomethine ylide derived product **12** in 85% yield. Facile isomerization to the azomethine ylide once again precluded trapping of the intermediate carbonyl ylide. The inability of the

(11) The 1,3-sigmatropic shift of **26** to **6** is faster than the loss of carbon monoxide and formaldehyde.

azomethine ylide to undergo intramolecular cycloaddition across the unactivated C–C double bond is in accord with FMO theory in that type-I dipoles require electron-deficient dipolarophiles which possess low-lying LUMO levels.^{12–15} MNDO calculations (AM1) show that cyclic carbonyl ylides of type **2** are ca. 15 kcal/mol higher in their heat of formation than the corresponding azomethine ylides.¹⁶ Some of this energy difference is presumably responsible for the facility with which the dipole reorganization occurs.¹⁷

The high efficiency of the dipole cascade, in conjunction with the intriguing chemistry of the resulting cycloadducts, presents numerous synthetic possibilities. We are continuing to pursue further extensions of the “dipole interconversion” process and will report additional findings at a later date.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health. Use of the high-field NMR spectrometer used in these studies was made possible through a NSF equipment grant.

Supplementary Material Available: X-ray data for compound **6** (8 pages). Ordering information is given on any current masthead page.

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Macromolecular Stereochemistry: The Out-of-Proportion Influence of Optically Active Comonomers on the Conformational Characteristics of Polyisocyanates. The Sergeants and Soldiers Experiment¹

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The Italian school of polymer stereochemistry long ago demonstrated that copolymers prepared from achiral and chiral vinyl monomers show disproportionately high optical activities. Although the optical rotatory dispersion of the responsible backbone electronic transitions could not be directly observed, this characteristic was reasonably attributed to induced chiral conformations of the polymer chain.^{2,3} In the present work, we have repeated this type of experiment on poly(alkyl isocyanates), which are known to adopt stiff helical conformations in solution,⁴ and have discovered highly temperature and solvent dependent (Table

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