Tetrahedron Vol. 48, No. 36, pp. 7565-7580, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Azomethine Ylide Generation via the Dipole Cascade‡

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(*Received in USA 9 June* 1992)

Abstract: A series of N-acyl 2-diazo-3-oxobutanoates, when treated with a catalytic quantity of a rhodium(II) carboxylate, were found to afford substituted pyrroles derived from an azomethine ylide intermediate. The initial reaction involves generation of the expected carbonyl ylide dipole by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the neighboring amide group. The primary cycloadduct undergoes a subsequent rearrangement-fragmentation reaction to give the pyrrole derivative. When the α-position of the α-diazoketone was blocked with two methyl groups, the rhodium(II)-catalyzed cycloaddition with dimethyl acetylenedicarboxylate led to the carbonyl ylide cycloadduct in high yield. MNDO calculations show that the cyclic carbonyl ylide derived from ethyl 2-diazo-4-dibenzoylamino-3-oxobutyrate is 3.3 kcal lower in its heat of formation than the corresponding azomethine ylide. This thermodynamic difference in stability of dipoles nicely accounts for why the carbonyl ylide cycloadduct is the major product from the rhodium(II) catalyzed reaction of ethyl 2-diazo-4-dibenzoylamino-3-oxobutyrate.

Azomethine ylides have represented attractive synthetic building blocks for alkaloids[1] since Huisgen's initial observation of reversible thermal conrotatory electrocyclic ring opening of substituted aziridines and their subsequent trapping.[2] While these dipoles are versatile synthetic intermediates especially useful for 1,3-dipolar cycloaddition reactions, they are prone to undergo numerous side reactions under the thermal and/or photolytic conditions used to cleave the aziridine ring.[3-5] Consequently there is a continuing need to develop mild and versatile procedures for the generation of azomethine ylides. Studies conducted in these[6] and other laboratories[7-12] have shown that the desilylation of α-(trimethylsilyl)ammonium salts represents a convenient method for ylide generation. More recently we described the use of α-cyanomethylaminosilanes as valuable dipole precursors.[13] Other routes to azomethine ylides include (a) the thermolysis of benzaldimines[14,15], (b) thermal N-alkylamino ester/aldehyde condensation[16], (c) carbene insertion into an imine nitrogen lone pair[17], (d) treatment of trialkylamine N-oxides with LDA[18], (e) 1,2-prototropy in X=YZH systems[19], (f) decarboxylative transamination of α-amino acids[20] and (g) controlled reduction of oxazolium salts.[21] While many of these techniques are synthetically useful, most suffer from some limitations. In searching for alternate ways to form azomethine ylides, we introduced a new strategy for ylide formation in which the key step involved a dipole rearrangement.[22] This reaction, which we termed a *"dipole cascade"*, involves three distinct classes of 1,3-dipoles. It is initiated by a rhodium(II)-catalyzed diazo ketone cyclization onto a neighboring carbonyl group to generate a carbonyl ylide dipole[23-26] which then undergoes a subsequent proton shift. As part of our long standing interest in the chemistry of 1,3-dipoles, we have undertaken a more detailed investigation of the *dipole-cascade* with the hope of gaining an appreciation of the synthetic applicability of the reaction. The results reported below summarize various aspects of this effort.

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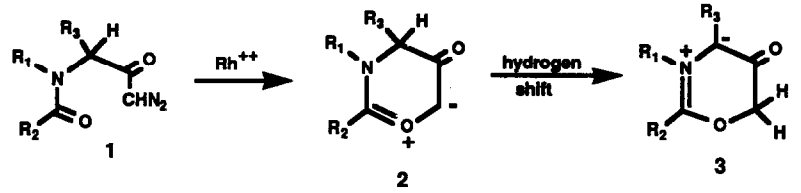
‡ *Dedicated with respect and admiration to Professor Charles W. Rees, one of the leading pioneers in the area of heterocyclic chemistry, on the occasion of his official retirement from Imperial College.*

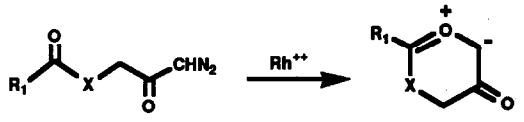
Dipole Cascade



1 2 3

Results and Discussion

Recent papers from these laboratories have described a route to oxapolycyclic ring systems which involves the tandem cyclization-cycloaddition reaction of a transient rhodium carbenoid.[27] As indicated below, a cyclic carbonyl ylide intermediate was generated by treatment of a diazoalkanedione (**4a**) with rhodium(II) carboxylates. In an effort to extend this methodology to other carbonyl-containing compounds,[28] we examined the rhodium(II) catalyzed behavior of (S)-1-acetyl-2-(1-diazoacetyl)pyrrolidine (6).[22] Decomposition of **6** in the presence of

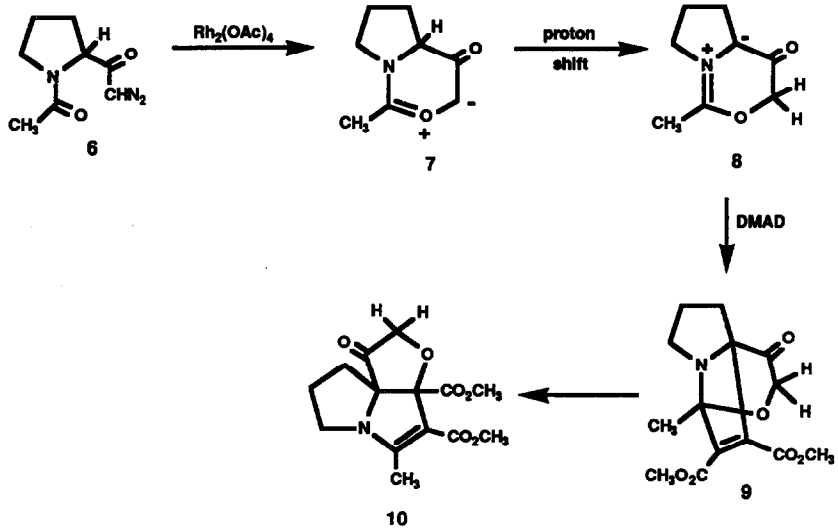


4a ; X=CH 2
4b; X=NR

5a ; X=CH 2
5b; X=NR

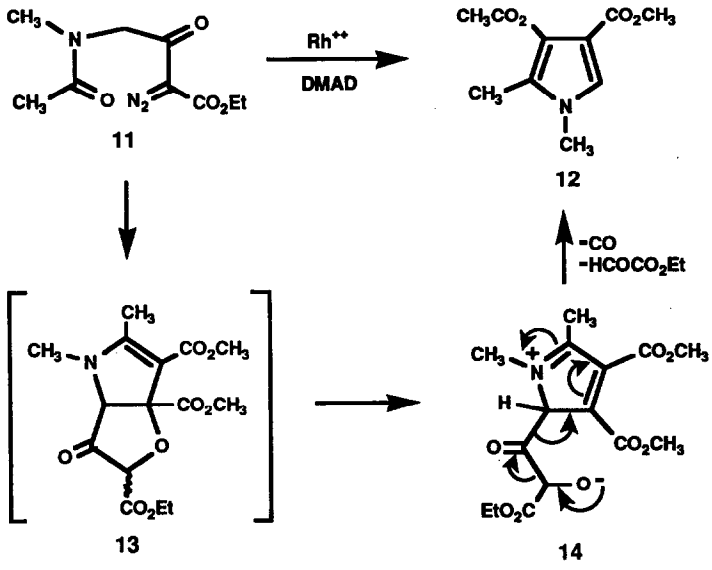
DMAD at 25°C gave mainly the 3+2-cycloadduct **10**. The formation of this novel product involves generation of the expected carbonyl ylide dipole **7** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. Isomerization of **7** to azomethine ylide **8** is followed by 1,3-dipolar cycloaddition with DMAD. The initially formed cycloadduct **9** undergoes a subsequent alkoxy 1,3-shift to generate the tricyclic dihydropyrrolizine ring system **10**.

Scheme I



6 7 8 9 10

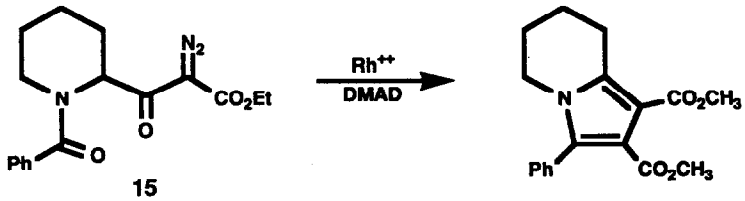
In order to further evaluate the generality of the *dipole cascade* process, we decided to study the rhodium(II) catalyzed behavior of a series of related α-diazo ketoacyl amides. To facilitate investigation of the fundamental aspects of the process, we utilized substrates devoid of unnecessary functionality. The synthetic objective was to construct substrates of general type **1** in which the amido carbonyl group could cyclize to give the six-ring dipole **2**. Along these lines, we investigated the $Rh_2(OAc)_4$ catalyzed reaction of ethyl 4-[(acetyl)methylamino]-2-diazo-3-oxobutanoate (**11**) and found that dimethyl 1,2-dimethylpyrrole dicarboxylate (**12**) was the only identifiable product (54%) that could be isolated from the crude reaction mixture. By analogy to the results encountered with



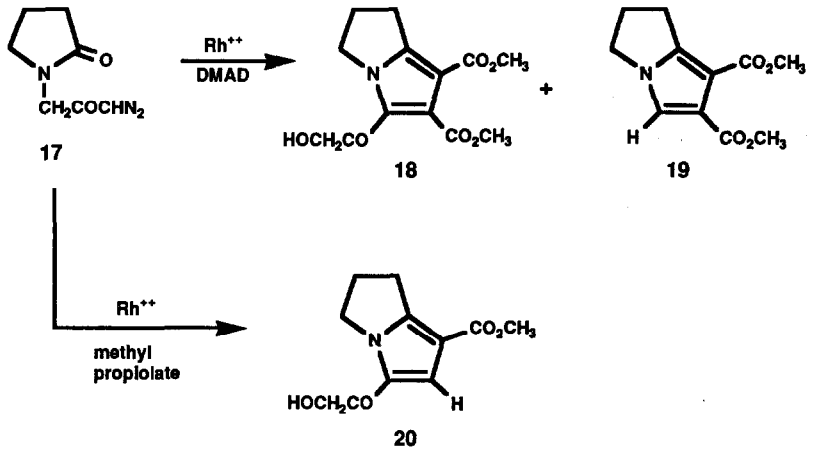
11 **12** **13** **14**

the N-acetyl pyrrolidine system **6**[22], we believe that the formation of **12** proceeds by a related mechanism. The *dipole cascade* pathway (see Scheme I) produces the azomethine ylide cycloadduct **13** which is subsequently converted to pyrrole **12** (*i.e.*, **11**→**13**→**14**→**12**).

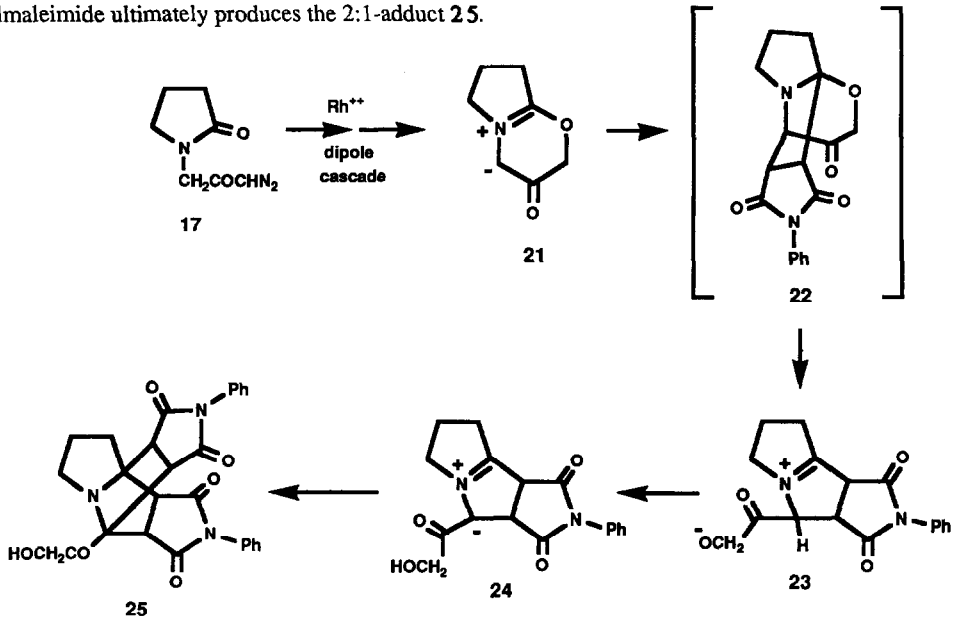
The cycloaddition reaction of diazo keto amide **15** and DMAD proceeded in a similar manner, giving rise to pyrrole **16** as the only isolable product in 60% yield. A key finding occurred when the cycloaddition of **17** was carried out in the presence of several different dipolarophiles. With DMAD, the reaction produced a 2:1-mixture of pyrroles **18** and **19**. The cycloaddition with methyl propiolate proceeded in a highly regioselective manner, giving only pyrrole **20** in 76% isolated yield. Interestingly, the reaction of **17** with N-phenylmaleimide gave the 2:1-cycloadduct **25** as the major product. The formation of **25** strongly supports the involvement of an azomethine



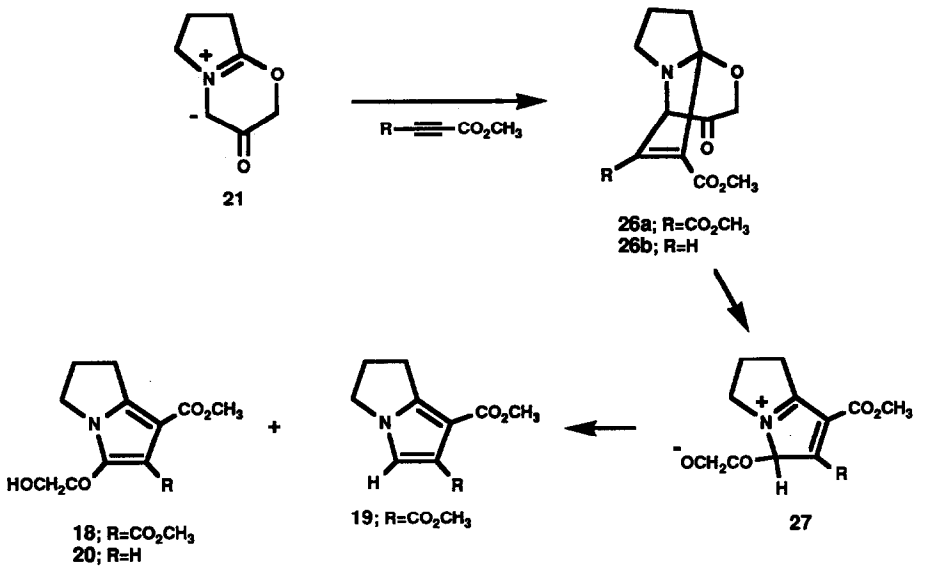
15 **16**



ylide intermediate (i.e. **21**) which undergoes rapid 1,3-dipolar cycloaddition with the added dipolarophile. The initially formed 1:1-cycloadduct **22** ring opens very easily to give zwitterion **23** and this is followed by an internal proton transfer to produce the rearranged 1,3-dipole **24**. Reaction of this azomethine ylide with additional N-phenylmaleimide ultimately produces the 2:1-adduct **25**.

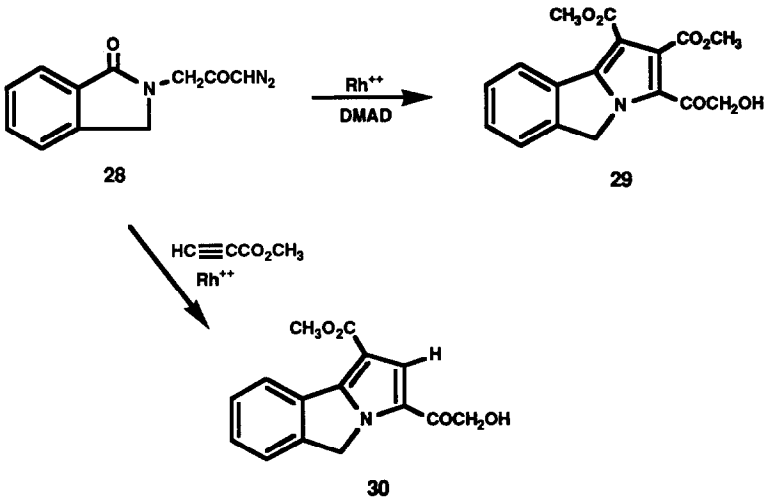


Cycloaddition of azomethine ylide **21** with DMAD gives **26** which subsequently fragments to afford zwitterion **27**. This species can either transfer a proton from C to O to produce **18** or undergo loss of CH_2O and CO to generate pyrrole **19**. The regiospecific reaction of **21** with methyl propiolate is perfectly consistent with the proposed mechanism. According to frontier molecular orbital (FMO) theory,[29] regioselectivity is the result of best overlap of the interacting orbitals; i.e., the atoms with the largest coefficients of appropriate symmetry combine preferentially. The cycloaddition reaction of azomethine ylide **21** favors formation of the 3+2-adduct **26b** which

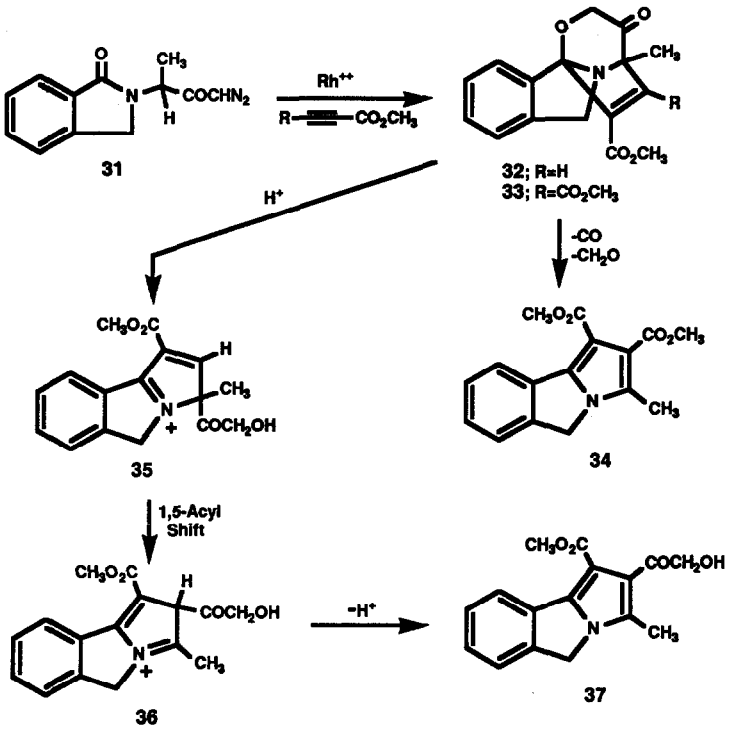


ultimately gives rise to pyrrole **20**.

The rhodium(II) catalyzed reactions of diazo 1-oxo-1H-isoindole **28** proceeded in a similar manner when DMAD and methyl propiolate were used as the dipolarphiles, giving rise to pyrroles **29** and **30** in 50% and 72% yield, respectively. An analogous cycloaddition was also encountered with the mono-methylated diazo ketoamide **31**. In this case, however, the initially formed dipolar cycloadduct **32** derived from methyl propiolate could actually be isolated. Cycloadduct **32** displayed a very characteristic AB pattern at δ 3.90 (d, 1H, J=17.0 Hz) and 4.13 (d, 1H, J=17.0 Hz). This compound was quantitatively converted to **37** upon silica gel chromatography or upon

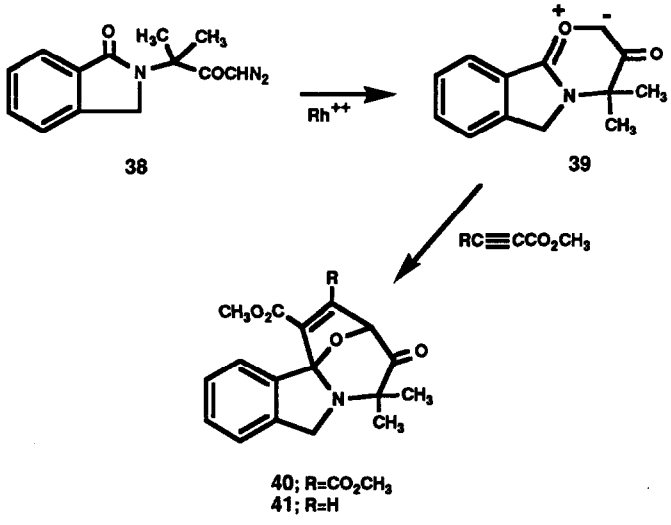


standing at room temperature for several hours. The formation of **37** from **32** involves ring opening to produce iminium ion **35** as a transient species. In this case, a 1,5-acyl shift to the unsubstituted carbon occurs faster than fragmentation giving the rearranged iminium ion **36** which subsequently loses a proton to produce pyrrole **37**. With

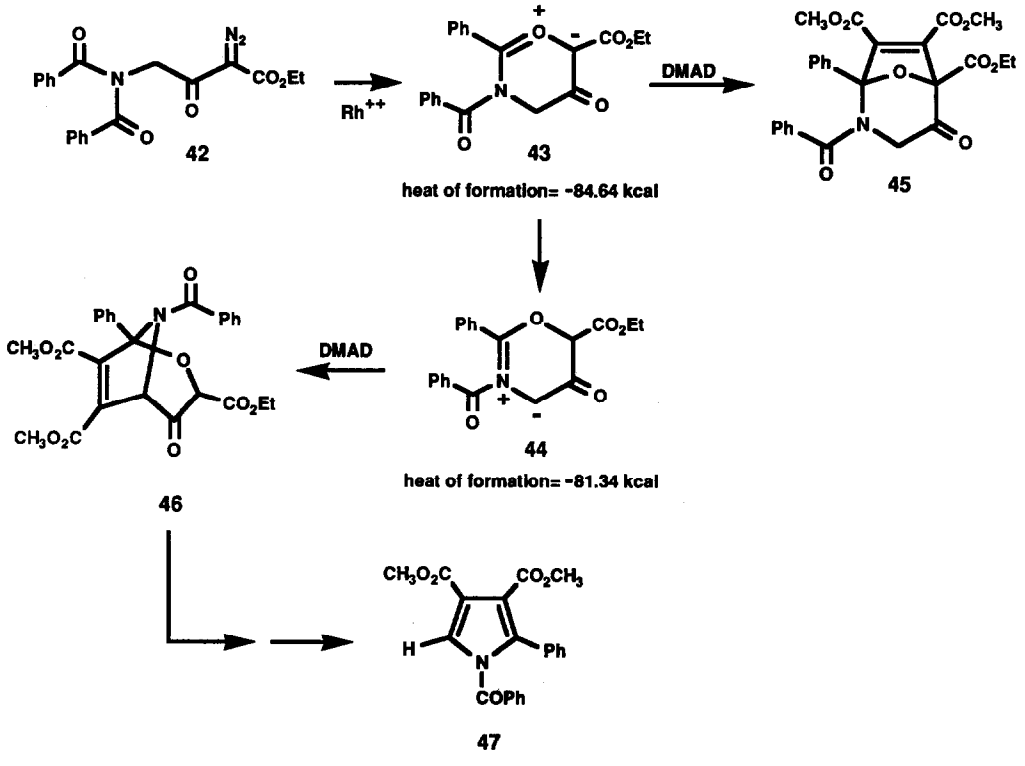


DMAD, only pyrrole **34** was formed (presumably *via* **33**).

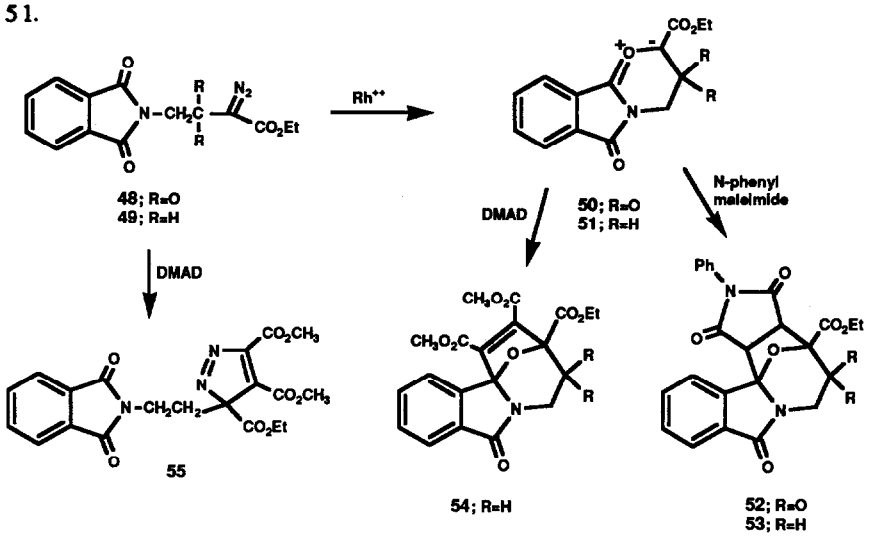
We have also investigated the rhodium(II) catalyzed behavior of the dimethylated diazo 1-oxo-1H-isoindole system **38**. With this compound, cycloaddition can only take place from the initially formed carbonyl ylide **39** since the α-position of the dipole is blocked by the two methyl groups. Indeed, treatment of **38** with either DMAD or methyl propiolate afforded the expected carbonyl ylide derived cycloadducts **40** and **41** in good yield.



Semi-empirical molecular orbital calculations have indicated that the heat of formation of cyclic carbonyl ylides of type **2** are generally 10-15 kcal/mol higher in energy than the corresponding azomethine ylides of type **3**.[22] We assume that the relative energy differences of the two dipoles will parallel the rate in which the carbonyl ylide dipole rearranges to the thermodynamically more stable azomethine ylide. Comparison of the calculated heats of formation of the two dipoles showed that the only exception to the "*stability rule*" comes from a case where the cyclizing carbonyl was part of an imide functionality.[22] In order to ascertain whether this is generally true, we have carried out MOPAC calculations on the two different dipoles derived from ethyl 2-diazo-4-dibenzoylamino-3-oxo-butyrate (**42**). Global minima for each dipole were found by making use of the multiconformer generation in Model (TTY, Conf, Statistical Coordinate) followed by batch minimization using Bakmdl.[30] The particular parameters used were those of the NOH (no hydrogen) force field developed by Still and implemented by Steliou in the program Model. The resulting lowest energy conformation was submitted for a semi-empirical determination of the heat of formation. Calculations were performed in the MOPAC package which includes the PM3 parameters. The MNDO calculations reveal a 3.3 kcal energy difference, with the carbonyl ylide dipole possessing the more negative heat of formation. This would suggest that the rhodium-catalyzed reaction of diazo imide **42** should give predominantly an unrearranged cycloadduct. Indeed, this was borne out experimentally. Exposure of **42** to $Rh_2(tfa)_4$ in benzene with DMAD afforded a mixture of two products. The minor component (31%) corresponds to pyrrole **47** which is derived from azomethine ylide **44**. The other product **45** is derived from carbonyl ylide **43** and the fact that it is the major component (54%) is perfectly in accord with the MOPAC calculations.



We also investigated the rhodium(II) catalyzed reaction of the diazophthalimide derivatives **48** and **49**. When **48** was treated with N-phenylmaleimide in the presence of $Rh_2(OAc)_4$ in refluxing benzene, cycloadduct **52** was obtained as the exclusive product in 87% yield. Similar treatment of the less activated diazophthalimidoester **49** with N-phenylmaleimide and DMAD afforded cycloadducts **53** (92%) and **54** (79%) derived from the carbonyl ylide dipole **51**.



This observation indicates, that at least in this situation, the N-acyl substituted carbonyl ylides (i.e., **50** and **51**) cycloadd with the added dipolarophile at a much faster rate than rearrangement to the corresponding azomethine ylides. In the absence of a catalyst, **49** undergoes facile 1,3-dipolar cycloaddition with DMAD across the diazo group to give 3H-pyrazole **55** in high yield.

In conclusion, 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.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in oven dried glassware under an atmosphere of extra dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-hexane mixture as the eluent unless specified otherwise.

Preparation and Cycloaddition of Ethyl 4-(acetylmethylamino)-2-diazo-3-oxobutanoate (11) with Dimethyl Acetylenedicarboxylate. A 2.5 g sample of N-acetyl sarcosine[31] was treated sequentially with N,N'-carbonyldiimidazole and the dianion of hydrogen ethyl malonate according to the standard Rapoport procedure[32] to give ethyl 4-[acetylmethylamino]-3-oxobutanoate as a colorless oil in 63% yield; IR (neat) 1760, 1740, 1660, 1420 and 1200 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.30 (t, 3H, J=7.0 Hz), 2.10 (s, 3H), 3.05 (s, 3H), 4.45 (s, 2H), and 4.20 (q, 2H, J=7.0 Hz). This compound was subjected to typical diazo transfer conditions to give ethyl 4-[(acetyl)methyl-amino]-2-diazo-3-oxobutanoate (**11**) as a yellow oil in 76% yield; IR (neat) 2160, 1745, 1730, 1650, 1490, 1380 and 1240 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J=7.3 Hz), 2.17 (s, 3H), 3.03 (s, 3H), 4.27 (q, 2H, J=7.3 Hz), and 4.60 (s, 2H).

A solution containing 110 mg of **11** and 0.072 mL of DMAD in 5 mL of $CHCl_3$ was treated with 5 mg of

Rh (II) octanoate for 2 h at reflux. Removal of solvent under reduced pressure and chromatography of the residue afforded 56 mg (54%) of dimethyl 1,2-dimethylpyrrole-3,4-dicarboxylate (**12**) as a light yellow solid; mp 86-87°C (lit[33] mp 88-89°C); IR (KBr) 1750, 1710, 1400, 1300, 1280 and 1100 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 3.52 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), and 7.07 (s, 1H); Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C 56.77; H, 6.23; N, 6.54.

Preparation and Cycloaddition of 2-Diazo-3-(N-benzoylpiperidinyl)-3-oxopropanoate (15) with Dimethyl Acetylenedicarboxylate. To a solution containing 1.45 g of N-benzoylpipecolinic acid[34] in 50 mL of THF was added 1.2 g of N,N'-carbonyldiimidazole and the resulting solution was stirred for 12 h at rt. A 1.25 g sample of hydrogen ethyl malonate was treated with 9.5 mL of a 2.0 N isopropyl magnesium solution at 0°C for 30 min, then at 25°C for another 30 min and finally at 40°C for another 30 min to generate the dianion as its magnesium chelate. To this solution at 0°C was added the acylimidazole solution and a gummy precipitate began to form immediately. The mixture was allowed to warm to rt and was further stirred for 4 h, poured onto a ice-cold 1.0 M phosphoric acid solution and extracted with EtOAc. The organic extracts were washed with a saturated $NaHCO_3$ solution, brine, and dried over $MgSO_4$. Removal of the solvent and chromatography of the residue gave ethyl 3-(N-benzoylpiperidinyl)-3-oxopropanoate as a colorless oil: IR (neat) 1755, 1725, 1660, 1640, 1450, 1285 and 1005 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, J=6.9 Hz), 1.42 (m, 4H), 1.70 (m, 2H), 3.05 (m, 1H), 3.55 (s, 2H), 3.60 (m, 1H), 4.07 (q, 2H, J=6.9 Hz), 5.38 (d, 1H, J=4.1 Hz), and 7.38 (s, 5H).

A solution containing 500 mg of the above compound and 412 mg of p-acetamidobenzide sulfonyl azide[35] in 15 mL of CH_3CN was treated with 0.46 mL of Et_3N at rt. The mixture was stirred at 25°C for 4 h, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give 510 mg (94%) of ethyl 2-diazo-3-(N-benzoylpiperidinyl)-3-oxopropanoate (**15**) as a light yellow oil: IR (neat) 2145, 1728, 1720, 1660, 1640, 1420, 1380 and 1320 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J=7.1 Hz), 1.75 (m, 4H), 1.96 (m, 2H), 3.60 (m, 2H), 4.25 (q, 2H, J=7.1 Hz), 5.95 (d, 1H, J=5.0 Hz), and 7.40 (s, 5H).

A solution containing 300 mg of **15** and 0.15 mL of DMAD in 10 mL of benzene was treated with 5 mg of Rh (II) octanoate at 90°C for 60 min. After cooling to rt, the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 170 mg (60%) of dimethyl-3-phenyl-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (**16**) as a white solid; mp 125-126°C; IR (KBr) 1740, 1715, 1550, 1470, and 1220 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.82 (m, 4H), 3.12 (m, 2H), 3.64 (s, 3H), 3.72 (m, 2H), 3.80 (s, 3H), and 7.38 (m, 5H); HRMS Calcd. for $C_{18}H_{19}NO_4$: 313.1314. Found: 313.1315.

Preparation and Cycloaddition of 1-(3-Diazo-2-propanone)-2-oxo-pyrrolidine (17) with Dimethyl Acetylenedicarboxylate. A solution containing 500 mg of 2-oxo-1-pyrrolidineacetic acid[36] in 20 mL of benzene was treated with 730 mg of PCl_5. The solution was stirred at rt for 90 min and at 60°C for 90 min. The solvent was removed under reduced pressure and the residue was taken up in 30 mL of CH_2Cl_2 and the solution was filtered. The filtrate was treated with 10 mmol of CH_2N_2 in ether at rt and was stirred for 12 h. Removal of the solvent followed by chromatography gave 350 mg (61%) of 1-(3-diazo-2-propanone)-2-oxopyrrolidine (**17**) as a yellow solid; mp 47-48°C; IR (KBr) 2140, 1750, 1545, 1380, 1245 and 1100 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.05 (tt, 2H, J=7.9 and 7.5 Hz), 2.40 (t, 2H, J=7.9 Hz), 3.42 (t, 2H, J=7.1 Hz), 3.99 (s, 2H), and 5.36 (s, 1H).

A solution containing 100 mg of **17** and 0.089 mL of DMAD in 3 mL of $CHCl_3$ was treated with 5 mg of Rh (II) octanoate dimer. The mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the resulting residue was subjected to flash silica chromatography giving rise to two products. The major compound isolated (55%) was identified as dimethyl 5-(2-hydroxyethanone)-2,3-dihydro-1H-pyrrolizine-6,7-dicarboxylate (**18**); mp 95-96°C; IR (KBr) 1740, 1660, 1400, 1250 and 1110 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.57 (tt, 2H, J=7.6 and 7.4 Hz), 3.05 (t, 2H, J=7.6 Hz), 3.58 (brt, 1H, J=3.7 Hz), 3.80 (s, 3H), 4.00 (s, 3H), 4.40 (t, 2H, J=7.4 Hz) and 4.52 (d, 2H, J=3.7 Hz); HRMS Calcd. for $C_{13}H_{15}NO_6$: 281.0899. Found: 281.0891.

The minor product (21%) was identified as 6,7-dicarboxymethoxy-2,3-dihydropyrrolizine (**19**)[37]; mp 85-86°C; IR (KBr) 1740, 1400, 1290, 1200, 1120 and 1080 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.50 (tt, 2H, J=7.4 and

7.2 Hz), 3.05 (t, 2H, J=7.4 Hz), 3.80 (s, 6H), 3.98 (t, 2H, J=7.2 Hz), and 7.16 (s, 1H); HRMS Calcd. for $C_{11}H_{13}NO_4$: 223.0844. Found: 223.0842.

Cycloaddition of 1-(3-Diazo-2-propanone)-2-oxo-pyrrolidine (17) with Methyl Propiolate. A solution containing 200 mg of diazo ketoamide **17** and 0.086 mL of methyl propiolate in 10 mL of CH_2Cl_2 was treated with 5 mg of Rh (II) octanoate for 3 h. The solvent was removed under reduced pressure and the resulting residue was subjected to chromatography to give 204 mg (76%) of methyl 5-(2-hydroxyethanone)-2,3-dihydro-1H-pyrrolizine-7-carboxylate (**20**); mp 156-157°C; IR ($CHCl_3$) 1710, 1655, 1440, 1245 and 1090 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.57 (pent, 2H, J=7.5 Hz), 3.09 (t, 2H, J=7.5 Hz), 3.29 (t, 1H, J=4.6 Hz exchanges with D_2O), 3.81 (s, 3H), 4.36 (t, 2H, J=7.5 Hz) 4.65 (d, 2H, J=4.6 Hz), and 7.31 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.8, 48.2, 50.7, 63.3, 108.5, 120.9, 123.2, 149.7, 163.7, and 187.4; Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.17; H, 5.87; N, 6.28. Found: C, 59.21; H, 5.87; N, 6.22.

Cycloaddition of 1-(3-Diazo-2-propanone)-2-oxo-pyrrolidine (17) with N-Phenylmaleimide. A solution containing 250 mg of diazo ketoamide **17** and 779 mg of N-phenylmaleimide in 13 mL of CH_2Cl_2 was treated with 5 mg of Rh (II) octanoate for 3.5 h. The solution was filtered and the white solid was collected and recrystallized from CH_2Cl_2-hexane to give 100 mg of the 2:1-cycloadduct **25**; mp 235-236°C; IR ($CHCl_3$) 1715, 1510, 1390 and 1290 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.20 (pent, 2H, J=7.2 Hz), 2.53 (t, 2H, J=7.2 Hz), 2.97 (t, 2H, J=7.2 Hz), 3.15 (d, 2H, J=7.3 Hz), 3.21 (t, 1H, J=6.3 Hz exchanges with D_2O), 4.04 (d, 2H, J=7.3 Hz), 4.78 (d, 2H, J=6.3 Hz), 7.17-7.20 (m, 4H), and 7.39-7.49 (m, 6H); ^{13}C-NMR (CD_3CN, 75 MHz) δ 18.9, 27.6, 42.5, 50.3, 54.9, 67.1, 75.5, 80.8, 125.8, 128.1, 128.5, 131.6, 172.2, 174.7, and 204.4; HRMS Calcd. for $C_{27}H_{18}N_3O_6$: 485.1587. Found: 485.1610.

Preparation and Cycloaddition of 2,3-Dihydro-1-oxo-1H-isoindole-2-(1-diazo-2-propanone) (28) with Dimethyl Acetylenedicarboxylate. A solution containing 0.80 g of 2,3-dihydro-1-oxo-1H-isoindole-2-acetic acid[38] in 5 mL of dry benzene was treated with 0.91 g of PCl_5. The solution was stirred at rt for 90 min and then at 50°C for an additional 90 min. The mixture was cooled to rt, filtered and the solvent was removed under reduced pressure. The residue was taken up in 15 mL of dry CH_2Cl_2 and then treated with 15 mmol of diazomethane in ether at rt. The mixture was stirred overnight at rt. Removal of the solvent followed by chromatography of the residue gave 45 mg (50%) of 2,3-dihydro-1-oxo-1H-isoindole-2-(1-diazo-2-propanone) (**28**) as a yellow solid; mp 119-120°C; IR ($CHCl_3$) 2140, 1700, 1650 and 1370 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 4.33 (s, 2H), 4.50 (s, 2H), 5.43 (s, 1H), 7.47 (t, 2H, J=8.3 Hz), 7.54 (m, 1H) and 7.87 (d, 1H, J=8.3 Hz).

A solution containing 100 mg of **28** and 0.086 mL of DMAD in 5 mL of dry CH_2Cl_2 was treated with 5 mg of Rh (II) octanoate at rt. The mixture was stirred for 1 hr and the solvent was removed under reduced pressure and the residue was recrystallized to give dimethyl 3-(2-hydroxyethanone)-1H-pyrrolo[2,1-a]-isoindole-1,2-dicarboxylate (**29**) (50%), mp 185-186°C; IR ($CHCl_3$) 1730, 1710, 1655, 1280 and 1155 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.39 (t, 1H, J=3.7 Hz), 3.94 (s, 3H), 4.01 (s, 3H), 4.61 (d, 2H, J=3.7 Hz), 5.39 (s, 2H), 7.45-7.60 (m, 3H), and 8.43 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.3, 52.7, 53.4, 64.5, 106.5, 121.8, 122.3, 123.9, 127.1, 128.0, 128.6, 129.1, 141.6, 145.4, 162.4, 165.5, and 187.8; HRMS Calcd. for $C_{17}H_{15}NO_6$: 329.0899. Found: 329.0897.

Cycloaddition of 2,3-Dihydro-1-oxo-1H-isoindole-2-(1-diazo-2-propanone) (28) with Methyl Propiolate. A solution containing 200 mg of **28** in 10 mL of dry CH_2Cl_2 and 0.083 mL of methyl propiolate was treated with 5 mg of Rh(II) octanoate at rt. The mixture was stirred for 1 h and the solvent was removed under reduced pressure. Chromatography of the residue gave methyl 3-(2-hydroxyethanone)-1H-pyrrolo[2,1-a]-isoindole-1-carboxylate (**30**) (72%); mp 186-187°C; IR ($CHCl_3$) 1715, 1655, 1440, 1280, 1200 and 770 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.33 (t, 1H, J=3.7 Hz exchanges with D_2O), 3.94 (s, 3H), 4.73 (d, 2H, J=3.7 Hz), 5.28 (s, 2H), 7.47 (m, 2H), 7.55 (m, 1H), and 8.49 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 59.8, 52.5, 63.6, 108.3, 121.0, 122.2, 123.7, 124.0, 127.8, 128.1, 129.7, 141.8, 146.6, 163.5, and 187.2; HRMS Calcd for $C_{14}H_{13}NO_4$: 271.0845. Found: 271.0849.

Preparation and Cycloaddition of 2,3-Dihydro-1-oxo-1H-isoindole-2-(1-diazo-3-methyl-2-

propanone) (31) with Dimethyl Acetylenedicarboxylate. A solution containing 2.0 g of 2,3-dihydro-1-oxo-1H-isoindole-2-(α-methyl)acetic acid[38] in 20 mL of dry benzene was treated with 2.13 g of PCl_5. The solution was stirred at rt for 90 min and then at 50°C for an additional 90 min. The solution was cooled to rt, filtered and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 and was treated with 35 mmol of CH_2N_2 in ether at rt and was stirred overnight. Removal of the solvent followed by chromatography gave 1.4 g (63%) of 2,3-dihydro-1-oxo-1H-isoindole-2-(1-diazo-3-methyl-2-propanone) (**31**) as a yellow solid; mp 58-59°C; IR ($CHCl_3$) 2130, 1680, 1645, 1470, 1455, 1409, 1369, 1325, and 1148 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, 3H, J=7.0 Hz), 4.42 (s, 2H), 5.07 (q, 1H, J=7.0 Hz), 5.48 (s, 1H), 7.46 (m, 2H), 7.549 (m, 1H), and 7.85 (m, 1H).

A solution containing 100 mg of **31** and 0.08 mL of DMAD in 5 mL of dry CH_2Cl_2 under N_2 was treated with 5 mg of Rh (II) octanoate at rt. The mixture was stirred for 2 h and the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give dimethyl 3-methyl-1H-pyrrolo[2,1a]-isoindole-1,2-dicarboxylate (**34**) in 65% isolated yield as a yellow solid; mp 183-184°C (lit[38] mp 185-187°C); IR ($CDCl_3$) 2950, 1694 (br), 1441, 1290, 1220 and 1175 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 4.72 (s, 2H), 7.20-7.40 (m, 3H), and 8.04-8.10 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11.3, 48.7, 51.2, 51.3, 106.1, 115.7, 122.6, 122.7, 127.0, 128.3, 131.7, 131.7, 140.1, 140.3, 164.7 and 165.6; Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.44; H, 5.28; N, 4.87.

Cycloaddition of 2,3-Dihydro-1-oxo-1H-isoindole-2-(1-diazo-3-methyl-2-propanone) (31) with Methyl Propiolate. A solution containing 200 mg of **31** and 0.078 mL of methyl propiolate in 10 mL of dry CH_2Cl_2 was treated with 5 mg of Rh (II) octanoate at rt. The mixture was stirred for 1.5 hr and the solvent was removed under reduced pressure to initially give cycloadduct **32** (95% NMR yield); NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 3H), 3.82 (s, 3H), 3.90 (d, 1H, J=17.0Hz), 4.13 (d, 1H, J=17.0 Hz), 4.35 (d, 1H, J=17.6 Hz), 4.50 (d, 1H, J=17.6 Hz), 5.78 (s, 1H), 7.38-7.50 (m, 3H), and 8.79-8.82 (m, 1H). Silica gel chromatography of this compound resulted in rearrangement to methyl 2-(2-hydroxyethanone)-3-methyl-1H-pyrrolo-[2,1-a]isoindole-1-carboxylate (**37**) in 84% yield; mp 133-134°C; IR ($CHCl_3$) 1690, 1662, 1420, 1255 and 1163 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.51 (bs, 1H), 3.95 (s, 3H), 4.68 (s, 2H), 4.84 (s, 2H), 7.35 (m, 1H), 7.44 (m, 2H), and 8.21 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11.5, 48.3, 50.8, 67.7, 104.5, 120.7, 122.3, 122.6, 127.1, 127.9, 130.9, 132.3, 140.0, 140.6, 164.1, and 198.1; Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.14; H, 5.36; N, 4.81.

Preparation and Cycloaddition of 2,3-Dihydro-1-oxo-1H-isoindole-2-(1-diazo-3,3-dimethyl-2-propanone) (38) with Dimethyl Acetylenedicarboxylate. To a solution containing 7.15 g of methyl 2-bromomethyl benzoate and 7.45 g of methyl 2-aminoisobutyrate[39] in 70 mL of methanol was added 6.54 mL of Et_3N and the mixture was heated at reflux for 48 h. The solution was cooled to rt, filtered and the solvent was removed under reduced pressure. The residue was taken up in 75 mL of CH_2Cl_2 and extracted with a 1.0 N HCl solution, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 4.0 g (55%) of methyl 2,3-dihydro-1-oxo-1H-isoindole-2-(α,α-dimethyl) acetate as a yellow solid; mp 92-93°C ; IR ($CHCl_3$) 1760, 1700 and 1217 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.65 (s, 6H), 3.74 (s, 3H), 4.50 (s, 2H), 7.41-7.6 (m, 3H), and 7.80 (m, 1H).

A solution containing 2.0 g of the above compound in 20 mL of dioxane was treated with 10.6 mL of a 1N KOH solution and the mixture was stirred overnight. The solution was then acidified to pH 2-3 with a 1.0 N HCl solution and was extracted using a continuous extraction apparatus with CH_2Cl_2 for 24 h. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to give 1.45 g (77%) of 2,3-dihydro-1-oxo-1H-isoindole-2-(α,α-dimethyl)-acetic acid as a white solid; mp 243-244°C; IR (KBr) 3300-2400, 1710, 1678, 1403, 1308, 1256, 1217 and 1180 cm^{-1}; NMR (DMSO-d_6, 300 MHz) δ 1.51 (s, 6H), 4.56 (s, 2H), 7.39-7.70 (m, 4H) and 12.46 (s, 1H).

A solution containing 1.0 g of the above acid in 10 mL of dry benzene was treated with 0.97 g of PCl_5. The solution was stirred at rt for 90 min and then at 50°C for an additional 90 min. After cooling to rt, the mixture was

filtered and the solvent was removed under reduced pressure. The resulting residue was taken up in 10 mL of CH_2Cl_2 and was treated with 14 mmol of CH_2N_2 in ether at rt. The solution was stirred overnight and the solvent was removed under reduced pressure. Flash silica gel chromatography of the residue gave 340 mg (30%) 2,3-dihydro-1-oxo-1H-isoindole-2-(1-diazo-3,3-dimethyl-2-propanone) (**38**) as a yellow solid; mp 194-195°C; IR ($CHCl_3$) 2110, 1700, 1690 and 1355 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.57 (s, 6H), 4.48 (s, 2H), 5.41 (s, 1H), 7.35-7.60 (m, 3H), and 7.73-7.90 (m, 1H).

A solution containing 50 mg of **38** and 0.038 mL of DMAD was treated with 5 mg of Rh(II) octanoate at rt. The mixture was stirred for 1.25 hr and the solvent was removed under reduced pressure. Flash silica gel chromatography using an 1:1 hexane-EtOAc mixture as the eluent followed by recrystallized from CH_2Cl_2-hexane gave 36 mg (48%) of dimethyl 7,7-dimethyl-9,11a-epoxy-8-oxo-7,8,9,11a-tetrahydro-5H-azepino-[2,1a]isoindole-1,2-dicarboxylate (**40**) as a white solid; mp 173-174°C; IR ($CHCl_3$) 3000, 2950, 1735, 1725, 1690, 1431, 1285, 1260 and 1090 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 3H), 1.86 (s, 3H), 3.15 (d, 1H, J=4.6 Hz), 3.44 (d, 1H, J=4.6 Hz), 3.73 (s, 3H), 3.86 (s, 3H), 5.86 (s, 1H), 7.40-7.52 (m, 3H), and 7.77 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.7, 24.6, 50.4, 51.9, 52.0, 55.3, 57.0, 57.9, 122.7, 123.3, 128.5, 131.7, 132.3, 139.4, 139.7, 164.0, 164.1, and 168.3; Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.70; H, 5.34; N, 3.84.

Cycloaddition of 2,3-Dihydro-1-oxo-1H-isoindole-2-(1-diazo-3,3-dimethyl-2-propanone) (38) with Methyl Propiolate. A solution containing 100 mg of **38** and 0.037 mL of methyl propiolate in 10 mL of dry CH_2Cl_2 was treated with 5 mg of Rh(II) octanoate at rt. The mixture was stirred for 1.5 h, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 75 mg (61%) of methyl 7,7-dimethyl-9,11a-epoxy-8-oxo-7,8,9,11a-tetrahydro-5H-azepino[2,1-a]isoindole-1-carboxylate (**41**); mp 157-158°C; IR ($CHCl_3$) 2990, 2975, 1710, 1590, 1430, 1295 and 1065 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 1.25 (s, 3H), 3.71 (s, 3H), 4.47 (q, 2H, J=16.7 Hz), 4.94 (d, 1H, J=2.2 Hz), 6.87 (t, 1H, J=7.3 Hz), 7.03 (t, 1H, J=7.3 Hz), 7.18 (d, 1H, J=6.9 Hz), 7.43 (d, 1H, J=6.9 Hz), and 7.62 (d, 1H, J=2.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.5, 25.1, 61.2, 61.9, 62.8, 69.0, 102.0, 118.7, 120.3, 124.8, 125.0, 145.2, 146.4, 147.1, 154.5, 163.1, and 207.8; Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 67.96; H, 5.75; N, 4.62.

Preparation and Cycloaddition of Ethyl 2-Diazo-4-dibenzoylamino-3-oxo-butyrate (42) with Dimethyl Acetylenedicarboxylate. N,N-Dibenzoylglycyl chloride was prepared from 500 mg of N,N dibenzoylglycine and 370 mg of PCl_5 in 10 ml of dry dioxane according to the procedure of Sheehan and Corey.[40] A solution of this material in 10 mL of THF at 0°C was added to 10 mL of a 0.5 M THF solution of the magnesium dianion of hydrogen ethyl malonate.[2] The reaction was allowed to warm to 25°C overnight and was quenched with a 1 M aqueous phosphoric acid solution. The reaction was extracted with ether, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash silica gel chromatography afforded 421 mg (63%) of ethyl 4-dibenzoylamino-3-oxo-butyrate as a pale yellow oil; IR (neat) 1740, 1700, 1670, 1600, 1500, 1330, 1290, 1120, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.20 (t, 3H, J=7.0 Hz), 3.57 (s, 2H), 4.20 (q, 2H, J=7.0 Hz), 5.00 (s, 2H), 7.0-7.3 (m, 6H) and 7.4-7.6 (m, 4H).

To a solution containing 421 mg of the above β-keto ester and 160 mg of mesyl azide in 2.5 mL of dry CH_3CN at 25°C was added 241 mg of Et_3N. The reaction was stirred for 2 h and worked up according to the method of Taber[41]. Purification by flash silica gel chromatography afforded 325 mg (72%) of ethyl 2-diazo-4-dibenzoylamino-3-oxo-butyrate (**42**) as a bright yellow oil; IR (neat) 2100, 1720, 1680, 1480, 1340, 1150, 810 and 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.33 (t, 3H, J=7 Hz), 4.37 (q, 2H, J=7 Hz), 5.30 (s, 2H), 7.13-7.33 (m, 6H) and 7.50-7.67 (m, 2H).

To a solution containing 58 mg of **42** and 65 mg of DMAD in 0.3 mL of dry benzene at 25°C was added 5 mg of Rh(II) trifluoroacetate. Gas evolution was rapid and continuous for about 10 min. The reaction was stirred for an additional 15 min and was concentrated under reduced pressure. Flash silica gel chromatography of the residue afforded a mixture of two products. The first fraction isolated from the column contained 45 mg (51%) of 2-benzoyl-5-carboethoxy-6,7-dicarbomethoxy-8-oxa-4-oxo-1-phenyl-2-azabicyclo[3.2.1]oct-6-ene (**45**) as a col-

orless oil; IR ($CHCl_3$) 1730, 1700, 1670, 1615, 1460, 1330, 1270, 1240, 1100, 1030, and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, 3H, J=7.0 Hz), 3.40 (s, 3H), 3.75 (s, 3H), 4.32 (q, 2H, J=7.0), 5.30 (s, 2H), and 7.11-7.51 (m, 10 H); Anal. Calcd for $C_{26}H_{23}NO_9$: C, 63.27; H, 4.70; N, 2.84. Found: C, 63.14; H, 4.68; N, 2.71.

The second fraction contained 30 mg (31%) of dimethyl N-benzoyl-2-phenylpyrrole-3,4-dicarboxylate (**47**) as a light yellow solid; mp 113-114°C; IR (KBr) 1740, 1360, 1260, 1170 and 970 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3H), 3.83 (s, 3H), 7.22-7.34 (m, 5H), 7.41 (m, 2H), 7.58 (m, 1H), 7.61 (s, 1H), and 7.70 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.2, 51.7, 115.9, 118.8, 127.0, 127.4, 127.9, 128.1, 128.8, 129.3, 129.9, 131.1, 133.5, 135.7, 162.6, 164.6, and 167.3; Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.35; H, 4.88; N, 3.99. Found: C, 68.33; H, 4.83; N, 3.93.

Preparation and Cycloaddition of Ethyl 2-Diazo-3-oxo-4-phthalimidobutyrate (48) with N-Phenylmaleimide. To a solution containing 1.0 g of N-phthalimido glycine[42] in 25 mL of THF was added 948 mg of carbonyl diimidazole and the resulting solution was allowed to stir for 14 h at rt. A 965 mg sample of hydrogen ethyl malonate was treated with 7.3 mL of a 2.0 N isopropyl magnesium chloride solution at 0°C for 30 min, then at 25°C for 45 min, and finally at 40°C for another 30 min to generate the dianion as its magnesium chelate. To this solution at 0°C was added the imidazole-phthalimido glycine solution. The mixture was allowed to warm to rt and was further stirred for an additional 4 h, poured into an ice-cold 1.0 M phosphoric acid solution and extracted with EtOAc. The organic extracts were washed with a saturated Na_2CO_3 solution, brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography producing 711 mg (53%) of ethyl-3-oxo-4-phthalimido butyrate as a white crystalline solid: mp 105-106°C, IR ($CHCl_3$) 1790, 1730, 1420, 1400, 1325, and 1095 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.33 (t, 3H, J=7.5 Hz), 4.38 (q, 2H, J=7.5 Hz), 4.97 (s, 2H), and 7.65-8.00 (m, 4H).

A solution containing 934 mg of the above compound and 831 mg of *p*-acetamidobenzene azide in 12 mL of CH_3CN was treated with 1.42 mL of Et_3N at 0°C. The solution was stirred at 0°C for 1.5 h and at 25°C for 12 h. The solvent was removed under reduced pressure and the resulting residue was taken up in 15 mL of CH_2Cl_2. After filtration, the solvent was removed under reduced pressure and the residue was purified by chromatography giving 531 mg (52%) of ethyl-2-diazo-3-oxo-4-phthalimidobutyrate (**48**) as a pale yellow crystalline solid: mp 149-150°C, IR ($CHCl_3$) 2150, 1780, 1720, 1665, 1410, 1310, and 935 cm^{-1}, NMR ($CDCl_3$, 90 MHz) δ 1.33 (t, 3H, J=7.5 Hz), 4.38 (q, 1H, J=7.5 Hz), 4.97 (s, 2H), and 7.65-8.00 (m, 4H); Anal. Calcd. for $C_{14}H_{11}N_3O_5$: C, 55.81; H, 3.68; N, 13.95. Found: C, 55.80; H, 3.68; N, 13.95.

A solution containing 284 mg of **48** and 179 mg of N-phenylmaleimide in 9.5 mL of benzene together with 5 mg of Rh(II) acetate was placed in an oil bath preheated to 100°C. The solution was heated at reflux for 2 h and then the solution was allowed to cool to rt. The white solid that formed was recrystallized from a CH_2Cl_2-hexane solution to give ethyl 4,12b-epoxy-3a,4,5,6,12b,12c-hexahydro-1,3,5,8-tetraoxo-1H-pyrrolo[3,4-k]5H-azepino[2,1-a]isoindole-4-carboxylate (**52**) (53%) as a white crystalline solid, mp 249-250°C; IR ($CHCl_3$) 1750, 1725, 1391, 1299, 1208, and 1075 cm^{-1}, NMR ($CDCl_3$, 300 MHz) δ 1.41 (t, 3H, J=7.1 Hz), 3.98 (d, 1H, J=7.6 Hz), 4.16 (d, 1H, J=7.6 Hz), 4.30 (d, 1H, J=18.9 Hz), 4.37-4.57 (m, 2H), 4.85 (d, 1H, J=18.9 Hz), 7.30-7.40 (m, 3H), 7.47-7.67 (m, 5H), and 7.89 (d, 1H, J=8.3 Hz); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 13.9, 47.5, 50.4, 51.8, 61.8, 88.3, 94.6, 123.3, 125.1, 127.1, 129.1, 129.3, 131.5, 131.8, 132.2, 132.3, 136.8, 162.3, 163.2, 171.8, 172.2 and 191.5; Anal. Calcd. for $C_{24}H_{18}N_2O_7$: C, 64.57; H, 4.06; N, 6.28. Found: C, 64.29; H, 4.08; N, 6.18.

Preparation and Cycloaddition of Ethyl 2-Diazo 4-Phthalimidobutyrate (49) with N-Phenylmaleimide. A suspension containing 54 g of potassium phthalimide and 71 g of ethyl 4-bromobutyrate in 300 mL of dry DMF was heated at reflux and maintained for 24 h. The reaction was cooled to 25°C, poured into water and extracted with ether. The combined organic extracts were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 84 g of a pale yellow solid which was recrystallized from CH_2Cl_2-hexane to give 47 g (63%) of ethyl 4-phthalimido butyrate as a white solid, mp 64-65°C; IR ($CDCl_3$) 1780, 1720, 1620, 1480, 1430, 1380, 1200, 900 and 720 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.23 (t, 3H, J=7 Hz), 1.85-2.17 (m, 2H),

2.23-2.56 (m, 2H), 3.77 (t, 2H, J=7 Hz), 4.10 (q, 2H, J=7 Hz) and 7.63-7.97 (m, 4H).

To a suspension of NaH (97 mg of a 60% suspension in oil) in 3 mL of dry benzene at 0°C was added one drop of anhydrous ethanol, followed by the dropwise addition of 211 mg of the above phthalimido butyrate and 180 mg of ethyl formate. The reaction was allowed to warm to 25°C and was stirred for 12 h after which 490 mg of mesyl azide was introduced. Stirring was continued for 4 h and then the mixture was quenched with water, washed with a 10% NaOH solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash silica gel chromatography afforded 162 mg (69%) of ethyl 2-diazo 4-phthalimidobutyrate (**49**) as a yellow oil; IR (neat) 2100, 1780, 1720, 1680, 1470, 1340, 1150, 1030, 980, and 720 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, 3H, J=7.1 Hz), 2.68 (t, 2H, J=6.5 Hz), 3.86 (t, 2H, J=6.5 Hz), 4.11 (q, 2H, J=7.1 Hz), and 7.30-7.47 (m, 4H).

A solution containing 113 mg of N-phenylmaleimide and 5 mg of Rh(II) octanoate in 0.5 mL of CH_2Cl_2 was treated dropwise with a solution containing 37 mg of diazoester **49** in 0.2 mL of CH_2Cl_2. Removal of the solvent indicated a 92% yield of the carbonyl ylide derived cycloadduct **53** as judged by NMR spectroscopy. An analytically pure sample was obtained by recrystallization from CH_2Cl_2-hexane followed by recrystallization from acetone to give cycloadduct **53** as a white solid, mp 239-240°C, IR ($CHCl_3$) 1795, 1760, 1740, 1610, 1480, 1300, 1290, 1080, 920, and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, 3H, J=7.1 Hz), 2.13 (ddd, 1H, J=13.7, 12.1 and 6.8 Hz), 2.42 (dd, 1H, J=13.7 and 4.8 Hz), 3.38 (ddd, 1H, J=14.5, 12.1 and 4.8 Hz), 3.63 (d, 1H, J=7.5 Hz), 3.86 (d, 1H, J=7.5 Hz), 4.30 (q, 2H, J=7.1 Hz), 4.51 (dd, 1H, J=14.5 and 6.8 Hz) and 7.31-7.86 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.3, 29.5, 32.4, 50.1, 52.0, 61.9, 84.7, 94.1, 122.9, 124.6, 125.8, 128.7, 128.8, 130.7, 131.1, 132.0, 136.2, 163.6, 166.8, 171.0, and 172.5; Anal. Calcd. for $C_{24}H_{20}N_2O_6$: C, 66.65; H, 4.66; N, 6.48. Found: C, 66.36; H, 4.74; N, 6.41.

Reaction of Ethyl 2-Diazo 4-Phthalimidobutyrate (49) with Dimethyl Acetylenedicarboxylate. To a solution containing 22 mg of DMAD and 5 mg of Rh (II) octanoate in 0.2 mL of dry CH_2Cl_2 was slowly added a solution containing 37 mg of diazo ester **49** in 0.5 mL of CH_2Cl_2. Removal of the solvent followed by flash silica gel chromatography gave ethyl 10,11-dicarbomethoxy-9,11a-epoxy-1,2,3,4,7,8 hexahexahydro-5-oxo-2H-azepino-[2,1-a]isoindole-4-carboxylate (**54**) (79%) as a colorless oil; IR (neat) 1760, 1740, 1635, 1625, 1470, 1410, 1260, 960, and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3H, J=7.1 Hz), 2.28 (dd, 1H, J=13.6 and 5.6 Hz), 2.41 (ddd, 1H, J=13.5, 11.6 and 7.1 Hz), 3.34 (ddd, 1H, J=13.5, 11.6 and 5.6 Hz), 3.53 (s, 3H), 3.88 (s, 3H), 4.28 (q, 2H, J=7.1 Hz), 4.36 (dd, 1H, J=13.6 and 7.1 Hz), 7.53-7.63 (m, 3H), and 7.80-7.83 (m, 1H); MS 401 (M^+), 369, 355, 342, 328, 295, 268, 240 (base), 208, 182, 160 and 120; Anal. Calcd. for $C_{20}H_{19}NO_8$: C, 59.83; H, 4.77; N, 3.49. Found: C, 59.71; H, 4.65; N, 3.28.

Dipolar Cycloaddition Reaction of Ethyl 2-Diazo 4-Phthalimidobutyrate (49) with Dimethyl Acetylenedicarboxylate. A solution containing 48 mg of diazoester **49** and 29 mg of DMAD was allowed to stir in 0.5 mL of $CDCl_3$ for 12 h. Removal of the solvent left a colorless oil whose structure was assigned as 3H-pyrazole (**55**) on the basis of its spectral properties: IR ($CDCl_3$) 1770, 1750, 1740, 1580, 1380, 1280, 1010, and 880 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, 3H, J=7.1 Hz), 3.55 (s, 3H), 3.81 (s, 3H), 3.55 (m, 2H), 4.03 (t, 2H, J=6.5 Hz), 4.50 (q, 2H, J=7.1 Hz), and 7.63-7.73 (m, 4H). This compound readily rearranged to the N-carboethoxy pyrazole **56** upon silica gel chromatography: IR ($CDCl_3$) 1740, 1720, 1400, 1310, 1240, 1120, and 1050 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.32 (t, 2H, J=6.8 Hz), 3.83 (s, 3H), 3.91 (s, 3H), 4.03 (t, 2H, J=6.8 Hz), 7.24-7.71 (m, 2H), and 7.78 (m, 2H); MS 357 (M^+), 325, 296, 210, 160 (base), 122, 104 and 77; Anal. Calcd. for $C_{17}H_{15}N_3O_6$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.06; H, 4.15; N, 11.57.

Acknowledgement: We gratefully acknowledge support of this work by the National Institutes of Health (CA-26751). Use of the high-field NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

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† Recipient of a Graduate Fellowship from the Organic Chemistry Division of the American Chemical Society sponsored by Pfizer, Inc., 1990-1991.

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