1,3-Dipolar Cycloadditions of (4*R**,5*R**)-1-Alkylidene-4-(benzoylamino)-5-phenyl-3-pyrazolidinon-1-azomethine Imines

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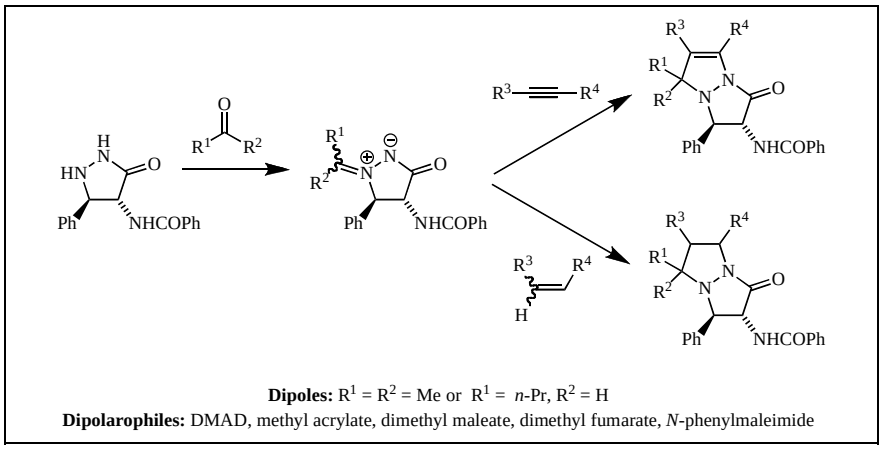

1,3-Dipolar cycloadditions of azomethine imines **3a** and **3b**, available by acid-catalyzed treatment of 3-pyrazolidinone **1** with acetone (**2a**) and butyraldehyde (**2b**), respectively, were studied. Reactions of **3a** with DMAD (**4**) afforded a mixture of products **9** and **10a**, whilst treatment of **3b** with DMAD (**4**) gave a mixture of compound **9** and epimeric cycloadducts **10/10'b**. On the other hand, cycloadducts **13a,b–16a,b** were isolated as single diastereomers in 9–37% yields upon reactions of **3a,b** with olefinic dipolarophiles **5–8**. The structures of cycloadducts **9**, **10a**, **10/10'b**, and **13a,b–16a,b** were determined by ^{1}H nmr and NOESY spectroscopy. The structure of compound **13a** was confirmed by X-ray diffraction.

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INTRODUCTION

1,3-Dipolar cycloadditions are useful methods for the preparation of five-membered heterocycles. They enable access to polyfunctional compounds with multiple asymmetric centers, usually with excellent stereocontrol [1]. Asymmetric cycloadditions in chiral nitrone, nitrile oxide, and azomethine ylide series are well elaborated, however, much less examples have been reported in chiral azomethine imine series [1–4]. Stable chiral azomethine imines have been prepared from pyridazine-diazoalkane cycloadducts [5–9], 3-pyrazolidinones [10–22], and 1,3,4-oxadiazin-2-ones [23–26]. Generally, 1,3-dipolar cycloadditions of such cyclic chiral azomethine imines to various dipolarophiles were accompanied by high facial and *endo*/*exo*-selectivity and afforded the corresponding functionalized fused pyrazolones with a bridgehead N–N structural element [4–26].

The importance of 3-pyrazolidinones rose significantly in the last decades, due to applicability in industrial processes, and because several 3-pyrazolidinone derivatives exhibit biological activities [10–12,27]. An important group of fused pyrazolidinone analogues are 2-(acylamino)-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-7-carboxylates, which are useful scaffolds for the preparation of conformationally constrained peptide mimetics [10–12,28]. A common method for the preparation of pyrazolo[1,2–*a*]pyrazolones is 1,3-dipolar cycloaddition of pyrazolidinon-1-azomethine imine to a suitable dipolarophile, first introduced by Dorn [29] and Oppolzer [30].

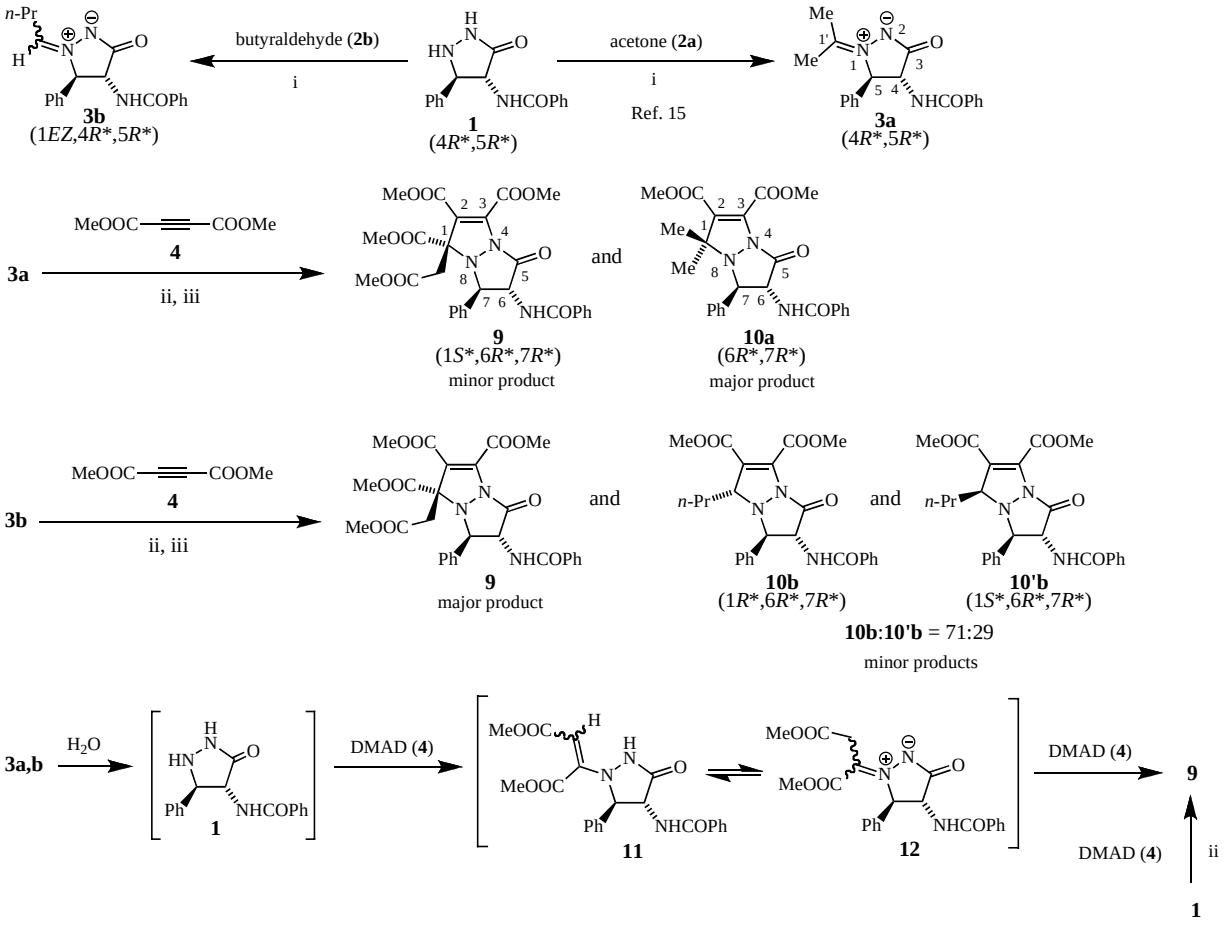
In the last decade, a part of our research interest has also been devoted to the chemistry of 3-pyrazolidinones and their fused analogues [13–15,20–22,31,32]. In this connection, we have previously reported 1,3-dipolar cycloadditions of (1'*Z*,4*R**,5*R**)-1-(arylmethylidene)-4-(benzoylamino)-5-phenyl-3-pyrazolidinon-1-azomethine imines to various dipolarophiles. The regiochemistry and stereochemistry of these cycloaddition reactions was controlled by the stereodirecting group in chiral dipole, by the *ortho*-substituents at the aromatic ring, and by the structure of the dipolarophile [13, 20–22]. In contrast to 1-arylmethylidene substituted 3-pyrazolidinone-1-azomethine imines, 1,3-dipolar cycloadditions of 1-alkylidene substituted analogues have not been studied yet. Herein, we report 1,3-dipolar cycloadditions of (4*R**,5*R**)-1-alkylidene-4-benzoylamino-5-phenyl-3-pyrazolidinon-1-azomethine imines **3a** and **3b** to dimethyl acetylenedicarboxylate (DMAD) (**4**), methyl acrylate (**5**), dimethyl maleate (**6**), dimethyl fumarate (**7**), and *N*-phenylmaleimide (**8**).

RESULTS AND DISCUSSION

Starting compound, *N*-[(4*R**,5*R**)-3-oxo-5-phenylpyrazolidin-4-yl]benzamide (**1**), was prepared from *N*-benzoylglycine according to the literature procedure [13]. Next, azomethine imines **3a** [15] and **3b** were prepared by acid-catalyzed treatment of **1** with acetone (**2a**) and butyraldehyde (**2b**) in 70% and 60% yield, respectively, according to the general literature procedure for the preparation of 3-pyrazolidinone-1-azomethine imines [13]. In contrast to closely related 1-arylmethylidene analogues, which exist as the (*Z*)-isomers, exclusively [13,20], the dipole **3b** exists in dimethyl sulfoxide-d_6 solution as a 1:1 mixture of both isomers. Then, reactions of dipoles **3a,b** with dimethyl acetylenedicarboxylate (DMAD) (**4**), methyl acrylate (**5**), dimethyl maleate (**6**), dimethyl fumarate (**7**), and *N*-phenylmaleimide (**8**) in refluxing anisole were studied. Heating of dipole **3a** with 1 equiv. of DMAD (**4**) followed by chromatographic separation gave compounds **9** and **10a** in 16% and 33% yield, respectively. Similarly, treatment of **3b** with DMAD (**4**) afforded a mixture of compound **9** and epimeric cycloadducts **10b** and **10'b**. Further chromatographic separation then furnished compound **9** in 34% yield and a mixture of **10b** and **10'b** in a ratio of 71:29, respectively, in 8% yield. Formation of **9** could be explained by hydrolysis of azomethine imine **3** into the starting pyrazolidinone **1**, which undergoes 1,4-addition to DMAD (**4**) to give the Michael-adduct **11**. Isomerisation of **11** gives the dipole **12**, which reacts with the second equivalent of DMAD to furnish compound **9**. The proposed mechanism was supported by another experiment, where **1** was treated with two equivalents of DMAD in refluxing anisole to afford **9** as the only product in 71% yield (Scheme 1).

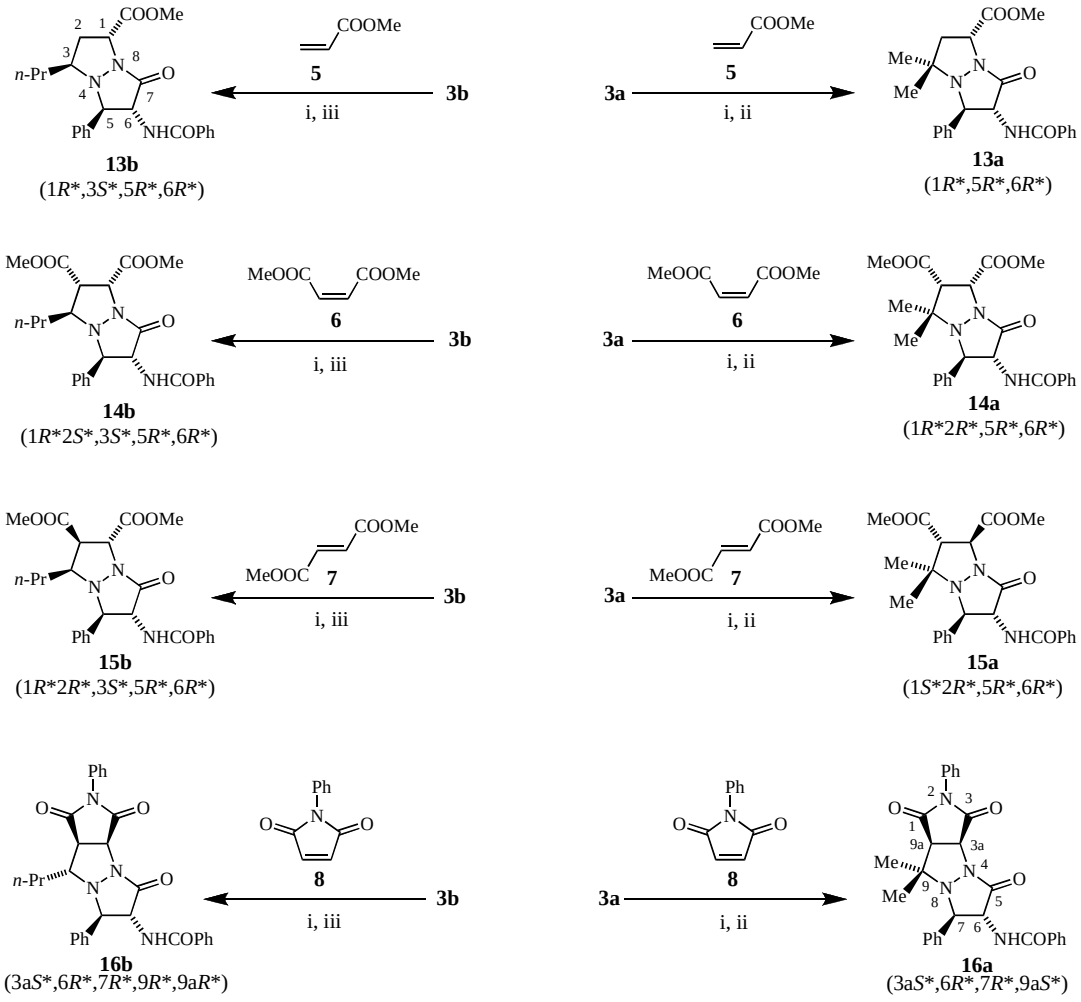
Heating of azomethine imine **3a,b** with olefinic dipolarophiles **5–8** in anisole, on the other hand, produced the corresponding cycloadducts **13a,b–16a,b** as the major products according to tlc. Compounds **13a,b–16a,b** were then isolated as single diastereomers in 9–37% yields. (Scheme 2).

Scheme 1



Reagents and conditions: (i) ethanol, CF_3COOH (cat.), reflux; (ii) anisole, reflux; (iii) chromatographic separation.

Scheme 2



Reagents and conditions: (i) anisole, reflux; (ii) chromatographic purification; (iii) crystallization from Et_2O.

With exception of **10/10'b**, all other cycloadducts, **9**, **10a**, and **13a,b–16a,b** were isolated as single diastereomers. This might indicate, that cycloadditions of chiral dipoles **3a,b** were stereoselective. However, isolation of single diastereomers itself does not prove stereoselectivity of cycloadditions, since the isolated yields of cycloadducts **9**, **10**, and **13–16** were only moderate. Unfortunately, unambiguous determination of stereoselectivity by ^{1}H nmr was not possible, because the ^{1}H nmr spectra of the crude reaction mixtures were very complex due to presence various by-products and impurities. Nevertheless, stereoselective cycloadditions might seem reasonable for reactions of dipole **3a** lacking a prochiral center at C(1'). For cycloadditions of the (1'*EZ*)-dipole **3b**, however, formation of at least two diastereomeric cycloadducts would be expected. Accordingly, reaction of **3b** with DMAD (**4**) gave a mixture of the (1*R**,6*R**,7*R**)-isomer **10b** and the (1*S**,6*R**,7*R**)-epimer **10'b**. On the other hand, isolation of single diastereomers **9**, **10a**, and **13a,b–16a,b** could be explained by the loss of the minor isomer(s) during chromatographic or crystallization workup. By analogy with cycloadditions of 1-arylmethylidene analogues [13,20–22] it could be presumed, that preferential approach of dipolarophiles **4–8** took place from the less hindered face of dipoles **3a,b**. The structures of the isolated cycloadducts **13**, **14**, and **16** indicate, that stereocontrol of these cycloadditions was analogous to that, observed previously in reactions to their *ortho*-unsubstituted 1-arylmethylidene analogues [20,21]: cycloadditions of methyl acrylate (**5**) and dimethyl maleate (**6**) were *endo*-selective, whilst cycloadditions of *N*-phenylmaleimide (**8**) were *exo*-selective. Reactions of both dipoles, **3a** and (*EZ*)-**3b**, can be explained by the concerted 1,3-dipolar cycloaddition mechanism [33] (Figure 1, see also Schemes 1 and 2).

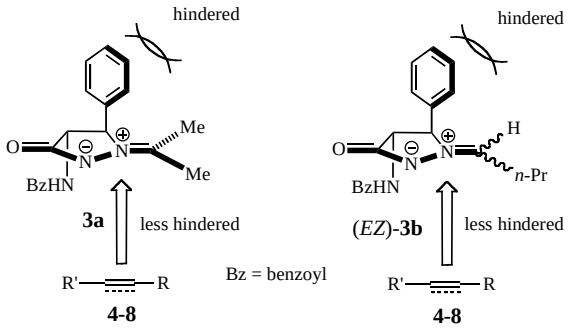
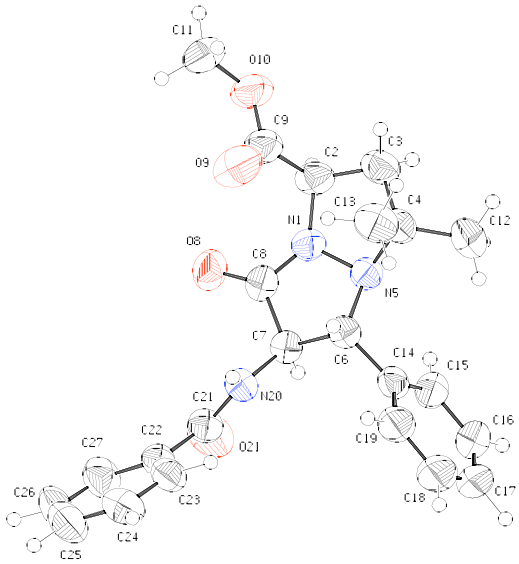


Figure 1.

The structures of novel compounds **3b**, **9**, **10a**, **10/10'b**, and **13a,b**–**16a,b** were determined by spectroscopic methods (ir, ^{1}H and ^{13}C nmr, NOESY spectroscopy, and ms) and by elemental analyses for C, H, and N. Compound **13a** was not obtained in analytically pure form. Its identity was confirmed by ^{13}C nmr, ei-hrms, and by X-ray diffraction (Figure 2).

The relative configurations of cycloadducts **9**, **10b, 13b**, and **14a,b**–**16a,b** were determined by NOESY spectroscopy. Absence of n.O.e. between *H*–C(7) and H_2C(1') in compound **9**, between *H*–C(1) and *H*–C(7) in compound **10b**, and between *H*–C(7) and *H*–C(9) in compound **16b** was in agreement with *anti*-orientation between these nuclei. On the other hand, the *syn*-orientation between *H*–C(3) and *H*–C(5) in compounds **13b–15b** was established on the basis of a strong n.O.e. between these two protons. Next, a strong n.O.e. between *H*–C(2) and *H*–C(3) in compound **15b** was in agreement with (2*R**,3*S**)-configuration, while absence of n.O.e. between *H*–C(2) and *H*–C(3) in compound **14b** and between *H*–C(9) and *H*–C(9a) in compound **16b** supported the *trans*-orientation of the corresponding nuclei. The (1*R**,2*R**)-configuration of compounds **14a** and the (1*S**,2*R**)-configuration of **15a** were established on the basis of n.O.e. between *H*–C(5) and Me_a–C(3) and n.O.e. between Me_b–C(3) and *H*–C(2). Absence of n.O.e. between Me_a–C(3) and *H*–C(2) and between Me_b–C(3) and *H*–C(5) supported the proposed configurations of compounds **14a** and **15a**. In the same manner, the (*S**)-configuration at position 9a in compound **16a** was determined by n.O.e. between Me_a–C(9) and *H*–C(9a) and between Me_a–C(9) and *H*–C(7) as well as by the absence of n.O.e. between Me_b–C(9) and *H*–C(9a) and between Me_b–C(9) and *H*–C(7) (Figure 3).



ORTEP view of compound **13a.**

Figure 2

In conclusion, (4*R**5*R**)-1-alkylidene-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imines **3a** and **3b**, are easily available from the parent pyrazolidinone **1** and acetone (**2a**) and butyraldehyde (**2b**), respectively. Both

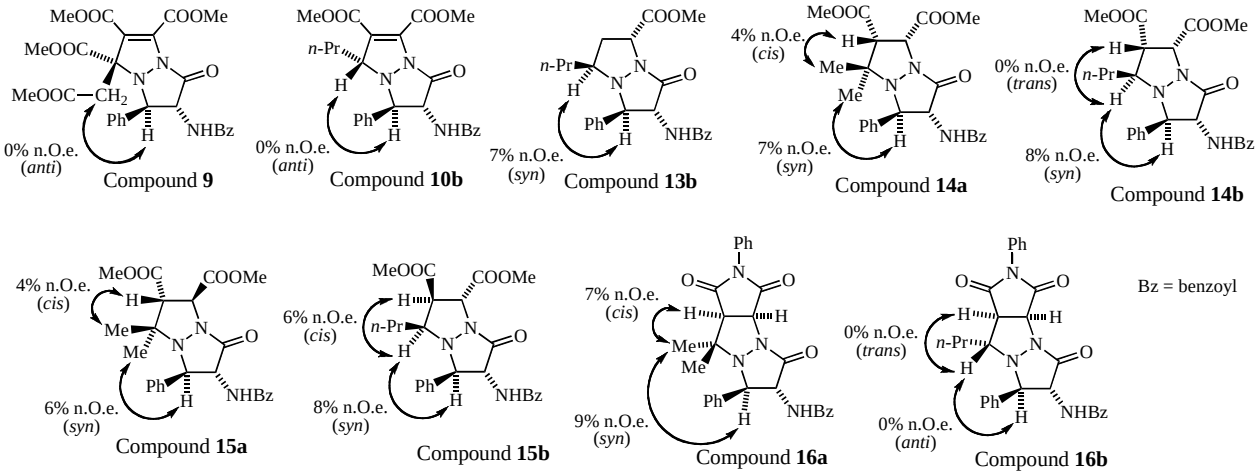


Figure 3

dipoles undergo 1,3-dipolar cycloadditions to acetylenic and olefinic dipolarophiles **4–8** to give the corresponding cycloadducts **9–16** in low to moderate yields. With exception of cycloadduct **10/10'b**, the other cycloadducts were isolated as single diastereomers. Most probably, isolation of isomerically pure cycloadducts was due to the loss of the other isomer(s) during isolation rather than due to the high stereoselectivity of cycloadditions. Stereocontrol of cycloadditions seems analogous to that, observed previously in cycloadditions to their *ortho*-unsubstituted 1-arylmethylidene analogues [20–22], *i.e.* approach of dipolarophiles took place predominantly from the less hindered face of dipoles **3**, cycloadditions of methyl acrylate (**5**) and dimethyl maleate (**6**) were *endo*-selective, whilst cycloadditions of *N*-phenylmaleimide (**8**) were *exo*-selective. In order to get a better insight into the reactivity and selectivity of 1,3-dipolar cycloadditions to 1-alkylidene substituted 3-pyrazolidinone-1-azomethine imines, a further study on related dipoles is in progress.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using dimethyl sulfoxide-d_6 and deuteriochloroform as solvents with tetramethylsilane as the internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Column chromatography was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). The isomer ratios were determined by ^{1}H nmr.

Butyraldehyde (**2b**), dimethyl acetylenedicarboxylate (**4**), methyl acrylate (**5**), dimethyl maleate (**6**), dimethyl fumarate (**7**), and *N*-phenylmaleimide (**8**) are commercially available (Sigma-Aldrich). Compounds **1** [13] and **3a** [15] were prepared according to the literature procedures.

(1'*EZ*,4*R,5*R**)-4-(Benzoylamino)-1-butylidene-3-oxo-5-phenylpyrazolidinium Inner Salt** (**3b**). A mixture of **1** (5.626 g, 0.020 mole), anhydrous ethanol (60 ml), and butyraldehyde (**2b**) (2.16 ml, 0.022 mole) was refluxed for 5 minutes. Then, 20 drops of trifluoroacetic acid were added through a reflux condenser and refluxing was continued for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was triturated with diethyl ether (60 ml). The precipitate was collected by filtration and washed with diethyl ether (50 ml) to give **3b** as a white solid. Yield: 4.017 g (60%), mp 220–226°; ir: NH 3318, CO 1703, 1685, 1643 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 0.43 (t, 3H, CH_3 (*isomer a*), J = 6.0 Hz), 0.65 (m, 3H, 3H of CH_2), 0.86 (m, 1H, 1H of CH_2), 0.94 (t, 3H, CH_3 (*isomer b*), J = 6.9 Hz), 1.40 (m, 2H, CH_2), 2.22 (m, 1H, 1H of CH_2), 2.82 (m, 1H, 1H of CH_2), 4.32 (d, 1H, 5–H (*isomer a*), J = 11.4 Hz), 4.59 (t, 1H, 4–H (*isomer a*), J = 9.0 Hz), 4.69 (s, 1H, 1'–H (*isomer a*)), 4.76 (d, 1H, 5–H (*isomer b*), J = 9.0 Hz), 5.01 (dd, 1H, 4–H (*isomer b*), J = 11.4, 8.7 Hz), 7.25–7.60 (m, 16H, phenyl protons), 7.84 (m, 4H, phenyl protons), 8.97 (d, 1H, NH (*isomer a*), J = 8.4 Hz), 9.07 (d, 1H, NH (*isomer b*), J = 8.7 Hz), 10.13 (s, 1H, 1'–H (*isomer b*)). *Anal.* Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.33; H, 6.31; N, 12.31.

Methyl [(1*S,6*R**,7*R**)-6-(Benzoylamino)-6,7-dihydro-1,2,3-tris(methoxycarbonyl)-5-oxo-7-phenyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazol-1-yl]acetate** (**9**). A mixture of **1** (0.281 g, 0.001 mole), anisole (5 ml), and DMAD (**4**) (0.282 g, 0.002 mole) was refluxed for 4 hours. Volatile components were evaporated in vacuo and the residue was triturated with diethyl ether (5 ml). The precipitate was collected by filtration and washed with diethyl ether (2 ml) to give **9** as a yellow solid. Yield: 0.400 g (71%). Yellow solid; mp 205–206° (from toluene); ir: NH 3300, CO 1722, 1700 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.50 and 3.00 (2d, 2H, 1:1, CH_2), 3.70, 3.76, 3.85, and 3.95 (4s, 12H, 1:1:1:1, 4×OMe), 4.53 (d, 1H, 7–H, J = 10.9 Hz), 5.04 (dd, 1H, 6–H, J = 7.9, 10.9 Hz), 6.70 (br s, 1H, NH), 7.3–7.5 (m, 8H, phenyl protons), 7.70 ppm (d, 2H, phenyl protons, J = 8.3 Hz). *Anal.* Calcd. for $C_{28}H_{27}N_3O_{10}$: C, 59.47; H, 4.81; N, 7.43. Found: C, 59.64; H, 4.84; N, 7.35.

General Procedures for the Reaction of Azomethine Imines 3a,b with Dipolarophiles 4–8.

Procedure A. A mixture of dipole **3a** or **3b** (0.001 mole), anisole (5 ml), and dipolarophile **4–8** (0.001 mole) was heated under reflux for 7 hours. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography (CC, ethyl acetate–hexanes). Fractions containing the product were combined and evaporated in vacuo to give cycloadducts **9**, **10a**, **10/10'b**, and **13a–16a**.

Procedure B. A mixture of dipole **3b** (0.335 g, 0.001 mole), anisole (5 ml), and dipolarophile **5–8** (0.001 mole) was heated under reflux for 7 hours. Volatile components were evaporated *in vacuo* and the residue was triturated with diethyl ether (5 ml). The precipitate was collected by filtration and washed with diethyl ether (2 ml) to give cycloadducts **13b–16b**.

The following compounds were prepared in this manner:

Methyl [(1*S,6*R**,7*R**)-6-(Benzoylamino)-6,7-dihydro-1,2,3-tris(methoxycarbonyl)-5-oxo-7-phenyl-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazol-1-yl]acetate (9) and Dimethyl (6*R**,7*R**)-6-(Benzoylamino)-6,7-dihydro-1,1-dimethyl-5-oxo-7-phenyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-2,3-dicarboxylate (10a).** These compounds were prepared from **3a** (0.321 g, 0.001 mole) and DMAD (0.142 g, 0.001 mole); Procedure A, CC (ethyl acetate–hexanes, 1:1).

Data for compound 9. Yield: 0.090 g (16%); physical and spectral data for compound **9** are given above.

Data for compound 10a. Yield: 0.152 g (33%) of a yellow solid, mp 119–121° (from toluene); ir: NH 3335, CO 1754, 1737, 1709, 1650 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.28 and 1.46 (2s, 6H, 1:1, 2×Me), 3.74 and 3.94 (2s, 6H, 1:1, 2×OMe), 4.81 (d, 1H, 7–H, J = 11.1 Hz), 4.86 (dd, 1H, 6–H, J = 6.4, 11.1 Hz), 6.65 (d, 1H, NH, J = 6.4 Hz), 7.34–7.41 (m, 5H, phenyl protons), 7.45–7.52 (m, 3H, phenyl protons), 7.68–7.73 (m, 2H, phenyl protons). *Anal.* Calcd. for $C_{25}H_{25}N_3O_6$: C, 64.79; H, 5.44; N, 9.07. Found: C, 64.77; H, 5.61; N, 9.30.

Methyl [(1*S,6*R**,7*R**)-6-(Benzoylamino)-6,7-dihydro-1,2,3-tris(methoxycarbonyl)-5-oxo-7-phenyl-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazol-1-yl]acetate (9), Dimethyl (1*R**,6*R**,7*R**)-6-(Benzoylamino)-6,7-dihydro-5-oxo-7-phenyl-1-propyl-1*H*,5*H*-pyrazolo-[1,2–*a*]pyrazole-2,3-dicarboxylate (10b), and Its Minor (1*S**, 6*R**,7*R**)-Isomer 10'b**. These compounds were prepared from **3b** (0.335 g, 0.001 mole) and DMAD (0.142 g, 0.001 mole); Procedure A, CC (ethyl acetate–hexanes, 1:1).

Data for compound 9. Yield: 0.191 g (34%); physical and spectral data for compound **9** are given above.

Data for compounds 10/10'b. Yield: 0.041 g (8%) of a yellow solid, **10b**:**10'b** = 71:29, mp 202–209° (from toluene); ir: NH 3339, CO 1736, 1652 cm^{-1}; ^1H nmr (deuteriochloroform): δ *major isomer* **10b** 0.74 (t, 3H, $CH_2CH_2CH_3$, J = 7.1 Hz), 1.31 (m, 2H, $CH_2CH_2CH_3$), 1.67 (m, 2H, $CH_2CH_2CH_3$), 3.82 and 3.93 (2s, 6H, 1:1, 2×OMe), 4.38 (d, 1H, 7–H, J = 11.4 Hz), 4.51 (dd, 1H, 1–H, J = 3.3, 4.9 Hz); 5.17 (dd, 1H, 6–H, J = 8.2, 11.4 Hz), 6.45 (d, 1H, NH, J = 8.3 Hz), 7.32–7.50 (m, 8H, phenyl protons), 7.70–7.78 (m, 2H, phenyl protons); *minor isomer* **10'b** 0.85 (t, 3H, $CH_2CH_2CH_3$, J = 7.2 Hz), 3.75 and 3.98 (2s, 6H, 1:1, 2×OMe), 4.48 (dd, 1H, 1–H, J = 4.1, 6.1 Hz); 4.69 (dd, 1H, 6–H, J = 7.6, 10.0 Hz), 4.96 (d, 1H, 7–H, J = 10.1 Hz), 6.56 (d, 1H, NH, J = 7.6 Hz). *Anal*. Calcd. for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.22; H, 5.82; N, 8.82.

Methyl (1*R,5*R**,6*R**)-6-(Benzoylamino)tetrahydro-3,3-dimethyl-7-oxo-5-phenyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-1-carboxylate** (**13a**). This compound was prepared from **3a** (0.321 g, 0.001 mole) and methyl acrylate (**5**) (0.086 g, 0.001 mole); Procedure A, CC (ethyl acetate–hexanes, 2:1). Yield: 0.068 g (17%) of a white solid, mp 175–185° (from toluene); ir: NH 3310, CO 1741, 1693, 1661 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.84 and 1.27 (2s, 6H, 1:1, 2×Me), 2.20 (dd, 1H, 2–Ha, J = 2.2, 13.1 Hz), 2.70 (dd, 1H, 2–Hb, J = 11.3, 12.8 Hz), 3.83 (s, 3H, OMe), 4.25 (d, 1H, 5–H, J = 11.6 Hz), 4.38 (dd, 1H, 1–H, J = 3.1, 11.1 Hz), 5.27 (dd, 1H, 6–H, J = 8.2, 11.6 Hz), 6.84 (d, 1H, NH, J = 8.2 Hz), 7.30–7.39 (m, 5H, phenyl protons), 7.42–7.52 (m, 3H, phenyl protons), 7.70–7.74 (m, 2H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 20.4, 27.2, 47.3, 51.9, 53.2, 59.6, 63.2, 68.8, 127.6, 127.7, 128.5, 128.6, 128.7, 128.9, 129.0, 129.1, 161.7, 167.5, 170.0; ei-ms: m/z 407 (M^+). Ei-hrms Calcd. for $C_{23}H_{25}N_3O_4$: m/z 407.184507 (M^+). Found: m/z 407.185250 (M^+).

Methyl (1*R,3*S**,5*R**,6*R**)-6-(Benzoylamino)tetrahydro-7-oxo-5-phenyl-3-propyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-1-carboxylate** (**13b**). This compound was prepared from **3b** (0.335 g, 0.001 mole) and methyl acrylate (**5**) (0.086 g, 0.001 mole); Procedure B. Yield: 0.157 g (37%) of a white solid, mp 173–174° (from toluene); ir: NH 3346, CO 1737, 1720, 1645 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.67 (t, 3H, $CH_2CH_2CH_3$, J = 6.7 Hz), 1.09 (m, 2H, $CH_2CH_2CH_3$), 1.67 (m, 2H, $CH_2CH_2CH_3$), 2.44 (m, 2H, 2–CH_2), 3.05 (m, 1H, 3–H), 3.85 (s, 3H, OMe), 4.14 (d, 1H, 5–H, J = 11.5 Hz), 4.42 (dd, 1H, 1–H, J = 3.0, 6.9 Hz), 5.39 (dd, 1H, 6–H, J = 8.3, 11.5 Hz), 6.61 (d, 1H, NH, J = 8.3 Hz), 7.30–7.41 (m, 5H, phenyl protons), 7.44–7.51 (m, 3H, phenyl protons), 7.70–7.75 (m, 2H, phenyl protons). *Anal*. Calcd. for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.59; H, 6.50; N, 10.16.

Dimethyl (1*R,2*R**,5*R**,6*R**)-6-(Benzoylamino)tetrahydro-3,3-dimethyl-7-oxo-5-phenyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-1,2-dicarboxylate** (**14a**). This compound was prepared from **3a** (0.321 g, 0.001 mole) and dimethyl maleate (**6**) (0.144 g, 0.001 mole); Procedure A, CC (ethyl acetate–hexanes, 2:1). Yield: 0.086 g (18%) of a white solid, mp 222–230° (from toluene); ir: NH 3325, CO 1749, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 and 1.36 (2s, 6H, 2×Me), 3.65 (d, 1H, 2–H, J = 10.2 Hz), 3.74 and 3.86 (s, 6H, 2×OMe), 4.31 (d, 1H, 5–H, J = 11.0 Hz), 4.53 (dd, 1H, 1–H, J = 1.2, 10.2 Hz), 5.25 (dd, 1H, 6–H, J = 8.3, 11.0 Hz), 6.74 (d, 1H, NH, J = 8.3 Hz), 7.30–7.40 (m, 5H, phenyl protons), 7.43–7.51 (m, 3H, phenyl protons), 7.69–7.74 (m, 2H, phenyl protons). *Anal*. Calcd. for $C_{25}H_{27}N_3O_6$: C, 64.50; H, 5.85; N, 9.03. Found: C, 64.27; H, 5.82; N, 9.29.

Dimethyl (1*R,2*S**,3*S**,5*R**,6*R**)-6-(Benzoylamino)tetrahydro-7-oxo-5-phenyl-3-propyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-2,3-dicarboxylate** (**14b**). This compound was prepared from **3b** (0.335 g, 0.001 mole) and dimethyl maleate (**6**) (0.144 g, 0.001 mole); Procedure B. Yield: 0.178 g (37%) of a white solid, mp 173–174°; ir: NH 3356, CO 1740, 1724, 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.53 (t, 3H, $CH_2CH_2CH_3$, J = 7.0 Hz), 1.05 (m, 2H, $CH_2CH_2CH_3$), 1.21 (m, 2H, $CH_2CH_2CH_3$), 3.42 (ddd, 1H, 3–H, J = 3.1, 4.5, 11.1 Hz), 3.58 (dd, 1H, 2–H, J = 8.8, 11.1 Hz), 3.72 and 3.81 (2s, 6H, 1:1, 2×OMe), 4.21 (d, 1H, 5–H, J = 11.9 Hz), 4.64 (dd, 1H, 1–H, J = 0.7, 8.8 Hz), 5.46 (dd, 1H, 6–H, J = 8.7, 11.9 Hz), 6.63 (d, 1H, NH, J = 8.7 Hz), 7.31–7.40 (m, 5H, phenyl protons), 7.46–7.51 (m, 3H, phenyl protons), 7.69–7.73 (m, 2H, phenyl protons). *Anal*. Calcd. for $C_{26}H_{29}N_3O_6$: C, 65.12; H, 6.10; N, 8.76. Found: C, 64.98; H, 6.28; N, 8.70.

Dimethyl (1*S,2*R**,5*R**,6*R**)-6-(Benzoylamino)tetrahydro-3,3-dimethyl-7-oxo-5-phenyl-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate** (**15a**). This compound was prepared from **3a** (0.321 g, 0.001 mole) and dimethyl fumarate (**7**) (0.144 g, 0.001 mole); Procedure A, CC (ethyl acetate–hexanes, 2:1). Yield: 0.060 g (13%) of a white solid, mp 206–208° (from toluene); ir: NH 3316, CO 1744, 1694, 1664 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 and 1.15 (s, 6H, 1:1, 3–Me), 3.42 (d, 1H, 2–H, J = 8.2 Hz), 3.81 and 3.83 (2s, 6H, 1:1, 2×OMe), 4.53 (d, 1H, 5–H, J = 10.4 Hz), 4.83 (dd, 1H, 6–H, J = 7.4, 10.4 Hz), 5.08 (d, 1H, 1–H, J = 8.2 Hz), 6.91 (d, 1H, NH, J = 7.4 Hz), 7.30–7.38 (m, 5H, phenyl protons), 7.44–7.54 (m, 3H, phenyl protons), 7.70–7.73 (m, 2H, phenyl protons). *Anal*. Calcd. for $C_{25}H_{27}N_3O_6$: C, 64.50; H, 5.85; N, 9.03. Found: C, 64.29; H, 5.89; N, 9.22.

Dimethyl (1*R,2*R**,3*S**,5*R**,6*R**)-6-(Benzoylamino)tetrahydro-7-oxo-5-phenyl-3-propyl-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-1,2-dicarboxylate** (**15b**). This compound was prepared from **3b** (0.335 g, 0.001 mole) and dimethyl fumarate (**6**) (0.144 g, 0.001 mole); Procedure B. Yield: 0.044 g (9%) of a white solid, mp 194–196° (from toluene); ir: NH 3337, CO 1761, 1734, 1707, 1645 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.61 (t, 3H, $CH_2CH_2CH_3$, J = 7.2 Hz), 0.98 (m, 2H, $CH_2CH_2CH_3$), 1.09 and 1.25 (2m, 2H, 1:1, $CH_2CH_2CH_3$), 3.18 (dt, 1H, 3–H, J = 6.4 Hz), 3.70 and 3.75 (2s, 6H, 1:1, 2×OMe), 3.80 (dd, 1H, 2–H, J = 1.9, 6.4 Hz), 4.35 (d, 1H, 5–H, J = 12.1 Hz), 4.52 (d, 1H, 1–H, J = 1.7 Hz), 5.07 (dd, 1H, 6–H, J = 9.1, 12.1 Hz), 7.29–7.39 (m, 3H, phenyl protons), 7.41–7.58 (m, 5H, phenyl protons), 7.80–7.84 (m, 2H, phenyl protons), 8.98 (d, 1H, NH, J = 9.0 Hz). *Anal*. Calcd. for $C_{26}H_{29}N_3O_6$: C, 65.12; H, 6.10; N, 8.76. Found: C, 65.02; H, 6.11; N, 8.88.

(3a*S,6*R**,7*R**,9a*S**)-6-(Benzoylamino)tetrahydro-9,9-dimethyl-7-phenyl-5*H*–pyrazolo[1,2–*a*]pyrrolo[3,4–*c*]pyrazole-1,3,5(2*H*,3a*H*)-trione** (**16a**). This compound was prepared from **3a** (0.321 g, 0.001 mole) and *N*-phenylmaleimide (**7**) (0.173 g, 0.001 mole); Procedure A, CC (ethyl acetate–hexanes, 2:1). Yield: 0.152 g (31%) of a white solid, mp 164–165° (from toluene); ir: NH 3316, CO 1788, 1719, 1653 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 and 1.43 (2s, 6H, 1:1, 2×Me), 3.40 (d, 1H, 9a–H, J = 7.9 Hz), 4.56 (dd, 1H, 6–H, J = 6.7, 9.7 Hz), 4.68 (d, 1H, 7–H, J = 9.7 Hz), 5.26 (d, 1H, 3a–H, J = 7.9 Hz), 6.90 (d, 1H, NH, J = 6.7 Hz), 7.30–7.37 (m, 6H, phenyl protons), 7.39–7.45 (m, 4H, phenyl protons), 7.46–7.54 (m, 3H, phenyl protons) 7.72–7.78 (m, 2H, phenyl protons). *Anal*. Calcd. for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33. Found: C, 70.31; H, 5.40; N, 11.34.

(3a*S,6*R**,7*R**,9*R**,9a*R**)-6-(Benzoylamino)tetrahdyro-7-phenyl-9-propyl-5*H*-pyrazolo[1,2–*a*]pyrrolo[3,4-*c*]pyrazole-1,3,5(2*H*,3a*H*)-trione** (**16b**). This compound was prepared from **3b** (0.335 g, 0.001 mole) and *N*-phenylmaleimide (**7**) (0.173 g, 0.001 mole); Procedure B. Yield: 0.114 g (28%) of a white solid, mp 273–274° (from toluene); ir: NH 3333, CO 1796, 1727, 1647 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.99 (t, 3H, $CH_2CH_2CH_3$, J = 7.2 Hz), 1.34 (m, 2H, $CH_2CH_2CH_3$), 1.63 and 1.78 (2m, 2H, 1:1, $CH_2CH_2CH_3$), 3.73 (m, 2H, 9–H, 9a–H), 4.58 (dd, 1H, 6–H, J = 7.0, 10.3 Hz), 4.84 (d, 1H, 7–H, J = 10.3 Hz), 5.19 (d, 1H, 3a–H, J = 8.0 Hz), 6.72 (d, 1H, NH, J = 6.9 Hz), 7.32–7.46 (m, 10H, phenyl protons), 7.48–7.55 (m, 3H, phenyl protons), 7.75–7.80 (m, 2H, phenyl protons). *Anal*. Calcd. for $C_{30}H_{28}N_4O_4$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.62; H, 5.65; N, 10.88.

X-Ray Structure Analysis for Compound 13a. Single crystal X-ray diffraction data of compound **13a** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software [34]. DENZO and SCALEPACK [35] were used for indexing and scaling of the data and the structure was solved by means of SIR97 [36]. Refinement and plotting were done using Xtal3.4 [37] program package. Crystal structure was refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina [38] weighting scheme was used.

Crystallographic data (excluding structure factors) for compound **13a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 647967. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk

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