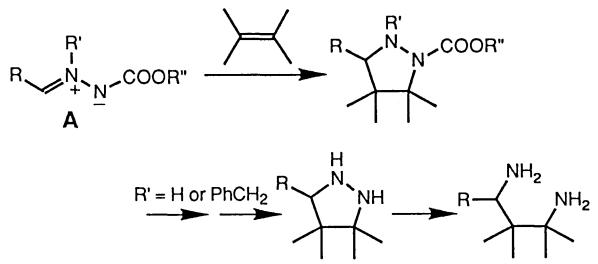
Triethylamine-Mediated Generation of a Synthetic Equivalent of Parent Azomethine Imine by Condensation of Ethyl 3-Benzylcarbazate with Paraformaldehyde

Shuji KANEMASA,* Naoki TOMOSHIGE, Eiji WADA, and Otohiko TSUGE*
Institute of Advanced Material Study, and Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816
(Received April 27, 1989)

A synthetic equivalent of parent azomethine imine is accessible by simple heating of ethyl 3-benzylcarbazate with paraformaldehyde under reflux in toluene in the presence of triethylamine, which effectively suppresses the undesired formation of imine dimers. The resulting imines can be trapped with a variety of dipolarophiles.

The cycloaddition of azomethine imine 1,3-dipoles with olefin dipolarophiles offers a short synthetic method for producing pyrazolidine derivatives.[1] The pyrazolidines which have been synthesized by this route are derivatives bearing at least one *N*-substituent.[2] To the best of our knowledge, not only the parent azomethine imine, itself, but also its synthetic equivalent is unknown.

We planned to establish a route leading to a synthetic equivalent of the parent azomethine imine 1,3-dipole. Cycloadditions of this synthetic equivalent with olefins and a subsequent removal of the *N*-substituents would produce *N*-unsubstituted pyrazolidines. Therefore, the cycloadducts would serve as functionalized cyclic hydrazines in heterocyclic synthesis; a reductive cleavage of the nitrogen-nitrogen bond of *N*-unsubstituted pyrazolidines would provide a new synthetic way to functionalized 1,3-diamines.



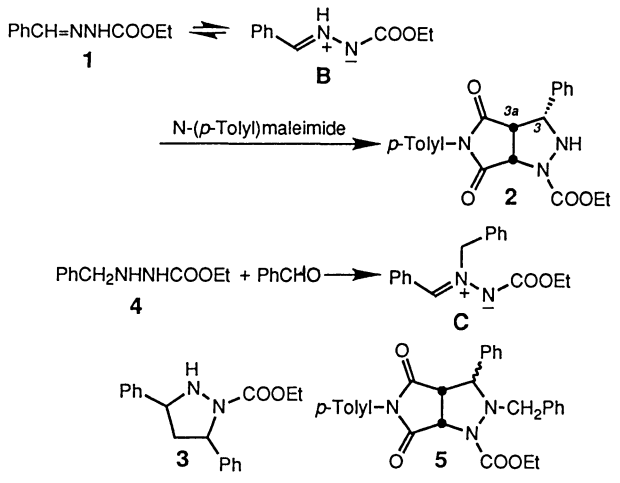
The synthetic equivalent of our choice is azomethine imine **A**, which bears an anion-stabilizing ester group at the terminal nitrogen and the central nitrogen is either unsubstituted or substituted by a removable benzyl group.

In the present work we investigated the condensation of ethyl 3-benzylcarbazate with formaldehyde and its equivalent reactions. It was found that triethylamine could effectively inhibit the formal dimerization of the transient azomethine imine. The generation procedure is simply carried out by heating ethyl 3-benzylcarbazate with paraformaldehyde and triethylamine in toluene in the presence of a dipolarophile.

Results and Discussion

Hydrazones undergo thermal[3] or acid-catalyzed tautomerism[4] generating azomethine imines bearing an unsubstituted nitrogen **A** (R′=H). Ethyl 3-benzylidenecarbazate (**1**) was selected as an imine precursor and its thermal tautomerism was investigated since **1** has an array of functionalities similar to that of the imines of α-amino esters whose thermal tautomerism is known to generate ester-stabilized azomethine ylides.[5]

Heating hydrazone **1** with *N*-(*p*-tolyl)maleimide under reflux in toluene for 72 h gave a single stereoisomer of cycloadduct **2** in 39% yield (Scheme 1). The structure of **2** was assigned as being a 3,3a-cis isomer on the basis of $J_{3\text{-}3a}$=8.8 Hz, indicating the endo-selective cycloaddition of azomethine imine **B**. However, the poor reactivity cancels the advantage of high stereoselectivity. Attempts to trap imine **B** with less reactive olefins, such as methyl acrylate and crotonate (each excess in a sealed tube), were unsuccessful, and attempts to activate hydrazone **1** by the aid of lithium bromide/triethylamine[6] were all in vain. The use of 1-benzylidene-2-(*p*-tolylsulfony)hydrazine, instead of **1**, produced no cycloadducts.



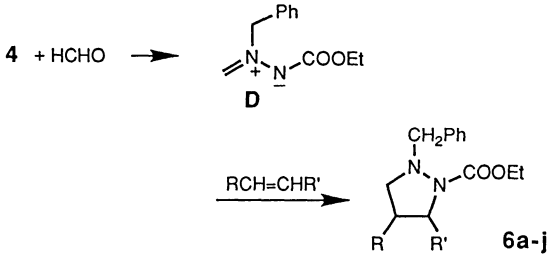
Scheme 1.

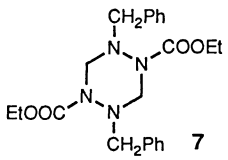
Although boron trifluoride etherate[4] showed some catalysis in a hydrazone-azomethine imine tautomerism of **1**, a 5 : 1 stereoisomeric mixture of cycloadduct **3** was obtained only in 38% yield in a reaction with styrene. Similar boron trifluoride-catalyzed reactions with butyl vinyl ether or *N*-(*p*-tolyl)maleimide gave no cycloadducts.

The next generation method employed was the condensation of carbonyl compounds with 1,2-disubstituted hydrazines.[1] For this purpose, hydrazone **1** was reduced with either zinc borohydride or a borane/pyridine complex into ethyl 3-benzylcarbazate (**4**).

Heating **4** with benzaldehyde under reflux in toluene resulted in a quantitative generation of azomethine imine **C**, which was captured by *N*-(*p*-tolyl)maleimide to give a 73:27 mixture of endo and exo isomers of cycloadduct **5** (Scheme 1). Both isomers, which were separated from each other by silica-gel column chromatography by using hexane-ethyl acetate, were assigned on the basis of $J_{3\text{-}3a}$.

In expectation of the generation of a synthetic equivalent of the parent azomethine imine, a reaction of hydrazine **4** with paraformaldehyde was performed under reflux in toluene with a continuous removal of water by the aid of a Dean-Stark trap. The azomethine imine **D** generated was trapped with several olefins such as *N*-(*p*-tolyl)maleimide, dimethyl fumarate, and styrene (Scheme 2). Even when two equimolar amounts of the olefins were employed, the yields of the corresponding cyloadducts **6a,b,d** were low (Table 1, Entries 1, 6, 11). In all these cases, the cycloadducts were accompanied by diethyl 2,5-dibenzylperhydro-1,2,4,5-tetrazine-1,4-dicarboxylate (**7**), the formal dimer of imine **D**, in 15 to 50% yields. Although the yield of **6d** went up to 73% when a large excess of styrene (13 equiv) was used, side-product **7** was still formed in 10% yield (Entry 12).





6a: R,R' = CON(*p*-Tolyl)CO (cis)
6b: R = R' = COOMe (trans)
6c: R = R' = COOMe (cis)
6d: R = H, R' = Ph
6e: R,R' = $CH_2C_6H_4$-*o* (cis)
6f: R = H, R' = COOMe
6g: R = COOMe, R' = H
6h: R = Me, R' = COOMe (trans)
6i: R = COOMe, R' = Me (trans)
6j: R = H, R' = OBu-*n*

Scheme 2.

The azomethine imine **D**, thus generated, failed to react with less reactive olefins, such as methyl acrylate and crotonate, dimer **7** being the only product (Entries 23, 25). As anticipated, dimer **7** was formed also in the absence of dipolarophiles. Thus, heating **4** with paraformaldehyde under reflux in toluene produced 24% of **7** after 2 h, and 79% after 42 h. Under these reaction conditions, a thermal cleavage of dimer **7** did not take place, indicating no possibility for the regeneration of azomethine imine **D** by the thermolysis of **7**.

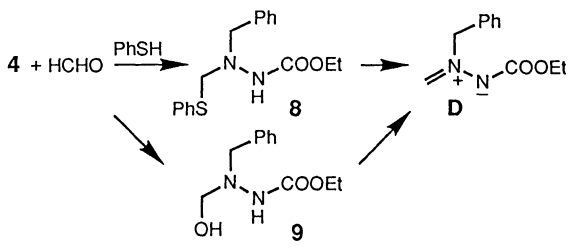
When dipolarophiles are not highly reactive in the simple heating method (Method A), the formation of side-product **7** becomes critical.

Molecular sieves of 4A were used to remove the water formed during the condensation (Method B). Under these conditions, the formation of dimer **7** was significantly suppressed in the reactions with styrene and butyl vinyl ether, so that the relative yields of cycloadducts **6d,j** slightly increased (Entries 13, 28). However, no significant improvement was observed in the reaction with *N*-(*p*-tolyl)maleimide (Entry 2).

The 2-(phenylthiomethyl) derivative of hydrazine **4** is the second precursor of azomethine imine **D** of our choice. Treatment of **4** with aqueous formaldehyde, and then benzenethiol in ethanol at room temperature, gave ethyl 3-benzyl-3-(phenylthiomethyl)carbazate (**8**) in 93% yield (Scheme 3), which is sufficiently stable to be purified by coluumn chromatography over silica gel.

Simple heating of **8** generated azomethine imine **D** which was trapped with electron-deficient activated dipolarophiles, such as *N*-(*p*-tolyl)maleimide and dimethyl maleate, to afford the corresponding cycloadducts **6a,c**. Although the formation of dimer **7** was effectively suppressed during this procedure, the slow generation of imine **D** resulted in the recovery of some starting precursor **8**, even after the lapse of long reaction times (Entries 4, 9). More troublesome, especially in the reaction with *N*-(*p*-tolyl)maleimide as a highly reactive Michael acceptor, was the Michael addition of phenylthiol nucleophile, arising from the elimination of **8**. A considerable amount of *N*-(*p*-tolyl)-2-(phenylthio)succinimide was produced. Poor stereospecificity in the reaction with dimethyl maleate was another disadvantage (Entry 9).

The base-induced azomethine imine generation by treating **8** with sodium hydride, in *N*,*N*-dimethyl-



Scheme 3.

Table 1. Cycloaddition of Azomethine Imine **D** with Olefinic Dipolarophiles

Entry	Olefin	Method[a,b]	Solvent	Additive	Time/h	Product (yield/%)[c]			
						6		**7**	Others
1	*N*-(*p*-Tolyl)maleimide	A[d]	Toluene		6	**6a**	41	38	
2	*N*-(*p*-Tolyl)maleimide	B	Toluene		10	**6a**	41	42	
3	*N*-(*p*-Tolyl)maleimide	C	Toluene		50	**6a**	93	0	
4	*N*-(*p*-Tolyl)maleimide	D	THF		45	**6a**	67	0	(15)[e], (23)[f]
5	*N*-(*p*-Tolyl)maleimide	E	Toluene		11	**6a**	61	5	
6	Dimethyl fumarate	A	Toluene		7	**6b**	70	15	
7	Dimethyl fumarate	C	Toluene		50	**6b**	93	0	
8	Dimethyl maleate	A	Toluene		7	**6c**	41	44	
9	Dimethyl maleate	D	Toluene		44	**6c**	19	0	(42)[e], (31)[g]
10	Dimethyl maleate	E	Toluene	AcOH(cat)	20	**6c**	50	23	
11	Styrene	A	Toluene		23	**6d**	34	50	
12	Styrene	A[h]	Toluene		3	**6d**	73	10	
13	Styrene	B	Toluene		23	**6d**	51	34	
14	Styrene	C	Toluene		50	**6d**	88	0	
15	Styrene	D	Xylene		96	**6d**	32	0	(37)[e]
16	Styrene	D	Xylene	AcOH (1 equiv)	50	**6d**	48	0	(24)[e]
17	Styrene	D	Xylene	AcOH (10 equiv)	50	**6d**	18	35	(10)[e]
18	Styrene	E	Xylene	AcOH (cat)	4	**6d**	35	49	
19	Styrene	E	Xylene	CF_3COOH (cat)	4	**6d**	0	92	
20	Styrene	E	Toluene	NEt_3 (1.2 equiv)	24	**6d**	56	8	
21	Styrene	E	Toluene	NEt_3 (3 equiv)	50	**6d**	72	0	
22	Indene	E	Toluene	NEt_3 (3 equiv)	50	**6e**	76	0	
23	Methyl acrylate	A	Toluene		72	**6f, g**	0	85	
24	Methyl acrylate	C	Toluene	NEt_3 (3 equiv)	50	**6f, g**	96[i]	0	
25	Methyl crotonate	A	Toluene		12	**6h, i**	0	60	
26	Methyl crotonate	C	Toluene	NEt_3 (3 equiv)	15	**6h, i**	42[j]	0	(20)[k]
27	Butyl vinyl ether	A	Toluene		21	**6j**	37	10	
28	Butyl vinyl ether	B	Toluene		21	**6j**	58	0	
29	Butyl vinyl ether	C	Toluene	NEt_3 (3 equiv)	50	**6j**	80	0	

a) Unless otherwise referred, all reactions were carried out by heating a mixture of a precursor, paraformaldehyde (1.5—2 equiv), and a dipolarophile (2 equiv) under reflux in the solvent shown above with continiuous removal of water by the aid of a Dean-Stark trap. b) As methods A to E, see experimental section. c) Yield of isolated products based on **4** or **8**. d) One equivalent of the maleimide was used. e) Recovered **8**. f) *N*-(*p*-Tolyl)-2-(phenylthio)succinimide. g) The fumarate adduct **6b**. h) A large excess (13 equiv) of styrene was used. i) **6f**: 50%; **6g**: 46%. j) **6h**: 14%; **6i**: 28%. k) Ethyl 4-benzylperhydro-1,3,4-oxadiazole-3-carboxylate.

formamide (DMF) at 0 °C in the presence of butyl vinyl ether, formed complex mixture of many compounds. It was found, however, that the imine generation was effected by an acid catalysis. Thus, the reaction of **8** with styrene was catalyzed by one equivalent of acetic acid, but the formation of dimer **7** was also facilitated in the presence of a large excess of acetic acid (Entries 15—17).

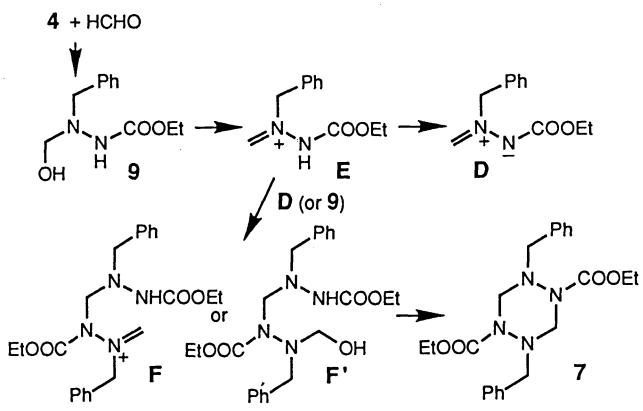
The reaction of hydrazine **4** with aqueous formaldehyde in ethanol at room temperature and evaporation of all the volatile materials left an unstable liquid which was assigned to be ethyl 3-benzyl-3-(hydroxymethyl)carbazate (**9**) on the basis of the ^1H NMR spectrum. The use of **9** as a precursor of azomethine imine **D** was investigated next.

The generation of azomethine imine **D** by the thermal or acid-catalyzed dehydration of (hydroxymethyl)hydrazine **9** accompanied the formation of significant amounts of dimer **7** (Entries 5, 10, 18), and the use of a strong acid catalyst, such as trifluoroacetic acid, resulted in a quantitative formation of dimer **7** (Entry 19). To our delight, however, triethylamine was found to effectively suppress the formation of dimer **7** (Entries 20—22).

We examined the direct generation route of imine **D** by heating hydrazine **4** with paraformaldehyde in the presence of excess (3 equiv) triethylamine. This procedure (Method C) worked well for a variety of olefinic dipolarophiles to produce the corresponding cycloadducts **6a,b,d,j** in excellent yields (Entries 3, 7, 14, 29). Even with less reactive olefins, such as methyl acrylate and crotonate, imine **D** underwent a smooth cycloaddition to give cycloadducts **6f,g** and **6h,i** (Entries 24, 26).

It is apparent that the condensation of hydrazine **4** with formaldehyde initially forms (hydroxymethyl)-hydrazine **9**, which then eliminates water leading to iminium intermediate **E** (Scheme 4). The direct formation of dimer **7** through the cycloaddition dimerization of azomethine imine **D** is thermally forbidden.[7] The most likely path is the nucleophilic addition of azomethine imine **D** or (hydroxymethyl)hydrazine **9** to the iminium intermediate **E** leading to **F** or **F'**. Either of them undergoes a ready cyclization to give dimer **7**.

In the presence of a weak acid catalyst, the dehydra-



Scheme 4.

tion of **9** is facilitated to accumulate iminium salt **E**. The generation of imine **D** competes with the coupling reaction leading to **F** or **F'**. When the catalyst is strongly acidic, deprotonation of **E** becomes difficult, so that the dimer formation becomes a major path. On the other hand, triethylamine catalyzes the deprotonation stage of **E** leading to azomethine imine **D** while minimizing the opportunity for a coupling reaction.

The removal of both the ester and benzyl substituents from the cycloadducts **6a—j** can be readily performed by acid- or base-catalyzed hydrolysis and catalytic hydrogenation on Pd/C, respectively. The use of the resulting heterocycles in organic synthesis is now under investigation; the results will soon be published elsewhere.

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 and A-702 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on JEOL FX-100 (100 MHz for ^{1}H NMR and 25.05 MHz for ^{13}C NMR) and GSX-270 (270 MHz for ^{1}H NMR and 67.94 MHz for ^{13}C NMR) instruments. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were measured with a JEOL-01SG-2 spectrometer at an ionization energy of 70 eV. Elemental analyses were performed on a Hitachi 026 CHN analyzer. For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silica gel 60 (Merck) were employed. Flash chromatography was carried out on an EYELA EF-10 apparatus using a column (20×180 mm) packed with Silica gel 60 (Merck, size: 0.04—0.063 mm).

Ethyl 3,3a-*cis*-3a,6a-*cis*-4,6-Dioxo-3-phenyl-5-(*p*-tolyl)-perhydropyrrolo[3,4-*c*]pyrazole-1-carboxylate (2): A mixture of **1** (0.191 g, 1 mmol) and *N*-(*p*-tolyl)maleimide (0.15 g, 0.8 mmol) was heated under reflux in toluene (4 ml) for 72 h. The mixture was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (2:1 v/v) to give **2** (0.117 g, 39%): Colorless prisms (diethyl ether-hexane); mp 203—205 °C; IR (KBr) 3210, 1710, 1365, and 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.36 (3H, t, J=7.2 Hz, COOEt), 2.35 (3H, s, *p*-Me), 3.83 (1H, dd, $J_{3a\text{-}3}$=8.8 and $J_{3a\text{-}6a}$=8.1 Hz, 3a-H), 4.32 (2H, m, COOEt), 4.67 (1H, t, $J_{3\text{-}3a}$= $J_{3a\text{-}NH}$=8.8 Hz, 3-H), 4.98 (1H, br d, J=8.8 Hz, NH), 5.48 (1H, d, $J_{6a\text{-}3a}$=8.1 Hz, 6a-H), and 7.0—7.5 (9H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=14.56 (COOEt), 21.19 (*p*-Me), 52.01 (COOEt), 61.97 (3a-C), 63.37 (6a-C), 66.45 (3-C), 125.41, 127.11, 128.65, 128.81, 129.02, 129.82, 133.37, 138.93 (each Ph), 156.74 (COOEt), 171.89, and 172.94 (each CON). Found: C, 66.66; H, 5.68; N, 10.93%. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.47; H, 5.59; N, 11.08%.

Ethyl 3,5-Diphenyl-1-pyrazolidine-1-carboxylate (3): A solution of **1** (0.191 g, 1 mmol), styrene (0.17 ml, 1.5 mmol), and trifluoroborane etherate (0.16 ml, 1.3 mmol) in dichloromethane (5 ml) was stirred at room temperature for 20 h. The solvent was evaporated in vacuo, and the residue was treated with saturated aqueous sodium hydrogencarbonate; the mixture was then extracted with diethyl ether (25 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel with hexane-ethyl acetate (5:1 v/v) to give the major stereoisomer of **3** (0.112 g, 38%) which was contaminated by a trace of the minor isomer: Colorless liquid; IR (neat) 3250, 1695, 1325, and 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) major isomer: δ= 1.2—1.3 (3H, COOEt), 2.46 (1H, dt, J_{gem}=12.8 and $J_{4\text{-}3}$=$J_{4\text{-}5}$=6.6 Hz, one of 4-H), 2.81 (1H, ddd, J_{gem}=12.8, $J_{4\text{-}3}$=8.1, and $J_{4\text{-}5}$=4.4 Hz, the other of 4-H), 4.0—4.3 (2H, m, COOEt), 4.62 (1H, dd, $J_{3\text{-}4}$=6.6 and 4.4 Hz, 3-H), 5.02 (1H, dd, $J_{5\text{-}4}$=8.1 and 6.6 Hz, 5-H), and 7.2—7.5 (10H, m, Ph); minor isomer: δ=2.17, 3.10 (each 1H, m, 4-H), 4.34 (1H, dd, $J_{3\text{-}4}$=10.6 and 5.4 Hz, 3-H), and 5.24 (1H, t, $J_{5\text{-}4}$= 9.2 Hz, 5-H); ^{13}C NMR ($CDCl_3$) major isomer: δ=14.61 (COOEt), 45.41 (4-C), 60.96, 61.52, 61.67 (3-, 5-C, and COOEt), 125.76, 126.32, 127.17, 127.40, 128.58, 139.97, 142.30 (each Ph), and 156.12 (COOEt); minor isomer: δ=45.86, 61.88, 63.48, 63.58, 126.81, 127.12, 127.73, 128.25, 128.66, 128.69, 128.85, 129.05, and 142.30. Other ^{1}H and ^{13}C signals of the minor isomer are overlapping with those of the major isomer.

Ethyl 3,3a-*cis*-2-Benzyl-4,6-dioxo-3-phenyl-5-(*p*-tolyl)perhydropyrrolo[3,4-*c*]pyrazole-1-carboxylate (5): A mixture of **4** (0.04 g, 0.2 mmol), benzaldehyde (0.024 g, 0.2 mmol), and *N*-(*p*-tolyl)maleimide (0.038 g, 0.2 mmol) was heated under reflux in toluene (3 ml) for 24 h, during which time the water formed was removed by the aid of a Dean-Stark trap. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel to give 3,3a-*trans*-**5** (0.025 g, 27%) from the fraction eluted with hexane-ethyl acetate (5:1 v/v) and 3,3a-*cis*-**5** (0.069 g, 73%) with ethyl acetate. 3,3a-*cis*-**5**: Colorless prisms (diethyl ether-hexane); mp 98 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.44 (3H, t, J=7.3 Hz, COOEt), 2.26 (3H, s, *p*-Me), 3.72 (1H, t, $J_{3a\text{-}3}$=$J_{3a\text{-}6a}$=8.6 Hz, 3a-H), 4.12, 4.25 (each 1H, d, J_{gem}=12.7 Hz, $PhCH_2$), 4.42 (2H, m, COOEt), 4.76 (1H, d, $J_{6a\text{-}3a}$=8.6 Hz, 6a-H), 5.11 (1H, d, $J_{3\text{-}3a}$=8.6 Hz, 3-H), 6.21, 7.01 (each 2H, d, J=8.3 Hz, Ar), and 7.3—7.4 (10H, m, Ph); MS *m/z* (rel intensity, %) 469 (M^+, 1), 91 (base peak), and 44 (23). Found: C, 71.37; H, 6.06; N, 8.89%. Calcd for $C_{28}H_{27}N_3O_4$: C, 71.61; H, 5.81; N, 8.95%. 3,3a-*trans*-**5**: Colorless prisms (diethyl ether-hexane); mp 203—204 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.28 (3H, t, J=7.1 Hz, COOEt), 2.43 (3H, s, *p*-Me), 3.89 (1H, d, J_{gem}=12.5 Hz, one of $PhCH_2$), 3.96 (1H, dd, $J_{3a\text{-}6a}$=8.6 and $J_{3a\text{-}3}$=1.3 Hz, 3a-H), 4.1—4.4 (3H, m, COOEt and the other of $PhCH_2$), 4.89 (1H,

br s, 3-H), 5.43 (1H, d, J_{6a-3a}=8.6 Hz, 6a-H), and 7.3—7.5 (14H, m, Ar); MS *m/z* (rel intensity, %) 469 (M^+, 28), 278 (29), and 91 (base peak). Found: C, 71.73; H, 5.77; N, 8.93%. Calcd for $C_{28}H_{27}N_3O_4$: C, 71.61; H, 5.81; N, 8.95%.

General Proceudre for Cycloadditions of Azomethine Imine D with Olefinic Dipolarophiles Leading to 6a—j. The following five procedures were employed for the generation of **D** and its cycloaddition: Method A: A mixture of hydrazine **4** (0.194 g, 1 mmol), paraformaldehyde (1.5—2 mmol), and an olefin (2 mmol) was heated under reflux in toluene (3 ml) with a continuous removal of water by the aid of a Dean-Stark trap. Method B: Similar to Method A, except that the mixture was heated together with Molecular Sieves 4A (1 g). Method C: The same as Method A, except that the mixture was heated in the presence of triethylamine (0.3 g, 3 mmol). Method D: (Phenylthiomethyl)hydrazine **8** (0.316 g, 1 mmol) and an olefin (2 mmol) were heated in the solvent shown in Table 1 in the absence or presence of acetic acid. Method E: Hydrazine **4** (0.194 g, 1 mmol) was treated with aqueous formaldehyde in ethanol (4 ml) at room temperature for 1 h. The ethanol was evaporated in vacuo; then the residue was dissolved in water (25 ml), and extracted with dichloromethane (20 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was heated with an olefin (2 mmol) in the absence or presence of a catalyst.

After the reaction had come to completion, the mixture was evaporated in vacuo and the residue was purified by silica-gel chromatography. The eluent used was as follows: **6a**: ethyl acetate; **6b**: hexane-ethyl acetate (3 : 1 v/v); **6c**: hexane-ethyl acetate (5 : 1 v/v); **6d**: hexane-ethyl acetate (3:1 v/v); **6e**: hexane-ethyl acetate (3 : 1 v/v); **6f** and **6g**: hexane-ethyl acetate (2 : 1 v/v); **6h** and **6i**: hexane-ethyl acetate (3 : 1 v/v); **6j**: hexane-ethyl acetate (4 : 1 v/v).

Ethyl 3,3a-*cis*-2-Benzyl-4,6-dioxo-5-(*p*-tolyl)perhydropyrrolo[3,4-*c*]pyrazole-1-carboxylate (6a): Colorless needles (diethyl ether-hexane); mp 143 °C; IR (KBr) 1700, 1380, and 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (3H, t, J=7.2 Hz, COOEt), 2.41 (3H, s, *p*-Me), 3.35 (1H, dd, J_{gem}=12.8 and J_{3-3a}=8.7 Hz, one of 3-H), 3.64 (1H, br d, J_{gem}=12.8 Hz, the other of 3-H), 3.69 (1H, d, J_{gem}=12.0 Hz, one of $PhCH_2$), 3.77 (1H, dt, J_{3a-3}=J_{3a-6a}=8.7 and J_{3a-3}=1.5 Hz, 3a-H), 4.00 (1H, d, J_{gem}=12.0 Hz, the other of $PhCH_2$), 4.17 (2H, m, COOEt), 5.40 (1H, d, J_{6a-3a}=8.7 Hz, 6a-H), and 7.2—7.4 (9H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=14.34 (COOEt), 21.24 (*p*-Me), 47.57 (COOEt), 54.82 (3-C), 60.39, 62.78, 63.34 (each $PhCH_2$, 3a-, and 6a-C), 125.67, 128.02, 128.52, 129.01, 129.74, 130.08, 136.06, 139.17 (each Ar), 155.99 (COOEt), 173.66, and 176.58 (each CON); MS *m/z* (rel intensity, %) 393 (M^+, 36), 202 (31), and 91 (base peak). Found: C, 67.08; H, 5.90; N, 10.64%. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.15; H, 5.90; N, 10.68%.

Dimethyl 3,4-*trans*-1-Benzyl-2-ethoxycarbonyl-3,4-pyrazolidinedicarboxylate (6b): Colorless liquid; IR (neat) 1730, 1380, 1340, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.18 (3H, t, J=7.1 Hz, COOEt), 3.15 (1H, dd, J_{gem}=11.7 and J_{5-4}=10.6 Hz, one of 5-H), 3.36 (1H, dd, J_{gem}=11.7 and J_{5-4}=7.3 Hz, the other of 5-H), 3.7—3.8 (2H, m, 4-H and one of $PhCH_2$), 3.75, 3.83 (each 3H, s, COOMe), 4.0—4.2 (3H, m, COOEt and the other of $PhCH_2$), 4.96 (1H, J_{3-4}=8.1 Hz, 3-H), and 7.3—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.38, 48.32 (each COOEt), 52,73, 52.90 (each COOMe), 55.79 (5-H), 61,50, 62.19, 62.66 (each $PhCH_2$, 3-, and 4-C), 127,71, 128.38, 129.76, 136.78 (Ph), 154.90 (COOEt), 170.68, and 171.96 (each COOMe); MS *m/z* (rel intensity %) 350 (M^+, 26), 127 (24), 91 (base peak). Found: C, 58.40; H, 6.42; N, 8.05%. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.34; N, 8.00%.

Dimethyl 3,4-*cis*-1-Benzyl-2-ethoxycarbonyl-3,4-pyrazolidinedicarboxylate (6c): Colorless liquid; IR (neat) 1740, 1680, 1430, 1380, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (3H, t, J=7.0 Hz, COOEt), 3.27 (1H, dd, J_{gem}=11.0 and J_{5-4}=7.0 Hz, one of 5-H), 3.4—3.6 (2H, m, 4-H and the other of 5-H), 3.70, 3.76 (each 3H, s, COOMe), 3.97, 4.07 (each 1H, d, J_{gem}=12.3 Hz, $PhCH_2$), 4.17 (2H, q, J=7.0 Hz, COOEt), 4.85 (1H, d, J_{3-4}=8.8 Hz, 3-H), and 7.3—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.68, 47.01 (each COOEt), 52.71, 53.87 (each COOMe), 61.53, 62.25, 62.44 (each $PhCH_2$, 3-, and 4-C), 127.97, 128.69, 129.93, 137.11 (each Ph), 154.85 (COOEt), 170.16, and 170.31 (each COOMe); MS *m/z* (rel intensity, %) 350 (M^+, 12), 127 (22), 103 (20), 91 (base peak), and 58 (24). Found: C, 58.04; H, 6.33; N, 8.09%. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.34; N, 8.00%.

Ethyl 2-Benzyl-5-phenyl-1-pyrazolidinecarboxylate (6d): Colorless prisms (diethyl ether); mp 81—83 °C; IR (KBr) 1675, 1410, 1330, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.19 (3H, t, J=7.1 Hz, COOEt), 2.28 (1H, ddt, J_{gem}=13.0, J_{4-5}=8.2, and J_{4-3}=7.5 Hz, one of 4-H), 2.56 (1H, dddd, J_{gem}=13.0, J_{4-5}=8.2, and J_{4-3}=6.0 and 5.0 Hz, the other of 4-H), 3.0—3.1 (2H, m, 3-H), 3.85 (1H, d, J_{gem}=12.1 Hz, one of $PhCH_2$), 4.0—4.2 (2H, m, COOEt), 4.17 (1H, d, J_{gem}=12.1 Hz, the other of $PhCH_2$), 5.08 (1H, t, J_{5-4}=8.2 Hz, 5-H), and 7.2—7.5 (10H, m, Ph); MS *m/z* (rel intensity, %) 310 (M^+, 5) and 91 (base peak). Found: C, 73.44; H, 7.23; N, 9.11%. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.51; H, 7.16; N, 9.03%.

Ethyl 3a,8a-*cis*-2-Benzyl-1,2,3,3a,4,8a-hexahydroindeno-[1,2-*c*]pyrazole-1-carboxylate (6e): Pale yellow liquid; IR (neat) 1700, 1130, and 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24 (3H, t, J=7.1 Hz, COOEt), 2.9—3.4 (5H, m, 3-, 3a-, and 4-H), 3.58, 3.81 (each 1H, d, J_{gem}=12.1 Hz, $PhCH_2$), 4.1—4.2 (2H, m, COOEt), 5.73 (1H, d, J_{8b-3a}=6.6 Hz, 8b-H), and 7.1—7.7 (9H, m, Ar); MS *m/z* (rel intensity, %) 322 (M^+, 30), 159 (30), 115 (20), and 91 (base peak). HRMS Found: *m/z* 322.1683. Calcd for $C_{20}H_{22}N_2O_2$: M, 322.1680.

Ethyl 2-Benzyl-5-methoxycarbonyl-1-pyrazolidinecarboxylate (6f) and Ethyl 2-Benzyl-4-methoxycarbonyl-1-pyrazolidinecarboxylate (6g): 6f: Colorless liquid; IR (neat) 1740, 1690, 1420, and 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.18 (3H, t, J=7.1 Hz, COOEt), 2.3—2.5 (2H, m, 4-H), 2.9—3.2 (2H, m, 3-H), 3.73 (1H, d, J_{gem}=11.0 Hz, one of $PhCH_2$), 3.79 (3H, s, COOMe), 4.0—4.2 (3H, COOEt and the other of $PhCH_2$), 4.53 (1H, t, J_{5-4}=8.2 Hz, 5-H), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.43 (COOEt), 29.79 (4-C), 51.89 (3-C), 52.45 (COOMe), 59.91 (COOEt), 61.32, 61.88 (5-C and $PhCH_2$), 127.54, 128.33, 129.80, 137.38 (each Ph), 154.96 (COOEt), and 172.92 (COOMe); MS *m/z* (rel intensity, %) 292 (M^+, 29), 91 (base peak), and 69 (37). Found: C, 61.40; H, 7.13; N, 9.36%. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.62; H, 6.91; N, 9.58%. **6g**: Colorless liquid; IR (neat) 1740, 1690, 1430, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20 (3H, t, J=7.1 Hz, COOEt), 3.1—3.3 (3H, m, 3-H and one of 5-H), 3.69 (3H, s, COOMe), 3.81 (2H, s, $PhCH_2$), 3.8—4.0 (2H, m, 4-H and the other of 5-H), 4.11 (2H, m, COOEt), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.56 (COOEt), 43.24 (4-C), 47.33 (5-C), 52.25 (COOMe), 55.16 (3-C), 60.98, 61.64 (COOEt and $PhCH_2$), 127.70, 128.36, 129.69, 136.78 (each Ph), 155.29 (COOEt), and 172.64 (COOMe); MS *m/z* (rel intensity, %) 292 (M^+, 45), 219 (28), 201 (21), 129 (48), 97 (21), 91 (base

peak), and 69 (32). HRMS Found: m/z 292.1403. Calcd for $C_{15}H_{20}N_2O_4$: M, 292.1422.

Ethyl 4,5-*trans*-2-Benzyl-5-methoxycarbonyl-4-methyl-1-pyrazolidinecarboxylate (6h) and Ethyl 4,5-*trans*-2-Benzyl-4-methoxycarbonyl-5-methyl-1-pyrazolidinecarboxylate (6i): **6h:** Colorless liquid; IR (neat) 1740, 1690, 1420, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16 (3H, t, J=7.0 Hz, COOEt), 1.23 (3H, d, J=6.2 Hz, 4-Me), 2.68 (1H, t, $J_{gem}=J_{3\text{-}4}$=11.4 Hz, one of 3-H), 2.8—3.0 (1H, m, 4-H), 3.14 (1H, dd, J_{gem}=11.4 and $J_{3\text{-}4}$=6.2 Hz, the other of 3-H), 3.75 (1H, d, J_{gem}=12.1 Hz, one of $PhCH_2$), 3.83 (3H, s, COOMe), 4.0—4.1 (3H, m, COOEt and 5-H), 4.19 (1H, d, J_{gem}=12.1 Hz, the other of $PhCH_2$), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.40 (COOEt), 15.67 (4-Me), 38.57 (4-C), 52.51 (COOMe), 59.74 (COOEt), 61.80, 61.88 (3-C and $PhCH_2$), 67.14 (5-C), 127.50, 128.30, 129.83, 137.50 (each Ph), 154.98 (COOEt), and 172.94 (COOMe); MS m/z (rel intensity, %) 306 (M^+, 66), 233 (30), 91 (base peak), and 83 (26). Found: C, 62.79; H, 7.52; N, 9.15%. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.25; N, 9.14%. **6i**: Colorless liquid; IR (neat) 1740, 1690, 1420, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (3H, t, J=7.1 Hz, COOEt), 1.52 (3H, d, $J_{5\text{-}4}$=6.6 Hz, 5-H), 3.1—3.3 (3H, m, 3- and 4-H), 3.70 (3H, s, COOMe), 3.77, 4.00 (each 1H, d, J_{gem}=12.5 Hz, $PhCH_2$), 4.0—4.2 (2H, m, COOEt), 4.2—4.3 (1H, m, 5-H), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.51 (COOEt), 22.22 (5-Me), 50.88 (3-C), 52.24 (COOMe), 54.63 (4-C), 58.53 (COOEt), 61.55, 62.66 ($PhCH_2$ and 5-C), 127.73, 128.38, 129.74, 136.99 (each Ph), 155.80 (COOEt), and 171.74 (COOMe); MS m/z (rel intensity, %) 306 (M^+, 7), 111 (21), 91 (base peak), and 83 (39). HRMS Found: m/z 306.1586. Calcd for $C_{16}H_{22}N_2O_4$: M, 306.1578.

Ethyl 2-Benzyl-5-butoxy-1-pyrazolidinecarboxylate (6j): Colorless liquid; IR (neat) 1690, 1370, 1330, and 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.94 (3H, t, J=7.3 Hz, n-Bu), 1.22 (3H, t, J=7.1 Hz, COOEt), 1.3—1.5, 1.5—1.7 (each 2H, m, n-Bu), 2.2—2.3 (2H, m, 4-H), 3.0—3.2 (2H, m, 3-H), 3.52 (1H, dt, J_{gem}=9.5 and J=6.6 Hz, one of n-Bu), 3.65 (1H, dt, J_{gem}=9.5 and J=6.6 Hz, the other of n-Bu), 3.80 (1H, d, J_{gem}=12.1 Hz, one of $PhCH_2$), 4.0—4.2 (2H, m, COOEt), 4.27 (1H, d, J_{gem}=12.1 Hz, the other of $PhCH_2$), 5.53 (1H, dd, $J_{5\text{-}4}$=4.8 and 3.7 Hz, 5-H), and 7.2—7.5 (5H, m, Ph); MS m/z (rel intensity, %) 306 (M^+, 46), 233 (22), 143 (22), 91 (base peak), and 87 (23). HRMS Found: m/z 306.1941. Calcd for $C_{17}H_{26}N_2O_3$: M, 306.1942.

Diethyl 2,5-Dibenzylperhydro-1,2,4,5-tetrazine-1,4-dicarboxylate (7): A mixture of **4** (0.205 g, 1.1 mmol) and paraformaldehyde (0.054 g, 1.8 mmol) was heated under reflux in toluene (4 ml) for 42 h. The solvent was evaporated in vacuo and the residue was washed with hexane to give **7** (0.179 g, 79%): Colorless prisms (diethyl ether-hexane); mp 139—140 °C; IR (KBr) 1680, 1420, 1340, 1290, and 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (6H, t, J=7.0 Hz, COOEt), 4.08 (4H, br s, $PhCH_2$), 4.20 (4H, q, J=7.0 Hz, COOEt), 4.72 (4H, br s, 3- and 6-H), and 7.2—7.6 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.51, 55.04 (each COOEt), 56.28 ($PhCH_2$), 62.14 (3- and 6-C), 127.86, 128.35, 129.74, 135.75 (each Ph), and 155.85 (COOEt); MS m/z (rel intensity, %) 412 (M^+, 6), 279 (24), 250 (33), and 91 (base peak). Found: C, 63.80; H, 6.82; N, 13.47%. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.05; H, 6.86; N, 13.58%.

Ethyl 3-Benzyl-3-(phenylthiomethyl) carbazate (8): Hydrazine **4** (0.194 g, 1 mmol) was treated with aqueous formaldehyde (37% solution) in ethanol (3 ml) for 1 h at room temperature. The ethanol was evaporated in vacuo, the residue was dissolved in water (20 ml), and extracted with dichloromethane (25 ml×2). The combined extracts were dried over magnesium sulfate, and evaporated in vacuo; the residue was then heated with benzenethiol (0.11 g, 1 mmol) under reflux in toluene (3 ml) for 1 h. The toluene was evaporated in vacuo and the residue was chromatographed on silica gel with ethyl acetate to give **8** (0.294 g, 83%): Colorless solid (purified by silica-gel column chromatography); mp 65 °C; IR (KBr) 3300, 1690, 1515, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13 (3H, t, J=7.1 Hz, COOEt), 3.91 (2H, s, $PhCH_2$), 4.01 (2H, q, J=7.1 Hz, COOEt), 4.55 (2H, s, SCH_2), 6.22 (1H, br s, NH), and 7.1—7.5 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.58, 59.82 (each COOEt), 61.30 ($PhCH_2$), 64.31 (SCH_2), 127.12, 127.75, 128.43, 129.32, 129.39, 131.44, 136.00, 136.25 (each Ph), and 155.45 (COOEt); MS m/z (rel intensity, %) 207 (M^+ −109, 10), 109 (38), 91 (base peak), and 65 (30). Found: C, 64.46; H, 6.42; N, 8.75%. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.52; H, 6.38; N, 8..85%.

Ethyl 3-Benzyl-3-(hydroxymethyl)carbazate (9): Hydrazine **4** (0.194 g, 1 mmol) was treated with aqueous formaldehyde (37% solution) in ethanol (3 ml) for 1 h at room temperature. The ethanol was evaporated in vacuo; the residue was then dissolved in water (20 ml), and extracted with dichloromethadcne (25 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give viscous liquid of **9** (0.22 g, 98%) as an unstable compound, for which only IR and ^1H NMR spectra were recorded: IR (neat) 3300, 1700, 1240, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (3H, t, J=7.5 Hz, COOEt), 3.91 (2H, s, $PhCH_2$), 4.0—4.3 (3H, m, COOEt and OH), 4.38 (2H, s, CH_2OH), 4.92 (1H, s, OH), and 7.2—7.5 (6H, m, Ph and NH).

References

1) A. Padwa, "1,3-Dipolar Cycloaddition Chemistry," in "General Heterocyclic Chemistry Series," ed by E. C. Taylor and A. Weissberger, John Wiley & Sons, New York, Chichester, Brisbane, Toronto, Singapore (1984), Chap. 7, pp. 733—814.

2) a) W. Oppolzer, *Tetrahedron Lett.*, **1970**, 2199 and 3091; b) W. Oppolzer, *ibid.*, **1972**, 1707; c) J. W. Lown and B. E. Landberg, *Can. J. Chem.*, **53**, 3782 (1975).

3) H. Ogura, K. Kubo, Y. Watanabe, and T. Itoh, *Chem. Pharm. Bull.*, **21**, 2026 (1973); M. K. Saxena, M. N. Gudi, and M. V. George, *Tetrahedron*, **29**, 101 (1973); R. Grigg, J. Kemp, and N. Thompson, *Tetrahedron Lett.*, **1978**, 2827.

4) K. D. Hesse, *Liebigs Ann. Chem.*, **743**, 50 (1971); G, Le Fevre, S. Sinbabdhit, and J. Hamelin, *Tetrahedron*, **35**, 1821 (1979); R. M. Wilson, J. W. Rekers, A. B. Packard, and R. C. Elder, *J. Am. Chem. Soc.*, **102**, 1633 (1980).

5) R. Grigg, *Chem. Soc. Rev.*, **16**, 89 (1987).

6) Imines of α-amino esters were sufficiently activated by the action with lithium bromide and triethylamine (O. Tsuge, S. Kanemasa, and M. Yoshioka, *J. Org. Chem.*, **53**, 1384 (1989)).

7) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).