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Stereoselectivity of Cycloaddition of *N*-(Cyanomethyl)- and *N*-(α-Cyanobenzyl)imines with Olefinic Dipolarophiles. Synthetic Equivalents of Nitrile Ylide 1,3-Dipoles

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N-(Cyanomethyl)- and *N*-(α-cyanobenzyl)imines derived from a variety of aldehydes and ketones can tautomerize into *N*-protonated azomethine ylides which undergo cycloadditions with olefinic dipolarophiles. These cycloadditions are often accompanied by the elimination of HCN, mostly in a stereospecific manner, showing these imines to be synthetic equivalents of nonstabilized nitrile ylides. Stereoselectivity of the cycloadditions is discussed.

Since the discovery of imine–azomethine ylide tautomerism of the imines derived from α-amino esters,[1-3] a wide range of 1,3-dipolar cycloaddition reactions utilizing such imines have been applied to the synthesis of pyrrolidine- and pyrrole-2-carboxylates.[4,5] However, quite rare are cycloaddition examples leading to the formation of stereoselective cycloadducts.[1] Generally, a mixture of two or even more stereoisomers of cycloadducts is formed.[2,4,6]

It is only quite recent that stereochemical features of cycloaddition of heteroaromatic *N*-ylides as peripheral azomethine ylides with olefinic dipolarophiles have been unveiled.[7] Although a lot of examples for the cycloadditions of open-chained azomethine ylides have been reported,[8-15] it is so far very difficult to predict stereoselectivity of a given example of cycloaddition of an azomethine ylide with an olefin. This difficulty results partly from the lack of information on the structure of azomethine ylide which has participated in the cycloaddition.

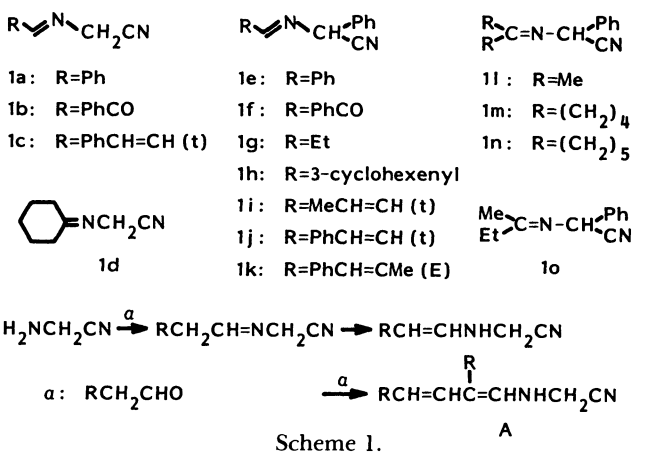
An *N*-protonated azomethine ylide generated through tautomerism of imine lies in equilibrium with the starting imine under the conditions of cycloaddition. Therefore, the most stable isomer of all possible *N*-protonated azomethine ylides should participate in the cycloaddition. Geometry of the most stable ylide isomer may be readily predictable on the basis of structure of the starting imine.[16]

In the previous communications, we have found that *N*-benzylidene derivatives of cyanomethylamine[17] and α-cyanobenzylamine[18] undergo cycloadditions with olefins as *N*-protonated azomethine ylides of cyano-stabilized type. Elimination of HCN from the cycloadducts leads to pyrrolines which correspond to cycloadducts of nonstabilized nitrile ylides with olefins. It is important that these azomethine ylides directly afford cycloadducts one oxidation state higher than those expected from simple azomethine ylides, because there is no general route available for nonstabilized nitrile ylides.

The analysis of stereoselectivity in cycloadditions of *N*-protonated azomethine ylides of cyano-stabilized type is a major purpose of the present report. Structures incorrectly assigned for some cycloadducts described in the previous communication[18] are to be revised here.

Results and Discussion

A variety of *N*-(cyanomethyl)- **1a—d** and *N*-(α-cyanobenzyl)imines **1e—o** were examined as possible tautomeric precursors of *N*-protonated azomethine ylides of cyano-stabilized type (Scheme 1). The imines are readily accessible from reactions of aldehydes or ketones with cyanomethylamine or α-cyanobenzylamine. In some cases, imines were generated only in situ and used for the cycloadditions without isolation. Although the corresponding imines are similarly formed from cyanomethylamine and aliphatic aldehydes, they have a tendency to react further with the second molecule of the aldehyde as reactive enamines to give dienamines **A** even when no excess of the aldehyde is used.



Scheme 1.

All the imines **1a—c** and **1e—k** derived from aldehydes are found to exist in single isomeric forms in solution (^{1}H NMR in $CDCl_3$), presumably in *E*-forms.[19]

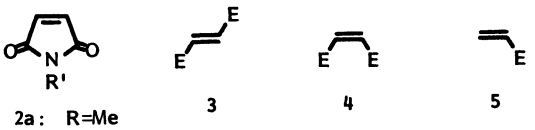
In the present work, these imines **1** were subjected to react with olefinic dipolarophiles such as *N*-methyl- **2a**, *N*-(*p*-nitrophenyl)maleimide **2b**, dimethyl

Table 1. Cycloaddition of **1a** with **2** Under Various Conditions

Entry	Maleimide	Reaction conditions				Product	Yield/%[a]	Isomer ratio[b]
		Solvent	Catalyst/mol%	Temp	Time/h			
1	**2a**	Toluene	—	Reflux	6.5	**6**	100	
2		MeCN	—	Reflux	62	**6**+**10**	100	**6** : **10**=3:1
3		MeCN	AcOH (5)	rt	24	**6**+**10**	100	**6** : **10**=1:1
4		MeCN	$(COOH)_2$ (0.1)	Reflux	17	**6**+**10**	99	**6** : **10**=1:1
5		AcOH	—	rt	13	**6**+**10**	83	**6** : **10**=1.8:1
6	**2b**	Toluene	—	Reflux	16	**7**	100	
7		MeCN	AcOH (10)	rt	30	**7**	100	

a) Isolated yield. b) Determined by ^{1}H NMR.

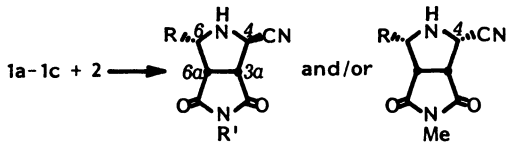
fumarate **3**, dimethyl maleate **4**, and methyl acrylate **5**. On the basis of stereostructure of cycloadducts formed, geometry of *N*-protonated azomethine ylides involved in the cycloaddition as well as stereoselectivity



2a: R=Me
2b: R=p-$NO_2C_6H_4$
E=COOMe

and stereospecificity of the cycloaddition is to be figured out. Synthetic versatility of these *N*-protonated azomethine ylides as synthons of nitrile ylides is next tested by elimination of HCN from the cycloadducts.

Reaction of *N*-(Cyanomethyl)imines with Maleimides. The reaction of *N*-(cyanomethyl)benzylideneamine **1a** with *N*-methylmaleimide **2a** took place cleanly, under reflux in toluene, to give a quantitative yield of cycloadduct **6** as a single stereoisomer (Scheme 2 and Table 1). However, under reflux in such a polar solvent as acetonitrile, the major product **6** was accompanied by its stereoisomer **10** in a 3:1 ratio (Entry 2 in Table 1). After investigation of the same reaction under a variety of conditions, it was found that this reaction was effectively catalyzed by weak acids such as acetic acid and oxalic acid (Entries 3 and 4).[20] Catalyzed cycloadditions occurred even at room temperature, a mixture of **6** and **10** being again obtained. Neither strong acids (CF_3COOH, *p*-TsOH) nor Lewis acids ($BF_3 \cdot Et_2O$, $Ti(OPr^i)_4$, $Al(OEt)_3$) were found to serve as effective catalysts, leading to recovery of the starting materials or complex mixture of many products.

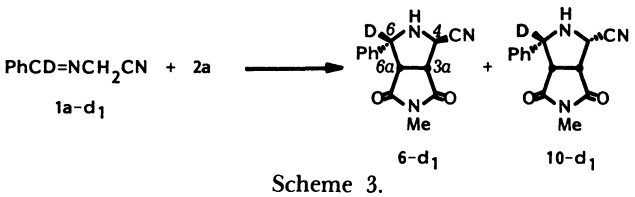


6: R=Ph, R'=Me
7: R=Ph, R'=p-$NO_2C_6H_4$
8: R=PhCO, R'=Me
9: R=PhCH=CH (t), R'=Me
10: R=Ph
11: R=PhCH=CH (t)

Scheme 2.

Similarly **1a** reacted with *N*-(*p*-nitrophenyl)maleimide **2b** to give single cycloadduct **7**, regardless of reaction conditions (Entries 6 and 7).

Stereostructures of **6** and **10** were assigned to be 3a,4-*trans*:6,6a-*cis* and 3a,4-*cis*:6,6a-*cis* cycloadducts, respectively, on the basis of spectral data, especially of the vicinal coupling constants (**6**: J_{3a-4}=0 and J_{6-6a}= 8.0 Hz; **10**: J_{3a-4}=J_{6-6a}=7.5 Hz). Signal assignment for the 6-H, a terminal of four consecutive methine hydrogens sitting on the newly formed five-membered ring, was accomplished by deuterium labeling. Monodeuterio derivatives **6**-d_1 and **10**-d_1 were prepared in the acid-catalyzed reaction of **1a**-d_1 with **2a** (Scheme 3).



Scheme 3.

Under non-catalytic conditions, which have shown high stereoselectivity in the reaction of **1a**, *N*-(cyanomethyl)benzoylmethyleneamine **1b** and -cinnamylideneamine **1c** reacted with **2a** giving 3a,4-*trans*:6,6a-*cis* cycloadducts **8**, **9** and 3a,4-*cis*:6,6a-*cis* isomer **11** (Scheme 2 and Table 2).

Four geometrical isomers **B1**—**4** are possible for the *N*-protonated azomethine ylides formed through tautomerism of **1a**—**c**, and these ylides can be interconverted readily to each other via an imine form under the reaction conditions (Fig. 1). Relative stability

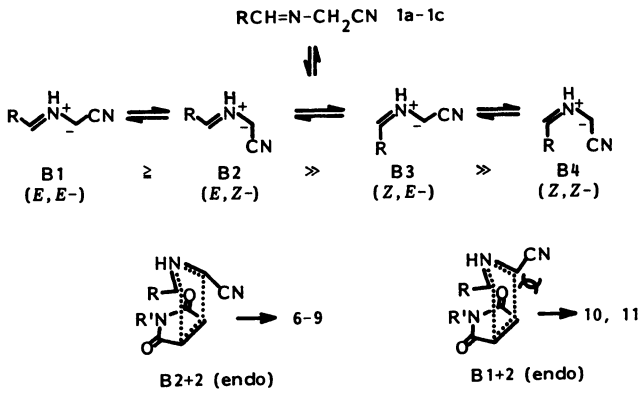


Fig. 1. Geometry of *N*-protonated azomethine ylides B generated from **1a**—**c** and stereochemistry of the cycloaddition with maleimides **2**.

Table 2. Cycloaddition of Imines **1** with Olefinic Dipolarophiles **2—5**

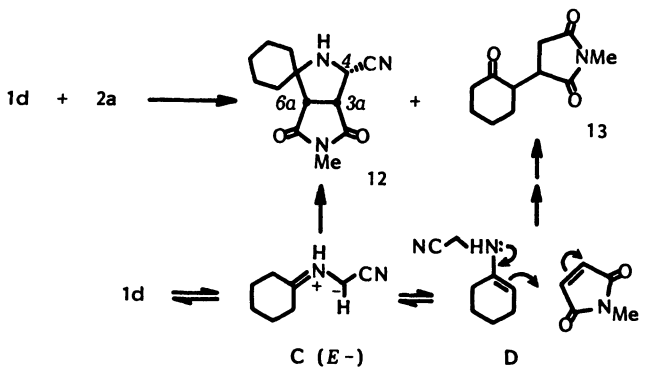
Imine	Olefin	Reaction conditions			Product	Yield/%[a]	Isomer ratio[b]	endo:exo[c]
		Solvent	Temp	Time/h				
1a	**2a**	Toluene	Reflux	6.5	**6**	100		100:0
	2b	Toluene	Reflux	16	**7**	100		100:0
1b	**2a**	$CHCl_3$	Reflux	4	**8**	100		100:0
1c	**2a**	Toluene	Reflux	14	**9+11**	100	**9** : **11**=2.3:1	100:0
1d	**2a**	Toluene	Reflux	15	**12+13**	15+50[d]		
1e	**2a**	Toluene	Reflux	6	**16+18**	92	**16** : **18**=2.3:1	70:30
		MeCN	Reflux	7	**16+18**	100	**16** : **18**=3.5:1	78:22
		MeCN[e]	Reflux	3	**16+18+20+22**	60+40[f]	**16** : **18**=6.7:1	87:13
	2b	Toluene	Reflux	6	**17+19+21+23**	92+8[g]	**17** : **19**=3.5:1	78:22
1f	**2a**	$CHCl_3$	Reflux	5 min	**14**	100		100:0
1g	**2a**	Toluene	Reflux	13	**24**	100		100:0
1h	**2a**	Toluene	Reflux	21	**25**	100		100:0
1i	**2a**	Toluene	Reflux	20	**26+29**	92	**26** : **29**=3.9:1	80:20
1j	**2a**	Toluene	Reflux	16	**27+30**	73	**27** : **30**=5:1	83:17
1k	**2a**	Toluene	Reflux	12	**28**	80		100:0
1l	**2a**	Toluene	Reflux	20	**31**	47		
1m	**2a**	Toluene	Reflux	36	**32**	83		
1n	**2a**	Toluene	Reflux	24	**33**	100		
1o	**2a**	Toluene	Reflux	19	**34**	30		
1a	**3**	Toluene	Reflux	24	**40+41**	86	**40** : **41**=1:1.9	100:0
		MeCN[h]	rt	38	**40+41**	72	**40** : **41**=2.2:1	100:0
1a	**4**	Toluene	Reflux	27	**42**	66		100:0
1e	**3**	Benzene	Reflux	8	**44+46**	100	**44** : **46**=3:1	75:25
		Toluene	Reflux	3	**44+47+46**	100	**44+47**:**46**=1.5+1.5:1	75:25
1e	**4**	Benzene	Reflux	15	**47**	100		100:0
1f	**3**	$CHCl_3$	Reflux	2	**45**	94		100:0
1j	**3**	Toluene	Reflux	20	**48+50**	76	**48** : **50**=2.5:1	71:29
	4	Toluene	Reflux	22	**48+52**	24+29[i]		100:0
1k	**3**	Toluene	Reflux	15	**49+51**	92	**49** : **51**=1.1:1	52:48
	4	Toluene	Reflux	23	**49**	76		100:0
1n	**3**	Toluene	Reflux	24	**53**	85		
	4	Toluene	Reflux	24	**53**	77		
1a	**5**	Neat	Reflux	12	**54+55**[j]	100	**54** : **55**=1.5:1	60:40
1e	**5**	Toluene	Reflux	6	**59+60**[k]	97	**59** : **60**=1.1:1	52:48[l]
1g	**5**	Neat	Reflux	22	**61+62**	93[m]		0:100[l]

a) All isolated yields as single isomer or as mixture of isomers. b) Determined on the basis of ^1H NMR spectrum of crude reaction mixture. c) The endo:exo ratio with respect to the imine carbon of **1**. d) The yields of **12** (15%) and **13** (50%). e) In the presence of AcOH (10 mol%). f) The yields of **16+18** (60%) and **20+22** (1:4, 40%). g) The yields of **17+19** (92%) and **21+23** (1:1, 8%). h) In the presence of AcOH (5 mol%). i) The yields of **48** (24%) and **52** (29%). j) Each two stereoisomers are included. k) **60** consists of two stereoisomers. l) The ratio of regioisomers (4-carboxylates: 3-carboxylates). m) The combined yield.

among them could be evaluated on the ground of steric repulsion.

Cyano moiety is only slightly bigger than hydrogen atom, while substituent R (Ph, PhCO, or PhCH=CH (t)) is much bulkier than any other substituents. Accordingly, the order of stability must be **B1**≧**B2**≫**B3**≫**B4**. The stereoselective cycloadducts **6—9** correspond to the ones formed through an endo approach of **2** to the second stable ylide **B2**, and the isomers **10** and **11** are endo cycloadducts of the most stable ylide **B1**. In the endo approach of **B1**, there exists some small steric repulsion between the cyano group and a carbonyl moiety of the maleimide **2**. So far we have no satisfactory explanation toward a question why acid catalysts have lowered stereoselectivity of the cycloaddition so much.

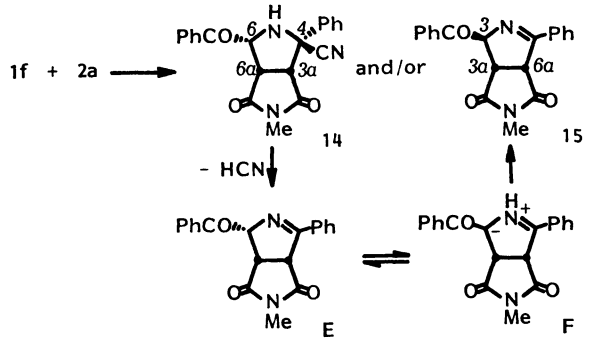
N-(Cyanomethyl)cyclohexylideneamine **1d**, generated in situ from cyclohexanone and cyanomethylamine under reflux in chloroform, reacted with **2a** under reflux in toluene to give only 15% of 3a,4-*cis* cycloadduct **12** (Scheme 4 and Table 2). Major product **13** was the Michael type adduct between cyclohexanone and **2a**. As described above (Scheme 1),



Scheme 4.

the imines derived from aliphatic aldehydes and cyanomethylamine readily tautomerize into enamines. In this case also, imine **1d** experienced competitive tautomerization, or the first formation of azomethine ylide and subsequent enamine formation, generating *N*-protonated azomethine ylide **C** and enamine **D**. The cycloaddition of **C**, that occupies sterically less hindered *E*-geometry, with **2a** produces **12** and the Michael addition of **D** forms a betaine intermediate which is then hydrolyzed into **13**.[21] Under acidic conditions (AcOH) both at room temperature and under reflux in acetonitrile, the Michael adduct **13** was the only product. This result looks reasonable since such polar conditions favor the Michael addition which is known to take place through a polar transition state.

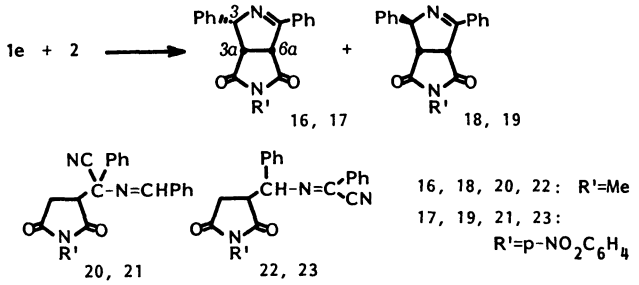
Reaction of *N*-(α-Cyanobenzyl)imines with Maleimides. *N*-(α-Cyanomethyl)benzoylmethyleneamine **1f** is found reactive toward maleimides. Thus, the reaction of **1f** with **2a** was completed in 5 min under reflux in chloroform to give a stereoselective cycloadduct **14** in a quantitative yield, which was assigned as one of 6,6a-*cis* isomers as shown in Scheme 5. Stereochemistry at the 4-position was tentatively determined on the basis of the most stable geometry for the *N*-protonated azomethine ylide generated from **1f**. This point will be discussed later.



Scheme 5.

When chromatographed over silica gel,[22] **14** underwent quantitative elimination of HCN to give **15** as a single stereoisomer in which the configuration of the 3-position was inverted. The prolonged reaction of **1f** with **2a** also furnished **15** as a side product. Probably **14** was first transformed into cis isomer **E** which then isomerized into **15** as a thermodynamically more stable product via azomethine ylide tautomer **F** (Scheme 5). In this isomerization, such a strongly electron-withdrawing substituent as benzoyl moiety is essential since imine-azomethine ylide tautomerism takes place only if α-hydrogen of imine is highly acidic.

A mixture of cis **16** and trans isomer **18** of HCN-eliminated cycloadduct was obtained in the reaction of *N*-(α-cyanobenzyl)benzylideneamine **1e** with **2a** under reflux in acetonitrile or toluene (Scheme 6, **16**:**18**=3.5—2.3:1). Under catalytic conditions (AcOH),



Scheme 6.

were formed two additional isomers **20** and **22** which were identified to be regioisomeric Michael adducts.

Similar reaction of **1e** with **2b** gave two HCN-eliminated cycloadducts **17**, **19** (3:1) and the Michael adducts **21**, **23** as minor products even under non-catalytic conditions (Table 2).[23]

This poor stereoselectivity between the 3- and 3a-positions of **16** and **18** (or **17** and **19**) is quite surprising. Four isomeric forms **G1—4** are again possible for the *N*-protonated azomethine ylide **G** formed by tautomerism of **1e** (Fig. 2). Unlike the preceding case (**B** in Fig. 1), **G1** must be by far the most stable since the additional phenyl moiety causes unfavorable steric repulsion in **G2**. Therefore, it is easily understood that only **G1** has participated in cycloaddition with **2**. Endo and exo approaches of **2a** to **G1** lead to the corresponding cycloadducts **H** and **I** whose stereospecific elimination of HCN produces cis **16** and trans isomer **18**. If this is the case, what is the reason for such poor stereoselectivity?

Before we try to explain this poor selectivity, we should rule out a possibility that **18** as a thermodynamically more stable isomer could have been secondarily derived from endo selective cycloadduct

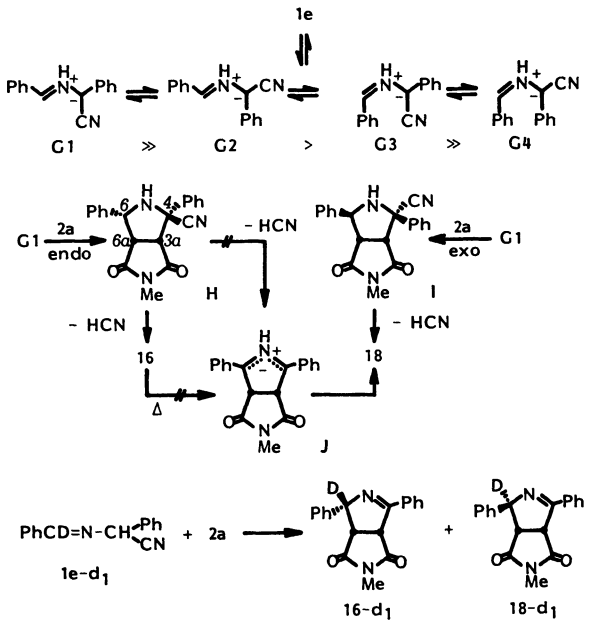
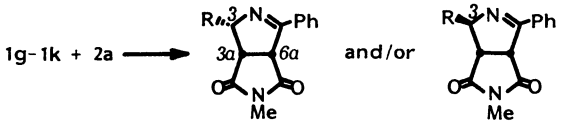


Fig. 2. Geometry of *N*-protonated azomethine ylide G generated from **1e** and stereochemistry of the cycloaddition with a maleimide **2a**.

H. Isomerization of **16** into **18** via azomethine ylide intermediate **J**, which resembles the inversion of **14** into **15** via **F** (Scheme 5), was first excluded by the fact that no trace of **18** was even detected on heating **16** under the reaction conditions of cycloaddition.[24] Direct formation of peripheral azomethine ylide intermediate **J** from **H** by 1,3-elimination of HCN was also excluded.[25] Cycloaddition of monodeuterio imine **1e**-d_1 with **2a** under the same conditions provided only a mixture of monodeuterio derivatives **16**-d_1 and **18**-d_1 of HCN-eliminated cycloadduct, indicating that stereochemistry at the 3-position of **16** and **18** has been already built up as it is now in the corresponding initial cycloadducts **H** and **I**. Thus, it is concluded that cycloaddition of **1e** with **2a** is nonstereoselective, forming two stereoisomeric cycloadducts **H** and **I**.

Both the phenyl substituents of **G1** can attractively interact with the carbonyl conjugation of **2a** allowing endo approach of both reagents.[26] However, this endo attractive interaction should be hindered by steric repulsion simultaneously growing among the same positions of these reacting molecules. As the phenyl groups are discouraged to share the same plane with the azomethine ylide triangle of **G1**,[27] steric repulsion on the endo approach becomes inevitable in this case. Accordingly the endo approach leading to **H** competes with the exo approach leading to **I**.

Similarly, *N*-(α-cyanobenzyl)alkylideneamines **1g—h** and -alkenylideneamines **1j—k** reacted with **2a** as *N*-protonated azomethine ylides to give 3,3a-*cis* **24—28** and/or 3,3a-*trans* isomers **29** and **30** of HCN-eliminated cycloadducts (Scheme 7 and Table 2). Stereoselectivity was found to depend upon substituents of imines **1**, and the cycloadditions of **1g—h** and **1k** were exclusively *endo*-selective.

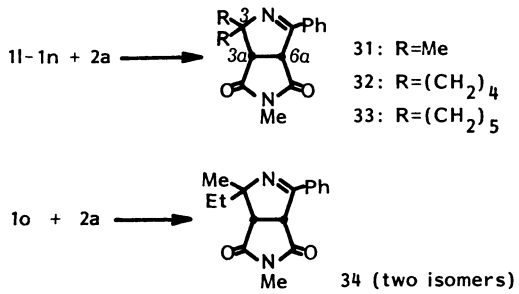


24: R=Et
25: R=3-cyclohexenyl
26: R=MeCH=CH (t)
27: R=PhCH=CH (t)
28: R=PhCH=CMe (E)
29: R=MeCH=CH (t)
30: R=PhCH=CH (t)

Scheme 7.

N-(α-Cyanobenzyl)imines **1l—o** derived from aliphatic ketones also reacted with **2a** giving HCN-eliminated cycloadducts **31—34** in good yields (Scheme 8 and Table 2).

Elimination of HCN from the Maleimide Cycloadducts. As mentioned above, most of the cycloadducts formed in the reactions of *N*-(α-cyanobenzyl)-imines **1e—o** with maleimides **2** undergo spontaneous elimination of HCN under the conditions of cycloaddition, indicating that these imines are useful

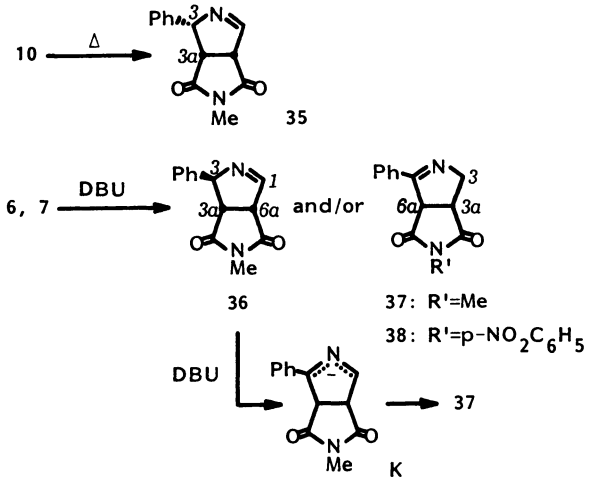


31: R=Me
32: R=$(CH_2)_4$
33: R=$(CH_2)_5$
34 (two isomers)

Scheme 8.

as synthetic equivalents of benzonitrile methylides. On the other hand, the cycloadducts from *N*-(cyanomethyl)imines **1a—d** are substituted with a cyano moiety. Therefore, some of these cycloadducts were subjected to thermal or base-catalyzed elimination of HCN.

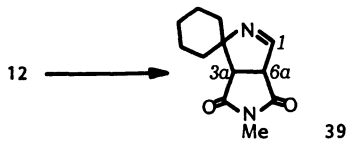
On heating in xylene, the all-*cis* cycloadduct **10** underwent slow elimination of HCN to give **35** with retention of configuration (Scheme 9 and Table 3), while its isomer **6** was recovered unchanged under the same conditions. In the presence of a catalytic amount of DBU, elimination occurred to give a mixture of 3,3a-*trans* isomer **36** and double bond-migrated product **37** whose ratio was found to change depending upon reaction time. The thermodynamically most stable isomer **37** was quantitatively obtained when **36** was heated in xylene for a long time in the presence of DBU. It is understood that both inversion of stereochemistry at the 3-position and double bond migration have occurred via the common anionic intermediate **K**.



Scheme 9.

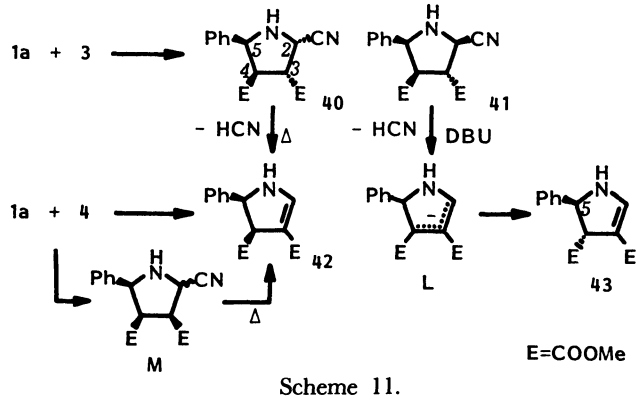
As spiro cycloadduct **12** has no possibility of secondary change after elimination of HCN, its elimination was carried out under reflux in xylene in the presence of a catalytic amount of DBU. A quantitative yield of **39** was obtained (Scheme 10 and Table 3).

Reaction with Fumarate, Maleate, and Acrylate. We further continued to study cycloaddition reactions of **1** with acyclic olefins such as dimethyl fumarate



Scheme 10.

3 and maleate 4. Reaction of **1a** with 3 gave two stereoisomeric cycloadducts **40** and **41** whose ratio was found to depend upon reaction conditions (Scheme 11 and Table 2). They were assigned as *r*-2, *c*-3, *t*-4, *t*-5 **40** and *r*-2, *t*-3, *c*-4, *c*-5 isomer **41** on the basis of the corresponding coupling constants as well as the magnetic shielding by a phenyl group at the 5-position toward the adjacent ester moiety cis to the phenyl.



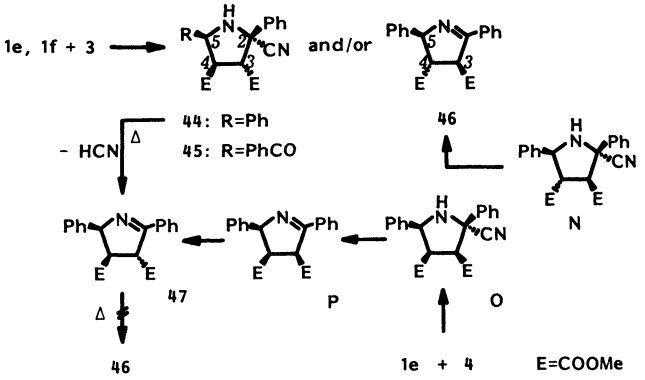
Scheme 11.

Cycloadduct **40** experienced slow elimination of HCN when heated in toluene to afford 4,5-*cis* 2-pyrroline **42** in which cis configuration at the 4- and 5-positions was retained. On the other hand, its isomer **41** suffered from no elimination until it was heated under reflux in toluene in the presence of a catalytic amount of DBU. The only product was 4,5-*trans* 2-pyrroline **43**. This inversion leading to **43** as a thermodynamically more stable isomer was presumably caused via allyl anion intermediate **L**.

Reaction of **1a** with the maleate **4** under reflux in toluene did not stop at a stage of cycloaddition but further reached to the complete elimination of HCN. The formation of 4,5-*cis* 2-pyrroline **42** as a single product indicates that cycloaddition between **1a** and **4** was exclusively *endo*-selective to form cis cycloadduct **M**.

Thus, cycloadditions of **1a** with both 3 and **4** are so highly stereoselective around one of the two newly formed C–C bonds that cycloadducts formed are exclusively 4,5-*cis* isomers. In contrast, reaction of **1e** bearing an additional phenyl substituent with 3 showed poor stereoselectivity.

Reaction of **1e** with 3 under reflux in benzene produced a mixture of 4,5-*cis* cycloadduct **44** and 4,5-*trans* isomer **46** of HCN-eliminated cycloadduct in a 3:1 ratio (Scheme 12 and Table 2). Under reflux in toluene, 4,5-*cis* isomer **47** of HCN-eliminated cycloadduct was newly formed (**44**:**47**:**46**=1.5:1.5:1), which was found to produce in a quantitative yield by thermal elimination of HCN of **44** with retention of stereochemistry. As **47** did not isomerize into **46** under the conditions of cycloaddition, **46** must be a product formed from 4,5-*trans* cycloadduct **N** through stereospecific HCN elimination reaction. After all, endoselectivity around the 4- and 5-positions was only 75% in this case.



Scheme 12.

Similar cycloaddition of **1e** with **4**, however, occurred very cleanly to give a quantitative yield of **47** as a single isomer. As we now know that epimerization at the 5-position of 1-pyrroline hardly takes place under thermal conditions, formation of **47** is easily explained by the following mechanism: Cycloaddition between **1e** and **4** first forms 4,5-*cis* cycloadduct **O** which then loses HCN under the conditions of cycloaddition. *r*-3, *c*-4, *c*-5 1-Pyrroline **P** undergoes epimerization at the 3-position through imine-enamine tautomerism.[28] Such tautomerization is frequently observed on pyrroline ring systems in which double bond is settled to the thermodynamically most stable location as seen in some examples **42**, **43**, **46**, and **47**.[29]

Not only to maleimides (Scheme 5) but also to 3, reactive imine **1f** underwent stereoselective cycloaddition under mild reaction conditions to give 4,5-*cis* cycloadduct **45**.

High stereoselectivity in cycloadditions of **1a** with both 3 and **4** was predictable on the ground of attractive interaction working between the phenyl moiety of **1a** and one of esters of 3 and **4**. As shown in Fig. 3, this is the only possible attractive interaction and there exists no serious steric hindrance among substituents. As a result, stereochemistry of cycloaddition was controlled by this interaction providing 4,5-*cis* products **40**—**42** in all cases. On the other hand, there are two possible endo interactions in the reaction of **1e** with 3 since **1e** participates to cycloaddition in the most stable form **G1**. Accordingly, stereoselectivity between the 4- and 5-positions was poor and a mixture of 4,5-*cis* **44** and 4,5-*trans* cycloadduct **N** was formed. In the cycloaddition of **1e** with **4**, the both ester groups of **4** can possitively interact with the both phenyl groups of **G1**. Unlike the rigid

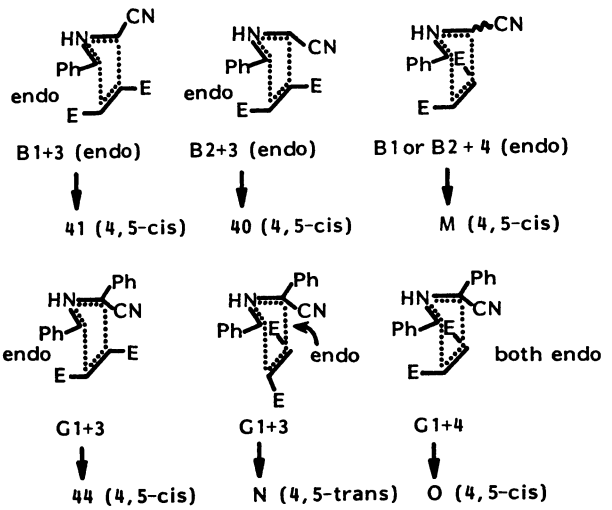
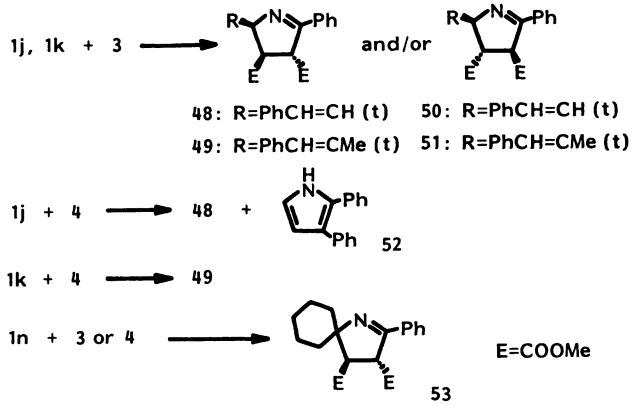


Fig. 3. Stereochemistry of cycloaddition of **1a** and **1e** with fumarate **3** and maleate **4**.

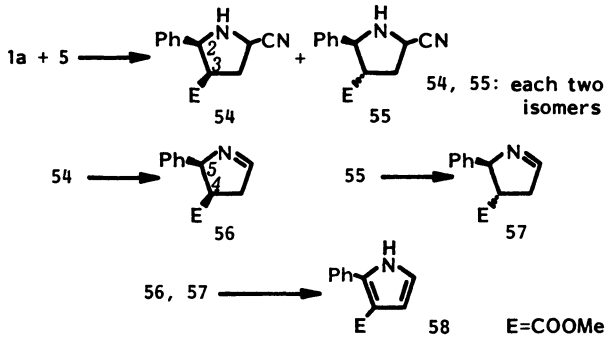
carbonyl conjugation of maleimides **2**, the ester groups of **4** can rotate around a C–C bond in such a direction as steric repulsion is minimized and also attractive interaction is maximized. Accordingly, the cycloaddition of **1e** with **4** was highly *endo*-selective forming cycloadduct **O**.

Similar reactions of **1j—k** with **3** furnished both mixtures of 4,5-*cis* **48**, **49** and 4,5-*trans* isomers **50**, **51** of HCN-eliminated cycloadducts (Scheme 13 and Table 2). However, the cycloadditions with **4** were exclusively *endo*-selective. 4,5-*cis* Isomers **48** and **49** were the only products in the reactions of **1j** and **1k**, respectively. Pyrrole **52** is the product formed by a 1,5-cyclization of imine **1j** followed by elimination of HCN. Spiro 1-pyrroline **53** carrying two ester groups trans to each other was obtained in either of reactions of **1n** with **3** and **4**.



Scheme 13.

Although reaction of **1a** with methyl acrylate **5** gave only very poor yields of cycloadducts or HCN-eliminated cycloadducts under reflux in toluene or in acetonitrile in the absence or presence of AcOH, heating **1a** in **5** gave a quantitative yield of mixture of four cycloadducts. Two of the four were separated from the other two and they were assigned as mixtures of two isomers of 2,3-*cis* **54** and 2,3-*trans* cycloadduct **55** on the basis of the following conversion as well as spectral data (Scheme 14). The both mixtures **54** and **55** underwent smooth elimination of HCN affording 4,5-*cis* **56** and 4,5-*trans* 1-pyrroline **57** with retention of configuration, respectively. Both 1-pyrrolines **56** and **57** were further converted into the same pyrrole-3-carboxylate **58** by dehydrogenation with chloranil, indicating that the cycloaddition of **1a** with **5** was exclusively regioselective. As regioselectivity in this and related cycloadditions is most likely to result, at least in part, from endo attractive interaction among the substituents as shown later, comparable formation of *exo*-cycloadducts **55** in this case is



Scheme 14.

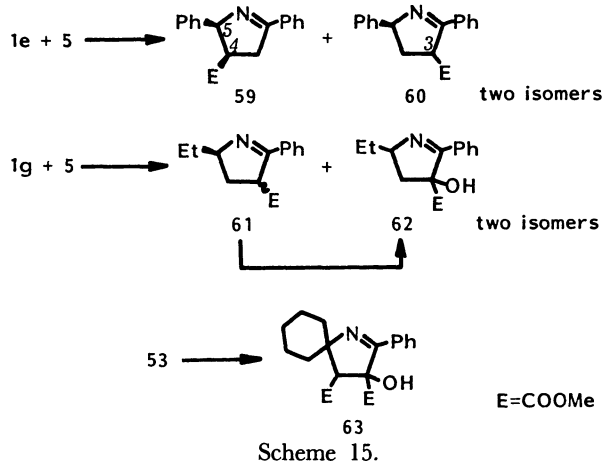
Table 3. Elimination of Hydrogen Cyanide from Cycloadducts

Cycloadduct	Reaction conditions				Product (yield/%)[a]			
	Solvent	Catalyst[b]	Temp	Time/h				
14	c)	silica gel	rt	—	**15** (100)			
10	Xylene	—	Reflux	19	**35** (60)			**10** (40)
6	Xylene	DBU	Reflux	7		**36** (19)	**37** (68)	
7	Xylene	DBU	Reflux	7			**38** (83)	
12	Xylene	DBU	Reflux	9	**39** (100)			
40	Xylene	—	Reflux	9	**42** (42)			**40** (58)
41	Toluene	DBU	Reflux	12.5		**43** (100)		
44	$CHCl_3$	silica gel	rt	—	**47** (100)			
	Toluene	—	Reflux	3	**47** (70)			
54	Toluene	DBU[d]	Reflux	17	**56** (82)			
55	Toluene	DBU	Reflux	18	**57** (81)			

a) All isolated yields. b) A catalytic amount of DBU was used. c) Chloroform–diethyl ether (3:1). d) Heating **54** under reflux in xylene in the absence of DBU gave a mixture of **56** and **54**.

quite surprising. We have so far no idea for the origin of exo cycloaddition.

Imine **1e** carrying two phenyl groups which can possitively interact with ester moiety reacted with **5** providing two regioisomeric HCN-eliminated cycloadducts **59** and **60** (Scheme 15 and Table 2). Stereochemistry at the 3-position of **60** is not important since easy epimerization is known to take place at this position.[29]



Scheme 15.

As anticipated, reaction of **1g** with **5** was regioselective giving single regioisomer **61** of HCN-eliminated cycloadduct. Probably endo interaction between the phenyl and ester groups resulted in such outstanding regioselectivity.

Surprisingly, **61** was easily air-oxidized at the 3-position forming mixture of two stereoisomeric 3-hydroxy-1-pyrrolines **62**. Similar air oxidation took place on **53** which was quantitatively oxidized into **63** under oxygen atmosphere.

Experimental

General. Melting points were determined on a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were taken with a JASCO IRA-1 or a JASCO A-702 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-40 (90 MHz) or a JEOL FX-100 instrument (100 MHz) and ^{13}C NMR spectra on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were measured with a JEOL JMS-01SG-2 spectrometer at 70 eV of ionization energy. Elementary analyses were performed on a Hitachi 026 CHN micro analyzer. Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck) or of aluminum oxide 60 F-254 type-E (Merck). Visualization was made with ultraviolet light (254 and 365 nm), iodine, molybdophosphoric acid (5% in ethanol), or *p*-anisaldehyde (5% in ethanol containing 5% of sulfuric acid). For preparative column chromatography, Wakogel C-200, C-300 (Wako) and Silicagel 60 (Merck) were employed. Flash chromatography was carried out on an EYELA EF-10 apparatus using a column (20×180 mm) packed with Silicagel 60 (Merck, size 0.04—0.063 mm). Preparative high performance liquid chromatography (HPLC) was performed on a Kusano KHLC-201 apparatus with a UV-detector Uvilog-III using a column (22×300 mm) packed with silica gel (Wakogel LC-50H). Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type-V at about 50 °C unless otherwise cited.

Benzene, toluene, and xylene were distilled over sodium and stored on sodium wire.

General Procedure for the Preparation of 1. A mixture of each equimolar amounts of cyanomethylamine or α-cyanobenzylamine and carbonyl compounds was refluxed in an appropriate solvent under the elimination of water formed by means of a Dean-Stark trap. The solvents and reaction times are as follows: In chloroform: **1b** (10 min); **1c** (1.5 h); **1d** (5 h); **1e** (30 min); **1f** (5 min); **1g** (4 h); **1i** (30 min); **1k** (30 min); **1m** (4 h); **1n** (2.5 h); **1o** (2.5 h). In dichloromethane: **1a** (1 h). In toluene at 60 °C: **1j** (15 min). In acetone: **1l** (30 min). These imines are not highly stable and **1b**, **1f**, and **1j** are too unstable to be separated. Accordingly, the most imines **1** were prepared immediately prior to their use and they were used for the following cycloaddition reactions after the evaporation of solvent in vacuo. Some spectral and analytical data are given as follows: **1a**: IR (neat) 2240 and 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.53 (2H, d, J=2.0 Hz, CH_2), 7.30—7.75 (5H, m, Ph), and 8.42 (1H, d, J=2.0 Hz, CH=N); ^{13}C NMR ($CDCl_3$) δ=45.73 (t, CH_2), 115.49 (s, CN), 128.06, 128.26, 131.23 (each d), 134.35 (s), and 164.27 (d, CH=N). **1c**: ^{1}H NMR ($CDCl_3$) δ=4.43 (2H, br, CH_2), 6.78—7.45 (7H, m, Ph and CH=CH), and 8.09 (1H, br d, J=7.5 Hz, CH=N). **1d**: ^{1}H NMR ($CDCl_3$) δ=1.55—1.90 (6H, m, CH_2), 2.15—2.40 (4H, m, CH_2), and 4.14 (2H, s, CH_2). **1e**: Colorless prisms (hexane); mp 51.5—52 °C; IR (KBr) 2210 and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=5.80 (1H, d, J=2.0 Hz, CH), 7.10—8.20 (10H, m. Ph), and 8.65 (1H, d, J=2.0 Hz, CH=N); MS m/z 220 (M^+). Found: C, 81.71; H, 5.46; N, 12.68%. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72%. **1g**: ^{1}H NMR ($CDCl_3$) δ=1.10 (3H, t, Et), 2.36 (2H, m, Et), 5.41 (1H, br s, CH), 7.26 (5H, br s, Ph), and 7.95 (1H, br d, CH=N). **1h**: ^{1}H NMR ($CDCl_3$) δ=1.30—2.75 (7H, m, CH_2 and CH), 5.46 (1H, s, CH), 5.60 (2H, m, CH=CH), 7.26 (5H, br s, Ph), and 7.90 (1H, d, J=4.5 Hz, CH=N). **1i**: IR (neat) 2230 and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.84 (3H, d, J=5.0 Hz, Me), 5.45 (1H, s, CH), 6.20 (2H, m, CH=CH), 7.15—7.30 (5H, m, Ph), and 8.05 (1H, dd, J=7.0 and 1.5 Hz, CH=N); MS m/z 184 (M^+). HRMS Found: m/z 184.0970. Calcd for $C_{12}H_{12}N_2$: M, 184.0999. **1j**: ^{1}H NMR ($CDCl_3$) δ=5.55 (1H, d, J=1.5 Hz, CH), 6.80 (1H, dd, J=16.0 and 7.5 Hz, PhCH=C<u>H</u>), 7.05 (1H, d, J=16.0 Hz, PhC<u>H</u>=CH), 7.10—7.40 (10H, m, Ph), and 8.22 (1H, dd, J=7.5 and 1.5 Hz, CH=N). **1k**: Colorless prisms (hexane); mp 68—70 °C; IR (KBr) 2230 and 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.07 (3H, s, Me), 5.55 (1H, s, CH), 6.80 (1H, br s, CH=), 7.10—7.40 (10H, m, Ph), and 8.14 (1H, s, CH=N); MS m/z 260 (M^+). Found: C, 82.85; H, 6.24; N, 10.78%. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76%. **1l**: IR (neat) 2190 and 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.95, 2.05 (each 3H, s, Me), 5.26 (1H, s, CH), and 7.10—7.50 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=19.65, 54.36, 119.19, 127.48, 129.24, 135.95, and 174.77. **1m**: ^{1}H NMR ($CDCl_3$) δ=1.70—2.30 (8H, m, CH_2), 4.89 (1H, s, CH), and 7.10—7.50 (5H, m, Ph). **1n**: ^{1}H NMR ($CDCl_3$) δ=1.50—2.50 (10H, m, CH_2), 5.43 (1H, s, CH), and 7.10—7.50 (5H, m, Ph). **1o**: ^{1}H NMR ($CDCl_3$) δ= 1.05 (3H, t, Et), 2.10 (3H, s, Me), 2.34 (2H, m, Et), 4.76 (1H, s, CH), and 7.10—7.50 (5H, m, Ph).

The deuterio derivatives **1a**-d_1 and **1e**-d_1 were similarly

prepared from the reactions with benzaldehyde-d_1 which was synthesized from phenylglyoxlic acid.[30]

General Procedure for the Cycloadditions of 1 with 2. The reactions of **1** with **2** were performed according to the following general procedure unless otherwise stated: A mixture of each equimolar amounts of **1** and **2** in a solvent (10—15 ml for 1 mmol of **1** or **2**) was allowed to react until either of the starting materials was all consumed (checked on TLC). The solvents and reaction conditions are listed in Tables 1 and 2. After the solvent was evaporated to dryness in vacuo, the residue was subjected to a ^{1}H NMR measurement to know the purity of products and then chromatographed over silica gel using chloroform, chloroform–diethyl ether, or chloroform–ethyl acetate (10—20:1 v/v). When a reaction was carried out in the presence of catalyst, the crude reaction mixture was first poured into water and extracted with chloroform or dichloromethane. The extract was washed with aqueous sodium hydrogencarbonate and water, dried over anhydrous magnesium sulfate, and evaporated in vacuo.

Reaction of 1a with 2a Leading to 6 and/or 10. The results are given in Table 1 (entries 1 to 5). **6**: Colorless prisms (benzene–hexane); mp 152—153 °C; IR (KBr) 3300, 2220, and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.40 (1H, br, NH), 2.85 (3H, s, NMe), 3.45 (1H, t, J_{6a-3a}=J_{6a-6}=8.0 Hz, 6a-H), 3.54 (1H, d, J_{3a-6a}=8.0 Hz, 3a-H), 4.66 (1H, s, 4-H), 4.78 (1H, d, J_{6-6a}=8.0 Hz, 6-H), and 7.18—7.38 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.14 (q, NMe), 47.66, 49.51, 49.85 (each d, 3a-, 4-, and 6a-C), 63.26 (d, 6-C), 118.66 (s, CN), 126.99, 128.45, 128.55, 136.00 (s), 174.01, and 175.24 (each s, CON); MS *m/z* (rel. intensity, %) 255 (M^+, 29), 144 (76), 143 (base peak), and 77 (49).

Found: C, 66.04; H, 5.13; N, 16.24%. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46%.

10: Colorless prisms (acetone–hexane); mp 199—200 °C; IR (KBr) 3300, 2250, and 1690 cm^{-1}: ^{1}H NMR (DMSO-d_6) δ=2.50 (1H, br, NH), 2.72 (3H, s, NMe), 3.42 (1H, t, J_{6a-3a}=J_{6a-6}=7.5 Hz, 6a-H), 3.56 (1H, t, J_{3a-4}=J_{3a-6a}=7.5 Hz, 3a-H), 4.22 (1H, d, J_{4-3a}=7.5 Hz, 4-H), 4.32 (1H, d, J_{6-6a}=7.5 Hz, 6-H), and 7.16—7.32 (5H, m, Ph); ^{13}C NMR (DMSO-d_6) δ=24.46 (q, NMe), 46.59, 47.85, 48.58 (each d, 3a-, 4-, and 6a-C), 62.91 (d, 6-C), 117.44 (s, CN), 127.09, 127.62, 137.62 (s), 174.40, and 174.99 (each s, CON); MS *m/z* (rel. intensity, %) 255 (M^+, 13), 228 (33), 144 (70), 143 (base peak), 117 (70), 115 (72), 90 (50), 89 (56), and 77 (39).

Found: C, 65.71; H, 5.09; N, 16.11%. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46%.

Reaction of 1a with 2b Leading to 7. The results are given in Table 1 (Entries 6 and 7): Colorless needles (benzene–hexane); mp 148—149 °C; IR (KBr) 3350, 2230, and 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.53 (1H, br, NH), 3.64 (1H, t, J_{6a-3a}=J_{6a-6}=8.0 Hz, 6a-H), 3.76 (1H, d, J_{3a-6a}=8.0 Hz, 3a-H), 4.80 (1H, s, 4-H), 4.96 (1H, d, J_{6-6a}=8.0 Hz, 6-H), 7.22—7.40 (7H, m, Ar), and 8.10—8.30 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=47.56, 49.90, 50.20 (each d, 3a-, 4-, and 6a-C), 63.64 (d, 6-C), 118.13 (s, CN), 124.35, 126.28, 126.93, 128.75, 129.05, 135.39 (s), 136.62, 146.89 (each s), 172.20, and 173.43 (each s, CON); MS *m/z* (rel. intensity, %) 362 (M^+, 6), 143 (53), 117 (47), 115 (51), 90 (base peak), and 89 (53).

Found: C, 63.26; H, 3.91; N, 15.27%. Calcd for $C_{19}H_{14}N_4O_4$: C, 62.98; H, 3.89; N, 15.46%.

Reaction of 1b with 2a Leading to 8. A mixture of cyanomethylamine (162 mg, 2.89 mmol) and phenylglyoxal (440 mg, 2.89 mmol) in chloroform (30 ml) was heated under reflux for 10 min. After **2a** (321 mg, 2.89 mmol) was added, the mixture was allowed to react under the conditions shown in Table 2 to give **8**: Colorless prisms (benzene); mp 210—211 °C; IR (KBr) 3310, 2240, 1780, and 1700 cm^{-1}; ^{1}H NMR (CD_3CN) δ=2.71 (3H, s, NMe), 3.32 (1H, m, NH), 3.65 (1H, dd, J_{3a-4}=1.4 and J_{3a-6a}=7.7 Hz, 3a-H), 3.91 (1H, t, J_{6a-3a}=J_{6a-6}=7.7 Hz, 6a-H), 4.66 (1H, dd, J_{4-3a}=1.4 and J_{4-NH}=5.2 Hz, 4-H), 5.03 (1H, dd, J_{6-6a}=7.7 and J_{6-NH}=9.0 Hz, 6-H), 7.30—7.70 (3H, m, Ph), and 7.85—8.06 (2H, m, Ph); ^{13}C NMR (DMSO-d_6) δ=24.94 (q, NMe), 49.42, 50.18, 51.66 (each d, 3a-, 4-, and 6a-C), 64.59 (d, 6-C), 119.95 (s, CN), 128.42, 128.95, 133.77 (each d), 136.07 (s), 175.54 (2×C, s, CON), and 195.31 (s, PhCO); MS *m/z* (rel. intensity, %) 283 (M^+, 1), 178 (base peak), 106 (68), 93 (38), and 77 (25).

Found: C, 63.58; H, 4.67; N, 14.64%. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83%.

Reaction of 1c with 2a Leading to 9 and 11. A mixture of cyanomethylamine (112 mg, 2 mmol) and cinnamaldehyde (264 mg, 2 mmol) in chloroform (20 ml) was heated under reflux for 1.5 h on molecular sieves 4A. The molecular sieves was filtered off and the chloroform was evaporated in vacuo. To the residue were added dry toluene (20 ml) and **2a** (222 mg, 2 mmol). The mixture was allowed to react under the conditions shown in Table 2 to give a mixture of **9** and **11**. **9**: Colorless needles (acetone–hexane); mp 175—176 °C; IR (KBr) 3450, 3320, 2220, 1765, and 1690 cm^{-1}; ^{1}H NMR (CD_3CN) δ=2.86 (3H, s, NMe), 3.44 (1H, t, J_{6a-3a}=J_{6a-6}=8.0 Hz, 6a-H), 3.60 (1H, d, J_{3a-6a}=8.0 Hz, 3a-H), 4.22 (1H, dd, J_{6-6a}=8.0 and $J_{6\text{-}CH=}$=7.2 Hz, 6-H), 4.51 (1H, s, 4-H), 6.10 (1H, dd, $J_{=CH\text{-}6}$=7.2 and J_{trans}=16.0 Hz, PhCH=C<u>H</u>), 6.66 (1H, d, J_{trans}=16.0 Hz, PhC<u>H</u>=CH), and 7.20—7.50 (5H, m, Ph); MS *m/z* (rel. intensity, %) 281 (M^+, 83), 170 (base peak), and 169 (74).

Found: C, 68.50; H, 5.44; N, 14.78%. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94%.

11: Colorless prisms (acetone–hexane); mp 209—210 °C; IR (KBr) 3450, 3310, 2230, 1765, and 1690 cm^{-1}; ^{1}H NMR (CD_3CN) δ=2.88 (3H, s, NMe), 3.30 (1H, t, J_{6a-3a}=J_{6a-6}=7.5 Hz, 6a-H), 3.49 (1H, t, J_{3a-4}=J_{3a-6a}=7.5 Hz, 3a-H), 3.89 (1H, dd, J_{6-6a}=7.5 and $J_{6\text{-}CH=}$=7.1 Hz, 6-H), 4.14 (1H, d, J_{4-3a}=7.5 Hz, 4-H), 6.14 (1H, dd, $J_{=CH\text{-}6}$=7.1 and J_{trans}=16.0 Hz, PhCH=C<u>H</u>), 6.60 (1H, d, J_{trans}=16.0 Hz, PhC<u>H</u>=CH), and 7.20—7.50 (5H, m, Ph); MS *m/z* (rel. intensity, %) 281 (M^+, 40), 254 (46), 170 (45), 169 (68), 168 (38), 143 (54), 115 (base peak), and 77 (35).

Found: C, 68.07; H, 5.31; N, 15.16%. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94%.

Reaction of 1d with 2a Leading to 12 and 13. A mixture of cyanomethylamine (153 mg, 2.73 mmol) and cyclohexanone (276 mg, 2.73 mmol) in dry chloroform (30 ml) was heated under reflux for 5 h. The solvent was removed by evaporation in vacuo. To the residue were added dry toluene (30 ml) and **2a** (303 mg, 2.73 mmol). The mixture was allowed to react under the conditions shown in Table 2 and chromatographed over silica gel. An elution with chloroform–diethyl ether (20:1) gave **13** (285 mg, 50%) and the followed fraction with chloroform–diethyl ether (10:1) afforded **12** (101 mg, 15%). The same reaction in the presence of acetic acid gave only **13** (70—72%).

12: Colorless prisms (benzene–hexane); mp 158—159 °C; IR (KBr) 3330, 2920, 2840, 2240, 1770, and 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20—2.20 (10H, m, CH_2), 2.50 (1H, br,

NH), 2.94 (1H, d, J_{6a-3a}=7.8 Hz, 6a-H), 3.00 (3H, s, NMe), 3.50 (1H, t, $J_{3a-4}=J_{3a-6a}$=7.8 Hz, 3a-H), and 4.28 (1H, d, J_{4-3a}=7.8 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ=22.59, 23.00 (each t, CH_2) 25.24 (2×C, t and q, CH_2 and NMe), 34.47, 36.00 (each t, CH_2), 47.06, 47.94, 53.59 (each d, 3a-, 4-, and 6a-C), 64.65 (s, 6-C), 117.59 (s, CN), 174.95, and 175.48 (each s, CON); MS *m/z* (rel. intensity, %) 247 (M^+, 20), 204 (base peak), 191 (28), and 119 (38).

Found: C, 62.99; H, 6.94; N, 16.92%. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99%.

13: Colorless needles (benzene-hexane); mp 122—123 °C; IR (KBr) 2900, 2830, and 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.40—2.84 (12H, m, CH_2 and CH), and 3.00 (3H, s, NMe); ^{13}C NMR ($CDCl_3$) δ=24.94 (q, NMe), 24.77, 27.06, 31.83, 31.94 (each t, CH_2), 41.18 (d, CH), 41.77 (t, CH_2), 50.36 (d, CH), 177.01, 179.54 (each s, CON), and 210.54 (s, CO); MS *m/z* (rel. intensity, %) 209 (M^+, 35), 113 (base peak), and 97 (88).

Found: C, 63.27; H, 7.26; N, 6.82%. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69%.

Reaction of 1f with 2a Leading to 14 and/or 15. A mixture of α-cyanobenzylamine (563 mg, 3.7 mmol) and phenylglyoxal (489 mg, 3.7 mmol) in dry chloroform (30 ml) was heated under reflux for 5 min and **2a** (411 mg, 3.7 mmol) was added. The mixture was refluxed for 5 min and the solvent was evaporated in vacuo to give **14** (1.328 g, 100%). Continued heating for 1 h afforded a mixture of **14** and **15** (1:1). The latter **15** was obtained in a quantitative yield when **14** was chromatographed over silica gel with chloroform–diethyl ether (3:1).

14: Colorless prisms; mp 157—158 °C; IR (KBr) 3350, 1780, 1710, and 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=2.70 (3H, s, NMe), 4.16 (1H, dd, J_{6a-3a}=9.0 and J_{6a-6}=10.0 Hz, 6a-H), 4.96 (1H, d, J_{3a-6a}=9.0 Hz, 3a-H), 6.20 (1H, br, NH), 6.36 (1H, d, J_{6-6a}=10.0 Hz, 6-H), and 7.20—8.10 (10H, m, Ph); MS *m/z* (rel. intensity, %) 332 (M^+—HCN, 10), 142 (22), 115 (65), and 105 (base peak).

Found: C, 70.14; H, 4.82; N, 11.58%. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69%.

15: Pale yellow prisms (acetone-hexane); mp 285—286 °C; IR (KBr) 1740 and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.88 (3H, s, NMe), 4.30 (1H, dd, J_{3a-3}=2.6 and J_{3a-6a}=8.5 Hz, 3a-H), 4.66 (1H, dd, J_{6a-3}=2.9 and J_{6a-3a}=8.5 Hz, 6a-H), 6.02 (1H, dd, J_{3-3a}=2.6 and J_{3-6a}=2.9 Hz, 3-H), and 7.20—8.30 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.25 (q, NMe), 45.79 (d, 3a-C), 56.60 (d, 6a-C), 79.55 (d, 3-C), 128.28, 128.63, 129.57, 131.45, 131.69, 133.86, 134.74, 167.44 (s, 1-C), 173.01, 177.54 (each s, CON), and 193.62 (s, PhCO); MS *m/z* (rel. intensity, %) 331 (M^+—H, 8), 330 (33), 140 (29), 113 (24), 105 (40), and 77 (base peak).

Found: C, 72.48; H, 4.30; N, 8.63%. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%.

Reaction of 1e with 2a Leading to 16, 18 and/or 20, 22. Under the conditions shown in Table 2, a mixture of **16**, **18** and/or **20**, **22** was obtained. **16**: Colorless prisms (benzene); mp 178—179 °C; IR (KBr) 1780, 1700, and 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.60 (3H, s, NMe), 3.94 (1H, dd, J_{3a-3}=10.0 and J_{3a-6a}=9.0 Hz, 3a-H), 4.60 (1H, dd, J_{6a-3a}=9.0 Hz, 6a-H), 5.85 (1H, d, J_{3-3a}=10.0 Hz, 3-H), 6.96—7.50 (8H, m, Ph), and 8.10 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.72 (q, NMe), 49.49 (d, 3a-C), 56.71 (d, 6a-C), 77.20 (d, 3-C), 127.11, 128.16, 128.34, 128.46, 129.57, 131.63, 131.86, 137.09, 144.59, 144.84, 167.26 (s, 1-C), 173.01, and 174.14 (each s, CON); MS *m/z* (rel. intensity, %) 306 (M^+, 5), 304 (base peak), 219 (23), and 115 (48).

Found: C, 74.10; H, 5.83; N, 9.27%. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15%.

18: Colorless prisms (benzene-hexane); mp 162—163 °C; IR (KBr) 1775, 1700, and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.95 (3H, s, NMe), 3.56 (1H, dd, J_{3a-3}=3.0 and J_{3a-6a}=8.5 Hz, 3a-H), 4.66 (1H, dd, J_{6a-3}=2.5 and J_{6a-3a}=8.5 Hz, 6a-H), 5.65 (1H, dd, J_{3-3a}=3.0 and J_{3-6a}=2.5 Hz, 3-H), 7.28—7.50 (8H, m, Ph), and 8.20 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.19 (q, NMe), 53.48 (d, 3a-C), 56.40 (d, 6a-C), 75.74 (d, 3-C), 126.17, 127.64, 128.40, 128.81, 129.57, 131.57, 131.75, 142.02, 166.32 (d, 1-C), 172.90, and 177.00 (each s, CON); MS *m/z* (rel. intensity, %) 306 (M^+, 4), 304 (base peak), 219 (15), and 115 (23).

Found: C, 74.66; H, 5.92; N, 9.22%. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15%.

20: Colorless prisms (benzene-hexane); mp 136—137 °C; IR (KBr) 2140, 1775, 1700, and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.68 (2H, d, J=7.0 Hz, CH_2), 2.82 (3H, s, NMe), 3.57 (1H, t, J=7.0 Hz, CH), 7.10—7.55 (8H, m, Ph), 7.80 (2H, m, Ph), and 8.53 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$) δ=24.83 (q, NMe), 31.47 (t, CH_2), 50.24 (d, CH), 71.12 (s, q-C), 117.07 (s, CN), 126.18, 126.71, 129.13, 129.36, 129.66, 132.54, 134.60, 136.59, 163.13 (d, CH=N), 174.01, and 174.66 (each s, CON); MS *m/z* 333 (M^+, 15), 228 (base peak), and 115 (16).

Found: C, 72.03; H, 5.78; N, 12.68%. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.61%.

22: Colorless viscous oil; IR (neat) 2210, 1775, 1700, and 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.70 (2H, d, J=6.5 Hz, CH_2), 2.84 (3H, s, NMe), 3.46 (1H, q, J=6.5 Hz, CH), 5.43 (1H, d, J=6.5 Hz, CH), 7.20—7.55 (8H, m, Ph), and 8.00 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.71 (q, NMe), 31.24 (t, CH_2), 46.47 (d, CH), 71.65 (d, CH), 109.71 (s, CN), 126.72, 127.24, 127.83, 128.18, 128.95, 129.19, 133.01, 133.24, 137.83, 142.60 (s, C=N), 175.89, and 176.83 (each s, CON); MS *m/z* 333 (M^+, 10), 220 (18), 219 (base peak), 115 (27), and 105 (50).

Found: C, 71.84; H, 5.71; N, 12.64%. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.61%.

Reaction of 1e with 2b Leading to 17, 19 and/or 21, 23. The result is given in Table 2. **17**: Colorless needles (benzene-hexane); mp 265—266 °C; IR (KBr) 1780, 1720, and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.20 (1H, t, $J_{3a-6a}=J_{3a-3}$=9.0 Hz, 3a-H), 4.90 (1H, d, J_{6a-3a}=9.0 Hz, 6a-H), 6.15 (1H, d, J_{3-3a}= 9.0 Hz, 3a-H), and 6.90—8.40 (14H, m, Ar); MS *m/z* (rel. intensity, %) 411 (M^+, 77), 219 (31), 193 (base peak), and 115 (39).

Found: C, 70.16; H, 4.35; N, 10.15%. Calcd for $C_{24}H_{17}N_3O_4$: C, 70.06; H, 4.17; N, 10.21%.

19: Colorless prisms (benzene-hexane); mp 239—241 °C; IR (KBr) 1780, 1720, and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 3.85 (1H, dd, J_{3a-3}=3.0 and J_{3a-6a}=9.0 Hz, 3a-H), 4.95 (1H, dd, J_{6a-3}=3.0 and J_{6a-3a}=9.0 Hz, 6a-H), 5.90 (1H, t, $J_{3-3a}=J_{3-6a}$=3.0 Hz, 3-H), and 7.30—8.45 (14H, m, Ar); MS *m/z* (rel. intensity, %) 411 (M^+, 51), 219 (36), 193 (base peak), and 115 (46).

Found: C, 69.87; H, 4.03; N, 10.17%. Calcd for $C_{24}H_{17}N_3O_4$: C, 70.06; H, 4.17; N, 10.21%.

21: Colorless prisms (benzene-hexane); mp 250—252 °C; IR (KBr) 2250, 1780, 1720, and 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.90 (2H, m, CH_2), 4.35 (1H, m, CH), 7.30—8.30 (14H, m, Ar), and 8.80 (1H, s, CH=N); MS *m/z* (rel. intensity, %) 438 (M^+, 14), 220 (18), 219 (base peak), and 115 (15).

Found: C, 68.27; H, 4.25; N, 12.50%. Calcd for $C_{25}H_{18}N_4O_4$:

C, 68.48; H, 4.14; N, 12.78%.

23: Colorless prisms (benzene-hexane); mp 195—196 °C; IR (KBr) 2240, 1775, 1710, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.91 (1H, dd, J_{gem}=18.0 and J=9.0 Hz, one of CH_2), 3.10 (1H, dd, J_{gem}=18.0 and J=6.0 Hz, the other of CH_2), 3.63 (1H, ddd, J=9.0, 7.0, and 6.0 Hz, CH), 5.53 (1H, d, J=7.0 Hz, CH), and 7.22—8.32 (14H, m, Ar); MS *m/z* (rel. intensity, %) 438 (M^+, 13), 220 (21), 219 (base peak), and 115 (21).

Found: C, 68.12; H, 4.23; N, 12.49%. Calcd for $C_{25}H_{18}N_4O_4$: C, 68.48; H, 4.14; N, 12.78%.

Reaction of 1g with 2a Leading to 24. A mixture of propionaldehyde (300 mg, 5.17 mmol) and α-cyanobenzylamine (230 mg, 1.74 mmol) in dry chloroform was heated under reflux for 4 h. After the solvent and the excess aldehyde were removed by evaporation in vacuo, toluene (20 ml) and **2a** (215 mg, 1.94 mmol) were added to the residue. The mixture was allowed to react under the conditions given in Table 2 to give **24**: Colorless prisms (ethyl ether-hexane); mp 91—92 °C; IR (KBr) 2930, 1760, 1690, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16 (3H, t, Et), 1.20—1.32, 1.90—2.25 (each 1H, m, Et), 2.88 (3H, s, NMe), 3.66 (1H, t, J_{3a-3}=J_{3a-6a}=9.5 Hz, 3a-H), 4.32—4.64 (2H, m, 3- and 6a-H), 7.30—7.52 (3H, m, Ph), and 7.96—8.20 (2H, m, PH); ^{13}C NMR ($CDCl_3$) δ=12.12 (q, Et), 24.94 (q, NMe), 25.94 (t, Et), 47.18 (d, 3a-C), 56.89 (d, 6a-C), 75.18 (d, 3-C), 128.48, 129.48, 131.30, 132.48 (each d), 164.72 (s, 1-C), 173.54, and 175.95 (each s, CON); MS *m/z* 256 (M^+, 22), 228 (42), 170 (30), 145 (44), 144 (23), 143 (25), 142 (59), 130 (base peak), 115 (80), 104 (67), and 77 (30).

Found: C, 70.11; H, 6.27; N, 10.78%. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%.

Reaction of 1h with 2a Leading to 25. A mixture of 3-cyclohexene-1-carbaldehyde (128 mg, 1.16 mmol) and α-cyanobenzylamine (119 mg, 0.902 mmol) was heated under reflux in dry chloroform (10 ml) for 2 h. The solvent was evaporated in vacuo. To the residue were added dry toluene (10 ml) and **2a** (111 mg, 1 mmol). The mixture was allowed to react under the conditions shown in Table 2 giving **25** as mixture of threo and erythro isomers (1:1): Colorless prisms (benzene-hexane); mp 167—168 °C; IR (KBr) 2980, 2860, 1750, 1670, and 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24—2.62 (7H, m, CH_2 and CH), 2.90 (3H, s, NMe), 3.68, 3.74 (each 0.5H, t, J_{3a-3}=J_{3a-6a}=9.0 Hz, 3a-H), 4.28—4.66 (2H, m, 3- and 6a-H), 5.70 (2H, m, CH=CH), 7.30—7.52 (3H, m, Ph), and 7.96—8.20 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.00 (q, NMe), 25.41, 25.41, 28.76, 31.18, 35.18, 36.18 (CH_2 and CH), 46.30, 46.53 (each d, 3a-C), 56.83 (d, 6a-C), 77.30, 78.59 (each d, 3-C), 126.30, 127.19, 128.42, 131.30 (each d), 132.42 (s), 165.07 (s, 1-C), 173.36, 175.89, and 176.18 (each s, CON); MS *m/z* (rel. intensity, %) 308 (M^+, 18), 228 (71), 200 (33), 170 (25), 143 (base peak), 142 (40), 116 (21), 115 (75), 104 (26), 91 (32), 80 (21), 79 (40), and 77 (51).

Found: C, 74.22; H, 6.52; N, 8.95%. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08%.

Reaction of 1i with 2a Leading to 26 and 29. The result is given in Table 2: **26**: Colorless prisms (benzene-hexane); mp 108—109 °C; IR (KBr) 1775, 1690, and 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.68 (3H, d, J=7.0 Hz, Me), 2.85 (3H, s, NMe), 3.67 (1H, t, J_{3a-3}=J_{3a-6}=9.0 Hz, 3a-H), 4.46 (1H, d, J_{6a-3a}=9.0 Hz, 6a-H), 5.15 (1H, dd, J_{3-3a}=9.0 and $J_{3\text{-}CH=}$=6.0 Hz, 3-H), 5.40—5.85 (2H, m, MeC<u>H</u>=C<u>H</u>), 7.35 (3H, m, Ph), and 8.05 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.94 (q, Me), 25.00 (q, NMe), 48.47 (d, 3a-C), 56.71 (d, 6a-C), 74.48 (d, 3-C), 127.36, 128.65, 129.71, 129.89, 131.71, 132.18, 137.42, 166.30 (s, 1-C), 173.48, and 175.36 (each s, CON); MS *m/z* (rel. intensity, %) 268 (M^+, 20), 210 (11), 182 (22), and 115 (base peak).

Found: C, 71.39; H, 5.88; N, 10.22%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

29: Colorless prisms (hexane); mp 150—151 °C; IR (KBr) 1770, 1700, and 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.70 (3H, d, Me), 2.90 (3H, s, NMe), 3.36 (1H, dd, J_{3a-3}=4.0 and J_{3a-6a}=8.0 Hz, 3a-H), 4.57 (1H, dd, J_{6a-3}=2.0 and J_{6a-3a}=8.0 Hz, 6a-H), 5.00 (1H, m, 3-H), 5.25—5.93 (2H, m, MeC<u>H</u>=C<u>H</u>), 7.35 (3H, m, Ph), and 8.05 (1H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.77 (q, Me), 25.14 (q, NMe), 51.12 (d, 3a-C), 56.05 (d, 6a-C), 76.56 (d, 6-C), 114.55, 126.41, 128.56, 129.05, 129.59, 131.25, 131.64, 132.08, 165.87 (s, 1-C), 173.44, and 177.39 (each s, CON); MS *m/z* (rel. intensity, %) 268 (M^+, 21), 193 (base peak), 115 (30), and 105 (21).

Found: C, 71.54; H, 6.06; N, 10.27%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

Reaction of 1j with 2a Leading to 27 and 30. A mixture of cinnamaldehyde (264 mg, 2 mmol) and α-cyanobenzylamine (264 mg, 2 mmol) in toluene (10 ml) was heated at 60 °C for 5 min and then **2a** (222 mg, 2 mmol) was added. The mixture was allowed to react under the conditions given in Table 2.

27: Colorless needles (benzene-hexane); mp 153—154 °C; IR (KBr) 1780, 1700, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.85 (3H, s, NMe), 3.88 (1H, dd, J_{3a-3}=9.0 and J_{3a-6a}=8.0 Hz, 3a-H), 4.64 (1H, d, J_{6a-3a}=8.0 Hz, 6a-H), 5.42 (1H, dd, J_{3-3a}=9.0 and $J_{3\text{-}CH=}$=6.0 Hz, 3-H), 6.30 (1H, dd, J=6.0 and J_{trans}=18.0 Hz, PhCH=C<u>H</u>), 6.60 (1H, d, J_{trans}=18.0 Hz, PhC<u>H</u>=CH), 7.20—7.54 (8H, m, Ph), and 8.20 (2H, m, Ph); MS *m/z* (rel. intensity, %) 330 (M^+, 53), 245 (23), 219 (23), and 115 (base peak).

Found: C, 76.36; H, 5.47; N, 8.41%. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48%.

30: Colorless prisms (benzene-hexane); mp 145—146 °C; IR (KBr) 1770 and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.95 (3H, s, NMe), 3.50 (1H, dd, J_{3a-3}=3.2 and J_{3a-6a}=8.3 Hz, 3a-H), 4.68 (1H, dd, J_{6a-3}=2.5 and J_{6a-3a}=8.3 Hz, 6a-H), 5.26 (1H, ddd, J_{3-3a}=3.2, J_{3-6a}=2.5, and $J_{3\text{-}CH=}$=6.0 Hz, 3-H), 6.26 (1H, dd, J=6.0 and J_{trans}=16.0 Hz, PhCH=C<u>H</u>), 6.68 (1H, d, J_{trans}=16.0 Hz, PhC<u>H</u>=CH), 7.20—7.50 (8H, m, Ph), and 8.18 (2H, m, Ph); MS *m/z* (rel. intensity, %) 330 (M^+, base peak), 245 (29), 219 (27), and 115 (96).

Found: C, 76.61; H, 5.58; N, 8.41%. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48%.

Reaction of 1k with 2a Leading to 28. The result is shown in Table 2: Colorless prisms (benzene-hexane); mp 149—150 °C; IR (KBr) 1770, 1690, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.92 (3H, d, J=1.0 Hz, Me), 2.74 (3H, s, NMe), 3.72 (1H, t, J_{3a-3}=J_{3a-6a}=9.0 Hz, 3a-H), 4.42 (1H, d, J_{6a-3a}=9.0 Hz, 6a-H), 5.13 (1H, d, J_{3-3a}=9.0 Hz, 3-H), 6.13 (1H, br, PhC<u>H</u>=), 6.90—7.40 (8H, m, Ph), and 8.07 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=18.24 (q, Me), 25.00 (q, NMe), 48.18 (d, 3a-C), 56.77 (d, 6a-C), 79.47 (d, 3-C), 126.83, 127.71, 128.30, 128.65, 129.13, 129.77, 131.83, 132.12, 136.18, 136.48, 167.07 (s, 1-C), 173.30, and 175.07 (each s, CON); MS *m/z* (rel. intensity, %) 344 (M^+, 31), 233 (33), and 115 (base peak).

Found: C, 76.92; H, 5.92; N, 8.10%. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13%.

Reaction of 1l with 2a Leading to 31. A mixture of α-cyanobenzylamine (240 mg, 1.82 mmol) and acetone (20 ml) was heated under reflux for 30 min. The acetone was evaporated in vacuo and **2a** (222 mg, 2 mmol) was added to the residue. The mixture was allowed to react under the conditions shown in Table 2 to give **31**: Colorless prisms

(benzene-hexane); mp 176—177 °C; IR (KBr) 2940, 1750, 1690, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33, 1.46 (each 3H, s, Me), 2.85 (3H, s, NMe), 3.25 (1H, d, J_{3a-6a}=8.5 Hz, 3a-H), 4.55 (1H, d, J_{6a-3a}=8.5 Hz, 6a-H), 7.20—7.50 (3H, m, Ph), and 7.90—8.20 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.94 (q, NMe), 25.47, 32.12 (each q, Me), 53.89 (d, 3a-C), 57.18 (d, 6a-C), 75.30 (s, 3-C), 128.48, 129.48, 131.30 (each d), 132.36 (s), 162.37 (s, 1-C), 173.43, and 176.01 (each s, CON); MS *m/z* (rel. intensity, %) 256 (M^+, 47), 255 (23), 170 (25), 156 (30), 145 (89), 115 (37), 104 (base peak), 103 (25), 96 (20), and 77 (30).

Found: C, 70.50; H, 6.35; N, 10.61%. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%.

Reaction of 1m with 2a Leading to 32. A mixture of cyclopentanone (175 mg, 2.08 mmol) and α-cyanobenzylamine (238 mg, 1.80 mmol) in dry chloroform (20 ml) was heated under reflux for 4 h. The solvent was evaporated in vacuo and **2a** (222 mg, 2 mmol) in dry toluene (20 ml) was added to the residue. The mixture was allowed to react under the conditions shown in Table 2 giving **32**: Colorless prisms (benzene-hexane); mp 148—149 °C; IR (KBr) 2930, 1750, 1680, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.56—3.20 (8H, m, CH_2), 2.91 (3H, s, NMe), 3.38 (1H, d, J_{3a-6a}=8.7 Hz, 3a-H), 4.60 (1H, d, J_{6a-3a}=8.7 Hz, 6a-H), 7.24—7.50 (3H, m, Ph), and 7.92—8.16 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=23.65, 24.24 (each t, CH_2), 24.95 (q, NMe), 35.24, 43.24 (each t, CH_2), 52.65 (d, 3a-C), 56.89 (d, 6a-C), 85.42 (s, 3-C), 128.42, 129.42, 131.13 (each d), 132.60 (s), 162.01 (s, 1-C), 173.54, and 176.18 (each s, CON); MS *m/z* (rel. intensity, %) 282 (M^+, base peak) 281 (36), 241 (23), 171 (35), 170 (24), and 104 (22).

Found: C, 72.58; H, 6.51; N, 9.89%. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92%.

Reaction of 1n with 2a Leading to 33. A mixture of cyclohexanone (100 mg, 1.02 mmol) and α-cyanobenzylamine (119 mg, 0.902 mmol) in dry chloroform was heated under reflux for 2.5 h. The solvent was removed through evaporation in vacuo and **2a** (111 mg, 1 mmol) in dry toluene (10 ml) was added to the residue. The mixture was allowed to react under the conditions shown in Table 2 affording **33**: Colorless prisms (benzene-hexane); mp 200—201 °C; IR (KBr) 2890, 1750, 1680, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.25—2.20 (10H, m, CH_2), 2.89 (3H, s, NMe), 3.24 (1H, d, J_{3a-6a}=8.5 Hz, 3a-H), 4.58 (1H, d, J_{6a-3a}=8.5 Hz, 6a-H), 7.25—7.50 (3H, m, Ph), and 8.00—8.20 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=23.18 (q, NMe), 22.88, 24.88, 25.77, 34.94, 41.83 (each t, CH_2), 54.47 (d, 3a-C), 56.30 (d, 6a-C), 78.24 (s, 3-C), 128.42, 129.54, 131.07 (each d), 132.83 (s), 161.77 (s, 1-C), 173.66, and 175.95 (each s, CON); MS *m/z* (rel. intensity, %) 296 (M^+, 40), 241 (20), 185 (36), 168 (24), 157 (20), 156 (82), 155 (240), 154 (23), 115 (base peak), and 104 (54).

Found: C, 73.13; H, 6.79; N, 9.36%. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45%.

Reaction of 1o with 2a Leading to 34. A mixture of 2-butanone (75 mg, 1.04 mmol) and α-cyanobenzylamine (119 mg, 0.902 mmol) in dry chloroform (10 ml) was heated under reflux for 2.5 h. The solvent was evaporated in vacuo and **2a** (111 mg, 1 mmol) in dry toluene (10 ml) was added to the residue. The mixture was allowed to react under the conditions shown in Table 2 giving **34** as mixture of two stereoisomers (1:1) whose separation through chromatography was unsuccessful: ^1H NMR ($CDCl_3$) δ=0.92 (2×3H, t, Et), 1.32, 1.44 (each 3H, s, Me), 1.55—2.10 (2×2H, m, Et), 2.86, 2.89 (each 3H, s, NMe), 3.26, 3.30 (each 1H, d, J_{3a-6a}= 9.0 Hz, 3a-H), 4.53, 4.61 (each 1H, d, J_{6a-3a}=9.0 Hz, 6a-H), 7.20—7.50 (2×3H, m, Ph), and 7.90—8.15 (2×2H, m, Ph).

General Procedure for the Elimination of HCN from the Maleimide Cycloadducts. The elimination reactions were performed under the conditions shown in Table 3. After the reactions were completed, the solvent was evaporated in vacuo and the residue was chromatographed over silica gel with hexane-ethyl acetate (9:1). The results are given in Table 3.

35: Obtained as mixture with the starting material **10** (**35**:**10**=6:4) which could not be removed through chromatography. ^1H NMR of **35** (in CD_3CN) δ=2.59 (3H, s, NMe), 3.69 (1H, dd, J_{3a-3}=10.0 and J_{3a-6a}=8.8 Hz, 3a-H), 4.19 (1H, dt, J_{6a-1}=J_{6a-3}=1.3 and J_{6a-3a}=8.8 Hz, 6a-H), 5.60 (1H, ddd, J_{3-1}=2.7, J_{3-3a}=10.0, and J_{3-6a}=1.3 Hz, 3-H), 6.85—7.10 (3H, m, Ph), 7.16—7.32 (2H, m, Ph), and 7.72 (1H, dd, J_{1-3}= 2.7 and J_{1-6a}=1.3 Hz, 1-H).

36: Colorless prisms (benzene-hexane); mp 153—154 °C; IR (KBr) 1700 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.99 (3H, s, NMe), 3.41 (1H, dd, J_{3a-3}=3.0 and J_{3a-6a}=8.5 Hz, 3a-H), 4.26 (1H, dd, J_{6a-3a}=8.5 and J_{6a-1}=2.0 Hz, 6a-H), 5.64 (1H, dd, J_{3-1}=5.5 and J_{3-3a}=3.0 Hz, 3-H), 7.16—7.50 (5H, m, Ph), and 7.78 (1H, br, 1-H); MS *m/z* (rel. intensity, %) 228 (M^+, 38), 143 (28), 117 (base peak), 115 (34), and 77 (17).

Found: C, 68.61; H, 5.40; N, 12.03%. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%.

37: Colorless prisms (benzene-hexane); mp 125—126 °C; IR (KBr) 1765, 1700, 1690, and 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.89 (3H, s, NMe), 3.64 (1H, dt, J_{3a-3}=6.0, 8.0 and J_{3a-6a}=8.0 Hz, 3a-H), 4.32—4.66 (3H, m, 1- and 6a-H), and 7.26—8.20 (5H, m, Ph); MS *m/z* (rel. intensity, %) 228 (M^+, 40), 117 (base peak), 115 (23), and 77 (13).

Found: C, 68.31; H, 5.38; N, 12.08%. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%.

38: Yellow prisms (benzene-hexane); mp 133—134 °C; IR (KBr) 1710 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.90 (1H, ddd, J_{3a-3}=6.0, 7.5 and J_{3a-6a}=9.0 Hz, 3a-H), 4.57 (2H, m, 3-H), 4.79 (1H, dt, J_{6a-3}=2.0 and J_{6a-3a}=9.0 Hz, 6a-H), 7.20—7.60 (5H, m, Ar), and 8.00—8.32 (4H, m, Ar); MS *m/z* (rel. intensity, %) 335 (M^+, 21), 117 (base peak), and 77 (25).

Found: C, 64.80; H, 4.42; N, 12.00%. Calcd for $C_{18}H_{13}N_3O_4$: C, 64.48; H, 3.91; N, 12.53%.

39: Colorless needles (hexane); mp 92—93 °C; IR (KBr) 2930, 2840, 1755, 1690, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20—2.20 (10H, m, CH_2), 2.90 (3H, s, NMe), 3.05 (1H, d, J_{3a-6a}=8.5 Hz, 3a-H), 4.14 (1H, dd, J_{6a-1}=1.0 and J_{6a-3a}=8.5 Hz, 6a-H), and 7.45 (1H, d, J_{1-6a}=1.0 Hz, 1-H); ^{13}C NMR ($CDCl_3$) δ=22.88, 23.00 (each t, CH_2), 24.94 (q, NMe), 25.47, 34.59, 41.24 (each t, CH_2), 51.77 (d, 3a-C), 58.71 (d), 90.36 (s, 3-C), 155.95 (d, 1-C), 173.54, and 175.83 (each s, CON); MS *m/z* (rel. intensity, %) 220 (M^+, 70), 113 (29), 109 (60), 108 (28), 81 (23), 66 (37), 58 (35), and 42 (base peak).

Found: C, 65.48; H, 7.35; N, 12.46%. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72%.

General Procedure for the Cycloadditions of 1 with 3 and 4. A mixture of each equimolar amounts of **1** and **3** (or **4**) in a solvent (10—15 ml for 1 mmol of **1**) was allowed to react until either of the starting materials was consumed (checked on TLC). After the solvent was evaporated in vacuo, the residue was subjected to a ^1H NMR measurement to know the purity of products and then chromatographed over silica gel using chloroform, chloroform-diethyl ether, or chloroform-ethyl acetate (10:1). The solvents, reaction conditions, and results are listed in Table 2.

Reaction of 1a with 3 Leading to 40 and 41. This reaction under reflux in toluene or at room temperature in acetonitrile in the presence of acetic acid gave **40** and **41** which were separated through column chromatography over silica gel with chloroform–diethyl ether (10:1). **40**: Colorless prisms (benzene–hexane); mp 123—124 °C; IR (KBr) 3320, 2980, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.44 (1H, br, NH), 3.09 (3H, s, 4-COOMe), 3.77 (1H, dd, J_{4-3}=8.6 and J_{4-5}=9.6 Hz, 4-H), 3.78 (3H, s, 3-COOMe), 4.02 (1H, dd, J_{3-2}=7.2 and J_{3-4}=8.6 Hz, 3-H), 4.68 (1H, d, J_{2-3}=7.2 Hz, 2-H), 4.88 (1H, d, J_{5-4}=9.6 Hz, 5-H), and 7.16—7.40 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=49.47, 49.59 (each d, 3- and 4-C), 50.36, 51.83 (each q, COOMe), 52.89 (d, 2-C), 63.06 (d, 5-C), 118.65 (s, CN), 127.77, 128.36 (each d), 138.42 (s), 169.72, and 171.36 (each s, COOMe); MS *m/z* (rel. intensity, %) 288 (M^+, 5), 177 (82), 169 (39), 144 (56), 143 (base peak), 119 (26), 117 (31), 116 (44), 115 (67), 104 (34), and 77 (36).

Found: C, 62.60; H, 5.67; N, 9.78%. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72%.

41: Colorless prisms (benzene–hexane); mp 97—97.5 °C; IR (KBr) 3290, 2200, and 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 2.50 (1H, br, NH), 3.18 (3H, s, 4-COOMe), 3.54 (1H, dd, J_{3-2}=8.4 and J_{3-4}=6.5 Hz, 3-H), 3.77 (3H, s, 3-COOMe), 3.90 (1H, dd, J_{4-3}=6.5 and J_{4-5}=9.6 Hz, 4-H), 4.30 (1H, d, J_{2-3}= 8.4 Hz, 2-H), 4.60 (1H, d, J_{5-4}=9.6 Hz, 5-H), and 7.20—7.36 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=49.65, 50.53 (each d, 3- and 4-C), 51.95, 52.42 (each q, COOMe), 53.06 (d, 2-C), 64.48 (d, 5-C), 119.12 (s, CN), 127.24, 128.48 (each d), 137.95 (s), 170.89, and 171.18 (each s, COOMe); MS *m/z* (rel. intensity, %) 288 (M^+, 4), 177 (81), 169 (29), 162 (21), 144 (base peak), 143 (90), and 115 (29).

Found: C, 62.48; H, 5.54; N, 9.65%. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.71%.

Reaction of 1a with 4 Leading to 42. The result is shown in Table 2: Colorless prisms (benzene–hexane); mp 120—122 °C; IR (KBr) 3300, 1720, and 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.08 (3H, s, 4-COOMe), 3.61 (3H, s, 3-COOMe), 4.12 (1H, dd, J_{4-5}=12.3 and J_{4-2}=1.0 Hz, 4-H), 4.84 (1H, br, NH), 5.30 (1H, dd, J_{5-1}=1.6 and J_{5-4}=12.3 Hz, 5-H), 7.20—7.36 (5H, m, Ph), and 7.46 (1H, dd, J_{2-1}=3.0 and J_{2-4}=1.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=50.48, 51.12 (each q, COOMe), 52.14 (d, 4-C), 66.08 (d, 5-C), 100.29 (s, 3-C), 127.14, 127.96 (each d), 137.66 (d), 150.62 (d, 2-C), 166.07, and 171.24 (each s, COOMe); MS *m/z* (rel. intensity, %) 261 (M^+, 35), 202 (base peak), 170 (45), 143 (50), 117 (21), and 115 (34).

Found: C, 64.38; H, 5.84; N, 5.57%. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36%.

Elimination of HCN from 40 and 41 Leading to 42 and 43. When **40** was heated under reflux in xylene, **42** was obtained. In the presence of a catalytic amount of DBU, **41** was converted into **43**. The reaction conditions and results are given in Table 3.

43: Colorless liquid; IR (neat) 3320, 1730, 1670, 1650, and 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.64, 3.74 (each 3H, s, COOMe), 3.80 (1H, br, NH), 3.82 (1H, dd, J_{4-5}=7.0 and J_{4-2}=1.0 Hz, 4-H), 5.11 (1H, d, J_{5-4}=7.0 Hz, 5-H), 7.10—7.40 (5H, m, Ph), and 7.45 (1H, d, J_{2-4}=1.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=50.77, 52.47 (each q, COOMe), 55.24 (d, 4-C), 67.65 (d, 5-C), 100.53 (s, 3-C), 126.07, 128.42, 129.13 (each d), 142.19 (s), 149.24 (d, 2-C), 166.19, and 174.60 (each s, COOMe); MS *m/z* (rel. intensity, %) 261 (M^+, 17), 202 (67), 201 (70), 170 (60), 158 (22), 143 (65), 142 (26), 131 (34), 117 (60), 116 (33), 115 (base peak), 104 (23), 103 (28), 90 (42), 89 (42), and 77 (39).

HRMS Found: *m/z* 261.0994. Calcd for $C_{14}H_{15}NO_4$: M, 261.1000.

Reaction of 1e with 3 Leading to 44, 46, and/or 47. The separation of these products was carried out as follows: Column chromatography of the mixture over silica gel with chloroform gave pure **44** and a mixture of **46** and **47**. This mixture was then subjected to HPLC (solvent: diethyl ether–hexane (7:3)), **46** and **47** being separated.

44: Colorless prisms (benzene–hexane); mp 131—133 °C; IR (KBr) 3350, 2230, and 1740 cm^{-1}; ^1H NMR (CD_3CN) δ=3.06 (3H, s, 4-COOMe), 3.56 (1H, br, NH), 3.62 (3H, s, 3-COOMe), 3.80—4.05 (2H, m, 3- and 4-H), 5.00 (1H, m, changed to dd (J=6.0 and 3.0 Hz) when treated with D_2O, 5-H), and 7.30—8.10 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ= 50.56 (d, 4-C), 51.72, 52.51 (each q, COOMe), 58.42 (d, 3-C), 62.13 (d, 5-C), 66.33 (s, 2-C), 119.20 (s, CN), 126.64, 127.80, 128.16, 128.34, 128.65, 129.38, 136.93 (s), 137.97 (s), 169.21, and 171.16 (each s, COOMe); MS *m/z* (rel. intensity, %) 337 (M^+—HCN, 43), 277 (base peak), and 115 (29).

Found: C, 69.21; H, 5.53; N, 7.69%. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.09; H, 5.62; N, 7.61%.

46: Colorless prisms (benzene–hexane); mp 138—140 °C; IR (KBr) 1740 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.50 (1H, t, J_{4-3}=J_{4-5}=8.0 Hz, 4-H), 3.60, 3.76 (each 3H, s, COOMe), 4.70 (1H, dd, J_{3-4}=8.0 and J_{3-5}=2.0 Hz, 3-H), 5.52 (1H, dd, J_{5-4}=8.0 and J_{5-3}=2.0 Hz, 5-H), 7.20—7.42 (8H, m, Ph), and 7.87 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=52.76 (2×C, q, COOMe), 56.30 (d, 4-C), 79.24 (d, 3-C), 127.13, 127.42, 127.90, 128.37, 128.83, 131.36, 133.01, 142.30, 168.54 (s, 2-C), 171.90, and 173.18 (each s, COOMe); MS *m/z* (rel. intensity, %) 337 (M^+, 19), 277 (base peak), and 115 (39).

Found: C, 71.12; H, 5.68; N, 4.21%. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%.

47: Colorless prisms (benzene–hexane); mp 106—107 °C; IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.14, 3.70 (each 3H, s, COOMe), 4.00 (1H, dd, J_{4-3}=5.0 and J_{4-5}=9.0 Hz, 4-H), 4.92 (1H, dd, J_{3-4}=5.0 and J_{3-5}=2.0 Hz, 3-H), 5.95 (1H, dd, J_{5-3}=2.0 and J_{5-4}=9.0 Hz, 5-H), and 7.20—8.20 (10H, m, Ph); MS *m/z* (rel. intensity, %) 337 (M^+, 48), 277 (99), 193 (base peak), and 115 (36).

Found: C, 71.20; H, 5.83; N, 4.08%. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%.

This compound **47** was also obtained from the reaction of **1e** with **4** (Table 2).

Reaction of 1f with 3 Leading to 45. The result is shown in Table 2: Colorless prisms (benzene–hexane); mp 96—97 °C; IR (KBr) 3300, 1730, and 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.72 (1H, br, NH), 3.26, 3.66 (each 3H, s, COOMe), 3.86 (1H, d, J_{3-4}=9.0 Hz, 3-H), 4.22 (1H, t, J_{4-3}=J_{4-5}=9.0 Hz, 4-H), 5.30 (1H, d, J_{5-4}=9.0 Hz, 5-H), and 7.30—8.04 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=50.06, 52.18 (each q, COOMe), 52.83 (d, 3-C), 59.42 (d, 4-C), 62.00 (d, 5-C), 67.95 (s, 2-C), 119.30 (s, CN), 126.42, 128.77, 129.01, 129.19, 129.71, 134.18, 135.24, 136.42, 168.95 (s, COOMe), 170.77 (s, COOMe), and 196.25 (s, PhCO); MS *m/z* (rel. intensity, %) 365 (M^+—HCN, 9), 105 (base peak), and 77 (36).

Found: C, 67.47; H, 5.16; N, 7.10%. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14%.

Reaction of 1j with 3 Leading to 48 and 50. A mixture of cinnamaldehyde (132 mg, 1 mmol) and α-cyanobenzylamine (132 mg, 1 mmol) in toluene (10 ml) was heated under reflux for 15 min. After **3** (144 mg, 1 mmol) was added, the mixture was allowed to react under the conditions shown in Table 2. Although **48** and **50** could not be separated each other through

column chromatography, **48** was identical with one of two products (**48** and **52**) formed in the reaction of **1e** with **4** (Table 2).

48: Viscous liquid; IR (neat) 1700, 1680, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.53, 3.60 (each 3H, s, COOMe), 3.75 (1H, dd, J_{4-3}=6.0 and J_{4-5}=9.0 Hz, 4-H), 4.72 (1H, dd, J_{3-4}=6.0 and J_{3-5}=2.0 Hz, 3-H), 5.30 (1H, ddd, J_{5-3}=2.0, J_{5-4}=9.0, and $J_{5\text{-}CH=}$=8.0 Hz, 5-H), 5.96 (1H, dd, J_{trans}=15.0 and J=8.0 Hz, PhCH=C<u>H</u>), 6.62 (1H, d, J_{trans}=15.0 Hz, PhC<u>H</u>=CH), 7.07—7.33 (8H, m, Ph), and 7.80 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=52.24 (2×C, q, COO<u>Me</u>), 52.89 (d, 4-C), 56.83 (d, 3-C), 75.89 (d, 5-C), 125.83, 126.78, 127.30, 128.01, 128.42, 128.77, 131.42, 132.96, 133.60, 136.83, 169.25 (s, <u>C</u>OOMe), and 171.42 (s, <u>C</u>OOMe); MS *m/z* (rel. intensity, %) 363 (M^+, 53), 304 (59), 272 (57), and 115 (base peak).

Found: C, 72.94; H, 5.64; N, 3.85%. Calcd for $C_{21}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85%.

50: Contaminated with **48**; ^1H NMR ($CDCl_3$) δ=3.36 (1H, t, J_{4-3}=J_{4-5}=6.0 Hz, 4-H), 3.60, 3.70 (each 3H, s, COOMe), 4.60 (1H, dd, J_{3-4}=6.0 and J_{3-5}=2.0 Hz, 3-H), and 5.06 (1H, dt, J_{5-3}=2.0 and J_{5-4}=$J_{5\text{-}CH=}$=6.0 Hz, 5-H); MS *m/z* 363 (M^+).

Found: C, 72.58; H, 5.79; N, 4.02%. Calcd for $C_{21}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85%.

52: Colorless prisms (hexane); mp 130—131 °C; IR (KBr) 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.30 (1H, t, J_{4-5}=J_{4-NH}=2.0 Hz, 4-H), 6.72 (1H, t, J_{5-4}=J_{5-NH}=2.0 Hz, 5-H), 7.04—7.30 (10H, m, Ph), and 8.00 (1H, br, NH); MS *m/z* 219 (M^+).

Found: C, 87.70; H, 6.20; N, 6.38%. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39%.

Reaction of 1k with 3 Leading to 49 and 51. This reaction under the conditions shown in Table 2 afforded a mixture of **49** and **51** which could not be separated each other through column chromatography. The isomer **49** was also obtained as a single product in the reaction of **1k** with **4** (Table 2).

49: Viscous liquid; IR (neat) 1730 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.82 (3H, d, J=1.5 Hz, Me), 3.53, 3.62 (each 3H, s, COOMe), 3.85 (1H, dd, J_{4-3}=5.0 and J_{4-5}=9.0 Hz, 4-H), 4.75 (1H, dd, J_{3-4}=5.0 and J_{3-5}=1.5 Hz, 3-H), 5.26 (1H, dd, J_{5-3}=1.5 and J_{5-4}=9.0 Hz, 5-H), 6.47 (1H, br s, CH=), 7.10—7.40 (8H, m, Ph), and 7.85 (2H, m, Ph); MS *m/z* (rel. intensity, %) 377 (M^+, 42), 318 (35), and 115 (base peak).

Found: C, 72.84; H, 6.02; N, 3.58%. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71%.

51: Contaminated with **49**; ^1H NMR ($CDCl_3$) δ=1.90 (3H, d, J=1.5 Hz, Me), 3.50 (1H, dd, J_{4-3}=6.0 and J_{4-5}=5.0 Hz, 4-H), 3.57, 3.72 (each 3H, s, COOMe), 4.62 (1H, dd, J_{3-4}= 6.0 and J_{3-5}=2.0 Hz, 3-H), 4.95 (1H, dd, J_{5-3}=2.0 and J_{5-4}= 5.0 Hz, 5-H), and 6.40 (1H, br s, =CH); MS *m/z* 377 (M^+).

Found: C, 73.27; H, 6.18; N, 3.74%. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71%.

Reaction of 1n with 3 or 4 Leading to 53. The both reactions under the conditions shown in Table 2 gave the same product **53** as single isomer: Colorless viscous liquid; IR (neat) 1720 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16—2.20 (10H, m, CH_2), 3.20 (1H, d, J_{4-3}=7.5 Hz, 4-H), 3.60, 3.72 (each 3H, s, COOMe), 4.70 (1H, d, J_{3-4}=7.5 Hz, 3-H), 7.20—7.40 (3H, m, Ph), and 7.70—7.85 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=22.76, 23.41, 25.94, 34.47, 39.77 (each t, CH_2), 52.06, 52.53 (each q, COO<u>Me</u>), 56.77, 58.71 (each d, 3- and 4-C), 78.71 (s, 5-C), 128.02, 128.54, 130.60 (each d), 133.89 (s), 163.95 (s, 2-C), 172.25, and 172.30 (each s, <u>C</u>OOMe); MS *m/z* (rel. intensity, %) 329 (M^+, base peak), 270 (94), 242 (41), 210 (26), 185 (61), 182 (22), and 104 (35).

HRMS Found: *m/z* 329.1689. Calcd for $C_{19}H_{23}NO_5$: M, 329.1626.

General Procedure for the Cycloadditions of 1 with 5. These cycloadditions were carried out acoording to the general procedures mentioned above for the reactions with **2—4**, except that methyl acrylate **5** was used in large excess or as a reaction solvent. The reaction conditions and results are listed in Table 2.

Reaction of 1a with 5 Leading to 54 and 55. This reaction gave four stereoisomers of the corresponding cycloadduct. Mixture of two isomers **54** was separated from mixture of the other two **55** (**54**:**55**=1.5:1) through sequential procedures of column chromatography over silica gel (chloroform–diethyl ether (20:1)) and preparative thin layer chromatography on silica gel (the same eluent as above).

54: A 4:5 mixture of two stereoisomers; colorless liquid; IR (neat) 3330, 2230, 1730, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.10—2.80 (3H, m, CH_2 and CH), 3.07, 3.15 (3H, each s, COOMe), 3.20—4.70 (3H, m, CH and NH), and 7.14 (5H, br s, Ph); ^{13}C NMR ($CDCl_3$) δ=32.41, 33.06 (each t, 4-C), 46.00, 47.12, 47.83, 48.77 (each d, 3- and 5-C), 63.65, 64.12 (each d, 2-C), 120.72, 121.30 (each s, CN), 126.89, 127.54, 127.71, 127.95 (each d), 138.48, 139.19 (each s), 171.66, and 172.31 (each s, <u>C</u>OOMe); MS *m/z* (rel. intensity, %) 230 (M^+, 13), 177 (19), 162 (19), 144 (base peak), 143 (79), 117 (25), and 104 (18).

HRMS Found: *m/z* 230.1050. Calcd for $C_{13}H_{14}N_2O_2$: M, 230.1054.

55: A 2:3 mixture of two stereoisomers; colorless liquid; IR (neat) 3320, 2205, 1725, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.10—3.00 (3H, m, CH_2 and CH), 3.30—4.80 (3H, m, CH and NH), 3.57, 3.62 (3H, each s, COOMe), and 7.18 (5H, br s, Ph); MS *m/z* (rel. intensity, %) 230 (M^+, 30), 229 (42), 183 (22), 169 (22), 156 (55), 154 (69), 143 (47), 117 (57), 116 (61), 115 (base peak), and 91 (88).

HRMS Found: *m/z* 230.1048. Calcd for $C_{13}H_{14}N_2O_2$: M, 230.1054.

Elimination of HCN from 54 and 55 Leading to 56 and 57. The elimination was performed under the conditions listed in Table 3. The HCN-eliminated products **56** and **57** were purified through column chromatography over silica gel with chloroform–diethyl ether (5:1).

56: Pale yellow liquid; IR (neat) 1730 and 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.80 (2H, m, 3-H), 3.08 (3H, s, COOMe), 3.50 (1H, ddd, J_{4-3}=9.6, 6.0 and J_{4-5}=9.2 Hz, 4-H), 5.52 (1H, ddd, J_{5-2}=2.0, J_{5-3}=4.0, and J_{5-4}=9.2 Hz, 5-H), 7.00—7.44 (5H, m, Ph), and 7.80 (1H, dt, J_{2-3}=1.0, 1.0 and J_{2-5}=2.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=40.24 (t, 3-C), 46.30 (d, 4-C), 51.36 (q, COO<u>Me</u>), 78.83 (d, 5-C), 127.66, 128.13 (each d), 138.07 (s), 167.24 (d, 2-C), and 172.65 (s, <u>C</u>OOMe); MS *m/z* (rel. intensity, %) 203 (M^+, 15), 144 (34), 143 (20), 117 (42), 90 (23), and 43 (base peak).

HRMS Found: *m/z* 203.0932. Calcd for $C_{12}H_{13}NO_2$: M, 203.0945.

57: Pale yellow liquid; IR (neat) 1735, 1720, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.90—3.04 (3H, m, CH_2 and CH), 3.70 (3H, s, COOMe), 5.36 (1H, m, 5-H), 7.00—7.44 (5H, m, Ph), and 7.66 (1H, br, 2-H); ^{13}C NMR ($CDCl_3$) δ=41.53 (t, 3-C), 49.18 (d, 4-C), 52.36 (q, COO<u>Me</u>), 79.89 (d, 5-C), 126.54, 127.60, 128.83 (each d), 142.54 (s), 165.59 (d, 2-C), and 174.77 (s, <u>C</u>OOMe); MS *m/z* (rel. intensity, %) 203 (M^+, 22), 144 (66), 143 (61), 117 (base peak), 116 (27), 115 (54), 104 (34), 91 (33), 90 (66), 89 (55), and 77 (28).

HRMS Found: *m/z* 203.0907. Calcd for $C_{12}H_{13}NO_2$: M,

203.0945.

Dehydrogenation of 56 and 57 Leading to 58. A mixture of equivalent amounts of **56** (or **57**) and DDQ in dry benzene was heated under reflux for 30 min. The residue was chromatographed over silica gel with chloroform–diethyl ether (10:1) to give pure **58** (41% from **56**: **42% from 57**): Beige liquid; IR (neat) 3310, 1700, 1685, and 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.69 (3H, s, COOMe), 6.70, 6.74 (each 1H, d, J=1.0 Hz, 4- and 5-H), 7.20—7.60 (5H, m, Ph), and 8.50 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ=50.90 (q, COOMe), 111.68 (s, 3-C), 112.09 (d, 4-C), 117.88 (d, 5-C), 128.12, 128.88 (each d), 132.10 (s), 137.25 (s, 2-C), and 165.62 (s, COOMe); MS *m/z* (rel. intensity, %) 201 (M^+, 66), 170 (base peak), 115 (61), 114 (29), and 89 (17).

HRMS Found: *m/z* 201.0790. Calcd for $C_{12}H_{11}NO_2$: M, 201.0790.

Reaction of 1e with 5 Leading to 59 and 60. The crude reaction mixture was chromatographed over silica gel with chloroform to give pure **59** and mixture of stereoisomers **60** of HCN-eliminated cycloadduct. This mixture could not be separated by HPLC.

59: Colorless prisms (hexane); mp 104—105 °C; IR (KBr) 1730 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.12 (3H, s, COOMe), 3.06—3.28 (1H, m, one of 3-H), 3.46—3.83 (2H, m, the other of 3-H and 4-H), 5.85 (1H, m, 5-H), 7.04—7.48 (8H, m, Ph), and 7.92 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=37.88 (t, 3-C), 47.89 (d, 4-C), 51.12 (q, COOMe), 78.39 (d, 5-C), 127.54, 127.95, 130.93, 133.66, 138.48, 172.41 (s, COOMe), and 173.18 (s, COOMe); MS *m/z* (rel. intensity, %) 279 (M^+, 35), 220 (72), 193 (base peak), and 115 (25).

Found: C, 77.48; H, 6.17; N, 5.10%. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01%.

60: A 2:1 mixture of two stereoisomers; colorless liquid; IR (neat) 1740 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.96—2.28 (1H, m, one of 4-H), 2.66—3.05 (1H, m, the other of 4-H), 3.54, 3.60 (3H, each s, COOMe), 4.16 (1/3H, dt, J=8.0, 2.0, and 2.0 Hz, 3-H), 4.34 (2/3H, dt, J=8.0, 2.0, and 2.0 Hz, 3-H), 5.26 (1/3H, dt, J=8.0, 8.0, and 2.0 Hz, 5-H), 5.47 (1H, dt, J=8.0, 8.0, 2.0 Hz, 5-H), 6.15—6.40 (8H, m, Ph), and 6.76—7.00 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=38.00, 38.88 (each t), 52.41 (q, 2×C), 54.29, 54.59 (each d), 75.55, 75.77 (each d), 124.36, 126.72, 127.00, 127.30, 128.01, 128.42, 128.71, 129.36, 130.89, 131.12, 133.36, 133.65, 143.12, 143.83, 169.40 (s), 169.77 (s), 172.42, and 173.12 (each s); MS *m/z* (rel. intensity, %) 279 (M^+, 40), 220 (65), 193 (93), 192 (base peak), and 115 (49).

Found: C, 77.14; H, 5.89; N, 4.94%. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01%.

Reaction of 1g with 5 Leading to 61 and 62. A mixture of propionaldehyde (530 mg, 9.14 mmol) and α-cyanobenzylamine (792 mg, 6 mmol) was heated under reflux in chloroform (60 ml) in the presence of molecular sieves 5A for 6 h. The molecular sieves was filtered off and the solvent was evaporated in vacuo. To the residue was added methyl acrylate **5** (3g, 30 mmol) and the mixture was refluxed for 22 h. The solvent was evaporated in vacuo and the residue was chromatographed over silica gel to give **61** (from chloroform–diethyl ether (20:1), 896 mg, 65%) and **62** (from chloroform–diethyl ether (10:1), 443 mg, 30%). Cycloadduct **61** gradually changes into **62** when its solution is allowed to stand on exposure to air. The other product **62** consists of two stereoisomers which can be separated by repeated column chromatography over silica gel.

61: Pale yellow liquid; IR (neat) 1730 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90—2.20 (7H, m, Et and CH_2), 3.56 (3H, s, COOMe), 3.60 (1H, m, 3-H), 4.20 (1H, m, 5-H), 7.10—7.40 (3H, m, Ph), and 7.60—7.90 (2H, m, Ph); MS *m/z* (rel. intensity, %) 231 (M^+, 19), 212 (55), 172 (19), 170 (36), 145 (29), 144 (base peak), 130 (40), 116 (42), 115 (27), and 104 (86).

HRMS Found: *m/z* 231.1256. Calcd for $C_{14}H_{17}NO_2$: M, 231.1258.

One isomer of **62**: Colorless needles (benzene–hexane); mp 129—130 °C; IR (KBr) 3100, 2960, 1755, and 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.06 (3H, t, Et), 1.40—2.16 (2H, m, Et), 1.88 (1H, dd, J_{gem}=13.3 and J_{4-5}=7.0 Hz, one of 4-H), 2.66 (1H, dd, J_{gem}=13.3 and J_{4-5}=7.0 Hz, the other of 4-H), 3.74 (3H, s, COOMe), 3.86 (1H, s, OH), 4.12 (1H, m, 5-H), 7.20—7.48 (3H, m, Ph), and 7.70—7.90 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=10.82 (q, Et), 29.47 (t, Et), 44.83 (t, 4-C), 53.65 (q, COOMe), 71.24 (d, 5-C), 86.83 (s, 3-C), 128.01, 128.65, 130.65 (each d), 132.42 (s), 168.65 (s, 2-C), and 175.60 (s, COOMe); MS *m/z* (rel. intensity, %) 247 (M^+, 28), 144 (base peak), 130 (28), 104 (72), 102 (26), 85 (26), and 77 (24).

Found: C, 67.86; H, 6.93; N, 5.68%. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66%.

The other isomer of **62**: Colorless needles (benzene–hexane); mp 147—148.5 °C; IR (KBr) 3100, 1740, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.04 (3H, t, Et), 1.40—2.45 (4H, m, Et and CH_2), 3.68 (3H, s, COOMe), 4.00 (1H, br s, OH), 4.30 (1H, m, 5-H), 7.20—7.44 (3H, m, Ph), and 7.64—7.84 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=11.13 (q, Et), 29.10 (t, Et), 45.21 (t, 4-C), 53.52 (q, COOMe), 72.27 (d, 5-C), 86.52 (s, 3-C), 127.83, 128.66, 130.61 (each d), 132.56 (s), 167.91 (s, 2-C), and 175.85 (s, COOMe); MS *m/z* (rel. intensity, %) 247 (M^+, 25), 144 (base peak), 130 (37), 104 (90), 103 (22), 102 (29), and 83 (29).

Found: C, 68.15; H, 6.96; N, 5.73%. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66%.

Air Oxidation of 53 Leading to 63. A solution of **53** in chloroform was stirred at room temperature under oxygen atmosphere for 2 d. The solvent was evaporated in vacuo to give a quantitative yield of **63**: Colorless prisms (hexane); mp 124—125 °C; IR (KBr) 3460, 1710, and 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.01—2.20 (10H, m, CH_2), 3.24 (1H, s, 4-H), 3.71, 3.78 (each 3H, s, COOMe), 4.30 (1H, s, OH), 7.20—7.44 (3H, m, Ph), and 7.70—7.90 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=22.59, 23.48, 26.06, 33.77, 40.71 (each t), 52.18, 53.89 (each q, COOMe), 68.95 (d, 4-C), 78.53 (s, 5-C), 87.77 (s, 3-C), 128.25, 128.60, 130.72 (each d), 132.42 (s), 164.78 (s, 2-C), 170.77, and 173.99 (each s, COOMe); MS *m/z* (rel. intensity, %) 345 (M^+, 22), 242 (base peak), 210 (20), 185 (22), 183 (21), 182 (39), 155 (22), 129 (30), 123 (30), 122 (23), 104 (40), and 77 (22).

Found: C, 66.00; H, 6.69; N, 4.29%. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06%.

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