Stereoselective Azepine-Ring Formation Through Ene Reactions of 3-(Alk-2-enyl)amino-2-cyanoacrolein Derivatives

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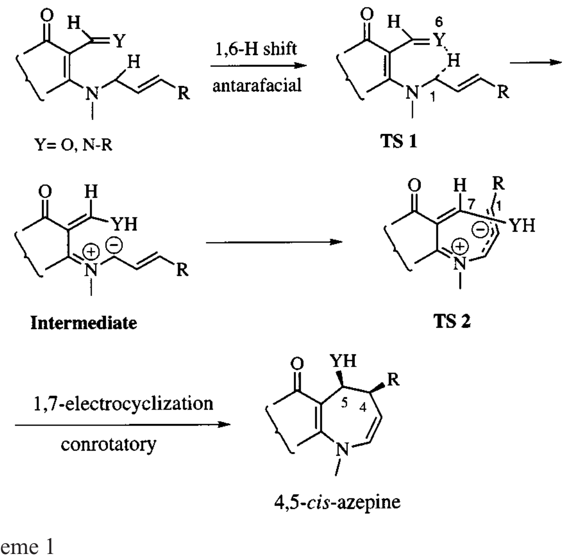
The reaction of 3-[*N*-(alk-2-enyl)benzylamino]-2-cyanoacroleins **9** with primary amines **12** and **13** gave 4,5-dihydro-1*H*-azepines **14** and **15** stereoselectively, through an intramolecular ene reaction of the imine derivatives of **9**. Similarly, carbonyl–ene reaction of acrolein derivatives **9**, and olefin–ene reaction of their conjugated diene compounds **22**, and **24**–**27** are also discussed. These ene reactions established an efficient synthetic approach toward monocyclic azepine ring formation.

Introduction

In previous papers,[1] we reported the stereoselective azepine ring formation through the thermal imine– and carbonyl–ene reactions at the periphery of heterocyclic systems. The investigation on their mechanisms based on PM3 molecular orbital (MO) calculations, and utilizing a chiral substrate, revealed that the azepine ring formation consisted of two consecutive orbital-allowed reactions; the [1,6] sigmatropic shift of the allylic hydrogen (TS 1), generating a conjugated azomethine ylide (Intermediate), and its [1,7] electrocyclic ring closure (TS 2) (Scheme 1).[1b] In order to develop the scopes of the azepine ring formation, further PM3 MO calculations of the model compounds were performed. Preliminary results of the calculations[2] proposed that the heterocyclic system in the above substrates was not necessary for the azepine ring formation, and that 3-(*N*-allylmethylamino)acrolein derivatives **1** (Y = O; NMe) could perform the carbonyl– and imine–ene reactions to afford azepines **2**, as well as 2-(*N*-allylmethylamino)-3-formylpyrido[1,2-*a*]pyrimidine and its *N*-methylimine **3**[1b] (Figure 1). We describe here the successful extension of the azepine ring formation to 3-(alk-2-enyl)aminoacroleins and the generality of the ring-closing ene reactions in this system, leading to functionalized monocyclic 4,5-dihydro-1*H*-azepines.[3]



Scheme 1

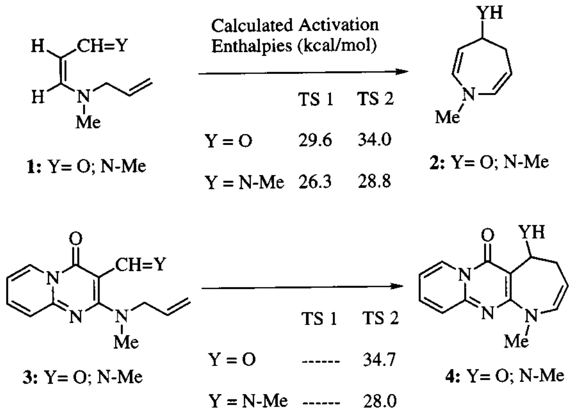


Figure 1. Activation enthalpies in the ene reactions of the model compounds **1** and **3** calculated by PM3 method

Results and Discussion

A starting material 3-(*N*-allylbenzyl)aminoacrolein (**6**) was prepared in a moderate yield from 1,1,3,3-tetramethoxypropane and *N*-allylbenzylamine (**5a**), as is shown in Scheme 2. Thermal reaction of acrolein derivative **6** in re-

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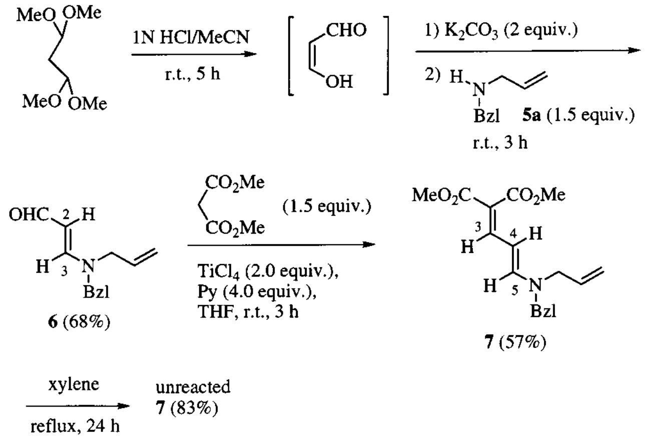
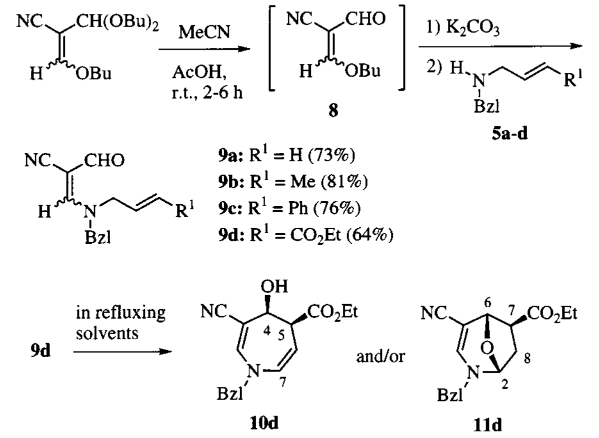
fluxing solvents gave only disappointing results; the starting **6** was recovered at lower temperatures (below 100 °C), while the reaction at elevated temperatures (above 140 °C) gave mixtures of unidentified products, probably due to the decomposition of acrolein derivative **6**. Condensation of **6** with dimethyl malonate in the presence of pyridine and titanium tetrachloride[4] gave conjugated diene compound **7**. Thermal reaction of **7** in refluxing xylene for 24 h gave only the unchanged **7** in 83% yield. The ^{1}H NMR spectrum of conjugated diene compound **7** showed that it existed exclusively as an *E*-isomer, which makes it impossible to perform the ene reaction (Scheme 2). We concluded that the unfavorable equilibrium between the *E*-isomer and the less stable *Z*-isomer, and the conformational flexibility of the substrates **6** and **7** were responsible for the failure of the ene reactions. Therefore, we decided to introduce an electron-withdrawing substituent, such as a cyano group, into the reaction substrate, so as to facilitate the *E*/*Z*-isomerization.



Scheme 2

Carbonyl Ene Reaction of 3-(Alk-2-enyl)amino-2-cyanoacroleins 9

We prepared 2-cyanoacrolein derivatives; the reaction of 3-butoxy-2-cyanoacrolein (**8**), obtained from commercially available 1,3,3-tributoxy-2-cyanopropene,[5] with *N*-allyl- (**5a**), *N*-[(*E*)-but-2-enyl]- (**5b**), *N*-[(*E*)-cinnamyl]- (**5c**), and *N*-[3-ethoxycarbonyl-(*E*)-prop-2-enyl]benzylamine (**5d**) gave the corresponding 3-[*N*-(alk-2-enyl)benzylamino]-2-cyanoacroleins **9a–d** in good yields, as inseparable mixtures of two geometric isomers (Scheme 3). The carbonyl–ene reaction of acrolein derivatives **9a–c** was examined. For the reaction of **9a–c**, refluxing conditions in toluene or xylene gave only recovered starting material, while harsher conditions resulted in their decomposition, giving many unidentified products together with unchanged **9a–c**. A good result was only obtained in the reaction of **9d** (R^1 = CO$_2$Et); heating **9d** (isomeric ratio = 2/3) in refluxing toluene for 24 h gave azepine **10d** and acrolein derivative **9d** (in an unchanged isomeric ratio) in 52% and 24% yield, respectively. The same reaction in refluxing xylene for 20 h gave 1,3-oxazine **11d** (56%) and a trace amount of **10d**. 1,3-Oxazine



Scheme 3

11d seems to be a secondary product from azepine **10d**, in which a nucleophilic attack of the hydroxyl group at the 7-position of **10d**, corresponding to the α-position of the enamine moiety, gives a bridged product **11d**. The structural confirmation of **10d** and **11d** was accomplished on the basis of their elemental analyses, and a comparison of their spectroscopic data with those of the related azepine and 1,3-oxazine derivatives.[1] The relative stereochemistry between the 4- and 5-H of azepine **10d** was deduced to be *cis* from the coupling constant ($J_{4-5} \approx 0$ Hz). This suggests that this type of ene reaction proceeds in a strict stereoselective manner.[1b] The *exo*-configuration of the ethoxycarbonyl group at the 7-position of 1,3-oxazine **11d** was also confirmed by the coupling constant between the bridge-head proton (6-H) and 7-H ($J_{6-7} \approx 0$ Hz; 7-H: *endo*). These findings, as well as the reason that an electron-withdrawing substituent on the alkenyl moiety facilitated the ene reactions at the periphery of heterocyclic systems, were discussed in our previous reports.[1]

Ene Reaction of Imines from 3-(Alk-2-enyl)amino-2-cyanoacroleins 9

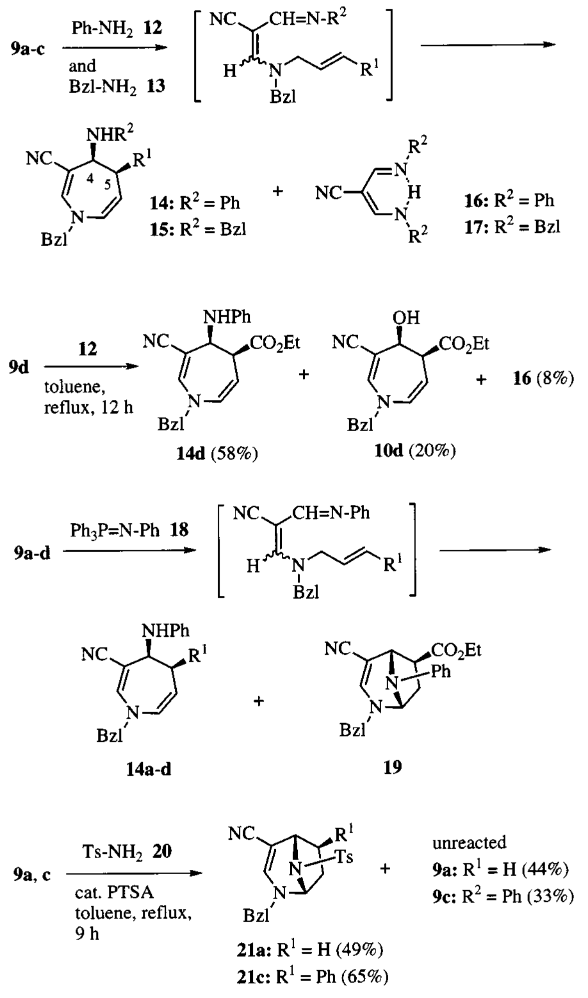
Our next concern was focused on the ene reaction of imine derivatives of acroleins **9**. The reaction of acrolein derivative **9a** with aniline (**12**) and benzylamine (**13**) in refluxing xylene gave azepine derivatives **14a** and **15a**, respectively, in good yields via the corresponding imine formation. Similar reaction of acrolein **9b** with amines **12** and **13** gave azepines

Table 1. Ene reaction of imines of 3-[*N*-(Alk-2-enyl)benzylamino]-2-cyanoacroleins **9**

Run	Acrolein	R^1	Reagent	Conditions[a]	Product (yield/%)[b]
1	**9a**	H	**12**	xylene, 1 h	**14a** (83)
2	**9a**	H	**13**	xylene, 1 h	**15a** (68)
3	**9b**	Me	**12**	xylene, 3 h	**14b** (72)
4	**9b**	Me	**13**	xylene, 3 h	**15b** (57)
5	**9c**	Ph	**12**	benzene, 24 h	**14c** (28), **16** (55)
6	**9c**	Ph	**13**	benzene, 18 h	**15c** (36), **17** (46)
7	**9a**	H	**18**	benzene, 24 h	**14a** (72)
8	**9b**	Me	**18**	benzene, 18 h	**14b** (77)
9	**9c**	Ph	**18**	benzene, 18 h	**14c** (81)
10	**9d**	CO$_2$Et	**18**	benzene, 18 h	**14d** (74), **19** (8)

[a] Performed in refluxing solvents. [b] Based on isolated products.

14b and **15b**. On the other hand, in the reaction of *N*-cinnamyl substrate **9c** with amines **12** and **13**, the azepine ring formation was found not to be a major reaction. Acrolein derivative **9c** preferably reacted with two mol of the corresponding amine to give vinamidine derivatives **16** (55%) and **17** (46%)[6] as the major products, together with the desired azepines **14c** (28%) and **15c** (36%), respectively (Table 1 and Scheme 4). Furthermore, similar one-pot reaction of acrolein **9d** in the presence of aniline (**12**) gave azepines **14d** and **10d**, where the imine–ene reaction was competitive with the carbonyl–ene reaction.



Scheme 4

To suppress the vinamidine formation, an aza-Wittig reaction was used for the imine synthesis; the reaction of acrolein derivatives **9a–d** with *N*-(triphenylphosphoranylidene)aniline (**18**) in refluxing benzene gave the desired azepines **14a–d**, and further bicyclized pyrimidine **19**, in moderate to good yields (Table 1 and Scheme 4).

The reaction of acrolein derivatives **9a** and **9c** with *p*-toluenesulfonamide (**20**) in refluxing toluene in the presence of *p*-toluenesulfonic acid (PTSA) gave pyrimidine derivatives **21a** and **21c**, respectively, in moderate yields (Scheme 4).

Ene Reaction of Conjugated Diene Derivatives from 3-(Alk-2-enyl)amino-2-cyanoacroleins 9

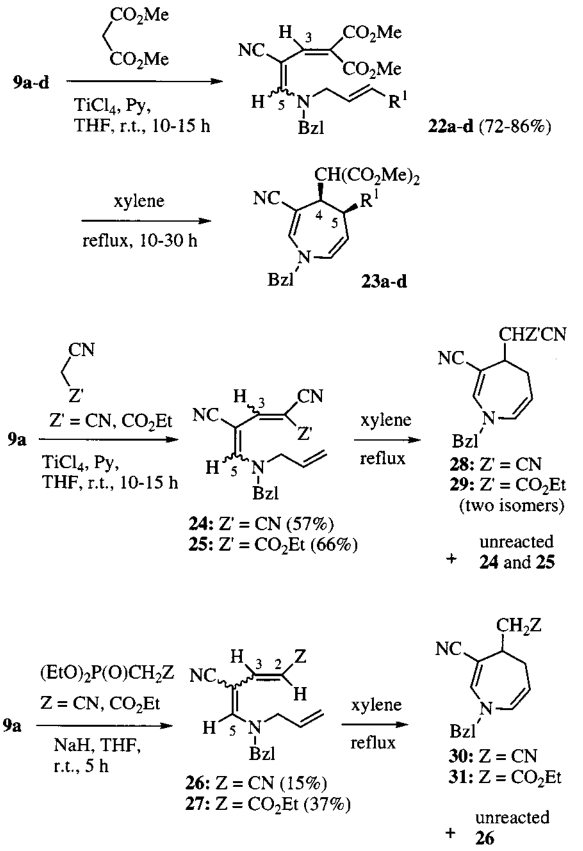
Condensation of acrolein derivatives **9a–d** with dimethyl malonate gave conjugated dienes **22a–d** in good yields. Compounds **22** were obtained as inseparable (ca. 2:3) mixtures of two geometric isomers, which were utilized for the ene reaction without further purification (Scheme 5). Heating compounds **22a–d** in refluxing xylene gave azepines **23a–d** as sole products in good yields. The 4,5-*cis* configuration of azepines **23b–d** was also deduced on the basis of the coupling constants ($J_{4-5} \approx 0$ Hz), and unambiguously confirmed by single crystal X-ray analysis of **23d**[7] (Table 2 and Scheme 5). Thermal cyclization reaction of 2-(alk-2-enyl)amino-2,4-pentadienenitriles leading to 4,5-dihydroazepines has been found in the literature.[8] Therein, the same reaction mechanism for the formation of the azepines as that discussed in this paper was proposed.

Finally, to elucidate the effect of the substituent(s) of the terminal olefinic moiety on the reactivity, we prepared four other conjugated dienes; similar condensation of acrolein derivative **9a** with malononitrile and ethyl cyanoacetate, and the Horner–Emmons reactions of **9a** gave conjugated dienes **24–27** in poor to moderate yields. Thermal reaction of the mono-substituted substrates **26** and **27** in refluxing xylene for 40–60 h gave azepines **30** and **31** in good yields. Interestingly, similar reaction of the ω,ω-disubstituted compounds **24** and **25** also provided azepines **28** and **29**, yet in poor yields, together with the unchanged starting materials **24** and **25** as the major components. A prolonged reaction of **24** (for 4 d) in refluxing xylene gave almost the same

Table 2. Ene reaction of conjugated diene compounds **22** and **24–27**

Run	Vinyl Compound	R^1	Z	Z′	Time/h	Azepine (yield/%)[a]	Recovered (yield/%)[a]
1	**22a**	H	CO_2Me	CO_2Me	24	**23a** (76)	
2	**22b**	Me	CO_2Me	CO_2Me	30	**23b** (77)	
3	**22c**	Ph	CO_2Me	CO_2Me	24	**23c** (76)	
4	**22d**	CO_2Et	CO_2Me	CO_2Me	10	**23d** (98)	
5	**24**	H	CN	CN	48	**28** (4)	**24** (83)
6	**24**	H	CN	CN	96	**28** (5)	**24** (80)
7	**25**	H	CN	CO_2Et	48	**29** (31)	**25** (51)
8	**26**	H	CN	H	24	**30** (42)	**26** (33)
9	**27**	H	CO_2Et	H	24	**31** (83)	

[a] Based on isolated products.



Scheme 5

results (Table 2). The exact reason remains unclear why the ω,ω-disubstituted substrates **24** and **25** exhibited a lower reactivity for the ene reaction than ω,ω-disubstituted **22a** and mono-substituted **26** and **27**. We suggest, however, that the electron-withdrawing substituents such as cyano and methoxycarbonyl groups would stabilize the conjugated diene forms with the push-pull electronic properties more than the azepine derivatives, and that the *retro*-ene reaction of the formed azepines would also proceed leading to the starting conjugated dienes.

Conclusion

We have reported azepine ring formations through the thermal carbonyl–, imine–, and olefin–ene reactions of 3-[*N*-(alk-2-enyl)benzyl]amino-2-cyanoacrolein derivatives. These ene reactions lead to azepine derivatives effectively and stereoselectively, and therefore, provide an efficient synthetic approach toward functionalized monocyclic 4,5-dihydro-1*H*-azepines. Further details on the mechanistic aspects and investigations on the effect of the 2-position of the acrolein derivatives are in progress and will be reported elsewhere.

Experimental Section

General: Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. – IR spectra were measured on a JASCO IR-Report-100 spectrophotometer from samples as KBr pellets or NaCl discs. – ^{1}H NMR spectra were measured on a JEOL EX-270 and/or EX-400 spectrometers (270 and 400 MHz, respectively) and ^{13}C NMR spectra were measured on a JEOL EX-270 spectrometer (67.8 MHz) in deuterated-chloroform solutions unless otherwise stated. Tetramethylsilane was used as internal standard, and *J* values are given in Hz. Splitting patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad signal; and ov, overlapping signals. – Mass spectra were determined on a JEOL JMS-SX102A spectrometer. – Elemental analyses were performed on a Yanagimoto MT-5 CHN analyzer. – All nonaqueous reaction were run under positive pressure of argon or nitrogen. All solvents were dried by standard methods before use. The progress of reactions was monitored by TLC (silica gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or silica gel 60 (230–400 mesh, Merck).

Preparation of Starting Materials – General Procedure

Preparation of 3-(Allybenzylamino)acrolein (6): A solution of tetramethoxypropane (0.83 g, 5.1 mmol) in 1 N HCl/MeCN (6 mL) was stirred at room temp. for 5 h, and anhydrous potassium carbonate (1.41 g, 10.2 mmol) was added to the reaction mixture. To the mixture was added amine **5a** (1.18 g, 8 mmol), and the resulting mixture was stirred at room temp. for 3 h. Precipitates were filtered off and the filtrate was evaporated to dryness, which was subjected to column chromatography on silica gel with hexane/ethyl acetate (1:1) as an eluent to afford acrolein derivative **6** (0.693 g, 68%).

3-(Allybenzylamino)acrolein (**6**): Pale yellow oil. – $C_{13}H_{15}NO$: calcd. 201.1153; observed *m*/*z* (EI) 201.1160. – This compound was a (2:3) mixture of two isomers in [D$_6$]DMSO. – ^{1}H NMR ([D$_6$]DMSO): major isomer: δ = 3.84 (br d, *J* = 5.0 Hz, 2 H, >NC*H*$_2$–CH=), 4.61 (s, 2 H, C*H*$_2$Ph), 5.14–5.33 (ov, 3 H, 2-H and =CH$_2$), 5.97 (m, 1 H, –C*H*=CH$_2$), 7.33–7.44 (ov, 5 H, Ph), 7.73 (br d, *J* = 12.9 Hz, 1 H, 3-H; *trans*), 9.78 (br d, *J* = 7.9 Hz, 1 H, 1-H). Assigned signals for minor isomer: δ = 4.01 (br d, *J* = 4.6 Hz, 2 H, >NC*H*$_2$–CH=), 4.49 (s, 2 H, C*H*$_2$Ph), 5.71 (m, 1 H, –C*H*=CH$_2$), 7.58 (br d, *J* = 12.9 Hz, 1 H, 3-H; *trans*), 9.09 (br d, *J* = 7.9 Hz, 1H, 1-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 50.0, 50.9 (>N*C*H$_2$–CH=), 57.6, 58.2 (*C*H$_2$Ph), 101.6, 101.8 (2-C), 117.5, 118.5 (=*C*H$_2$), 127.0, 127.3, 127.9, 128.6, 131.0, 133.6, 136.0, 136.5 (–*C*H=CH$_2$ and Ph–C), 160.3 (3-C), 188.2 (1-C).

Preparation of 3-(Allybenzylamino)-2-cyanoacrolein (9a): A solution of 1,3,3-tributoxy-2-cyanopropene (1.48 g, 5.2 mmol) and AcOH (0.374 g, 6.2 mmol) in MeCN (20 mL) was stirred at room temp. for 6 h and anhydrous potassium carbonate (1.08 g, 7.8 mmol) was added to the reaction mixture. To the mixture was added amine **5a** (1.18 g, 8 mmol), and the resulting mixture was stirred at room temp. for an additional 2 h. The usual workup by column chromatography on silica gel with hexane/ethyl acetate (1:1) as an eluent afforded acrolein derivative **9a** (0.86 g, 73%).

3-(Allybenzylamino)-2-cyanoacrolein (9a): Yellow oil. – $C_{14}H_{14}N_2O$ (226.3): calcd. C 74.31, H 6.24, N 12.38; found C 74.69, H 6.46, N 12.64. This compound was a (2:3) mixture of two geometric isomers in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): major isomer: δ = 3.95 (d, *J* = 6.3 Hz, 2 H, >NC*H*$_2$–CH=), 4.98 (s, 2 H, C*H*$_2$Ph), 5.24–5.42 (ov, 2 H, =CH$_2$), 5.83 (m, 1 H, –C*H*=CH$_2$), 7.24–7.42 (ov, 6-H, 3-H and Ph), 9.19 (br, 1 H, 1-H). Assigned signals for minor isomer: δ = 4.26 (d, *J* = 5.6 Hz, 2 H, >NC*H*$_2$–CH=), 4.58 (s, 2 H, C*H*$_2$Ph), 9.16 (br, 1 H, 1-H). – ^{13}C NMR (CDCl$_3$): δ = 50.7, 52.1 (>N*C*H$_2$–CH=), 59.4, 61.3 (*C*H$_2$Ph), 86.0 (2-C), 115.0 (CN), 119.4, 121.4 (=*C*H$_2$), 127.6, 128.0, 128.4, 128.9, 129.0, 129.2, 129.5, 130.5, 133.4, 137.7 (–CH=CH$_2$ and Ph–C), 160.2, 160.3 (3-C), 186.4, 186.7 (1-C).

3-{Benzyl[(*E*)-but-2-enyl]amino}-2-cyanoacrolein (9b): Yellow oil. – $C_{15}H_{16}N_2O$ (240.3): calcd. C 74.97, H 6.71, N 11.66; found C 74.89, H 6.76, N 11.74. This compound was a (2:3) mixture of two geometric isomers in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): major isomer: δ = 1.76 (d, J = 5.6 Hz, 3 H, Me), 3.86 (d, J = 6.9 Hz, 2 H, >NCH_2–CH=), 4.98 (s, 2 H, CH_2Ph), 5.40–5.80 (ov, 2 H, –CH=CH–), 7.21–7.43 (ov, 6 H, 3-H and Ph), 9.23 (br, 1 H, 1-H). Assigned signals for minor isomer: δ = 1.78 (d, J = 5.6 Hz, 3 H, Me), 4.21 (d, J = 5.0 Hz, 2 H, >NCH_2–CH=), 4.58 (s, 2 H, CH_2Ph). – ^{13}C NMR (CDCl$_3$) δ = 17.8 (Me), 50.5, 51.2 (>NCH$_2$–CH=), 59.1, 61.0 (CH$_2$Ph), 86.0 (2-C), 115.1 (CN), 122.5, 123.1, 127.7, 128.0, 128.5, 129.1, 129.3, 132.4, 134.2, 133.5, 133.9 (–CH=CH– and Ph–C), 156–162 (br, 3-C), 186.2 (1-C).

3-{Benzyl[(*E*)-cinnamyl]amino}-2-cyanoacrolein (9c): Pale yellow oil. – $C_{20}H_{18}N_2O$ (302.4): calcd. C 79.44, H 6.00, N 9.27; found C 79.21, H 5.90, N 9.41. This compound was a (2:3) mixture of two geometric isomers in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): major isomer: δ = 4.09 (d, J = 7.3 Hz, 2 H, >NCH_2–CH=), 5.03 (s, 2 H, CH_2Ph), 6.13 (m, 1 H, >NCH$_2$–CH=), 6.56 (d, J = 15.8 Hz, 1 H, =CH–Ph), 7.24–7.48 (ov, 11 H, 3-H and Ph), 9.24 (br, 1 H, 1-H). Assigned signals for minor isomer: δ = 4.44 (d, J = 5.0 Hz, 2 H, >NCH_2–CH=), 4.61 (s, 2 H, CH_2Ph). – ^{13}C NMR (CDCl$_3$): δ = 50.2, 51.8 (>NCH$_2$–CH=), 59.0, 61.0 (CH$_2$Ph), 85.7 (2-C), 115.5, 115.7 (CN), 120.5, 121.1, 126.4, 127.4, 127.9, 128.1, 128.2, 128.3, 128.4, 128.7, 128.9, 129.0, 133.4, 133.7, 134.7, 135.0, 135.3, 136.1 (–CH=CH– and Ph–C), 160.2, 160.3 (3-C), 186.7 (1-C).

3-{Benzyl-[2-ethoxycarbonyl-(*E*)-(prop-2-enyl)]amino}-2-cyanoacrolein (9d): yellow oil. – $C_{17}H_{18}N_2O_3$ (298.3): calcd. C 68.44, H 6.08, N 9.39; found C 68.39 H, 5.90, N 9.31. This compound was a (1:2) mixture of two geometric isomers in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): major isomer: δ = 1.42 (ov, 3 H, CH$_2$CH_3), 4.06 (d, J = 7.3 Hz, 2 H, >NCH_2–CH=), 4.19–4.28 (ov, 2 H, CH_2CH$_3$), 5.00 (s, 2 H, CH_2Ph), 5.95 (d, J = 15.8 Hz, 1 H, =CH–Es), 6.83 (m, 1 H, –CH=CH–Es), 7.15–7.65 (ov, 6 H, 3-H and Ph), 9.26 (br, 1 H, 1-H). Assigned signals for minor isomer: δ = 4.43 (d, J = 5.0 Hz, 2 H, >NCH_2–CH=), 4.57 (s, 2 H, CH_2Ph), 5.95 (d, J = 15.8 Hz, 1 H, =CH–Es). – ^{13}C NMR (CDCl$_3$): δ = 14.1 (CH$_2$$CH_3$), 48.8, 52.7 (>N$CH_2$–CH=), 57.0, 60.8 ($CH_2$Ph), 61.0, 62.1 ($CH_2CH_3$), 85.7 (br, 2-C), 115.5, 115.7 (CN), 124.4, 125.0, 127.7, 128.0, 128.8, 129.3, 129.4, 132.9, 133.3 (–CH=CH–Es and Ph–C), 139.0 (–CH=CH–Es), 160.2, 160.3 (3-C), 165.0 (CO$_2$), 186.7 (1-C).

Condensation of Acrolein Derivative 6 with Dimethyl Malonate–General Procedures

Preparation of Conjugated Diene Compound 7: To a solution of TiCl$_4$ (0.24 mL, 2.2 mmol) in THF (10 mL), cooled at 0 °C, was added the acrolein derivative **6** (0.22 g, 1.1 mmol) and dimethyl malonate (0.23 g, 1.8 mmol), and the mixture was stirred at the same temp. for 1 h. Pyridine (0.35 mL, 4.4 mmol) was added to the reaction mixture and stirred at room temp. for an additional 3 h. To quench the reaction, water was added and the solvent was evaporated. The residue was extracted with ethyl acetate. The organic layer was dried and evaporated to dryness, and the residue was subjected to column chromatography on silica gel with hexane/ethyl acetate (2:1) as an eluent to afford diene compound **7** (0.197 g, 57%).

Conjugated Diene 7: yellow oil. – $C_{18}H_{21}NO_4$: calcd. 315.1453; observed m/z (EI) 315.1459. This compound was a single isomer in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): δ = 3.75, 3.77 (each s, each 3 H, OMe), 3.81 (d, J = 5.9 Hz, 2 H, >NCH_2–CH=), 4.43 (s, 2 H, CH_2Ph), 5.23 (ov, 2 H, =CH$_2$), 5.72 (m, 1 H, –CH=CH$_2$), 6.33 (br t, J = 12.5 Hz, 1 H, 4-H), 7.12 (d, J = 12.9 Hz, 1 H, 3-H), 7.19–7.40 (ov, 5 H, Ph), 7.70 (d, J = 12.5 Hz, 1 H, 5-H). – ^{13}C NMR (CDCl$_3$): δ = 50.5 (>NCH$_2$–CH=), 51.2, 51.5 (OMe), 59.0 (CH$_2$Ph), 98.0 (2-C), 107.1 (4-C), 119.3 (=CH$_2$), 127.6, 126.2, 128.9, 130.5, 135.5 (–CH=CH$_2$ and Ph–C), 154.3, 155.9 (3- and 5-C), 167.2, 167.3 (CO$_2$).

Conjugated Diene 22a: Pale yellow plates from hexane/ethyl acetate; m.p. 72–73 °C. – $C_{19}H_{20}N_2O_4$: calcd. 340.1423; observed m/z (EI) 340.1517. This compound was a (2:3) mixture of two geometric isomers in [D$_6$]DMSO. – ^{1}H NMR ([D$_6$]DMSO): major isomer: δ = 3.62–3.67 (ov, 6 H, OMe), 4.20 (br d, J = 5.9 Hz, 2 H, >NCH_2–CH=), 4.58 (br s, 2 H, CH_2Ph), 5.16–5.30 (ov, 2 H, =CH$_2$), 5.76–5.83 (m, 1 H, –CH=CH$_2$), 7.17–7.41 (ov, 6 H, 5-H and Ph), 8.18 (br s, 1 H, 3-H). Assigned signals for minor isomer: δ = 3.98 (br d, J = 6.4 Hz, 2 H, >NCH_2–CH=), 4.93 (br s, 2 H, CH_2Ph), 8.02 (s, 1 H, 3-H).

Conjugated Diene 22b: Pale yellow plates from hexane/ethyl acetate; m.p. 92–93 °C. – $C_{20}H_{22}N_2O_4$ (354.4): calcd. 67.78, H 6.26, N 7.90; found C 67.28, H 6.31, N 7.68. $C_{20}H_{22}N_2O_4$: calcd. 354.1732; observed m/z (EI) 354.1733. This compound was a (2:3) mixture of two geometric isomers in [D$_6$]DMSO. – ^{1}H NMR ([D$_6$]DMSO): major isomer: δ = 1.66 (br d, J = 5.6 Hz, 3 H, =CH–Me), 3.64, 3.67 (each s, each 3 H, OMe), 4.11 (br d, J = 5.2 Hz, 2 H, >NCH_2–CH=), 4.58 (br s, 2 H, CH_2Ph), 5.42–5.46 (ov, 2 H, =CH$_2$), 5.63–5.70 (br, 1 H, –CH=CH$_2$), 7.24–7.43 (ov, 6 H, 5-H and Ph), 8.12 (s, 1 H, 3-H). Assigned signals for minor isomer: δ = 3.62, 3.65 (each s, each 3 H, OMe), 3.89 (br d, J = 5.6 Hz, 2 H, >NCH_2–CH=), 4.91 (br, 2 H, CH_2Ph), 8.00 (s, 1 H, 3-H).

Conjugated Diene 22c: Pale yellow amorphous; m.p. 48–49 °C. – $C_{25}H_{24}N_2O_4$: calcd. 416.1888; observed m/z (EI) 416.1892. This compound was a (2:3) mixture of two geometric isomers in [D$_6$]DMSO. – ^{1}H NMR ([D$_6$]DMSO): major isomer: δ = 3.70, 3.72 (each s, each 3 H, OMe), 4.41 (br d, J = 5.3 Hz, 2 H, >NCH_2–CH=), 4.70 (s, 2 H, CH_2Ph), 6.22–6.53 (ov, 1 H, =CH–Ph), 6.53–6.70 (ov, 1 H, –CH=CHPh), 7.29–7.46 (ov, 6 H, 5-H and Ph), 8.27 (br s, 1 H, 3-H). Assigned signals for minor isomer: δ = 3.67, 3.72 (each s, each 3 H, OMe), 4.08 (br d, J = 6.9 Hz, 2 H, >NCH_2–CH=), 5.04 (s, 2 H, CH_2Ph), 8.16 (br s, 1 H, 3-H).

Conjugated Diene 22d: Pale yellow amorphous; m.p. 40–43 °C. – $C_{22}H_{24}N_2O_6$ (412.4): calcd. 64.06, H 5.87, N 6.79; found C 64.18, H 6.02, N 6.75. This compound was a (1:3) mixture of two geometric isomers in [D$_6$]DMSO. – ^{1}H NMR ([D$_6$]DMSO): major isomer: δ = 1.29 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3), 3.72, 3.75 (each s, each 3 H, OMe), 4.20 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.45 (br d, J = 5.9 Hz, 2 H, >NCH_2–CH=), 4.68 (br s, 2 H, CH_2Ph), 5.93 (br d, J = 15.8 Hz, 1 H, =CHEs), 6.82–6.99 (ov, 1 H, –CH=CHEs), 7.33–7.47 (ov, 6 H, 5-H and Ph), 8.28 (s, 1 H, 3-H). Assigned signals for minor isomer: δ = 4.20 (1 H, br d, J = 6.0 Hz, >NCH_2–CH=), 5.03 (br s, 2 H, CH_2Ph), 6.09 (br d, J = 15.5 Hz, 1 H, =CHPh), 8.09 (s, 1 H, 3-H).

Similar condensation of acrolein **9a** with malononitrile and ethyl cyanoacetate gave conjugated diene compounds **24** and **25**, respectively.

Conjugated Diene 24: Pale yellow prisms from hexane/ethyl acetate; m.p. 99–100 °C. – $C_{17}H_{14}N_4$ (274.3): calcd. 74.43, H 5.14, N 20.43; found C 74.39, H 5.29, N 20.25. This compound was a (2:3) mixture of two geometric isomers in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): major isomer: δ = 3.94 (d, J = 6.3 Hz, 2 H, >NCH_2–CH=), 4.56 (s, 2 H, C*H*$_2$Ph), 5.27 (ov, 2 H, =CH$_2$), 5.70–5.97 (ov, 1 H, –C*H*=CH$_2$), 7.04 (s, 1 H, 5-H), 7.21–7.47 (ov, 6 H, 3-H and Ph). Assigned signals for minor isomer: δ = 4.40 (d, *J* = 5.6 Hz, 2 H, >NC*H*$_2$–CH=), 5.10 (s, 2 H, C*H*$_2$Ph), 7.11 (s, 1 H, 5-H).

Conjugated Diene 25: Pale yellow prisms from hexane/ethyl acetate; m.p. 92–93 °C. – $C_{19}H_{19}N_3O_2$ (321.4): calcd. 71.01, H 5.96, N 13.08; found C 70.81 H, 5.95, N 13.11. This compound was a (2:3) mixture of two geometric isomers in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): major isomer: δ = 1.33 (t, *J* = 6.9 Hz, 3 H, CH$_2$C*H*$_3$), 4.40 (d, *J* = 5.6 Hz, 2 H, >NC*H*$_2$–CH=), 4.28 (m, 2 H, C*H*$_2$CH$_3$), 4.54 (s, 2 H, C*H*$_2$Ph), 5.36 (ov, 2 H, =CH$_2$), 5.73–5.96 (m, 1 H, –C*H*=CH$_2$), 7.22–7.53 (ov, 6 H, 5-H and Ph), 7.63 (s, 1 H, 3-H). Assigned signals for minor isomer: δ = 3.91 (d, *J* = 5.9 Hz, 2 H, >NC*H*$_2$–CH=), 5.10 (s, 2 H, C*H*$_2$Ph), 7.68 (s, 1 H, 3-H).

Horner–Emmons Reaction of Acrolein Derivative 9a Leading to Conjugated Diene Compound 26: To a THF solution (8 mL) of diethyl cyanomethylphosphonate (0.12 mL, 0.78 mmol), cooled at 0 °C, was added sodium hydride (0.02 g, 0.99 mmol), and the mixture was stirred at the same temp. for 1 h. A solution of acrolein derivative **9a** (0.161 g, 0.71 mmol) in THF (1 mL) was added to the mixture, and the mixture was stirred for an additional 5 h. After quenching the reaction with water, the solvent was evaporated and the residue was taken up in ethyl acetate. The ethyl acetate was evaporated to dryness, and the residue was subjected to column chromatography on silica gel with hexane/ethyl acetate (2:1) as an eluent to afford conjugated diene compound **26** (0.267 g, 15%).

Conjugated Diene 26: yellow oil. – $C_{14}H_{15}N_4$ (249.3): calcd. C 77.08, H 6.15, N 16.68%; found C 76.86, H 6.14, N 16.54. This compound was a (3:7) mixture of two geometric isomers in [D$_6$]DMSO. – ^{1}H NMR ([D$_6$]DMSO): major product: δ = 4.09 (br, 2 H, >NC*H*$_2$–CH=), 4.47 (br s, 2 H, C*H*$_2$Ph), 5.04 (d, *J* = 20.0 Hz, 1 H, 2-H), 5.16–5.19 (ov, 2 H, =CH$_2$), 5.74 (m, 1 H, –C*H*=CH$_2$), 7.15–7.36 (ov, 6 H, 5-H and Ph), 7.75 (br s, 1 H, 3-H). Assigned signals for minor isomer: δ = 3.89 (br, 2 H, >NC*H*$_2$–CH=), 4.81 (br s, 2 H, C*H*$_2$Ph), 7.63 (br s, 1 H, 3-H).

Similarly, diene compound **27** was obtained in 37% yield.

Conjugated Diene 27: Colorless prisms from hexane/benzene; m.p. 49–50 °C. – $C_{18}H_{20}N_2O_2$ (296.4): calcd. C 72.95, H 6.80, N 9.45; found C 72.69, H 6.69, N 9.46. This compound was almost a single isomer in CDCl$_3$. – ^{1}H NMR (CDCl$_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 4.08 (br, 2 H, >NC*H*$_2$–CH=), 4.18 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.61 (br, 2 H, C*H*$_2$Ph), 5.21–5.36 (ov, 2 H, =CH$_2$), 5.77–5.83 (ov, 1 H, –C*H*=CH$_2$), 5.88 (d, *J* = 15.2 Hz, 1 H, 2-H), 6.98 (s, 1 H, 5-H), 7.20–7.43 (ov, 6 H, 3-H and Ph).

Carbonyl Ene Reaction–General Procedures. – Thermal Reaction of Acrolein Derivative 9d: A solution of acrolein derivative **9d** (0.148 g, 0.50 mmol) in toluene (3 mL) was heated under reflux for 24 h, and then evaporated to dryness. The resulting residue was subjected to column chromatography on silica gel with hexane/ethyl acetate (3:1) to afford unchanged **9d** (24%) and azepine **10d** (0.077 g, 52%). Similar reaction of **9d** in refluxing xylene for 20 h and the usual workup gave 1,3-oxazine **11d** (58%) and azepine **10d** (trace) together with many unidentified products.

Azepine Derivative 10d: Pale yellow paste. – IR (NaCl): ṽ = 3460 cm^{-1}, 2180, 1590. – ^{1}H NMR (CDCl$_3$): δ = 1.28 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$), 2.68 (br, 1 H, OH; exchanged with D$_2$O), 3.49 (ddd, *J* = 1.3, 1.6, and 5.6 Hz, 1 H, 5-H), 4.15–4.27 (ov, 2 H, C*H*$_2$CH$_3$), 4.53 (s, 2 H, C*H*$_2$Ph), 4.98 (br d, *J* = 5.9 Hz, 1 H, 4-H; changed to br s after the treatment with D$_2$O), 5.30 (dd, *J* = 5.6 and 9.2 Hz, 1 H, 6-H), 6.05 (br d, *J* = 9.2 Hz, 1 H, 7-H), 6.85 (br s, 1 H, 2-H), 7.19–7.42 (ov, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 14.2 (CH$_2$*C*H$_3$), 50.1 (5-C), 58.9 (*C*H$_2$CH$_3$), 61.3 (*C*H$_2$Ph), 68.8 (4-C), 105.8 (3-C), 107.0 (6-C), 121.9 (CN), 126.0, 128.2, 129.1, 136.8 (Ph–C), 131.0 (7-C), 146.8 (2-C), 172.3 (CO$_2$). – $C_{17}H_{18}N_2O_3$ (298.3): calcd. C 68.44, H 6.08, N 9.39; found C 68.66, H 6.12, N 9.44.

1,3-Oxazine 11d: yellow oil. – IR (NaCl): ṽ = 2180 cm^{-1}, 1600. – ^{1}H NMR (CDCl$_3$): δ = 1.26 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$), 2.24 (dd, *J* = 8.9 and 13.5 Hz, 1 H, 8-H), 2.62 (ddd, *J* = 3.0, 6.3, and 13.5 Hz, 1 H, 8-H), 3.44 (dd, *J* = 3.0 and 8.9 Hz, 1 H, 7-H), 4.14 (q, *J* = 7.3 Hz, 2 H, C*H*$_2$CH$_3$), 4.31 (s, 2 H, C*H*$_2$Ph), 4.92 (s, 1 H, 6-H), 5.12 (d, *J* = 6.3 Hz, 1 H, 2-H), 6.78 (s, 1 H, 4-H), 7.2–7.42 (ov, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 14.2 (CH$_2$*C*H$_3$), 44.0 (8-C), 48.1 (7-C), 56.9 (*C*H$_2$Ph), 61.0 (*C*H$_2$CH$_3$), 79.0 (6-C), 87.2 (2-C), 103.7 (5-C), 122.0 (CN), 126.1, 128.2, 129.3, 136.8 (Ph–C), 144.6 (4-C), 172.1 (CO$_2$). – $C_{17}H_{18}N_2O_3$ (298.3): calcd. C 68.44, H 6.08, N 9.39; found C 68.51, H 6.22, N 9.30.

Imine Ene Reaction–General Procedures. – Reaction of the Acrolein Derivative 9a and Aniline (12): A solution of acrolein derivative **9a** (0.219 g, 0.97 mmol) and aniline (**12**; 0.093 g, 1.1 mmol) in xylene (5 mL) was heated under reflux for 3 h. The solvent was evaporated to dryness, and the residue was subjected to column chromatography on silica gel with hexane/ethyl acetate (3:1) as an eluent to afford azepine **14a** (0.242 g, 83%).

Azepine Derivative 14a: Pale yellow prisms from hexane/benzene; m.p. 120–121 °C. – IR (KBr): ṽ = 3340 cm^{-1}, 2180, 1600. – ^{1}H NMR (CDCl$_3$): δ = 2.56 (m, 2 H, 5-H$_2$), 3.68 (br, 1 H, 4-H), 4.50 (s, 2 H, C*H*$_2$Ph), 4.55 (br, 1 H, NH), 4.98 (m, 1 H, 6-H), 5.96 (td, *J* = 1.3 and 7.6 Hz, 1 H, 7-H), 6.68–6.82, 7.15–7.42 (ov, total 11 H, 2-H and Ph). – ^{13}C NMR (CDCl$_3$): δ = 33.4 (5-C), 53.6 (4-C), 62.2 (*C*H$_2$Ph), 89.7 (3-C), 108.5 (6-C), 114.0, 118.3, 126.9, 128.3, 129.1, 129.3, 136.3, 146.0 (Ph–C), 122.5 (CN), 132.2 (7-C), 145.6 (2-C). – $C_{20}H_{19}N_3$ (301.4): calcd. C 79.70, H 6.35, N 13.94; found C 79.76, H 6.38, N 13.93.

Azepine Derivative 15a: Pale yellow prisms from hexane/benzene; m.p. 72–74 °C. – IR (KBr): ṽ = 3310 cm^{-1}, 2175, 1600. – ^{1}H NMR (CDCl$_3$): δ = 1.49 (br, 1 H, NH), 2.47–2.55 (ov, 2 H, 5-H$_2$), 3.82 (dd, *J* = 2.6 and 5.0 Hz, 1 H, 4-H), 3.93, 3.98 (each d, *J* = 16.8 Hz, each 1 H, –NHC*H*$_2$Ph), 4.49 (s, 2 H, 1–C*H*$_2$Ph), 5.45 (ddd, *J* = 5.9, 6.3, and 8.9 Hz, 1 H, 6-H), 5.88 (br dd, *J* = 1.3 and 8.9 Hz, 1 H, 7-H), 6.82 (d, *J* = 1.3 Hz, 1 H, 2-H), 7.18–7.39 (ov, 10 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 33.6 (5-C), 50.5 (NH*C*H$_2$Ph), 58.0 (4-C), 62.3 (1–CH$_2$Ph), 89.9 (3-C), 109.4 (6-C), 123.4 (CN), 126.8, 126.9, 127.0, 128.2, 129.0, 136.5, 140.1 (Ph–C), 131.8 (7-C), 145.6 (2-C). – $C_{21}H_{21}N_3$ (315.4): calcd. C 79.96, H 6.71, N 13.32; found C 80.02, H 6.64, N 13.57.

Azepine Derivative 14b: Pale yellow prisms from hexane/benzene; m.p. 114–115 °C. – IR (KBr): ṽ = 3360 cm^{-1}, 2180, 1600. – ^{1}H NMR (CDCl$_3$): δ = 1.15 (d, *J* = 5.9 Hz, 3 H, 5-Me), 2.86 (m, 1 H, 5-H), 3.43 (br d, *J* = 7.6 Hz, 1 H, 4-H), 4.40 (d, *J* = 7.6 Hz, 1 H, NH), 4.48 (s, 2 H, C*H*$_2$Ph), 4.76 (dd, *J* = 4.6 and 9.6 Hz, 1 H, 6-H), 5.87 (td, *J* = 1.6 and 9.6 Hz, 1 H, 7-H), 6.70–6.75, 7.15–7.40 (ov, total 11 H, 2-H and Ph). – ^{13}C NMR (CDCl$_3$): δ = 19.3 (5-Me), 38.7 (5-C), 58.2 (4-C), 63.4 (*C*H$_2$Ph), 90.3 (3-C), 113.6 (6-C), 113.8, 118.0, 126.9, 128.3, 129.1, 129.3, 136.4, 146.7 (Ph–C), 122.8 (CN), 129.8 (7-C), 145.1 (2-C). – $C_{21}H_{21}N_3$ (315.4): calcd. C 79.96, H 6.71, N 13.32; found C 80.15, H 6.76, N 13.15.

Azepine Derivative 15b: Pale yellow prisms from hexane/ether; m.p. 70–72 °C. – IR (KBr): ṽ = 3300 cm^{-1}, 2170, 1600. – ^{1}H NMR (CDCl$_3$): δ = 1.13 (d, *J* = 6.9 Hz, 3 H, 5-Me), 1.38 (br, 1 H, NH), 2.67 (m, 1 H, 5-H), 3.55 (dd, *J* = 0.7 and 1.0 Hz, 1 H, 4-H), 3.93, 4.09 (each d, *J* = 13.2 Hz, each 1 H, NHCH_2Ph), 4.48 (s, 2 H, 1-CH_2Ph), 4.73 (dd, *J* = 4.6 and 9.2 Hz, 1 H, 6-H), 5.76 (1 H, td, *J* = 1.7 and 9.2 Hz, 7-H), 6.82 (1 H, d, *J* = 1.0 Hz, 2-H), 7.17–7.43 (10 H, ov, Ph). – ^{13}C NMR (CDCl$_3$): δ = 19.4 (5-Me), 38.7 (5-C), 40.7 (NHCH$_2$Ph), 62.2 (1-CH$_2$Ph), 63.2 (4-C), 90.0 (3-C), 115.5 (6-C), 123.6 (CN), 126.8, 126.9, 128.1, 128.2, 128.3, 128.8, 126.6, 140.4 (Ph–C), 129.1 (7-C), 145.1 (2-C). – $C_{22}H_{23}N_3$ (329.4): calcd. C 80.21, H 7.04, N 12.76; found C 79.95, H 7.01, N 12.58.

Azepine Derivative 15c: we did not succeed in isolating this compound in a pure form. The structure was deduced by the ^{1}H NMR spectral data of the crude mixture as follows: δ = 3.91 (d, *J* = 6.0 Hz, 2 H, 5-H$_2$), 3.94 (d, *J* = 12.7 Hz, 1 H, 4-NHC*H*HPh), 4.50 (s, 2 H, 1-CH_2Ph), 5.98 (br d, *J* = 9.4 Hz, 1 H, 7-H), 6.82 (br s, 1 H, 2-H).

Azepine Derivative 14d: Colorless paste. – IR (KBr): ṽ = 3360 cm^{-1}, 2180, 1680, 1600. – ^{1}H NMR (CDCl$_3$): δ = 1.21 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3), 3.54–3.70 (ov, 2 H, 5-H and NH), 4.52 (s, 2 H, CH_2Ph), 5.03 (br s, 1 H, 4-H), 5.41 (dd, *J* = 5.0 and 9.6 Hz, 1 H, 6-H), 6.07 (br d, *J* = 9.6 Hz, 1 H, 7-H), 6.71–6.79 (ov, 4 H, 2-H and Ph), 7.16–7.41 (ov, 8 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 14.1 (CH$_2$$CH_3$), 49.0 (5-C), 57.0 (4-C), 62.0 (CH$_2$CH$_3$), 62.7 (CH$_2$Ph), 107.0, 107.4 (3- and 6-C), 122.0 (CN), 114.1, 118.3, 126.4, 128.0, 129.1, 129.3, 136.7, 146.3 (Ph–C), 130.1 (7-C), 145.5 (2-C), 172.0 (CO$_2$). – $C_{23}H_{23}N_3O_2$ (373.4): calcd. C 73.97, H 6.21, N 11.25; found C 74.09, H 6.38, N 11.11.

Aza-Wittig Reaction of Acrolein Derivative 9c with Iminophosphorane 18: A solution of acrolein derivative **9c** (0.11 g, 0.36 mmol) and iminophosphorane **18** (0.14 g, 0.40 mmol) in benzene was heated under reflux for 24 h, and the solvent was evaporated to dryness. The residue was subjected to column chromatography on silica gel with hexane/ethyl acetate (3:1) as an eluent to afford azepine **14c** (0.111 g, 81%).

Azepine Derivative 14c: Pale yellow prisms from hexane/benzene; m.p. 135–137 °C. – IR (KBr): ṽ = 3340 cm^{-1}, 2180 1590. – ^{1}H NMR (CDCl$_3$): δ = 3.63 (br d, *J* = 9.2 Hz, 1 H, NH), 4.01 (d, *J* = 5.9 Hz, 1 H, 5-H), 4.56 (s, 2 H, CH_2Ph), 4.67 (br d, *J* = 9.2 Hz, 1 H, 4-H), 5.12 (dd, *J* = 5.9 and 9.6 Hz, 1 H, 6-H), 6.07 (br dd, *J* = 1.3 and 9.6 Hz, 1 H, 7-H), 6.83 (d, *J* = 1.3 Hz, 1 H, 2-H), 6.59–6.74, 7.12–7.44 (ov, total 15 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 49.7 (5-C), 57.2 (4-C), 62.6 (CH$_2$Ph), 90.5 (3-C), 110.8 (6-C), 114.1, 118.3, 127.1, 128.4, 128.5, 129.2, 129.3, 130.6, 136.2, 141.6, 144.4 (Ph–C), 121.9 (CN), 130.6 (7-C), 145.9 (2-C). – $C_{26}H_{23}N_3$ (377.5): calcd. C 82.73, H 6.14, N 11.13; found C 82.45, H 6.16, N 10.88.

Similar reaction of acrolein derivative **9d** with **18** gave the desired azepine **14d** together with a small amount of pyrimidine **19**, which could not be isolated in a pure form. The structure of **19** was deduced from the ^{1}H-NMR spectral data of the crude mixture as follows: δ = 2.24 (dd, *J* = 9.0 and 13.2 Hz, 8-H), 2.60 (m, 8-H), 4.40 (s, CH_2Ph), 4.90 (s, 6-H), 5.15 (d, *J* = 6.3 Hz, 2-H).

Reaction of Acrolein Derivative 9a with *p*-Toluenesulfonamide (20) in the Presence of PTSA: A solution of acrolein derivative **9a** (0.194 g, 0.86 mmol), sulfonamide **20** (0.162 g, 0.94 mmol), and a small amount of PTSA in toluene (5 mL) was heated under reflux for 9 h. Usual workup by column chromatography on silica gel with hexane/ethyl acetate (5:1) and (1:1) as eluents, gave pyrimidine **21a** (0.161 g, 49%) and unchanged **9a** (44%) respectively.

Pyrimidine Derivative 21a: Colorless prisms from hexane/benzene; m.p. 74–75 °C. – IR (KBr): ṽ = 2180 cm^{-1}, 1600, 1330, 1150. – ^{1}H NMR (CDCl$_3$): δ = 1.87 (m, 1 H, 8-H), 2.11–2.20 (ov, 3 H, 7-H$_2$ and 8-H), 2.46 (s, 3 H, Me), 4.03, 4.19 (each d, *J* = 14.2 Hz, each 1 H, CH_2Ph), 4.29 (br d, *J* = 2.3 Hz, 1 H, 6-H), 5.05 (br d, *J* = 4.6 Hz, 1 H, 2-H), 6.12 (s, 1 H, 4-H), 7.15–7.39, 7.72–7.83 (ov, total 9 H, Ar). – ^{13}C NMR (CDCl$_3$): δ = 21.6 (Me), 36.5 (8-C), 38.4 (7-C), 56.6 (6-C), 58.1 (CH$_2$Ph), 72.4 (2-C), 80.2 (5-C), 119.6 (CN), 126.5, 127.9, 128.4, 128.7, 129.1, 129.3, 134.9, 144.3 (Ar–C), 144.0 (4-C). – $C_{21}H_{21}N_3O_2S$ (379.4): calcd. C 66.47, H 5.58, N 11.08; found C 66.38, H 5.67, N 11.20.

Pyrimidine Derivative 21c: Colorless prisms from hexane/benzene; m.p. 91–92 °C. – IR (KBr): ṽ = 2180 cm^{-1}, 1600, 1345, 1150. – ^{1}H NMR (CDCl$_3$): δ = 2.19 (ddd, *J* = 4.0, 5.6, and 13.5 Hz, 1 H, 8-H), 2.39 (m, 1 H, 7-H), 2.43 (s, 3 H, Me), 3.64 (dd, *J* = 4.0 and 8.9 Hz, 1 H, 8-H), 4.10, 4.29 (each d, *J* = 13.5 Hz, each 1 H, CH_2Ph), 4.27 (s, 1 H, 6-H), 5.19 (d, *J* = 5.6 Hz, 1 H, 2-H), 6.21 (s, 1 H, 4-H), 7.14–7.42 (ov, 12 H, Ar), 7.74 (br d, *J* = 8.6 Hz, 2 H, Ar). – ^{13}C NMR (CDCl$_3$): δ = 21.5 (Me), 46.4 (8-C), 56.3 (7-C), 58.1 (CH$_2$Ph), 62.1 (6-C), 72.8 (2-C), 79.5 (5-C), 119.5 (CN), 126.3, 126.3, 127.0, 127.9, 128.4, 128.6, 129.1, 129.2, 134.8, 135.5, 142.9, 144.3 (Ar–C), 143.5 (4-C). – $C_{27}H_{25}N_3O_2S$ (455.6): calcd. C 71.18, H 5.53, N 9.22; found C 71.55, H 5.63, N 9.41.

Olefin Ene Reaction. – General Procedures. – Thermal Reaction of Conjugated Diene Compound 22a: A solution of conjugated diene compound **22a** (0.345 g, 1.0 mmol) in toluene (5 mL) was heated under reflux for 24 h and usual purification by silica gel column chromatography [with hexane/ethyl acetate (3:1)] gave azepine **23a** (0.267 g, 76%).

Azepine Derivative 23a: Pale yellow prisms from hexane/ethyl acetate; m.p. 69–70 °C. – IR (KBr): ṽ = 2180 cm^{-1}, 1750, 1730, 1600. – ^{1}H NMR (CDCl$_3$): δ = 2.52 (ov, 2 H, 5-H$_2$), 3.41 [d, *J* = 10.6 Hz, 1 H, 4-C*H*(CO$_2$Me)$_2$], 3.58 (td, *J* = 4.0 and 10.6 Hz, 1 H, 4-H), 3.74, 3.81 (each s, each 3 H, OMe), 4.48 (s, 2 H, CH_2Ph), 4.89 (m, 1 H, 6-H), 5.87 (ddd, *J* = 1.3, 1.6, and 9.2 Hz, 1 H, 7-H), 6.76 (d, *J* = 1.3 Hz, 1 H, 2-H), 7.19–7.43 (ov, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 31.4 (5-C), 42.8 (4-C), 53.1, 53.2 (OMe), 58.9 [CH(CO$_2$Me)$_2$], 62.8 (CH$_2$Ph), 86.3 (3-C), 109.3 (6-C), 122.8 (CN), 127.3, 128.7, 129.5, 136.7 (Ph–C), 132.3 (7-C), 147.2 (2-C), 168.3 (CO$_2$). – $C_{19}H_{20}N_2O_4$ (340.4): calcd. C 67.04, H 5.92, N 8.23; found C 66.91, H 5.93, N 8.18.

Azepine Derivative 23b: Pale yellow prisms from hexane/ethyl acetate; m.p. 99–100 °C. – IR (KBr): ṽ = 2180 cm^{-1}, 1730, 1720, 1600. – ^{1}H NMR (CDCl$_3$): δ = 1.03 (d, *J* = 7.3 Hz, 3 H, 5-Me), 2.76 (m, 1 H, 5-H), 3.46 [d, *J* = 10.6 Hz, 1 H, 4-C*H*(CO$_2$Me)$_2$], 3.60 (br d, *J* = 10.7 Hz, 1 H, 4-H), 3.75, 3.76 (each s, each 3 H, OMe), 4.47 (s, 2 H, CH_2Ph), 4.72 (br, 1 H, 6-H), 5.79 (ddd, *J* = 1.3, 1.7, and 9.6 Hz, 1 H, 7-H), 6.75 (d, *J* = 1.3 Hz, 1 H, 2-H), 7.20–7.42 (ov, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 19.9 (5-Me), 37.4 (5-C), 46–48 (br, 4-C), 52.6, 52.7 (OMe), 57.1 [CH(CO$_2$Me)$_2$], 62.1 (CH$_2$Ph), 86.1 (3-C), 114.9 (6-C), 122.3 (CN), 126.9, 128.2, 129.0, 136.2 (Ph–C), 129.6 (7-C), 146.3 (2-C), 167.9, 168.4 (CO$_2$). $C_{20}H_{22}N_2O_4$ (354.4): calcd. 67.78, H 6.26, N 7.90%; found C 67.57, H 6.26, N 7.89%.

Azepine Derivative 23c: Pale yellow prisms from hexane/ethyl acetate; m.p. 150–151 °C. – IR (KBr): ṽ = 2180 cm^{-1}, 1730, 1600. – ^{1}H NMR (CDCl$_3$): δ = 3.43, 3.70 (each br s, each 3 H, OMe), 3.52 [d, *J* = 9.3 Hz, 1 H, 4-C*H*(CO$_2$Me)$_2$], 3.85 (br d, *J* = 9.3 Hz, 1 H, 4-H), 4.01 (br, 1 H, 5-H), 4.52 (s, 2 H, CH_2Ph), 5.21 (dd, *J* = 5.1 and = 9.6 Hz, 1 H, 6-H), 6.01 (ddd, *J* = 1.7, 2.0, and 9.6 Hz, 1 H, 7-H), 6.86 (d, *J* = 1.7 Hz, 1 H, 2-H), 7.18–7.45 (ov, 10 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 47.6 (5-C), 48.0 (br, 4-C), 52.5, 52.8 (OMe), 56.4 [CH(CO$_2$Me)$_2$], 62.2 (CH$_2$Ph), 86.4 (3-C), 110.5 (6-C), 121.8 (CN), 127.1, 127.2, 128.1, 128.3, 128.5, 129.1, 136.1, 141.1 (Ph–C), 130.6 (7-C), 146.6 (2-C), 167.5, 167.8 ($\mathrm{CO_2}$). – $\mathrm{C_{25}H_{24}N_2O_4}$ (416.5): calcd. C 72.10, H 5.81, N 6.73; found C 71.85, H 5.91, N 6.62.

Azepine Derivative 23d: Colorless prisms from hexane/ethyl acetate; m.p. 101–102 °C. – IR (KBr): $\tilde{\nu}$ = 2180 $\mathrm{cm^{-1}}$, 1730, 1600 cm. – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 1.32 (t, J = 6.9 Hz, 3 H, $\mathrm{CH_2C}\mathit{H}_3$), 3.36 [br, 1 H, 4-$\mathrm{C}\mathit{H}\mathrm{(CO_2Me)_2}$], 3.44 (br, 1 H, 4-H), 3.68, 3.78 (each s, each 3 H, OMe), 3.78 (br, 1 H, 5-H), 4.18 (ov, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 4.52 (s, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 5.37 (br, 1 H, 6-H), 5.99 (td, J = 1.7 and 9.6 Hz, 1 H, 7-H), 6.80 (br s, 1 H, 2-H), 7.20–7.43 (ov, 5 H, Ph). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 14.0 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 45.1 (br, 5-C), 47.2 (4-C), 52.7, 52.8 (OMe), 57.9 [br, $\mathit{C}\mathrm{H(CO_2Me)_2}$], 61.7 ($\mathit{C}\mathrm{H_2CH_3}$), 62.4 ($\mathit{C}\mathrm{H_2Ph}$), 85.7 (3-C), 106.7 (6-C), 121.8 (CN), 126.9, 128.4, 129.1, 135.9 (Ph–C), 130.5 (7-C), 146.6 (2-C), 167.3, 167.5, 170.9 ($\mathrm{CO_2}$). – $\mathrm{C_{22}H_{24}N_2O_6}$ (412.4): calcd. C 64.07, H 5.86, N 6.79; found C 63.80, H 5.86, N 6.76. The structure of this compound was confirmed by single crystal X-ray analysis.

Azepine Derivative 28: We did not succeed in isolating this compound, however, its formation was confirmed by the ^{1}H NMR spectral data of the crude mixture as follows: δ = 2.50 (m, 5-$\mathrm{H_2}$), 4.85 (m, 6-H), 6.70 (s, 2-H).

Azepine Derivative 29: Yellow oil. – $\mathrm{C_{19}H_{19}N_3O_2}$ (321.4): calcd. C 71.01, H 5.96, N 13.08; found C 70.50, H 6.04, N 12.58. – $\mathrm{C_{19}H_{19}N_3O_2}$: calcd. 321.1477; observed m/z (EI) 321.1466. This compound was obtained as an inseparable (3:7) mixture of two diastereomers. The structures of **29** were supported by their spectral data as follows: – ^{1}H NMR ($\mathrm{CDCl_3}$): major isomer: δ = 1.37 (t, J = 7.3 Hz, 3 H, $\mathrm{CH_2C}\mathit{H}_3$), 2.39–2.74 (m, 2 H, 5-$\mathrm{H_2}$), 3.44–3.57 [ov, 2 H, 4-H and 4-$\mathrm{C}\mathit{H}\mathrm{(CO_2Et)CN}$], 4.34 (q, J = 7.3 Hz, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 4.48 (s, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 5.08 (ddd, J = 1.3, 5.3, and 8.9 Hz, 1 H, 6-H), 5.93 (br d, J = 8.9 Hz, 1 H, 7-H), 6.82 (d, J = 1.3 Hz, 1 H, 2-H), 7.20–7.43 (ov, 5H, Ph). Assigned signals for the minor isomer: δ = 1.34 (t, J = 7.3 Hz, 3 H, $\mathrm{CH_2C}\mathit{H}_3$), 2.39–2.50 (ov, 2 H, 5-$\mathrm{H_2}$), 4.28 (q, J = 7.3 Hz, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 5.00 (m, 1 H, 6-H), 5.92 (br d, J = 8.9 Hz, 1 H, 7-H), 6.89 (d, J = 1.7 Hz, 1 H, 2-H). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 13.9 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 30.7, 31.0 (5-C), 42.9, 43.0 (4-C), 44.0, 44.6 (4-$\mathit{C}\mathrm{H_2CO_2Et}$), 62.5, 62.6 ($\mathit{C}\mathrm{H_2CH_3}$), 63.1, 63.4 ($\mathit{C}\mathrm{H_2Ph}$), 84.0, 84.4 (3-C), 108.6, 108.8 (6-C), 114.8, 115.2 (3-CN), 121.5 (CN), 126.9, 128.5, 129.1, 135.9 (Ph–C), 132.8 (7-C), 147.0 (2-C), 164.5 ($\mathrm{CO_2}$).

Azepine Derivative 30: Yellow oil. – IR (NaCl): $\tilde{\nu}$ = 2180 $\mathrm{cm^{-1}}$, 1600. – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.39–2.69 (ov, 4 H, 5-$\mathrm{H_2}$ and 4-$\mathrm{C}\mathit{H}_2\mathrm{CN}$), 3.13 (m, 1 H, 4-H), 4.47 (s, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 5.08 (m, 1 H, 6-H), 5.92 (td, J = 1.6 and 8.9 Hz, 1 H, 7-H), 6.77 (d, J = 1.6 Hz, 1 H, 2-H), 7.18–7.43 (ov, 5 H, Ph). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 24.4 (5-C), 31.3 (4-C), 38.9 ($\mathit{C}\mathrm{H_2CN}$), 62.3 ($\mathit{C}\mathrm{H_2Ph}$), 86.1 (3-C), 109.3 (6-C), 117.4 ($\mathrm{CH_2}\mathit{C}\mathrm{N}$), 121.8 (3-CN), 126.9, 128.4, 129.1, 136.1 (Ph–C), 132.7 (7-C), 146.1 (2-C). – $\mathrm{C_{16}H_{15}N_3}$: calcd. 249.1266; observed m/z (EI) 249.1255.

Azepine Derivative 31: Yellow oil. – IR (KBr): $\tilde{\nu}$ = 2180 $\mathrm{cm^{-1}}$, 1730, 1600. – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 1.20 (t, J = 7.2 Hz, 3 H, $\mathrm{CH_2C}\mathit{H}_3$), 2.21–2.59 (ov, 4 H, 5-$\mathrm{H_2}$ and 4-$\mathrm{C}\mathit{H}_2\mathrm{CO_2Et}$), 3.16 (m, 1 H, 4-H), 4.09 (q, J = 7.2 Hz, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 4.48 (s, 2 H, $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 4.88 (td, J = 5.6 and 8.9 Hz, 1 H, 6-H), 5.77 (td, J = 1.7 and 8.9 Hz, 1 H, 7-H), 6.62 (d, J = 1.6 Hz, 1 H, 2-H), 7.10–7.33 (ov, 5 H, Ph). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 14.1 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 32.0 (5-C), 38.7 (4-C), 41.4 (4-$\mathit{C}\mathrm{H_2CO_2Et}$), 60.5 ($\mathit{C}\mathrm{H_2CH_3}$), 62.1 ($\mathit{C}\mathrm{H_2Ph}$), 88.4 (3-C), 109.8 (6-C), 122.6 (3-CN), 127.3, 128.7, 129.5, 136.6 (Ph–C), 131.7 (7-C), 145.4 (2-C), 171.3 ($\mathrm{CO_2}$). – $\mathrm{C_{18}H_{20}N_2O_2}$ (296.4): calcd. C 72.95, H 6.80, N 9.45; found C 73.03, H 6.71, N 9.29.

Single-Crystal X-ray Structure Analysis of Azepine 23d[6]

Single crystals of compound **23d** were obtained as prisms from propan-2-ol. A crystal of approximate dimensions 0.160 × 0.600 × 1.00 mm was used for data collection. All measurements were made on a Rigaku AFC5S diffractometer by employing graphite-monochromated Mo-K_α radiation. The unit cell dimensions were obtained by least-squares analysis of 25 reflections within the range of $20.1 < 2\theta < 26.0°$. The crystal data for compound **23d** are given: crystal system: monoclinic; space group: Cc; cell constants: a = 8.188(8) Å, b = 29.86(1) Å, c = 9.168(7) Å^{-3}, V = 2135(3) Å^3; β = 107.71(6)°; Z value: 4; $D_{\mathrm{calcd.}}$ = 1.283 g cm^{-3}. The ω-2θ scan technique to a maximum 2θ-value of 53.9° was used. Scans of (1.57 + 0.30 tan θ)° were made at a speed 16° min^{-1}. A total of 2081 observed reflections (unique: 1936; R_{int} = 0.046) were collected. All calculations were performed using TEXAN program.[9] Atoms other than hydrogen were refined anisotropically. The structures were solved by direct methods (SIR)[10] and refined by least-squares to R 0.054 (R_{w} 0.054) for compound **23d**.

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