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Nitrone Cycloadditions to 1,2-Diphenylcyclopropenes and Subsequent Transformations of the Isoxazolidine Cycloadducts

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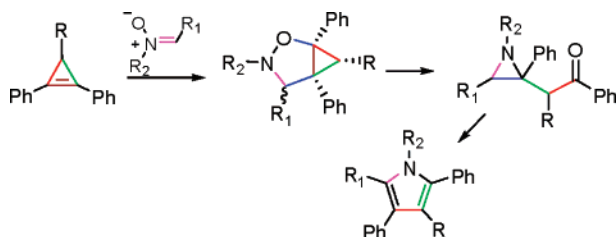
1,3-Dipolar cycloaddition of *C*-aryl,*N*-aryl (or *N*-methyl) nitrones with a number of 1,2-diphenylcyclopropenes substituted at the C[3] position occurs with the formation of expected "normal" cycloadducts (with *N*-methylnitrones) and products of their subsequent transformations. Among them are corresponding α-acetophenyl aziridines and tetra (or penta)-arylpyrroles. Aziridines and the normal cycloadducts can be also thermally converted to such arylpyrroles with moderate to good yields. Substitution at the C[3] position of cyclopropenes by an electron acceptor group decreases the reactivity of cyclopropenes.

The release of strain upon any type of addition or cycloaddition onto alkenes with three-membered carbon units such as cyclopropenes,[1] methylenecyclopropanes,[2] and bicyclopropy-lidenes[3] results in enhanced reactivity. This makes such alkenes especially attractive for synthetic applications.[1a−c,2,3] Among such strained compounds, cyclopropenes possess the most highly strained double C,C bond.[1] We demonstrated earlier the significance of electronic factors in determining the reactivity of cyclopropenes in the cycloaddition reaction with carbonyl ylides.[4] Corresponding cycloadducts with carbonyl ylides were formed in yields of up to 92% with cyclopropenes, but no reaction was observed or the yields of adducts were less than 5% in the case of 3-acceptor-substituted cyclopropenes. Frontier molecular orbital (FMO) analysis and the global electrophilicity index ω have been used to clarify the relative reactivity patterns.[4] We decided to examine whether these results are restricted to reactions with carbonyl ylides only. Among other 1,3-dipoles, nitrones have similar FMO characteristics and electrophilicity to the carbonyl ylides studied earlier.[5] Whereas 1,3-dipolar cycloadditions of nitrones with methylenecyclopropanes and bicyclopropylidenes have been investigated in great detail,[2,3a] there is only a single report of cycloaddition of an electron-deficient nitrone with 3,3-dimethylcyclopropene.[6] In this paper, we wish to report the first systematic study of 1,3-dipolar cycloaddition of nitrones with cyclopropenes.

1,2-Diphenylcyclopropenes monosubstituted at the C[3] position (**1a−e**) were selected for investigation (Scheme 1). This enabled us to vary electronic properties of the substituent at the C[3] position. We performed 1,3-dipolar cycloaddition reactions with *C*-aryl-*N*-phenylnitrones **2a−d** and *C*-phenyl-*N*-methylnitrone **2e** (Scheme 1). In general, the reactions studied here differ in both reaction conditions and products formed. The results can be arranged into three distinct groups.

I. Reactions of *C*-phenyl-*N*-methylnitrone **2e** and cyclopropenes **1a,b** (benzene, reflux, 10−15 h) afforded expected "normal" cycloadducts **3a** and **3b** in yields of about 30% (Table 1, entries 5 and 8). Preferably the endo isomer of cycloadduct

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(1) Reviews: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (c) *Methods of Organic Chemistry (Houben-Weyl)*; de Meijere, A., Ed.; Thieme: Stuttgart, Germany, 1997; Vol. E17a−d. (d) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271. (e) Dolbier, W. R., Jr.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071. (f) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (g) Deem, M. L. *Synthesis* **1972**, 675. (h) Deem, M. L. *Synthesis* **1982**, 701.

(2) Reviews: (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (b) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (c) Goti, A.; Cordero, F. M.; Brandi, A. *Top. Curr. Chem.* **1996**, *178*, 1.
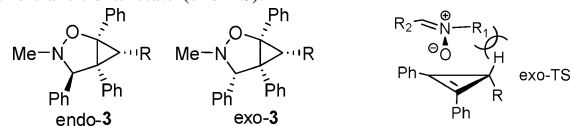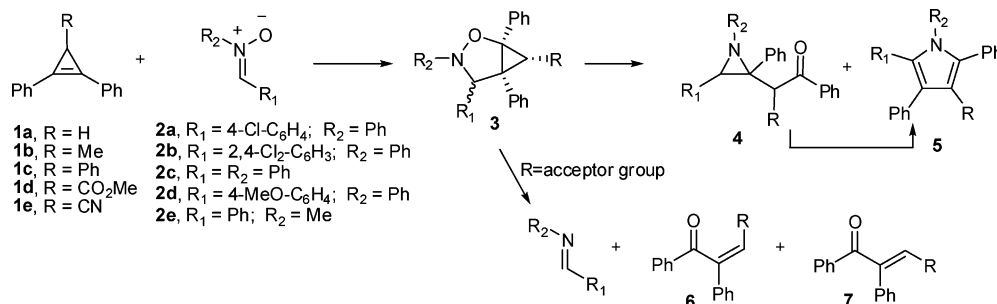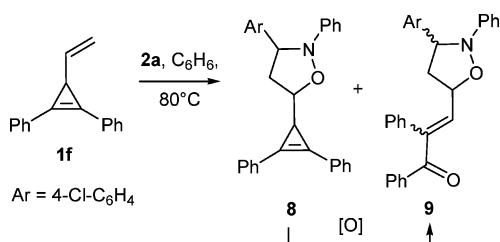
(3) Reviews: (a) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89. (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Zh. Org. Khim.* **1996**, *32*, 1607; *Russ. J. Org. Chem. (Engl. Transl.)* **1996**, *32*, 1555.

(4) (a) Diev, V. V.; Kostikov, R. R.; Gleiter, R.; Molchanov, A. P. *J. Org. Chem.* **2006**, *71*, 4066. (b) Molchanov, A. P.; Diev, V. V.; Kopf, J.; Kostikov, R. R. *Russ. J. Org. Chem (Engl. Transl.)* **2004**, *40*, 431.

(5) For reviews on the 1,3-dipolar cycloaddition of nitrones, see: (a) Jones, R. C. F.; Martin, J. N. In *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; pp 1−81. (b) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, Germany, 1988. (c) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 83−168.

(6) Akmanova, N. A.; Sagitdinova, K. F.; Balenkova, E. S. *Khim. Geterotsikl. Soedin.* **1982**, 1192; *Chemistry of Heterocyclic Compounds (Engl. Transl.)* **1982**, *18*, 910. In the reaction of *C,N*-diphenylnitrone with 1,3,3-trimethylcyclopropene, products were not identified: see ref 1h.

(7) The unfavorable steric interactions between the proton at the C[3] position of the cyclopropene ring and substituent R₁ of nitrones can occur in exo transitional state (exo-TS):

endo-3   exo-3   exo-TS

TABLE 1. Results of Reactions of Nitrones with 3-Substituted 1,2-Diphenylcyclopropenes

entry	cyclopropene	nitrone	3/yield (%)	4/yield (%)	5/yield (%)	6/yield (%)	7/yield (%)
1[a]	**1a**	**2a**	–	**4a**/61 (76)[b]	**5a**/14 (69)[c]	–	–
2[a]	**1a**	**2b**	–	**4b**/56 (74)[b]	**5b**/12 (70)[c]	–	–
3[a]	**1a**	**2c**	–	**4c**/57	**5c**/26	–	–
4[a]	**1a**	**2d**	–	**4d**/50	**5d**/6	–	–
5[d]	**1a**	**2e**	**3a**/29[e]	–	–	–	–
6[a]	**1b**	**2a**	–	**4e**/–	**5e**/60	–	–
7[a]	**1b**	**2c**	–	**4f**/16 (32)[b]	**5f**/13 (26)[b]	–	–
8[d]	**1b**	**2e**	**3b**/35[f]	–	**5g**/26[g]	**6a**/–[g]	**7a**/52[g]
9[d]	**1c**	**2a**	–	–	**5h**/18[h]	**6b**/–	**7b**/57
10[d]	**1c**	**2e**	–	–	–	–	–
11[i]	**1d**	**2a**	–	–	**5i**/8[h]	**6c**/22	**7c**/30
12[i]	**1d**	**2c**	–	–	**5j**/7[h]	**6c**/21	**7c**/36
13[i]	**1d**	**2d**	–	–	**5k**/8	**6c**/25	**7c**/33
14[i]	**1d**	**2e**	–	–	–	–	–
15[i]	**1e**	**2a**	–	–	–	**6d**/31	**7d**/65
16[i]	**1e**	**2c**	–	–	–	**6d**/26	**7d**/47
17[i]	**1e**	**2d**	–	–	–	**6d**/21	**7d**/43

[a] Conditions: benzene/acetonitrile, reflux, 1−3 h. [b] Yield based on recovered cyclopropenes. [c] Yield is based on the thermolysis of aziridines (benzene, reflux). [d] Conditions: benzene, reflux, 10−15 h (entries 9 and 10, 100 h). [e] Diastereomeric ratio (endo/exo) = 82:18. [f] Diastereomeric ratio (endo/exo) > 98:2. [g] Conditions: **3b**, o-xylene, reflux, 3 h. [h] Calculated yields from ^{1}H NMR spectra of fractions enriched with corresponding products; analytically pure samples could not be obtained. [i] Conditions: toluene, reflux, 25−35 h (entry 14, 100 h).

SCHEME 1. General Scheme of Reactions of Nitrones with 3-Substituted 1,2-Diphenylcyclopropenes

1a, R = H
1b, R = Me
1c, R = Ph
1d, R = CO$_2$Me
1e, R = CN

2a, R$_1$ = 4-Cl-C$_6$H$_4$; R$_2$ = Ph
2b, R$_1$ = 2,4-Cl$_2$-C$_6$H$_3$; R$_2$ = Ph
2c, R$_1$ = R$_2$ = Ph
2d, R$_1$ = 4-MeO-C$_6$H$_4$; R$_2$ = Ph
2e, R$_1$ = Ph; R$_2$ = Me

SCHEME 2. Cycloaddition of Nitrone 2a to 3-Vinyl-1,2-diphenylcyclopropene 1f

Ar = 4-Cl-C$_6$H$_4$

3a was formed (exo:endo 18:82)[7] in the cycloaddition reaction of 1,2-diphenylcyclopropene **1a**, and only the endo cycloadduct **3b** was observed in the reaction of 3-methyl-1,2-diphenylcyclopropene **1b**. The anti-disposition of the methyl group relative to the isoxazolidine ring in cycloadduct **3b** corresponds to the approach of the dipolarophile from the least hindered face of cyclopropene **1b**. Reaction of *N*-methylnitrone **2e** with cyclopropenes **1c** (R = Ph) and **1d** (R = CO$_2$Me) did not give any products even on heating the reaction mixture for 100 h (starting cyclopropenes were recovered from reaction mixtures).

II. Reactions of diarylnitrones **2a−d** and cyclopropenes **1a,b** (Table 1, entries 1−4, 6, 7, and 9) proceeded under milder conditions (benzene/acetonitrile, reflux, 1−3 h) and afforded separable mixtures of aziridines **4**[8] (30−60% yield) and tetraarylpyrroles **5** (6−60% yield). Remarkably, the reaction of diarylnitrone **2a** with triphenylcyclopropene **1c** was much slower (benzene, reflux, 100 h), giving pentaarylpyrrole **5h** (18%) and ketone **7b** (57%). Formation of these unexpected aziridines and

pyrroles can be considered as a result of rearrangement of the initially formed normal cycloadducts of nitrone and cyclopropene (see below for discussion).

III. Reactions of nitrones **2** with acceptor-substituted cyclopropenes **1d,e** belong to the third group (Table 1, entries 11−17). In this case, the reactions proceeded at both higher temperatures and for prolonged times (toluene, reflux, 25−35 h) and afforded complex mixtures containing isomeric ketones **6** and **7**.[9] That the reactions with acceptor-substituted cyclopropenes require more vigorous conditions is consistent with a diminished reactivity of cyclopropenes found in our previous

(8) Only one isomer of aziridines **4** was isolated from the reaction mixtures. For the most stable aziridine **4b**, X-ray analysis did not give reliable result (R factor = 0.14; for a view, see Supporting Information). The obtained aziridine **4a** appeared to be somewhat unstable in solutions in air, slowly furnishing the corresponding pyrrole **5a**. However, the rather stable aziridine **4b** can be obtained in the reaction of diarylnitrone **2b**. The stability of aziridines was also found to be dependent on the nature of the substituent R in the α-position. Thus, the corresponding aziridine **4e** formed in the reaction of 3-methyl-1,2-diphenylcyclopropene **1b** (Table 1, entry 6) can only be detected by TLC. This aziridine underwent complete transformation to the pyrrole **5e** on silica gel.

(9) Besides ketones, products of decomposition of Schiff bases were formed (corresponding aldehydes) as well as compounds **A−F** (see Supporting Information). The latter are products of the 1,3-dipolar cycloaddition of nitrones to the double C,C bond of the initially formed unsaturated ketones. Dipolar cycloadditions with different unsaturated carbonyl compounds are well documented (see ref 5).

A−F, R=CO$_2$Me, CN
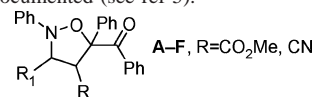
SCHEME 3. Proposed Mechanisms of the Formation of Aziridines, Pyrroles, Enamines, and Ketones Starting from Cyclopropenes and Nitrones
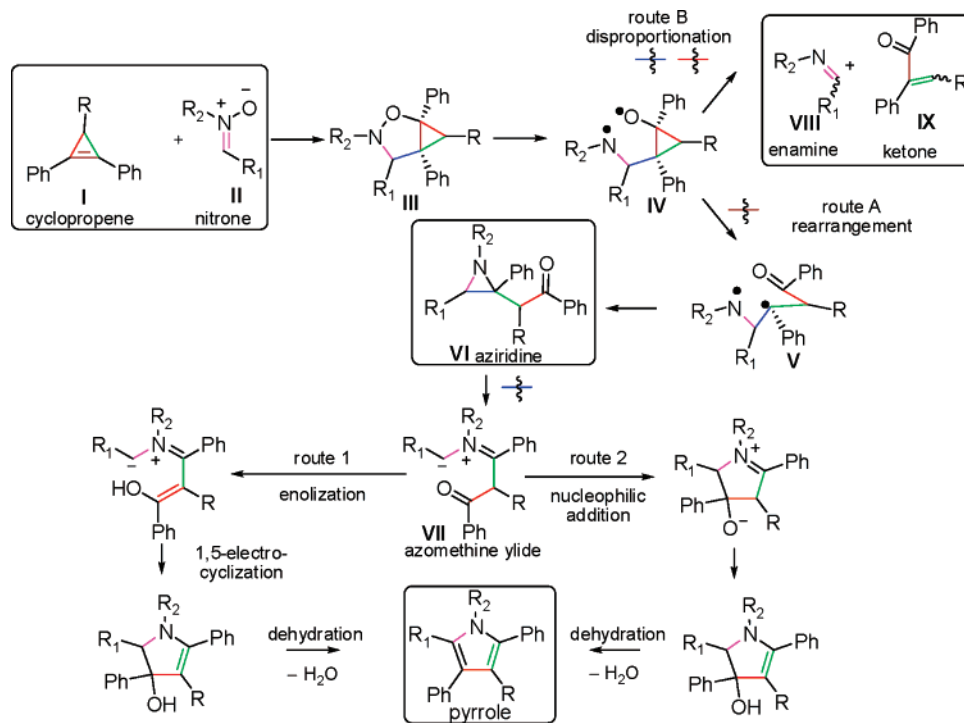
study of cycloadditions of carbonyl ylides to 3-substituted 1,2-diphenylcyclopropenes **1a**−**e**.[4] The reactivity of cyclopropenes **1a**−**e** with nitrones, however, is not so strongly affected by the electronic nature of the substituent at the cyclopropene C[3] position as in the case of carbonyl ylides.

We also studied thermolysis reactions with several of the obtained products (Scheme 1, Table 1, footnotes c and g). When subjected to thermolysis in refluxing benzene, aziridines **4a**,**b** underwent conversion to pyrroles **5a**,**b** (70%). Heating the normal cycloadduct **3b** in refluxing *o*-xylene until complete consumption of starting material (3 h) afforded a separable mixture of 1,2-diphenylbut-2-en-1-one **7a** (52%) and pentasubstituted pyrrole **5g** (26%).

In contrast to cycloaddition of nitrones **2a**−**e** with cyclopropenes **1a**−**e**, the reaction of 3-vinyl-1,2-diphenylcyclopropene **1f** with diarylnitrone **2a** (benzene, reflux, 1 h) proceeded with the formation of cyclopropenyl isoxazolidine **8** as a single isomer (10%) and a mixture of four isomeric isoxazolidines **9** (48%) (Scheme 2). All products in this reaction correspond to the cycloaddition of nitrone dipole to the vinylic C,C double bond of cyclopropene **1f**. The initially formed cycloadducts **8** containing the cyclopropene moiety are unstable and can be easily oxidized by air to form isomeric isoxazolidines **9**.[10] This result demonstrates that the C,C double bond of the three-membered ring is significantly less active toward cycloaddition of nitrone than vinylic double bond. This could be due to the more polar nature of the vinylic double bond.[11]

A preliminary attempt to rationalize the mechanism of these transformations can be proposed (Scheme 3). The initial step of the process is presumed to be a normal 1,3-dipolar cycloaddition reaction of cyclopropenes **I** with nitrones **II** to form

cycloadducts **III**. These cycloadducts **III** are thermally unstable in the case of diarylnitrones, whereas with *N*-methylnitrone, they can be isolated. Then, the isoxazolidine cycloadducts **III** undergo a thermally induced homolytic cleavage of the weak N−O bond, giving intermediate biradical **IV**.[12] The presence of the strained three-membered ring fused on the adjacent position to the O-centered radical in **IV** can lead to ring opening of the cyclopropane with formation of the more stable biradical **V** (Scheme 3, route A).[13] The latter undergoes ring contraction to the rather stable aziridine **VI**. Another possible transformation of biradical intermediate **IV** is disproportionation (route B) with the formation of the corresponding enamine **VIII** and isomeric ketones **IX**. The presence of an acceptor group at the cyclopropane ring in biradicals **IV** derived from cyclopropenes **1d**,**e** seems to facilitate such disproportionation. It is not clear whether pyrroles isolated directly from reaction mixtures are formed from aziridines or other intermediate species. The data, however, indicate that isolated aziridines can be thermally converted to

(11) According to B3LYP/6-31G* calculations, the terminal vinylic carbon atom of 3-vinyl-1,2-diphenylcyclopropene **1f** has the greatest negative charge (−0.3, Lowdin). The charges on another vinylic carbon atom and carbons of the cyclopropenyl double bond are close to 0. Remarkably, carbonyl ylide cycloadditions to cyclopropene **1f** proceed to the C,C double bond of the three-membered ring (see ref 4). Also, we can suggest that the difference between steric screening of double bonds in both synclinal and periplanar conformations of vinylcyclopropene **1f** (see Supporting Information) is not enough to explain regiochemical outcome of the reaction.

(12) For recent examples of closely related isomerization of 4-isoxazolines to aziridines, see: (a) Friebolin, W.; Eberbach, W. *Tetrahedron* **2001**, *57*, 4349. (b) Ishikawa, T.; Kudoh, T.; Yoshida, J.; Yasuhara, A.; Manabe, S.; Saito, S. *Org. Lett.* **2002**, *4*, 1907.

(13) For reviews on N−O bond cleavage in nitrone−alkylidenecyclopropane cycloadducts, see ref 2. For closely related N−O bond cleavage in nitrile oxide−cyclopropene cycloadducts, see: Zaitseva, L. G.; Chizhov, I. G.; Bolesov, I. G. *Zh. Org. Khim.* **1975**, *11*, 1347; *Russ. J. Org. Chem. (Engl. Transl.)* **1975**, *11*, 1333. In addition, analogous ketones have been reported in this work.

(10) Taking into account that the two isomeric products **9** can be obtained from a single isomer of **8**, the initial formation of two isomeric cyclopropenyl isoxazolidines **8** can be proposed. Only the more stable isomer was isolated.

final pyrroles with good yields. A mechanism involving opening of the aziridine ring to an azomethine ylide **VII** followed by either enolization of its carbonyl group with subsequent 1,5-electrocyclization (Scheme 3, route 1) or intramolecular nucleophilic addition of azomethine ylide to a carbonyl group (Scheme 3, route 2) can be proposed to account for the observed rearrangement patterns.[14]

In conclusion, we have reported a previously unknown reaction cascade that involves 1,3-dipolar cycloaddition of 1,2-diphenylcyclopropenes to *C*-aryl,*N*-aryl (or *N*-methyl) nitrones with the formation of bicyclic isoxazolidine products. Subsequent transformations of the isoxazolidines give sterically hindered polyarylsubstituted aziridines and pyrroles. A plausible mechanism has been proposed which includes formation of biradicals and their rearrangements. Theoretical calculations are underway in our lab to study these mechanistically interesting transformations of biradicals. The obtained results also suggest the significance of substitution at the C^3 position of cyclopropenes by an electron acceptor group.

Experimental Section

Typical Procedure for the Cycloaddition Reactions of Nitrones with Cyclopropenes. To a solution of *C*-(2,4-dichlorophenyl)-*N*-phenylnitrone **2b** (230 mg, 0.87 mmol, 1.14 equiv) in benzene/acetonitrile (1:1, 5 mL) was added 1,2-diphenylcyclopropene **1a** (146 mg, 0.76 mmol). After heating the reaction mixture at 80 °C for 1 h in argon atmosphere, solvents were evaporated under reduced pressure. The residue was chromatographed on a silica gel column eluting with a mixture of hexane/ethyl acetate to afford aziridine **4b** (190 mg, 0.42 mmol, 56%) and tetraarylpyrrole **5b** (37 mg, 0.08 mmol, 12%). **4b**: mp 115−117 °C; ^{1}H NMR δ 3.30 (d, 1H, $J = 17.4$ Hz), 3.87 (s, 1H), 3.88 (d, 1H, $J = 17.4$ Hz), 6.93−6.96 (m, 1H), 7.02−7.22 (m, 7H), 7.28−7.43 (m, 8H), 7.51 (t, 1H, $J = 8.0$ Hz), 7.75 (d, 2H, $J = 6.5$ Hz); ^{13}C NMR δ 43.5, 49.4, 54.0, 121.0, 123.4, 126.9, 127.3, 128.1, 128.4, 128.6, 128.9, 129.7, 130.6, 133.3, 133.5, 133.6, 134.6, 137.5, 138.7, 149.2, 196.6. Anal. Calcd for $C_{28}H_{21}Cl_2NO$: C, 73.37; H, 4.62; N, 3.06. Found: C, 73.27; H, 4.51; N, 2.79. **5b**: mp 70−71 °C; ^{1}H NMR δ 6.80 (s, 1H), 7.03−7.05 (m, 2H), 7.12−7.28 (m, 15H), 7.33−7.34 (m, 1H); ^{13}C NMR δ 109.8, 125.0, 125.4, 126.9, 127.22, 127.25, 127.5, 127.8, 128.5, 128.8, 128.9, 128.99, 129.02, 129.7, 130.5, 131.7, 133.1, 133.7, 135.3, 137.5, 138.9, 143.3. MS (EI) *m/z* (%): 439 [M] (100), 199 (24), 165 (13), 105 (40), 77 (84). Anal. Calcd for $C_{28}H_{21}ClN$: C, 76.37; H, 4.35; N, 3.18. Found: C, 76.07; H, 4.10; N, 3.10.

Supporting Information Available: Details of experimental procedures, spectroscopic data of the reaction products **3**−**9**, and X-ray crystal structure and a CIF file for **3b** and **5g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Note the proposed mechanism needs more clarification. Thus, it is problematic to demonstrate whether enolization of azomethine ylide or direct intramolecular nucleophilic addition occurs (route 1 vs 2). For the possibility of conversion of aziridines to pyrroles via 1,5-electrocyclization of transient azomethine ylide, see: (a) Padwa, A.; Dean, D.; Mazzu, A.; Vega, E. *J. Am. Chem. Soc.* **1973**, *95*, 7168. (b) Huisgen, R. *Angew. Chem.* **1980**, *92*, 979. (c) For recent review on conjugated azomethine ylides, see: Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873. (d) For review on 1,5-dipolar cyclizations, see: Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181.