JOC*Note*

Highly Efficient and Site-Selective [3 + 2] Cycloaddition of Carbene-Derived Ambident Dipoles with Ketenes for a Straightforward Synthesis of Spiro-Pyrrolidones

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Received April 11, 2007

The [3 + 2] cycloaddition reaction of 2-arylthiocarbamoyl benzimidazolium, -imidazolinium, and -triazolium inner salts (the ambident C−C−N and C−C−S 1,3-dipoles derived from carbenes) with ketenes proceeded efficiently in a highly site-selective manner to produce the C−C−N cycloaddition products benzimidazoline-, imidazolidine-, or triazoline spiro-pyrrolidones in 58−93% yields. Theoretical calculation suggests a stepwise mechanism for the reaction and indicates that the C−C−N cycloaddition of the dipoles with ketenes is both a dynamically and thermodynamically favored reaction pathway. Their easy availability, high reactivity, and reaction selectivity render the benzimidazolium, -imidazolinium, and -triazolium inner salts powerful and versatile 1,3-dipoles in the construction of novel spiro heterocyclic systems, which are not easily accessible by other methods.

Huisgen's [3 + 2] dipolar cycloaddition reactions constitute one of the most powerful protocols in organic synthesis.[1] For more than half a century, 1,3-dipolar cycloadditions have been widely applied in the construction of various five-membered heterocycles and in the synthesis of natural products and of bioactive organic compounds.[2] Most of the known 1,3-dipolar compounds, such as diazoalkanes, azides, nitrile ylides, nitrile imines, nitrile oxides, azomethine ylides, nitrones, carbonyl ylides, and carbonyl imines, are heteroatom-centered dipoles containing only one dipolar species. The 1,3-dipolar cycloaddition reactions of a carbon-centered 1,3-dipole and of a compound containing two or more dipolar species are uncommon.[3]

Ketenes[4] are versatile reactive intermediates in cycloaddition reactions.[5] The well-known Staudinger ketene−imine[6] and ketene−alkene[7] [2 + 2] cycloadditions have become the most popular route to β-lactam and cyclobutanone derivatives. Ketenes are also good dienophiles in [4 + 2] cycloaddition reactions.[8] Both the [2 + 2] and [4 + 2] cycloadditions can take place across either the C═C or the C═O bond of the ketenes. By comparison with the numerous reports of [2 + 2] and [4 + 2] cycloaddition reactions of ketenes, only a few examples of [3 + 2] cycloaddition with 1,3-dipoles are documented in the literature. For example, ketenes have been reported to undergo [3 + 2] cycloaddition with nitrones,[9] nitrile oxides,[10] and azomethine ylides.[11] By contrast with [2 + 2] and [4 + 2] cycloadditions, only the C═C bond of ketenes is involved in the above-reported [3 + 2] reactions.

Nucleophilic *N*-heterocyclic carbenes are known to react with aryl or acyl isothiocyanates to form stable zwitterionic inner salts.[3,12] However, these formal carbon-centered bis-dipoles have not attracted much attention, and their [3 + 2] cycloaddition reactions have remained largely unexplored.[3a,b] Very recently, we found that the 2-arylthiocarbamoyl benzimidazolium **1** and imidazolinium inner salts **2** (which are readily derived from the reaction of imidazoline and benzimidazole carbenes with aryl isothiocyanates) are unique ambident C^+-C-S^- and C^+-C-N^- bis-dipolar compounds able to react with a few dipolarophiles.[3c,d] For example, our experimental and theoretical studies[3d] have shown that zwitterions **1** or **2** acted as C^+-C-S^- dipoles toward stronger electrophilic and somewhat sterically hindered dipolarophiles such as dimethyl acetylenedicarboxylate and dibenzoylacetylene to afford imidazole spiro-thiophene derivatives. On the other hand, upon the treatment with weaker electrophilic and less hindered dipolarophiles such as ethyl

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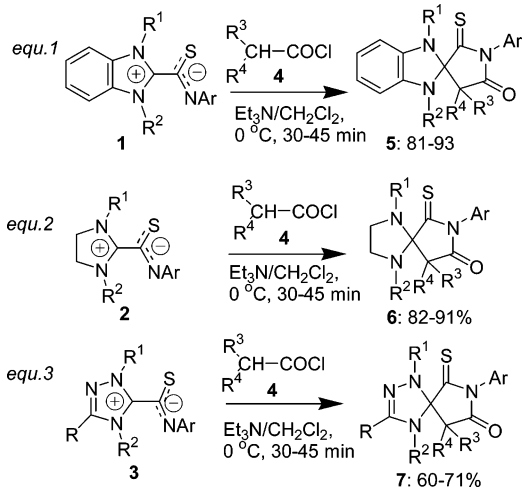
10.1021/jo070759u CCC: $37.00
Published on Web 07/13/2007

SCHEME 1. Reactions of 2-Arylthiocarbamoyl Benzimidazolium 1, -Imidazolinium 2, and -Triazolium Inner Salts 3 with Acyl Chloride in the Presence of Triethylamine



propiolate, methyl acrylate, and acrylonitrile, **1** or **2** behaved as C^+-C-N^- species and produced imidazole spiro-pyrrole derivatives. No reaction was observed when the less active and also sterically hindered dipolarophiles, such as methyl 2-butynoate, methyl crotonate, diethyl fumarate, and fumaronitrile, were used. However, the behavior of these ambident dipoles toward strong and less hindered dipolarophiles has not been examined. To gain a deep insight into the reactivity and particularly the site selectivity of such ambident C^+-C-S^- and/or C^+-C-N^- dipolar compounds, we undertook the current study of their reaction with ketenes.

The carbon-centered bis-dipoles, namely, 2-arylthiocarbamoyl benzimidazolium **1,** imidazolinium **2**, or triazolium inner salts **3**, were prepared from the reaction of aryl isothiocyanates with the corresponding carbenes generated in situ from the benzimidazolium, imidazolinium, or triazolium salts, respectively.[3c,d,11e] Since ketenes are conveniently generated by the elimination of HCl from an acyl chloride using a base, we initially examined the reaction of *N*,*N*′-dibenzyl-2-phenylthiocarbamoyl benzimidazolium inner salt **1a** with isobutyl chloride **4a** in the presence of triethylamine.

At 0 °C, the reaction of **1a** with **4a** and triethylamine in dichloromethane proceeded rapidly and efficiently to afford a red product **5a** in 93% isolated yield after 30−45 min. Encouraged by this result, we studied the reaction between various benzimidazolium inner salts **1a**−**f** and different acyl chlorides **4a**−**d** (Scheme 1, eq 1). To our delight, as summarized in Table 1, all reactions except that of **1a** with **4d** took place efficiently to produce spiro[benzimidazoline-2,3′-pyrrolidine]-2′-thioxo-5′-ones **5a**−**i** in the yields of 81−93%. No reaction was observed between dipole **1a** and the bulky diphenylacetyl chloride **4d**, most probably because of steric hindrance of two phenyl groups of **4d** in the cyclization process (Table 1, entry 10).

To test the generality of the reaction, we then extended the 1,3-dipolar substrates to imidazolinium **2** and triazolium inner salts **3**. Under identical conditions, both **2** and **3** reacted equally well with acyl chloride to furnish imidazolidine spiro-pyrrolidones **6a**−**d** in 82−91% and triazoline spiro-pyrrolidones **7a**,**b** in 60−71%, respectively (eqs 2 and 3 in Scheme 1 and Table 2).

The structures of all products were fully characterized by spectroscopic data and microanalysis. Both the spectroscopic data and microanalysis indicated that all products **5**, **6**, and **7**

TABLE 1. Preparation of Spiro[benzimidazoline-2,3′-pyrrolidine]-2′-thioxo-5′-ones 5

	starting materials		product
entry	**1**: R^1, R^2, Ar	**4**: R^3, R^4 or **11**: R^3	yield (%)
1	**1a**: Bn, Bn, Ph	**4a**: Me, Me	**5a** 93
2	**1a**: Bn, Bn, Ph	**4b**: H, Bn	**5b** 91
3	**1a**: Bn, Bn, Ph	**4c**: R^3, $R^4 = (CH_2)_5$	**5c** 90
4	**1b**: Bn, Bn, *p*-MeOPh	**4a**: Me, Me	**5d** 85
5	**1c**: Bn, Bn, *p*-ClPh	**4a**: Me, Me	**5e** 85
6	**1d**: *p*-ClBn, *p*-ClBn, Ph	**4a**: Me, Me	**5f** 87
7	**1d**: *p*-ClBn, *p*-ClBn, Ph	**4b**: H, Bn	**5g** 85
8	**1e**: Et, Bn, Ph	**4a**: Me, Me	**5h** 81
9	**1f**: Bu, Bn, Ph	**4a**: Me, Me	**5i** 83
10	**1a**: Bn, Bn, Ph	**4d**: Ph, Ph	*a*
11	**1a**: Bn, Bn, Ph	**11a**: Bn	**5b** 58
12	**1a**: Bn, Bn, Ph	**11b**: CH_2CH_2Ph	**5j** 66
13	**1d**: *p*-ClBn, *p*-ClBn, Ph	**11c**: $CH(CH_3)_2$	**5k** 58

[a] No reaction was observed.

TABLE 2. Preparation of the Spiro[imidazolidine-2,3′-pyrrolidine]-2′-thioxo-5′-ones 6 and Spiro[triazoline-2,3′-pyrrolidine]-2′-thioxo-5′-ones 7

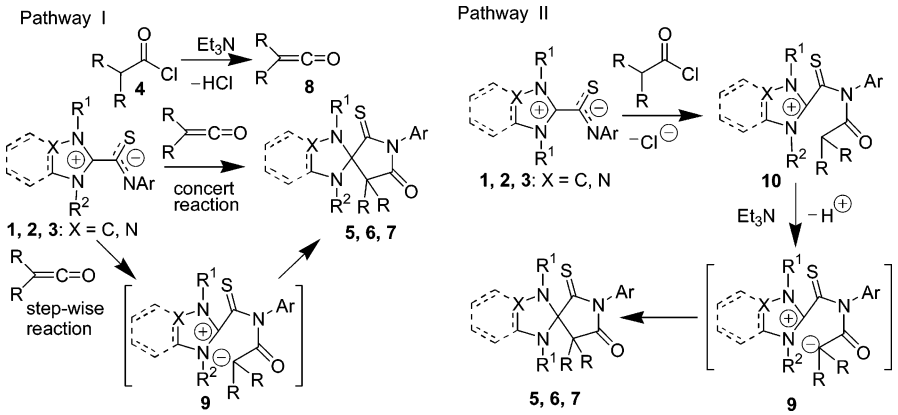
	starting materials		product
entry	**2**: R^1, R^2, Ar **3**: R, R^1, R^2, Ar	**4**: R^3, R^4	yield (%)
1	**2a**: Bn, Bn, Ph	**4a**: Me, Me	**6a** 82
2	**2a**: Bn, Bn, Ph	**4c**: R^3, $R^4 = (CH_2)_5$	**6b** 91
3	**2b**: *p*-ClBn, *p*-ClBn, Ph	**4a**: Me, Me	**6c** 85
4	**2b**: *p*-ClBn, *p*-ClBn, Ph	**4b**: H, Bn	**6d** 83
5	**3a**: Ph, Ph, Ph, Ph	**4a**: Me, Me	**7a** 71
6	**3b**: *p*-MePh, Ph, Ph, *p*-ClPh	**4a**: Me, Me	**7b** 60

were the 1 + 1 adducts of the two reactants with the loss of HCl. To identify the product beyond doubt, the structure of 1,3-dibenzyl-1′-phenyl-4′,4′-dimethylspiro[benzimidazoline-2,3′-pyrrolidine]-2′-thioxo-5′-one **5a** was determined unambiguously by single-crystal X-ray diffraction analysis (Figure S1 in Supporting Information).

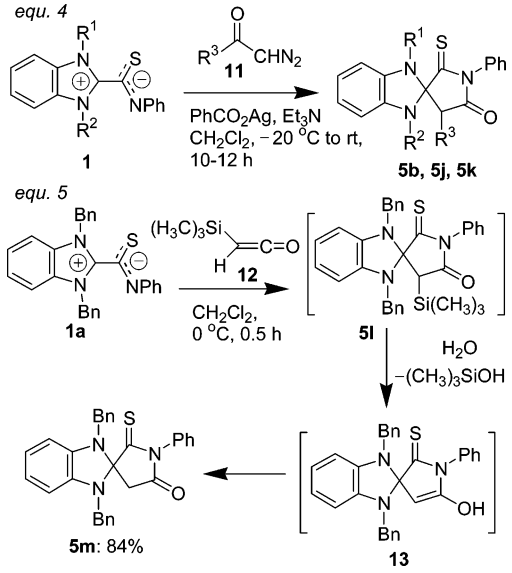
The formation of the heterocycle spiro-pyrroles **5**, **6**, and **7** could follow two different reaction pathways. As depicted in Scheme 2, pathway I was through a concert or a stepwise [3 + 2] cycloaddition between the C−C−N moiety of the dipole **1**, **2**, or **3** with a ketene **8**, generated in situ from the elimination of HCl from acyl chloride in the presence of triethylamine. Alternatively, pathway II shows N-acylation of the dipole **1**, **2**, or **3** to give intermediate **10**. Deprotonation and intramolecular cyclization of **10** leads to the formation of product (Scheme 2).

To clarify the reaction pathways, the reaction of 1,3-dipoles with ketenes was examined using a different ketene precursor.

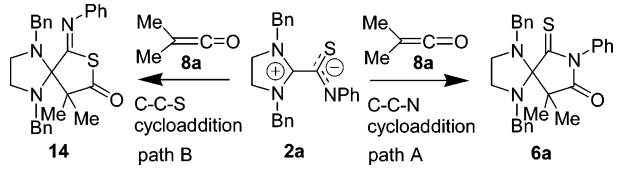
SCHEME 2. Proposed Mechanisms for the Reaction of Dipoles 1, 2, and 3 with Acyl Chlorides in the Presence of Triethylamine



SCHEME 3. Reaction of 2-Arylthiocarbamoyl Benzimidazolium Inner Salts 1 with Ketenes



SCHEME 4



Thus, the reaction of 1,3-dipoles **1** with α-diazoketones **11** catalyzed by $PhCO_2Ag$ was studied and did result in the formation of spiro heterocycles **5**, albeit more slowly (10−12 h) and in slightly lower yields (58−66%) (Scheme 3, eq 4, and Table 1, entries 11−13). The relatively slow reaction between **1** and **11** in the presence of $PhCO_2Ag$ might be due to the slow rearrangement of α-diazoketones to ketenes. Alternatively, the interaction of a Ag^+ cation with the anion center of the dipole could reduce the reactivity of dipole.

To further clarify the mechanism, a stable trimethylsilylketene **12**[13] was prepared and reacted with the dipole **1a**. As expected, at 0 °C and in dichloromethane, the interaction between **1a** and silylketene **12** proceeded rapidly and efficiently, and the reaction was finished within 30 min. HRMS analysis indicated that the crude products contained both the expected product **5l** and its desilylated derivative **5m**. However, the product **5l** was not isolated because it was very unstable and converted completely into the desilylated product **5m** in chromatographic or recrystallized workup. Finally, compound **5m** was isolated in 84% by recrystallization (This product was unstable to silica gel or neutral Al_2O_3, decomposing partially to the starting material **1a**) (eq 5 in Scheme 3 and pS5-S6 in Supporting Information).

The aforementioned reactions indicate clearly that the 2-arylthiocarbamoyl benzimidazolium, -imidazolinium, and -triazolium inner salts are highly efficient C−C−N rather than C−C−S 1,3-dipoles in [3 + 2] cycloaddition reaction with ketenes. Comparing the cycloaddition between dipoles **1** or **2** and ketenes with the reactions of dipoles with electron-deficient alkynes,[3c,d] it is noteworthy that the dipoles have similar reactivity toward ketenes, dimethyl acetylenedicarboxylate, and dibenzoylacetylene. However, the site selectivity in the reaction of ambident dipoles with ketenes was in sharp contrast to that with DMAD or with dibenzoylacetylene. To elucidate the highly site-selective 1,3-dipolar cycloaddition reactions between ambident dipoles and ketenes, we undertook a theoretical study using the density functional theory method to investigate the detailed mechanisms of the two possible pathways depicted in Scheme 4. Three transition-state structures (Figure S2 in Supporting Information) were derived for the two different pathways. The present calculations indicated a stepwise mechanism for a C−C−N 1,3-dipolar cycloaddition but a concerted mechanism for a C−C−S 1,3-dipolar cycloaddition. The relative energies for all stationary points calculated at the B3LYP/6-31G(*d*) level are summarized in Table 3.

In the C−C−N cycloaddition (path A), the first step is the nucleophilic attack of N1 on C5 via transition state A-TS1 (Figure S2 in Supporting Information), in which the key distances of N1−C5 and C3−C4 are 1.952 and 3.393 Å, respectively. The nucleophilic attack results in a zwitterionic intermediate A-INT1, which is calculated to be located in a shallow minimum, 1.1 (1.8) kcal/mol lower than A-TS1 (data in parentheses correspond to $\Delta G_{CH_2Cl_2}$). In A-INT1, the N1−C5 bond is formed with a distance of 1.556 Å while C4 is still 3.098 Å far away from C3. The C3−C4 bond forms with a barrier of only 2.8 (3.5) kcal/mol relative to the intermediate. At transition state A-TS2, the critical N1−C5 and C3−C4 bond distances are 1.486 and 2.471 Å, respectively. As indicated in Table 3, A-TS2 is the rate-limiting step in dichloromethane. Different from the C−C−N cycloaddition, a concerted transition

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TABLE 3. Calculated Relative Electronic Energies, Enthalpies, Entropies, and Free Energies of 1,3-Dipolar Cycloaddition between 2a and 8a at the B3LYP/6-31G(*d*) Level

	$\Delta E^{t\,a}$ (298 K) kcal/mol	ΔH^{t} (298 K) kcal/mol	$\Delta S^{\ddagger}$ (298 K) cal/mol K	ΔG_{gas} (298 K) kcal/mol	$\Delta G_{CH_2Cl_2}$ (298 K) kcal/mol
2a+8a	0	0	0	0	0
A-TS1	7.4	6.9	−50.3	21.9	23.3
A-INT1	5.7	5.1	−53.5	20.8	21.5
A-TS2	7.3	6.0	−58.7	23.6	25.0
6a	−13.4	−14.7	−60.5	3.3	6.9
B-TS1	16.5	17.7	−57.0	32.5	34.7
14	−8.1	−9.5	−61.1	8.8	14.1

[a] The activation barrier with zero-point energy correction.

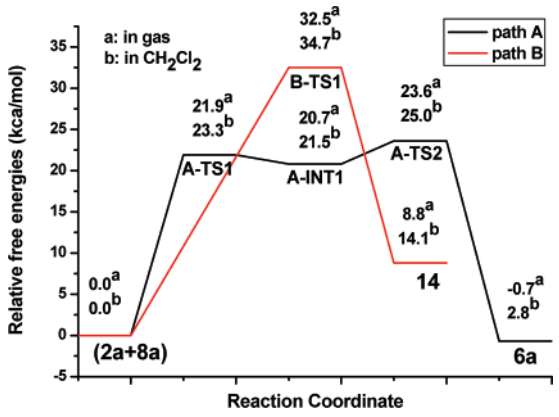

FIGURE 1. Potential energy profile for the 1,3-dipolar cycloaddition between **2a** and **8a**.

state B-TS1 (Figure S2 in Supporting Information) was optimized for the C−C−S cycloaddition (path B) and the associated relative free energy was found to be 32.5 (34.7) kcal/mol, indicating that this path is not possible kinetically, which is in good agreement with our experimental results. In B-TS1, S1−C5 has already been formed with a distance of 1.953 Å, while the distance of C3−C4 is 2.524 Å. Our IRC calculations confirmed that no intermediate could be located between the reactant and product in the C−C−S pathway, revealing a concerted but asynchronous mechanism. As indicated in Table 3 and Figure 1, the transition states and the product in the C−C−N cycloaddition of **2a** with dimethyl ketene **8a** have much lower relative free energies than those of the C−C−S cycloaddition. Therefore, the C−C−N cycloaddition of **2** with ketene **8** is both a dynamically and thermodynamically favored reaction pathway.

In conclusion, we have demonstrated that the ambident dipolar compounds, 2-arylthiocarbamoyl benzimidazolium **1**, -imidazolinium **2**, and -triazolium inner salts **3**, act as highly reactive and site-selective C−C−N 1,3-dipoles toward ketenes. Theoretical calculation suggests a stepwise mechanism for the [3 + 2] cycloaddition reaction between the dipoles and ketenes. The easy availability, high reactivity, and selectivity render the benzimidazolium, -imidazolinium, and -triazolium inner salts powerful and versatile 1,3-dipoles in the synthesis of novel benzimidazoline-, imidazolidine-, and triazoline spiro-pyrrolidones, which are not easily accessible by other methods.

Experiment Section

1. General Procedure for the Reaction of 2-Arylthiocarbamoyl Benzimidazolium 1, -Imidazolinium 2, and -Triazolium Inner Salts 3 with Acyl Chlorides in the Presence of Triethylamine. Under nitrogen atmosphere, 2-arylthiocarbamoyl benzimidazolium **1**, -imidazolinium **2**, or -triazolium inner salt **3** (1 mmol) was dissolved in the solution of dry triethylamine (5 mL) and dichloromethane (15 mL). To this mixture cooled in an ice bath, the solution of an acyl chloride (4 mmol) in dry dichloromethane (5 mL) was added dropwise within 5−10 min. The reaction mixture was then stirred at 0 °C for 30−45 min. After removal of the dichloromethane, the residue was diluted with ethyl acetate (50 mL) to precipitate the triethylamine hydrochloride. After filtering the salt and evaporating the solvent, we isolated the products **5**, **6**, or **7**, respectively, by flash chromatography on a neutral Al_2O_3 column eluting with a mixture of petroleum ether (30−60 °C) and ethyl acetate (20:1).

1,3-Dibenzyl-1′-phenyl-4′,4′-dimethylspiro[benzimidazoline-2,3′-pyrrolidine]-2′-thioxo-5′-one 5a: 93%, mp 167−168 °C; IR υ (cm^{-1}) 1749, 1596, 1496; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.46−7.50 (m, 3H), 7.38−7.41 (m, 8H), 7.33 (t, J = 6.2 Hz, 2H), 6.99 (d, J = 6.7 Hz, 2H), 6.60 (dd, J = 5.4, 3.2 Hz, 2H), 6.12 (dd, J = 5.3, 3.2 Hz, 2H), 4.60 (d, J = 17.6 Hz, 2H), 4.56 (d, J = 17.5 Hz, 2H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 201.5, 181.1, 140.8, 137.3, 133.8, 129.40, 129.36, 128.8, 127.3, 127.1, 126.5, 119.4, 105.9, 100.6, 51.9, 48.5, 21.4; MS (MALDI-TOF): 504 (M + 1). Anal. Calcd for $C_{32}H_{29}N_3OS$: C, 76.31; H, 5.80; N, 8.34. Found: C, 76.27; H, 5.81; N, 8.28.

2. General Procedure for the Reaction of 2-Arylthiocarbamoyl Benzimidazolium Inner Salts 1 with Ketenes Generated from α-Diazoketones. Under nitrogen atmosphere and at −20 °C, the solution of $PhCO_2Ag$ (0.8 mmol) in triethylamine (2 mL) was added to the α-diazoketones in dry dichloromethane (5 mL), and the mixture was stirred at −20 °C for 1 h. To the reaction mixture, the solution of 2-arylthiocarbamoyl benzimidazolium inner salts **1** (1 mmol) in dichloromethane (20 mL) was added slowly within 1 h. The reaction temperature was raised slowly, and the reaction mixture was then stirred at room temperature for 10−12 h. After removal of the solvent, the products **5** were isolated by flash chromatography on a neutral Al_2O_3 column eluting with a mixture of petroleum ether (30−60 °C) and ethyl acetate (20:1).

1,3-Dibenzyl-1′-phenyl-4′-(2-phenyl)ethylspiro[benzimidazoline-2,3′-pyrrolidine]-2′-thioxo-5′-one 5j: 66%, mp 167−169 °C; IR υ (cm^{-1}) 1748, 1599, 1495; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.53 (t, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.33−7.42 (m, 10H), 7.26 (t, J = 7.3 Hz, 2H), 7.14−7.19 (m, 5H), 6.64 (t, J = 7.5 Hz, 1H), 6.52 (t, J = 7.5 Hz, 1H), 6.22 (d, J = 7.3 Hz, 1H), 6.03 (d, J = 7.4 Hz, 1H), 4.68 (d, J = 16.8 Hz, 1H), 4.38 (d, J = 16.1 Hz, 1H), 4.30 (d, J = 16.1 Hz, 1H), 4.22 (d, J = 16.8 Hz, 1H), 3.08 (dd, J = 8.0, 5.5 Hz, 1H), 2.94−3.00 (m, 1H), 2.79−2.85 (m, 1H), 2.35−2.40 (m, 1H), 2.21−2.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 202.1, 176.9, 141.2, 140.9, 139.8, 137.7, 136.1, 133.7, 129.5, 128.9, 128.8, 128.5, 128.4, 127.6, 127.5, 127.4, 126.9, 126.8, 126.2, 119.9, 118.8, 106.9, 104.5, 97.8, 49.7, 49.5, 46.8, 33.9, 26.5; MS (MALDI-TOF): 580 (M + 1). Anal. Calcd for $C_{38}H_{33}N_3OS$: C, 78.72; H, 5.74; N, 7.25. Found: C, 78.80; H, 5.98; N, 7.25.

Acknowledgment. This work was supported by the National Natural Science Foundation of China for Distinguished Young Scholars (No. 20525207), National Natural Science Foundation of China (No. 20672013), Program for New Century Excellent Talents in University (No. NCET-04-0143), and the "PCSIRT".

Supporting Information Available: Experimental procedures for the preparation of products **5**, **6**, and **7**; full characterization and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **5**, **6**, and **7**; ORTEP drawing of single-crystal structure and single-crystal data of **5a** (CIF); and computational method and calculated data for the reaction of 1,3-dipole **2a** with dimethyl ketene. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070759U