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1,3-Dipolar Cycloaddition Reactions of Vinylidenecyclopropane-Diesters with Aromatic Diazomethanes Generated in Situ

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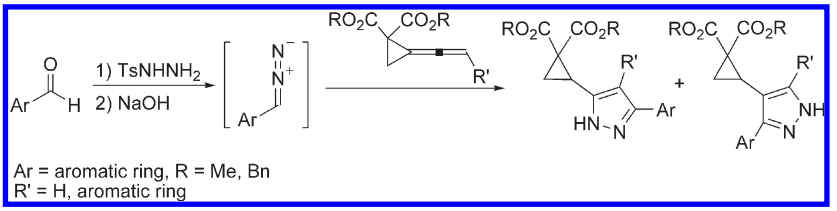

1,3-Dipolar cycloaddition reactions of VDCP-diesters with aromatic diazomethanes generated in situ from the corresponding aromatic aldehydes and tosylhydrazine mediated by base produce pyrazole derivatives in good yields under mild conditions. A plausible reaction mechanism has been proposed on the basis of control experiments along with the discussion on the regioselectivity.

Introduction

Diazo compounds are remarkably versatile building blocks in organic synthesis, which are known to take part in 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles,[1] although they are also known to be toxic and potentially explosive. Recently a new method based on the Bamford−Stevens reaction[2] has been reported for generating aromatic diazomethanes from stable tosylhydrazone derivatives in situ,[3] which has proven to be a highly effective and safe alternative to handling aryldiazomethanes and has been employed in the sulfur ylide-mediated synthesis of epoxides from carbonyl compounds, aziridination of imines, cyclopropanation of alkenes, homologation of aldehydes, Wittig reactions, and preparation of pyrazoles via [3+2] cycloadditions with alkenes and alkynes.[4] Vinylidenecyclopropanes (VDCPs) as highly strained small rings have an allene moiety connected by a cyclopropane. Thus far, the chemistry of vinylidenecyclopropanes (VDCPs) has been extensively explored in our laboratory and other groups during the last several years. Many novel intramolecular rearrangements and intermolecular cycloaddition reactions with carbon−carbon or carbon−heteroatom multiple bonds such as imines, aldehydes, nitriles as well as α,β-unsaturated ketones could take place smoothly either upon heating and photoirradiation[5]

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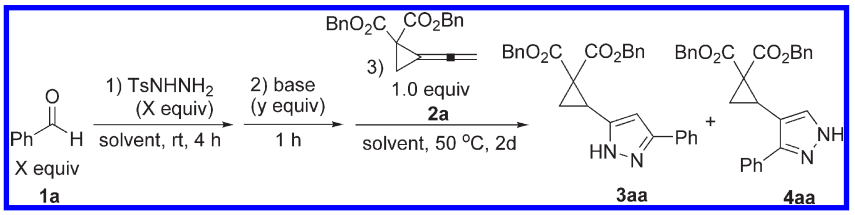
TABLE 1. Optimization of the [3+2] Cycloaddition Reaction Conditions[a]



				total yield of the product (%)[b]	
entry	*X* equiv	solvent	base (*y* equiv)	**3aa**	**4aa**
1	1.0	CH_3CN	5.0 M NaOH (1.0)	16	18
2	2.0	CH_3CN	5.0 M NaOH (2.0)	25	30
3	4.0	CH_3CN	5.0 M NaOH (4.0)	20	25
4	0.8	CH_3CN	5.0 M NaOH (0.8)	9	16
5[c]	2.0	CH_3CN	5.0 M NaOH (2.0)	trace	
6[d]	2.0	CH_3CN	5.0 M NaOH (2.0)		
7	2.0	CH_3CN	NaH (2.0)	complex	
8	2.0	CH_3CN	NaOEt (2.0)	10	13
9	2.0	CH_3CN	KO^{t}Bu (2.0)	trace	
10	2.0	CH_3CN	10.0 M NaOH (2.0)	26	45
11	2.0	CH_3CN	20.0 M NaOH (2.0)	complex	
12	2.0	DCE	10.0 M NaOH (2.0)	17	30
13	2.0	THF	10.0 M NaOH (2.0)	28	56
14	2.0	toluene	10.0 M NaOH (2.0)	22	30

[a]All the reactions were carried out by stirring benzaldehyde **1a** and $TsNHNH_2$ in the solvent (2.0 mL) for 4 h at room temperature followd by adding the base with stirring for an additional 1 h. Then VDCP-diester **2a** (0.2 mmol) in the same solvent (4.0 mL) was added and the reaction mixture was stirred at 50 °C for 2 d unless otherwise specified. [b]Isolated yields. [c]The phase transfer catalyst (PTC) $BnEt_3NCl$ (10 mol %) was added. [d]Lewis acid $BF_3 \cdot OEt_2$ (10 mol %) was added.

or catalyzed/mediated by Lewis acids and Brønsted acids, giving the corresponding rearranged products as well as the cycloadducts in moderate to good yields under mild conditions.[6−8] In our recent work, we have found that VDCPs with geminal installation of two EWGs at the cyclopropane ring could undergo formal [3+3] cycloaddition reaction with 1,3-dipolar nitrones catalyzed by $Yb(OTf)_3$.[9] We anticipated that cycloaddition reactions of VDCP-diesters[10] with 1,3-dipolar diazo compounds could also take place smoothly under mild conditions. To our delight, it was found that such a cycloaddition takes place with the triple bond tautomerized from the allene moiety rather than the original allene moiety or the cyclopropane of VDCP-diesters, affording a one-pot procedure for the preparation of pyrazole derivatives. In this paper, we wish to report this cycloaddition reaction of VDCP-diesters with aromatic diazomethanes generated in situ under mild conditions.

Results and Discussion

To determine the best cycloaddition conditions, initial examinations were carried out with VDCP-diester **2a** and benzaldehyde **1a** as the substrates and the results are summarized in Table 1. We found that the corresponding cycloadducts **3aa** and **4aa** were obtained in the total yield of 34% from the cycloaddition of VDCP-diester **2a** (0.2 mmol) with phenyl diazomethane generated in situ from benzaldehyde **1a** (0.2 mmol, 1.0 equiv) and tosylhydrazine (0.2 mmol, 1.0 equiv) mediated by the base of 5.0 M aqueous NaOH solution (40 μL, 1.0 equiv) in CH_3CN (6.0 mL) (Table 1, entry 1). Changing the employed amount of benzaldehyde **1a** from 4.0 equiv to 0.8 equiv, we found that the highest yield was obtained using 2.0 equiv of benzaldehyde **1a** (Table 1, entries 2−4). We also examined some additives such as phase transfer catalyst ($BnEt_3NCl$) (Bn = $C_6H_5CH_2$) (10 mol %) and Lewis acid $BF_3 \cdot OEt_2$ (10 mol %) in this reaction, but no improvements were observed in both

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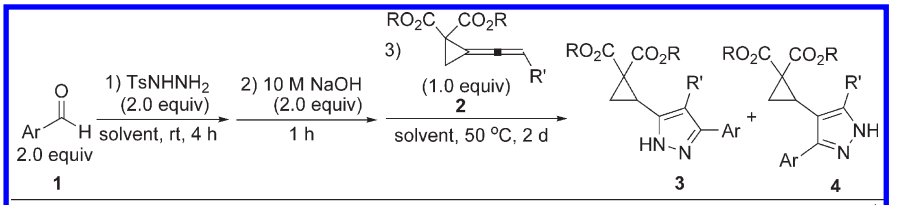
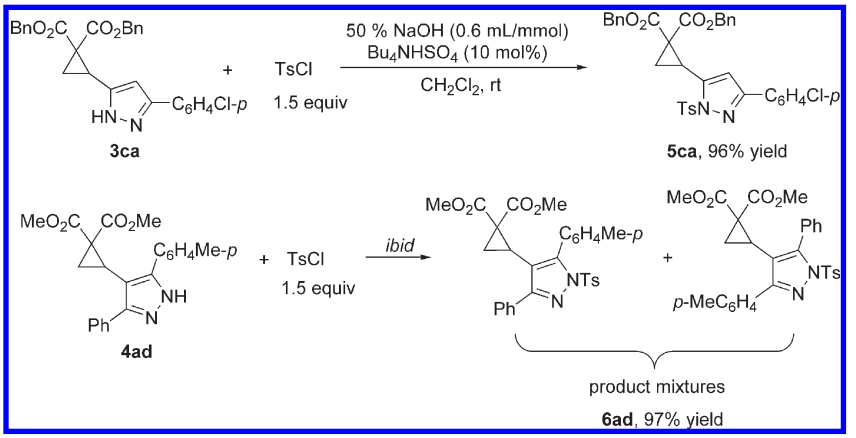
TABLE 2. Scope of the [3+2] Cycloaddition Reaction of VDCP-Diesters 2 with Aromatic Diazomethanes Generated in Situ from Corresponding Aromatic Aldehydes 1[a]



entry	1, Ar		R	R'	solvent	yield of the product (%)[b] 3	4
1	**1b**, *p*-MeC_6H_4	**2a**	Bn	H	THF	**3ba**, 30	**4ba**, 50
2	**1c**, *p*-ClC_6H_4	**2a**	Bn	H	THF	**3ca**, 30	**4ca**, 53
3	**1a**, Ph	**2b**	Me	H	CH_3CN[c]	**3ab**, 25	**4ab**, 47
4	**1a**, Ph	**2c**	Me	Ph	THF	-	**4ac**, 68
5	**1a**, Ph	**2c**	Me	Ph	CH_3CN	-	**4ac**, 80
6	**1a**, Ph	**2d**	Me	*p*-MeC_6H_4	CH_3CN	-	**4ad**, 76
7	**1a**, Ph	**2e**	Me	*p*-ClC_6H_4	CH_3CN	-	**4ae**, 82
8	**1b**, *p*-MeC_6H_4	**2c**	Me	Ph	CH_3CN	-	**4bc**, 85
9	**1d**, *p*-BrC_6H_4	**2c**	Me	Ph	CH_3CN	-	**4dc**, 88
10	**1e**, *m*-$MeOC_6H_4$	**2c**	Me	Ph	CH_3CN	-	**4ec**, 79
11	**1f**, *o*-ClC_6H_4	**2c**	Me	Ph	CH_3CN	-	**4fc**, 85
12	**1g**, *o,m*-$Cl_2C_6H_3$	**2c**	Me	Ph	CH_3CN	-	**4gc**, 72
13	**1h**, 	**2c**	Me	Ph	CH_3CN	-	**4hc**, 81
14	**1a**, Ph	**2f**	Me	Bn	CH_3CN	-	**4af**, 10

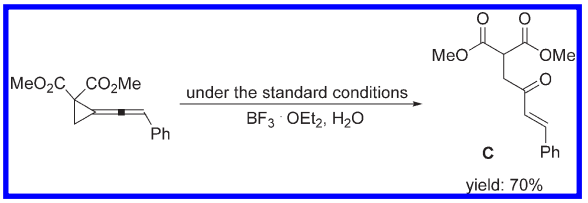
[a]All the reactions were carried out by stirring aromatic aldehydes **1** (0.4 mmol, 2.0 equiv) and $TsNHNH_2$ (0.4 mmol, 2.0 equiv) in THF (or CH_3CN) (2.0 mL) for 4 h at room temperature followd by adding 10.0 M NaOH (40 μL, 2.0 equiv) with stirring for an additional 1 h. Then VDCP-diesters **2** (0.2 mmol, 1.0 equiv) in THF (or CH_3CN) (4.0 mL) were added and the reaction mixture was stirred at 50 °C for 2 d unless otherwise specified. [b]Isolated yields. [c]In THF, a trace amount of **3ab** and **4ab** was formed.

SCHEME 1. Transformations of Pyrazole Derivatives 3ca and 4ad with TsCl



cases (Table 1, entries 5 and 6).[11] Other bases were also tested and it was found that aqueous NaOH solution afforded a better result than those of NaH, NaOEt, or KO^{t}Bu (Table 1, entries 7 to 9). Moreover, we also examined the effect of the concentration of NaOH aqueous solution on the reaction outcome. Products **3aa** and **4aa** were obtained in a higher total yield (71%) in the presence of 10.0 M of NaOH aqueous solution, while raising the concentration further to 20.0 M resulted in complex product mixtures (Table 1, entries 10 and 11). The examination of solvent effect in CH_3CN, 1,2-dichloroethane (DCE), toluene, and tetrahydrofuran (THF) revealed that THF was the solvent of choice, affording **3aa** and **4aa** in 84% total yield (Table 1, entries 12−14).

(11) With the addition of $BF_3 \cdot OEt_2$, we mainly obtained the cyclopropane ring-opening product C in 70% yield of VDCP-diester attacked by H_2O.



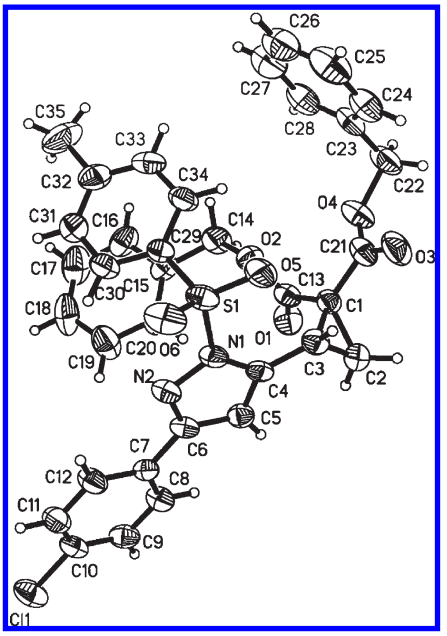


FIGURE 1. ORTEP drawing of **5ca**.

With the optimal reaction conditions in hand, we next examined the scope and limitations of the cycloaddition reaction of VDCP-diesters **2** with various aromatic diazomethanes generated in situ from the corresponding aromatic aldehydes **1** and tosylhydrazine and the results of these experiments are summarized in Table 2. In the reactions of VDCP-diester **2a** with aromatic diazomethanes generated in situ from aromatic aldehyde **1b** bearing a Me group or aromatic aldehyde **1c** having a chloro substituent at the para-position of the benzene ring, a pair of the desired products **3ba** and **4ba** as well as **3ca** and **4ca** were obtained in good total yields of 80% and 83%, respectively, under the standard conditions (Table 2, entries 1 and 2). As for VDCP-diester **2b**, in which R is a methyl group, a trace of the desired products **3ab** and **4ab** was obtained in THF, but they could be obtained in 25% and 47% yield, respectively, in CH_3CN (Table 2, entry 3). The change of the employed solvent also should be made for VDCP-diesters **2c**, **2d**, and **2e** with an aromatic ring connected to the allene moiety because higher yield of the desired product **4ac** was obtained when the reaction of VDCP-diester **2c** with the diazomethane generated from **1a** was carried out in CH_3CN than that in THF (Table 2, entries 4 and 5). It should be emphasized here that in this case, the cycloadduct **4ac** was obtained in 80% yield as the sole product presumably due to the steric effect of the phenyl group (R′) and the aromatic group (Ar) which may impair the formation of cycloadduct **3**. The regioselective [3+2] cycloaddition reactions of VDCP-diesters **2c**, **2d**, and 2e with aromatic diazomethanes generated in situ from aromatic aldehydes **1** proceeded smoothly under the standard conditions and showed a broad substrate scope with respect to a variety of electronically and structurally diverse aromatic aldehydes **1**. Irrespective of the electron-poor and electron-rich substituents on the aromatic rings of the aldehydes **1** or at the ortho- or meta-positions, the corresponding [3+2] cycloadducts were obtained in good yields (Table 2, entries 6−12). As for the heteroaromatic aldehyde **1h**, a similar result was obtained (Table 2, entry 13). However,

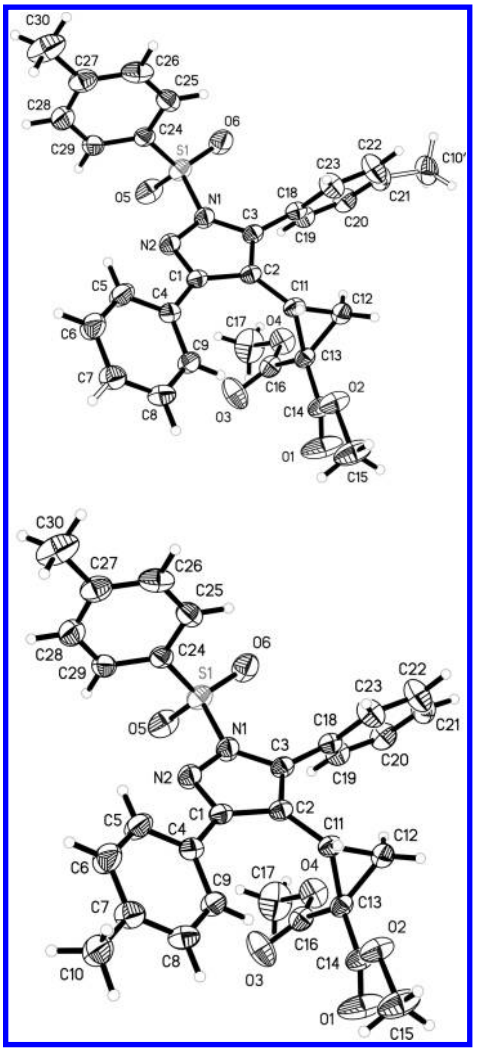


FIGURE 2. ORTEP drawing of **6ad**.[14]

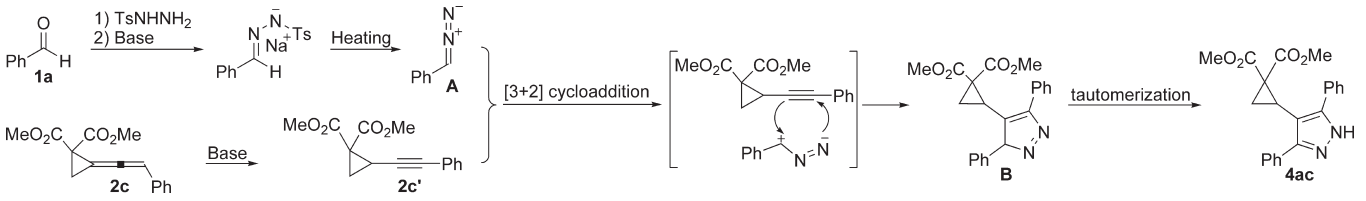
applying VDCP-diester **2f** with an aliphatic substituent (Bn = $C_6H_5CH_2$) on the allene moiety to this reaction provided the desired product **4af** in 10% yield under the standard reaction conditions (Table 2, entry 14).

The structures of the cycloadducts **3ca** and **4ad** were unambiguously determined by the X-ray diffraction of the corresponding products **5ca** and **6ad** through further transformation by treatment with *p*-toluenesulfonyl chloride (TsCl) under basic conditions (Scheme 1). Their ORTEP drawings are shown in Figures 1 and 2, respectively, and their CIF data are presented in the Supporting Information.[12,13] In the case of **4ad**, the pyrazole ring possesses two nitrogen atoms which are adjacent to two aromatic rings respectively, favoring an anionic equilibrium between these two nitrogen atoms in the presence of a base. Therefore, they can react with TsCl to give the corresponding product mixtures, respectively. As for **3ca**, there is only one aromatic ring

(12) The crystal data of **5ca** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 755464. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

(13) The crystal data of **6ad** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 752526. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

SCHEME 2. A Plausible Reaction Mechanism



adjacent to the nitrogen atom, disfavoring such an anionic equilibrium, thus only one product is formed (Scheme 1, see the Supporting Information for the details).

On the basis of the above results, a plausible mechanism for this [3+2] cycloaddition reaction of VDCP-diesters **2** with aromatic diazomethanes generated in situ from the corresponding aromatic aldehydes **1** with tosylhydrazine mediated by base is tentatively outlined in Scheme 2 by using VDCP-diester **2c** and benzaldehyde **1a** as an example. First, condensation of tosylhydrazine with benzaldehyde **1a** followed by treatment with an aqueous solution of NaOH leads to a solution of benzaldehyde tosylhydrazone sodium salt, which upon heating to 50 °C gives a reddish solution of phenyl diazomethane **A**. Meanwhile, under the basic condition, VDCP-diester **2c** tautomerizes to its alkyne isomer **2c′**,[15] which furnishes intermediate **B** through [3+2] cycloaddition with phenyl diazomethane **A**. The proton transfer in intermediate **B** affords the final product **4ac**. The high regioselectivity observed in these 1,3-dipolar cycloadditions of VDCP-diesters **2c**, **2d**, and **2e** can be explained from two points of view: one is the steric interaction of the substituents on the reactants and the other is the atomic orbital coefficients of the HOMO (diazo compound)-LUMO (alkyne) favor the interaction expected for this type of cycloaddition, which is in keeping with previous literature reports involving cycloadditions onto arylacetylenes.[16] As for VDCP-diesters **2a** and **2b**, probably because of the absence of the aromatic ring connected to the allene moiety, the regioselectivity is poor in the cycloaddition process, resulting in two regioisomers.

In conclusion, we have disclosed a one-pot method for the preparation of pyrazole derivatives by 1,3-dipolar cycloadditions of VDCP-diesters with aromatic diazomethanes generated in situ from the corresponding aromatic aldehydes and tosylhydrazine. VDCP-diesters with an allene moiety connecting to an aromatic group can undergo [3+2] cycloaddition reactions with diazomethanes via tautomerization, affording a series of pyrazole derivatives in good yields with high regioselectivities under mild reaction conditions. Efforts are underway to further elucidate the reaction mechanism and to understand the scope and limitations of this process.

Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded at 400 (or 300) and 100 (or 75) MHz, respectively. Mass and HRMS spectra were recorded by EI and ESI method. Organic solvents used were dried by standard methods when necessary. Satisfactory CHN microanalyses were obtained with an analyzer. Commercially obtained reagents were used without further purification. All these reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was carried out with use of silica gel at increased pressure.

General Procedure for the Cycloaddition Reaction of VDCP-Diesters with Aromatic Diazomethanes. The aromatic aldehyde **1** (0.4 mmol, 2.0 equiv) and tosylhydrazine (0.4 mmol, 2.0 equiv) were dissolved in THF or CH_3CN (2.0 mL) and the mixture was stirred at room temperature for 4 h. The 10 M aqueous NaOH solution (40 μL, 2.0 equiv) was added into the reaction mixtures and stirring was continued for an additional hour. Then, VDCP-diester **2** (0.2 mmol) in THF or CH_3CN (4.0 mL) was added and the above reaction mixture was warmed to 50 °C and stirred continuously for 2 days. After the reaction was finished (monitored by TLC plates), the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography to afford the desired products **3** and/or **4**.

General Procedure for the Reaction of Pyrazole Derivatives with TsCl. To a solution of pyrazole derivative **3** or **4** (0.20 mmol) and tetrabutylammonium hydrogen sulfate (0.02 mmol, 10 mol %) in CH_2Cl_2 (5.0 mL) was added 50% NaOH aqueous solution (120 μL). After the mixture was stirred for a few minutes, TsCl (0.30 mmol, 1.5 equiv) was added to the reaction mixture and the solution was then stirred vigorously at room temperature (20 °C). When the reaction was completed (monitored by TLC plates), the solution was poured into water and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the desired products **5** or **6**.

Compound 3aa: light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.84 (dd, J = 9.6, 5.2 Hz, 1H, CH), 2.22 (dd, J = 9.6, 5.2 Hz, 1H, CH), 3.20 (dd, J = 9.2, 8.0 Hz, 1H, CH), 4.89 (d, J = 12.0 Hz, 1H, CH_2), 4.94 (d, J = 12.0 Hz, 1H, CH_2), 5.14 (d, J = 12.4 Hz, 1H, CH_2), 5.23 (d, J = 12.4 Hz, 1H, CH_2), 6.36 (s, 1H, CH), 7.02 (d, J = 6.8 Hz, 2H, Ar), 7.09−7.15 (m, 3H, Ar), 7.28−7.42 (m, 8H, Ar), 7.58 (d, J = 6.8 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 19.7, 24.9, 37.0, 67.4, 67.5, 102.0, 125.5, 127.96, 128.04, 128.20, 128.25, 128.5, 128.8, 130.5, 135.0, 135.2, 144.3, 147.1, 166.6, 169.1; IR (CH_2Cl_2) ν 3033, 2925, 1727, 1498, 1455, 1380, 1322, 1273, 1193, 1128, 959, 764, 695 cm^{-1}; MS (%) m/z 452 (M^+, 3), 361 (17), 318 (18), 263 (9), 108 (14), 91 (100), 79 (11), 65 (7); HRMS (EI) calcd for $C_{28}H_{24}N_2O_4$ 452.1736, found 452.1738.

Compound 4aa: light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.80 (dd, J = 9.6, 5.2 Hz, 1H, CH), 2.06 (dd, J = 9.6, 5.2 Hz, 1H, CH), 3.13 (t, J = 9.6 Hz, 1H, CH), 4.83 (d, J = 12.0 Hz, 1H, CH_2), 4.89 (d, J = 12.0 Hz, 1H, CH_2), 5.16 (d, J = 12.8 Hz, 1H, CH_2), 5.29 (d, J = 12.8 Hz, 1H, CH_2), 6.95−6.97 (m, 2H, Ar), 7.11−7.17 (m, 3H, Ar), 7.25−7.33 (m, 9H, Ar), 7.57−7.58 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 20.4, 24.6, 37.5, 67.2, 67.3, 127.4, 127.7, 127.9, 128.0, 128.1, 128.16, 128.21, 128.3, 128.49, 128.50, 128.6, 129.5, 135.1, 135.5, 166.5, 169.2; IR (CH_2Cl_2) ν 3341, 3033, 2929, 1728, 1497, 1455, 1382, 1319, 1130, 737, 697 cm^{-1}; MS (%) m/z 452 (M^+, 2), 361 (9), 318 (10),

(14) The ORTEP drawing of **6ad** is the mixture of two isomers which cannot be separated by silica gel chromatography.

(15) During our preparation of the VDCP-diesters under the basic conditions, we observed the formation of the corresponding alkyne isomers and the NMR spectroscopic data of **2c′** are presented in the Supporting Information.

(16) (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. I. (b) Bastide, J.; Henri-Rousseau, O. *Bull. Soc. Chim. Fr.* **1973**, 2294–2296.

263 (5), 108 (8), 91 (100), 79 (8), 65 (5); HRMS (EI) calcd for $C_{28}H_{24}N_2O_4$ 452.1736, found 452.1731.

Compound 4ac: light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.49 (dd, J = 8.8, 4.8 Hz, 1H, CH), 1.57 (dd, J = 8.8, 4.8 Hz, 1H, CH), 3.08 (s, 3H, OCH_3), 3.36 (t, J = 8.8 Hz, 1H, CH), 3.72 (s, 3H, OCH_3), 7.34−7.40 (m, 6H, Ar), 7.60−7.62 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 22.4, 24.0, 36.5, 52.0, 52.6, 108.8, 127.8, 128.1, 128.4, 131.1, 167.0, 170.2; IR (CH_2Cl_2) ν 3328, 2952, 1731, 1604, 1493, 1437, 1370, 1328, 1290, 1132, 775, 732, 698 cm^{-1}; MS (%) m/z 376 (M^+, 34), 344 (26), 301 (25), 257 (100), 244 (91), 228 (16), 128 (17), 104 (12), 77 (34), 57 (17); HRMS (EI) calcd for $C_{22}H_{20}N_2O_4$ 376.1423, found 376.1422.

Compound 5ca: colorless solid; mp 127−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.98 (dd, J = 9.6, 5.6 Hz, 1H, CH), 2.04 (dd, J = 8.0, 6.8 Hz, 1H, CH), 2.31 (s, 3H, CH_3), 3.74 (t, J = 9.2 Hz, 1H, CH), 4.73 (d, J = 12.0 Hz, 1H, CH_2), 4.77 (d, J = 12.0 Hz, 1H, CH_2), 5.24 (d, J = 12.0 Hz, 1H, CH_2), 5.34 (d, J = 12.0 Hz, 1H, CH_2), 6.17 (s, 1H, CH), 6.88−6.91 (m, 2H, Ar), 7.04−7.08 (m, 3H, Ar), 7.11 (d, J = 8.8 Hz, 2H, Ar), 7.32−7.39 (m, 7H, Ar), 7.62 (d, J = 8.4 Hz, 2H, Ar), 7.89 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 20.1, 21.6, 24.1, 37.8, 67.4, 67.7, 105.5, 127.5, 127.8, 127.9, 128.0, 128.2, 128.4, 128.6, 128.7, 129.7, 134.6, 134.9, 135.0, 135.2, 143.1, 145.5, 152.8, 165.8, 168.3; IR (CH_2Cl_2) ν 2941, 2911, 1729, 1597, 1381, 1193, 1134, 1091, 813, 698, 667, 583 cm^{-1}; MS-ESI (%) m/z 641.3 ($M + H^+$); HRMS (ESI) calcd for $C_{35}H_{29}ClN_2NaO_6S$ 663.1327, found 663.1336.

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Supporting Information Available: Spectroscopic data of all the new compounds and detailed descriptions of experimental procedures as well as CIF data of **5ca** and **6ad**. This material is available free of charge via the Internet at http://pubs.acs.org.