Regiochemistry in 1,3-Dipolar Cycloadditions of the Azomethine Ylide Formed from Diethyl Aminomalonate and Paraformaldehyde

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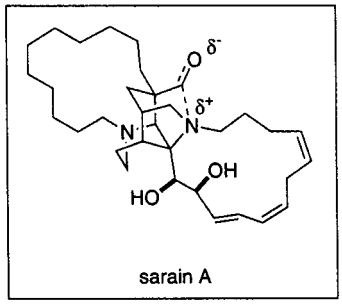
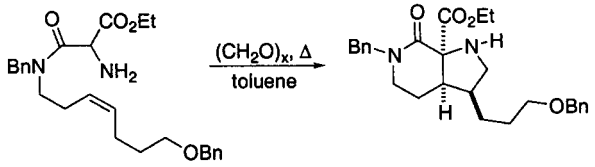
Abstract: The azomethine ylide derived from the condensation of diethyl aminomalonate with paraformaldehyde undergoes 1,3-dipolar cycloadditions with acrylate and propiolate derivatives. Contrary to a previous report, these reactions yield mixtures of regioisomers generally favoring the 2,2,3-trisubstituted product. However, the relative quantity of the 2,2,4-trisubstituted product formed increases with an increase in the size of the activating group on the dipolaroplile.

In 1989, we began studies directed toward the total synthesis of the marine sponge metabolite sarain A.[1] In a key step of our synthesis of the core structure of sarain A, an unactivated olefin undergoes an intramolecular 1,3-dipolar cycloaddition (1,3-DC) with an azomethine ylide to provide a fused, bicyclic pyrrolidine (Scheme 1). This transformation is conveniently performed by stirring the amine precursor with paraformaldehyde in toluene at reflux.[1e]

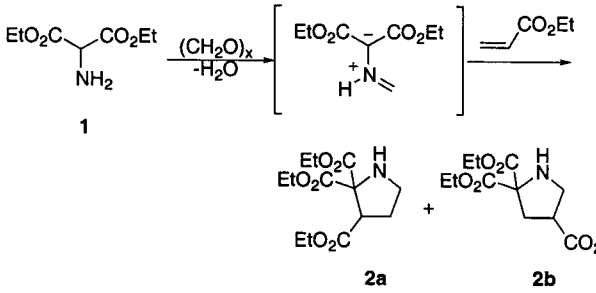
The precedent for this procedure was provided by earlier reports of *inter*molecular 1,3-DC employing diethyl aminomalonate (**1**) as the amine substrate.[2,3] In 1980, Amornraksa and Grigg utilized arylaldehydes to generate azomethine ylides which were trapped with symmetrical, activated dipolarophiles.[2a] Later, Husinec and co-workers reported the successful use of paraformaldehyde in similar reactions.[2b] These authors included unsymmetrical dipolarophiles, but claimed to observe complete regioselectivity in product formation. We speculated that an intermolecular 1,3-DC might permit us to improve the efficiency of our synthesis by increasing the convergence of the route.

Scheme 1





Scheme 2



We began by repeating a previously reported 1,3-DC (Scheme 2) as described by Husinec.[2b] Freshly distilled **1** was stirred with paraformaldehyde and ethyl acrylate in toluene at reflux for 13 h. A Dean−Stark trap was employed to remove the water formed through the course of the reaction. After the allotted time, the reaction was cooled to room temperature, and the toluene was removed in vacuo. The crude product mixture was examined by ^{1}H NMR spectroscopy. Contrary to the earlier report, the crude material contained a mixture of two regioisomers. The isomers were separated by HPLC and their structures determined spectroscopically. Analysis of the ^{1}H NMR spectra led us to conclude that the major isomer was 2,2,3-trisubstituted pyrrolidine **2a** rather than 2,2,4-trisubstituted pyrrolidine **2b**, as previously reported.

The characteristic coupling patterns of the carbon-bound protons on the pyrrolidine ring proved most valuable in establishing the regiochemistry of the cycloadduct isomers. In the case of **2b**, four distinct dd were expected for the four protons at C-3 and C-5. The remaining proton bound to C-4 was expected to appear as a more complicated multiplet. On the other hand, the ^{1}H NMR spectrum of **2a** would possess only one dd for the proton at C-3 with greater splitting for the four other protons, at C-4 and C-5. Indeed, exactly these patterns are observed for the two cycloadduct isomers isolated. However, as noted above, the major isomer was in fact **2a**, not **2b**.

With the results for the 1,3-DC with ethyl acrylate in hand, we chose to optimize the reaction conditions and explore the impact of changing the dipolarophile. We

(1) For our progress toward the synthesis of sarain A, see: (a) Henke, B. R,; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056. (b) Sharp, M. J.; Heathcock, C. H. *Tetrahedron. Lett.* **1994**, *35*, 3651. (c) Griffith, D. A.; Heathcock, C. H. *Tetrahedron. Lett.* **1995**, *36*, 2381. (d) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp M. J. *Synlett* **1995**, 467. (e) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616.

(2) (a) Amornraksa, K.; Grigg, R. *Tetrahedron Lett.* **1980**, *21*, 2197. (b) Husinec, S.; Savic, V.; Porter, A. E. A *Tetrahedron Lett.* **1988**, *29*, 6649

(3) For reviews of 1,3-dipolar cycloadditions of azomethine ylides, see: (a) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A, Ed.; Wiley: New York, 1984; Vol. 1 Chapter 6. (b) Vedejs, E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1988; Vol. 1, p 33. (c) Tsuge O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1989; Vol. 45, p 231. (d) Tsuge O.; Kanemasa, S. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1993; Vol. 3, p 99. (e) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1993; Vol. 3, p 161.

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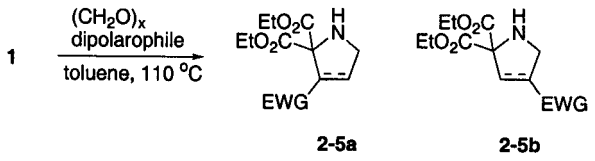
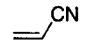
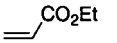
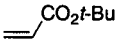
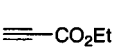
Table 1. 1,3-Dipolarcycloadditions: Yields and Regioselectivity



entry	dipolarophile	products	ratio	%yield
1		**3a:3b**	5:1	61
2		**2a:2b**	3:1	78
3		**4a:4b**	1:1	68
4		**5a:5b**	1:1.2	42

found that the Dean−Stark trap was unnecessary and had no impact on reaction rate or product distribution. Furthermore, we found that when employing ethyl acrylate as the dipolarophile, the reaction was complete in less than 4 h. We were disappointed to find that ethyl crotonate yielded no pyrrolidine cycloadducts. However, Husinec had already reported the failure of β-substituted α,β-unsaturated ketones to undergo 1,3-DC, so the ethyl crotonate results were not surprising.[2b] We then limited our study to commercially available β-unsubstituted dipolarophiles.

We successfully employed acrylonitrile, *tert*-butyl acrylate, and ethyl propiolate as dipolarophiles. The yields and regioselectivities of these experiments are reported in Table 1. The structures of the acrylonitrile and the *tert*-butyl acrylate cycloadducts (**3a**,**b** and **4a**,**b**, respectively) were determined analogously to the ethyl acrylate case discussed above. The structures for the corresponding ethyl propiolate cycloadducts (**5a**,**b)** could not be established unambiguously by 1-dimensional ^{1}H NMR spectroscopy. However, catalytic hydrogenation of these pyrrolines provided pyrrolidines **2a** and **2b**, thereby clarifying the regioselectivity of the ethyl propiolate 1,3-DC.

For entries 1−3 (Table 1), as the size of the dipolarophile activating group increases, more of the less sterically congested 2,2,4-trisubstituted product is obtained. The electronics of the various dipolarophiles are not expected to differ significantly, so the trend seems to point to a steric effect. When ethyl propiolate serves as the dipolarophile (entry 4), the regioselectivity reverses, though only moderately. The source of this reversal is unclear, and either electronics and/or sterics may come into play.

We have reexamined the 1,3-DC of a few simple commercial dipolarophiles with the azomethine ylide generated from **1** and paraformaldehyde. In contrast to the previous report, we have found these reactions not to be regiospecific. Upon further study, we have uncovered a small, but observable, steric effect based on the size of the dipolarophile activating group.

Experimental Section

General Procedures. All solvents for reactions and extraction were reagent grade and used as received. Paraformaldehyde was dried over P_2O_5 under high vacuum. Other reagents were used as obtained, without additional purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were acquired in deuterated chloroform ($CDCl_3$). HPLC purification was performed on a Dynamax 60-A column with HPLC grade solvents. Reactions were performed under an N_2 atmosphere.

General Procedure for 1,3 Dipolar Cycloadditions. Commercial diethyl aminomalonate hydrochloride was converted to its free amine by stirring in ethanol with excess potassium carbonate for about 1 h. The solids were then filtered and the ethanol removed in vacuo. Diethyl aminomalonate (**1**) was subsequently distilled at reduced pressure (10 Torr) using a Kugelrohr apparatus. This material was stored in a refrigerator, and it maintained its integrity for several days as determined by ^{1}H NMR. The amine **1** (1.5 mmol, 263 mg) was dissolved in toluene (7.5 mL), and paraformaldehyde (1.5 mmol, 45 mg) and dipolarophile (1.5 mmol) were added to the mixture. The reaction flask was fitted with a Dean−Stark apparatus (this precaution was later determined to be unnecessary) and heated to reflux. After 13 h, the mixture was cooled, and the toluene was removed in vacuo. Unless otherwise noted, addition of anisole (1.5 mmol, 16.3 μL) as an internal standard permitted the determination of % yield by ^{1}H NMR of the crude reaction mixture. Product ratios were also established by ^{1}H NMR of the crude reaction mixture. Although most of the pairs of regioisomers could be resolved by TLC, we found purification by flash chromatography less satisfactory than normal phase HPLC for the isolation of the cycloadducts.

Dipolar Cycloddition with Ethyl Acrylate as the Dipolarophile. Employing ethyl acrylate (153 mg, 163 μL) as the dipolarophile in the foregoing procedure, two regioisomers were obtained as a 3:1 mixture in 88% yield as determined by crude NMR (68% isolated yield after HPLC). The major isomer proved to be **2a**.

Ethyl (±)-2,3-Bis(ethoxycarbonyl)pyrrolidine-2-carboxylate (2a). Pale yellow oil: ^{1}H NMR δ 1.22 (t, 3H, J = 7.4 Hz), 1.23 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.5 Hz), 2.02−2.10 (m, 1H), 2.19−2.28 (m, 1H), 2.97 (ddd, 1H, J = 5.4, 7.5, 9.9 Hz), 3.25 (dt, 1H, J = 7.2, 9.9 Hz), 3.75 (dd, 1H, J = 5.1, 8.2), 4.04−4.29 (m, 6H); ^{13}C NMR δ 13.9, 13.9, 14.0, 30.6, 45.8, 49.6, 60.9, 62.0, 62.1, 75.1, 169.5, 170.0, 172.6; IR (thin film) 3356, 1736 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_6$ C, 54.35**;** H, 7.37; N, 4.88. Found: C, 54.12; H, 7.35; N, 5.16.

Ethyl (±)-2,4-Bis(ethoxycarbonyl)pyrrolidine-2-carboxylate (2b). Pale yellow oil: ^{1}H NMR δ 1.23 (t, 3H, J = 7.3 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.3 Hz), 2.51 (dd, 1H, J = 7.8, 13.7 Hz), 2.74 (dd, 1H, J = 8.3, 13.7 Hz), 3.01−3.09 (m, 1H), 3.23 (dd, 1H, J = 7.1, 10.2 Hz), 3.28 (dd, 1H, J = 7.7, 10.2 Hz), 4.13 (q, 2H, J = 7.3 Hz), 4.16−4.28 (m, 4H); ^{13}C NMR δ 14.0, 14.0, 14.1, 35.7, 43.7, 50.0, 60.9, 62.0, 62.0, 72.2, 170.8, 171.0, 173.1; IR 3353, 1735 cm^{-1}.

Dipolar Cycloddition with Acrylonitrile as the Dipolarophile. Employing acrylonitrile (80 mg, 99 μL) as the dipolarophile in the foregoing procedure, two regioisomers were obtained as a 4.8:1 mixture in 69% yield as determined by crude NMR (61% isolated yield after HPLC). The major isomer proved to be **3a**. The minor isomer could not be isolated in pure form.

Ethyl (±)-3-Cyano-2-ethoxycarbonylpyrrolidine-2-carboxylate (3a). Pale yellow oil: ^{1}H NMR δ 1.27 (t, 3H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz), 2.17−2.24 (m, 1H), 2.30−2.39 (m, 1H), 2.84 (br s, 1H), 3.06 (ddd, 1H, J = 5.4, 7.0, 10.1 Hz), 3.34 (dt, 1H, J = 7.1, 10.1 Hz), 3.84 (dd, 1H, J = 5.4, 7.7 Hz) 4.15−4.37 (m, 4H); ^{13}C NMR δ 13.8, 13.9, 31.3, 35.1, 45.8, 62.7, 63.1, 74.7, 118.6, 168.4, 168.7; IR (thin film) 3352, 2244, 1736 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_4$ C, 54.99**;** H, 6.71; N, 11.66. Found: C, 55.04; H, 6.50; N, 11.63.

Ethyl (±)-4-Cyano-2-ethoxycarbonylpyrrolidine-2-carboxylate (3b). Pale yellow oil. ^{1}H NMR δ 1.26 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.55 (dd, 1H, J = 8.0, 13.7 Hz), 2.85 (dd, 1H, J = 8.2, 13.7 Hz), 3.05 (pentet, 1H, J = 7.7 Hz), 3.26 (dd, 1H, J = 7.6, 10.1 Hz), 3.39 (dd, 1H, J = 7.0, 10.2 Hz), 4.18−4.31 (m, 4H); ^{13}C NMR δ 13.9, 14.0, 28.2, 36.7, 50.7, 62.4, 62.6, 71.4, 119.8, 170.0, 170.1; IR 3345, 2243, 1731 cm^{-1}.

Dipolar Cycloddition with *tert*-Butyl Acrylate as the Dipolarophile. Employing *tert*-butyl acrylate (192 mg, 219 μL) as the dipolarophile in the foregoing procedure, two regioisomers were obtained as a 1:1 mixture in 83% yield as determined by crude NMR (68% isolated yield after HPLC).

Ethyl (±)-3-*tert*-Butoxycarbonyl-2-ethoxycarbonylpyrrolidine-2-carboxylate (4a). Pale yellow oil. ^{1}H NMR δ 1.18 (t, 3H, J = 7.1 Hz), 1.35 (s, 9H), 1.92−1.99 (m, 1H), 2.15−2.24 (m, 1H), 2.91 (ddd, 1H, J = 4.4, 7.7, 9.6 Hz), 2.98 (br s, 1H), 3.17 (q, 1H, J = 8.2 Hz), 3.59 (dd, 1H, J = 4.0, 8.3 Hz), 4.00−4.10 (m, 1H), 4.11−4.27 (m, 1H); ^{13}C NMR δ 13.8, 27.7, 30.9, 45.5, 50.3, 61.7, 61.9, 74.7, 80.9, 169.5, 170.0, 171.7; IR (thin film) 3358, 1737 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_6$ C, 57.13**;** H, 7.99; N, 4.44. Found: C, 57.24; H, 7.92; N, 4.52

Ethyl (±)-4-*tert*-Butoxycarbonyl-2-ethoxycarbonylpyrrolidine-2-carboxylate (4b). Pale yellow oil. ^{1}H NMR δ 1.16 (t, 3H, J = 7.1 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.34 (s, 9H), 2.37 (dd, 1H, J = 7.9, 13.6 Hz), 2.61 (dd, 1H, J = 8.3, 13.6 Hz), 2.86 (br s), 2.84−2.92 (m, 1H), 3.08−3.17 (m, 2H), 4.05−4.20 (m, 4H); ^{13}C NMR δ 13.8, 13.8, 27.7, 35.5, 44.5, 49.8, 61.7, 61.8, 72.0, 80.6, 170.7, 170.9, 172.1; IR (thin film) 3352, 1728 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_6$ C, 57.13**;** H, 7.99; N, 4.44. Found: C, 57.09; H, 8.05; N, 4.74.

Dipolar Cycloddition with Ethyl Propiolate as the dipolarophile. Amine **1** (5.7 mmol, 1.0 g) was dissolved in toluene (30 mL). To this mixture were added ethyl propiolate (5.7 mmol, 559 mg, 578 μL) and paraformaldehyde (5.7 mmol, 171 mg). The reaction mixture was heated to reflux and stirred 12 h before cooling to room temperature. The toluene was removed in vacuo and *o*-dinitrobenzene (0.58 mmol, 100.5 mg) was added as an NMR standard. Two regioisomers were obtained as a 1.2:1 mixture in 58% yield as determined by crude NMR (43% isolated yield after HPLC). The major isomer proved to be **5b**.

Ethyl (±)-2,3-Bis(ethoxycarbonyl)-3-pyrroline-2-carboxylate (5b). Pale yellow oil. ^{1}H NMR δ 1.26 (t, 6H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.2 Hz), 3.13 (br s, 1H), 4.04 (d, 1H, J = 2.2 Hz), 4.18−4.25 (m, 6H), 6.71 (t, 1H, J = 2.2 Hz); ^{13}C NMR δ 13.9, 14.1, 52.8, 60.9, 62.4, 79.8, 135.2, 138.1, 162.9, 169.3; IR 3362, 1730, 1643 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_6$ C, 54.73; H, 6.71; N, 4.91 Found: C, 54.46; H, 6.73; N, 5.19.

Ethyl (±)-2,4-Bis(ethoxycarbonyl)-3-pyrroline-2-carboxylate (5a). Pale yellow oil. ^{1}H NMR δ 1.27 (t, 6H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.97 (br s, 1H), 4.00 (d, 1H, J = 2.1 Hz), 4.17−4.31 (m, 6H), 6.98 (t, 1H, J = 2.1 Hz); ^{13}C NMR δ 13.9, 14.1, 53.3, 60.7, 62.2, 77.9, 133.2, 143.6, 162.3, 170.1; IR 3362, 1733, 1639 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_6$ C, 54.73; H, 6.71; N, 4.91 Found: C, 54.52; H, 6.74; N, 5.16.

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