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Synthesis of Fluorous and Nonfluorous Polycyclic Systems by One-Pot, Double Intramolecular 1,3-Dipolar Cycloaddition of Azomethine Ylides

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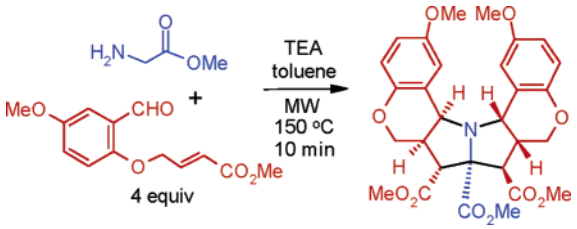
ABSTRACT



Under microwave irradiation, a one-pot, double intramolecular [3 + 2]-cycloaddition reaction of azomethine ylides leads to formation of a novel hexacyclic ring system. The major diastereomer is isolated, and its stereochemistry is determined by X-ray crystal structure analysis.

Intramolecular [3 + 2]-cycloaddition of azomethine ylides has the power to construct complex cyclic systems from relatively simple precursors.[1,2] This important aspect of 1,3-dipolar cycloaddition chemistry has been well studied in recent years. Aziridine-tethered alkenes,[3] *O*-allyl or *O*-propargyl salicylaldehydes,[4] and several other systems[5] have been developed for the synthesis of bicyclic, tricyclic, and even more complex ring skeletons. Reactions on solid-support[4g,6] or under microwave irradiation[4i] have also been investigated. We report here our discovery of a double intramolecular cyclization of *O*-allylic salicylaldehydes that forms a novel hexacyclic system containing fluorous or nonfluorous substitution groups in a stereoselective fashion.

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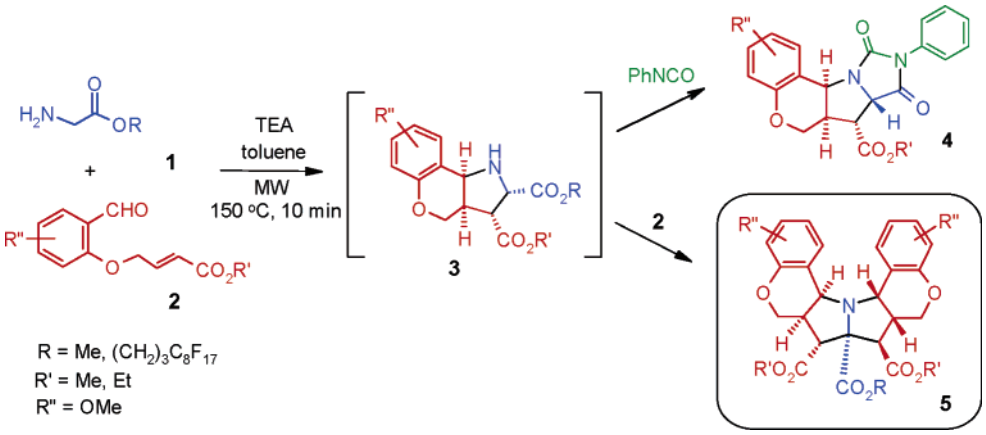
Scheme 1. Formation of the Unexpected Dicycloaddition Product **5**



In our continuous efforts on the application of fluorous technologies for the synthesis of library scaffolds for small molecules,[7] we recently reported the use of perfluorooctylsulfonyl benzaldehydes for intermolecular 1,3-dipolar cycloaddition reactions followed by Suzuki coupling reactions to produce biaryl-substituted proline derivatives.[8] In a new project, we intended to use a similar approach to construct a druglike tetracyclic scaffold **4** (Scheme 1). We envisioned that an azomethine ylide generated from the condensation of fluorous aminoester **1** (R = $CH_2CH_2CH_2C_8F_{17}$)[9a] with *O*-allyl salicylaldehyde **2** could undergo intramolecular 1,3-dipolar cycloaddition to form a tricyclic proline intermediate **3**. The urea generated by reaction of **3** with an isocyanate could spontaneously cyclized to form hydantoin-fused tetracyclic product **4** (Scheme 1).[4g,9]

The cycloaddition reaction was conducted under microwave irradiation (250 W, 150 °C, 10 min) using triethylamine (TEA) as a base and toluene as a solvent. An excess amount (2.0 equiv) of **2** was used to consume the fluorous aminoester **1** (1.0 equiv) so that the desired product **3** could be easily isolated from the reaction mixture by fluorous solid-phase extraction (F-SPE).[10] To our surprise, LC-MS analysis of the reaction mixture revealed that in addition to the desired product **3**, there was another major peak with a molecular mass compatible with double cycloaddition product **5**. The ratio of mono- and dicycloaddition products was about 45:55.[11] To the best of our knowledge, such a reaction is unprecedented, and the hexacyclic ring system is novel. We decided to investigate the synthetic utility of this new reaction sequence, which generates four rings and seven stereocenters in one-pot.

The formation of the dicycloaddition product was proportional to the number of equivalents of allylic salicylaldehyde **2** (Table 1). When 1.25 equiv of **2** was used, LC-MS analysis of the reaction mixture indicated that the ratio of dicycloaddition product **5** to monocycloaddition product **3** was 4:96. The amount of the dicycloaddition product increased significantly with increasing equivalence of **2**. The ratio of di- to monocycloaddition products was 80:20 when 4.0 equiv of **2** was used. Under the optimized conditions,[12] we conducted three reactions using different starting materials (**1** and **2**) and produced three analogues, including a nonfluorous **5c** and two fluorous (**5a** and **5b**) compounds with the methoxy substitution at different positions on the benzene rings. In addition to the major diastereomer, a small

Table 1. Equivalents of **2a** and Ratio of **5a** to **3a**

equiv of **2a**	ratio of **5a**:**3a**
1.25	4:96
2.5	55:45
4.0	80:20
8.0	78:22

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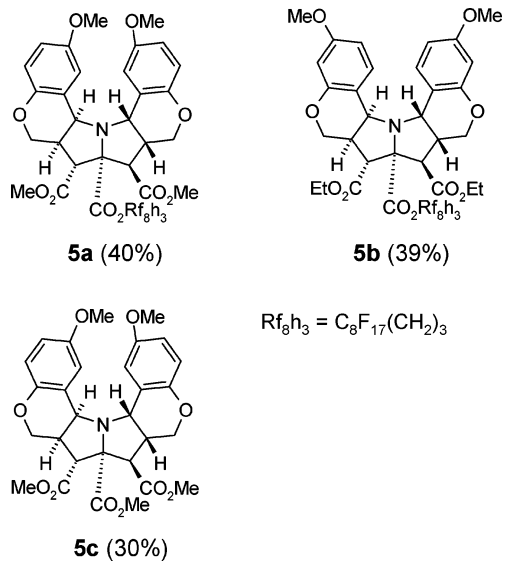
(11) Ratio of **5a**:**3a** was determined by LC-MS with a C18 column and UV 254 detection.

amount (10−15%) of minor diastereomers of dicycloaddition products was also detected from the reaction mixture by LC-MS. Only the major diastereomer was successfully isolated from the reaction mixture by flash chromatography or HPLC (Scheme 2). The yield listed in Scheme 2 is for the single diastereomer after chromatography purification.

Scheme 2. Major Diastereomer of **5**



Our next effort was to determine the stereochemistry of the major diastereomer isolated from the dicycloaddition mixture. Both ^{1}H NMR and ^{13}C NMR analyses indicated that **5a**, **5b**, and **5c** were not C_2-symmetric molecules. Two-dimensional NMR analyses, including COSY, HMBC, HMQC, NOESY, and ROESY of **5b**, could not provide conclusive information. Finally, the stereochemistry assignment was accomplished by X-ray crystal structure analysis of **5c** (Figure 1). It was found that three stereocenters on one side of the molecule are cis to each other, while the other three stereocenters on the other side of the molecule are cis to each other. These two groups of substituents are trans to each other.

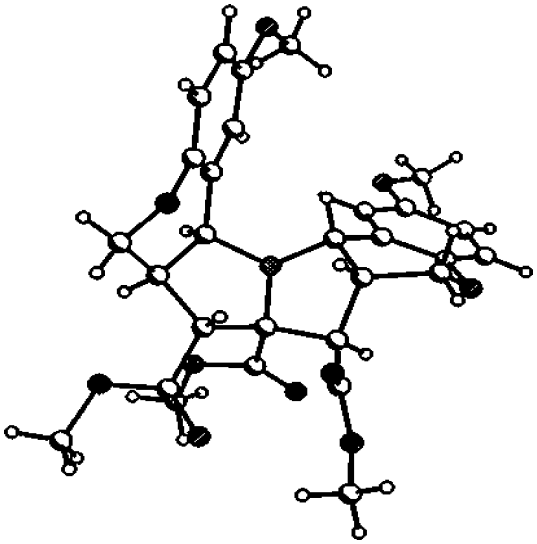


Figure 1. X-ray structure of compound **5c**.

On the basis of the stereochemical information provided by the X-ray analysis, a mechanism is proposed to explain the formation of the major diastereomer of the dicycloaddition product **5** (Scheme 3). Because the CO_2R group from the azomethine ylide side chain and the CO_2R' group from the allylic side chain are two hindered groups, the transition state of **6** could be oriented in such a way that those two ester groups are trans to each other, leading to formation of monocycloaddition product **3** with two cis-fused hydrogen atoms. A similar orientation could also be applied to azomethine ylide **7**, which leads to formation of the final product **5** with the stereochemistry shown in Scheme 3.

In summary, we have discovered a one-pot, double intramolecular [3 + 2]-cycloaddition reaction of azomethine ylides to form a novel hexacyclic ring system containing

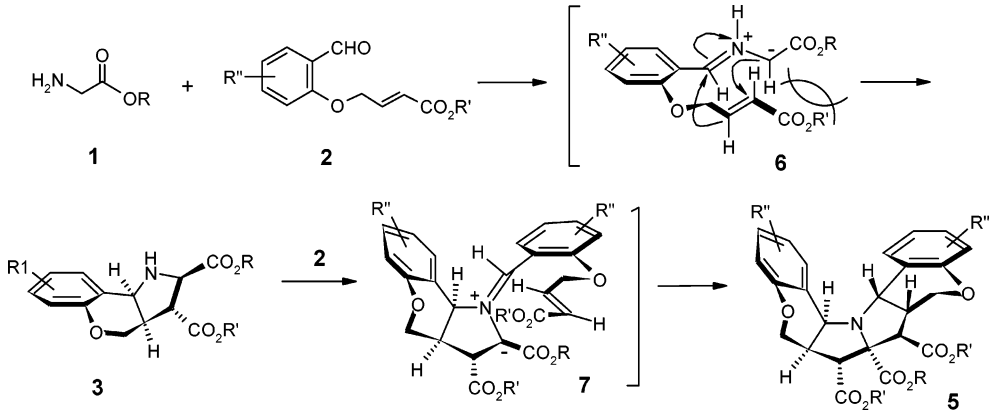
(12) **General Procedures for Dicycloaddition Reactions.** A mixture of TFA salt of aminoester **1** (0.1 mmol),[9a] *O*-allyl salicylaldehyde **2** (0.4 mmol), and 20 μL of TEA, in 1 mL of toluene, was irradiated in a single-mode microwave cavity at 250 W, 150 °C, for 10 min. The reaction mixture was concentrated and loaded onto a 5 g Fluoro*Flash* cartridge in 0.5 mL of CH_2Cl_2 and eluted with 20 mL of 80:20 MeOH/H_2O to remove monofluorous components, including TEA and its salt. The fluorous fraction containing mono- and dicycloaddition products was collected by elution with 20 mL of acetone. Further purification of the fluorous mixture by flash column chromatography gave single diastereomers **5a** and **5b**, respectively. The reaction mixture containing nonfluorous dicycloaddition product **5c** was purified by HPLC without conducting F-SPE. The crystal of **5c** was obtained by crystallization from MeOH/$CHCl_3$.

(13) Analytical data for **5a**: ^{1}H NMR ($CDCl_3$) δ 1.63−1.93 (m, 2H), 1.93−2.25 (m, 2H), 2.50−2.68 (m, 1H), 3.32−3.50 (m, 1H), 3.52 (d, J = 8.5 Hz, 1H), 3.65 (s, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.88−4.04 (m, 5H), 4.07 (d, J = 12.5 Hz, 1H), 4.11−4.23 (m, 2H), 4.97 (d, J = 8.5 Hz, 1H), 6.65 (s, 2H), 6.75−7.04 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.9, 27.7 (t, J = 84 Hz), 40.2, 44.0, 48.0, 50.6, 52.1, 52.2, 55.6, 60.5, 63.9, 64.3, 69.8, 79.0, 103−125 (m), 113.6, 114.7, 115.2, 116.1, 117.3, 118.9, 122.8, 127.1, 147.6, 151.5, 154.0, 154.3, 171.3, 171.7, 172.4; MS (APCI) m/z 1000 (M + 1); HRMS calcd for $C_{39}H_{35}NO_{10}F_{17}$ 1000.1990, found 1000.2021.

(14) Analytical data for **5b**: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.3 Hz, 3H), 1.29 (t, J = 7.3 Hz, 3H), 1.70−1.88 (m, 2H), 1.93−2.18 (m, 2H), 2.35−2.50 (m, 1H), 3.30−3.50 (m, 1H), 3.59 (d, J = 8.6 Hz, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 3.88−4.18 (m, 12H), 4.18−4.35 (m, 4H), 4.97 (d, J = 8.6 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.5, 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 8.5, 2.4 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.9, 27.8 (t, J = 84 Hz), 40.7, 43.8, 48.1, 49.8, 53.6, 55.1, 55.3, 59.6, 61.0, 61.3, 63.6, 64.3, 69.0, 78.9, 100.7, 102.8, 103−125 (m), 108.6, 108.7, 114.2, 118.3, 130.5, 132.2, 154.2, 158.3, 159.4, 160.4, 171.3, 171.7, 172.2; MS (APCI) m/z 1028 (M + 1); HRMS calcd for $C_{41}H_{39}NO_{10}F_{17}$ 1028.2303, found 1028.2317.

(15) Analytical data for **5c**. ^{1}H NMR ($CDCl_3$) δ 2.52−2.68 (m, 1H), 3.32−3.48 (m, 1H), 3.50 (d, J = 8.1 Hz, 1H), 3.61 (s, 3H), 3.66 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 3.92−4.06 (m, 5H), 4.06−4.19 (m, 2H), 4.98 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 1.6 Hz, 2H), 6.80 (dd, J = 8.8, 2.8 Hz, 1H), 6.86 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.2, 43.7, 48.1, 50.7, 52.1, 52.2, 52.4, 54.2, 55.6, 55.7, 60.2, 64.3, 69.4, 78.9, 113.7, 114.6, 115.1, 116.0, 117.2, 118.7, 122.6, 127.0, 147.5, 151.3, 153.9, 154.1, 171.5, 171.7, 172.5; MS (APCI) m/z 554 (M + 1); HRMS calcd for $C_{29}H_{32}NO_{10}$ 554.2026, found 554.2014.

Scheme 3. Proposed Mechanism for Formation of the Major Diastereomer of Dicycloaddition Product **5**



fluorous or nonfluorous substitution groups in a stereoselective fashion. This new reaction sequence extends the scope of intramolecular 1,3-dipolar cycloaddition chemistry in the construction of highly condensed ring skeletons.

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Supporting Information Available: NMR and mass spectra for dicycloaddition products **5a**−**c**, and X-ray analysis data for **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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