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Synthesis and Inverse Electron Demand Diels−Alder Reactions of 3,6-Bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine

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The synthesis of 3,6-bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine (**2**) and the scope of its reactivity in inverse electron demand Diels−Alder reactions are disclosed representing the first systematic study of the [4 + 2] cycloaddition reactions of 3,6-diacyl-1,2,4,5-tetrazines.

1,2,4,5-Tetrazines serve as useful precursors for the preparation of a variety of natural products bearing pyrrole ring systems.[1,2] The methodology is based on an inverse electron demand Diels−Alder reaction of an electron-deficient 1,2,4,5-tetrazine with an electron-rich dienophile to form a 1,2-diazine, followed by a reductive ring contraction to yield the corresponding pyrrole (Figure 1).[2] Typically, this has been conducted utilizing the readily accessible dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**)[3] which exhibits exceptional reactivity participating in [4 + 2] cycloaddition reactions with electron-rich, unactivated, and even electron-deficient dienophiles including a select set of heterodienophiles.[4] In the course of studies on the total synthesis of ningalin D and purpurone,[5] we elected to examine the extension of these studies to the novel 3,6-dibenzoyl-1,2,4,5-tetrazine **2**, thereby incorporating 3,6-dicarboxylate functionalization into the substrate prior to cycloaddition. We are aware of only two earlier reports on the synthesis of 3,6-dibenzoyltetrazines, and their reactivity as azadienes was not investigated.[6,7] More recently, Snyder and co-workers

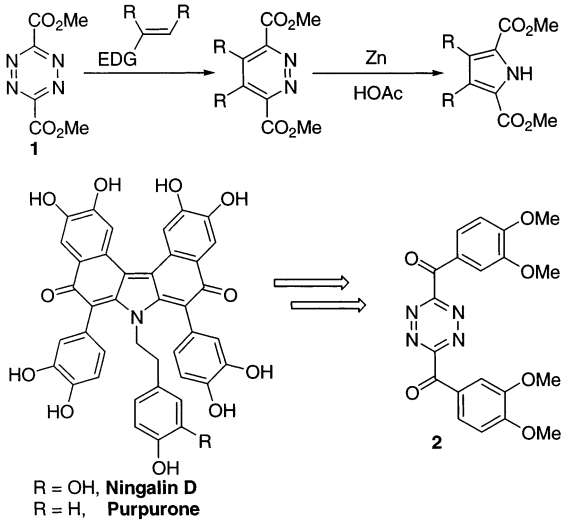

FIGURE 1.

have reported the synthesis of methyl 6-acetyl-1,2,4,5-tetrazine-3-carboxylate and 3,6-diacetyl-1,2,4,5-tetrazine, the only known additional acyl-substituted 1,2,4,5-tetrazines, and have examined their reactivity in a select series of Diels−Alder cycloadditions.[8] Thus, prior reports detailing the synthesis of 3,6-diacyl-1,2,4,5-tetrazines and their participation in Diels−Alder reactions are limited. Herein, we report our findings regarding the synthesis of **2** and its reactivity in Diels−Alder cycloadditions.

Tetrazine **2** was synthesized in five steps and in 28% overall yield from commercially available 3,4-dimethoxybenzaldehyde (**3**) as depicted in Scheme 1. The preparation commenced with the formation of TMS-protected 3,4-dimethoxybenzaldehyde cyanohydrin **4**[9] (TMSCN, ZnI_2) in quantitative yield.[10] Treatment of **4** with saturated ethanolic HCl[11] promoted ethanol addition to the nitrile

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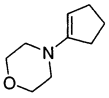
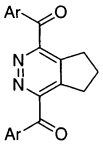
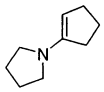
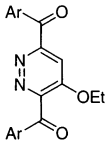
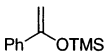
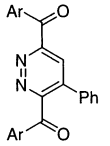
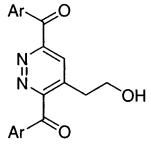
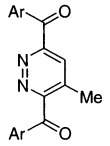
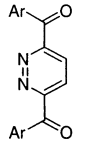
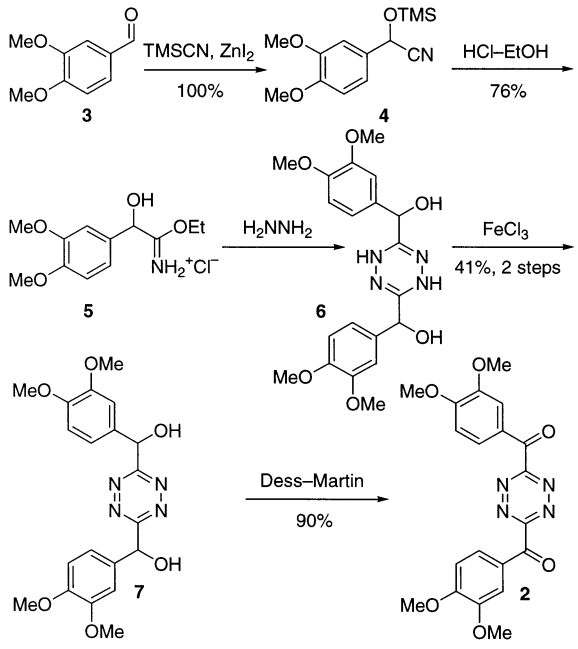
TABLE 1. Diels–Alder Reactions of 3,6-Bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine (2) with Alkenes

entry	dienophile	equiv	conditions	product	yield (%)
1	**8a** 	5	toluene, 23 °C, 3 h, then 10% HOAc/C_6H_6, 23 °C, 16 h	**9a** 	60
2	**8b** 	5	toluene, 60 °C, 0.5 h	**9a**	90
3	**8c** 	5	$CHCl_3$, 45 °C, 10 min, then 10% HOAc/C_6H_6, 23 °C, 1.5 h	**9c** 	64
4	**8d** 	3	toluene, 23 °C, 2 h	**9d** 	86
5	**8e** 	5	$CHCl_3$, 50 °C, 5 min, then $CHCl_3$, 23 °C, 3 h	**9e** 	80
6	**8f** 		neat, 4 °C, 4 d	**9f** 	73
7	**8g** 	12 2	1,4-dioxane, 23 °C, 72 h 1,4-dioxane, 35 °C, 48 h	**9g** 	100 95–98
8	**8h** 	9	toluene, 110 °C, 17 h	**9g**	100

SCHEME 1



and deprotection of the benzylic alcohol to provide **5**.[12,13] Imidate **5** was most conveniently purified by repeated washings with Et_2O or EtOAc, and the off-white solid was then added in portions to neat hydrazine hydrate[7,14–16] at 0 °C to afford the 1,4-dihydrotetrazine **6**. Like **5**, the dihydrotetrazine **6** could be conveniently purified by repeated washings with EtOAc[14] to afford **6** as a white solid, although air oxidation to the more soluble tetrazine during this purification may result in a loss of material in the EtOAc trituration. Deliberate oxidation of the 1,4-dihydrotetrazine **6** was accomplished by treatment with ferric chloride[17] in EtOH/H_2O to provide tetrazine **7** as a bright pink solid (41%, two steps). Final oxidation of the benzylic alcohols with Dess–Martin periodinane[18] then afforded **2** (90%) as a bright orange solid. Tetrazine **2** was

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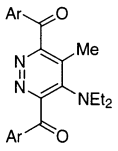
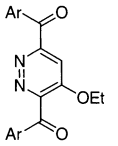
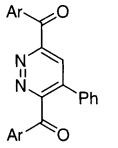
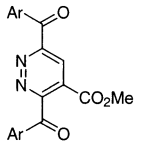
TABLE 2. Diels-Alder Reactions of 3,6-Bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine (2) with Alkynes

entry	dienophile		equiv	conditions	product		yield (%)
1	**14a**	Me—≡—NEt_2	2 1	1,4-dioxane, 23 °C, 2 h 1,4-dioxane, 23 °C, 2 h	**15**		100 94
2	**14b**	≡—OEt	5	benzene, 60 °C, 3.5 d	**9c**		66
3	**14c**	≡—Ph	10	toluene, 110 °C, 2 d	**9d**		70
4	**14d**	≡—CO_2Me	5	1,4-dioxane, 95 °C, 5 d	**16**		65
5	**14e**	Ph—≡—Ph	3	mesitylene, 100 °C, 1 d or 160 °C, 5 h	—		no reaction

slightly soluble in $CHCl_3$, CH_2Cl_2, toluene, and DMF above 23 °C but insoluble in diethyl ether, benzene, tetrahydrofuran, and 1,4-dioxane at ambient temperatures. Exposure of **2** to protic solvents including methanol resulted in its rapid decomposition while **7** was stable to methanol over prolonged exposure times (>2 days). Neither tetrazine **7** nor **2** was stable to conventional silica gel chromatography; however, both could be purified by simple trituration with CH_2Cl_2 or MeOH (for **7**) or EtOAc (for **2**) due to their minimal solubilities in these solvents. An alternative synthesis of **2** via base-catalyzed dimerization of α-diazo-3,4-dimethoxyacetophenone[7] was unsuccessful, although this was not investigated in detail.

The reactivity of **2** in Diels−Alder cycloadditions with a variety of dienophiles was examined, and representative results are summarized in Tables 1 and 2. Tetrazine **2** participated in inverse electron demand Diels−Alder reactions with both electron-rich and neutral alkenes **8a**−**h** and alkynes **14a**−**d**, providing the 1,2-diazine cycloadducts in good yields.[19] As previously observed with Diels−Alder cycloadditions of 3,6-bis(methylthio)-1,2,4,5-tetrazine[20] and 6-[(*tert*-butyloxycarbonyl)amino]-3-(methylthio)-1,2,4,5-tetrazine,[21] the slow step of the reaction cascade with electron-rich olefinic dienophiles typically was the aromatization step. Enamines, enol ethers, and ketene acetals underwent rapid, room-temperature [4 + 2] cycloaddition with concomitant loss of N_2, and the aromatization step involving the loss of an alcohol or secondary amine was often incomplete under mild reaction conditions. This aromatization could be facilitated by treatment of the intermediate crude product mixture with 10% HOAc/C_6H_6 (v:v). For example, the elimination of morpholine from entry 1 (Table 1) was effected by treatment with 10% HOAc/C_6H_6, whereas the aromatization for the entry 2 enamine was completed by extending the reaction time under more vigorous conditions (toluene, 60 °C, 30 min) to provide diazine **9a**. Notably, the initial [4 + 2] cycloadditions of the enamines **8a** and **8b** with tetrazine **2** were complete at 23 °C (<5 min). Similarly, entry 3 employed acid treatment to complete the loss of ethanol, while entries 4 and 5 (Table 1) simply required additional reaction time (2−3 h) at ambient temperature to complete aromatization following a cycloaddition that was complete in 5 min (50 °C). Thus, as expected, the electron-rich alkenes **8a**−**g**, including enamines, enol ethers, and ketene acetals, undergo facile [4 + 2] cycloadditions under mild conditions. Although longer reaction times were required, Diels−Alder reactions with 2-methoxypropene (entry 6) could be observed even at temperatures as low as 4 °C. Not surprisingly, the [4 + 2] cycloaddition with the less electron-rich vinyl acetate (**8h**, 110 °C, 17 h) required higher reaction temperatures.

Although not extensively investigated, tetrazine **2** was found to participate in effective [4 + 2] cycloadditions with selected heterodienophiles including *S*-alkyl thioimidates[4] providing the corresponding 1,2,4-triazine (eq 1). Analogous to prior observations with **1**,[4] thioimidates proved more effective than either imidates or amidines (X = SCH_3 > OCH_3, NH_2) that in our prior studies was shown to be the result of an optimal combination of properties. That is, the thioimidates are

(19) The reactions were monitored by the disappearance of baseline tetrazine on TLC and dissolution of the initial orange slurry to provide a clear solution.

(20) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415. Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240. For the preparation of 3-methoxy-6-methylthio-1,2,4,5-tetrazine, see: Sakya, S. M.; Groskopf, K. K.; Boger, D. L. *Tetrahedron Lett.* **1997**, *38*, 3805.

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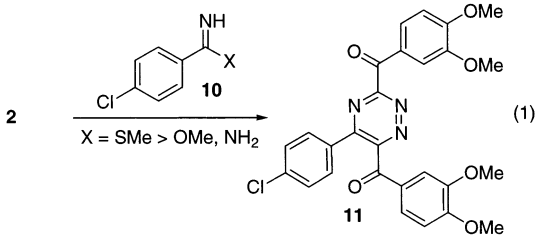
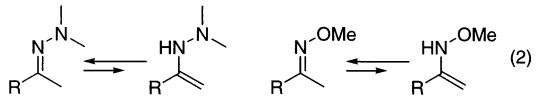
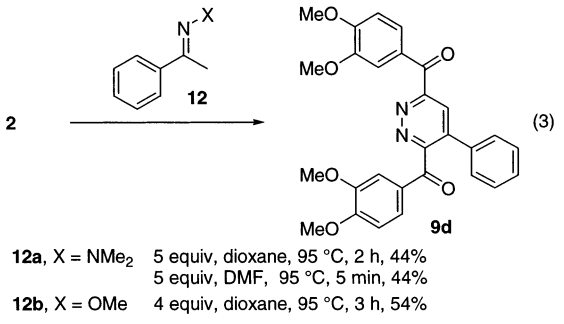


10a, X = SMe 2 equiv, dioxane, 50 °C, 17 h, 61%
10 equiv, toluene, 90 °C, 48 h, 57%
(followed by 10% HOAc–benzene)
10b, X = OMe 2 equiv, dioxane, 90 °C, 17 h, 31%
10c, X = NH_2 2 equiv, dioxane, 90 °C, 17 h, 32%

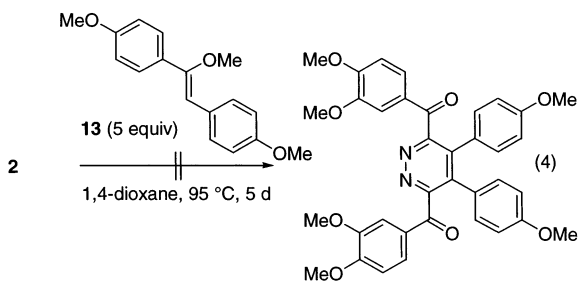
sufficiently electron-rich to participate effectively in the [4 + 2] cycloaddition reaction (NH_2 > OCH_3 ≥ SCH_3) *and* the thiomethyl group is a sufficiently good leaving group to permit subsequent aromatization (SCH_3 > OCH_3 > NH_2) competitive with further dihydrotriazine reaction with a substrate. Tetrazine **2** was also found to serve as an effective trap of typically inaccessible electron-rich dienophiles generated by in situ tautomerization of a more stable precursor (eq 2). Such tactics enlisting the



in situ generation of reactive electron-rich dienophiles substantially increases the scope of cycloadditions available to tetrazine **2**. For example, **2** underwent facile Diels−Alder cycloaddition with dimethylhydrazone **12a** (eq 3) and the oxime **12b** upon in situ tautomerization of the carbon−nitrogen double bond (eq 2) to allow cycloaddition across the carbon−carbon double bond. Finally, it was evident from attempted cycloadditions with a variety of dienophiles bearing bulky substituents that steric hindrance can be a factor limiting the reactivity of **2**. For example, cycloadditions with enol ether **13**[22] could not be effected even at temperatures in excess of 140 °C (eq 4). In this regard, tetrazine **2** is not as broadly reactive as the diester **1**.



12a, X = NMe_2 5 equiv, dioxane, 95 °C, 2 h, 44%
5 equiv, DMF, 95 °C, 5 min, 44%
12b, X = OMe 4 equiv, dioxane, 95 °C, 3 h, 54%



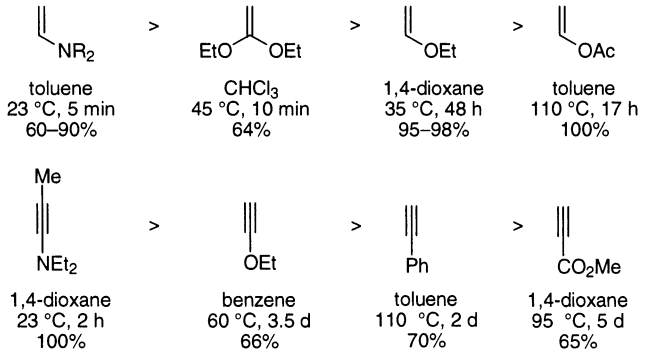


FIGURE 2. Relative dienophile reactivity toward **2**.

Diels−Alder cycloadditions were also observed with alkynyl dienophiles (Table 2), as demonstrated by formation of the 1,2-diazines **15** (100%) and **9c** (66%) upon reaction with the ynamine **14a** (entry 1, 23 °C, 2 h) and ethoxyacetylene (entry 2, 60 °C, 3.5 d), respectively. Higher reaction temperatures were required for [4 + 2] cycloaddition with phenylacetylene (**14c**, 110 °C, 2 d). Tetrazine **2** even exhibited limited reactivity toward the electron-poor alkyne methyl propiolate although satisfactory conversions were observed only after prolonged reaction times (**14d**, 95 °C, 5 d, 65%). Typically, the alkyne dienophiles were not as reactive as the corresponding alkenes (e.g., **8g** > **14b**) but they follow reactivity trends expected on the basis of the electronic properties of their substituents (Figure 2).

Conclusions

The synthesis of tetrazine **2**, by an approach applicable to a range of 3,6-dibenzoyl-1,2,4,5-tetrazines, and its reactivity in inverse electron demand Diels−Alder reactions were described representing the first systematic study of the [4 + 2] cycloaddition reactions of a 3,6-diacyl-1,2,4,5-tetrazine. Tetrazine **2** was shown to readily undergo [4 + 2] cycloadditions with electron-rich and neutral alkenes and alkynes and even a select electron-deficient dienophile to provide substituted 1,2-diazines in good yields defining a broadly reactive and useful class of heterocyclic azadienes.

Experimental Section

3,4-Dimethoxymandelimidic Acid Ethyl Ester Hydrochloride (5). 2-(3,4-Dimethoxyphenyl)-2-(trimethylsilyloxy)-acetonitrile **4**[9] (1.60 g, 6.02 mmol) as prepared by the procedure of Isobe[10] was treated with saturated HCl−EtOH (20 mL) at 0 °C for 16 h. Removal of the solvent and washing of the crude solid with Et_2O (2 × 30 mL) provided **5** (1.26 g, 76%) as an off-white solid: mp 125−127 °C (lit. mp[12] 129−149 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.68 (br s, 2H), 7.23 (br s, 1H), 7.08 (s, 1H), 6.98 (s, 2H), 5.47 (s, 1H), 4.46 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 179.5, 149.2, 148.7, 129.7, 119.3, 111.6, 110.4, 70.6, 69.7, 55.5 (2C), 13.3; IR (film) ν_{max} 3234, 1643, 1514 cm^{-1}; ESIMS m/z 274 ($C_{12}H_{18}ClNO_4$ − H^- requires 274).

(3,4-Dimethoxyphenyl)[6-[(3,4-dimethoxyphenyl)hydroxymethyl]-1,2,4,5-tetrazin-3-yl]methanol (7). Imidate **5** (3.28 g, 11.90 mmol) was added in portions over 15 min to a stirring solution of hydrazine monohydrate (2.6 mL) at 0 °C.

(22) Krow, G. R.; Michener, E. *Synthesis* **1974**, 572.

After 3 h, the hydrazine was removed to provide crude 1,4-dihydrotetrazine **6**. The 1,4-dihydrotetrazine could be purified by trituration with EtOAc[14] to provide **6** as a white solid as a near 1:1 mixture of two diastereomers: ^{1}H NMR (DMSO-d_6/D_2O, 400 MHz) δ 7.01 (s, 1H), 6.97 (s, 1H), 6.87 (s, 2H), 6.84 (s, 2H), 5.05 (s, 1H), 5.03 (s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H); MALDIFTMS (DHB) *m*/*z* 417.1761 ($C_{20}H_{24}N_4O_6 + H^+$ requires 417.1769). A slurry of the crude 1,4-dihydrotetrazine in EtOH (80 mL) at 75 °C was treated with a solution of $FeCl_3$ (2.89 g, 17.8 mmol) in H_2O (27 mL). The reaction solubilized and became bright pink within 15 min. After an additional 15 min, the reaction was cooled to 25 °C, diluted with CH_2Cl_2, washed with H_2O (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. Trituration of the crude solid with CH_2Cl_2 or MeOH (400 mL) afforded **7** (1.02 g, 41%) as a bright pink solid: mp 171−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, J = 1.8 Hz, 2H), 7.04 (dd, J = 1.8, 8.2 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 6.34 (s, 2H), 3.88 (s, 6H), 3.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5 (2C), 149.7 (2C), 149.6 (2C), 132.1 (2C), 119.5 (2C), 111.5 (2C), 109.7 (2C), 74.5 (2C), 56.2 (4C); IR (film) ν_{max} 3377, 1591, 1512 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 437.1414 ($C_{20}H_{22}N_4O_6 + Na^+$ requires 437.1431).

Analogous oxidations of crude **6** enlisting 0.2 equiv (vs 1.5 equiv) of $FeCl_3$ (open to air, 38%), DDQ (1 equiv, THF, 0−23 °C, 20 h), or nitrous gas[3] (CH_2Cl_2, 0 °C, 45 min) provided comparable conversions.

3,6-Bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine (2). A stirring solution of **7** (329 mg, 0.793 mmol) in CH_2Cl_2 (53 mL) under Ar at 23 °C was treated with Dess−Martin periodinane (1.01 g, 2.38 mmol). After 3.5 h, the orange slurry was treated with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL) and stirred for 15 min at 23 °C before the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. Trituration with EtOAc (2 × 10 mL) afforded pure **2** (292 mg, 90%) as a bright orange solid: mp 195−196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 2.0 Hz, 2H), 7.58 (dd, J = 2.0, 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 4.02 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.5, 164.6, 155.8, 150.0, 128.3, 127.3, 111.6, 110.5, 56.6, 56.5; IR (film) ν_{max} 1665, 1595, 1515 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 433.1104 ($C_{20}H_{18}N_4O_6 + Na^+$ requires 433.1118).

3,6-Bis(3,4-dimethoxybenzoyl)cyclopenta[*d*]pyridazine (9a). From 8b. A solution of **2** (8.8 mg, 0.021 mmol) in toluene (150 μL) under Ar at 60 °C was treated with a solution of 1-pyrrolidino-1-cyclopentene (**8b**, 14.4 mg, 0.105 mmol) in toluene (100 μL). After 30 min, the reaction mixture was cooled to 23 °C and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 0−20% EtOAc/CH_2Cl_2 gradient elution) provided **9a** (8.5 mg, 90%) as a light yellow solid: mp >250 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (m, 4H), 6.91 (d, J = 8.8 Hz, 2H), 3.97 (s, 12H), 3.28 (t, J = 7.6 Hz, 4H), 2.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.2 (2C), 155.7 (2C), 154.5 (2C), 149.4 (2C), 148.1 (2C), 128.9 (2C), 127.9 (2C), 112.2 (2C), 110.2 (2C), 56.4 (2C), 56.3 (2C), 31.8 (2C), 24.1; IR (film) ν_{max} 1642, 1577, 1512 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 449.1695 ($C_{25}H_{24}N_2O_6 + H^+$ requires 449.1707).

From 8a. A solution of **2** (10 mg, 0.024 mmol) and 4-(1-cyclopenten-1-yl)morpholine (**8a**, 19.6 mg, 0.12 mmol) in toluene (120 μL) was stirred at 23 °C for 3 h during which time the reaction solution changed from orange to yellow. A 10% HOAc−benzene solution (v/v) was added to promote elimination of the amine for aromatization of the Diels−Alder product. After 16 h, the solvent was removed in vacuo, and the product was purified by PTLC (SiO_2, 2:1 EtOAc/hexanes) to yield **9a** (6.4 mg, 60%) as a light yellow solid.

3,6-Bis(3,4-dimethoxybenzoyl)-4-ethoxypyridazine (9c). From 8c. A stirring solution of **2** (8.9 mg, 0.022 mmol) in $CHCl_3$ (220 μL) under Ar was treated with ketene diethyl acetal (**8c**, 14 μL, 0.11 mmol) and warmed to 45 °C. The reaction solubilized within 1 min, and the reaction was cooled to 23 °C after an additional 9 min. The solvent was removed under reduced pressure, and the residue was redissolved in 10% HOAc−benzene (500 μL) and stirred at 23 °C for 1.5 h to induce aromatization before reconcentration. Flash chromatography (SiO_2, 1.5 × 8 cm, 0−20% EtOAc/CH_2Cl_2 gradient elution) provided **9c** (6.4 mg, 64%) as yellow needles: mp 171−173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J = 1.8, 8.5 Hz, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.65 (s, 1H), 7.33 (dd, J = 1.8, 8.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 3.982 (s, 3H), 3.976 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.8, 189.7, 159.5, 157.0, 154.8, 154.5, 153.0, 149.6, 149.2, 129.0, 128.4, 128.2, 127.1, 113.0, 111.0, 110.3, 110.2, 109.4, 65.3, 56.4 (2C), 56.3 (2C), 14.2; IR (film) ν_{max} 1661, 1590, 1515 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 453.1666 ($C_{24}H_{24}N_2O_7 + H^+$ requires 453.1656).

From 14b. A stirring solution of **2** (9.1 mg, 0.022 mmol) in benzene (220 μL) under Ar was treated with ethoxyacetylene (**14b**, 40 wt % solution in hexanes, 27 μL, 0.11 mmol). The reaction was warmed at 60 °C for 3.5 d before the cooled reaction mixture was concentrated under reduced pressure. Flash chromatography (SiO_2, 1.5 × 8 cm, 0−10% EtOAc/CH_2Cl_2 gradient elution) afforded **9c** (6.6 mg, 66%) as a yellow solid.

3,6-Bis(3,4-dimethoxybenzoyl)-4-phenylpyridazine (9d). From 8d. A solution of **2** (6.0 mg, 15 μmol) and 1-phenyl-1-(trimethylsiloxy)ethylene (**8d**, 4.5 μL, 44 μmol) in toluene (75 μL) was stirred at 23 °C for 2 h during which time the orange color was discharged and the solution turned yellow. The solvent was removed in vacuo, and the crude material was purified by PTLC (SiO_2, 2:1 EtOAc/hexanes) to yield **9d** (6.0 mg, 86%) as a pale yellow solid: mp 145−147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 8.08 (dd, J = 1.8, 8.2 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.37−7.45 (m, 6H), 6.97 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.00 (s, 6H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 191.6, 189.6, 159.2, 158.5, 154.7, 154.5, 149.5, 149.2, 141.0, 137.3, 134.4, 133.3, 130.1, 129.4, 128.7, 128.5, 128.3, 128.2, 127.3, 125.3, 112.8, 111.1, 110.3, 110.2, 56.4 (2C), 56.3, 56.2; IR (film) ν_{max} 1661, 1651, 1592, 1514 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 485.1695 (M + H$^+$, $C_{28}H_{24}N_2O_6$ requires 485.1707).

From 14c. A solution of **2** (6.0 mg, 0.015 mmol) and phenylacetylene (**14c,** 16.2 μL, 0.15 mmol) in toluene (75 μL) was warmed at 110 °C for 2 d. PTLC (SiO_2, 2:1 EtOAc/hexanes) afforded **9d** (5.0 mg, 70%) as a pale yellow solid.

From 12a. Tetrazine **2** (10.4 mg, 0.025 mmol) was treated with a solution of dimethylhydrazone **12a** (20.3 mg, 0.125 mmol) in 1,4-dioxane (250 μL) under Ar and warmed at 95 °C for 2 h. The cooled reaction mixture was concentrated and flash chromatography (SiO_2, 1.5 × 8 cm, 25−50% EtOAc/hexanes gradient elution) afforded **9d** (5.3 mg, 44%) as a pale yellow solid. Alternatively, **2** (13.7 mg, 0.033 mmol) was treated with a solution of **12a** (27.1 mg, 0.167 mmol) in DMF (330 μL) under Ar and warmed at 95 °C for 5 min. The cooled reaction mixture was concentrated, and flash chromatography (SiO_2, 1.5 × 8 cm, 25−50% EtOAc/hexanes gradient elution) afforded **9d** (7.0 mg, 44%) as a pale yellow solid.

From 12b. A solution of **2** (10.0 mg, 0.024 mmol) and acetophenone (*O*-methyl)oxime (**12b**, 14.5 mg, 0.097 mmol) in dioxane (120 μL) was stirred at reflux for 3 h during which time the orange color was discharged and the solution turned yellow. The solvent was removed in vacuo, and the crude material was purified by PTLC (SiO_2, 2:1 EtOAc/hexanes) to yield **9d** (6.4 mg, 54%).

3,6-Bis(3,4-dimethoxybenzoyl)-4-(2-hydroxyethyl)-pyridazine (9e). A stirring solution of **2** (10.7 mg, 0.026 mmol) in $CHCl_3$ (260 μL) under Ar was treated with 2,3-dihydrofuran (**8e**, 10 μL, 0.130 mmol) and warmed at 50 °C for 5 min. The cooled solution was maintained at 23 °C for 3 h to allow complete aromatization before concentration under reduced pressure. Flash chromatography (SiO_2, 1.5 × 8 cm, 0−30%

EtOAc/CH_2Cl_2 gradient elution) afforded **9e** (9.4 mg, 80%) as an off-white solid: mp 207−209 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1H), 8.03 (dd, J = 2.1, 8.5 Hz, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.43 (dd, J = 2.1, 8.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 3.99 (m, 5H), 3.98 (s, 3H), 3.97 (s, 6H), 3.04 (t, J = 6.2 Hz, 2H), 2.36 (t, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.0, 189.8, 160.0, 158.2, 155.0, 154.5, 149.5, 149.2, 140.6, 129.8, 128.9, 128.3, 128.2, 128.1, 112.8, 111.6, 110.2, 62.0, 56.5, 56.4, 56.3 (2C), 34.5; IR (film) ν_{max} 3395, 1646, 1580, 1513 cm^{-1}; MALDIFTMS (DHB) m/z 453.1651 ($C_{24}H_{24}N_2O_7$ + H^+ requires 453.1656).

3,6-Bis(3,4-dimethoxybenzoyl)-4-methylpyridazine (9f). Tetrazine **2** (6.0 mg, 0.015 mmol) was dissolved in 2-methoxypropene (**8f**, 105 μL, 1.10 mmol). The mixture was stirred for 4 d at 4 °C, during which time the solution changed color from orange to yellow. The solvent was removed in vacuo, and the crude product was purified by PTLC (SiO_2, 50% EtOAc/hexanes) to yield **9f** (4.4 mg, 73%) as a pale yellow solid: mp 134−135 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 1H), 8.02 (dd, J = 1.8, 8.6 Hz, 1H), 7.85 (d, J = 1.8 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.39 (dd, J = 1.8, 8.4 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.973 (s, 3H), 3.967 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.4, 191.7, 154.9, 154.5, 149.6, 149.2, 138.9, 132.5, 131.2, 129.8, 128.8, 128.4, 128.2, 127.6, 112.8, 111.4, 110.3, 110.2, 56.5, 56.4, 56.3 (2C), 18.4; IR (film) ν_{max} 1650 cm^{-1}; MALDIFTMS (DHB) m/z 423.1534 (M + H^+, $C_{23}H_{22}N_2O_6$ requires 423.1551).

3,6-Bis(3,4-dimethoxybenzoyl)pyridazine (9g). From 8h. A solution of **2** (6.0 mg, 0.015 mmol) and vinyl acetate (**8h**, 12.6 μL, 0.014 mmol) in toluene (72 μL) was warmed at 110 °C for 17 h. The solvent was removed in vacuo, and the material was purified by PTLC (SiO_2, 2:1 EtOAc/hexanes) to yield **9g** (6.0 mg, 100%) as a pale yellow solid: mp 210−211 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (s, 2H), 8.00 (dd, J = 2.0, 8.5 Hz, 2H), 7.83 (d, J = 2.0 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 3.99 (s, 6H), 3.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 189.4 (2C), 158.7 (2C), 154.4 (2C), 149.1 (2C), 128.6 (2C), 128.0 (4C), 112.4 (2C), 110.0 (2C), 56.2 (2C), 56.1 (2C); IR (film) ν_{max} 1654, 1593, 1517 cm^{-1}; MALDIFTMS (DHB) m/z 409.1391 (M + H^+, $C_{22}H_{20}N_2O_6$ requires 409.1394).

From 8g. A solution of **2** (101 mg, 0.246 mmol) in dioxane (1.20 mL) was treated with ethyl vinyl ether (**8g**, 45 μL, 0.48 mmol) and stirred at 35 °C for 48 h. At the end of the reaction, the solution had changed in color from orange to yellow. The solvent was removed in vacuo, and the product was precipitated with MeOH and collected by filtration to afford **9g** (94.8 mg, 95%).

3,6-Bis(3,4-dimethoxybenzoyl)-5-(*p*-chlorophenyl)-1,2,4-triazine (11). From 10a. A solution of **2** (17.9 mg, 0.044 mmol) and the free base[23] of *S*-methyl (*p*-chlorophenyl)-thioimidate hydroiodide[4] (**10a**, 27.4 mg, 0.087 mmol) in dioxane (225 μL) was warmed at 50 °C for 17 h. The solvent was removed in vacuo, and the product was purified by chromatography (SiO_2, 1 × 10 cm, 2:1 EtOAc/hexanes) to yield **11** (13.8 mg, 61%) as a red solid: mp 135−136 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (m, 2H), 8.02 (m, 2H), 7.74 (d, J = 1.8 Hz, 2H), 6.93−6.90 (m, 4H), 3.98 (s, 6H), 3.95 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.1, 192.9, 170.3, 169.2, 168.8, 160.3, 157.7, 154.6, 152.4, 152.3, 141.3, 135.9, 132.4, 129.7, 129.5, 126.8, 126.7, 118.8, 118.6, 112.8, 112.6, 110.3, 110.2, 56.5 (2C), 56.4, 56.3; IR (film) ν_{max} 1651, 1592, 1515 cm^{-1}; MALDIFTMS (DHB) m/z 520.1263 ($C_{27}H_{22}ClN_3O_6$ + H^+ requires 520.1270).

From 10b. A solution of **2** (14.7 mg, 0.036 mmol) in dioxane (180 μL) was treated with the free base[23] of *O*-methyl (*p*-chlorophenyl)imidate hydrochloride (**10b**, 14.8 mg, 0.072 mmol), and the reaction mixture was stirred at 90 °C for 17 h. The reaction mixture was cooled and the solvent removed under reduced pressure. Chromatography (SiO_2, 1 × 10 cm, 2:1 EtOAc/hexanes) afforded **11** (5.8 mg, 31%).

From 10c. A solution of **2** (15.4 mg, 0.036 mmol) in dioxane (185 μL) was treated with the free base[23] of *p*-chlorobenzene-1-carboximidamide hydrochloride (**10c**, 14.0 mg, 0.0731 mmol), and the reaction mixture was stirred at 90 °C for 17 h. The reaction mixture was cooled and the solvent removed under reduced pressure. Chromatography (SiO_2, 1 × 10 cm, 2:1 EtOAc/hexanes) afforded **11** (6.0 mg, 32%).

4-(*N*,*N*-Diethylamino)-3,6-bis(3,4-dimethoxybenzoyl)-5-methylpyridazine (15). Tetrazine **2** (10 mg, 0.024 mmol) in dioxane (120 μL) was treated with 1-(*N*,*N*-diethylamino)-1-propyne (**14a**, 7 μL, 0.048 mmol) at 23 °C. Rapid evolution of N_2 was observed, as the reaction changed from an orange slurry to a red solution. After 2 h, the solvent was removed in vacuo, and the crude material purified by PTLC (SiO_2, 2:1 EtOAc/hexanes) to yield **15** (11.9 mg, 100%) as a yellow solid: mp 65−66 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.71 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.49 (dd, J = 1.8, 8.4 Hz, 1H), 7.39 (dd, J = 1.8, 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 3.972 (s, 3H), 3.965 (s, 3H), 3.960 (s, 3H), 3.955 (s, 3H), 3.12 (q, J = 7.0 Hz, 4H), 2.26 (s, 3H), 1.06 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 193.0, 191.8, 155.4, 154.7 (2C), 154.4, 149.9, 149.6, 149.4, 131.3, 129.2, 129.0, 127.6, 127.3, 111.5, 111.2, 110.2 (2C), 56.4 (2C), 56.3 (2C), 46.4 (2C), 15.1, 13.7 (2C); IR (film) ν_{max} 1661, 1652, 1593, 1515 cm^{-1}; MALDI−FTMS (DHB) m/z 494.2297 (M + H^+, $C_{27}H_{31}N_3O_6$ requires 494.2286).

3,6-Bis(3,4-dimethoxybenzoyl)-4-carbomethoxypyridazine (16). A stirring solution of **2** (10.5 mg, 0.026 mmol) in 1,4-dioxane (260 μL) under Ar was treated with methyl propiolate (**14d**, 11 μL, 0.128 mmol) and warmed at 95 °C for 5 d. The reaction mixture was concentrated, and the crude product was purified by flash chromatography (SiO_2, 1.5 × 8 cm, 0−5% EtOAc/CH_2Cl_2 gradient elution) to afford **16** (7.9 mg, 65%) as a yellow oil: ^{1}H NMR (CD_3CN, 400 MHz) δ 8.50 (s, 1H), 7.82 (dd, J = 2.0, 8.5 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 2.0, 8.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.892 (s, 3H), 3.886 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 191.2, 189.9, 164.7, 160.3, 160.0, 155.81, 155.78, 150.6, 150.3, 130.5, 129.5, 128.9, 128.6, 128.5, 127.4, 113.6, 111.9, 111.6, 111.5, 56.4 (2C), 56.3 (2C), 53.9; IR (film) ν_{max} 1738, 1667, 1651, 1593, 1515 cm^{-1}; MALDIFTMS (DHB) m/z 467.1445 ($C_{24}H_{22}N_2O_8$ + H^+ requires 467.1449).

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Supporting Information Available: ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The salt was partitioned between $CHCl_3$ (1.5 mL) and 10% aqueous $NaHCO_3$ (1.5 mL) and the organic phase was concentrated to provide the free base.