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Inverse Electron Demand Diels-Alder Reactions of 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine and 2,4,6-Tris(methylthio)-1,3,5-triazine: Pyrimidine Introduction†

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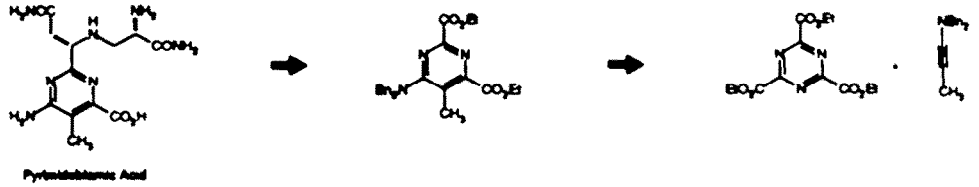
Abstract: A full investigation of the scope of the participation of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (1a) and 2,4,6-tris(methylthio)-1,3,5-triazine (1b) in inverse electron demand Diels-Alder reactions suitable for the preparation of functionalized 5,6-disubstituted pyrimidines is detailed. The use of the resulting [4 + 2] cycloadducts as immediate precursors to the parent 4,5-disubstituted pyrimidines is described.

In recent efforts we have detailed the use of a series of inverse electron demand Diels-Alder reactions of electron-deficient heterocyclic azadienes in [4 + 2] cycloaddition reactions with electron-rich dienophiles comprising a general approach to the introduction of a full range of heteroaromatic systems, Scheme I.[2-14]

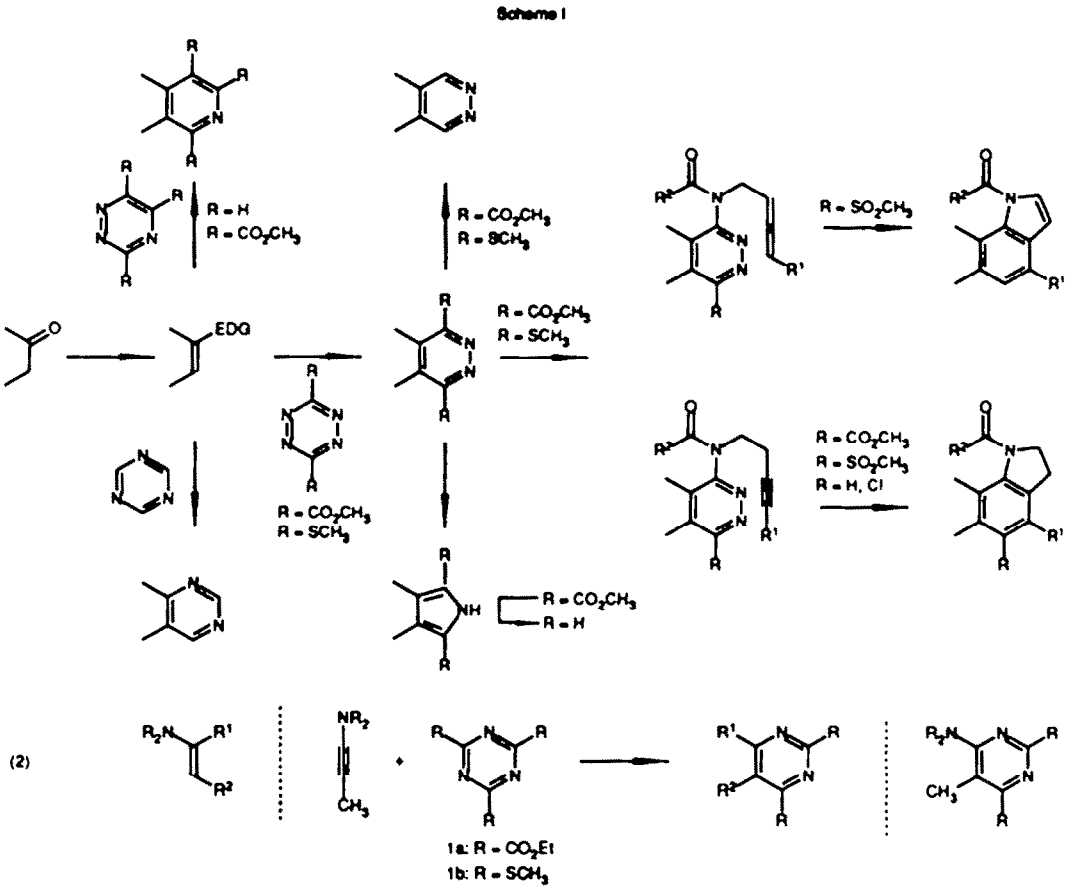
This approach has proven well-suited for the introduction of highly substituted and highly functionalized heteroaromatic systems difficult to assemble by alternative methodology and consequently has found application in the total syntheses of a range of naturally occurring materials.[8-13] In a continued exploration of the inverse electron demand Diels-Alder reactions of heterocyclic azadienes and in efforts to extend the 1,3,5-triazine →pyrimidine Diels-Alder reaction[3] to the total synthesis of pyrimidoblamic acid,[15] the heteroaromatic segment of the bleomycin, equation 1, the potential use of 2,4,6-trisubstituted-1,3,5-triazines has been under investigation. Herein, we detail our efforts on the investigation of the scope of the [4 + 2] cycloaddition reactions of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (1a)[3,16] and 2,4,6-tris(methylthio)-1,3,5-triazine (1b)[17] with electron-rich dienophiles suitable for the preparation of functionalized 5,6-disubstituted pyrimidines, equation 2.



Pyrimidoblamic Acid

† This paper is dedicated to Professor E. C. Taylor on the occasion of his 65th birthday.

Scheme I



[4 + 2] Cycloaddition Reactions of 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (1a). Ynamines, electron-rich alkynes, and enamines, electron-rich alkenes, were found to participate in well-defined [4 + 2] cycloaddition reactions with 2 4,6-tris(ethoxycarbonyl)-1,3,5-triazine (1a), Table I. In the case of ynamines, the room temperature [4 + 2] cycloaddition reaction is followed by a subsequent retro Diels-Alder reaction (40-100°C) with loss of ethyl cyanoformate and with direct generation of the 5-substituted 2,4-bis(ethoxycarbonyl)-6-dialkylaminopyrimidines, Scheme II (Table I, entries 1-2).

The [4 + 2] cycloaddition reaction of 1a with enamines 2c-2h was found to proceed (25-100°C) in conventional organic solvents (CH_3CN, dioxane, diglyme, CH_2Cl_2) to provide the stable, isolable [4 + 2] cycloadducts which only sluggishly and poorly undergo a retro Diels-Alder reaction and final aromatization to provide the 5,6-disubstituted 2,4-bis(ethoxycarbonyl)pyrimidines, Scheme III. The initial [4 + 2] cycloadducts proved remarkably stable and capable of purification by conventional means (silica gel chromatography); Table I, entries 9-11. Initial attempts to thermally promote the retro Diels-Alder reaction (100-200°C, 4 → 5) were only modestly successful and were hampered by the subsequent, problematic aromatization step (5 → 3) requiring the loss of secondary amine (pyrrolidine, morpholine); Table I, entries 3d-e and 8a. In the search for reaction conditions which would promote both the retro Diels-Alder reaction and subsequent aromatization, the exposure of the isolated

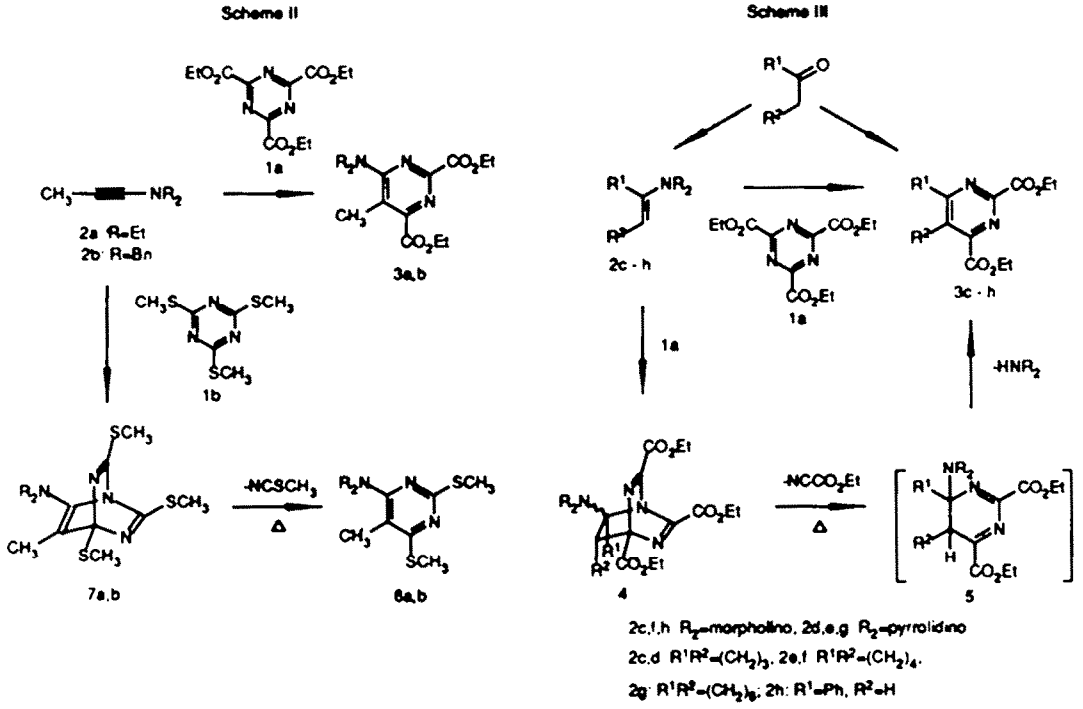
Table I.

[4 + 2] Cycloaddition Reactions of 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (1a).

Entry	Dienophile	equiv	Conditions	Pyridine[a]	%Yield[b]
1a	2a[c]	2	dioxane, 101°C, 2 h	3a	83
b		2	dioxane, 60°C, 24 h		67
2a	2b[d]	1.7	CH_3CN, 82°C, 12 h	3b	73
b		2	dioxane, 101°C, 21 h		95
3a	2c[e]	2	dioxane, 101°C, 4 h 4N HCl, 101°C, 12 h	3c	68
b		2	CH_2Cl_2, 40°C, 12 h CH_2Cl_2, CH_3COOH, 100°C, 11 h		62[g]
c		2	CH_2Cl_2, CH_3COOH, 100°C, 20 h		58[f]
d		2	dioxane, 25°C, 2 h 101°C, 14 h		28[h,i]
e		2	CH_3CN, 82°C, 15 h		20[h,i]
4a	2d[e]	2	CH_2Cl_2, CH_3COOH, 85°C, 20 h	3c	36[f]
b		2	CH_2Cl_2, 40°C, 2 h CH_2Cl_2, CH_3COOH, 100°C, 11 h		26[g]
5a	2e[e]	2	dioxane, 101°C, 12 h 4N HCl, 101°C, 24 h	3e	33
b		2	CH_2Cl_2, 40°C, 4 h CH_2Cl_2, CH_3COOH, 100°C, 12 h		32[g]
c		2	CH_2Cl_2, CH_3COOH, 90°C, 17 h		30[f]
6a	2f[e]	2	CH_2Cl_2, CH_3COOH, 100°C, 20 h	3e	72[f]
7a	2g[e]	2	CH_2Cl_2, CH_3COOH, 90°C, 16 h	3g	75[f]
8a	2h[e]	2	diglyme, 120°C, 4 h 145°C, 24 h	3h	41[h]
b		2	CH_2Cl_2, CH_3COOH, 90°C, 13 h		31[f]
9a	2c	2	CH_3CN, 82°C, 12 h	4c	66
b		2	dioxane, 101°C, 6 h		34
c		2	dioxane, 65°C, 12 h		23[j]
10a	2d	2	CH_3CN, 82°C, 16 h	4d	91
b		2	dioxane, 101°C, 14 h		45[k]
11a	2e	2	CH_3CN, 82°C, 17 h	4e	49

[a] All products exhibited the expected or previously reported ^1H NMR, IR, and EI/CIMS characteristics consistent with the assigned structure. All new compounds provided satisfactory HRMS exact mass information. [b] All yields are based on pure material isolated by chromatography (SiO_2). [c] Available commercially from Fluka. [d] Ireland, R. E.; Anderson, R. C.; Badond, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisinonge, S.; Wilcox, C. S. J. Am. Chem. Soc. 1983, 105, 1988. [e] The morpholino and pyrrolidino enamines were prepared in benzene with the aid of the azeotropic removal of water (2c,d,e,f): Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovic, J.; Terrell, R. J. Am. Chem. Soc. 1963, 85, 207; or with the aid of 4 Å molecular sieves (2g,h): Taguchi, K.; Westheimer, F. H. J. Org. Chem. 1971, 36, 1570. [f] Methylene chloride:acetic acid (1:1) was used as the reaction solvent. [g] The reaction was first conducted in methylene chloride until the [4 + 2] was complete (TLC) before acetic acid (CH_2Cl_2:HOAc, 1:1) was added. [h] The reaction product consisted of both the [4 + 2] cycloadduct 4 and the final pyrimidine product 3. [i] The [4 + 2] cycloadduct was isolated, then subjected to treatment with p-toluenesulfonic acid/benzene (reflux). The yield is based on two steps. [j] 13% of 3c and 17% of 1a were isolated. [k] 28% of 3c was isolated.

enamine [4 + 2] cycloadducts 4 to 4N hydrochloric acid-dioxane (Table I, entries 3a and 5a), catalytic anhydrous p-toluenesulfonic acid (Table I, entries 3d and 3e), or acetic acid (Table I, entries 3b, 4b, and 5b) proved to catalyze both the retro Diels-Alder reaction requiring the loss of ethyl cyanoformate and the subsequent, final aromatization step providing a suitable two-step process for pyrimidine generation. This two-step sequence could be reduced to the anticipated, single operation by conducting the [4 + 2] cycloaddition reaction in methylene chloride-acetic acid (1:1), thus providing reaction conditions which do not hamper the initial [4 + 2] cycloaddition reaction (40°C) and which serve to facilitate the subsequent retro Diels-Alder reaction and final aromatization step (40-100°C); Table I, entries 3c, 4a, 5c, 6a, 7a, and 8b.



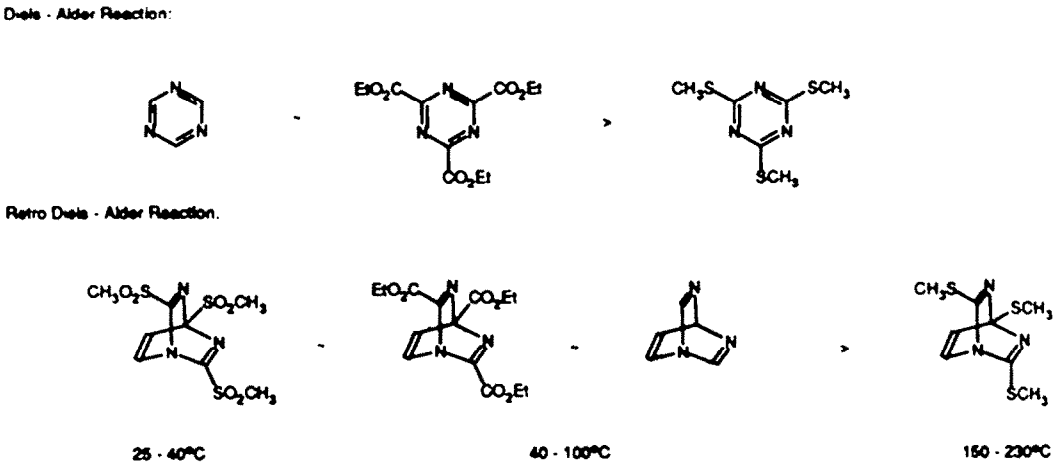
A range of electron-rich (1,1-dimethoxyethylene, N-vinylpyrrolidin-2-one, and 1-phenyl-1-trimethylsilyloxyethylene) and electron-deficient (dimethyl acetylenedicarboxylate, p-naphthoquinone) alkynes and alkenes failed to react with 1a.

[4 + 2] Cycloaddition Reactions of 2,4,6-Tris(methylthio)-1,3,5-triazine (1b). Ynamines, nucleophilic alkynes, proved to be the sole nucleophilic dienophiles sufficiently reactive to participate in productive [4 + 2] cycloaddition reactions with 2,4,6-tris(methylthio)-1,3,5-triazine (1b), Table II. In contrast to prior studies of the reaction of ynamines with 1,3,5-triazines including the parent ring system[3] and 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine,[3a] the initial ynamine 1,3,5-triazine [4 + 2] cycloadducts 7 proved stable, isolatable by standard chromatographic techniques, and remarkably resistant to thermolytic retro Diels-Alder reaction

with the loss of methylthiocyanate ($CH_3SC{\equiv}N$), Scheme II. Consequently, the [4 + 2] cycloaddition of 1b with ynamines may be carried out with the intermediate isolation and characterization of the initial 1,3,5-triazine [4 + 2] cycloadduct 7 (100°C) and followed with the subsequent thermolytic (150-230°C) or acid-catalyzed (p-TsOH, 100°C) retro Diels-Alder reaction. Alternatively, the thermolytic [4 + 2] cycloaddition may be carried out (100°C, 150-230°C) under conditions which provide the 6-substituted 5-dialkylamino-2,4-bis(thiomethyl)pyrimidine 6 directly. Consistent with past observations[18] in which the presence of appropriately placed electron-withdrawing substituents serve to accelerate the retro Diels-Alder reaction of bicyclo[2.2.2]hexenes, bicyclo[2.2.2]hexadienes, and bicyclo[2.2.2]hexatrienes; the clean S-oxidation of the thermally stable [4 + 2] cycloadduct 7b (6.5 equiv mCPBA, -5 to 23°C, CH_2Cl_2) with in situ generation of the corresponding tris(methanesulfonyl) derivative 9 preceeded a low temperature (≤ 25°C) retro Diels-Alder reaction proceeding with the loss of methanesulfonylcyanate ($CH_3SO_2C{\equiv}N$) and afforded 6-(N,N-dibenzylamino)-5-methyl-2,4-bis(methanesulfonyl)pyrimidine (10), equation 3. Thus, in contrast to the thermal stability of the [4 + 2] cycloadduct 7b which suffers a retro Diels-Alder reaction only at temperatures of 150-230°C, the retro Diels-Alder reaction of the corresponding tris(methanesulfonyl)derivative 9 readily occurs at temperatures less than 25°C, Figure I.

In contrast to the observations with 1,3,5-triazine[3] and 1a, enamines failed to react with 1b, Figure I. In addition, the electron-deficient dienophiles (p-naphthoquinone, dimethyl acetylenedicarboxylate) failed to participate in [4 + 2] cycloaddition reactions with 1b.

Figure I



Preparation of the Parent 4,5-Disubstituted Pyrimidines. Reductive desulfurization (Raney nickel) of the 2,4-bis(methylthio)pyrimidine [4 + 2] cycloadducts provides an approach to the preparation of the parent 4,5-disubstituted pyrimidines. In a representative example,

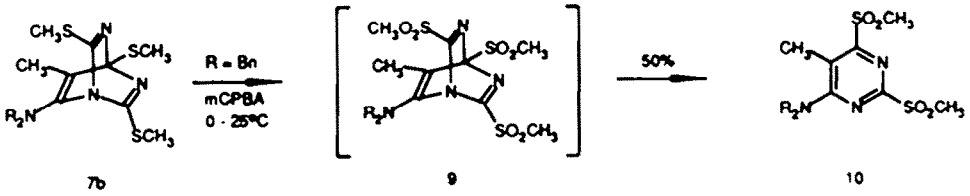
Table II.

[4 + 2] Cycloaddition Reactions of 2,4,6-Tris(methylthio)-1,3,5-triazine (1b).

Entry	Dienophile	equiv	Conditions	Pyrimidine[a]	%Yield[b]
1	2a[c]	2	dioxane, 101°C, 12 h DMF, 100°C, 15 h 155°C, 30 h	6a	86[e]
		2	dioxane, 101°C, 12 h p-TsOH, 101°C, 7 h	6a	76
		2	CH_2Cl_2, 25°C, 65 h 13 kbar	--	--
2	2b[d]	2	diglyme, 150°C, 24 h 162°C, 24 h TIPB, 230°C, 36 h	6b	66[f]
		2	diglyme, 150°C, 16 h TIPB, 230°C, 36 h	6b	58[g]
3	2a	2	dioxane, 101°C, 16 h	7a	93
4	2b	2	diglyme, 150°C, 24 h 162°C, 24 h	7b	69[h]

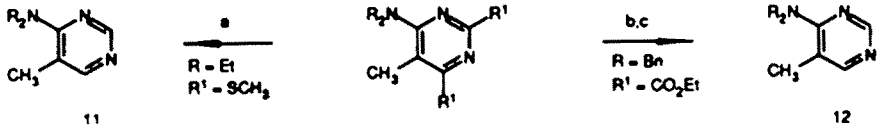
[a] All products exhibited the expected or previously reported ^1H NMR, IR, and EI/CIMS characteristics consistent with the assigned structure. All new compounds provided satisfactory HRMS exact mass information. [b] All yields are based on pure material isolated by chromatography (SiO_2). [c] Commercially available from Fluka.
[d] Ireland, R. E.; Anderson, R. C.; Badond, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisinongs, S.; Wilcox, C. S. J. Am. Chem. Soc. 1983, 105, 1988. [e] Yield based on two steps: cycloaddition (93%), retro Diels-Alder reaction (92%). [f] Yield based on two steps: cycloaddition (69%), retro Diels-Alder reaction (96%). [g] Yield based on two steps: cycloaddition (60%), retro Diels-Alder reaction (96%). [h] 23% of starting 1b recovered.

(3)



7b 9 10

(4)



11 12

(a) 34 Equiv Ra-Ni, aqueous dioxane, 101°C, 20 h, 46%. (b) 1 M NaOH, 25°C, 4 h, 100%.
(c) 1:1 CH_3CO_2H and $(CH_3CO)_2O$, 120°C, 30 h, 52%.

reductive desulfurization of 6a (34 equiv Raney nickel, aqueous dioxane)[19,20] provided 4-(N,N-diethylamino)-5-methylpyrimidine (11, 46%), equation 4. The two-step decarboxylation of the 2,4-bis(ethoxycarbonyl)pyrimidine [4 + 2] cycloadducts provides an alternative approach to the preparation of the parent 4,5-disubstituted pyrimidines. In a representative example, exhaustive ethyl ester hydrolysis of 3b followed by acid-catalyzed decarboxylation of the corresponding dicarboxylic acid provided 4-(N,N-dibenzylamino)-5-methylpyrimidine (12, 52%).

Experimental Section

Proton nuclear magnetic spectra (^{1}H NMR) were recorded on a Varian XL-200, General Electric QE-300, or Varian FT-80 spectrometer and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (0.00 ppm). Infrared spectra (IR) were recorded on a Perkin Elmer 1420 or Perkin-Elmer Model 1800 FTIR as KBr pellets (solids) and thin films (liquids). Melting points (mp) were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Electron impact mass spectra (EIMS) and chemical ionization mass spectra (CIMS) were recorded on a Finnegan 4000 spectrometer. Electron impact (EI) and chemical ionization (CI) high resolution mass spectra (HRMS) were recorded on a Kratos MS-50 spectrometer. Flash chromatography (chromatography)[21] was performed on 230-400 mesh silica gel. Tetrahydrofuran (THF), ether (Et_2O), and diglyme (diethylene glycol dimethyl ether) were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2), chloroform ($CHCl_3$), and acetonitrile (CH_3CN) were distilled from phosphorus pentoxide. Mesitylene, dioxane, N,N-dimethylformamide (DMF), toluene, xylene, and triisopropylbenzene (TIPB, Aldrich Chemical Co.) were distilled from calcium hydride. Acetic acid was distilled over chromium trioxide and acetic anhydride. All extraction and chromatographic solvents: ethyl ether (Et_2O), ethyl acetate (EtOAc), and hexane were distilled prior to use. All other solvents and reagents were used as received from commercial sources. All Diels-Alder reactions and other reactions requiring anhydrous conditions or an inert atmosphere were conducted under a positive pressure of nitrogen or argon.

2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (1a). 1,3,5-Triazine 1a was prepared following the procedure described by Ott.[16] Neat ethyl cyanoformate (5.0 g, 50.5 mmol) and hydrochloric acid (0.25 g, 6.85 mmol, 5%) at room temperature (48 h) afforded pure 1a (4.24 g, 5.0 g theoretical, 85%). Mp 170.5 - 171.5°C (ethanol, white needles; lit. mp 165°C);[16] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (9H, t, J = 7.2 Hz, $-OCH_2\underline{CH_3}$), 4.59 (6H, q, J = 7.2 Hz, $-O\underline{CH_2}CH_3$); IR (KBr) ν_{max} 2980, 1745, 1625, 1530, 1465, 1380, 1235, 1010, 940, 860, 740 cm^{-1}; EIMS, m/e (relative intensity), 298(M^+ + H, 2), 282(2), 253(13), 225(100), 197(32), 168(2), 152(6), 125(21), 107(12), 98(10), 79(7), 56(30); CIMS (2-methylpropane), m/e 298(M^+ + 1, base).

2,4,6-Tris(methylthio)-1,3,5-triazine (1b). A solution of trithiocyanuric acid (2.54 g, 14.3 mmol) in 1.0 N aqueous sodium hydroxide (43 mL, 43 mmol, 3.0 equiv) was treated with methyl iodide (6.11 g, 43 mmol, 3.0 equiv) and the resulting reaction mixture was stirred at room temperature for 2 hours during which time 1b precipitated from the reaction solution. Ethanol (25 mL) was added, the solid was collected by filtration, and washed with water (10 mL) and ethanol (10 mL). Recrystallization from acetic acid afforded the pure 1b (2.76 g, 3.14 g theoretical, 88%) as pale yellow needles: mp 188-188.5°C (lit. mp 188°C);[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (9H, s, $-SCH_3$); IR (KBr) ν_{max} 2926, 2843, 2399, 1477, 1410, 1321, 1240, 980, 856, 783 cm^{-1}; EIMS, m/e (relative intensity) 219(M^+, 100), 204(13), 186(10), 173(3), 158(50), 131(2), 110(7), 99(26), 74(32); CIMS (2-methylpropane), m/e 220(M^+ + 1, base).

[4 + 2] Cycloaddition Reactions of 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (1a) with Enamines (2c-2h). General Procedure for the Preparation of 5,6-Disubstituted 2,4-Bis(ethoxycarbonyl)pyrimidines: 2,4-Bis(ethoxycarbonyl)-5H-6,7-dihydrocyclopentapyrimidine (3c). A solution of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (1a, 53 mg, 0.18 mmol) in methylene chloride and acetic acid (1:1, 0.36 mL) under argon was treated with morpholinocyclopent-1-ene (2d, 55 mg, 0.36 mmol, 2.0 equiv) at 25°C and the resulting reaction solution was warmed at 100°C (20 h). The cooled reaction mixture was diluted with methylene chloride (15 mL) and washed with saturated aqueous sodium bicarbonate (2 x 15 mL). The aqueous extracts were washed with methylene chloride (2 x 25 mL) and the combined organic extracts were dried over potassium carbonate. Flash chromatography (SiO_2, 15 cm x 1.2 cm, 60% Et_2O-

petroleum ether eluant) afforded pure 3c (27 mg, 47 mg theoretical, 58%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (3H, t, J = 7.4 Hz, $-CH_2\underline{CH_3}$), 1.47 (3H, t, J = 7.4 Hz, $-CH_2\underline{CH_3}$), 2.25 (2H, p, J = 7.8 Hz, $-CH_2\underline{CH_2}CH_2-$), 3.21 (2H, t, J = 7.9 Hz, $-\underline{CH_2}CH_2CH_2-$), 3.39 (2H, t, J = 7.7 Hz, $-CH_2CH_2\underline{CH_2}-$), 4.52 (2H, q, J = 7.4 Hz, $-O\underline{CH_2}CH_3$), 4.52 (2H, q, J = 7.4 Hz, $-O\underline{CH_2}CH_3$); IR (film) ν_{max} 2964, 2932, 2855, 1743, 1572, 1557, 1401, 1381, 1239, 1197, 1124, 1023 cm^{-1}; EIMS, m/e (relative intensity), 265(M^+ + H, 1), 192(26), 164(3), 146(7), 118(28), 89(20), 72(16), 65(6), 57(18) 45(100); CIMS (2-methylpropane), m/e 265(M^+ + 1, base); EIHRMS, m/e calcd. for $C_{13}H_{16}N_2O_4$ 264.1110, found 264.1105.

General Procedure for the [4 + 2] Cycloaddition Reaction of Ynamines with 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (1a) and 2,4,6-Tris(methylthio)-1,3,5-triazine (1b): 2,4-Bis(ethoxycarbonyl)-6-(N,N-dibenzylamino)-5-methylpyrimidine (3b). A solution of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (1a, 1.22 g, 4.11 mmol) in dioxane (10 mL) under argon was treated with 1-N,N-dibenzylamino-1-propyne (2b, 1.93 g, 8.22 mmol, 2.0 equiv)[22] at 25°C and the resulting reaction solution was warmed at 101°C (21 h). Removal of the solvent in vacuo and flash chromatography (SiO_2, 15 cm x 4 cm, 20-40% EtOAc-hexane gradient elution) afforded pure 3b (1.69 g, 1.78 g theoretical, 95%) as a light orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (3H, t, J = 7.2 Hz, $-CH_2\underline{CH_3}$), 1.42 (3H, t, J = 7.2 Hz, $-CH_2\underline{CH_3}$), 2.36 (3H, s, $-CH_3$), 4.44 (2H, q, J = 7.2 Hz, $-\underline{CH_2}CH_3$), 4.45 (2H, q, J = 7.2 Hz, $-\underline{CH_2}CH_3$), 4.73 (4H, s, $-\underline{CH_2}Ph$), 7.32 (10H, m, Ph); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 165.79 ($-\underline{C}O_2Et$), 165.74 ($-\underline{C}O_2Et$), 163.66 (C-2), 157.93 (C-6), 153.18 (C-4), 136.94, 128.53, 127.90 and 127.41 (four C_6H_5), 116.26 (C-5), 62.07 (two $-CH_2Ph$), 52.42 (two $-\underline{CH_2}CH_3$), 16.00 ($-CH_3$), 14.08 ($-\underline{CH_2}CH_3$), 13.97 ($-\underline{CH_2}CH_3$); IR (film) ν_{max} 3029, 2982, 2935, 1739, 1560, 1496, 1453, 1427, 1243, 1222, 1091, 700 cm^{-1}; EIMS, m/e (relative intensity), 342(3), 196(4), 146(1), 134(18), 118(3), 106(43), 91(100), 79(11), 77(15), 65(23), 51(11); CIMS (2-methylpropane), m/e 434(M^+ + 1, base); CIHRMS, m/e calcd. for $C_{25}H_{27}N_3O_4$ 434.2080, found 434.2054.

2,4-Bis(ethoxycarbonyl)-6-(N,N-diethylamino)-5-methylpyrimidine (3a). Table I, entry 1a: 1a (53 mg, 0.18 mmol) and 1-N,N-diethylamino-1-propyne (2a, 40 mg, 0.36 mmol, 2 equiv) afforded pure 3a (46 mg, 55 mg theoretical, 83%) as a pale yellow oil identical in all comparable respects with authentic material:[3a] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (6H, t, J = 7 Hz, $-NCH_2\underline{CH_3}$), 1.41 (6H, t, J = 7.2 Hz, $-OCH_2\underline{CH_3}$), 2.32 (3H, s, $-CH_3$), 3.54 2(4H, q, J = 7 Hz, $-N\underline{CH_2}CH_3$), 4.43 (2H, q, J = 7.2 Hz, $-O\underline{CH_2}CH_3$), 4.44 (2H, q, J = 7.2 Hz, $-O\underline{CH_2}CH_3$); IR (film) ν_{max} 2981, 2936, 1738, 1565, 1524, 1502, 1432, 1379, 1236, 1176, 1064, 825 cm^{-1}.

2,4-Bis(ethoxycarbonyl)-5,6,7,8-tetrahydroquinazoline (3e). Table I, entry 6a: 1a (54 mg, 0.18 mmol) and 2f (61 mg, 0.37 mmol, 2 equiv) afforded pure 3e (37 mg, 51 mg theoretical, 72%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (3H, t, J = 7.2 Hz, $-CH_2\underline{CH_3}$), 1.49 (3H, t, J = 7.2 Hz, $-CH_2\underline{CH_3}$), 1.90 (4H, m, $-CH_2\underline{CH_2}\underline{CH_2}CH_2-$), 3.01 (2H, t, J = 6.1 Hz, $-CH_2CH_2CH_2\underline{CH_2}-$), 3.08 (2H, t, J = 6.1 Hz, $-\underline{CH_2}CH_2CH_2CH_2-$), 4.46 (2H, q, J = 7.2 Hz, $-\underline{CH_2}CH_3$), 4.53 (2H, q, J = 7.2 Hz, $-\underline{CH_2}CH_3$); IR (film) ν_{max} 2939, 2869, 1737, 1554, 1450, 1403, 1380, 1307, 1198, 1145, 1024, 866, 751 cm^{-1}; EIMS, m/e (relative intensity), 278(M^+, 13), 232(11), 206(100), 178(3), 160(10), 132(18), 104(4), 92(1), 79(14), 65(2), 55(3); CIMS (2-methylpropane), m/e 279(M^+ + 1, base); EIHRMS, m/e calcd. for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1268.

2,4-Bis(ethoxycarbonyl)-5H-6,7,8,9-tetrahydrocycloheptapyrimidine (3g). Table I, entry 7a: 1a (80 mg, 0.27 mmol) and 2g (89 mg, 0.54 mmol, 2 equiv) afforded pure 3g (59 mg, 79 mg theoretical, 75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (3H, t, J = 7.6 Hz, $-CH_2\underline{CH_3}$), 1.46 (3H, t, J = 7.6 Hz, $-CH_2\underline{CH_3}$), 1.76 (4H, m), 1.94 (2H, m), 2.95 (2H, m), 3.21 (2H, m), 4.48 (2H, q, J = 7.6 Hz, $-\underline{CH_2}CH_3$), 4.54 (2H, q, J = 7.6 Hz, $-\underline{CH_2}CH_3$); IR (film) ν_{max} 2982, 2930, 2858, 1742, 4559, 1403, 1381, 1241, 1189, 1126, 1020, 863, 744 cm^{-1}; EIMS, m/e (relative intensity), 292(M^+, 8), 277(2), 263(23), 247(4), 235(5), 220(100), 190(26), 172(14), 158(9), 146(66),

130(8), 118(23), 91(45), 77(27), 65(21), 55(35); CIMS (2-methylpropane), m/z 293(M^+ + 1, base); EIHRMS, m/z calcd. for $C_{15}H_{20}N_2O_4$ 292.1423, found 292.1423.

2,4-Bis(ethoxycarbonyl)-6-phenylpyrimidine (3h). Table I, entry 8a: 1a (69 mg, 0.23 mmol) and 2h (87 mg, 0.46 mmol, 2 equiv) afforded pure 3h (28 mg, 69 mg theoretical, 41%) as an orange solid: mp 114-115°C (white needles, ethanol-water); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (3H, t, J = 7.1 Hz, $-CH_2\underline{CH_3}$), 1.50 (3H, t, J = 7.1 Hz, $-CH_2\underline{CH_3}$), 4.55 (2H, q, J = 7.1 Hz, $-\underline{CH_2}CH_3$), 4.57 (2H, q, J = 7.1 Hz, $-\underline{CH_2}CH_3$), 7.58 (3H, m), 8.27 (2H, m), 8.53 (1H, s); IR (KBr) ν_{max} 2924, 2853, 1740, 1579, 1535, 1450, 1382, 1247, 1226, 1204, 1089, 1025, 724 cm^{-1}; EIMS, m/z (relative intensity), 301(M^+ + H, 1), 256(4), 228(100), 200(9), 182(8), 155(32), 128(37), 105(29), 84(31), 77(37), 63(2), 51(14); CIMS (2-methylpropane), m/z 301(M^+ + 1, base); EIHRMS, m/z calcd. for $C_{16}H_{16}N_2O_4$ 300.1110, found 300.1105.

4c. Table I, entry 9a: 1a (46 mg, 0.15 mmol) and 2c (42 mg, 0.31 mmol, 2 equiv) afforded 4c (44 mg, 67 mg theoretical, 66%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (9H, m, $-OCH_2\underline{CH_3}$), 2.00 (3H, m), 2.65 (6H, m), 3.75 (6H, m), 4.35 (6H, m, $-O\underline{CH_2}CH_3$); IR (film) ν_{max} 3357, 2978, 2871, 1719, 1641, 1466, 1393, 1371, 1311, 1280, 864, 730 cm^{-1}; EIMS, m/z (relative intensity), 435(M^+ + H, 2), 361(100), 287(24), 266(21), 225(19), 220(16), 192(14), 136(90), 125(9), 120(15), 108(12), 97(11), 81(22), 70(58), 55(49); CIMS (2-methylpropane), m/z 435(M^+ + 1, base); EIHRMS, m/z calcd. for $C_{21}H_{30}N_4O_6$ 434.2165, found 434.2166.

4d. Table I, entry 10a: 1a (53 mg, 0.18 mmol) and 2d (55 mg, 0.36 mmol, 2 equiv) afforded 4d (73 mg, 81 mg theoretical, 91%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (9H, m, $-OCH_2\underline{CH_3}$), 1.95 (3H, m), 2.65 (6H, m), 3.75 (6H, m), 4.35 (6H, m, $-O\underline{CH_2}CH_3$); IR (film) ν_{max} 3407, 2962, 2854, 1719, 1647, 1457, 1372, 1270, 1117, 1021 cm^{-1}; EIMS, m/z (relative intensity), 451(M^+ + H, 1), 377(12), 303(5), 253(4), 225(24), 197(12), 153(100), 138(10), 125(16), 108(16), 95(23), 84(23), 71(15), 67(55), 55(27); CIMS (2-methylpropane), m/z 451(M^+ + 1, base); CIHRMS, m/z calcd. for $C_{21}H_{30}N_4O_7$ 451.2193, found 451.2148.

4e. Table I, entry 11a: 1a (96 mg, 0.32 mmol) and 2e (98 mg, 0.69 mmol, 2 equiv) afforded 4e (71 mg, 145 mg theoretical, 49%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (9H, m, $-OCH_2\underline{CH_3}$), 1.60-3.65 (17H, m), 4.35 (6H, m, $-O\underline{CH_2}CH_3$); IR (film) ν_{max} 3406, 3363, 2940, 2876, 1722, 1647, 1623, 1465, 1370, 1321, 1264, 1195, 1086, 732 cm^{-1}; EIMS, m/z (relative intensity), 379(26), 375(27), 306(48), 296(7), 280(6), 260(4), 253(14), 225(14), 160(17), 150(100), 134(6), 122(7), 110(8), 84(25), 79(12), 70(32), 55(25); CIMS (2-methylpropane), m/z 449(M^+ + 1, base); EIHRMS, m/z calcd. for $C_{22}H_{32}N_4O_6$ 448.2322, found 448.2326.

2,4-Bis(methylthio)-6-(N,N-diethylamino)-5-methylpyridine (6a). Table II, entry 1: 1b (44 mg, 0.20 mmol) and 1-N,N-diethylamino-1-propyne (2a, 45 mg, 0.40 mmol, 2 equiv) afforded pure 8a (45 mg, 52 mg theoretical, 86%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (6H, t, J = 7.0 Hz, $-CH_2\underline{CH_3}$), 2.13 (3H, s, $-CH_3$), 2.53 (3H, s, $-SCH_3$), 2.55 (3H, s, $-SCH_3$), 3.38 (4H, q, J = 7.0 Hz, $-\underline{CH_2}CH_3$); IR (film) ν_{max} 2970, 2925, 2870, 1528, 1428, 1377, 1343, 1309, 1293, 1179, 1046, 862, 802 cm^{-1}; EIMS, m/z (relative intensity), 257(M^+, 37), 242(13), 228(100), 214(43), 181(1), 171(2), 153(1), 112(14), 72(29); CIMS (2-methylpropane), m/z 258(M^+ + 1, base); EIHRMS, m/z calcd. for $C_{11}H_{19}N_3S_2$ 257.1020, found 257.1016.

2,4-Bis(methylthio)-6-(N,N-dibenzylamino)-5-methylpyrimidine (6b). Table II, entry 2: 1b (55 mg, 0.25 mmol) and 1-N,N-dibenzylamino-1-propyne (2b, 118 mg, 0.50 mmol, 2 equiv)[22] afforded pure 8b (63 mg, 96 mg theoretical, 66%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.10 (3H, s, $-CH_3$), 2.33 (3H, s, $-SCH_3$), 2.48 (3H, s, $-SCH_3$), 4.48 (4H, s, $-\underline{CH_2}Ph$), 7.18 (10H, m, Ph); IR (film) ν_{max} 3062, 3028, 2925, 1736, 1603, 1586, 1523, 1451, 1343, 1131, 1067, 958, 737 cm^{-1}; EIMS, m/z (relative intensity) 381(M^+, 4), 355(4), 290(100), 221(6), 189(5), 169(1.5), 147(11), 131(2), 112(11), 91(51), 73(27), 65(7), 55(1); CIMS (2-methylpropane), m/z 382(M^+ + 1, base); EIHRMS, m/z calcd. for $C_{21}H_{23}N_3S_2$ 381.1333, found 381.1339.

7a. Table II, entry 3: 1b (44 mg, 0.20 mmol) and 1-N,N-diethylamino-1-propyne (2a, 45 mg, 0.40 mmol, 2 equiv) afforded pure 7a (62 mg, 67 mg theoretical, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, t, J = 7.1 Hz, $-CH_2\underline{CH_3}$), 1.17 (3H, t, J = 7.1 Hz, $-CH_2\underline{CH_3}$), 1.89 (3H, s, $-CH_3$), 2.22 (3H, s, $-SCH_3$), 2.34 (3H, s, $-SCH_3$), 2.36 (3H, s, $-SCH_3$), 3.20 (4H, q, J = 7.1 Hz, $-\underline{CH_2}CH_3$); IR (film) ν_{max} 2974, 2925, 1610, 1555, 1479, 1462, 1320, 1249, 1166, 1086, 836 cm^{-1}; EIMS, m/e (relative intensity), 330(M^+, 21), 315(100), 283(11), 257(3), 242(10), 228(3), 217(40), 210(11), 168(11), 143(20), 112(29), 99(16), 81(29), 74(29), 68(23), 56(33); CIMS (2-methylpropane), m/e 331(M^+ + 1, base); EIHRMS, m/e calcd. for $C_{13}H_{22}N_4S_3$ 330.1007, found 330.1008.

7b. Table II, entry 4: 1b (55 mg, 0.25 mmol) and 1-N,N-dibenzylamino-1-propyne[22] (2b, 118 mg, 0.50 mmol, 2 equiv) afforded pure 7b (79 mg, 114 mg theoretical, 69%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.93 (3H, s, $-CH_3$), 2.23 (3H, s, $-SCH_3$), 2.45 (3H, s, $-SCH_3$), 4.27 (1H, d, J = 15 Hz, $-CH\underline{H}Ph$) and 4.35 (1H, d, J = 15 Hz, $-CH\underline{H}Ph$), 4.46 (1H, d, J = 16 Hz, $-CH\underline{H}Ph$) and 4.66 (1H, d, J = 16 Hz, $-CH\underline{H}Ph$), 7.28 (10H, m, Ph); IR (film) ν_{max} 2925, 2853, 1734, 1605, 1560, 1496, 1472, 1453, 1431, 1313, 1221, 1145, 1097, 909, 837, 732 cm^{-1}; EIMS, m/e (relative intensity) 454(M^+, 14), 439(79), 407(3), 381(1.5), 290(3), 223(1), 173(2), 144(2), 104(6), 91(100), 85(3), 74(3), 69(5), 65(10), 55(8); CIMS (2-methylpropane), m/e 455(M^+ + 1, base); EIHRMS, m/e calcd. for $C_{23}H_{26}N_4S_3$ 454.1320, found 454.1318.

2,4-Bis(methylsulfonyl)-6-(N,N-dibenzylamino)-5-methylpyrimidine (10). A solution of 7b (69 mg, 0.15 mmol) in methylene chloride (0.76 mL) was treated with m-chloroperbenzoic acid (mCPBA, 210 mg, 6.5 equiv of 80%) at -5°C. The resulting reaction mixture was allowed to warm to 25°C (1 h) and further stirred for 16 h. The reaction mixture was treated with saturated aqueous sodium sulfite (10 mL, 15 min) and extracted with diethyl ether (3 x 20 mL). The ether extracts were washed with half saturated aqueous sodium bicarbonate solution (5 x 25 mL) and were dried over magnesium sulfate. Flash chromatography (SiO_2, 15 cm x 1.2 cm, 40% ethyl acetate-hexane) afforded pure 2,4-bis(methanesulfonyl)-6-(N,N-dibenzylamino)-5-methylpyrimidine (10, 34.0 mg, 67.6 theoretical, 50%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (3H, s, $-CH_3$), 3.01 (3H, s, $-SO_2CH_3$), 3.41 (3H, s, $-SO_2CH_3$), 4.83 (4H, s, $-CH_2Ph$), 7.20-7.37 (10H, m, -Ph); IR (film) ν_{max} 3066, 2966, 2886, 2276, 2206, 1756, 1586, 1541, 1526, 1481, 1456, 1386, 1341, 1161, 1146, 1096, 1051, 981, 941, 836, 756, 726 cm^{-1}; EIMS, m/e (relative intensity) 446(M^+ + H, 1), 354(17), 211(6), 169(1), 139(2), 115(1), 104(4), 91(100), 77(3), 65(21), 57(3), 51(3); CIMS (2-methylpropane), m/e 446(M + 1, base).

4-(N,N-Diethylamino)-5-methylpyrimidine (11). A solution of 2,4-bis(methylthio)-6-(N,N-diethylamino)-5-methylpyrimidine (6a, 43 mg, 0.17 mmol) in aqueous dioxane (1 mL) was treated with Raney nickel (1.46 g wet, 34 equiv)[19,20] at 25°C and the resulting reaction mixture was warmed at 101°C (20 h). The Raney nickel was removed by filtration (ethyl acetate wash) through Celite. Chromatography (SiO_2, 100% ethyl acetate) afforded pure 4-(N,N-diethylamino)-5-methylpyrimidine (11, 12.8 mg, 27.8 mg theoretical, 46%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$), 1.23 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$), 2.27 (3H, s, $-CH_3$), 3.52 (4H, q, J = 7 Hz, $-\underline{CH_2}CH_3$), 7.99 (1H, s, C4-H), 8.49 (1H, s, C2-H); IR (film) ν_{max} 2970, 2925, 2855, 1535, 1452, 1343, 1248, 1226, 953, 769 cm^{-1}.

4-(N,N-Dibenzylamino)-5-methylpyrimidine (12). 2,4-Bis(ethoxycarbonyl)-6-(N,N-dibenzylamino)-5-methylpyrimidine (3b, 75 mg, 0.17 mmol) was treated with 1 M aqueous sodium hydroxide (2 mL) and the resulting solution was stirred at 25°C (4 h). The reaction mixture was diluted with water (15 mL) and washed with diethyl ether (2 x 15 mL). The aqueous layer was acidified to pH = 1, extracted with ethyl acetate (2 x 20 mL), and the combined organic extracts were dried over sodium sulfate. Removal of the solvent under reduced pressure afforded the 6-(N,N-dibenzylamino)-5-methylpyrimidine-2,4-dicarboxylic acid as yellow solid. A

solution of the resulting pyrimidine dicarboxylic acid in 1:1 acetic acid and acetic anhydride was warmed at 120°C (30 h). The cooled reaction mixture was treated with half saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were washed with half saturated aqueous sodium bicarbonate (15 mL x 3) and dried over potassium carbonate. Flash chromatography (SiO_2, 15 cm x 1.2 cm, 100% ethyl acetate) afforded pure 4-(N,N-dibenzylamino)-5-methylpyrimidine (12, 26 mg, 50 mg theoretical, 52%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (3H, s, $-CH_3$), 4.82 (4H, s, $-CH_2Ph$), 7.30 (10H, m, -Ph), 8.07 (1H, s, C4-H), 8.59 (1H, s, C2-H); IR (film) ν_{max} 3029, 2924, 1709, 1650, 1578, 1535, 1495, 1452, 1422, 1403, 1359, 1248, 1226, 1028, 953, 773 cm^{-1}; EIMS, m/z (relative intensity), 290(M^+ + H, 3), 289(M^+, 2), 198(100), 148(2), 106(17), 91(58), 79(3), 65(13), 55(1); CIMS (2-methylpropane), m/z 290(M + 1, base); EIHRMS, m/z calcd. for $C_{19}H_{19}N_3$ 289.1579, found 289.1579.

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