Direct Conversion of Heteroaromatic Esters to Methyl Ketones with Trimethylaluminum: Nonsymmetrically Disubstituted 1,2,4,5-Tetrazines

Marc Girardot, Rana Nomak, and John K. Snyder*

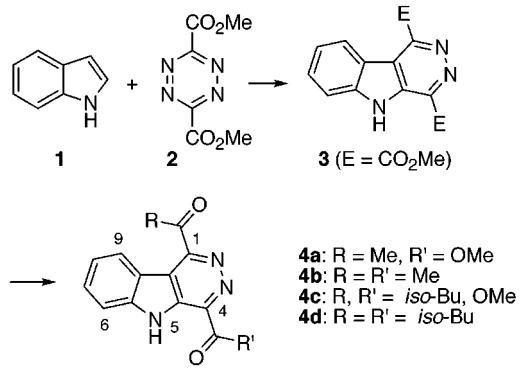
Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

Received July 31, 1998

Several years ago it was noted that the inverse electron demand Diels−Alder reaction of indole (**1**) with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**2**) gave dimethyl 5*H*-pyridazino[4,5-b]indole-1,4-dicarboxylate (**3**) in excellent yields (Scheme 1).[1] A key part of our plans to use **3** as a starting point for the synthesis of several carbazole alkaloids required regioselective transformation of one of the ester groups. However, efforts to effect the selective transformation of either of the ester groups using alkyl aluminum reagents often produced varying amounts of ketones. For example, Weinreb amidation[2] of **3** with Me_3Al and various amines frequently gave the monoketone **4a** and/or the diketone **4b** as minor products. Similarly, attempted reduction of the ester group(s) to the primary alcohol(s) using DIBAL-H often gave rise to mono and diketones **4c** and **4d** in annoyingly significant amounts. It was thus serendipitously realized that a direct conversion of these heteroaromatic esters to ketones may be possible with trialkylaluminum reagents. Since distinction of the two ester groups of **3** is critical to our future synthetic applications, a more in-depth investigation was undertaken. Application of this chemistry to the substituent-desymmetrization of **2** through monoketonization of its dihydroprecursor was also successful, thereby enabling the production of nonsymmetrically disubstituted 1,2,4,5-tetrazines[3] for further inverse electron demand Diels−Alder reactions.[4] Though such tetrazine systems are potentially important in heterocyclic synthesis, there are no other examples, of which we are aware, of 1,2,4,5-tetrazines with differentiated carbonyl substituents. More typically symmetric 3,6-dicarboalkoxy substituents are distinguished following cycloadditions of tetrazine **2**.[5]

As briefly mentioned in an earlier communication, the reaction of **3** with Me_3Al gave **4a** in 72% yield[6] (Table 1, item 1); the C1 acetyl regioisomer was identified by an NOE of H9 (δ 9.07, d, J = 8.2 Hz) upon irradiation of the acetyl methyl singlet (δ 3.09, s, 3 H).[7] Regioselective addition to the more electron deficient C1 ester group was easily rationalized from basic resonance considerations: electron donation from N5 renders the C4 carboxylate less electron deficient than the C1 carboxylate. While diketone **4b** was also produced as a minor product in this reaction, treatment of **4a** with additional Me_3Al at 0 °C gave **4b** in 41% yield (item 2), along with varying amounts of tertiary alcohols from further methylation of either ketone; when the reaction was performed at room temperature, the tertiary alcohols became the main products.[8]

Scheme 1



Brief examination of this ketonization with other heteroaromatic esters indicated that the chemistry was general as long as the ester functionality resided next to a ring nitrogen. When the ring nitrogen was remote from

* To whom correspondence should be addressed. Tel: (617) 353-2621, 2575. Fax: (617) 353-6466. E-mail: snyder@chem.bu.edu.

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(2) (a) Basha, A.; Lipton, M. F.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174. (b) Lipton, M. F.; Weinreb, S. M. In *Org. Synth., Collect Vol. VI.;* Noland, W. E., Ed.; John Wiley & Sons: New York, 1988; pp 492−495. (c) Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 1231−1233.

(3) For reviews of 1,2,4,5-tetrazine preparations: (a) Wiley, P. F. In *Chemistry of* 1,2,3-Triazines, and 1,2,4-Triazines, Tetrazines, and Pentazines. Wiley, P. F.; Neunhoeffer, H. *Chemistry of Heterocyclic Compounds Monograph 33*; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1978; pp 1077−1083. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 555−572. For some examples of unsymmetrically disubstituted 1,2,4,5-tetrazine preparations since these reviews, see: (c) Mueller, K.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 2541−2544. (d) Seitz, G.; Goegre, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355−4358. (e) Gleiter, R.; Schehlmann, V.; Spanget-Larson, J.; Fischer, H.; Neugebauer, F. A. *J. Org. Chem.* **1988**, *53*, 5756−5762. (f) Fields, S. C.; Parker, M. H.; Erickson, W. R. *J. Org. Chem.* **1994**, *59*, 8284−8287. (g) Panek, J. S.; Zhu, B. *Tetrahedron Lett.* **1996**, *37*, 8151−8154. (h) Sakya, S.; Groskopf, K. K.; Boger, D. L. *Tetrahedron Lett.* **1997**, *38*, 3805−3808. (i) Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329−6337. (j) Sauer, J.; Heldmann, D. K. *Tetrahedron* **1998**, *54*, 4297−4312.

(4) For reviews of inverse electron demand Diels−Alder reactions, see: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869−2939. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781−793. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Organic Chemistry Monograph 47; Academic: New York, 1987; Chapter 10. Recent overview: (d) Boger, D. L. *J. Heterocycl. Chem.* **1996**, *33*, 1519−1531.

(5) Some examples. (a) streptonegrin synthesis: Boger, D. L.; Panek, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 5745−5754. (b) Prodigiosin synthesis: Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499−2402; Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405−1415. (c) PDE-I and −II synthesis: Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250−3252. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717−2727.

(6) Daly, K.; Nomak, R.; Snyder, J. K. *Tetrahedron Lett.* **1997**, *38*, 8611−8614.

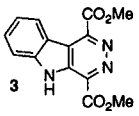
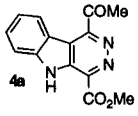
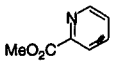
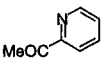
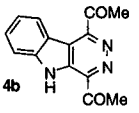
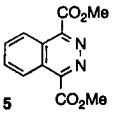
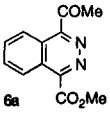
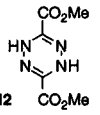
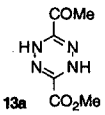
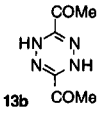
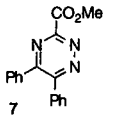
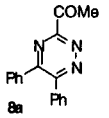
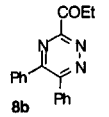
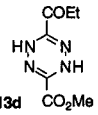
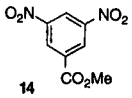
(7) We have used analogous NOE's in the past to assign regioisomers of heterocycles derived from indole cycloadditions, ref 6, also: Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257−3269.

(8) For the use of trialkylaluminum reagents to alkylate ketones and aldehydes: (a) Meisters, A.; Mole, T. *Aust. J. Chem.* **1974**, *27*, 1655−1663. (b) Starowieyski, K. B.; Becalska, A.; Okninski, A. *J. Organomet. Chem.* **1985**, *293*, 7−17. (c) Teague, S. J. *Tetrahedron Lett.* **1996**, *37*, 5751−5754.

10.1021/jo9815352 CCC: $15.00
Published on Web 12/02/1998

Table 1. Conversion of Esters to Ketones with Trimethyl- and Triethylaluminum[a]

$ArCO_2Me + R_3Al \rightarrow ArCOR$

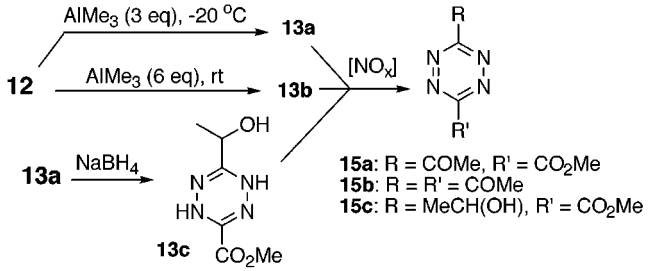
item	$ArCO_2Me$	R	product	yield,[b] %	item	$ArCO_2Me$	R	product	yield,[b] %
1	 **3**	Me	 **4a**	72	7	 **9**	Me	 **10**	54
2	**4a**	Me	 **4b**	41	8	 **11**	Me	-	0
3	 **5**	Me	 **6a**	48	9	 **12**	Me	 **13a**	80
4	**5**	Me	 **6b**	67	10	**12**	Me	 **13b**	43
5	 **7**	Me	 **8a**	42	11	**13a**	Me		41
6	**7**	Et_3Al	 **8b**	36	12	**12**	Et	 **13d**	25
					13	 **14**	Me	-	0

[a] See Experimental Section for conditions. [b] Isolated yields.

the ester group as in methyl nicotinate, no reaction occurred (item 8), nor was any reaction observed with methyl 3,5-dinitrobenzoate under comparable conditions (item 13). Thus, an electron-deficient ester carbonyl by itself was insufficient for conversion to the ketone. Analogous alkylation was also observed with Et_3Al (items 6 and 12). As many of these examples demonstrate, simple stoichiometric considerations and temperature control enable selective formation of monoketones from substrates with two potentially reactive ester groups. It was also found, however, that the activity of the Me_3Al reagent varied considerably with age and from batch to batch. Thus, the number of "equivalents" needed for optimal selective ketonization was variable, and overmethylation to produce diketones and alcohols was common with fresh batches of Me_3Al if more than 1 equiv was used. Direct conversion of a diester to diketone was also possible by using more Me_3Al (items 4 and 10). Given the selectivity for the ketonization of esters adjacent to a ring nitrogen, a single acyclic analogue, phenylglycine methyl ester, was also examined, but no reaction ensued.

While tetrazine **2** did not react cleanly with Me_3Al, the synthetic precursor of **2**, 1,4-dihydro-1,2,4,5-tetrazine (**12**),[9] did react with Me_3Al to produce mono- and diketones **13a** and **13b**, respectively, depending upon the reaction conditions (Table 1, items 9 and 10). Borohydride reduction of **13a** gave alcohol **13c** (Scheme 2). Aromatization of **13a**−**c** by exposure to nitrous gases[9] gave tetrazines **15a**−**c** (>95% crude yields, >98% purity by ^1H NMR) which proved to be very good, electron deficient heteroaromatic azadienes for inverse electron demand Diels−Alder chemistry (Table 2). The cycloaddition of **15a** with benzyne gave an excellent yield of cycloadduct **6a** (84%, Table 2, item 1), which was also produced in lower yield (48%) from the monoketonization of **5** (Table 1, item 3). Tetrazine **15b** also underwent a cycloaddition with benzyne to produce **6b**, albeit in lower yield (39%, item 6). Lower yields of cycloadducts from **15a** were also obtained with the sole enamine examined (Table 2, item 4), likely due to the reaction of the amine formed in the course of the adduct aromatization with the starting tetrazine.

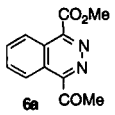
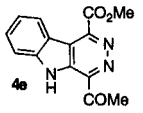
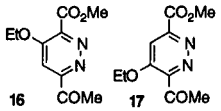
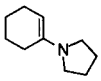
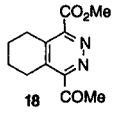
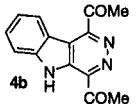
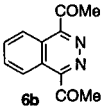
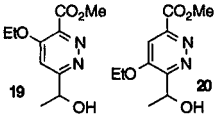
Scheme 2



With nonsymmetric, electron rich dienophiles, the regioselectivity of the cycloaddition was dependent upon the nucleophilicity of the dienophile. Cycloadditions of **15a** with indole (**1**) showed excellent regioselectivity with

(9) (a) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer, J. *J. Org. Chem.* **1985**, *50*, 5377−5379. (b) Boger, D. L.; Panek, J. S.; Patel, M. *Org. Synth.* **1991**, *70*, 79−92.

Table 2. Cycloadditions of 1,2,4,5-Tetrazines 15a−c[a]

item	tetrazine	dienophile	product	yield,[b] %
1	**15a**		 **6a**	84
2	**15a**	 **1**	 **4e**	72
3	**15a**		 **16** **17**	91 (1:1)
4	**15a**		 **18**	44
5	**15b**	 **1**	 **4b**	52
6	**15b**		 **6b**	39
7	**15c**		 **19** **20**	63 (96:4)

[a] See Experimental Section for conditions. [b] Isolated yields.

the nucleophilic indole-C3 adding to C4 of **15a** to produce **4e** in 72% isolated yield (Table 2, item 2) with barely detectable amounts of regioisomer **4a** apparent in the ^{1}H NMR spectrum of the product mixture (**4e**:**4a**, 98:2 by NMR integration). Cycloadduct **4e** was identified by an NOE of H9 (δ 8.87, d, J = 8.2 Hz) upon irradiation of the ester methyl singlet (δ 4.20, s, 3 H).[7] Presumably this regioselectivity is favored by increased stabilization of the developing negative charge by the more electron withdrawing ketone carbonyl rather than the ester carbonyl in a stepwise, or concerted, highly nonsynchronous process.[10] The regioselectivity of this cycloaddition therefore complements the ketonization of **3** with Me_3Al which produced **4a** exclusively (Table 1, item 1). Diketotetrazine **15b** also reacted readily with indole to produce **4b** (52%, Table 2, item 5), the same compound produced from stepwise diketonization of **3** (41%, Table 1, item 2).

In contrast to the excellent regioselectivity of indole, the reaction of **15a** with ethoxyacetylene gave a 1:1 mixture of regioisomers **16** and **17** (Table 2, item 3); the regioisomers were distinguished by NOE's following separation (Experimental Section). The monoalcohol tetrazine **15c** was considerably less reactive than **15a** and **15b**, though **15c** did undergo cycloadditions with ethoxyacetylene to produce **19** in 63% yield (item 7), with NOE's distinguishing this regioisomer (Experimental Section). A second compound tentatively assigned as regioisomer **20** was also detected in the ^{1}H NMR spectrum of the crude reaction mixture, though insufficient quantities were isolated for complete characterization.

The transformation of carboxyl compounds to ketones is a very common synthetic procedure that may proceed from several different starting points. Carboxylic acids may be directly converted to methyl ketones with methyllithium;[11] acid chlorides are known to produce ketones upon reaction with trialkylaluminum reagents typically in the presence of a Lewis acid catalyst,[12] while Weinreb amides are commonly converted to ketones upon reaction with Grignard or alkyllithium reagents,[13] though a few isolated examples of amide to ketone conversions have been reported with trimethylaluminum.[14] In contrast, the direct conversion of esters to ketones is relatively rare[15] since further alkylation of the ketones is difficult to prevent.[8,16] The lower reactivity of trimethylaluminum in comparison to Grignard reagents allows for practical monoketonization of diesters and also for the excellent regioselectivity displayed in the monoketonization of diester **3**.

The selective conversion of esters adjacent to ring nitrogen suggests that an intramolecular alkylation pathway with initial complexation of the trialkylaluminum reagent with the neighboring nitrogen may be operating. This would account for the lack of reactivity under these conditions with dinitrobenzoate ester **14**. The higher yields of ketonization obtained with dihydrotetrazine **12** and pyridazinoindole **3** in comparison to other heterocycles in Table 1 are due to extensive repetition, and hence optimization for the products from these two reactions (**4a**, **4e**, and **15**) are key starting points for syntheses currently under way in our labs. Higher yields may also be expected from the remaining ketonizations shown in Table 1 with similar optimization, and the cycloadditions of **15a** and **15b** with appropriate dienophiles may provide an alternative route to the same ketones.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra data were recorded at 93.94 kG (^{1}H 400 MHz, ^{13}C 100 MHz), 70.50 kG (^{13}C 75.0 MHz), or 63.41 kG (^{13}C 67.5 MHz), at ambient temperature

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in $CDCl_3$ unless otherwise noted. Proton chemical shifts are reported in parts per million (ppm) relative to internal reference: the residual $CHCl_3$ resonance at δ 7.24. All exchangeable protons were confirmed as such by the addition of D_2O. For ^{13}C NMR, the center line of the $CDCl_3$ triplet was used as the internal reference: δ 77.0. Unless otherwise noted, each carbon resonance represents a single carbon (relative intensity); inverse gated decoupled spectra were used for carbon resonance integration to establish relative intensities >1 C. Melting points were determined in capillaries and are uncorrected. Dichloromethane was distilled immediately prior to use from calcium hydride. All reactions were carried out in oven-dried (105 °C) glassware under a dry argon atmosphere. All chromatography refers to flash chromatography performed using silica gel-60 (43−60 μm). Trimethylaluminum (2.0 M in hexanes) was purchased from Fluka and used as received. Triethylaluminum (1.9 M in toluene) and ethyl ethynyl ether (50% in hexanes) were purchased from Aldrich and used as received. It is important to note that the number of equivalents of trialkylaluminum reagent required for the ketonizations depended upon the "freshness" of the reagent. Thus, in each procedure, the reagent is noted as "aged" or "new".

Methyl 1-Acetyl-5*H*-pyridazino[4,5-*b*]indole-4-carboxylate (4a). To a solution of **3**[1a] (0.123 g, 0.432 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise with stirring $Al(CH_3)_3$ (aged, 2.0 M in hexanes, 0.86 mL, 1.728 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature over 30 min, stirred for 24 h at room temperature, then quenched by the addition of 1 N HCl (5 mL), and stirred for 30 min. The layers were separated, and the aqueous layer extracted with CH_2Cl_2/EtOAc (1:1, 3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, and then the solvent was removed in vacuo to afford crude **4a**. Chromatography (CH_2Cl_2) gave pure **4a** (83.6 mg, 72% yield) as a yellow crystalline solid: mp 218−220 °C; IR (KBr) ν_{max} 3372, 1700, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (br s, ex, NH), 9.07 (bd, J = 8.2 Hz, 1 H), 7.74 (ddd, J = 8.2, 6.7, 1.2 Hz, 1 H), 7.67 (dd, 1 H, J = 8.2, 1.2 Hz, 1 H), 7.48 (dd, J = 6.7, 8.2 Hz, 1 H), 4.20 (s, 3 H), 3.09 (s, 3 H);^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.0, 166.1, 151.1, 141.1, 137.9, 136.6, 131.3, 127.9, 122.9, 120.0, 118.8, 111.9, 53.4, 28.3; EIHRMS (70 eV) m/z 269.0811 ([M]$^+$, 100%), calcd for $C_{14}H_{11}N_3O_3$ 269.0800.

1,4-Diacetyl-5*H*-pyridazino[4,5-*b*]indole (4b). Method A. To a solution of **4a** (0.040 g, 0.149 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise with stirring $Al(CH_3)_3$ (aged, 2.0 M in hexanes, 0.30 mL, 0.595 mmol) at −78 °C. The reaction mixture was allowed to warm to −20 °C over 30 min and then stirred at this temperature for 24 h. The reaction was quenched by the addition of 1 N HCl (2 mL) and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2/EtOAc (1:1, 3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, and then the solvent was removed in vacuo to afford crude **4b**. Chromatography (CH_2Cl_2) gave pure **4b** (14.0 mg, 41%) as a yellow crystalline solid. **Method B.** To a solution of tetrazine **15b** (32.0 mg, 0.193 mmol) in anhydrous CH_2Cl_2 (10 mL) was added a solution of indole (22.6 mg, 0.193 mmol) also in anhydrous CH_2Cl_2 (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 6 h and then solvent removed in vacuo. Chromatography as above gave pure **4b** (25.0 mg, 52%): mp 216−217 °C; IR (KBr) ν_{max} 3340, 1701, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (br s, ex, NH), 9.05 (d, J = 8.2 Hz, 1 H), 7.72 (ddd, J = 7.9, 7.0, 1.0, 1 H), 7.66 (dd, J = 7.9, 1.0, 1 H), 7.48 (ddd, J = 8.2, 7.0, 1.0, 1 H), 3.11 (s, 3 H), 3.08 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.4, 200.8, 151.0, 141.6, 141.3, 136.3, 131.2, 127.8, 122.9, 120.5, 118.6, 112.0, 28.4, 26.5; EIHRMS (70 eV) m/z 253.0866 ([M]$^+$, 48.3%), calcd for $C_{14}H_{11}N_3O_2$ 253.0851.

Methyl 4-Acetylphthalazine-1-carboxylate (6a). Method A. To a solution of dimethyl phthalazine-1,4-dicarboxylate[7] (**5**, 18.0 mg, 0.073 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise with stirring $Al(CH_3)_3$ (new, 2.0 M in hexanes, 0.14 mL, 0.073 mmol) at −45 °C. The reaction mixture was stirred at −45 °C for 12 h and then quenched by the addition of 1 N HCl (10 mL) and stirred for 10 min, warmed to 0 °C, and stirred for an additional 30 min and then allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **6a**. Chromatography (CH_2Cl_2/EtOAc, 5:1) gave pure **6a** (8.1 mg, 48% yield). **Method B.** To a mixture of tetrazine **15a** (37.0 mg, 0.203 mmol) and anthranilic acid (84 mg, 0.406 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added isoamylnitrite (93 μL, 0.480 mmol). The reaction mixture was stirred at this temperature for 1 h and then concentrated in vacuo, and the residue was purified by chromatography (CH_2Cl_2/EtOAc, 5:1) to give **6a** (62.3 mg, 84% yield) as a light yellow crystalline solid: mp 124−126 °C; IR (KBr) ν_{max} 1724, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (dd, J = 7.0, 1.8 Hz, 1 H), 8.63 (dd, J = 7.5, 1.8 Hz, 1 H), 8.04−7.96 (m, 2 H), 4.14 (s, 3 H), 2.97 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 200.9, 164.8, 153.4, 151.5, 134.3, 133.5, 126.1, 125.4 (2C), 124.4, 53.5, 28.9; EIHRMS (70 eV) m/z 230.0694 ([M]$^+$, 13.9%), calcd for $C_{12}H_{10}N_2O_3$ 230.0691.

1,4-Diacetylphthalazine (6b). Method A. To a solution of dimethyl phthalazine-1,4-dicarboxylate[7] (**5**, 70.0 mg, 0.285 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise with stirring $Al(CH_3)_3$ (new, 2.0 M in hexanes, 0.43 mL, 0.854 mmol) at −30 °C. The reaction mixture was stirred at −30 °C for 24 h and then quenched by the addition of 1 N HCl (10 mL) and stirred for 10 min, warmed to 0 °C and stirred for an additional 30 min and then allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **6b**. Chromatography (CH_2Cl_2) gave pure **6b** (40.1 mg, 67% yield). **Method B.** To a mixture of tetrazine **15b** (14.0 mg, 0.084 mmol) and anthranilic acid (23.1 mg, 0.169 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added isoamylnitrite (34 μL, 0.253 mmol). The reaction mixture was stirred at this temperature for 1.5 h and then concentrated in vacuo, and the residue was purified by chromatography (CH_2Cl_2) to give **6a** (7.0 mg, 39% yield) as a light yellow crystalline solid: mp 121−122 °C; IR (KBr) ν_{max} 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94−8.90 (m, 1 H), 8.02−7.98 (m, 1 H), 2.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 154.0, 134.1, 126.1, 125.0, 29.1; EIHRMS (70 eV) m/z 214.0741 ([M]$^+$, 1.4%), calcd for $C_{12}H_{10}N_2O_2$ 214.0742.

3-Acetyl-5,6-diphenyl-1,2,4-triazine (8a).[17] To a solution of ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate (**7**)[18] (63.0 mg, 0.216 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise with stirring $Al(CH_3)_3$ (aged, 2.0 M in hexanes, 0.32 mL, 0.649 mmol) at −78 °C. The reaction mixture was allowed to slowly warm to −20 °C over 30 min, stirred for 24 h at this temperature, then quenched by the addition of 1 N HCl (10 mL) at −20 °C followed by stirring for 10 min, warming to 0 °C, and stirring for an additional 30 min, and allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **8a**. Chromatography (CH_2Cl_2/EtOAc, 10:1) gave pure **8a** (25.0 mg, 42% yield) as a light yellow crystalline solid: mp 166−167 °C (lit. 159.5−161.5 °C,[17a] 162−163 °C[17b]); IR (KBr) ν_{max} 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.60 (m, 4 H), 7.46−7.32 (m, 6 H), 2.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 158.0, 156.84, 156.80, 134.8, 134.7, 131.3, 130.5, 129.9 (2C), 129.6 (2C), 128.79 (2C), 128.71 (2C), 27.3; CIHRMS (NH_3, 140 eV) m/z 276.1160 ([M + H]$^+$, 6.4%), calcd for $C_{17}H_{13}N_3O$ 276.1137.

3-Propionyl-5,6-diphenyl-1,2,4-triazine (8b). To a solution of **7** (184.0 mg, 0.632 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise with stirring $Al(CH_2CH_3)_3$ (aged, 1.9 M in toluene, 1.0 mL, 1.896 mmol) at −78 °C. The reaction mixture was allowed to slowly warm to −20 °C over 1 h, stirred for 24 h at this temperature, then quenched by the addition of 1 N HCl (5 mL), and stirred for 30 min. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL) The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **8b**. Chromatography (CH_2Cl_2) gave pure **8b** (62.0 mg, 36% yield) as a yellow solid: mp 107−108 °C; IR (KBr) ν_{max} 1718 cm^{-1}; ^{1}H NMR (400

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MHz, $CDCl_3$) δ 7.64−7.60 (m, 4 H), 7.48−7.32 (m, 6 H), 3.43 (q, J = 7.3 Hz, 2 H), 1.32 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.0, 158.0, 156.9, 156.7, 134.8, 134.7, 131.3, 130.4, 129.9 (2 C), 129.6 (2 C), 128.79 (2 C), 128.70 (2 C), 33.1, 7.8; EIHRMS (70 eV) *m/z* 289.1243 ([M]$^+$, 21.8%), calcd for $C_{18}H_{15}N_3O$ 289.1215.

2-Acetylpyridine (10). To a solution of methyl 2-picolinate (**9**) (150.0 mg, 1.095 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise with stirring $Al(CH_3)_3$ (aged, 2.0 M in hexanes, 1.10 mL, 2.190 mmol) at −78 °C. The reaction mixture was allowed to slowly warm to −20 °C over 30 min, then stirred for 12 h. The reaction was then quenched by the addition of 1 N HCl (5 mL) at −20 °C and stirred for 10 min, warmed to 0 °C, stirred for an additional 30 min, and then allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford **10** (71.5 mg, 54%) of >98% purity by ^{1}H NMR.[19]

Methyl 6-Acetyl-1,4-dihydro-1,2,4,5-tetrazine-3-carboxylate (13a). To a solution of **12**[9] (0.100 g, 0.50 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise with stirring $Al(CH_3)_3$ (aged, 2.0 M in hexanes, 0.75 mL, 1.50 mmol) at −78 °C. The reaction mixture was allowed to slowly warm to −20 °C over 1 h and then stirred for 12 h. The reaction was quenched by the addition of 1 N HCl (5 mL) at −20 °C, then stirred for 30 min, warmed to 0 °C, and stirred for an additional 30 min. The layers were separated and the aqueous layer extracted with CH_2Cl_2/EtOAc (1:1, 3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **13a**. Chromatography (CH_2Cl_2) gave pure **13a** (73.1 mg, 80%) as an orange crystalline solid: mp 157−158 °C; IR (KBr) ν_{max} 3315, 1724, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, ex, NH), 7.42 (br s, ex, NH), 3.90 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.4, 159.2, 142.5, 138.1, 53.7, 24.8; EIHRMS (70 eV) *m/z* 184.0604 ([M]$^+$, 100%), calcd for $C_6H_8N_4O_3$ 184.0596.

3,6-Diacetyl-1,4-dihydro-1,2,4,5-tetrazine (13b). To a solution of **12** (0.100 g, 0.50 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise with stirring $Al(CH_3)_3$ (aged, 2.0 M in hexanes, 1.5 mL, 3.000 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature over 2 h and stirred for 12 h at room temperature. The reaction was quenched by the addition of 1 N HCl (5 mL) and stirred for 30 min, then the layers were separated, and the aqueous layer was extracted with CH_2Cl_2/EtOAc (1:1, 3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **13b**. Chromatography (CH_2Cl_2) gave pure **13b** (36.4 mg, 43% yield) as a dark orange crystalline solid: mp 179−180 °C; IR (KBr) ν_{max} 3305, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, ex, NH), 2.40 (s, 3 H);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.6, 142.7, 24.7; EIHRMS (70 eV) *m/z* 168.0630 ([M]$^+$, 38.1%), calcd for $C_6H_8N_4O_2$ 168.0647.

Methyl 1,4-Dihydro-6-propionyl-1,2,4,5-tetrazine-3-carboxylate (13d). To a solution of **12** (0.100 g, 0.500 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise with stirring $Al(CH_2CH_3)_3$ (aged, 1.9 M in toluene, 1.05 mL, 2.050 mmol) at 0 °C. The reaction mixture was stirred for 12 h at 0 °C, then quenched by the addition of 1 N HCl (5 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2/EtOAc (1:1, 3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in vacuo to afford crude **13d**. Chromatography (CH_2Cl_2) gave pure **13d** (25.0 mg, 25% yield) as a dark orange crystalline solid: mp 102−103 °C; IR (KBr) ν_{max} 1720, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, ex, NH), 7.38 (br s, ex, NH), 3.88 (s, 3 H), 2.80 (q, J = 7.3 Hz, 2 H), 1.09 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 193.6, 159.2, 142.0, 138.2, 53.7, 30.7, 7.7; EIHRMS (70 eV) *m/z* 198.0759 ([M]$^+$, 4.3%), calcd for $C_7H_{10}N_4O_3$ 198.0753.

Methyl 6-(1-Hydroxyethyl)-1,4-dihydro-1,2,4,5-tetrazine-3-carboxylate (13c). To a mixture of **13a** (0.298 g, 1.600 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (0.031 mg, 0.809 mmol). The reaction mixture was stirred at 0 °C for 2 h and then quenched by the addition of 2 N HCl (10 mL), and the layers were immediately separated; then the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude **13c**. Chromatography (CH_2Cl_2/EtOAc, 5:1) gave pure **13c** (132.0 mg, 44% yield) as an orange solid: mp 73−74 °C; IR (KBr) ν_{max} 3340, 2958, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (br s, ex, NH), 7.14 (br s, ex, NH), 4.47 (dq, J = 5.1, 6.7 Hz, 1 H), 3.89 (s, 3 H), 2.19 (d, J = 5.1 Hz, ex, OH), 1.42 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6, 151.6, 139.9, 64.9, 53.5, 20.7; EIHRMS (70 eV) *m/z* 186.0763 ([M]$^+$, 100%), calcd for $C_6H_{10}N_4O_3$ 186.0753.

Methyl 6-Acetyl-1,2,4,5-tetrazine-3-carboxylate (15a). Dihydrotetrazine **13a** (270.0 mg, 1.452 mmol) was slurried in anhydrous CH_2Cl_2 (50 mL) and cooled to 0 °C. A stream of nitrous gases generated by the dropwise addition of 6 N $NaNO_2$ (5 mL) into concentrated HCl (4 mL)[9] was bubbled through the solution for 1 h. The color of the reaction changed from yellow to red upon introduction of the nitrous gases. Stirring was continued for 2 h; then the reaction mixture was allowed to warm to room temperature and stirred for 6 h. The solvent and excess nitrous gases were removed in vacuo to afford **15a** (265.0 mg, 99%, >98% pure by ^{1}H NMR) as a red crystalline solid, unstable to chromatography, that was used without further purification: mp 121−122 °C; UV (CH_3CN) λ_{max} nm (log ϵ) 216 (4.32), 260 (3.82), 310 (sh, 3.61), 518 (3.36); IR (KBr) ν_{max} 1752, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 1 H), 3.00 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 192.5, 160.4, 159.9, 158.9, 54.6, 27.5; EIHRMS (70 eV) *m/z* 182.0445 ([M]$^+$, 5.3%), calcd for $C_6H_6N_4O_3$ 182.0440.

3,6-Diacetyl-1,2,4,5-tetrazine (15b). Dihydrotetrazine **13b** (180.0 mg, 1.070 mmol) was slurried in anhydrous CH_2Cl_2 (70 mL) and cooled to 0 °C. A stream of nitrous gases generated by the dropwise addition of 6 N $NaNO_2$ (3.5 mL) into concentrated HCl (2 mL)[9] was bubbled through the solution for 0.5 h. The color of the reaction changed from orange to red upon introduction of the nitrous gases. Stirring was continued for 2 h; then the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvent and excess nitrous gases were removed in vacuo to afford **15b** (176.0 mg, 99%, >98% pure by ^{1}H NMR) as a red crystalline solid, unstable to chromatography, that was used without further purification. Due to limited solubility in $CDCl_3$, the ^{13}C NMR spectrum was recorded in CD_3CN (using the center line of the "CD_3" septet as the internal reference: δ 1.39). Mp 153−154 °C (dec); UV (CH_3CN) λ_{max} nm (log ϵ) 230 (3.31), 258 (3.23), 522 (2.68); IR (KBr) ν_{max} 1722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s); (400 MHz, CD_3CN, CHD_2CN as internal reference: δ 1.93) δ 2.92 (s); ^{13}C NMR (75.5 MHz, CD_3CN) δ 194.5, 160.8, 27.8; EIHRMS (70 eV) *m/z* 166.0499 ([M]$^+$, 4.8%), calcd for $C_6H_6N_4O_3$ 166.0491.

Methyl 6-(1-Hydroxyethyl)-1,2,4,5-tetrazine-3-carboxylate (15c). Dihydrotetrazine **13c** (214.0 mg, 1.150 mmol) was slurried in anhydrous CH_2Cl_2 (50 mL) and cooled to 0 °C. A stream of nitrous gases generated by the dropwise addition of 6 N $NaNO_2$ (4 mL) into concentrated HCl (3 mL)[9] was bubbled through the solution for 30 min. The color of the reaction changed from yellow to red immediately upon introduction of the nitrous gases. Stirring was continued for 2 h at 0 °C and then the reaction mixture was allowed to warm to room temperature. The solvent and excess nitrous gases were removed in vacuo to afford **15c** (211.0 mg, 97% yield, >98% pure by ^{1}H NMR) as a red crystalline solid unstable to chromatography and used without further purification: mp 86−87 °C; UV (CH_3CN) λ_{max} nm (log ϵ) 208 (4.36), 262 (4.28), 320 (sh), 528 (3.21); IR (KBr) ν_{max} 3496, 2980, 1758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (q, J = 6.7 Hz, 1 H), 4.14 (s, 3 H), 3.9−4.0 (br s, ex, OH), 1.75 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.5, 161.0, 159.0, 68.7, 54.3, 22.6; EIHRMS (70 eV) *m/z* 184.0593 ([M]$^+$, 11.6%), calcd for $C_6H_8N_4O_3$ 184.0596.

Methyl 4-Acetyl-5*H*-pyridazino[4,5-*b*]indole-1-carboxylate (4e). To a solution of tetrazine **15a** (41.0 mg, 0.225 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added a solution of indole (22.0 mg, 0.188 mmol) also in anhydrous CH_2Cl_2 (5 mL). The reaction mixture was stirred at this temperature for 6 h; then solvent was removed in vacuo keeping the temperature at 0 °C. Chromatography (CH_2Cl_2/EtOAc, 10:1) gave **4e** (36.2 mg,

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72%) as a yellow crystalline solid: mp 192−193 °C; IR (KBr) ν_{max} 3368, 1730, 1677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (br s, ex, NH), 8.87 (d, J = 8.2 Hz, 1 H), 7.72−7.65 (m, 2 H), 7.46 (dd, J = 6.4, 8.2 Hz, 1 H), 4.20 (s, 3 H), 3.05 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5, 165.7, 146.1, 141.4, 141.3, 135.9, 131.0, 126.9, 123.0, 121.8, 118.1, 112.2, 53.4, 26.3; EIHRMS (70 eV) *m/z* 269.0783 ([M]$^+$, 15.3%), calcd for $C_{14}H_{11}N_3O_3$ 269.0800.

Methyl 6-Acetyl-4-ethoxy-1,2-pyridazine-3-carboxylate (16) and Methyl 6-Acetyl-5-ethoxy-1,2-pyridazine-3-carboxylate (17). To a solution of tetrazine **15a** (90.0 mg, 0.495 mmol) in anhydrous CH_2Cl_2 (10 mL) was added a solution of ethyl ethynyl ether (50% in hexanes, 0.26 mL, 1.484 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 1 h, then warmed to room temperature, and stirred for an additional hour. The solvent was removed in vacuo and the residue purified by chromatography (CH_2Cl_2) giving **16** (50.4 mg, 46%) and **17** (50.4 mg, 46% yield) in order of elution. The regioisomers were distinguished from NOE experiments: irradiation of the acetyl methyl singlet in **16** (δ 2.85) led to an enhancement of the H4 singlet (δ 7.59), while irradiation of the methoxy singlet in **17** (δ 4.06) led to an enhancement of the H4 singlet (δ 7.69). **Methyl 6-Acetyl-4-ethoxy-1,2-pyridazine-3-carboxylate (16)**: colorless oil; IR (NaCl) ν_{max} 1724, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1 H), 4.24 (q, J = 6.8 Hz, 2 H), 4.01 (s, 3 H), 2.85 (s, 3 H), 1.48 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.1, 163.6, 156.9, 156.9, 147.6, 106.6, 65.4, 53.2, 26.3, 14.0; EIHRMS (70 eV) *m/z* 224.0787 ([M]$^+$, 25.5%), calcd for $C_{10}H_{12}N_2O_4$ 224.0797. **Methyl 6-Acetyl-5-ethoxy-1,2-pyridazine-3-carboxylate (17)**: colorless oil; IR (NaCl) ν_{max} 1728, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 4.25 (q, J = 6.9 Hz, 2 H), 4.06 (s, 3 H), 2.78 (s, 3 H), 1.51 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 197.5, 164.3, 156.9, 152.8, 150.4, 110.5, 65.4, 53.6, 29.2, 14.0; EIHRMS (70 eV) *m/z* 224.0796 ([M]$^+$, 78.2%), calcd for $C_{10}H_{12}N_2O_4$ 224.0797.

Methyl 4-Acetyl-5,6,7,8-tetrahydrophthalazine-1-carboxylate (18). To a solution of tetrazine **15a** (65.0 mg, 0.357 mmol) in anhydrous CH_2Cl_2 (30 mL) was added 1-(1-pyrrolidino)-cyclohexene[20] (161.0 mg, 1.000 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 4 h; then the solvent removed in vacuo to afford crude **18**. Chromatography (CH_2Cl_2/EtOAc, 5:1) gave pure **18** (36.8 mg, 44% yield) as a yellow solid: mp 85−86 °C; IR (KBr) ν_{max} 1724, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3 H), 3.06 (m, 2 H), 2.96 (m, 2 H), 2.81 (s, 3 H), 1.78 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.0, 165.4, 155.1, 152.9, 139.3, 138.9, 53.2, 29.1, 26.0, 25.8, 21.1, 20.8; CIHRMS (NH_3, 140 eV) *m/z* 234.1011 ([M]$^+$, 100%), calcd for $C_{12}H_{14}N_2O_3$ 234.1004.

Methyl 4-Ethoxy-6-(1-hydroxyethyl)-1,2-pyridazine-3-carboxylate (19) and Methyl 5-Ethoxy-6-(1-hydroxyethyl)-1,2-pyridazine-3-carboxylate (20). To a solution of tetrazine **15c** (22.0 mg, 0.120 mmol) in anhydrous CH_2Cl_2 (10 mL) was added a solution of ethyl ethynyl ether (50% in hexanes, 33 μL, 0.380 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 48 h. The solvent was removed in vacuo; chromatography (CH_2Cl_2) gave a mixture of **19**:**20** (96:4 by ^{1}H NMR, total 17.0 mg, 63%), which could not be further purified due to instability upon extensive exposure to silica gel**.** The 4-ethoxy regioisomer **19** was identified by an NOE of H5 (δ 7.07) upon irradiation of the carbinol resonance (δ 5.12). Light yellow oil; IR (NaCl) ν_{max} 3329, 1742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1 H), 5.12 (q, J = 6.7 Hz, 1 H), 4.18 (q, J = 7.0 Hz, 2 H), 3.98 (s, 3 H), 1.55 (d, J = 6.7 Hz, 3 H), 1.47 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.1, 164.0, 157.1, 145.3, 105.7, 68.9, 65.0, 53.0, 24.3, 14.1; EIHRMS (70 eV) *m/z* 226.0947 ([M]$^+$, 36.5%), calcd for $C_{10}H_{14}N_2O_4$ 226.0953. Insufficient **20** was isolated for complete characterization.

Acknowledgment. We are grateful to the National Science Foundation (CHE-9501069) and the Boston University Undergraduate Research Opportunity Program (M.G.) for financial support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds, **4a**, **4b**, **4e**, **6a**, **6b**, **8a**, **8b**, **13a**−**d**, **15a**−**c**, **16**−**19** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9815352

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