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Intramolecular Diels–Alder Reactions of 1,2,4-Triazines. Routes to Condensed Pyrazines via Cycloaddition of Nitrile Dienophiles

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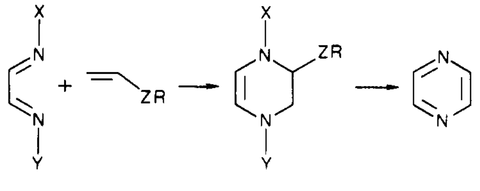
A synthetic route to benzopyrano[3,4-*b*]pyrazines and the first reported synthesis of the pyrazino[2,3-*c*]quinoline system are described whereby the fused pyrazine ring is constructed by an intramolecular nitrile/1,2,4-triazine Diels–Alder cycloaddition. Unsuccessful efforts to access thieno[2,3-*b*]pyrazines by an analogous strategy are detailed.

The intramolecular Diels–Alder reaction (IDA) of 1,2,4-triazines is a powerful and flexible approach to a broad array of condensed heterocyclic ring systems.[1] One of the practical consequences of the entropic assistance inherent in IDA reactions of substrates with three- and four-atom connecting chains is the compatibility of a wider array of diene/dienophile pairs. This additional flexibility can be attributed to a greater tolerance for energy differences between the interacting frontier orbitals, which arises from a reduction in the entropic component to the activation energy, which is substantial for the highly ordered Diels–Alder transition state.

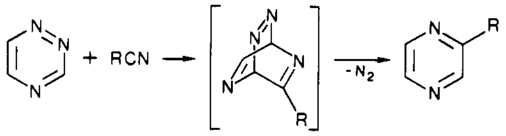
We have expanded the scope of the 1,2,4-triazine IDA reaction to include nitrile dienophiles as a potential route to condensed pyrazines. The few cycloaddition routes to pyrazines that have been reported lack generality and rely on the use of 1,4-diazadienes[2] (Scheme I), which are not readily available. In addition, access to the fully unsaturated pyrazine is not always possible. Our strategy relies on cycloaddition of a nitrile dienophile across C-3/C-6 of a 1,2,4-triazine followed by aromatization of the intermediate cycloadduct by extrusion of the N_2 bridge (Scheme II). The requisite regiochemical mode of cycloaddition for pyrazine formation, which requires addition of the nitrile nitrogen to C-6 of the 1,2,4-triazine, is the enforced mode in intramolecular cycloadditions of C-3 tethered nitrile dienophiles.

The dienophilic capacity of nitriles is normally extremely limited. Furthermore, the electron deficient nature of the nitrile group might be expected to render it incompatible for cycloaddition with electron-deficient 1,2,4-triazines. We are aware of only one example of nitrile cycloaddition with an electron-deficient heterocyclic azadiene.[3a,b] As a consequence, initial consideration was given to utilizing electron-rich nitrile equivalents (i.e. imino ethers, thio-

Scheme I



Scheme II



Scheme III

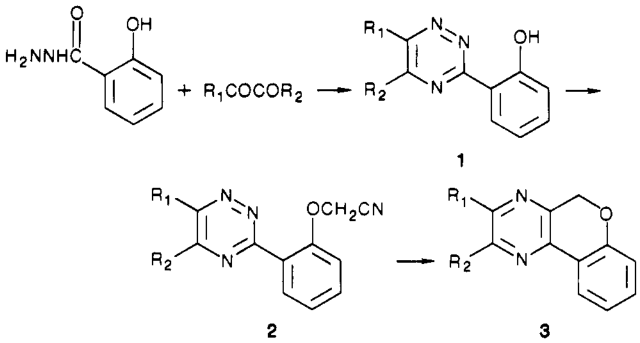


Table I. Synthesis of 3-(*o*-Hydroxyphenyl)-1,2,4-triazines[a] (1) (Scheme III)

α-diketone			1,2,4-triazine		
R	R′		R_1	R_2	% yield
Ph	Ph	**1a**	Ph	Ph	71
Ph	H	**1b**	Ph	H	19
		1c	H	Ph	26
Ph	CH_3	**1d**	Ph	CH_3	20
		1e	CH_3	Ph	28
CH_3	CH_3	**1f**	CH_3	CH_3	0

[a] Condensations were carried out in refluxing acetic acid with 1 equiv each of salicylic acid hydrazide and the dicarbonyl compound and a 20-fold excess of ammonium acetate. Unsymmetrical dicarbonyl compounds yielded 1,2,4-triazine mixtures which were separated by column chromatography.

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[1] (a) For a general discussion, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (b) Seitz, G.; Dietrich, S. *Arch. Pharm.* **1984**, *317*, 379. (c) Seitz, G.; Gorge, L. *Chem. Ztg.* **1984**, *108*, 331. (d) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1985**, *26*, 2419. (e) Seitz, G.; Gorge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (f) Seitz, G.; Dietrich, S. *Arch. Pharm.* **1985**, *318*, 1048 and 1051. (g) Taylor, E. C.; French, L. G. *Tetrahedron Lett.* **1986**, *27*, 1967. (h) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 431. (i) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 2107. (j) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. (k) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (l) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (m) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287. (n) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. (o) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. (p) Taylor, E. C.; Pont, J. L.; van Engen, D.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 5093. (q) Taylor, E. C.; Warner, J. C.; Pont, J. L. *J. Org. Chem.* **1988**, *53*, 800. (r) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 3568. (s) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Heterocycl. Chem.*, in press.

[2] (a) Pummerer, R.; Reuss, F. *Chem. Ber.* **1947**, *80*, 242. (b) Lora-Tamayo, M.; Ossorio, R. P.; Burta, M. S. *Chim. Soc. Espan. B.* **1954**, *50*, 765. (c) McFarland, J. W. *J. Org. Chem.* **1971**, *36*, 1842. (d) Friedrichsen, W.; Oeser, H.-G. *Chem. Ber.* **1975**, *108*, 31.

[3] (a) For the synthesis of a cyclopentenopyrimidine via intramolecular nitrile/pyrimidine cycloaddition, see: Davies, L. B.; Leci, O. A.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1293. (b) *N,N*-Dimethylcyanamide (which can be viewed as an electron-rich nitrile) has been reported to undergo cycloaddition with 3,6-dicarbomethoxy-1,2,4,5-tetrazine to give a 1,2,4-triazine (Seitz, G.; Overheu, W. *Chem. Zeit.* **1979**, *103*, 230).

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Table II. Williamson Ether Synthesis of Cyanomethyl Phenyl Ethers[a] (2) (Scheme III)

product	R_1	R_2	% yield
2a	Ph	Ph	45
2b	Ph	H	40
2c	H	Ph	43
2d	Ph	CH_3	36
2e	CH_3	Ph	14

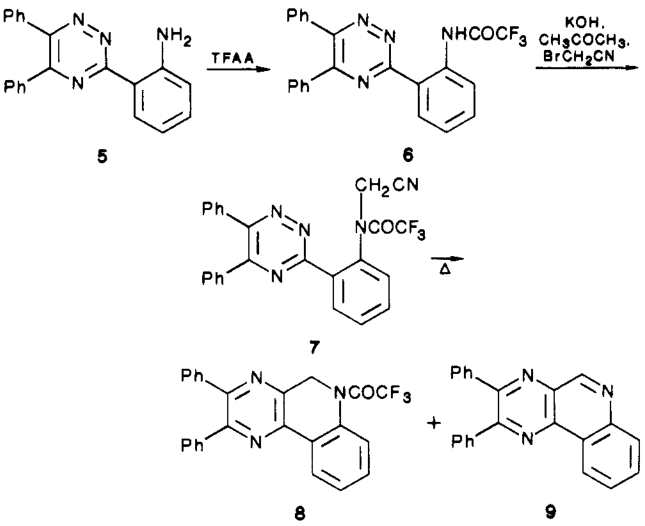
[a] Conditions: NaH, THF reflux, 23 h, 15-crown-5, 1.2 equiv of $BrCH_2CN$.

Table III. Synthesis of Benzopyrano[3,4-*b*]pyrazines[a] (3) (Scheme III)

starting material	product			% yield
		R_1	R_2	
2a	**3a**	Ph	Ph	45
2b	**3b**	Ph	H	39[b]
2d	**3d**	Ph	CH_3	47[c]
2e	**3e**	CH_3	Ph	12

[a] Cycloadditions effected by heating neat at 220–240 °C for 5–13 h. [b] 13 h reflux in diphenyl ether. [c] Reaction run for 5 h in refluxing 1,3,5-triisopropylbenzene.

Scheme IV

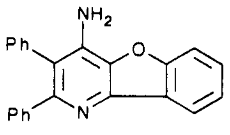


imidates, or amidines) in lieu of nitriles to achieve more favorable inverse electron demand mode matching of frontier orbital energies, but the ultimate selection of nitrile dienophiles for initial studies was based on ease of preparation of the cycloaddition precursors and the known propensity of amidines and imidates to react as dienophiles via their alkene tautomeric forms (*N*,*N*-ketene aminals and *N*,*O*-ketene aminals, respectively).[4] This proclivity was expected to be even more pronounced in many of the systems under study, as reaction in this manifold would yield 6,5,6- rather that 6,6,6-tricycles.

The following account details our efforts to utilize this 1,2,4-triazine–nitrile IDA approach to a series of bi- and tricyclic condensed pyrazine ring systems.

A single preparation of the benzopyrano[3,4-*b*]pyrazine ring system has been reported and relies on condensation of ethylenediamine with 3,4-chromandiones followed by oxidation.[5] Our cycloaddition-based methodology offers an attractive potential alternative for the construction of tricyclic pyrazines with a phenanthrene type nucleus. Thus, alkylation of 3-(*o*-hydroxyphenyl)-1,2,4-triazines with bromoacetonitrile would afford cyanomethyl phenyl ethers, which upon subsequent cycloaddition and rearomatization should provide the desired products (Scheme III). The 3-(*o*-hydroxyphenyl)-1,2,4-triazines **1a–e** were prepared utilizing a three-component condensation of salicylic acid hydrazide, α-dicarbonyl compound, and excess ammonium acetate (Table I). This 1,2,4-triazine ring synthesis works best for diaryl diketones and less well for aryl keto aldehydes and for aryl alkyl diketones. Diacetyl failed to provide any 1,2,4-triazine product.[6] Incorporation of the dienophilic side chain via a Williamson ether synthesis with bromoacetonitrile turned out to be complicated by the relatively low nucleophilicity of the derived phenoxides, a consequence of the sterically demanding, electron-withdrawing *o*-triazinyl moiety. Best yields were obtained by utilizing 15-crown-5 in conjunction with sodium hydride derived phenoxides in refluxing THF (Table II).

When heated in a capillary tube, 5,6-diphenyl-3-[2′-(cyanomethoxy)phenyl]-1,2,4-triazine (**2a**) melted at 169–171 °C. Further heating to approximately 210 °C was accompanied by slow gas evolution, which became vigorous at temperatures approaching 240 °C. This observation suggested that the desired cycloaddition might be occurring at these elevated temperatures. Accordingly, **2a** was heated neat under nitrogen at 225–235 °C for 8 h, and the resulting red gum was chromatographed on silica gel. One major product was isolated in addition to starting material, and spectral data confirmed structure **3a**, the product of intramolecular nitrile cycloaddition. An alternative product **4**, which might have arisen from cycloaddition of the ketenimine tautomer, is clearly ruled out by the absence of any evidence for an amino group in the IR and ^1H NMR spectra. The four other nitriles **2b–e** similarly underwent intramolecular cycloaddition to afford low to moderate yields of variously substituted benzopyrano[3,4-*b*]pyrazines **3b–e** (Table III).



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The benzopyrano[3,4-*b*]pyrazines **3a–e** are moderately high melting solids. ^1H NMR spectra display characteristic singlets in the range of δ 5.37–5.46 for the C-5 methylene protons, and the electron impact mass spectral fragmentation patterns reveal stable (100%) parent peaks as well as intense $M^+ - 1$ peaks for the tricyclic pyrylium ions formed upon loss of a hydrogen atom from C-5.

Neither the parent compound nor any derivatives of pyrazino[2,3-*c*]quinoline has been described in the literature. Since it appeared that a minor modification of the above methodology might provide a convenient entry into this unknown ring system (Scheme IV), 3-(2′-aminophenyl)-5,6-diphenyl-1,2,4-triazine[7] (**5**) was trifluoroacetylated, and the resulting trifluoroacetanilide **6** was N-alkylated with bromoacetonitrile and potassium hydroxide in aetone.[8] This method of monoalkylating aniline

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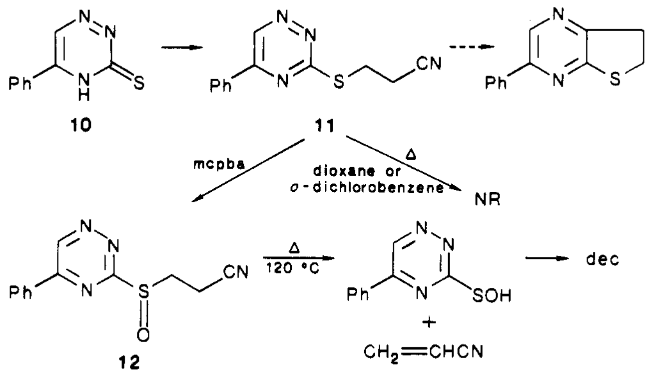
(4) Reaction of electron-rich nitrile dienophile equivalents via their alkene tautomeric forms in intermolecular reactions with 1,2,4,5-tetrazines has been observed. See, for example: (a) Seitz, G.; Overheu, W. *Arch. Pharm.* **1979**, *312*, 452. (b) Seitz, G.; Overheu, W. *Arch. Pharm.* **1977**, *310*, 936. (c) Figeys, H. P.; Mathy, A.; Dralants, A. *Synth. Commun.* **1981**, *11*, 655.

(5) Chiodini, L.; Di Ciommo, M.; Merlini, L. *J. Heterocycl. Chem.* **1981**, *18*, 23.

(6) The three-component 1,2,4-triazine ring synthesis employed is that reported by Atkinson, C. M.; Cossey, H. D. *J. Chem. Soc.* **1962**, 1805.

(7) As prepared by Atkinson and Cossey (see ref 6).

Scheme V



derivatives is chemoselective. Acylation of secondary amines within chains connecting diene and dienophile has been shown to facilitate IDA reactions.[9] The *N*-(cyanomethyl)trifluoroacetanilide **7**, when heated at reflux in diphenyl ether, afforded products that were separated by column chromatography and identified as 5,6-dihydro-2,3-diphenyl-6-trifluoroacetylpyrazino[2,3-*c*]quinoline (**8**) and the deacylated, fully aromatic 2,3-diphenylpyrazino-[2,3-*c*]quinoline (**9**).[10] The combined yield of cycloaddition products was 83%.

A related project was initiated with the aim of developing a nitrile/1,2,4-triazine IDA-based route to bicyclic fused pyrazines. The thieno[2,3-*b*]pyrazine ring system has attracted attention in our laboratories due to its presence in urothione[11] and in Form B of the molybdenum cofactor. Only a few approaches to this heterocycle have been described, all of which involve elaboration of the thiophene ring onto a functionalized pyrazine.[12] The alternative cyclocondensation strategy has not been pursued as the requisite 2,3-diaminothiophenes are difficult to prepare.[13] An approach that parallels the thieno[2,3-*b*]pyridine and thieno[2,3-*c*]pyridine syntheses recently developed in these laboratories[1b,l] would involve alkylation of a 1,2,4-triazine-3-thione with 3-bromopropionitrile, followed by an IDA to afford 6,7-dihydrothieno[2,3-*b*]-pyrazines, which would then be oxidized (Scheme V).

3-[(2′-Cyanoethyl)thio]-5-phenyl-1,2,4-triazine (**11**) was prepared in 68% yield by straightforward alkylation of the thione **10**.[14] However, attempts to effect cycloaddition in dioxane (101 °C, 48 h) and *o*-dichlorobenzene (179 °C, 21 h) returned unchanged starting material. Since our earlier work in the thienopyridine arena had shown that oxidation of the connecting chain sulfur atom facilitated cycloaddition,[15] we converted **11**, with 1 equiv of *m*-chloroperbenzoic acid, to the sulfinyltriazine **12**. When heated neat under nitrogen at 120 °C, this sulfoxide melted to a dark red oil, and gas evolution ensued. These observations suggested that the desired cycloaddition might indeed have occurred. However, ^{1}H NMR spectral data for the crude reaction mixture indicated the formation of acrylonitrile and unidentified 1,2,4-triazine products. Apparently, the sulfoxide functionality facilitates a retro-Michael reaction leading to acrylonitrile and a 1,2,4-triazine-3-sulfenic acid, which decomposes into a variety of 1,2,4-triazine products. Retro-Michael reactions of S-alkylated 1,2,4-triazine-3-thione derivatives at elevated temperatures proved to be a recurring problem,[16] and this approach to thienopyrazines was abandoned.

Experimental Section

General Methods. Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1320 instrument. ^{1}H NMR spectra were obtained with a JEOL FX-90Q 90-MHz instrument, and chemical shifts are reported in ppm downfield from TMS. Mass spectral data were obtained on AEI MS-902 and Kratos MS50TC spectrometers. Combustion analyses were performed at Eli Lilly and Co., Indianapolis, IN. Column chromatographic separations were carried out on Merck silica gel 60 (240–400 mesh). TLC analyses were performed on Bakerflex IB2-F plates, utilizing UV and iodine visualization. Preparative TLC was conducted on Analtech silica gel GF uniplates (1500 mm).

5,6-Diphenyl-3-(2′-hydroxyphenyl)-1,2,4-triazine (1a). To a solution of salicyl hydrazide (2.00 g, 13.2 mmol) and benzil (2.76 g, 13.2 mmol) in glacial acetic acid (30 mL) was added ammonium acetate (17.0 g. 294 mmol), and the solution was heated at reflux for 5.5 h. After cooling, the bright yellow precipitate that separated was collected by filtration, washed with water, and dried to provide 3.80 g of crude product. Recrystallization from DMF/ethanol afforded 3.05 g (71%) of **1a** as a crystalline yellow solid: mp 174–175 °C (lit.[17] 174–175 °C); IR (KBr) 3060, 1620, 1585, 1515, 1485, 1440, 1405, 1370, 1310, 1250, 1225, 1150, 1100, 1000, 820, 750, 695 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.53 (s, 1 H), 8.62 (d of d, J_o = 7.8 Hz, J_m = 1.9 Hz, 1 H), 7.78–6.93 (m, 13 H).

3-(2′-Hydroxyphenyl)-6-phenyl-1,2,4-triazine (1b) and 3-(2′-Hydroxyphenyl)-5-phenyl-1,2,4-triazine (1c). To a solution of phenylglyoxal monohydrate (2.80 g, 18.4 mmol) and salicyl hydrazide (2.80 g, 18.4 mmol) in glacial acetic acid (35 mL) was added ammonium acetate (21.3 g, 276 mmol), and the reaction mixture was heated at reflux for 3 h. The resulting dark red solution was concentrated to half its volume under reduced pressure and poured into water (150 mL). The aqueous mixture was extracted with methylene chloride (3 × 100 mL), and the combined organic layers were washed with water (125 mL) and dried over sodium sulfate. Evaporation of solvent under reduced pressure afforded a mixture of the 6- and 5-phenyl regioisomers **1b** and **1c**. Column chromatography on silica gel (100 g), eluting with a 50–75% methylene chloride/hexanes gradient, provided a fraction (R_f = 0.50, methylene chloride) containing 0.89 g (19%) of **1b**. Recrystallization from ethanol afforded 0.64 g (14%) of **1b** as a yellow solid: mp 171–173 °C; IR (KBr) 3045, 1610, 1585, 1485, 1455, 1440, 1395, 1245, 1080, 1000, 750, 680 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.39 (s, 1 H), 9.10 (s, 1 H), 8.16–8.09 and 7.61–7.13 (m, 9 H). Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.45; H, 4.65; N, 16.85.

A second fraction (R_f = 0.30, methylene chloride) provided 1.21 g (26%) of **1c**. Recrystallization from 80% ethanol afforded 0.96 g (21%) of **1c** as a yellow solid: mp 127–129 °C; IR (KBr) 3120, 3050, 1595, 1540, 1505, 1490, 1460, 1440, 1420, 1365, 1310, 1285, 1245, 1155, 1150, 1130, 1095, 1030, 1000, 990, 835, 810, 790, 745, 735, 680 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.64 (s, 1 H), 10.81 (s, 1 H), 8.65–8.22 and 7.67–6.94 (m, 9 H). Anal. Calcd for $C_{15}H_{11}N_3O$:

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(8) Secondary anilines are subsequently obtained via mild basic hydrolysis of the labile trifluoracetyl group. See: Johnstone, R. A. W.; Payling, D. W.; Thomas, L. *J. Chem. Soc. C* **1969**, 2223.

(9) For examples, see: Ciganek, E., *Org. React.* **1984**, *32*, 50.

(10) Formation of the completely aromatic heterocycle is probably a result of hydrolysis of the trifluoroacetyl group by adventitious water and subsequent air oxidation.

(11) Urothione: Taylor, E. C.; Reiter, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 285. Molybdenum cofactor: Kramer, S. P.; Johnson, J. L.; Ribeiro, A. A.; Millington, D. S.; Rajagopalan, K. V. *J. Biol. Chem.* **1987**, *262*, 16357.

(12) (a) Schneller, S. W.; Clough, F. W.; Hardee, L. E. *J. Heterocycl. Chem.* **1976**, *13*, 273. (b) Taylor, E. C.; Sabb, A. L. *J. Org. Chem.* **1988**, *53*, 5839.

(13) Schneller, S. W.; Clough, F. W. *J. Heterocycl. Chem.* **1975**, *12*, 513.

(14) Paudler, W. W.; Chen, T. K. *J. Heterocycl. Chem.* **1970**, *7*, 767.

(15) The impact of the oxidation state of the sulfur atom link (sulfide, sulfoxide, sulfone) in the connecting chain of terminal alkyne-substituted 1,2,4-triazines on the facility of cycloaddition has been discussed in terms of electronic and conformational effects. For details see ref 1l.

(16) Thermal elimination of sulfoxides with β-hydrogen atoms is well known; see: Durst, T. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: New York, 1979; Vol. 3, pp 140–144.

(17) CIBA Ltd. Belg. Pat. 615,619; *Chem. Abstr.* **1963**, *58*, 12583.

C, 72.28; H, 4.45; N, 16.86. Found: C, 72.05; H, 4.52; N, 16.89.

3-(2′-Hydroxyphenyl)-5-methyl-6-phenyl-1,2,4-triazine (1d) and 3-(2′-Hydroxyphenyl)-6-methyl-5-phenyl-1,2,4-triazine (1e). To a solution of 1-phenyl-1,2-propanedione (2.55 g, 17.2 mmol) and salicyl hydrazide (2.62 g, 17.2 mmol) in glacial acetic acid (30 mL) was added ammonium acetate (19.9 g, 258 mmol). The reaction mixture was heated at reflux for 2.5 h. Evaporation of solvent under reduced pressure afforded a red oil which was taken up in methylene chloride (100 mL) and decanted from an insoluble residue. The solution was washed with water (100 mL) and saturated sodium bicarbonate (100 mL) and dried over sodium sulfate. Evaporation of solvent under reduced pressure gave 3.0 g of a red oil which contained the above mixture of regioisomeric triazines. Column chromatography on silica gel (80 g) and elution with 1:1 methylene chloride/hexanes gave a fraction (R_f = 0.15), which afforded 0.91 g (20%) of **1d** as a white solid: mp 117–118 °C; IR (KBr) 3050, 1610, 1585, 1530, 1480, 1450, 1410, 1375, 1305, 1240, 1215, 1155, 1110, 1070, 1035, 1000, 820, 765, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.55 (s, 1 H), 8.55–8.44 and 7.75–6.90 (m, 9 H), 2.72 (s, 3 H). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.87; H, 5.04; N, 15.66.

A second fraction (R_f = 0.05) afforded 1.27 g (28%) of **1e** as a white solid: mp 115–117 °C; IR (KBr) 3060, 1600, 1590, 1500, 1485, 1405, 1385, 1355, 1310, 1255, 1205, 1150, 1100, 920, 890, 825, 755, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.50 (s, 1 H), 8.57–8.47 and 7.88–6.89 (m, 9 H), 2.87 (s, 3 H). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.13; H, 5.07; N, 15.74.

3-[2′-(Cyanomethoxy)phenyl]-5,6-diphenyl-1,2,4-triazine (2a). To a suspension of sodium hydride (0.28 g of a 60% mineral oil dispersion, 7.0 mmol) in dry THF (50 mL) stirred at room temperature under nitrogen was added **1a** (1.91 g, 5.88 mmol) portionwise over 5 min. Hydrogen evolution and the orange-red color of the phenoxide anion were noted. After 5 min, 15-crown-5 (0.01 mL) and bromoacetonitrile (0.83 g, 6.9 mmol) were added via syringe. The solution was heated at reflux for 23 h. After cooling, the precipitated sodium bromide was removed by filtration. Evaporation of solvent under reduced pressure provided a brown oil which was taken up in methylene chloride (50 mL), washed with 1% HCl (50 mL), and dried over sodium sulfate. Solvent was evaporated under reduced pressure to give a brown sludge which was purified by column chromatography over silica gel (50 g), with elution with methylene chloride. The fraction with R_f = 0.25 afforded 0.96 g (45%) of **2a** as a yellow solid: mp 146.5–147.5 °C; IR (KBr) 3120, 3070, 3040, 2990, 1600, 1580, 1495, 1450, 1385, 1365, 1295, 1275, 1220, 1170, 1085, 1030, 765, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19–8.10 and 7.79–7.37 (m, 14 H), 4.98 (s, 2 H). Anal. Calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.42; N, 15.37. Found: C, 75.52; H, 4.46; N, 15.25.

The following compounds were prepared analogously:

3-[2′-(Cyanomethoxy)phenyl]-6-phenyl-1,2,4-triazine (2b): from **1b** (0.61 g, 2.4 mmol); reflux period 22 h. Purification by column chromatography on silica gel (20 g) and elution with methylene chloride gave a fraction (R_f = 0.25), which afforded 0.28 g (40%) of **2b** as a red solid. The analytical sample was recrystallized from toluene/hexanes: mp 90.5–91 °C; IR (KBr) 3060, 2970, 1600, 1580, 1490, 1450, 1405, 1330, 1280, 1230, 1215, 1080, 1030, 760, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.11 (s, 1 H), 8.27–8.01 and 7.73–7.26 (m, 9 H), 4.96 (s, 2 H). Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 71.08; H, 4.42; N, 19.17.

3-[2′-(Cyanomethoxy)phenyl]-5-phenyl-1,2,4-triazine (2c): from **1c** (0.85 g, 3.4 mmol); reflux period 24 h. Purification by column chromatography on silica gel (30 g) and elution with methylene chloride gave a fraction (R_f = 0.10), which afforded 0.42 g (43%) of **2c** as a yellow solid: mp 145.5–146.5 °C; IR (KBr) 3060, 2990, 2950, 2920, 1600, 1580, 1535, 1495, 1455, 1440, 1390, 1365, 1320, 1285, 1225, 1115, 1070, 1025, 755, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.64 (s, 1 H), 8.34–8.00 and 7.67–7.22 (m, 9 H), 4.95 (s, 2 H). Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.61; H, 4.26; N, 19.12.

3-[2′-(Cyanomethoxy)phenyl]-5-methyl-6-phenyl-1,2,4-triazine (2d): from **1d** (1.00 g, 3.80 mmol); reflux period 41 h. Purification by column chromatography on silica gel (25 g) and elution with methylene chloride provided a fraction (R_f = 0.15) which afforded 0.42 g (36%) of **2d** as a pale yellow solid: mp 125–127 °C; IR (KBr) 3070, 3060, 2920, 1600, 1575, 1500, 1490, 1450, 1435, 1390, 1370, 1355, 1270, 1240, 1225, 1070, 1020, 760, 700, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07–7.98 and 7.76–7.26 (m, 9 H), 4.97 (s, 2 H), 2.71 (s, 3 H). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.68; N, 18.53. Found: C, 71.81; H, 4.61; N, 18.31.

3-[2′-(Cyanomethoxy)phenyl]-6-methyl-5-phenyl-1,2,4-triazine (2e): from **1e** (0.75 g, 2.8 mmol); reflux period 24 h. Purification by column chromatography on silica gel (15 g) and elution with methylene chloride followed by ethyl acetate provided a fraction (R_f = 0.10, methylene chloride), which afforded 0.12 g (14%) of **2e** as a yellow solid: mp 100.5–102.5 °C; IR (KBr) 3060, 2970, 1600, 1510, 1490, 1385, 1360, 1285, 1215, 1095, 1025, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14–7.30 (m, 9 H), 4.93 (s, 2 H), 2.90 (s, 3 H). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.33; H, 4.72; N, 18.64.

2,3-Diphenylbenzopyrano[3,4-*b*]pyrazine (3a). Compound **2a** (0.30 g, 0.824 mmol) was heated neat under nitrogen at 225–235 °C for 8 h. Column chromatography of the resulting red gum on silica gel (10 g) and elution with 1:3 methylene chloride/hexanes provided a fraction (R_f = 0.60, methylene chloride) which afforded 0.125 g (45%) of **3a** as a white solid: mp 169–171 °C; IR (KBr) 3100, 3080, 2990, 2940, 2870, 1605, 1460, 1410, 1390, 1300, 1275, 1235, 1210, 1165, 1035, 770, 760, 750, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.33–8.25 and 7.58–6.97 (m, 14 H), 5.46 (s, 2 H); LRMS, *m/z* (relative intensity) 336 (M^+, 100), 335 (56), 178 (2), 154 (6), 130 (16), 102 (28). Anal. Calcd for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.18; H, 4.76; N, 8.05.

3-Phenylbenzopyrano[3,4-*b*]pyrazine (3b). A solution of **2b** (0.074 g, 0.26 mmol) in diphenyl ether (1 mL) was heated at 225–235 °C under nitrogen for 13 h. The reaction mixture was passed through a short column of coarse silica gel which was then eluted first with petroleum ether to wash the solvent through and then with ether. The ether filtrate was evaporated under reduced pressure, and the residue was purified by preparative TLC on silica gel, developing with 1:4 ether/petroleum ether. The band with R_f = 0.55/ether afforded 0.026 g (39%) of **3b** as a yellow solid: mp 157–160 °C; IR (KBr) 3060, 2920, 1605, 1485, 1430, 1310, 1210, 905, 755, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 8.22–8.00 and 7.68–6.96 (m, 9 H), 5.42 (s, 2 H); HRMS calcd for $C_{17}H_{12}N_2O$ 260.0950, found 260.0937.

2-Methyl-3-phenylbenzopyrano[3,4-*b*]pyrazine (3d). A solution of **2d** (0.35 g, 1.2 mmol) in 1,3,5-triisopropylbenzene (5 mL) was heated at reflux under nitrogen for 5 h. The solution was filtered through a short column of coarse silica gel (15 g) with 1:3 ether/hexanes. The fraction with R_f = 0.55/methylene chloride afforded 0.15 g (47%) of **3d** as a yellow solid: mp 131–135 °C; IR (KBr) 3050, 2960, 1605, 1585, 1480, 1460, 1440, 1390, 1165, 1040, 835, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, J_o = 7.6 Hz, J_m = 2.0 Hz, 1 H), 7.56–6.93 (m, 8 H), 5.38 (s, 2 H), 2.67 (s, 3 H); LRMS, *m/z* (relative intensity) 274 (M^+, 100), 273 (97), 130 (19), 116 (20), 102 (19). Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.53; H, 5.06; N, 10.35.

3-Methyl-2-phenylbenzopyrano[3,4-*b*]pyrazine (3e). Compound **2e** (0.18 g, 0.60 mmol) was heated neat under nitrogen at 220–230 °C for 5 h. Purification by preparative TLC on silica gel with 1:4 ether/hexanes provided a band at R_f = 0.55/ether which afforded 0.202 g (12%) of **3e** as an off-white solid: mp 127–130 °C; IR (KBr) 3050, 2920, 2840, 1600, 1500, 1390, 1210, 1170, 1105, 1045, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, J_o = 7.7 Hz, J_m = 1.8 Hz, 1 H), 7.70–6.93 (m, 9 H), 5.37 (s, 2 H), 2.63 (s, 3 H); LRMS, *m/z* (relative intensity) 274 (M^+, 100) 273 (88), 130 (16), 115 (4), 102 (9); HRMS calcd for $C_{18}H_{14}N_2O$ 274.1106, found 274.1084.

5,6-Diphenyl-3-[2′-(trifluoroacetamido)phenyl]-1,2,4-triazine (6). To a suspension of 5,6-diphenyl-3-(2′-aminophenyl)-1,2,4-triazine[7] (3.00 g, 9.26 mmol) in anhydrous ether (25 mL) stirred at room temperature under nitrogen was added cautiously via syringe trifluoroacetic anhydride (5 mL). An exothermic reaction ensued immediately, and the orange color of the starting material quickly disappeared. After the mixture was stirred for 30 min, solvent and excess TFAA were removed by evaporation under reduced pressure, and the resulting yellow solid was dried in a vacuum oven to provide 3.80 g (98%) of **6** as a yellow powder. The analytical sample was prepared by recrystallization from benzene: mp 221–225 °C; IR (KBr) 1725, 1610, 1590, 1540, 1505, 1485, 1450, 1385, 1370, 1255, 1205, 1160, 900, 765, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 14.41 (br 1, H), 8.84–8.70

and 7.70–7.25 (m, 14 H). Anal. Calcd for $C_{23}H_{15}N_4OF_3$: C, 65.71; H, 3.60; F, 13.56; N, 13.33. Found: C, 66.00; H, 3.87; F, 13.35; N, 13.36.

3-[2′-[*N*-(Cyanomethyl)trifluoroacetamido]phenyl]-5,6-diphenyl-1,2,4-triazine (7). To a suspension of 6 (2.50 g, 5.95 mmol) in dry acetone (30 mL) was added bromoacetonitrile (2.85 g, 23.8 mmol). After the mixture was heated to reflux, powdered potassium hydroxide (1.50 g, 26.8 mmol) was added, and the mixture was refluxed for 10 min. The red mixture was filtered, and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (60 g), eluting with 3:1 methylene chloride/hexanes. A fraction with R_f = 0.15/methylene chloride contained 0.58 g (21%) of the alkylated, deacylated material, 3-[2′-[(cyanomethyl)amino]phenyl]-5,6-diphenyl-1,2,4-triazine. A second fraction (R_f = 0.10, methylene chloride) afforded 0.57 g (21%) of 7 as a bright yellow solid. The yield of 7 was augmented to 42% by reacylation of the deacylated material with excess TFAA in ether: mp 183–184 °C; IR (thin film) 3050, 1705, 1600, 1580, 1500, 1485, 1440, 1385, 1360, 1310, 1260, 1205, 1180, 1160, 1095, 995, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73–8.51 and 7.75–7.23 (m, 14 H), 4.79 (AB quartet, J_{gem} = 17.4 Hz, 2 H). Anal. Calcd for $C_{25}H_{16}F_3N_5O$: C, 65.36; H, 3.51; F, 12.40; N, 15.24. Found: C, 65.08; H, 3.29; F, 12.18; N, 15.31.

5,6-Dihydro-2,3-diphenyl-6-(trifluoroacetyl)pyrazino[2,3-*c*]quinoline (8) and 2,3-Diphenylpyrazino[2,3-*c*]quinoline (9). A solution of 7 (0.60 g, 1.3 mmol) in diphenyl ether (2 mL) was heated at reflux under nitrogen for 2 h. Purification by column chromatography on silica gel (20 g) with 30% ether/hexanes gave a fraction (R_f = 0.55, ether) that contained one product contaminated with diphenyl ether and a second fraction (R_f = 0.20), which afforded 0.21 g (47%) of 9 as a light orange solid: mp 177–178.5 °C; IR (thin film) 3050, 1610, 1580, 1525, 1420, 1380, 1355, 1210, 1075, 1015, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.58 (s, 1 H), 9.08 (m, 1 H), 8.23 (m, 1 H), 7.97–7.24 (m, 12 H); LRMS, m/z (relative intensity) 333 (M^+, 100) 332 (84), 230 (18), 167 (23), 127 (94). Anal. Calcd for $C_{23}H_{15}N_3$: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.65; H, 4.77; N, 12.31.

The first fraction was further purified by column chromatography on silica gel (15 g) with 1:4 ether/hexanes to afford 0.20 g (36%) of 8 as a white solid: mp 163–166 °C; IR (thin film) 3050, 1700, 1600, 1410, 1385, 1275, 1200, 1150, 1085, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.48–8.37 and 7.67–7.29 (m, 14 H), 5.21 (s, 2 H); LRMS, m/z (relative intensity) 431 (M^+, 100), 430 (36), 334 (23), 225 (7), 156 (20), 178 (16). Anal. Calcd for $C_{25}H_{16}F_3N_3O$: C, 69.20; H, 3.74; F, 13.21; N, 9.74. Found: C, 69.47; H, 3.99; F, 13.01; N, 9.94.

3-[(2′-Cyanoethyl)thio]-5-phenyl-1,2,4-triazine (11). A solution of 5-phenyl-1,2,4-triazine-3-thione (10)[14] (2.00 g, 10.5 mmol) and sodium hydroxide (0.42 g, 10.5 mmol) in water (100 mL) and ethanol (100 mL) was stirred at room temperature. 3-Bromopropionitrile (1.35 g, 10.5 mmol) was added in one portion, and the orange solution was heated at 65–70 °C for 20 h. The solution was concentrated by rotary evaporation, and a red oil separated. The aqueous mixture was extracted with methylene chloride (3 × 100 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of solvent under reduced pressure provided a deep red oil. Purification by column chromatography on silica gel (60 g) and methylene chloride elution afforded 1.67 g (68%) of 11 as a red solid. Recrystallization from isopropyl ether provided a yellow solid: mp 77–78 °C; IR (KBr) 3055, 3030, 2960, 2250, 1600, 1535, 1500, 1440, 1320, 1250, 760, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.42 (s, 1 H), 8.20–7.49 (m, 5 H), 3.56 (t, J = 6.8 Hz, 2 H), 3.00 (t, J = 6.8 Hz, 2 H). Anal. Calcd for $C_{12}H_{10}N_4S$: C, 59.49; H, 4.16; N, 23.12; S, 13.23. Found: C, 59.28; H, 3.89; N, 23.18; S, 13.00.

3-[(2′-Cyanoethyl)sulfinyl]-5-phenyl-1,2,4-triazine (12). To a solution of 11 (0.75 g, 3.1 mmol) in methylene chloride (15 mL) stirred in an ice bath was added a cold solution of *m*-chloroperbenzoic acid (0.65 g, 3.1 mmol based on 82.5% purity) in methylene chloride (15 mL) over 10 min. The solution was stirred at 0 °C for 2 h and then allowed to warm to room temperature. Chloroform (10 mL) was added, and the solution was washed with 1 N sodium carbonate (10 mL). The aqueous layer was back-extracted with chloroform (15 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of solvent under reduced pressure gave a yellow oil which upon trituration with a small portion of ethyl acetate provided a yellow solid. Additional material was obtained by diluting the ethyl acetate washings with ether; total yield of 12, 0.50 g (62%): mp 97–98 °C; IR (thin film) 3050, 3000, 2950, 2930, 2240, 1595, 1530, 1490, 1435, 1320, 1240, 1070, 755, 680 cm^{-1}; ^1H NMR (DMSO) δ 10.25 (s, 1 H), 8.48–8.37 and 7.72–7.63 (m, 5 H), 3.63 (m, 2 H), 2.97 (t, J = 7.3 Hz, 2 H); HRMS calcd for $C_{12}H_{10}N_4OS$ 258.0575, found 258.0570.

Registry No. 1a, 16086-60-5; **1b**, 118207-04-8; **1c**, 118207-07-1; **1d**, 118207-08-2; **1e**, 118207-09-3; **2a**, 106823-32-9; **2b**, 118207-10-6; **2c**, 118207-11-7; **2d**, 118207-12-8; **2e**, 118207-13-9; **3a**, 106823-36-3; **3b**, 118207-14-0; **3d**, 118207-15-1; **3e**, 118207-16-2; **5**, 89213-58-1; **6**, 106823-31-8; **7**, 106823-33-0; **8**, 106823-34-1; **9**, 106823-35-2; **10**, 15969-28-5; **11**, 118207-05-9; **12**, 118207-06-0; salicylhydrazine, 936-02-7; benzil, 134-81-6; phenyl glyoxal monohydrate, 1074-12-0; 1-phenyl-1,2-propanedione, 579-07-7; bromoacetonitrile, 590-17-0; 3-[2′-[(cyanomethyl)amino]phenyl]-5,6-diphenyl-1,2,4-triazine, 118207-17-3; 3-bromopropionitrile, 2417-90-5.

Synthesis of Pyridines by Diels–Alder Reactions of Hetero-Substituted 1,2,4-Triazines with Enamines and an Enaminone

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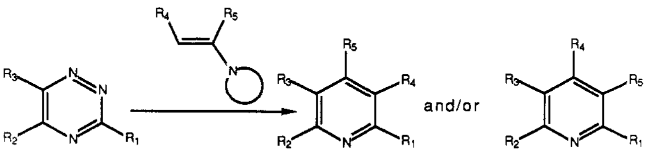
The use of (alkylthio)- and alkoxy-1,2,4-triazines in intermolecular inverse electron demand Diels–Alder reactions with enamine and enaminone dienophiles leads to highly functionalized pyridine derivatives.

Inverse electron demand intermolecular Diels–Alder reactions of 1,2,4-triazines with enamines to yield pyridines has been well documented and exploited (Scheme I).[2] However, the 1,2,4-triazines used in these reactions have been limited to the parent heterocycle ($R_1 = R_2 = R_3$ = H) or to carbon-substituted derivatives ($R_1 = R_2 = R_3$ = alkyl, aryl, or alkoxycarbonyl). Additionally, the enamines

Scheme I



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