Tandem Vicarious Nucleophilic Substitution of Hydrogen/Intramolecular Diels–Alder Reaction of 1,2,4-Triazines into Functionalized Cycloalkenopyridines[1)]

Danuta BRANOWSKA, Stanisław OSTROWSKI, and Andrzej RYKOWSKI*

Institute of Chemistry, University of Podlasie, ul. 3 Maja 54, PL-08-110 Siedlce, Poland.
Received October 9, 2001; accepted December 4, 2001

Synthesis of 2,3- and 3,4-cyclopentenopyridines, 5,6,7,8-tetrahydroquinolines and 5,6,7,8-tetrahydroisoquinolines from 1,2,4-triazine derivatives is reported. Introduction of an α-functionalized methyl substituent (*e.g.* arylsulphonyl, sulphonamide, sulphonic acid ester) into position 3- or 6- of triazines by vicarious nucleophilic substitution of hydrogen and subsequent alkylation with alkyl iodides bearing an acetylenic function in terminal position afforded valuable intermediates for intramolecular Diels–Alder reaction with inverse electron demand. When heated at higher temperature, these triazine derivatives gave the Diels–Alder cycloadducts, which, after spontaneous extrusion of nitrogen moiety, led to a variety of functionalized cycloalkenopyridine derivatives.

Key words cycloalkenopyridine; 1,2,4-triazine; Diels–Alder reaction; vicarious nucleophilic substitution

Substituted cycloalkenopyridines are found in a variety of naturally occuring, biologically active compounds, and a range of synthetic methods to this class of compounds exist.[2)] More recent approach employs a two-step intramolecular Diels–Alder cycloaddition/*retro*-cycloaddition reaction of 1,2,4-triazines with inverse electron demand, involving extrusion of nitrogen molecule.[3)] The approach used is outlined in Chart 1, and is focused on the construction of the key dienophilic intermediate. The synthesis of the latter is effected by nucleophilic displacement of methylsulphinate from 3-(methylsulphonyl)-1,2,4-triazine with active methylene compounds bearing the dienophilic side-chain on the reacting carbon atom. However, in some cases, a serious limitation for the above approach is rather difficult access to suitable substrates.[3)]

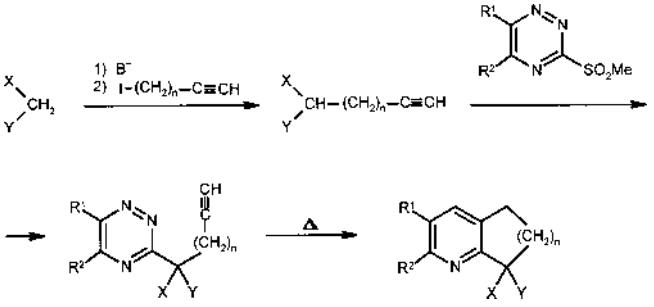

Chart 1

On the other hand, it is well documented that 1,2,4-triazines with functionalized alkyl substituents can be achieved in a more direct way by nucleophilic substitution of hydrogen.[4)] Among many variants of this process, the most general appears to be vicarious nucleophilic substitution (VNS), which proceeds when the reacting carbanion contains leaving group X at the carbanionic center.[5)] This reaction enables the preparation of a wide variety of the desired C-substituted derivatives *via* nucleophilic substitution of hydrogen in the 3-, 5- or 6-positions of the 1,2,4-triazine nucleus.[5a)] Subsequent alkylation of such obtained products (**9**, **10**) with alkyl iodides bearing an acetylenic unit in terminal position, followed by intramolecular cycloaddition involving the extrusion of molecular nitrogen, offered the synthesis of the titled cycloalkenopyridines possessing a high degree of complexity (Chart 2). It would be more difficult, or almost impossible, to achieve this by the intermolecular cycloaddition between triazine derivative and appropriately substituted enamine or other dienophile.

Continuing with our ongoing interest in the preparation of biologically active fused heterocycles, we present herein an improved synthesis of the cycloalkenopyridines functionalized in both rings, starting from 1,2,4-triazines, and using as the key steps: (1) vicarious nucleophilic substitution, and (2) intramolecular Diels–Alder reaction. The reaction sequence presented above has never been examined. We have started our investigations with easily available 5-phenyl- and 3-methylthio-5-phenyl-1,2,4-triazines (**1**, **2**). These highly electrophilic derivatives, when reacted with α-chloromethyl aryl sulphones (**3**: R=Ph, **4**: R=Tol), α-chloromethyl *N*,*N*-dialkyl sulphonamides (**5**: R=morpholino, **6**: R=pyrrolidino, **7**: R=NMe_2), and α-chloromethyl sulfonic acid ester (**8**: R=OCH_2-Bu^t), in the presence of an excess of potassium hydroxide in dimethyl sulfoxide (DMSO) at room temperature, resulted in formation of VNS products **9a**—**f** and **10a** in good yields (Chart 2, Table 1).

To establish optimal conditions for alkylation, the reaction of triazine **9a** with 5-iodo-1-pentyne (**11**) was investigated first. In order to optimize this step a variety of base/solvent systems were tested (NaH/THF, NaH/DMF, *tert*-BuOK/THF, KOH/DMSO, K_2CO_3/DMF, *etc.*) under various conditions: temperature (−40 to 155 °C) and reaction time (2 to 50 h). The highest yield of 5-phenyl-3-[1-(phenylsulphonyl)-5-hexynyl)-1,2,4-triazine (**13a**) was obtained in NaH/DMF at 0 °C (3 h, 94%), and the conditions found were applied to the preparation of the acetylenic key-intermediates **13b**—**i** and **14a**, **g**, respectively. The results of the alkylation of **9a**—**f** and **10a** with 4-iodo-1-butyne (**11**) and 5-iodo-1-pentyne (**12**) are compiled in Table 1. Isolation of the Diels–Alder precursors **13g**—**i** after the reaction of **9a**—**c** with 4-iodo-1-butyne (**12**) was complicated by their propensity to undergo

* To whom correspondence should be addressed. e-mail: rykowski@ap.siedlce.pl
© 2002 Pharmaceutical Society of Japan

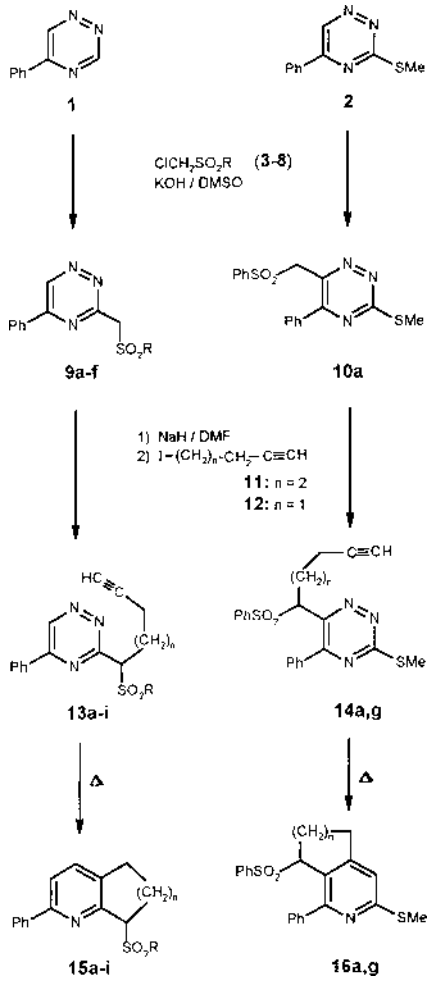

Chart 2

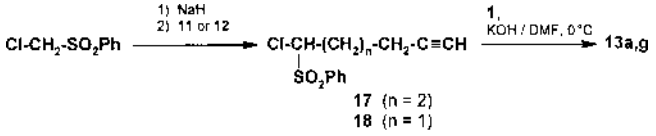

Chart 3

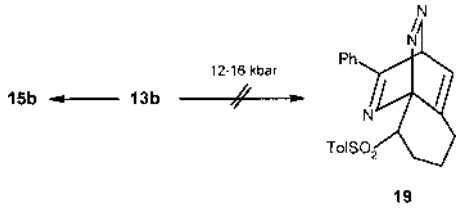

Chart 4

Table 1. Yields of the Products **9**, **13**, and **14** (Charts 1, 2, 3)

	R	Product (%)		*n*	R	Products (%)	
		9				**13**	**14**
a	Ph	74[a]	**a**	2	Ph	94[c]	50
b	Tol	87	**b**	2	Tol	66	—
c	Mrph[b]	70	**c**	2	Mrph[b]	83	—
d	Pyrl[b]	61	**d**	2	Pyrl[b]	82	—
e	NMe_2	68	**e**	2	NMe_2	74	—
f	OCH_2-Bu^t	77	**f**	2	OCH_2-Bu^t	26	—
			g	1	Ph	[c,d]	20
			h	1	Tol	[d]	—
			i	1	Mrph[b]	[d]	—

a) See lit.[5a]; also, compound **10a** (R=Ph) was obtained according to the method described earlier in the literature.[5a] *b*) Mrph stands for morpholine, Pyrl-for pyrrolidine. *c*) They were also obtained according to the scheme shown in Chart 3 (yields: **13a**, 26%; **13g**, 8%). *d*) Crude product was directly used in Diels–Alder cycloaddition.

Table 2. Cycloaddition Reactions and the Yields of Products

Substrate	*n*	Reaction time (h)	R	Product No	Yield (%)
13a	2	2	Ph	**15a**	76
13b	2	2	Tol	**15b**	58
13c	2	10	Mrph[a]	**15c**	81
13d	2	5	Pyrl[a]	**15d**	65
13e	2	4	NMe_2	**15e**	55
13f	2	3	OCH_2-Bu^t	**15f**	97
13g	1	0.5	Ph	**15g**	98[b]
13h	1	0.5	Tol	**15h**	82[b]
13i	1	3	Mrph[a]	**15i**	59[b]
14a	2	7	Ph	**16a**	27
14g	1	3	Ph	**16g**	29

a) Mrph stands for morpholine, Pyrl-for pyrrolidine. *b*) Yields for 2 steps.

fast [4+2]-cycloaddition. In some cases of formation of 5-membered rings, the cycloaddition occured spontaneously at 0 °C to 2,3-cyclopentenopyridines. To complete cycloaddition crude reaction mixtures containing **13g**—**i** were heated in bromobenzene to reflux for a short period of time to give the Diels–Alder cycloadducts, which, after spontaneous extrusion of nitrogen moiety, led to the desired products **15g**—**i** in good yields (Chart 2, Table 2). The bulky substituents (SO_2R) at the α-position of the side chains attached to C-3 or C-6 in triazine ring probably accelerated this process (Thorpe-Ingold effect[6]).

The intermediates **13a**, **13g** could be also obtained in one-step synthesis from the respective triazine derivative **1** in the reaction with tertiary carbanions **17** and **18** bearing dienophilic side-chain. However, attempts to prepare these compounds by this method, probably due to considerable steric hindrance, lead to the desired products (**13a**, **g**) only in low yield (Chart 3, Table 1).

Synthesis of several 5,6,7,8-tetrahydroquinoline derivatives, **15a**—**f**, proceeded analogously to the 2,3-cyclopentenopyridines **15g**—**i**. As expected, the rate of the cycloaddition reactions was substantially slower due to the longer carbon chain linking diene and dienophile. In order to optimize the yields, different solvents (dioxane, bromobenzene, 1,3,5-triisopropylbenzene, methylene chloride) were examined, and the best results were obtained for bromobenzene while the reaction mixture was heated to reflux. Terminal acetylenes tethered through a carbon atom at position 6- in compounds **14a**, **14g** afforded in 1,3,5-triisopropylbenzene 5,6,7,8-tetrahydroisoquinoline **16a** and 3,4-cyclopentenopyridine **16g**, respectively, in moderate yields (Table 2).

The attempts to isolate the cycloadduct **19**, which has never been observed before, failed. Several attempts to realize this on model compound **13b** in CH_2Cl_2 under high pressure (12—16 kbar, 20—60 °C) led directly to the product **15b**, or the starting material was recovered.

In conclusion, the tandem VNS and intramolecular inverse-electron-demand Diels–Alder reactions on 1,2,4-triazines constitute a versatile method for preparation of a vari-

ety of functionalized cycloalkenopyridines. Some of them are compounds of significant importance. They possess potent antishock,[7] tuberculostatic,[8,9] and antimalarial[10] properties. The biological tuberculostatic activity of the compounds described in this paper is now under investigation.[11]

Experimental

^{1}H-NMR spectra were recorded with Varian GEMINI-200 and Varian 360 spectrometers operating at 200 and 360 MHz, respectively. Coupling constants *J* are expressed in hertz [Hz]. IR spectra were measured with a Unicam SP-200 spectrometer and mass spectra were measured with an AMD 604 (AMD Intectra GmbH, Germany) spectrometer [electron impact and liquid secondary ion mass spectrometry (LSIMS) methods]; *m/z* values are given as a % of relative intensity. Melting points are uncorrected. TLC analysis was performed on aluminum foil plates precoated with silica gel 60F 254 Merck. Silica gel 200—300 mesh (Merck AG) was used for column chromatography.

The starting carbanion precursors were obtained according to methods described earlier in the literature: α-chloromethyl phenyl sulphone (**3**),[12] α-chloromethyl *p*-tolyl sulphone (**4**),[13] chloromethanesulphomorpholide (**5**),[14] *N*,*N*-pyrrolidino(chloromethane) sulphonamide (**6**),[14] *N*,*N*-dimethyl-(chloromethane)sulphonamide (**7**),[15] and neo-pentyl chloromethanesulphonate (**8**).[16]

Alkylation of α-Chloromethyl Phenyl Sulphone (3). General Procedure. To NaH (27 mg, 1.1 mmol; washed with Et_2O from 60% oil suspension) in DMF (3 ml) chloromethyl phenyl sulphone (**3**; 191 mg, 1.0 mmol) in DMF (3 ml) was added *via* syringe at 0 °C during 5 min. The mixture was stirred at this temperature under argon for *ca* 15 min. Then, 5-iodo-1-pentyne (214 mg, 1.1 mmol) in DMF (1 ml) was added, and the reaction mixture was stirred at 0 °C for 2 h. The mixture was poured onto water with ice, acidified with AcOH, and extracted with Et_2O (3×30 ml). The combined organic layers were dried with $MgSO_4$, and the crude product was purified by column chromatography using a $CHCl_3$/*n*-hexane (100 : 1) mixture as eluent to give 189 mg of the desired product **17**; oil, 74% yield. It was identified by IR and ^{1}H-NMR spectra: IR ($CHCl_3$) cm^{-1}: 3300, 1320, 1170; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.53—2.05 (5H, m), 2.10—2.74 (2H, m), 4.48—4.83 (1H, m), 7.40—7.60 (3H, m), 7.80—8.10 (2H, m).

Compound **18** was obtained analogously, according to the above procedure, using 4-iodo-1-butyne as alkylating agent; 73 mg; oil, 30% yield. It was identified by IR and ^{1}H-NMR spectra: IR ($CHCl_3$) cm^{-1}: 3300, 1330, 1170; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.53—2.57 (5H, m), 4.44—4.76 (1H, m), 7.40—7.72 (3H, m), 7.81—8.12 (2H, m).

Vicarious Nucleophilic Substitution of Hydrogen. General Prcedures Procedure A. KOH/DMSO System: To a stirred suspension of powdered KOH (4.0 g, 71 mmol) in anhydrous DMSO (20 ml) a solution of triazine derivative **1**—**2** (10.0 mmol) and a carbanion precursor (**3**—**8**; 11.0 mmol) in DMSO (5 ml) was added dropwise *via* syringe at room temp. during *ca* 5 min. After additional 1 h of stirring the mixture was poured onto water with ice and acidified with aqueous 5% HCl. The solid was filtered to give crude products **9a**—**f** and **10a**, which were purified by crystallization from an EtOH/H_2O mixture.

Procedure B. KOH/DMF System: To a stirred suspension of powdered KOH (600 mg, 10.7 mmol) in anhydrous DMF (6 ml) at 0 °C a solution of triazine **1** (158 mg, 1.0 mmol) and a carbanion precursor (**17**, **18**; 1.0 mmol) in DMF (3 ml) was added dropwise *via* syringe at 0 °C during *ca* 5 min. After additional 2 h of stirring at this temp., the mixture was poured onto water with ice, acidified with AcOH, and worked-up as in Procedure A to give the desired products: **13a**, 98 mg (26%), **13g**, 29 mg (8%).

5-Phenyl-3-phenylsulphonylmethyl-1,2,4-triazine (**9a**): Data see lit.[5a]

5-Phenyl-3-(toluene-4-sulphonylmethyl)-1,2,4-triazine (**9b**): mp 135—136 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.43 (3H, s), 4.94 (2H, s), 7.27—7.34 (2H, m), 7.49—7.63 (3H, m), 7.65—7.72 (2H, m), 8.01—8.07 (2H, m), 9.61 (1H, s). IR (KBr) cm^{-1}: 1350, 1160. *Anal.* Calcd for $C_{17}H_{15}N_3SO_2$: C, 62.75; H, 4.65. Found: C, 62.75; H, 4.68.

3-(Morpholine-4-sulphonylmethyl)-5-phenyl-1,2,4-triazine (**9c**): mp 155—156 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.32—3.38 (4H, m), 3.68—3.74 (4H, m), 4.83 (2H, s), 7.64—7.67 (3H, m), 8.21—8.28 (2H, m), 9.69 (1H, s). IR (KBr) cm^{-1}: 1350, 1160. *Anal.* Calcd for $C_{14}H_{16}N_4SO_3$: C, 52.49; H, 5.03; N, 17.49. Found: C, 52.70; H, 4.95; N, 17.61.

5-Phenyl-3-(pyrrolidine-1-sulphonylmethyl)-1,2,4-triazine (**9d**): mp 142—143 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.89—1.98 (4H, m), 3.29—3.37 (4H, m), 4.86 (2H, s), 7.58—7.66 (3H, m), 8.21—8.27 (2H, m), 9.67 (1H, s). IR (KBr) cm^{-1}: 1350, 1170. *Anal.* Calcd for $C_{14}H_{16}N_4SO_2$: C, 55.25; H, 5.30. Found: C, 55.39; H, 5.25.

N,*N*-Dimethyl-*C*-(5-phenyl-1,2,4-triazin-3-yl)-methanesulphonamide (**9e**): mp 173—174 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.91 (6H, s), 4.84 (2H, s), 7.54—7.67 (3H, m), 8.21—8.28 (2H, m), 9.68 (1H, s). IR (KBr) cm^{-1}: 1345, 1160. *Anal.* Calcd for $C_{12}H_{14}N_4SO_2$: C, 51.78; H, 5.07; N, 20.13. Found: C, 51.90; H, 5.02; N, 20.01.

(5-Phenyl-1,2,4-triazin-3-yl)-methanesulphonic Acid 2,2-Dimethyl-propyl Ester (**9f**): mp 159—160 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.96 (9H, s), 4.05 (2H, s), 4.95 (2H, s), 7.57—7.66 (3H, m), 8.20—8.26 (2H, m), 9.69 (1H, s). IR (KBr) cm^{-1}: 1380, 1130. *Anal.* Calcd for $C_{15}H_{19}N_3SO_3$: C, 56.06; H, 5.96; N, 13.07. Found: C, 56.29; H, 5.98; N, 12.55.

5-Phenyl-3-(1-phenylsulphonyl-hex-5-ynyl)-1,2,4-triazine (**13a**): mp 179—180 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.37—1.64 (4H, m), 1.90 (1H, t, *J*=2.7 Hz), 2.21 (2H, td, J_1=6.9, J_2=2.7 Hz), 4.88 (1H, dd, J_1=9.7, J_2=5.6 Hz), 7.41—7.74 (8H, m), 8.05—8.12 (2H, m), 9.59 (1H, s). IR (KBr) cm^{-1}: 3295, 1320, 1160. HR-MS *m/z*: 376.1135 (Calcd for $C_{21}H_{18}N_3SO_2$ (M−H): 376.1120). MS *m/z*: 377 (1, M^+), 312 (61), 285 (62), 237 (35), 236 (100), 208 (47), 183 (94), 102 (98), 77 (55). *Anal.* Calcd for $C_{21}H_{19}N_3SO_2$: C, 66.82; H, 5.07; N, 11.13. Found: C, 67.14; H, 4.82; N, 10.97.

5-Phenyl-3-(1-phenylsulphonyl-pent-4-ynyl)-1,2,4-triazine (**13g**): Unstable; spontaneously underwent to **15g**, for freshly prepared sample mp, IR, ^{1}H-NMR were measured. Mp 141—142 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.91 (1H, t, *J*=2.6 Hz), 2.09—2.28 (1H, m), 2.32—2.49 (1H, m), 2.63—2.85 (2H, m), 5.09 (1H, dd, J_1=10.0, J_2=5.0 Hz), 7.36—7.73 (8H, m), 8.04—8.10 (2H, m), 9.57 (1H, s). IR (KBr) cm^{-1}: 3290, 1320, 1170.

Alkylation of VNS Products 9a—f and 10a with Alkyl Iodides. General Procedure. The suspension of NaH (27 mg, 1.1 mmol; washed with Et_2O from 60% oil suspension) in DMF (3 ml), cooled to 0 °C, was stirred for 15 min under argon. Then, the triazine derivative (**9a**—**f** or **10a**) (1.0 mmol) and 5-iodo-1-pentyne (or 4-iodo-1-butyne) (1.0 mmol) in DMF (3 ml) was added *via* syringe at 0 °C during 5 min. The reaction mixture was stirred at 0 °C for *ca* 2—4 h (TLC monitoring). The mixture was poured onto water with ice, the precipitate was filtered, and the crude product was purified by column chromatography using a $CHCl_3$/*n*-hexane mixture (100 : 1) or $CHCl_3$ as eluent. Yields – see Table 1.

5-Phenyl-3-[1-(toluene-4-sulphonyl)-hex-5-ynyl]-1,2,4-triazine (**13b**): mp 172—173 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.35—1.65 (2H, m), 1.90 (1H, t, *J*=2.5 Hz), 2.21 (2H, td, J_1=7.0, J_2=2.5 Hz), 2.38 (3H, s), 2.55—2.70 (2H, m), 4.84 (1H, dd, J_1=9.7, J_2=5.4 Hz), 7.20—7.30 (2H, m), 7.50—7.65 (5H, m), 8.05—8.12 (2H, m), 9.58 (1H, s). IR (KBr) cm^{-1}: 3305, 1320, 1170. HR-MS *m/z*: 392.1442 (Calcd for $C_{22}H_{22}N_3SO_2$ (M+H): 392.1433). MS *m/z*: 392 (100, M+H), 236 (9), 209 (10), 176 (14), 155 (19), 154 (68), 137 (45), 136 (46). *Anal.* Calcd for $C_{22}H_{21}N_3SO_2$: C, 67.50; H, 5.41; N, 10.74. Found: C, 67.30; H, 5.35; N, 10.52.

3-[1-(Morpholine-4-sulphonyl)-hex-5-ynyl]-5-phenyl-1,2,4-triazine (**13c**): mp 164—165 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.37—1.70 (2H, m), 1.97 (1H, t, *J*=2.6 Hz), 2.25 (2H, td, J_1=7.0, J_2=2.6 Hz), 2.45—2.64 (1H, m), 2.68—2.92 (1H, m), 3.04—3.18 (2H, m), 3.25—3.38 (2H, m), 3.52—3.72 (4H, m), 4.85 (1H, dd, J_1=11.1, J_2=4.1 Hz), 7.59—7.67 (3H, m), 8.23—8.29 (2H, m), 9.69 (1H, s). IR (KBr) cm^{-1}: 3295, 1320, 1180. HR-MS *m/z*: 386.1413 (Calcd for $C_{19}H_{22}N_4SO_3$: 386.1413). MS *m/z*: 387 (54, M+H), 386 (2, M^+), 236 (9), 209 (7), 107 (28), 91 (17), 90 (14), 89 (19).

5-Phenyl-3-[1-(pyrrolidine-1-sulphonyl-hexyl)-5-ynyl]-1,2,4-triazine (**13d**): mp 153—154 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.41—1.67 (2H, m), 1.74—1.87 (4H, m), 1.94 (1H, t, *J*=2.6 Hz), 2.25 (2H, td, J_1=7.0, J_2=2.6 Hz), 2.47—2.65 (1H, m), 2.72—2.93 (1H, m), 2.96—3.09 (2H, m), 3.33—3.47 (2H, m), 4.91 (1H, dd, J_1=11.0, J_2=4.1 Hz), 7.53—7.66 (3H, m), 8.24—8.31 (2H, m), 9.67 (1H, s). IR (KBr) cm^{-1}: 3295, 1330, 1160. HR-MS *m/z*: 371.1540 (Calcd for $C_{19}H_{23}N_4SO_2$ (M+H): 371.1542). LSIMS(+) *m/z*: 371 (100, M+H). *Anal.* Calcd for $C_{19}H_{22}N_4SO_2$: C, 61.60; H, 5.99; N, 15.12. Found: C, 61.80; H, 5.89; N, 15.39.

1-(5-Phenyl-1,2,4-triazin-3-yl)-hex-5-yne-1-sulphonic Acid Dimethyl-amide (**13e**): mp 149—150 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.42—1.71 (2H, m), 1.96 (1H, t, *J*=2.6 Hz), 2.25 (2H, td, J_1=6.9, J_2=2.6 Hz), 2.45—2.63 (1H, m), 2.70—2.92 (1H, m), 2.77 (6H, s), 4.89 (1H, dd, J_1=11.0, J_2=4.1 Hz), 7.58—7.67 (3H, m), 8.24—8.30 (2H, m), 9.68 (1H, s). IR (KBr) cm^{-1}: 3295, 1320, 1160. HR-LSIMS *m/z*: 345.1386 (Calcd for $C_{17}H_{21}N_4SO_2$ (M+H): 345.1385. LSIMS(+) *m/z*: 345 (100, M+H). *Anal.* Calcd for $C_{17}H_{20}N_4SO_2$: C, 59.28; H, 5.85; N, 16.27. Found: C, 59.01; H, 5.61; N, 15.88.

1-(5-Phenyl-1,2,4-triazin-3-yl)-hex-5-yne-1-sulphonic Acid 2,2-Dimethyl-propyl Ester (**13f**): mp 64—65 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.91 (9H, s), 1.46—1.74 (2H, m), 1.96 (1H, t, *J*=2.6 Hz), 2.26 (2H, td, J_1=6.8, J_2=2.6 Hz), 2.53—2.90 (2H, m), 3.93 & 4.01 (2H, AB system, *J*=8.9 Hz), 4.97 (1H, dd, J_1=10.5, J_2=4.5 Hz), 7.53—7.69 (3H, m), 8.21—8.29 (2H,

m), 9.68 (1H, s). IR (KBr) cm^{-1}: 3300, 1320, 1160. HR-MS *m/z*: 372.1382 (Calcd for $C_{19}H_{22}N_3SO_3$ (M−CH_3): 372.1382). MS *m/z*: 372 (2, M−CH_3), 317 (4), 251 (4), 236 (100), 209 (17), 102 (91). *Anal.* Calcd for $C_{20}H_{25}N_3SO_3$: C, 61.99; H, 6.50; N, 10.84. Found: C, 62.20; H, 6.35; N, 10.63.

3-Methylsulphanyl-5-phenyl-6-(1-phenylsulphonyl-hex-5-ynyl)-1,2,4-triazine (**14a**): mp 155—156 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.93 (1H, t, J=2.6 Hz), 2.08—2.27 (2H, m), 2.35 (2H, td, J_1=5.9, J_2=2.6 Hz), 2.52—2.81 (2H, m), 2.68 (3H, s), 4.99 (1H, dd, J_1=10.7, J_2=4.4 Hz), 7.43—7.56 (3H, m), 7.57—7.67 (2H, m), 7.70—7.81 (5H, m). IR (KBr) cm^{-1}: 3290, 1320, 1170. HR-MS *m/z*: 423.1077 (Calcd for $C_{22}H_{21}N_3S_2O_2$: 423.1075. MS *m/z*: 423 (6, M^+), 390 (1), 376 (2), 358 (14), 312 (28), 209 (52), 133 (61), 125 (24), 104 (37), 89 (40), 77 (37). *Anal.* Calcd for $C_{22}H_{21}N_3S_2O_2$: C, 62.39; H, 5.00; N, 9.92. Found: C, 62.56; H, 5.00; N, 9.51.

3-Methylsulphanyl-5-phenyl-6-(1-phenylsulphonyl-pent-4-ynyl)-1,2,4-triazine (**14g**): mp 130—131 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.92 (1H, t, J=2.6 Hz), 2.08—2.84 (4H, m), 2.68 (3H, s), 5.00 (1H, dd, J_1=10.6, J_2=4.4 Hz), 7.43—7.67 (5H, m), 7.69—7.82 (5H, m). IR (KBr) cm^{-1}: 3290, 1320, 1170. HR-LSIMS *m/z*: 410.0997 (Calcd for $C_{21}H_{20}N_3S_2O_2$ (M+H): 410.0997. LSIMS(+) *m/z*: 410 (100, M+H). *Anal.* Calcd for $C_{21}H_{19}N_3S_2O_2$: C, 61.59; H, 4.68; N, 10.26. Found: C, 61.77; H, 4.54; N, 10.23.

Crude products **13g**—**i**, due to their instability, were directly used in Diels–Alder cycloaddition. An analytical sample of compound **13g** was purified by column chromatography for characterization (for data see above).

Cycloaddition Reaction. General Procedure. In a round-bottomed flask (100 ml) equipped with a reflux condenser, under argon, the triazine derivative (**13a**—**i**, 1.0 mmol) was dissolved in bromobenzene (20 ml; compounds **14a**, **g** in triisopropylbenzene), and the reaction mixture was heated to reflux. The reaction was monitored by TLC (reaction time–see Table 2). The solvent was distilled in vacuum and the residue was chromatographed using $CHCl_3$ as eluent to give the desired products **15a**—**i** and **16a**, **g**.

2-Phenyl-8-phenylsulphonyl-5,6,7,8-tetrahydroquinoline (**15a**): mp 174—175 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.83—1.97 (1H, m), 2.12—2.32 (1H, m), 2.35—2.54 (1H, m), 2.72—3.12 (3H, m), 4.68 (1H, dd, J_1=6.6, J_2=3.3 Hz), 7.24—7.66 (10H, m), 7.71—7.78 (2H, m). IR (KBr) cm^{-1}: 1320, 1160. HR-MS *m/z*: 349.1121 (Calcd for $C_{21}H_{19}NSO_2$: 349.1137). MS *m/z*: 349 (<1, M^+), 285 (23), 208 (100), 193 (13). *Anal.* Calcd for $C_{21}H_{19}NSO_2$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.05; H, 5.45; N, 3.99.

2-Phenyl-8-(toluene-4-sulphonyl)-5,6,7,8-tetrahydroquinoline (**15b**): mp 190—191 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.78—1.96 (1H, m), 2.10—2.30 (1H, m), 2.42 (3H, s), 2.36—2.60 (1H, m), 2.50—2.88 (1H, m), 2.92—3.11 (2H, m), 4.63 (1H, dd, J_1=6.6, J_2=3.0 Hz), 7.21—7.42 (7H, m), 7.49—7.63 (4H, m). IR (KBr) cm^{-1}: 1310, 1150. HR-LSIMS *m/z*: 364.1373 (Calcd for $C_{22}H_{22}NSO_2$ (M+H): 364.1371). LSIMS(+) *m/z*: 364 (100, M+H). *Anal.* Calcd for $C_{22}H_{21}NSO_2$: C, 72.70; H, 5.82, N, 3.85. Found: C, 72.77; H, 5.82; N, 3.87.

8-(Morpholine-4-sulphonyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**15c**): mp 184—185 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.78—1.94 (1H, m), 2.05—2.24 (1H, m), 2.30—2.54 (1H, m), 2.70—3.10 (3H, m), 3.24—3.44 (4H, m), 3.52—3.74 (4H, m), 4.58 (1H, dd, J_1=6.2, J_2=2.2 Hz), 7.41—7.58 (3H, m), 7.53 & 7.66 (2H, AB system, J=8.1 Hz), 8.02—8.10 (2H, m). IR (KBr) cm^{-1}: 1335, 1120. HR-LSIMS *m/z*: 359.1426 (Calcd for $C_{19}H_{23}N_2SO_3$ (M+H): 359.1429). LSIMS(+) *m/z*: 359 (70, M+H). *Anal.* Calcd for $C_{19}H_{22}N_2SO_3$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.79; H, 6.33; N, 7.70.

2-Phenyl-8-(pyrrolidine-1-sulphonyl)-5,6,7,8-tetrahydroquinoline (**15d**): mp 161—162 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.63—1.92 (5H, m), 2.06—2.26 (1H, m), 2.35—2.59 (1H, m), 2.70—2.88 (2H, m), 2.96—3.17 (3H, m), 3.37—3.51 (2H, m), 4.65 (1H, dd, J_1=6.4, J_2=2.4 Hz), 7.38—7.52 (3H, m), 7.54 & 7.65 (2H, AB system, J=8.1 Hz), 7.95—8.02 (2H, m). IR (KBr) cm^{-1}: 1310, 1155. HR-MS *m/z*: 343.1476 (Calcd for $C_{19}H_{23}N_2SO_2$ (M+H): 343.1480). MS *m/z*: 343 (<1, M+H), 209 (100), 208 (63), 193 (18), 128 (7), 83 (23). *Anal.* Calcd for $C_{19}H_{22}N_2SO_2$: C, 66.64; H, 6.48; N, 8.19. Found: C, 66.30; H, 6.59; N, 7.82.

2-Phenyl-5,6,7,8-tetrahydroquinoline-8-sulphonic Acid Dimethylamide (**15e**): mp 116—117 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.77—1.92 (1H, m), 2.07—2.26 (1H, m), 2.34—2.58 (1H, m), 2.69—3.10 (3H, m), 2.82 (6H, s), 4.62 (1H, dd, J_1=6.3, J_2=2.4 Hz), 7.37—7.54 (3H, m), 7.56 & 7.67 (2H, AB system, J=8.1 Hz), 8.01—8.08 (2H, m). IR (KBr) cm^{-1}: 1330, 1150. HR-LSIMS *m/z*: 317.1322 (Calcd for $C_{17}H_{21}N_2SO_2$ (M+H): 317.1324). LSIMS(+) *m/z*: 317 (100, M+H). *Anal.* Calcd for $C_{17}H_{20}N_2SO_2$: C, 64.53; H, 6.38; N, 8.86. Found: C, 64.44; H, 6.34; N, 8.67.

2-Phenyl-5,6,7,8-tetrahydroquinoline-8-sulphonic Acid 2,2-Dimethylpropyl Ester (**15f**): mp 84—85 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.89 (9H, s), 1.82—1.97 (1H, m), 2.12—2.45 (2H, m), 2.71—3.07 (3H, m), 3.93 & 3.96 (2H, AB system, J=9.2 Hz), 4.69—4.76 (1H, m), 7.35—7.51 (3H, m), 7.55 & 7.65 (2H, AB system, J=8.1 Hz), 7.97—8.04 (2H, m). IR (KBr) cm^{-1}: 1350, 1180. HR-MS *m/z*: 359.1556 (Calcd for $C_{20}H_{25}NSO_3$: 359.1555). MS *m/z*: 359 (4, M^+), 208 (100), 193 (14). *Anal.* Calcd for $C_{20}H_{25}NSO_3$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.90; H, 6.73; N, 3.80.

2-Phenyl-7-phenylsulphonyl-6,7-dihydro-5*H*-[1]pyrindine (**15g**): mp 152—153 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.53—2.74 (1H, m), 2.88—3.35 (3H, m), 4.75 (1H, dd, J_2=9.8, J_1=2.0 Hz), 7.32—7.39 (3H, m), 7.48—7.82 (9H, m). IR (KBr) cm^{-1}: 1320, 1160. HR-MS *m/z*: 335.0979 (Calcd for $C_{20}H_{17}NSO_2$: 335.0980). MS *m/z*: 335 (1, M^+), 271 (8), 194 (100). *Anal.* Calcd for $C_{20}H_{17}NSO_2$: C, 71.62; H, 5.11; N, 4.18. Found: C, 71.61; H, 4.81; N, 4.16.

2-Phenyl-7-(toluene-4-sulphonyl)-6,7-dihydro-5*H*-[1]pyrindine (**15h**): mp 150—151 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.49 (3H, s), 2.53—2.73 (1H, m), 2.87—3.33 (3H, m), 4.68—4.73 (1H, m), 7.29—7.38 & 7.54—7.68 (11H, 2×m). IR (KBr) cm^{-1}: 1310, 1150. HR-MS *m/z*: 349.1138 (Calcd for $C_{21}H_{19}NSO_2$: 349.1137). MS *m/z*: 349 (<1, M^+), 285 (13), 194 (100). *Anal.* Calcd for $C_{21}H_{19}NSO_2$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.21; H, 5.34; N, 3.99.

7-(Morpholine-4-sulphonyl)-2-phenyl-6,7-dihydro-5*H*-[1]pyrindine (**15i**): mp 131—132 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.49—2.72 (1H, m), 2.78—3.03 (2H, m), 3.27—3.48 (5H, m), 3.60—3.77 (4H, m), 4.71 (1H, dd, J_1=9.0, J_2=1.8 Hz), 7.42—7.55 (3H, m), 7.67 & 7.69 (2H, AB system, J=8.9 Hz), 8.02—8.10 (2H, m). IR (KBr) cm^{-1}: 1310, 1150. HR-LSIMS(+) *m/z*: 345.1273 (Calcd for $C_{18}H_{21}N_2SO_3$ (M+H): 345.1273). LSIMS(+) *m/z*: 345 (85, M+H), 195 (58), 194 (100). *Anal.* Calcd for $C_{18}H_{20}N_2SO_3$: C, 62.77; H, 5.86; N, 8.14. Found: C, 62.79; H, 5.79; N, 7.99.

3-Methylsulphanyl-1-phenyl-8-phenylsulphonyl-5,6,7,8-tetrahydroisoquinoline (**16a**): mp 165—166 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.78—1.96 (1H, m), 2.10—2.30 (1H, m), 2.38 (3H, s), 2.38—2.60 (1H, m), 2.71—3.11 (3H, m), 4.64 (1H, dd, J_1=6.6, J_2=3.2 Hz), 7.24—7.60 (9H, m), 7.70—7.80 (2H, m). IR (KBr) cm^{-1}: 1330, 1150. HR-MS *m/z*: 395.1013 (Calcd for $C_{22}H_{21}NS_2O_2$: 395.1014). MS *m/z*: 395 (1, M^+), 282 (60), 256 (21), 254 (100), 209 (22), 148 (30), 133 (18), 104 (8), 89 (10), 77 (10). *Anal.* Calcd for $C_{22}H_{21}NS_2O_2$: C, 66.81; H, 5.35; N, 3.54. Found: C, 66.63; H, 5.37; N, 3.80.

3-Methylsulphanyl-1-phenyl-7-phenylsulphonyl-6,7-dihydro-5*H*-[2]-pyrindine (**16g**): mp 201—202 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.39 (3H, s), 2.50—2.73 (1H, m), 2.88—3.11 (2H, m), 3.20—3.41 (1H, m), 4.71 (1H, dd, J_1=9.0, J_2=1.3 Hz), 7.30—7.72 (9H, m), 7.77—7.84 (2H, m). IR (KBr) cm^{-1}: 1320, 1155. HR-MS *m/z*: 381.0858 (Calcd for $C_{21}H_{19}NS_2O_2$: 381.0857). MS *m/z*: 381 (1, M^+), 240 (100), 225 (9), 224 (27), 223 (11), 193 (36).

References and Notes

1) Part 17 in "1,2,4-Triazines in Organic Synthesis." For part 16, see Rykowski A., Wolińska E., van der Plas H. C., *Khim. Geterotsikl. Soedin.* **2001**, 1549—1555.
2) Thummel R. P., "Carbocyclic Annelated Pyridines," in "Pyridine and Its Derivatives," Part 5, ed. by Newkome G. R., Vol. 14 in the series "The Chemistry of Heterocyclic Compounds," ed. by Weissberger A., Taylor E. C., Wiley-Interscience, New York, 1984, pp. 253—445.
3) Taylor E. C., Macor J. E., French L. G., *J. Org. Chem.*, **56**, 1807—1812 (1991).
4) Charushin V. N., Alexeev S. G., Chupakhin O. N., van der Plas H. C., *Adv. Heterocycl. Chem.*, **46**, 74—142 (1989).
5) *a*) Rykowski A., Makosza M., *Liebigs Ann. Chem.*, **1988**, 627–631; *b*) Makosza M., Wojciechowski K., *Heterocycles*, **54**, 445—474 (2001).
6) Jung M. E., *Synlett*, **1990**, 186—190.
7) Brown R. E., Lustgarten D. M., Stanaback R. J., Osborne M. W., Meltzer R. I., *J. Med. Chem.*, **7**, 232—235 (1964).
8) Meyers A. I., Schneller J., Ralhan N. K., *J. Org. Chem.*, **28**, 2944—2950 (1963).
9) Neilands L., *Khim. Geterotsikl. Soedin.*, **1970**, 647—650; *Chem. Abstr.*, **73**: 77013w (1970).
10) Dewar M. J. S., *J. Chem. Soc.*, **1944**, 615—619.
11) The samples are under investigation for tuberculostatic activity at the Southern Research Institute, Birmingham, U.S.A.
12) Mąkosza M., Goliński J., Baran J., *J. Org. Chem.*, **49**, 1488—1494 (1984).
13) Mąkosza M., Danikiewicz W., Wojciechowski K., *Liebigs Ann. Chem.*, **1987**, 711—715.
14) Christensen L. W., Seaman J. E., Truce W. E., *J. Org. Chem.*, **38**, 2243—2245 (1973).
15) Jacobsen H. J., Senning A., Kaae S., *Acta Chem. Scand.*, **25**, 3031—3035 (1971).
16) Mąkosza M., Goliński J., *Synthesis*, **1983**, 1023—1025.