Introduction of a Triflate Group into Sterically-hindered Positions in 1-Aryl-4,6-diamino-1,3,5-triazines and their Dimroth Rearrangement Products

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Decomposition of 1-(azidophenyl)-4,6-diamino-1,3,5-triazines **11-13** and their 4-amino-6-(azidoanilino)-1,3,5-triazine isomers **31-33** in trifluoromethanesulphonic acid at 0° led to the introduction of the triflate group (OSO_2CF_3) into the aryl group. This method can be employed to introduce a bulky substituent into the hindered position *ortho* to the triazinyl substituent. Dimroth rearrangement of 1-(aryl)-4,6-diamino-1,3,5-triazines is best effected in refluxing ethanolic pyridine.

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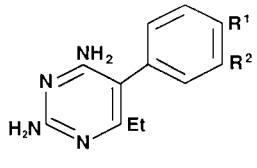
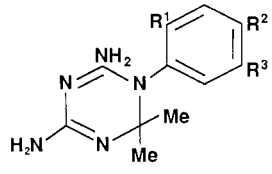
The atropisomerism (restricted rotation about a single bond) exhibited by 2,4-diamino-6-alkyl-5-arylpyrimidines gives rise to two enantiomeric rotational isomers. Detailed 2D nmr exchange experiments have confirmed the existence of multiple conformations in complexes of *Lactobacillus casei* dihydrofolate reductase (DHFR) with a range of DHFR-inhibitory diaminopyrimidines related in structure to the antimalarial drug pyrimethamine **1** [1]. By using a fluorine-labelled probe, fluoronitropyrimethamine **2**, and ^{19}F nmr, Tendler and co-workers [2] showed that the two rotomeric conformations are differentially associated to *Lactobacillus casei* DHFR, the ratio being 0.6:0.4 in the binary state and 0.3:0.7 in the ternary complex with $NADP^+$. Moreover, in an earlier paper [3] molecular modelling methods were employed to predict that only one of the rotomeric conformations of *m*-azidopyrimethamine **3** would associate tenaciously to the hydrophobic pocket in the active site of *Escherichia coli* DHFR.



	R^1	R^2	
1	Cl	H	(pyrimethamine)
2	F	NO_2	(fluoronitropyrimethamine)
3	Cl	N_3	(*m*-azidopyrimethamine)

1-Aryl-4,6-diamino-1,2-dihydro-6,6-dimethyl-1,3,5-triazines, readily synthesised by the notable '3-component synthesis' discovered by Modest [4] also exhibit atropisomerism. We have developed a method to introduce a bulky triflate group into the most hindered position in the aryl group and these new products are potential probes to explore selective binding of atropisomers in the 1,3,5-triazine series to their DHFR target.

The starting materials **4-7** required for the present work were synthesized by the Modest method involving interaction of the appropriate arylamine, cyanoguanidine and hy-



	R^1	R^2	R^3
4	H	Cl	H
5	H	H	NO_2
6	H	Cl	NO_2
7	Cl	H	NO_2
8	H	H	NH_2
9	H	Cl	NH_2
10	Cl	H	NH_2
11	H	H	N_3
12	H	Cl	N_3
13	Cl	H	N_3
14	OSO_2CF_3	H	NH_2
15	OSO_2CF_3	Cl	NH_2
16	Cl	OSO_2CF_3	NH_2

drochloric acid in refluxing acetone [4]. The nitrophenyl-derivatives **5-7** were reduced to the amines **8-10** with stannous chloride in hydrochloric acid or ethanol and the azides **11-13** prepared from the corresponding amines by diazotisation-azidation. The azide **11** was also formed as a hydrochloride salt by a 3-component synthesis. By keeping reaction conditions acidic and not recrystallising the free bases of the products we were able to preserve the 1-aryltriazine structures intact without observing rearrangements to isomeric 6-anilinotriazines.

Decomposition of the *m*-azidophenyltriazines **11-13** in trifluoromethanesulphonic acid (TFSA) in a trifluoroacetic acid (TFA)-trifluoroacetic anhydride (TFAA) mixture was effected at 0°. In the general case of a *m*-azidoarene **17**, formation and decomposition of the protonated azide **18** (Scheme 1) engenders a mesomeric carbocation **19a** ↔ nitrenium **19b** reactive species which suffers nucleophilic attack by the triflate counter-anion predominantly *para* to the incipient amino group to yield trisubstituted arenes **20** even in the presence of a bulky *meta*-substituent [5]. Thus when azide **12** was decomposed as above a single product (98%) was isolated. The aromatic region of the ^{1}H nmr spectrum showed only two sharp singlets at δ 6.95 and 7.47 for protons on C-2′ and C-5′ confirming structure **15** for this product. Clearly attack by triflate anion at C-2′ which would yield isomer **21** is sterically impeded by the *meta*-disposed functionalities in the reactive intermediate. Also nucleophilic attack by the 6-amino-group in the triazine ring in an intramolecular reaction to yield tricycle **22** is

Table 1 ^{1}H nmr Spectra[a] (δ-values) of 1-Aryl-4,6-diamino-1,3,5-triazines and 4-Amino-6-anilino-1,3,5-triazines

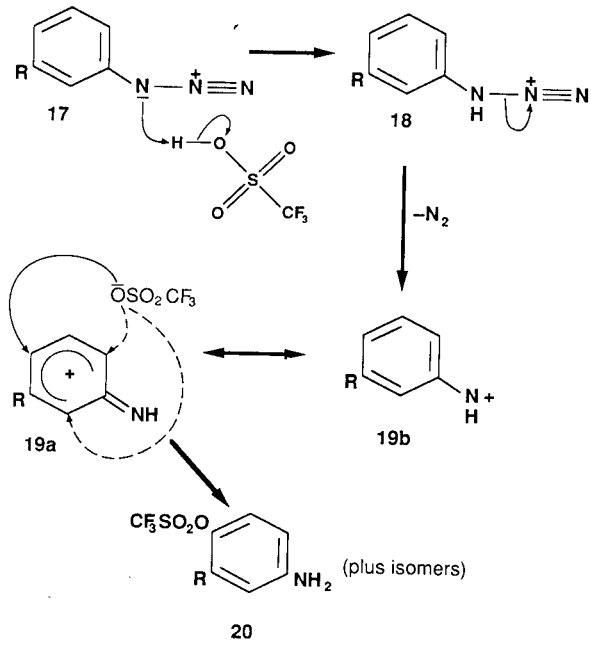
Compound	Solvent	2-Me	2-Me	2′-H	3′-H	4′-H	5′-H	6′-H
5[b]	B	1.37s	1.41s	8.23t	(NO_2)	8.39dd	------ 7.87m ------	
6[b]	B	------ 1.37s ------		8.20s	(NO_2)	(C1)	7.91d	7.77d
7[b]	B	1.24s	1.60s	(C1)	8.03d	8.39dd	(NO_2)	8.35d
8	A	------ 1.35s ------		6.75s	(NH_2)	6.74d	7.32t	6.43d
9	A	------ 1.38s ------		6.96s	(NH_2)	(C1)	7.50d	6.81d
10	A	1.23s	1.50s	(C1)	7.42d	6.92s	(NH_2)	7.00d
11	A	1.35s	1.36s	7.13s	(N_3)	7.26d	7.56t	7.21d
12	A	1.50s	1.52s	7.41d	(N_3)	(C1)	7.66d	7.24d
13	A	1.30s	1.59s	(C1)	7.66d	7.26dd	(N_3)	7.29d
14	A	1.47s	1.69s	(OSO_2CF_3)	7.46d	7.07dd	(NH_2)	7.03d
15	A	1.43s	1.64s	(OSO_2CF_3)	7.68s	(C1)	(NH_2)	7.13s
16	A	1.35s	1.53s	(C1)	7.02s	(OSO_2CF_3)	(NH_2)	6.74s
23	B	1.30s	1.52s	(OSO_2CF_3)	7.54s	(Cl)	(N_3)	7.02s
25	B	------ 1.31s ------		8.84	(NO_2)	8.02d	7.38t	7.58d
26	A	------ 1.58s ------		8.10d	(NO_2)	(C1)	7.59d	7.52dd
27	B	------ 1.48s ------		(C1)	7.85d	8.08dd	(NO_2)	8.57d
28	A	------ 1.36s ------		6.70s	(NH_2)	6.71d	7.15	6.56d
29	A	------ 1.42s ------		6.85d	(NH_2)	(C1)	7.27d	6.69dd
30	A	------ 1.46s ------		(C1)	7.29d	6.66dd	(NH_2)	6.77d
31	B	------ 1.41s ------		7.32m	(N_3)	6.58d	------ 7.32m ------	
32	A	------ 1.57s ------		7.31d	(N_3)	(C1)	7.49d	7.16dd
33	A	------ 1.58s ------		(C1)	7.60d	7.17d	(N_3)	7.26s
34	A	------ 1.51s ------		(OSO_2CF_3)	7.28d	6.82m	(NH_2)	7.03
35	A	------ 1.54s ------		(OSO_2CF_3)	7.56s	(C1)	(NH_2)	6.97s
36	A	------ 1.55s ------		(C1)	7.57s	(OSO_2CF_3)	(NH_2)	7.14s

Solvents: A, D_2O; B, [$^2H_6$]DMSO; C, [$^2H_4$]MeOH
[a]Spectra were recorded on a Bruker AC 250 spectrometer. [b]Hydrochloride salt: also shows absorption at δ 9.4-9.5 (br.s, NH^+).

thwarted by the strongly acidic conditions wherein the diaminotriazine fragment is diprotonated and hence non-nucleophilic. Decomposition of the *m*-azidophenyl triazine **11** also led to the introduction of a triflate group into the less-hindered position *ortho* to the triazinyl-substituent yielding compound **14** but in poor isolated yield (38%). When the *ortho*-position was blocked by a chloro group, as in azide **13**, the major product of the reaction (52%) was amine **16**. In these latter reactions other by-products, possibly isomeric, may be formed [6].

Elemental micro-analysis is an unreliable guide to purity in diamino-heterocycles notorious for undergoing partial solvation in the crystalline state; also 1-aryltriazine free bases do not normally give sharp melting points because of their propensity to undergo thermally-induced Dimroth rearrangements. Accordingly, all the compounds prepared in this work were characterised by ^{1}H nmr spectroscopy (see Table 1), mass spectrometry and, for the 1-aryltriazines, by the presence of a characteristic uv absorption in the range λ max 240-250 nm [4]. In a consistent manner all the 1-(*ortho*-substitutedphenyl)triazines showed two sharp singlets for the diastereotopic methyl groups in their ^{1}H nmr spectra with a separation ranging from 0.18-0.36 ppm (Table 1).

Scheme 1



Efforts to extend the scope of this reaction by incorporating alternative nucleophiles (from hydrogen halides, sodium halides, reactive methylenic substrates) in the de-

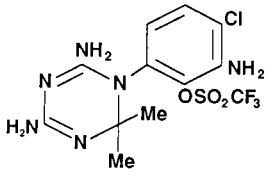
Table 2 Dimroth Rearrangements of 1-Aryl-4,6-diamino-1,3,5-triazines in Bases, and Physical Properties of the Products

Starting triazine	Method	Product	Yield (%)	Mp[a] (°C)	λ max. in water (nm)	ν max. in KBr (cm^{-1})
4[b]	A	**24**[c]	84	136-138[d]	255	
	B	**24**	95			
5[b]	A	**25**	82	130-132	257	
	B	**25**	98			
6[b]	A	**26**	62	154-156	260	
	B	**26**	98			
7[b]	A	**27**	75	142-144	252	
	B	**27**	99			
8[e]	A	**28**	71	180-182	237	
	B	**28**	50			
9[e]	B	**29**	86	150-152	230	
10[e]	B	**30**	57	216-218	243	
11[e]	B	**31**	70	150-155[f]	250	2100[g]
12[e]	B	**32**	43	135-137[f]	252	2100[g]
13[e]	B	**33**	13	165-170[f]	253	2120[g]

Methods: A, Sodium hydroxide-ethanol; B, Pyridine-ethanol.
[a]All compounds were crystallised from ethanol or aqueous ethanol. [b]Hydrocholoride salts. [c]Also isolated when the hydrochloride salt of **4** was refluxed in piperidine, morpholine and 98% hydrazine hydrate in 85%, 88% and 50% yields, respectively. [d]Ref 5. quotes mp 135-137°C. [e]Free base. [f]Melts with decomposition. [g]Azide group.

composition of azide **12** were not successful and only the same triflate **15** was isolated in high yields. Conversion of **15** to the corresponding azide **23** was routinely accomplished: however an attempt to intrude a second triflate group into the phenyl ring by decomposing **23** in TFSA led only to the formation of a complex unseparable mixture.

Facile Dimroth rearrangements are a feature of the chemistry of 1-aryltriazines [4]. In the present work we found that rearrangement of the nitrophenyltriazines **5-7** to the isomers **25-27** could be effected by hot ethanolic sodium hydroxide or preferably (95-100% yields) in refluxing ethanolic pyridine (Table 2). Rearrangements of the



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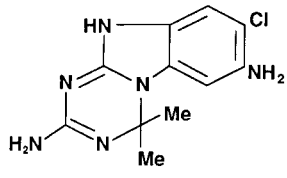

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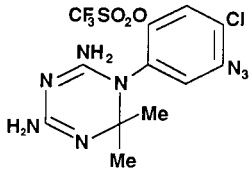

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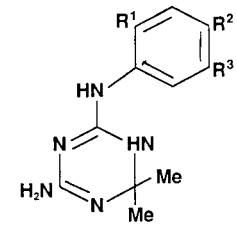
amines **8-10** and azides **11-13** proceeded in lower yields than from the corresponding nitro analogues. The efficiency of the latter rearrangements is due to the electron-withdrawing nitro groups which stabilise the transient dipolar acyclic species implicated as intermediates. In an effort to trap any (electrophilic) acyclic species generated in the rearrangement of the 1-aryltriazine **4** we conducted rearrangement in piperidine, morpholine or hydrazine hydrate: however only the corresponding 4-chloroanilino-isomer **24** was isolated. ^{1}H nmr spectroscopy provided a useful means to monitor conversions of 1-aryltriazines substituted in the *ortho* position. For example, because of restricted rotation about the pivotal inter-ring bond in the case of compound **7** the methyl groups are diastereoisotopic and appear as singlets of equal intensity at δ 1.24 and 1.60: these are replaced by a singlet at 1.48 in the Dimroth rearrangement product **27**.

Decomposition of the azidoanilinotriazines **31-33**, best prepared from the nitro compounds **25-27** by stannous chloride reduction to amines **28-30** followed by diazotisation-azidation, rather than the inefficient Dimroth rearrangement route, were converted to the triflates **34-36**, respectively, in poor to moderate yields in TFSA at 0°.



	R^1	R^2	R^3
24	H	Cl	H
25	H	H	NO_2
26	H	Cl	NO_2
27	Cl	H	NO_2
28	H	H	NH_2
29	H	Cl	NH_2
30	Cl	H	NH_2
31	H	H	N_3
32	H	Cl	N_3
33	Cl	H	N_3
34	OSO_2CF_3	H	NH_2
35	OSO_2CF_3	Cl	NH_2
36	Cl	OSO_2CF_3	NH_2

EXPERIMENTAL

Details of ^{1}H nmr spectra are recorded in Table 1. All compounds had appropriate molecular ions by EI mass spectrometry recorded on a VG Micromass 12 instrument operating at 70 eV, with a source temperature 200-300°. The ir spectra were recorded on a Mattson Instruments 2020 Galaxy Series FT-IR spectrometer as potassium bromide discs. The uv spectra were measured in 95% ethanol on a Unicam SP 8000 spectrometer: elsewhere ethanol refers to absolute ethanol.

Synthesis of 1-(Nitroaryl)-1,3,5-triazines by the Three-component Synthesis.

The known hydrochloride salt **5** was prepared by reacting 3-nitroaniline (0.1 molar equivalent), cyanoguanidine (0.11 molar equivalent), 10*N*-hydrochloric acid (10 ml) in refluxing acetone (100 ml) for 4 hours. The reaction mixture was cooled and the product (88%), mp 195-196° (lit [7] mp 195-196°) was collected and washed with acetone. The following new compounds were also prepared: 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(4-chloro-3-nitrophenyl)-1,3,5-triazine hydrochloride **6** (80%), mp 225-228° from aqueous ethanol; λ max 240 nm, from 4-chloro-3-nitroaniline; 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(2-chloro-5-nitrophenyl)-1,3,5-triazine hydrochloride **7** (51%), mp 220-225°, from water, λ max 242 nm, from 2-chloro-5-nitroaniline; and 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-azidophenyl)-1,3,5-triazine hydrochloride **11** (64%), mp 210° dec, from ethanol, ν max 2160 cm^{-1} (N_3), from 3-azidoaniline.

Anal. Calcd. for $C_{11}H_{14}N_8 \cdot HCl$: C, 44.8; H, 5.1; N, 38.0. Found: C, 44.9; H, 5.1; N, 38.2.

Reduction of 1-(Nitrophenyl)-1,3,5-triazines.

A suspension of the hydrochloride salt **5** (4.0 g), tin(II) chloride dihydrate (11 g) in 10*N*-hydrochloric acid (35 ml) was stirred at 20° for 24 hours. The white solid was collected, basified with 5*N*-sodium hydroxide solution at 0° and afforded 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-aminophenyl)-1,3,5-triazine free base **8**

(87%), mp 60-64°; λ max 240 nm. Similarly prepared were the following: 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-amino-4-chlorophenyl)-1,3,5-triazine **9** (96%), mp 150-155°; λ max 240 nm, from nitrotriazine **6**; and 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-amino-6-chlorophenyl)-1,3,5-triazine **10** (87%), mp 65-70°; λ max 241 nm, from nitrotriazine **7**.

Synthesis of 1-(Azidophenyl)-1,3,5-triazines.

A mixture of the 1-(3-aminophenyl)-1,3,5-triazine **8** (2.5 g) in 5*N*-hydrochloric acid (30 ml) was diazotised at 0° with a solution of sodium nitrite (0.76 g) in water (5 ml) over 1 hour. Sodium azide (2.86 g) was added, in portions, and the mixture was stirred at 0° until effervescence ceased (1 hour). 4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(3-azidophenyl)-1,3,5-triazine free base **11** (2.6 g, 90%) was precipitated from the mixture with excess 5*N*-sodium hydroxide solution at 0° and had mp 145-150° dec; λ max 245 nm, ν max 2140 cm^{-1} (N_3). Similarly prepared were the following: 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-azido-4-chlorophenyl)-1,3,5-triazine **12** (70%), mp 146-153° dec; λ max 246 nm, ν max 2140 cm^{-1} (N_3), from aminotriazine **9**; 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-azido-6-chlorophenyl)-1,3,5-triazine **13** (94%), mp 140-145° dec; λ max 249 nm, ν max 2120 cm^{-1} (N_3), from aminotriazine **10**; and 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-azido-4-chloro-6-trifluoromethanesulphonyloxyphenyl)-1,3,5-triazine **23** (75%), mp 160-161° dec; λ max 250 nm, ν max 2100 cm^{-1} (N_3), from aminotriazine **15**.

Decomposition of 1-(Azidophenyl)-1,3,5-triazines in Trifluoromethanesulphonic Acid.

The azidophenyltriazine free base **11** (0.9 g) was added in small portions to a stirred mixture of trifluoromethanesulphonic acid (5 ml), trifluoroacetic acid (8 ml) and trifluoroacetic anhydride (1 ml) at 0° until effervescence ceased. The stirred mixture was kept at 20° for 12 hours, basified with concentrated aqueous ammonia and the pink solid, 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-amino-6-trifluoromethylsulphonyloxyphenyl)-1,3,5-triazine **14** (38%), mp 118-120°; λ max 245 nm, was collected. Similarly prepared were the following: 4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(3-amino-4-chloro-6-trifluoromethylsulphonyloxyphenyl)-1,3,5-triazine **15** (98%), mp 170-174°; λ max 245 nm, from azidophenyltriazine **12**; and 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-amino-6-chloro-4-trifluoromethylsulphonyloxyphenyl)-1,3,5-triazine **16** (52%), mp 118-124°, λ max 241 nm, from azidophenyltriazine **13**.

Dimroth Rearrangements of 1-Aryl-1,3,5-triazines.

Two methods were employed to effect these rearrangements. In Method A (see Table 2) the triazine (1.0 g) was boiled (1.5 hours) in a mixture of aqueous 1*N*-sodium hydroxide (5 ml) and ethanol (5 ml). Products were collected and washed with water. In Method B the triazine (1.0 g) was refluxed in a mixture of pyridine (2 ml) and ethanol (5 ml) for 12 hours. Removal of solvents by vacuum evaporation afforded the rearranged products which were collected and washed with water.

Decomposition of 6-Anilino-1,3,5-triazines in Trifluoromethanesulphonic Acid.

The azidoanilinotriazine free base **31** (0.9 g) was decomposed in trifluoromethanesulphonic acid in a trifluoroacetic acid-trifluoroacetic anhydride mixture at 0° in the manner described above for the 1-(azidophenyl)-1,3,5-triazine isomer **11**. The product, 4-amino-6-(3-amino-6-trifluoromethylsulphonyloxyanilino)-1,2-dihydro-2,2-dimethyl-1,3,5-triazine **34** (60%) had mp 155-157°. Similarly prepared were the following: 4-amino-6-(3-amino-4-chloro-6-trifluoromethylsulphonyloxyanilino)-1,2-dihydro-2,2-dimethyl-1,3,5-triazine **35** (37%), mp 130-132°, from triazine **32**; 4-amino-6-(3-amino-6-chloro-4-trifluoromethylsulphonyloxyanilino)-1,2-dihydro-2,2-dimethyl-1,3,5-triazine **36** (55%), mp 120-122°, from triazine **33**.

REFERENCES AND NOTES

[1] B. Birdsall, S. J. B. Tendler, J. R. P. Arnold, J. Feeney, R. J. Griffin, M. D. Carr, J. A. Thomas, G. C. K. Roberts, and M. F. G. Stevens, *Biochemistry*, **29**, 9660 (1990).

[2] S. J. B. Tendler, R. J. Griffin, B. Birdsall, M. F. G. Stevens, G. C. K. Roberts, and J. Feeney, *FEBS Letters*, **240**, 201 (1988).

[3] C. E. Sansom, C. H. Schwalbe, P. A. Lambert, R. J. Griffin, and M. F. G. Stevens, *Biochim. Biophys. Acta*, **995**, 21 (1989).

[4] E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956).

[5] E. A. Bliss, R. J. Griffin, and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 2217 (1987).

[6] Recent work on the decomposition of 2-(4-azidophenyl)benzothiazoles in trifluoromethanesulphonic acid has revealed that mixtures of isomeric triflates and bimolecular coupling products can be formed: M. A. Castro and M. F. G. Stevens, *J. Chem. Soc., Chem. Commun.*, 869 (1992).

[7] R. J. A. Walsh, K. R. H. Wooldridge, D. Jackson, and J. Gilmour, *Eur. J. Med. Chem.*, **12**, 495 (1977).