A General Synthesis of *s*-Triazolo[1,5-*x*]diazines (I)

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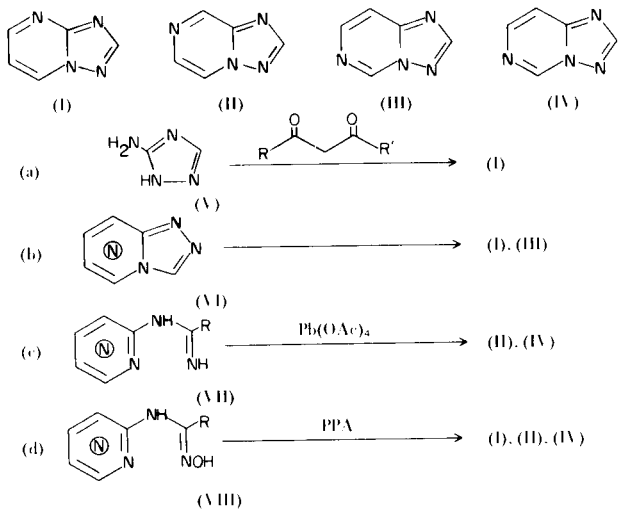
Treatment of 2-aminopyrimidine, a 4-aminopyrimidine, aminopyrazine, and 3-aminopyridazines with *O*-mesitylenesulfonylhydroxylamine gave the corresponding *N*-aminodiazinium salts in high yields. These salts could be transformed into *s*-triazolo[1,5-*a*]pyrimidines, *s*-triazolo[1,5-*a*]-pyrazines, *s*-triazolo[1,5-*c*]pyrimidines, and *s*-triazolo[1,5-*b*]pyridazines by treatment with acylating agents.

s-Triazolo[1,5-*x*]diazines (I-IV) have been prepared by the following four routes; (a) the reaction of 3-amino-*s*-triazole (V) with 1,3-dicarbonyl compounds (2), (b) a Dimroth rearrangement of *s*-triazolo[4,3-*a*]pyrimidines and *s*-tirazolo[4,3-*c*]pyrimidines (VI) (3), (c) oxidative cyclization of azinylamidines (VII, R = Me or Ph) with lead tetraacetate (4), and (d) a dehydrative cyclization of oximes (VIII) with polyphosphoric acid (5). However, route (a) is limited only to the preparation of *s*-triazolo[1,5-*a*]-pyrimidines (I) and route (b) is applicable only to the syntheses of I and *s*-triazolo[1,5-*c*]pyrimidines (III). Routes (c) and (d) appear to be more general for these ring systems, but have disadvantage in the scope due to the inherent synthetic difficulty of the intermediates VII (*e.g.*, R = H) and VIII (*e.g.*, R ≠ H).

Chart 1



Recently we have shown that *O*-mesitylenesulfonylhydroxylamine (MSH) (IX) (6) can easily aminate a variety of heteroaromatic amines to give the corresponding *N*-amino salts (7). We have now applied this *N*-amination

Chart 2

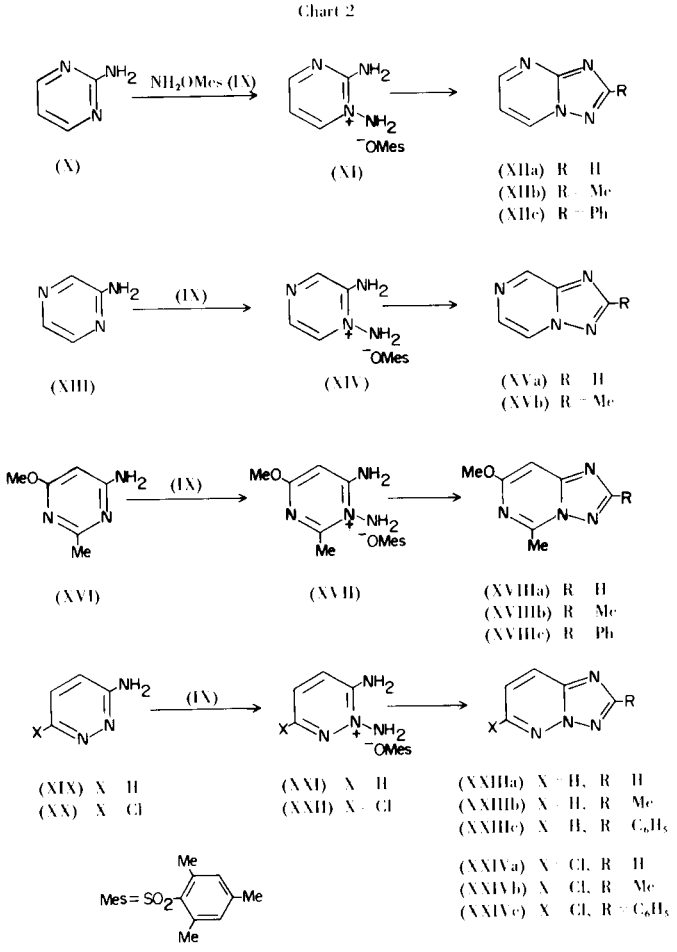


TABLE I

N-Aminodiazinium Mesitylenesulfonates

Compd.	M.p. °C	Yield %	Formula	Anal.	C%	H%	N%
XI	150-152	73	$C_{13}H_{18}N_4O_3S \cdot \frac{1}{2}H_2O$	Calcd.	48.89	5.99	17.54
				Found	49.21	6.26	17.79
XIV	205-206	87	$C_{13}H_{18}N_4O_3S$	Calcd.	50.31	5.85	18.06
				Found	50.19	5.94	18.27
XVII	181-182	84	$C_{15}H_{22}N_4O_4S$	Calcd.	50.84	6.26	15.81
				Found	50.93	6.27	15.51
XXI	139-140	72	$C_{13}H_{18}N_4O_3S$	Calcd.	50.31	5.85	18.06
				Found	50.27	5.99	17.75
XXII	244-245	89	$C_{13}H_{17}ClN_4O_3S$	Calcd.	45.29	4.97	16.24
				Found	45.17	5.08	16.24

reaction to a series of aminodiazines, and examined cyclization reaction of the resulting *N*-aminodiazinium salts, which might provide a novel and general route to *s*-triazolo[1,5-*x*]-diazine ring systems. The second step has already been successfully applied to the pyridine (8) and thiazole cases (9).

The desired *N*-aminodiazinium salts (XI, XIV, XVII, XXI, XXII) were obtained in high yields by treatment of the corresponding parent aminodiazines (X, XIII, XVI, XIX, XX) with MSH (IX) in chloroform at room temperature for 15 minutes (Table I). It should be noted that, except for the case of symmetric 2-aminopyrimidine (X), the amination could be expected to take place at either one of two nitrogen atoms in the ring, in principle. The fact that these *N*-aminodiazinium salts undergo cyclization with acylating agents indicates that the *N*-amination takes place preferentially at the nitrogen atom adjacent to the amino group. This may be related to the enhancement of the basicity of the nitrogen atom.

Cyclization of these *N*-aminodiazinium salts into *s*-triazolo[1,5-*x*]diazines was effected by heating with formic acid, acetic anhydride, and benzoyl chloride. The yields of the products largely depend on the reaction temperature. In general, the higher temperature gave the higher yeilds if the starting *N*-aminodiazinium salt or the product is stable at the temperature. Compounds (XIIa, XIIb, XVa, XVb, XXIIIa, XXIIIc, XXIVa, XXIVc) were identified by comparisons of the melting points or spectral data with the reported data.

It may be interesting to examine the effect of the second nitrogen atom in the six-membered ring on the uv and mass spectra. The positions of the uv absorption maxima of the heterocycles (XII, XV, XXIII) are not significantly affected by the position of the nitrogen atom in the six-membered ring. Thus, they in general have two main absorption maxima at 207-211 and 272-284 nm, while the 2-phenyl derivatives show rather complex spectra with the longest absorption maxima at 300-306 nm because of conjugation. For comparison, 2-methyl-*s*-triazolo[1,5-*a*]pyridine reportedly has absorption maxima at 217 and 273 nm (10). In the mass spectrum of XVa (11), the important fragmentation path involves the successive loss of HCN from the molecular ion, while the primary fragmentation path of XXIIIa is the loss of nitrogen from the molecular ion to give the ion at m/e 92 which further loses HCN. Compound XIIa shows both the fragmentations to give the ions at m/e 93 and 92.

EXPERIMENTAL

All melting points are uncorrected. The uv spectra were recorded on an Hitachi 124 spectrophotometer, nmr spectra on an Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Low and high resolution mass spectra were obtained with an Hitachi RMU-6D and a JEOL-JMS-01SG instrument with a direct inlet system, operating at 70 eV. Preparative tlc was carried out on Merck Alumina PF_{254}.

Material.

2-Aminopyrimidine (X) was obtained commercially. Aminopyrazine (XIII) (14), 4-amino-6-methoxy-2-methylpyrimidine (XVI) (15), 3-aminopyridazine (XIX) (16) and 3-amino-6-chloropyridazine (XX) (16), were prepared following procedures reported in the literature.

General Procedure for *N*-Aminodiazinium Mesitylenesulfonates (XI, XIV, XVII, XXI, and XXII).

To an ice-cooled solution of aminodiazines (2 mmoles) in chloroform (4 ml.) (in the cases of XIX and XX, methanol (4 ml.) was used) was added dropwise a solution of MSH (2 mmoles) in chloroform (4 ml.). The reaction mixture was stirred at room temperature for 15 minutes. After addition of ether, the precipitated crystals of *N*-aminodiazinium mesitylenesulfonates were collected and recrystallized from methanol-ether. The elemental analyses, yields, and melting points are summarized in Table I.

General Procedure for *s*-Triazolo[1,5-*x*]diazines.

N-Aminodiazinium mesitylenesulfonates were heated with formic acid, acetic anhydride, or benzoyl chloride. The reaction mixture was made alkaline with 20% sodium hydroxide and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and concentrated. The product was

isolated by preparative tlc using chloroform as solvent and purified further by recrystallization. In the cases of XXIIIa-c and XXIVa-c, the reaction proceeded cleanly to give a single product which was directly purified by recrystallization. Unless otherwise stated, recrystallization was carried out from chloroform-petroleum ether (b.p. 30-60°).

s-Triazolo[1,5-*a*]pyrimidine (XIIa).

Refluxing a solution of XI (621 mg.) in formic acid (2 ml.) for 1 hour gave XIIa, m.p. 144-145° [lit. (12) 140-142°], yield, 38 mg. (16%); uv λ max (ethanol): 208 nm (log ε 4.51), 272 (3.62); mass spectrum m/e (rel. intensity): 120 (M^+, 100), 93 (5), 92 (6), 66 (19), 65 (11); the nmr spectrum was in agreement with the published data (13).

Anal. Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 49.83; H, 3.36; N, 46.60.

2-Methyl-*s*-triazolo[1,5-*a*]pyrimidine (XIIb).

Heating a solution of XI (310 mg.) in acetic anhydride at 160° (bath temperature) for 4 hours gave XIIb, m.p. 132-132.5°, yield, 51 mg. (38%); uv λ max (ethanol): 211 nm (log ε 4.48), 278 (3.64); mass spectrum m/e (rel. intensity): 134 (M^+, 100), 106 (21), 93 (11), 80 (60), 66 (23); the nmr spectrum was in agreement with the published data (13).

Anal. Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.76; H, 4.62; N, 41.73.

2-Phenyl-*s*-triazolo[1,5-*a*]pyrimidine (XIIc).

Heating a solution of XI (931 mg.) in benzoyl chloride (2 ml.) at 150° (bath temperature) for 1 hour gave XIIc, m.p. 185-185.5°, yield, 47 mg. (8%); uv λ max (ethanol): 242 nm (4.49), 278 sh (3.96), 286 sh (3.85), 300 (4.04); nmr (deuteriochloroform): τ 1.10 (q, 1H, H-5, $J_{5,6}$ = 6.5, $J_{5,7}$ = 2.0 Hz), 1.19 (q, 1H, H-7, $J_{6,7}$ = 4.4, $J_{5,7}$ = 2.0 Hz), 2.90 (q, 1H, H-6, $J_{6,7}$ = 4.4, $J_{5,6}$ = 6.5 Hz), 1.53-1.70 (m, 2H), 2.39-2.55 (m, 3H); mass spectrum m/e (rel. intensity): 196 (M^+, 100), 195 (22), 170 (11), 143 (13).

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.33; H, 4.11; N, 28.56. Found: C, 67.06; H, 4.21; N, 28.30.

s-Triazolo[1,5-*a*]pyrazine (XVa).

Refluxing a solution of XIV (310 mg.) in formic acid (1 ml.) for 1 hour gave XVa, m.p. 125-126° [lit. (5) 127°], yield, 30 mg. (25%); uv λ max (ethanol): 207 nm (log ε 4.60), 280 (3.75); both the nmr (5) and mass spectra (11) were in agreement with the reported data.

Anal. Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 50.02; H, 3.47; N, 46.56.

2-Methyl-*s*-triazolo[1,5-*a*]pyrazine (XVb).

Heating a solution of XIV (310 mg.) in acetic anhydride (1 ml.) at 180° (bath temperature) for 5 minutes gave XVb, m.p. 130-132° [lit. (4a) 132°], yield, 64 mg. (48%); uv λ max (ethanol): 210 nm (log ε 4.46), 282 (3.63); mass spectrum m/e (rel. intensity): 134 (M^+, 100), 107 (6), 106 (9), 93 (14), 80 (14), 66 (74); the nmr spectrum was in agreement with the reported data (4b).

Anal. Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.44; H, 4.56; N, 41.71.

7-Methoxy-5-methyl-*s*-triazolo[1,5-*c*]pyrimidine (XVIIIa).

Heating a solution of XVII (1.77 g.) in formic acid (2 ml.) in a sealed tube at 180° for 15 minutes gave XVIIIa, m.p. 103-104°, yield, 10 mg. (1.2%); uv λ max (ethanol): 208 nm (log ε 4.43), 257 (3.93), 283 (3.53); nmr (deuteriochloroform): τ 1.80 (s, 1H, H-2), 3.23 (s, 1H, H-8), 6.00 (s, 3H, OCH_3), 7.07 (s, 3H, CH_3); mass spectrum: m/e 164 (M^+).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.33; H, 5.01; N, 34.14.

7-Methoxy-2,5-dimethyl-*s*-triazolo[1,5-*c*]pyrimidine (XVIIIb).

Heating a solution of XVII (354 mg.) in acetic anhydride (1 ml.) at 180° for 15 minutes gave XVIIIb, m.p. 136-137°, yield, 101 mg. (57%); uv λ max (ethanol): 211 nm (log ε 4.52), 258 (3.83), 283 (3.46); nmr (deuteriochloroform): τ 3.30 (s, 1H, H-8), 6.00 (s, 3H, OCH_3), 7.10 (s, 3H, CH_3), 7.45 (s, 3H, CH_3); mass spectrum: m/e 178 (M^+).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.93; H, 5.77; N, 31.59.

7-Methoxy-5-methyl-2-phenyl-*s*-triazolo[1,5-*c*]pyrimidine (XVIIIc).

Heating a solution of XVII (354 mg.) in benzoyl chloride (1 ml.) at 180° (bath temperature) for 15 minutes gave XVIIIc, m.p. 131-131.5° (from acetone), yield, 48 mg. (19%); uv λ max (ethanol): 245 nm (log ε 4.75), 283 sh (3.67), 296 (3.59); nmr (deuteriochloroform): τ 1.6-1.8 (m, 2H), 2.48-2.58 (m, 3H), 3.23 (s, 1H, H-8), 6.03 (s, 3H, OCH_3), 7.09 (s, 3H, CH_3); mass spectrum: m/e 240 (M^+).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.13; H, 5.04; N, 23.42.

s-Triazolo[1,5-*b*]pyridazine (XXIIIa).

Heating a solution of XXI (310 mg.) in formic acid (1 ml.) in a sealed tube at 200° (bath temperature) for 15 minutes gave XXIIIa, m.p. 157-158° [lit. (5) 138-142°], yield, 80 mg. (67%); uv λ max (ethanol): 208 nm (log ε 4.56), 277 (3.57); mass spectrum m/e (rel. intensity); 120 (M^+, 100, $C_5H_4N_4$), 92 (14, $C_5H_4N_2$), 65 (25, C_4H_3N). The nmr spectrum was in agreement with the reported data (5).

Anal. Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 50.01; H, 3.41; N, 46.18.

2-Methyl-*s*-triazolo[1,5-*b*]pyridazine (XXIIIb).

Heating a solution of XXI (310 mg.) in acetic anhydride (1 ml.) at 200° (bath temperature) gave XXIIIb, m.p. 110-112°, yield, 100 mg. (75%); uv λ max (ethanol): 211 nm (log ε 4.43), 284 (3.50); nmr (deuteriochloroform): τ 1.50 (q, 1H, H-6, $J_{6,7}$ = 4.5, $J_{6,8}$ = 2.0 Hz), 1.92 (q, 1H, H-8, $J_{7,8}$ = 9.5, $J_{6,8}$ = 2.0 Hz), 2.57 (q, 1H, H-7, $J_{7,8}$ = 9.5, $J_{6,7}$ = 4.5 Hz); mass spectrum m/e (rel. intensity): 134 (M^+, 100, $C_6H_6N_4$), 106 (9, $C_6H_6N_2$), 105 (7, $C_6H_5N_2$), 93 (1), 80 (8), 79 (13, C_5H_5N), 65 (36).

Anal. Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.90; H, 4.64; N, 41.84.

2-Phenyl-*s*-triazolo[1,5-*b*]pyridazine (XXIIIc).

Heating a solution of XXI (310 mg.) in benzoyl chloride (1 ml.) at 200° (bath temperature) for 15 minutes gave XXIIIc, m.p. 128° [lit. (4c) 131-132°], yield, 100 mg. (55%); uv λ max (ethanol): 239 nm (log ε 4.47), 247 sh (4.38), 277 sh (3.80), 284 (3.83), 306 (3.97); mass spectrum m/e (rel. intensity): 196 (M^+, 100, $C_{11}H_8N_4$), 168 (8, $C_{11}H_8N_2$), 142 (4), 141 (3), 140 (4), 103 (10). Mixed m.p. determination and comparison of the ir and nmr spectra with an authentic sample given by Prof. M. Tišler showed the two compounds to be identical.

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.33; H, 4.11; N, 28.56. Found: C, 67.38; H, 4.23; N, 28.73.

6-Chloro-*s*-triazolo[1,5-*b*]pyridazine (XXIVa).

Heating a solution of XXII (345 mg.) in formic acid (1 ml.) in a sealed tube at 200° for 30 minutes gave XXIVa, m.p. 144-145° [lit.

(5) 135-138°], yield, 120 mg. (78%); uv λ max (ethanol): 213 nm (log ε 4.49), 286 (3.49); mass spectrum: m/e 156, 154 (M^+). The nmr spectrum was in agreement with the reported data (5).

Anal. Calcd. for $C_5H_3ClN_4$: C, 38.85; H, 1.96; N, 36.25. Found: C, 39.04; H, 2.06; N, 36.27.

6-Chloro-2-methyl-*s*-triazolo[1,5-*b*]pyridazine (XXIVb).

Heating a solution of XXII (345 mg.) in acetic anhydride (1 ml.) at 210° (bath temperature) for 30 minutes gave XXIVb, m.p. 123°, yield, 146 mg. (87%); uv λ max (ethanol): 215 nm (log ε 4.49), 295 (3.57); nmr (deuteriochloroform): τ 1.92 (d, 1H, H-8, $J_{7,8}$ = 9.5 Hz), 2.54 (d, 1H, H-7, $J_{7,8}$ = 9.5 Hz), 7.33 (s, 3H, CH_3); mass spectrum: m/e 170, 168 (M^+).

Anal. Calcd. for $C_6H_5ClN_4$: C, 42.75; H, 2.96; N, 33.23. Found: C, 42.84; H, 3.01; N, 33.27.

6-Chloro-2-phenyl-*s*-triazolo[1,5-*b*]pyridazine (XXIVc).

Heating a solution of XXII (345 mg.) in benzoyl chloride (1 ml.) at 210° (bath temperature) for 15 minutes gave XXIVc, m.p. 197-198° [lit. (4c) 174-175°], yield 170 mg. (74%); uv λ max (ethanol): 244 nm (log ε 4.44), 250 sh (4.39), 278 sh (3.69), 286 (3.48), 318 (3.96); mass spectrum: m/e 232, 230 (M^+). Mixed m.p. determination and comparison of the ir and nmr spectra with a sample (melted at 194-195° in our hands) given by Prof. M. Tišler showed the two compounds to be identical.

Anal. Calcd. for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.16; H, 3.04; N, 23.99.

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