The Synthesis of Condensed 1,3,5-Triazinium Perchlorates from Diazaiminium Intermediates

George B. Okide

Department of Pharmaceutical Chemistry, University of Nigeria,
Nsukka, Nigeria

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The known azaiminium intermediate, 1-chloro-1,3-bis(dimethylamino)-3-phenyl-2-azaprop-2-en-1-ylium perchlorate **1** [1], reacts with 2-aminothiazole to yield the fully conjugated condensed 1,3,5-triazinium salt **7**. Various suitably substituted heterocyclic compounds react similarly to afford the corresponding condensed 1,3,5-triazinium salts. The diazaiminium intermediates **2-5** obtained from several secondary amides give identical products when treated with the same starting compounds. The procedure appears to be of wide application.

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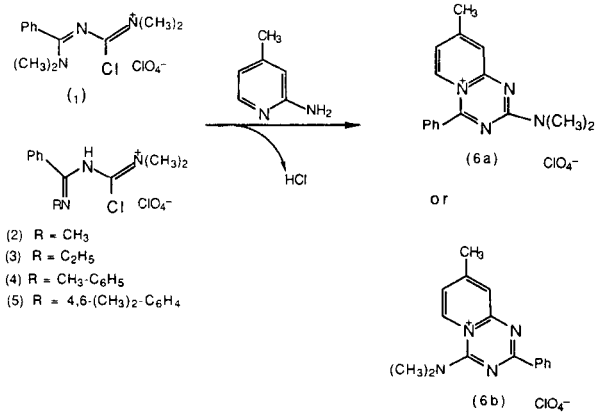
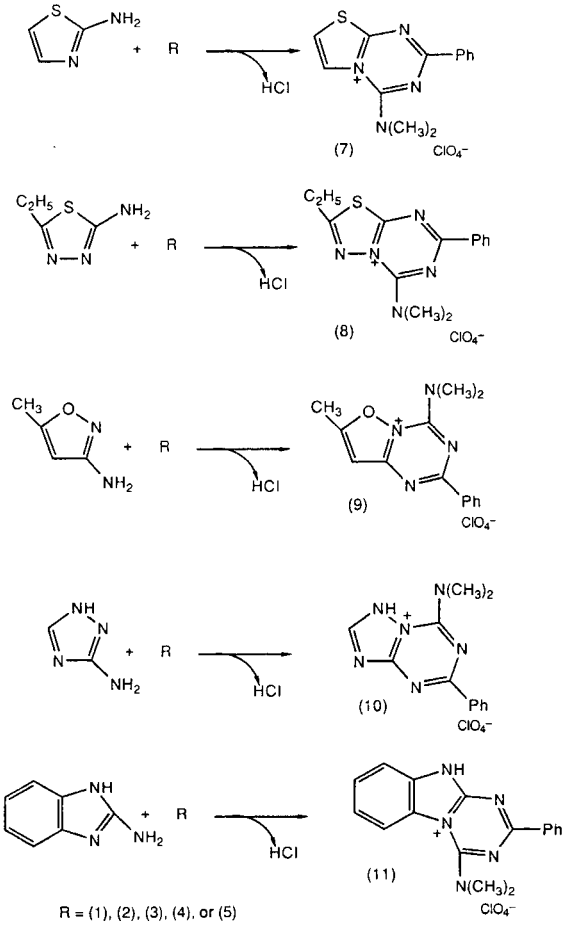
In an earlier report [1] we showed that azaiminium intermediates such as **1**, formed from the reaction of the tertiary amide *N,N*-dimethylbenzamide-phosphorus oxychloride complex and dimethylcyanamide when treated with 2-amino-4-methylpyridine afforded the condensed pyrido[1,2-*a*]-1,3,5-triazinium salt whose structure was unequivocally determined to be **6b** by X-ray crystallography and refinement. Identical intermediates **2-5** obtained from secondary amides reacted similarly to afford **6b**. The reaction was extended to other 2-aminopyridines as shown.

Scheme 1



The present work is an attempt to further extend the scope of this procedure. We have successfully prepared a variety of heteroatomic condensed 1,3,5-triazinium compounds as part of our continuing efforts to obtain target compounds to be screened for antimalarial activity. This objective was the result of the observation that the known prophylactic drug, proguanil, a biguanide, acts through the metabolite, a cyclized triazine cycloguanil [2]. It was, therefore, hoped that these compounds might possess some biological activity. We found that when **1, 2, 3, 4** or **5** was treated with 2-aminothiazole in refluxing acetonitrile the fully conjugated condensed 1,3,5-triazinium perchlorate **7** was obtained in about 40% yield. Similarly 2-amino-5-ethyl-1,3,4-thiadiazole, 3-amino-5-methylisoxazole, 3-amino-1,2,4-triazole and 2-aminobenzimidazole afforded **8, 9, 10** and **11**, respectively as shown.

Scheme 2



EXPERIMENTAL

Melting points were determined with a Gallenkamp electrically heated block and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer, incorporated with a data station, for nujol mulls on sodium chloride plates, unless stated otherwise. Ultraviolet spectra were recorded in the indicated solvent on a 402 spectrophotometer incorporated with a data station. The ^1H nmr spectra were recorded on a Bruker

WM 250 (250 MHz), a Nicolet NT 200 (200 MHz) or a Perkin Elmer R 32 (90 MHz) spectrometer. The data are recorded as the chemical shifts (δ) in parts per million (ppm) followed by integral, multiplicity and coupling constant (J in Hz) of the particular proton. Mass spectra were recorded with a Micromass instrument 16F, incorporated with a data system Vg 2000, at 35 and 70 electron volts. Thin-layer chromatography (tlc) was conducted with Merck 60GF254 precoated silica gel plates. Drying and/or purification of organic solvents was done as described by Riddick and Bunger [3].

General Procedure for the Preparation of the Condensed 1,3,5-Triazinium Perchlorates **7-11**.

The amino compound (6 mmoles) was added to a solution of 1-chloro-1,3-bis(dimethylamino)-3-phenyl-2-azaprop-2-enylium perchlorate (**1**) [1] (2.00 g, 6 mmoles) in acetonitrile (20 ml), and the solution was heated under reflux for 1 hour. It was allowed to cool and then poured into a large excess of crushed ice. When all the ice had melted the solid formed was collected and purified by crystallization from the solvent or solvent system.

The following perchlorates were obtained:

4-Dimethylamino-2-phenylthiazolo[3,2-*a*]-1,3,5-triazinium Perchlorate (**7**).

2-Aminothiazole (0.59 g, 6 mmoles) gave **7** in 40% yield (0.80 g), mp 257-258° from acetic acid; ir: ν max 1627 (C=N$^+$), 1600 (C=C), 1077 cm^{-1} (ClO_4^-); ^{1}H nmr (DMSO-d_6): δ 3.35 (3H, s, NMe), 3.56 (3H, s, NMe), 7.62-7.75 (3H, t, Ph, J = 7.50 Hz), 8.01 (1H, d, H-7, J = 5 Hz), 8.50 (2H, d, Ph, J = 7.50 Hz), 8.60 (1H, d, H-6, J = 5 Hz); ms: m/z 242 (10), 227 (3), 187 (100), 77 (33), 44 (5).

Anal. Calcd. for $C_{13}H_{13}ClN_4O_4S$: C, 43.76; H, 3.67; N, 15.70. Found: C, 44.00; H, 3.47; N, 15.90.

7-Ethyl-4-dimethylamino-2-phenyl-1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazinium Perchlorate (**8**).

2-Amino-5-ethyl-1,3,4-thiadiazole (0.77 g, 6 mmoles) gave **8** in 45% yield (1.03 g), mp 148-149° from acetonitrile/ethyl acetate; ir: ν max 1645 (C=N$^+$), 1596 (C=C), 1084 cm^{-1} (ClO_4^-); ^{1}H nmr (DMSO-d_6): δ 1.39 (3H, t, CMe, J = 7.50, 15.00); 3.30 (2H, q, CH_2, J = 7.50, 15.00), 3.63 (3H, s, NMe), 3.78 (3H, s, NMe), 7.63-7.83 (3H, m, Ph), 8.50 (2H, d, Ph, J = 7.50 Hz); ms: m/z 285 (14), 256 (24), 216 (6), 189 (100), 104 (25), 103 (20), 77 (58), 44 (43).

Anal. Calcd. for $C_{14}H_{16}ClN_5O_4S$: C, 43.57; H, 4.19; N, 18.15. Found: C, 43.40; H, 3.99; N, 18.00.

7-Methyl-4-dimethylamino-2-phenylisoxazolo[2,3-*a*]-1,3,5-triazinium Perchlorate (**9**).

3-Amino-5-methylisoxazole (0.58 g, 6 mmoles) gave **9** in 44% yield (0.92 g), mp 185-186° from acetic acid; ir: ν max 1645 (C=N$^+$), 1591 (C=C), 1092 cm^{-1} (ClO_4^-); ^{1}H nmr (DMSO-d_6): δ 3.37 (3H, s, CMe), 3.56 (3H, s, NMe), 3.70 (3H, s, NMe), 7.34 (1H, s, H-8), 7.60-7.66 (3H, m, Ph), 8.50 (2H, d, Ph, J = 7.50 Hz); ms: m/z 254 (11), 240 (55), 228 (49), 200 (100), 104 (21), 103 (5), 77 (27), 44 (53).

Anal. Calcd. for $C_{14}H_{15}ClN_4O_5$: C, 47.40; H, 4.26; N, 15.79. Found: C, 47.20; H, 4.23; N, 15.49.

4-Dimethylamino-2-phenyl-1,2,4-triazolo[4,3-*a*]-1,3,5-triazinium Perchlorate (**10**).

3-Amino-1,2,4-triazole (0.5 g, 6 mmoles) gave **10** in 37% yield (0.75 g), mp 246-248° from acetic acid; uv (acetonitrile): λ max 212 (ϵ 20,000), 256 nm (ϵ 41,000); ir: ν max 3331, 3140 (NH), 1670, 1625 (C=N$^+$), 1601, 1589 (C=C), 1071 cm^{-1} (ClO_4^-); ^{1}H nmr (DMSO-d_6): δ 3.51 (3H, s, NMe), 3.57 (3H, s, NMe), 7.57-7.67 (3H, m, Ph), 8.44 (2H, m, Ph), 8.46 (1H, s, H-7), 9.54 (1H, s, NH); ms: m/z 240 (100), 225 (17), 211 (25), 196 (6), 171 (99), 104 (17), 103 (15), 77 (21), 44 (26).

Anal. Calcd. for $C_{12}H_{13}ClN_6O_4$: C, 42.67; H, 3.85; N, 24.65. Found: C, 42.30; H, 3.65; N, 24.55.

4-Dimethylamino-2-phenyl-1,3,5-triazino[1,2-*a*]benzimidazolinium Perchlorate (**11**).

2-Aminobenzimidazole (0.77 g, 6 mmoles) gave **11** in 45% yield (1.03 g), mp 219-220° from acetic acid; uv (acetonitrile): λ max 210 (ϵ 19,500), 269 (ϵ 39,000), 352 nm (ϵ 10,200); ir: ν max 3332, (NH), 1654, 1628 (C=N$^+$), 1594 (C=C), 1098 cm^{-1} (ClO_4^-); ^{1}H nmr (DMSO-d_6): δ 3.29 (3H, s, NMe), 3.57 (3H, s, NMe), 7.20-7.40 (1H, br d, NH), 7.48-7.52 (1H, t, H-8, J = 7.50, 15.00 Hz), 7.56-7.68 (4H, m, H-7 & Ph), 7.76 (1H, d, H-6, J = 7.50 Hz), 8.00 (1H, d, H-9, J = 7.50 Hz), 8.50 (2H, dd, Ph); ms: m/z 289 (68), 274 (11), 259 (5), 245 (5), 219 (100), 103 (7), 77 (11), 44 (9).

Anal. Calcd. for $C_{17}H_{16}ClN_5O_4$: C, 52.34; H, 4.14; N, 17.97. Found: C, 52.70; H, 4.40; N, 18.10.

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