

Synthesis and reactions of [1,2,4]triazolo[1,5-*a*]pyrimidinium-2-aminides

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[1,2,4]Triazolo[1,5-*a*]pyrimidinium-2-aminides were synthesised by treating an appropriate triazolo[1,5-*a*]pyrimidinium salt with sodium hydroxide or from the reaction of 4-alkyl-3,5-diamino-1,2,4-triazoles with pentane-2,4-dione or 1,1,3,3-tetramethoxypropane.

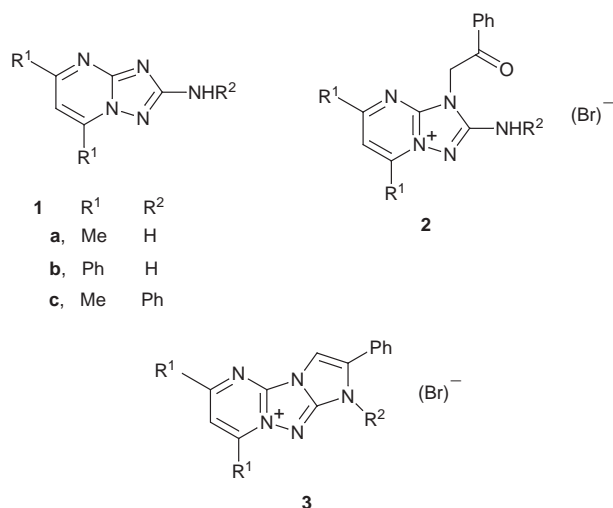
Introduction

The unusual rearrangement and dimerisation of certain putative [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides¹ and [1,2,4]triazolo[4,3-*a*][1,3,5]triazinium-3-aminides² have been described. We have also reported³ the preparation of [1,2,4]triazolo[1,5-*a*]pyrimidinium-2-olates and disclosed the interesting 1,3-dipolar cycloaddition reactions of these compounds with acetylenes and other derivatives. It was, therefore, of interest to investigate the synthesis and reactions of the related [1,2,4]triazolo[1,5-*a*]pyrimidinium-2-aminides.

Results and discussion

Synthesis

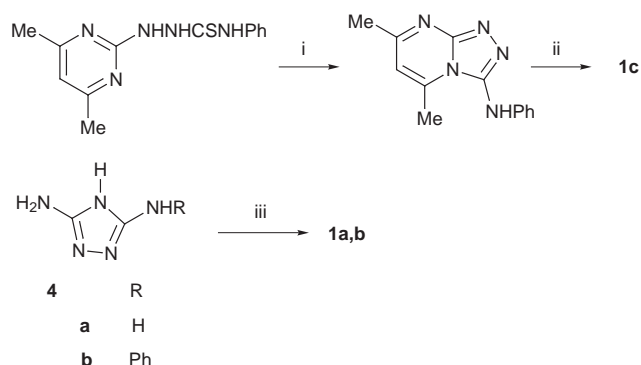
Alkylation reactions of heterocycles have been used for the synthesis of a number of mesoionic compounds, particularly 1,2,4-triazoliumolates,⁴⁻⁶ although mixtures of products were often obtained. Also in the synthesis of the tricyclic system (3) the preparation of the salts (2) by alkylation of 2-amino[1,2,4]triazolo[1,5-*a*]pyrimidines (1) was described.⁷ Thus, in this work



the alkylation of [1,2,4]triazolo[1,5-*a*]pyrimidines to yield the target betaines was attempted at the outset.

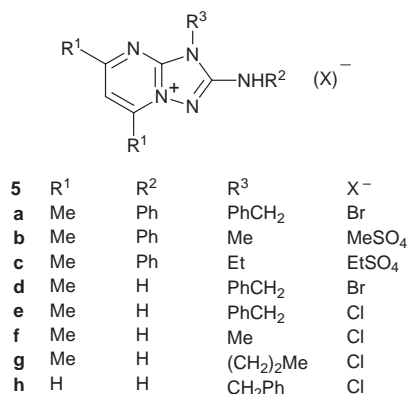
The desired precursor heterocycles, 2-amino-5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (1a) and the phenyl deriv-

ative (1c) were readily obtained through two routes. The latter (1c) was prepared through a Dimroth rearrangement⁸ of 5,7-dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine and this product proved to be identical to that obtained by treating 3-amino-5-phenylamino-1,2,4-triazole⁹ with pentane-2,4-dione (see Scheme 1); the triazole route was also used for



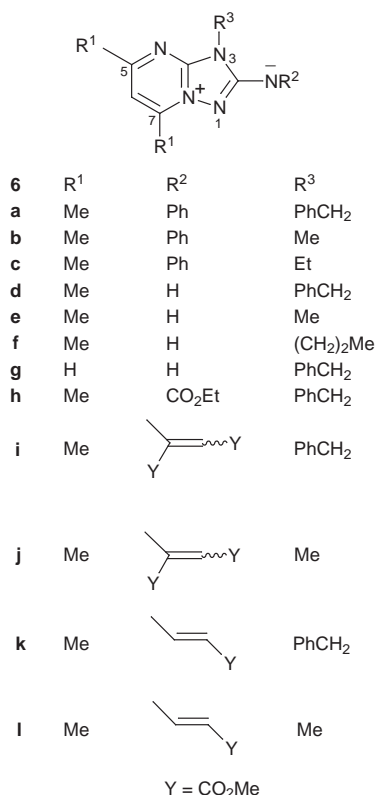
Scheme 1 Reagents: (i) DCC, toluene, (ii) 2 M aq. NaOH, (iii) pentane-2,4-dione.

synthesis of 1a. Alkylation of the triazolopyrimidines was initially carried out in boiling acetic acid, in which the phenyl derivative (1c) reacted with benzyl bromide to give the salt (5a) in 51% yield. Treatment of the salt 5a with Amberlite resin (OH



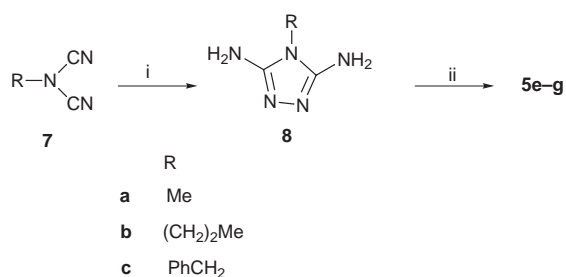
form) gave *N*-phenyl-3-benzyl-5,7-dimethyl-3*H*-8λ³-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum-2-aminide (6a) in 85% yield. The use of dialkyl sulfates as alkylating agents with the phenylamine 1c gave better results in dimethylformamide as solvent, giving

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the salts **5b** and **5c** in 63 and 42% yield, respectively; treatment of the latter (**5b,c**) with aqueous sodium hydroxide gave the betaines **6b** and **6c** in 69 and 91% yield, respectively. Attempted alkylation of the primary amine **1a** with dialkyl sulfates under these conditions gave complex mixtures, but with benzyl bromide, the salt **5d** was obtained in 41% yield. Treatment of the salt **5d** with aqueous sodium hydroxide gave the betaine **6d**, which was isolated as a dihydrate. Spectral data (IR, ¹H NMR) fully supported the structures **5d** and **6d** whereby alkylation had occurred at the 3-position. However, due to the limited success of this method for the preparation of the unsubstituted betaines (**5**, R² = H), an alternative, unambiguous route to these compounds was sought.

The new procedure for the preparation of 2-unsubstituted aminides **6d–f** involved the development of a synthetic route to 4-alkyl-3,5-diamino-1,2,4-triazoles (**8a–c**, Scheme 2). Alkyl



Scheme 2 Reagents: (i) N₂H₄·H₂O, (ii) CH₃COCH₂COCH₃, HCl.

dicyanamides **7a–c**, prepared by the method of Benders and Hackmann¹⁰ reacted with hydrazine hydrate to give the triazoles **8a–c** in 29–64% yield. Reaction of the diamino-1,2,4-triazoles with pentane-2,4-dione in ethanol in the presence of hydrochloric acid gave the 2-amino[1,2,4]triazolo[1,5-*a*]pyrimidinium chlorides **5e–g** as colourless crystalline solids in 74–93% yield. Treatment of salts **5e–g** with aqueous sodium hydroxide gave the betaines **6d–f** as yellow crystalline dihydrates, which rapidly darkened on attempted drying at temperatures >20 °C, in 42–78% yield. The benzyl derivative (**6d**) was identical (IR, ¹H NMR) to that obtained by the alkylation method, confirming that alkylation had occurred at the

3-position in the previous synthesis. A characteristic feature in the ¹H NMR spectra of compounds **5** and **6** is the appearance of the 7-Me resonance as a doublet (*J* ~ 0.8 Hz) although H-6 exists as a broadened resonance (see our earlier characterisation of [1,2,4]-triazolo[1,5-*a*]pyrimidinium-2-olates and -thiolates).³ Reaction of the diamino-1,2,4-triazole (**8c**) with 1,1,3,3-tetra-methoxypropane in ethanol and hydrochloric acid gave the pyrimidinium chloride **5h** in 86% yield, but attempted isolation of betaine **6g** by basification was unsuccessful.

Reactions

The betaines **6d–f**, unsubstituted on the exocyclic nitrogen atom, were not completely stable, but the mixtures of decomposition products did not include dimeric compounds analogous to the [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminide rearrangement products previously reported.^{1,2}

Acylation of the betaine **6d** with ethyl chloroformate in alkaline solution gave the stable ethoxycarbonyl derivative **6h**. Attempted 1,3-dipolar cycloaddition reactions of the betaines **6d** and **6e** with dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate were unsuccessful; an alternative process of conjugate addition occurred to give the adducts **6i–l**. Previous studies¹¹ of such additions to acetylenic esters have shown that the stereochemical outcome depends on a number of factors including the structure of the starting components, the solvent and reaction conditions. In this work the stereochemistry of adducts **6i,j** from DMAD was not determined but the analogous products **6k,l** derived from methyl propiolate were assigned as (*E*)-configuration from observation of relatively large coupling constants in the ¹H NMR spectra (*J* ~ 13 Hz) characteristic of *trans*-olefinic protons.

It is notable that the [1,2,4]triazolo[1,5-*a*]pyrimidinium betaines prepared in this work are stable and isolable, independent of whether the group on the exocyclic nitrogen is H (**6d–g**), Ph (**6a–c**) or an electron withdrawing moiety [e.g. CO₂Et (**6h**), C(CO₂Et)=CHCO₂Et (**6i**)]. Since the molecular dimerisation rearrangement of analogous [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides can be induced by an external base, it was decided to qualitatively evaluate the acidity of the methyl groups (R¹) in the pyrimidine ring of the aminides **6**. The ¹H NMR spectrum of phenyl derivative **6b** in deuterated methanol shows a single peak (δ 2.4) for the 7-methyl substituent with almost complete exchange of the 5-methyl protons (δ 2.5). The ¹H NMR spectrum of the betaine **6d** in deuterated methanol indicates almost total exchange of the protons of both the 5 and 7 methyl groups. Evaporation of the solution, dissolution in methanol and after 15 minutes re-evaporation gave a sample, the ¹H NMR of which recorded in CD₂Cl₂, showed the 5-methyl signal (δ 2.50) had reappeared, whereas the 7-methyl signal (δ 2.42) was still largely absent. These experiments indicate the ease with which these compounds may be deprotonated, particularly at the 5-methyl position.

Conclusions

[1,2,4]Triazolo[1,5-*a*]pyrimidinium-2-aminides (**6**), unsubstituted or substituted at the exocyclic nitrogen may be obtained as crystalline solids by two different synthetic methods. The aminides **6d,e** do not react with activated acetylenes through 1,3-dipolar cycloaddition but rather by conjugate addition of the exocyclic aminide nitrogen. Although the 5-methyl group of these compounds is readily deprotonated, unlike the isomeric [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides, no evidence of rearrangement and dimerisation of the compounds was found.

Experimental

Mps were determined on a Buchi 510 mp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781

spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on Bruker AM-250 or Bruker DPX 250 spectrometers with tetramethylsilane as internal standard. Chemical shifts were measured in ppm and coupling constants (J) in Hz. Mass spectra were obtained using a VG-Micromass-16F spectrometer using a direct insertion probe. Pre-coated Merck Kieselgel 60 F 254 plates were used for analytical TLC.

5,7-Dimethyl-3-phenylamino[1,2,4]triazolo[4,3-*a*]pyrimidine

A mixture of 1-(4,6-dimethylpyrimidin-2-yl)-4-(phenyl)thiosemicarbazide¹² (0.50 g, 1.8 mmol) and dicyclohexylcarbodiimide (0.57 g, 2.7 mmol) in toluene (20 ml) was heated under reflux for 1 h. The mixture was allowed to cool to room temperature and the precipitated product was collected by filtration. Recrystallisation of the crude product from propan-2-ol gave 5,7-dimethyl-3-phenylamino[1,2,4]triazolo[4,3-*a*]pyrimidine as yellow plates (0.28 g, 64%), mp 190–192 °C; ν_{max} (Nujol) 3160, 1630 and 750 cm^{-1} ; δ_{H} [(CD₃)₂CO] 2.49 (s, 3H, 7-CH₃), 2.68 (d, 3H, $J = 1$ Hz, 5-CH₃), 6.75–6.85 (m, 4H, 3 × Ar-H and H-6), 7.16–7.25 (m, 2H, Ar-H); δ_{C} [(CD₃)₂CO] 17.86, 25.17, 111.93, 115.39, 120.36, 130.00, 143.13, 144.75, 146.20, 153.88, 165.06; m/z (EI) 239 (100%) (M^+). This compound was not purified to analytical standard, but was used for the conversion to **1c**.

5,7-Dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine (**1c**)

Method A. A stirred mixture of 5,7-dimethyl-3-phenylamino[1,2,4]triazolo[4,3-*a*]pyrimidine (5.0 g, 21 mmol) and 2 M aqueous sodium hydroxide (100 ml) was heated at 70 °C for 2 h. The resulting mixture was cooled to room temperature and the product collected by filtration, washed with water (20 ml) and recrystallised from acetic acid to give 5,7-dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine (**1c**) as colourless needles (4.05 g, 81%), mp 285–286 °C (Found: C, 65.2; H, 5.6; N, 29.15. C₁₃H₁₃N₅ requires C, 65.25; H, 5.5; N, 29.25%); ν_{max} (Nujol) 3270, 1605, 1560 and 745 cm^{-1} ; δ_{H} [(CD₃)₂SO] 2.57 (s, 3H, 5-CH₃), 2.72 (br s, 3H, 7-CH₃), 6.81 (s, 1H, H-6), 6.88–7.66 (m, 5H, Ar-H); m/z (EI) 239 (100%) (M^+).

Method B. 3-Amino-5-phenylamino[1,2,4]triazole⁹ (20.0 g, 114 mmol) and pentane-2,4-dione (13.71 g, 137 mmol) were dissolved in propan-2-ol (400 ml) and the solution heated to reflux temperature for 48 h. The resulting slurry was cooled to room temperature and the solid collected by filtration. The solid was washed with propan-2-ol (200 ml) and dried *in vacuo* at 50 °C to afford a pale apricot solid (15.54 g, 57%). A second crop of product was collected from the filtrate, washed with propan-2-ol and dried *in vacuo* at 50 °C (7.80 g, 29%). Overall crude yield = 23.34 g, 86%. The crude product was recrystallised from dimethylformamide to afford the *title compound* as a white crystalline solid (21.74 g, 80%) mp 287–289 °C. This product was spectroscopically identical (IR, NMR) to the compound described above.

5,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**1a**)

3,5-Diamino[1,2,4]triazole (10.0 g, 100 mmol) and pentane-2,4-dione (10.1 g, 100 mmol) were dissolved in glacial acetic acid and the solution heated to reflux overnight. The resulting slurry was cooled to room temperature, the solid collected by filtration, washed with ethyl acetate and dried *in vacuo* at 50 °C to afford the *title compound* as pale yellow crystals (12.22 g, 75%), mp 355–357 °C (lit.,¹³ 357 °C).

3-Benzyl-5,7-dimethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum bromide (**5a**)

A mixture of 5,7-dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine (239 mg, 1 mmol) and benzyl bromide (855 mg, 5

mmol) in acetic acid (15 ml) was heated under reflux for 24 h. The resulting orange solution was cooled and the precipitate collected by filtration. The solid obtained was recrystallised from methanol to give 3-benzyl-5,7-dimethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum bromide (**5a**) as yellow needles (209 mg, 51%), mp 270 °C (decomp.) (Found: C, 58.55; H, 4.9; N, 16.9. C₂₀H₂₀BrN₅ requires C, 58.55; H, 4.9; N, 17.1%); ν_{max} (Nujol) 1620, 1565 and 758 cm^{-1} ; δ_{H} [(CD₃)₂SO] 2.69 (s, 3H, 5-CH₃), 2.81 (s, 3H, 7-CH₃), 5.79 (s, 2H, CH₂Ph), 7.13–7.51 (m, 8H, Ar-H), 7.22 (s, 1H, H-6), 7.78 (m, 2H, Ar-H), 10.42 (s, 1H, NH); δ_{C} [(CD₃)₂SO] 16.18 (C-7a), 24.41 (C-5a), 45.36 (N-CH₂), 115.49 (C-6), 119.90 (Ar-C), 124.20 (Ar-C), 127.26 (Ar-C), 128.15 (Ar-C), 128.71 (Ar-C), 129.16 (Ar-C), 133.68 (Ar-C), 137.47 (C-7), 145.50 (C-3a), 149.96 (Ar-C), 151.54 (C-2), 168.11 (C-5).

N-Phenyl-3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum-2-aminide (**6a**)

3-Benzyl-5,7-dimethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum bromide (**5a**) (200 mg, 0.5 mmol) was dissolved in hot methanol. To the resultant solution was added Amberlite resin [IRA 400 (OH form)] (200 mg) and the mixture stirred for 5 min then filtered. The filtrate was concentrated to give *N*-phenyl-3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum-2-aminide (**6a**) as golden needles (136 mg, 85%), mp 191–192 °C (Found: C, 72.7; H, 5.9; N, 21.1. C₂₀H₁₉N₅ requires C, 72.95; H, 5.8; N, 21.25%); ν_{max} (CHCl₃) 1625, 1612, 1578, 1555, 1140 and 690 cm^{-1} ; δ_{H} (CDCl₃) 2.63 (s, 3H, 5-CH₃), 2.71 (d, 3H, $J = 0.7$ Hz, 7-CH₃), 5.79 (br s, 2H, CH₂Ph), 6.91 (s, 1H, H-6), 6.95–7.85 (m, 10H, Ar-H); m/z 329 (89%) (M^+), 328 (57), 252 (20), 180 (25), 167 (100), 108 (28), 91 (99), 67 (18), 65(30), 28 (66).

3,5,7-Trimethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum methyl sulfate (**5b**)

5,7-Dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine (5.0 g, 21.0 mmol) was suspended in dimethylformamide (40 ml). The suspension was treated with dimethyl sulfate (3.16 g, 25.1 mmol) and the mixture heated at 100–110 °C for 1 h. The resulting dark green solution was cooled to room temperature for 30 min and the precipitated solid collected by filtration and rinsed through with dimethylformamide (10 ml). The filtrate was diluted with *tert*-butyl methyl ether (50 ml) over 15 min and the resulting slurry stirred for 10 min. The solid was collected by filtration, washed with 3 : 1 *tert*-butyl methyl ether–dimethylformamide (15 ml) and dried *in vacuo* at 50 °C to afford the *title compound* as a dark green solid (4.84 g, 63%); δ_{H} (d₆-DMSO) 2.72 (s, 3H, 5-CH₃), 2.80 (s, 3H, 7-CH₃), 3.36 (s, 3H, CH₃SO₄), 3.85 (s, 3H, N-CH₃), 7.18 (m, 1H, Ar-H), 7.47 (m, 2H, Ar-H), 7.68 (s, 1H, H-6), 7.78 (m, 2H, Ar-H); δ_{C} (d₆-DMSO) 16.0, 24.3, 29.4, 52.7, 114.9, 119.4, 123.9, 129.1, 137.5, 145.5, 149.3, 152.0, 167.7. This compound was not purified to analytical standard and was used immediately for the synthesis of **6b**.

N-Phenyl-3,5,7-trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum-2-aminide (**6b**)

3,5,7-Trimethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylum methyl sulfate (3.40 g, 9.3 mmol) was dissolved in water (100 ml). The resulting deep green solution was treated with 2 M aqueous sodium hydroxide (7.0 ml, 14.0 mmol) whereupon a solid immediately precipitated. The solid was collected by filtration, washed with water (50 ml) and dried *in vacuo* at 50 °C over P₂O₅ to afford a dark green solid (2.20 g, 94%). The crude product was recrystallised from propan-2-ol to afford the pure *title compound* as dark green needles (1.61 g, 69%) mp 216–218 °C (decomp.) (Found: C, 66.38; H, 6.02; N, 27.65. C₁₄H₁₅N₅ requires C, 66.38; H, 5.97; N, 27.65%); δ_{H} (CD₂Cl₂) 2.51 (s, 3H, 5-CH₃), 2.62 (s, 3H, 7-CH₃), 3.53 (s,

3H, N-CH₃), 6.68 (s, 1H, H-6), 6.81 (m, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 7.46 (m, 2H, Ar-H). δ_C (CD₂Cl₂) 16.9, 24.0, 27.2, 111.8, 119.5, 123.2, 128.4, 144.5, 150.1, 160.9.

5,7-Dimethyl-3-ethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium ethyl sulfate (5c)

5,7-Dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine (5.0 g, 21.0 mmol) was suspended in dimethylformamide (40 ml) and the suspension was treated with diethyl sulfate (3.87 g, 25.0 mmol). The mixture was heated at 100–110 °C for 24 h. The resulting deep green solution was cooled to room temperature and then to 0 °C whereupon a solid crystallised. The solid was collected by filtration, washed with cold DMF (10 ml) and dried *in vacuo* at 50 °C to afford the *title compound* as a pale pink solid (3.44 g, 42%) mp 208–210 °C (Found: C, 51.98; H, 5.89; N, 17.85; S, 8.20. C₁₇H₂₃N₅O₄S requires C, 51.90; H, 5.89; N, 17.80; S, 8.15%); δ_H (d₆-DMSO) 1.10 (t, 3H, *J* = 6.5 Hz, CH₂CH₃), 1.43 (t, 3H, *J* = 6.5 Hz, CH₂CH₃), 2.72 (s, 3H, 5-CH₃), 2.79 (s, 3H, 7-CH₃), 3.76 (q, 2H, *J* = 6.5 Hz, CH₂CH₃), 4.44 (q, 2H, *J* = 6.5 Hz, CH₂CH₃), 7.19 (m, 1H, Ar-H), 7.48 (m, 2H, Ar-H), 7.69 (s, 1H, H-6), 7.80 (m, 2H, Ar-H); δ_C (d₆-DMSO) 19.7, 21.7, 22.7, 31.0, 44.7, 67.8, 121.7, 126.4, 135.8, 144.2, 151.9, 156.0, 157.9, 174.4.

***N*-Phenyl-5,7-dimethyl-3-ethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide (6c).** 5,7-Dimethyl-3-ethyl-2-phenylamino-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium ethyl sulfate (3.0 g, 7.62 mmol) was dissolved in water (100 ml) with warming on a steam bath. The dark green solution was cooled to room temperature and treated, dropwise, with 2 M aqueous sodium hydroxide (4.0 ml, 8.0 mmol). The resulting green-yellow slurry was stirred at room temperature for one hour, the solid was collected by filtration, washed with water and dried *in vacuo* at 45 °C over P₂O₅ to afford the *title compound* as a yellow solid (1.85 g, 91%) mp 192–195 °C (decomp.) (Found: C, 67.34; H, 6.45; N, 26.16. C₁₅H₁₇N₅ requires C, 67.39; H, 6.41; N, 26.20%); δ_H (CD₂Cl₂) 1.40 (t, 3H, *J* = 6.5 Hz, CH₂CH₃), 2.50 (s, 3H, 5-CH₃), 2.60 (s, 3H, 7-CH₃), 4.14 (q, 2H, *J* = 6.5 Hz, CH₂CH₃), 6.66 (s, 1H, H-6), 6.80 (m, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 7.46 (m, 2H, Ar-H); δ_C (CD₂Cl₂) 13.3, 17.2, 24.3, 36.3, 111.9, 119.7, 123.4, 128.7, 144.6, 146.2, 150.4, 154.2, 161.1.

2-Amino-5,7-dimethyl-3-benzyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium bromide (5d)

5,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (3.0 g, 18.4 mmol) and benzyl bromide (3.72 g, 22.0 mmol) were heated together at 120 °C in DMF (60 ml) for 1.5 h. The dark greenish solution was allowed to cool to room temperature and then cooled to 0 °C for 30 min, whereupon a solid crystallised. The solid was collected by filtration, washed with cold DMF then dichloromethane and dried *in vacuo* at 40 °C to afford the *title compound* as a pale pink solid (2.5 g, 41%), mp 255–257 °C (Found: C, 50.21; H, 4.86; N, 20.92. C₁₄H₁₆N₅Br requires: C, 50.31; H, 4.83; N, 20.95%); δ_H (d₆-DMSO) 2.66 (s, 3H, 7-Me), 2.72 (s, 3H, 5-Me), 5.50 (s, 2H, CH₂Ph), 7.34–7.46 (m, 5H, Ph), 7.66 (s, 1H, H-6), 8.28 (s, 2H, NH₂); δ_C (d₆-DMSO) 15.7, 23.7, 44.4, 114.6, 133.3, 145.1, 148.6, 154.8, 165.9.

Alkyl dicyanamides (7a–c)

These compounds were prepared according to the method of Benders and Hackmann¹⁰ by reaction of cyanogen bromide with the appropriate amine in the presence of triethylamine. The following compounds were prepared.

Methyl dicyanamide (7a). This compound was prepared in quantitative crude yield and used for subsequent transformations without further purification.

Propyl dicyanamide (7b). Colourless liquid (12.0 g, 38%) bp 60–72 °C/2–3 mbar (lit.,¹⁰ bp 94–94.5 °C/12 Torr).

Benzyl dicyanamide (7c). Colourless liquid (10.0 g, 63%) bp 120–125 °C/0.1 mbar (lit.,¹⁰ bp 93–95 °C/0.2–0.3 Torr).

General method for the preparation of 4-alkyl-3,5-diamino-1,2,4-triazoles (8a–c)

A solution of the appropriate alkyl dicyanamide (1.0 equiv.) in industrial methylated spirits (IMS) was added over 30 min to a solution of hydrazine monohydrate (1.1 equiv.) in methylated spirits at 0 °C. The mixture was stirred at room temperature for 4–18 h. The reaction mixture was partially concentrated *in vacuo* and the crude products isolated by filtration. The crude products were recrystallised from ethanol. The following compounds were prepared.

3,5-Diamino-4-methyl-1,2,4-triazole (8a). Colourless needles (2.04 g, 29%), mp 265–273 °C (Found: C, 31.83; H, 6.18; N, 61.69%. C₃H₇N₅ requires C, 31.85; H, 6.24; N, 61.91%); ν_{\max} (Nujol) 3320, 3125 (N–H), 1650, 1630 and 1555 cm⁻¹; δ_H (d₆-DMSO) 3.11 (s, 3H, CH₃), 5.30 (br s, 4H, 2 × NH₂); δ_C (d₆-DMSO) 27.0, 150.8.

3,5-Diamino-4-propyl-1,2,4-triazole (8b). Colourless needles (7.60 g, 65%), mp 251–252 °C (Found: C, 42.43; H, 7.81; N, 49.51%. C₅H₁₁N₅ requires C, 42.53; H, 7.86; N, 49.61%); ν_{\max} (Nujol) 3330, 3120 (NH), 1635 and 1540 cm⁻¹; δ_H (CD₃OD) 0.93 (t, 3H, *J* = 7.5 Hz, CH₂CH₂CH₃), 1.70 (apparent sextet, 2H, *J* = 7.5, 8.0 Hz, CH₂CH₂CH₃), 3.63 (t, 2H, *J* = 7.5 Hz, CH₂CH₂CH₃); δ_C (CD₃OD) 11.0, 22.5, 43.8, 153.2.

3,5-Diamino-4-benzyl-1,2,4-triazole (8c). Colourless prisms (3.85 g, 64%), mp 285–298 °C (Found: C, 56.99; H, 5.89; N, 37.02%. C₉H₁₁N₅ requires C, 57.13; H, 5.86; N, 37.01%); ν_{\max} (Nujol) 3440, 3330, 3120 (NH), 1640, 1595 and 1550 cm⁻¹; δ_H (CD₃OD/DCl) 5.18 (br s, 2H + H₂O, CH₂Ph), 7.26–7.44 (m, 5H, ArH); δ_C (CD₃OD/DCl) 45.9, 127.8, 129.5, 130.1, 134.6, 151.5.

General method for the preparation of 3-alkyl-2-amino-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium chlorides (5e–h)

The appropriate 4-alkyl-3,5-diamino-1,2,4-triazole (1.0 equiv.), pentane-2,4-dione (1.1 equiv.) and concentrated hydrochloric acid (1.5 equiv.) were heated together at reflux in IMS for 1 h. The mixture was cooled to room temperature and partially concentrated *in vacuo*. The precipitated solid was collected by filtration, washed with cold IMS and dried *in vacuo* at 40 °C. The following compounds were prepared.

2-Amino-3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium chloride monohydrate (5e). Colourless needles (12.7 g, 88%), mp 270–280 °C (Found: C, 54.54; H, 5.94; N, 22.69; Cl, 11.65%. C₁₄H₁₆N₅Cl·H₂O requires C, 54.63; H, 5.89; N, 22.75; Cl, 11.52%); ν_{\max} (Nujol) 3510, 3450, 3320 (NH), 3040 and 1650 cm⁻¹; δ_H (CD₃OD) 2.72 (s, 3H, 5-CH₃), 2.78 (d, 3H, *J* = 0.8 Hz, 7-CH₃), 5.51 (s, 2H, CH₂Ph), 7.29–7.49 (m, 6H, 5 × ArH + 6-H).

2-Amino-3,5,7-trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium chloride (5f). Colourless needles (3.05 g, 81%), mp >300 °C (Found: C, 44.90; H, 5.67; N, 32.68; Cl, 16.72%. C₈H₁₂N₅Cl requires C, 44.97; H, 5.66; N, 32.78; Cl, 16.59%); ν_{\max} (Nujol) 3350, 3260 (NH), 1815 and 1665 cm⁻¹; δ_H (CD₃OD) 2.72 (s, 3H, 5-CH₃), 2.75 (d, 3H, *J* = 0.8 Hz, 7-CH₃), 3.76 (s, 3H, N-CH₃), 7.45 (s, 1H, 6-H).

2-Amino-5,7-dimethyl-3-propyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium chloride (5g). Colourless needles (2.53 g,

74%) mp 275–276 °C (decomp.) (Found: C, 49.55; H, 6.69; N, 28.75; Cl, 14.64%. C₁₀H₁₆N₅Cl requires C, 49.68; H, 6.67; N, 28.98; Cl, 14.67%; ν_{\max} (Nujol) 3330, 3210 (NH), 1655, 1600 and 1560 cm⁻¹; δ_{H} (CD₃OD) 1.15 (t, 3H, $J = 7.5$ Hz, CH₂CH₂CH₃), 1.92 (sextet, 2H, $J = 7.5$ Hz, CH₂CH₂CH₃), 2.73 (s, 3H, 5-CH₃), 2.78 (d, 3H, $J = 0.8$ Hz, 7-CH₃), 4.23 (t, 2H, $J = 7.5$ Hz, CH₂CH₂CH₃), 7.48 (s, 1H, 6-H).

2-Amino-3-benzyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium chloride (5h). 3,5-Diamino-4-benzyl-1,2,4-triazole (1.0 g, 5.3 mmol) and 1,1,3,3-tetramethoxypropane (0.88 ml, 5.3 mmol) were heated together at reflux in methylated spirits (15 ml) and concentrated hydrochloric acid (2 ml) for 1 h. The mixture was cooled to room temperature and the white solid collected by filtration, washed with cold water and dried *in vacuo* at 40 °C to afford the *title compound* as colourless needles (1.19 g, 86%), mp 275–277 °C (Found: C, 55.08; H, 4.69; N, 26.76; Cl, 13.52%. C₁₂H₁₂N₅Cl requires C, 55.07; H, 4.62; N, 26.76; Cl, 13.55%; ν_{\max} (Nujol) 3330, 3200 (N–H) and 1655 cm⁻¹; δ_{H} (CD₃OD) 5.64 (s, 2H, CH₂Ph), 7.44–7.58 (m, 5H, benzyl ArH), 7.78 (m, 1H, 6-H), 9.05 (m, 1H, 5-H), 9.32 (m, 1H, 7-H).

General method for the preparation of 5,7-dimethyl-3-alkyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminides (6d–f)

The appropriate 5,7-dimethyl-3-alkyl-2-amino[1,2,4]triazolo[1,5-*a*]pyrimidinium chloride was dissolved in water and the pH adjusted to 14 with 2.0 M aqueous sodium hydroxide. The mixture was chilled to 0 °C and the crystalline solid collected by filtration, washed with chilled water and dried *in vacuo* at room temperature over P₂O₅. The following compounds were prepared.

3-Benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide dihydrate (6d). Yellow plates (1.55 g, 78%), mp 156–158 °C (decomp.) (Found: C, 57.86; H, 6.57; N, 24.09%. C₁₄H₁₅N₅·2H₂O requires C, 58.12; H, 6.62; N, 24.20%; ν_{\max} (Nujol) 3450, 3310, 3270 (NH) and 1640 cm⁻¹; δ_{H} (CD₂Cl₂) 2.47 (s, 3H, 5-CH₃), 2.52 (d, 3H, $J = 0.8$ Hz, 7-CH₃), 3.47 (br s, 1H, NH), 5.13 (s, 2H, CH₂Ph), 6.68 (s, 1H, 6-H), 7.25–7.51 (m, 5H, ArH).

3,5,7-Trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide dihydrate (6e). Yellow needles (0.88 g, 56%), mp 176–179 °C (decomp.) (Found: C, 44.70; H, 7.11; N, 33.12%. C₉H₁₁N₅·2H₂O requires C, 45.06; H, 7.09; N, 32.84%; δ_{H} (CD₂Cl₂) 2.47 (s, 3H, 5-CH₃), 2.53 (d, 3H, $J = 0.8$ Hz, 7-CH₃), 3.42 (s, 3H, N-CH₃), 3.91 (br s, 1H, NH), 6.66 (s, 1H, 6-H).

5,7-Dimethyl-3-propyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide (6f). Yellow needles (0.18 g, 42%), mp 122–126 °C, ν_{\max} (thin solid film) 3370, 3260 (NH), 1653 and 1560 cm⁻¹; δ_{H} (CD₂Cl₂) 0.98 (t, 3H, $J = 7.5$ Hz, CH₂CH₂CH₃) 1.82 (sextet, 2H, $J = 7.5$ Hz, CH₂CH₂CH₃) 2.47 (s, 3H, 5-CH₃) 2.53 (d, 3H, $J = 0.8$ Hz, 7-CH₃) 3.72 (br s, 3H, NH + H₂O) 3.90 (t, 2H, $J = 7.5$ Hz, CH₂CH₂CH₃) 6.68 (s, 1H, 6-H).

N-Ethoxycarbonyl-3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide (6h)

To a solution of 3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide (0.5 g, 1.97 mmol) in dichloromethane (50 ml) was added 2 M aqueous sodium hydroxide (25 ml). To the vigorously stirred solution at 0 °C was then added ethyl chloroformate (0.21 ml, 2.17 mmol, 1.1 equiv.). The mixture was allowed to warm to room temperature during 0.5 h. when TLC (SiO₂, 90% CH₂Cl₂–10% MeOH) showed complete reaction. The CH₂Cl₂ layer was separated, washed with water (25 ml), dried (Na₂SO₄) and concentrated *in vacuo* to residue. The crude product was recrystallised from acetone to afford the *title compound* as off-white fluffy needles

(0.31 g, 48%) mp 193–195 °C (Found: C, 62.78; H, 5.94; N, 21.48%. C₁₇H₁₉N₅O₂ requires C, 62.75; H, 5.89; N, 21.53%; ν_{\max} (Nujol) 3050, 1630, 1580 and 1530 cm⁻¹; δ_{H} (CD₂Cl₂) 1.27 (t, 3H, $J = 7.5$ Hz, CH₂CH₃), 2.61 (s, 3H, 5-CH₃), 2.77 (d, 3H, $J = 0.8$ Hz, 7-CH₃), 4.09 (q, 2H, $J = 7.5$ Hz, CH₂CH₃), 5.31 (s, 2H, CH₂Ph), 6.97 (s, 1H, 6-H), 7.26–7.48 (m, 5H, ArH).

Reaction of 3,5,7-trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide with dimethyl acetylenedicarboxylate—formation of adduct 6j

To a solution of 3,5,7-trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide (0.1 g, 0.47 mmol) in dichloromethane (20 ml) at room temperature was added dimethyl acetylenedicarboxylate (0.1 g, 0.09 ml, 0.70 mmol). The yellow solution immediately became orange. The solution was stirred at room temperature for 2 h when TLC (SiO₂, 95% CH₂Cl₂–5% MeOH) showed no starting material remaining and one major, less polar product. The mixture was concentrated *in vacuo* to a residue which was recrystallised from IMS to afford the *adduct 6j* as orange needles (0.09 g, 70%) mp 214–216 °C (decomp.) (Found: C, 52.74; H, 5.40; N, 21.93. C₁₄H₁₇N₅O₄ requires C, 52.66; H, 5.37; N, 21.93%; δ_{H} (CD₂Cl₂) 2.63 (s, 3H, 5-CH₃), 2.75 (d, 3H, $J = 0.8$ Hz, 7-CH₃) 3.6 (s, 3H, N-CH₃), 3.62 (s, 3H, CO₂CH₃), 3.82 (s, 3H, CO₂CH₃), 6.04 (s, 1H, olefinic H), 6.97 (s, 1H, 6-H).

Reaction of 3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide with dimethyl acetylenedicarboxylate—formation of adduct 6i

To a solution of 3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide (0.1 g, 0.35 mmol) in dichloromethane (20 ml) at room temperature was added dimethyl acetylenedicarboxylate (0.09 ml, 0.73 mmol). The resulting orange solution was stirred at room temperature for 24 h. TLC analysis then showed a trace of starting material remaining and one major, less polar product. Solvent was removed *in vacuo* and the residue recrystallised from IMS to afford the *adduct (6i)* as yellow needles (0.1 g, 81%) mp 204–206 °C (Found: C, 60.77; H, 5.39; N, 17.79. C₂₀H₂₁N₅O₄ requires C, 60.75; H, 5.35; N, 17.71%; ν_{\max} (thin solid film) 1730, 1690, 1595 and 1530 cm⁻¹; δ_{H} (CD₂Cl₂) 2.62 (s, 3H, 5-CH₃), 2.69 (d, 3H, $J = 0.8$ Hz, 7-CH₃), 3.62 (s, 3H, CO₂CH₃), 3.83 (s, 3H, CO₂CH₃), 5.28 (s, 2H, CH₂Ph), 6.01 (s, 1H, olefinic H), 6.94 (s, 1H, 6-H), 7.25–7.56 (m, 5H, ArH).

Reaction of 3-benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide dihydrate with methyl propiolate—formation of adduct 6k

3-Benzyl-5,7-dimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide dihydrate (0.5 g, 1.73 mmol) and methyl propiolate (0.23 ml, 2.58 mmol) were stirred together in methylene chloride at room temperature for 18 h. The mixture was concentrated *in vacuo* to residue. The brown solid residue was triturated with ethanol and the yellow solid collected by filtration. The solid was recrystallised from ethanol to afford the *adduct 6k* as yellow needles (0.26 g, 45%), mp 193–195 °C (Found: C, 64.10; H, 5.76; N, 20.70%. C₁₈H₁₉N₅O₂ requires: C, 64.08; H, 5.68; N, 20.76%; ν_{\max} (Nujol) 1680, 1630 and 1570 cm⁻¹; δ_{H} (CD₂Cl₂) 2.58 (s, 3H, 5-CH₃), 2.69 (s, 3H, 7-CH₃), 3.64 (s, 3H, CO₂CH₃), 5.26 (s, 2H, CH₂Ph), 5.35 (d, 1H, $J = 13.0$ Hz, NCH=CHCO₂CH₃), 6.89 (s, 1H, H-6), 7.27–7.51 (m, 5H, Ph), 8.55 (d, 1H, $J = 13.0$ Hz, NCH=CHCO₂CH₃).

Reaction of 3,5,7-trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide dihydrate with methyl propiolate—formation of adduct 6l

3,5,7-Trimethyl-3H-8 λ^5 -[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylidium-2-aminide dihydrate (1.70 g, 7.97 mmol) and methyl

propiolate (0.84 ml, 9.44 mmol) were stirred together in methylene chloride (120 ml) at room temperature for 18 h. The precipitated solid was collected by filtration and recrystallised from ethanol to afford the *adduct* **61** as golden needles (0.97 g, 47%), mp 200–202 °C (Found: C, 55.20; H, 5.79; N, 26.93; O, 12.39%. C₁₂H₁₅N₅O₂ requires C, 55.16; H, 5.79; N, 26.80; O, 12.25%); ν_{\max} (Nujol) 3072, 1680 and 1630 cm⁻¹; δ_{H} (CD₂Cl₂) 2.64 (s, 3H, 5-CH₃), 2.75 (s, 3H, 7-CH₃), 3.61 (s, 3H, N-CH₃), 3.67 (s, 3H, CO₂CH₃), 5.35 (d, 1H, *J* = 13.0 Hz, NCH=CHCO₂CH₃), 7.08 (s, 1H, H-6), 8.56 (d, 1H, *J* = 13.0 Hz, NCH=CHCO₂CH₃).

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