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-amides 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.

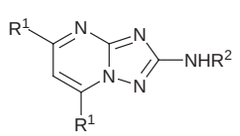
Introduction

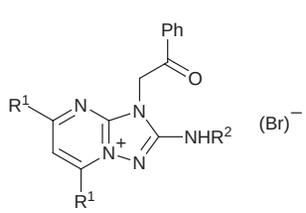
The unusual rearrangement and dimerisation of certain putative [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides[1] and [1,2,4]triazolo[4,3-*a*][1,3,5]triazinium-3-aminides[2] have been described. We have also reported[3] the preparation of [1,2,4]-triazolo[1,5-*a*]pyrimidinium-2-olates and disclosed the 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





1	R^1	R^2
a	Me	H
b	Ph	H
c	Me	Ph

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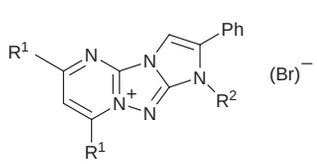

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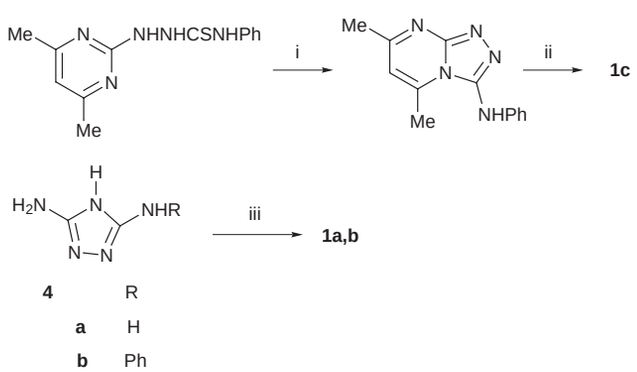
the alkylation of [1,2,4]triazolo[1,5-*a*]pyrimidines to yield the target betaines was attempted at the outset.

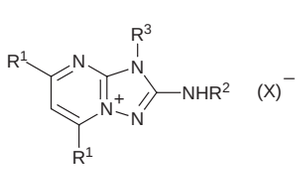
The desired precursor heterocycles, 2-amino-5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**1a**) and the phenyl derivative (**1c**) were readily obtained through two routes. The latter (**1c**) was prepared through a Dimroth rearrangement[8] of 5,7-dimethyl-2-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine and this product proved to be identical to that obtained by treating 3-amino-5-phenylamino-1,2,4-triazole[9] with pentane-2,4-dione (see Scheme 1); the triazole route was also used for



4	R
a	H
b	Ph

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



5	R^1	R^2	R^3	X^-
a	Me	Ph	$PhCH_2$	Br
b	Me	Ph	Me	$MeSO_4$
c	Me	Ph	Et	$EtSO_4$
d	Me	H	$PhCH_2$	Br
e	Me	H	$PhCH_2$	Cl
f	Me	H	Me	Cl
g	Me	H	$(CH_2)_2Me$	Cl
h	H	H	CH_2Ph	Cl

form) gave *N*-phenyl-3-benzyl-5,7-dimethyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-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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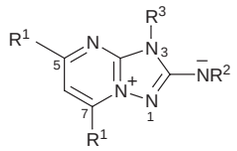
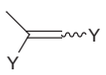
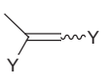
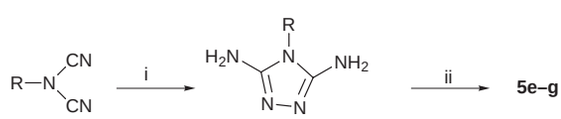


6	R^1	R^2	R^3
a	Me	Ph	$PhCH_2$
b	Me	Ph	Me
c	Me	Ph	Et
d	Me	H	$PhCH_2$
e	Me	H	Me
f	Me	H	$(CH_2)_2Me$
g	H	H	$PhCH_2$
h	Me	CO_2Et	$PhCH_2$
i	Me		$PhCH_2$
j	Me		Me
k	Me		$PhCH_2$
l	Me		Me

Y = CO_2Me

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, ^{1}H 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**, R^2 = 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



7 **8** **5e–g**

R	
a	Me
b	$(CH_2)_2Me$
c	$PhCH_2$

Scheme 2 *Reagents*: (i) $N_2H_4{\cdot}H_2O$, (ii) $CH_3COCH_2COCH_3$, HCl.

dicyanamides **7a–c**, prepared by the method of Benders and Hackmann[10] 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, ^{1}H 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 ^{1}H NMR spectra of compounds **5** and **6** is the appearance of the 7-Me resonance as a doublet ($J \sim 0.8$ 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-tetramethoxypropane 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 studies[11] 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 ^{1}H NMR spectra ($J \sim 13$ 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.* CO_2Et (**6h**), $C(CO_2Et)=CHCO_2Et$ (**6i**)]. Since the molecular dimerisative 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 (R^1) in the pyrimidine ring of the aminides **6**. The ^{1}H 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 ^{1}H 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 ^{1}H NMR of which recorded in CD_2Cl_2, 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. ^{1}H 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)thiosemicarbazide[12] (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 [$(CD_3)_2CO$] 2.49 (s, 3H, 7-CH_3), 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 [$(CD_3)_2CO$] 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. $C_{13}H_{13}N_5$ requires (C, 65.25; H, 5.5; N, 29.25%); ν_{max} (Nujol) 3270, 1605, 1560 and 745 cm^{-1}; δ_H [$(CD_3)_2SO$] 2.57 (s, 3H, 5-CH_3), 2.72 (br s, 3H, 7-CH_3), 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]triazole[9] (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-3*H*-8λ^5-[1,2,4]triazolo-[l,5-*a*]pyrimidin-8-ylium 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-8λ^5-[1,2,4]triazolo[1,5-a]pyrimidin-8-ylium bromide* (**5a**) as yellow needles (209 mg, 51%), mp 270 °C (decomp.) (Found: C, 58.55; H, 4.9; N, 16.9. $C_{20}H_{20}BrN_5$ requires C, 58.55; H, 4.9; N, 17.1%); ν_{max} (Nujol) 1620, 1565 and 758 cm^{-1}; δ_H [$(CD_3)_2SO$] 2.69 (s, 3H, 5-CH_3), 2.81 (s, 3H, 7-CH_3). 5.79 (s, 2H, CH_2Ph), 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 [$(CD_3)_2SO$] 16.18 (C-7a), 24.41 (C-5a), 45.36 (N-CH_2), 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]-pyrimidin-8-ylium-2-aminide (6a)

3-Benzyl-5,7-dimethyl-2-phenylamino-3*H*-8λ^5-[1,2,4]triazolo-[1,5-*a*]pyrimidin-8-ylium 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-8λ^5-[1,2,4]triazolo-[1,5-a]pyrimidin-8-ylium-2-aminide* (**6a**) as golden needles (136 mg, 85%), mp 191–192 °C (Found: C, 72.7; H, 5.9; N, 21.1. $C_{20}H_{19}N_5$ requires C, 72.95; H, 5.8; N, 21.25%); ν_{max} ($CHCl_3$) 1625, 1612, 1578, 1555, 1140 and 690 cm^{-1}; δ_H ($CDCl_3$) 2.63 (s, 3H, 5-CH_3), 2.71 (d, 3H, J = 0.7 Hz, 7-CH_3), 5.79 (br s, 2H, CH_2Ph), 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]-pyrimidin-8-ylium 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 (d_6-DMSO) 2.72 (s, 3H, 5-CH_3), 2.80 (s, 3H, 7-CH_3), 3.36 (s, 3H, CH_3SO_4), 3.85 (s, 3H, N-CH_3), 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 (d_6-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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]-pyrimidin-8-ylium-2-aminide (6b)

3,5,7-Trimethyl-2-phenylamino-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]-pyrimidin-8-ylium 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 P_2O_5 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. $C_{14}H_{15}N_5$ requires C, 66.38; H, 5.97; N, 27.65%); δ_H (CD_2Cl_2) 2.51 (s, 3H, 5-CH_3), 2.62 (s, 3H, 7-CH_3), 3.53 (s,

3H, N-CH_3), 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 (CD_2Cl_2) 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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. $C_{17}H_{23}N_5O_4S$ requires C, 51.90; H, 5.89; N, 17.80; S, 8.15%); δ_H (d_6-DMSO) 1.10 (t, 3H, J = 6.5 Hz, CH_2CH_3), 1.43 (t, 3H, J = 6.5 Hz, CH_2CH_3), 2.72 (s, 3H, 5-CH_3), 2.79 (s, 3H, 7-CH_3), 3.76 (q, 2H, J = 6.5 Hz, CH_2CH_3), 4.44 (q, 2H, J = 6.5 Hz, CH_2CH_3), 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 (d_6-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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-2-aminide (6c).** 5,7-Dimethyl-3-ethyl-2-phenylamino-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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 P_2O_5 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. $C_{15}H_{17}N_5$ requires C, 67.39; H, 6.41; N, 26.20%); δ_H (CD_2Cl_2) 1.40 (t, 3H, J = 6.5 Hz, CH_2CH_3), 2.50 (s, 3H, 5-CH_3), 2.60 (s, 3H, 7-CH_3), 4.14 (q, 2H, J = 6.5 Hz, CH_2CH_3), 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 (CD_2Cl_2) 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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. $C_{14}H_{16}N_5Br$ requires: C, 50.31; H, 4.83; N, 20.95%); δ_H (d_6-DMSO) 2.66 (s, 3H, 7-Me), 2.72 (s, 3H, 5-Me), 5.50 (s, 2H, CH_2Ph), 7.34–7.46 (m, 5H, Ph), 7.66 (s, 1H, H-6), 8.28 (s, 2H, NH_2); δ_C (d_6-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 Hackmann[10] 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%. $C_3H_7N_5$ 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 (d_6-DMSO) 3.11 (s, 3H, CH_3), 5.30 (br s, 4H, 2 × NH_2); δ_C (d_6-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%. $C_5H_{11}N_5$ requires C, 42.53; H, 7.86; N, 49.61%); ν_{max}(Nujol) 3330, 3120 (NH), 1635 and 1540 cm^{-1}; δ_H (CD_3OD) 0.93 (t, 3H, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.70 (apparent sextet, 2H, J = 7.5, 8.0 Hz, $CH_2CH_2CH_3$), 3.63 (t, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$); δ_C (CD_3OD) 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%. $C_9H_{11}N_5$ 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 (CD_3OD/DCl) 5.18 (br s, 2H + H_2O, CH_2Ph), 7.26–7.44 (m, 5H, ArH); δ_C (CD_3OD/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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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%. $C_{14}H_{16}N_5Cl{\cdot}H_2O$ 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 (CD_3OD) 2.72 (s, 3H, 5-CH_3), 2.78 (d, 3H, J = 0.8 Hz, 7-CH_3), 5.51 (s, 2H, CH_2Ph), 7.29–7.49 (m, 6H, 5 × ArH + 6-H).

2-Amino-3,5,7-trimethyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium chloride (5f). Colourless needles (3.05 g, 81%), mp >300 °C (Found: C, 44.90; H, 5.67; N, 32.68; Cl, 16.72%. $C_8H_{12}N_5Cl$ 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 (CD_3OD) 2.72 (s, 3H, 5-CH_3), 2.75 (d, 3H, J = 0.8 Hz, 7-CH_3), 3.76 (s, 3H, N-CH_3), 7.45 (s, 1H, 6-H).

2-Amino-5,7-dimethyl-3-propyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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%. $C_{10}H_{16}N_5Cl$ 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 (CD_3OD) 1.15 (t, 3H, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.92 (sextet, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$), 2.73 (s, 3H, 5-CH_3), 2.78 (d, 3H, J = 0.8 Hz, 7-CH_3), 4.23 (t, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$), 7.48 (s, 1H, 6-H).

2-Amino-3-benzyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium 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%. $C_{12}H_{12}N_5Cl$ 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 (CD_3OD) 5.64 (s, 2H, CH_2Ph), 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-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 P_2O_5. The following compounds were prepared.

3-Benzyl-5,7-dimethyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-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%. $C_{14}H_{15}N_5{\cdot}2H_2O$ requires C, 58.12; H, 6.62; N, 24.20%); ν_{max}(Nujol) 3450, 3310, 3270 (NH) and 1640 cm^{-1}; δ_H (CD_2Cl_2) 2.47 (s, 3H, 5-CH_3), 2.52 (d, 3H, J = 0.8 Hz, 7-CH_3), 3.47 (br s, 1H, NH), 5.13 (s, 2H, CH_2Ph), 6.68 (s, 1H, 6-H), 7.25–7.51 (m, 5H, ArH).

3,5,7-Trimethyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-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%. $C_8H_{11}N_5{\cdot}2H_2O$ requires C, 45.06; H, 7.09; N, 32.84%); δ_H (CD_2Cl_2) 2.47 (s, 3H, 5-CH_3), 2.53 (d, 3H, J = 0.8 Hz, 7-CH_3), 3.42 (s, 3H, N-CH_3), 3.91 (br s, 1H, NH), 6.66 (s, 1H, 6-H).

5,7-Dimethyl-3-propyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-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 (CD_2Cl_2) 0.98 (t, 3H, J = 7.5 Hz, $CH_2CH_2CH_3$) 1.82 (sextet, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$) 2.47 (s, 3H, 5-CH_3) 2.53 (d, 3H, J = 0.8 Hz, 7-CH_3) 3.72 (br s, 3H, NH + H_2O) 3.90 (t, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$) 6.68 (s, 1H, 6-H).

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

To a solution of 3-benzyl-5,7-dimethyl-3*H*-8λ^5-[1,2,4]triazolo-[1,5-*a*]pyrimidin-8-ylium-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 (SiO_2, 90% CH_2Cl_2–10% MeOH) showed complete reaction. The CH_2Cl_2 layer was separated, washed with water (25 ml), dried (Na_2SO_4) 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%. $C_{17}H_{19}N_5O_2$ requires C, 62.75; H, 5.89; N, 21.53%); ν_{max}(Nujol) 3050, 1630, 1580 and 1530 cm^{-1}; δ_H (CD_2Cl_2) 1.27 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.61 (s, 3H, 5-CH_3), 2.77 (d, 3H, J = 0.8 Hz, 7-CH_3), 4.09 (q, 2H, J = 7.5 Hz, CH_2CH_3), 5.31 (s, 2H, CH_2Ph), 6.97 (s, 1H, 6-H), 7.26–7.48 (m, 5H, ArH).

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

To a solution of 3,5,7-trimethyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]-pyrimidin-8-ylium-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 (SiO_2, 95% CH_2Cl_2–5% 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. $C_{14}H_{17}N_5O_4$ requires C, 52.66; H, 5.37; N, 21.93%); δ_H (CD_2Cl_2) 2.63 (s, 3H, 5-CH_3), 2.75 (d, 3H, J = 0.8 Hz, 7-CH_3) 3.6 (s, 3H, N-CH_3), 3.62 (s, 3H, CO_2CH_3), 3.82 (s, 3H, CO_2CH_3), 6.04 (s, 1H, olefinic H), 6.97 (s, 1H, 6-H).

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

To a solution of 3-benzyl-5,7-dimethyl-3*H*-8λ^5-[1,2,4]triazolo-[1,5-*a*]pyrimidin-8-ylium-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. $C_{20}H_{21}N_5O_4$ requires C, 60.75; H, 5.35; N, 17.71%); ν_{max}(thin solid film) 1730, 1690, 1595 and 1530 cm^{-1}; δ_H (CD_2Cl_2) 2.62 (s, 3H, 5-CH_3), 2.69 (d, 3H, J = 0.8 Hz, 7-CH_3), 3.62 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 5.28 (s, 2H, CH_2Ph), 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-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]-pyrimidin-8-ylium-2-aminide dihydrate with methyl propiolate—formation of adduct 6k

3-Benzyl-5,7-dimethyl-3*H*-8λ^5-[1,2,4]-triazolo[1,5-*a*]pyrimidin-8-ylium-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%. $C_{18}H_{19}N_5O_2$ requires: C, 64.08; H, 5.68; N, 20.76%.); ν_{max} (Nujol) 1680, 1630 and 1570 cm^{-1}; δ_H (CD_2Cl_2) 2.58 (s, 3H, 5-CH_3), 2.69 (s, 3H, 7-CH_3), 3.64 (s, 3H, CO_2CH_3), 5.26 (s, 2H, CH_2Ph), 5.35 (d, 1H, J = 13.0 Hz, NCH=$CHCO_2CH_3$), 6.89 (s, 1H, H-6), 7.27–7.51 (m, 5H, Ph), 8.55 (d, 1H, J = 13.0 Hz, NCH=$CHCO_2CH_3$).

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

3,5,7-Trimethyl-3*H*-8λ^5-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-ylium-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* **6l** as golden needles (0.97 g, 47%), mp 200–202 °C (Found: C, 55.20; H, 5.79; N, 26.93; O, 12.39%. $C_{12}H_{15}N_5O_2$ requires C, 55.16; H, 5.79; N, 26.80; O, 12.25%); ν_{max} (Nujol) 3072, 1680 and 1630 cm^{-1}; δ_H (CD_2Cl_2) 2.64 (s, 3H, 5-CH_3), 2.75 (s, 3H, 7-CH_3), 3.61 (s, 3H, N-CH_3), 3.67 (s, 3H, CO_2CH_3), 5.35 (d, 1H, J = 13.0 Hz, N*CH*=CHCO_2CH_3), 7.08 (s, 1H, H-6), 8.56 (d, 1H, J = 13.0 Hz, NCH=*CH*CO_2CH_3).

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