# Synthesis, reactions and theoretical studies of [1,2,4]triazolo[4,3-*c*]-pyrimidinium- and [1,2,4]triazolo[4,3-*a*]pyrazinium-3-aminides

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**[1,2,4]Triazolo[4,3-*c*]pyrimidinium-3-aminides 5a–h have been synthesised by treating pyrimidin-6-yl thiosemicarbazide derivatives 7f–n with dicyclohexylcarbodiimide (DCC). The above aminides 5a–h were slowly hydrolysed in water but very rapidly hydrolysed in 5 M aqueous hydrochloric acid to give substituted 1,2,4-triazole derivatives (*e.g.* 5a,d,g ⟶ 8e,a,f, respectively); related nucleophilic ring-opening reactions occurred when the aminides (*cf.* 5a–h) were treated with (separately) methanol and ethanol (*e.g.* 5d ⟶ 8c and 8d, respectively). A series of analogous [1,2,4]triazolo[4,3-*a*]pyrazinium-3-aminides 6a–e was prepared following the procedures described above. The pyrazinium aminides 6 are stable in aq. 2 M HCl, and a stable hydrochloride salt 13 was formed from one such substrate 6a.**

**The structure and electronic properties of condensed triazolium betaines 1, 5d, 6a and 15 have been studied using the semi-empirical PM3/COSMO method and with the *ab initio* 6-31 basis set; the implications of these results in respect of the potential of such betaines for molecular rearrangement are discussed.**

## Introduction

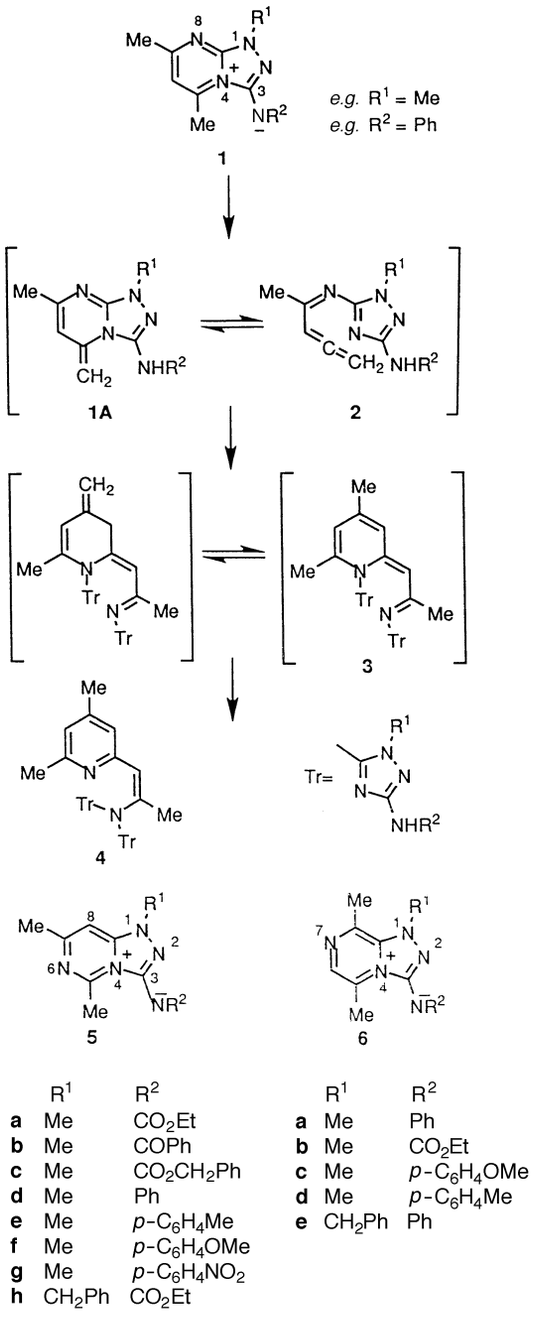
We have described the synthesis of 1,2,4-triazolo[1,5-*a*]-pyrimidinium-2-olates and -thiolates,[1] and of analogous condensed betaines in the 1,2,4-triazolo[4,3-*a*]pyridine and -pyrimidine series.[2] Of particular interest are 1,2,4-triazolo[4,3-*a*]pyrimidinium-3-aminides **1** certain examples of which (**1**, $R^2$ = electron-withdrawing group) are stable and isolable; in contrast, other (putative) compounds of this type in which $R^2$ is not an electron-withdrawing group (*e.g.* $R^2$ = Ph) undergo an unanticipated rearrangement leading to dimeric species unambiguously identified as 1,2,4-triazoles (**3** and **4**, Scheme 1).[2] We have tentatively suggested[2] a mechanism (Scheme 1) in which the juxtaposition of an appropriately substituted aminide function and a methyl substituent adjacent to the bridgehead nitrogen permits generation of a reactive iminoallenic intermediate **2**. This unusual behaviour encouraged us to attempt the synthesis of aminides in closely related ring systems in order to define the scope of this type of process. In this paper we describe the preparation and some reactions of aminides in the 1,2,4-triazolo[4,3-*c*]pyrimidine **5**, and 1,2,4-triazolo[4,3-*a*]pyrazine **6** systems; we also report results from theoretical studies of condensed triazolium betaines, including those described above, in an attempt to understand the factors governing rearrangement.

## Results and discussion

### 1,2,4-Triazolo[4,3-*c*]pyrimidinium-3-aminides

All condensed triazolium betaines described herein were synthesised from substituted hydrazino pyrimidines and pyrazines. (2,6-Dimethylpyrimidin-4-yl) hydrazine **7a** and the homologue **7b** were prepared in conventional fashion[3] from 4-chloro-2,6-dimethylpyrimidine[4] and either hydrazine hydrate or *N*-methylhydrazine, respectively. The *N*-benzyl derivative **7c** was prepared by a standard procedure[2] through alkylation of 6-benzylidenehydrazino-2,4-dimethylpyrimidine **7d** and acidic hydrolysis of the resulting *N*-benzyl derivative **7e**. The hydrazine derivatives were then treated with isothiocyanate derivatives to give a series of thiosemicarbazides (**7f–n**). With the exception of **7m**, the thiosemicarbazide derivatives (**7f–l** and **7n**) were successfully cyclised into the desired 1,2,4-triazolo[4,3-*c*]pyrimidinium-3-aminides (**5a–h**, 36–59%) by treating them with dicyclohexylcarbodiimide in acetone at room temperature. With one exception **5b**, the aminides were obtained analytically pure without recourse to recrystallisation or chromatography; indeed, such procedures caused slow hydrolysis of the betaines (see below), and the benzoyl derivative could not be purified to analytical standard. Spectroscopic data ($^1$H NMR, IR) were in accord with the proposed structures: assignments of chemical shifts for the 5-($\delta$ *ca.* 3.2) and 7-methyl ($\delta$ *ca.* 2.4) substituents were made by comparison with analogous 1,2,4-triazolo[4,3-*a*]pyrimidinium betaines **1**,[2] although there is an absence of coupling of H-8 to the C-7 methyl substituent in this case.

In contrast to our earlier observations on certain [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides, none of the aminides prepared in this study (**5a–h**) gave products of rearrangement; they were thermally stable at room temperature independent of whether the exocyclic *N*-substituent was electron-withdrawing (*e.g.* $CO_2Et$) or -donating (*e.g. p*-$MeOC_6H_4$). However, all the aminides **5a–h** were prone to hydrolysis, particularly in aqueous acid. For example, when suspensions of the orange aminides **5d,e** were stirred with water overnight, they gradually decolourised with formation of triazole derivatives (**8a,b**, respectively) of undefined, but probably *Z*-stereochemistry; the reaction occurred immediately when the hydrolysis was conducted at room temperature with 5 M aqueous hydrochloric acid (see **5a,d,g** ⟶ **8e,a,f**, respectively). A similar type of pyrimidine ring-opening by nucleophilic attack at C-5 occurred on treatment of the aminide **5d** with, separately, methanol and ethanol at room temperature (see **5d** ⟶ **8c** and **8d**, respectively). In this sense, the reactivity of these betaines resembles that of 'neutral' compounds in the series as exemplified by the Dimroth-type isomerisation, mediated through hydrolytic ring-opening, of 3-amino-7-methyl-5-propyl-[1,2,4]triazolo[4,3-*c*]pyrimidine (see *e.g.* **9** ⟶ **10** ⟶ **11**,

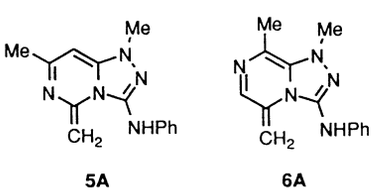



| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | Me | $CO_2Et$ |
| **b** | Me | COPh |
| **c** | Me | $CO_2CH_2Ph$ |
| **d** | Me | Ph |
| **e** | Me | $p$-$C_6H_4Me$ |
| **f** | Me | $p$-$C_6H_4OMe$ |
| **g** | Me | $p$-$C_6H_4NO_2$ |
| **h** | $CH_2Ph$ | $CO_2Et$ |

| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | Me | Ph |
| **b** | Me | $CO_2Et$ |
| **c** | Me | $p$-$C_6H_4OMe$ |
| **d** | Me | $p$-$C_6H_4Me$ |
| **e** | $CH_2Ph$ | Ph |

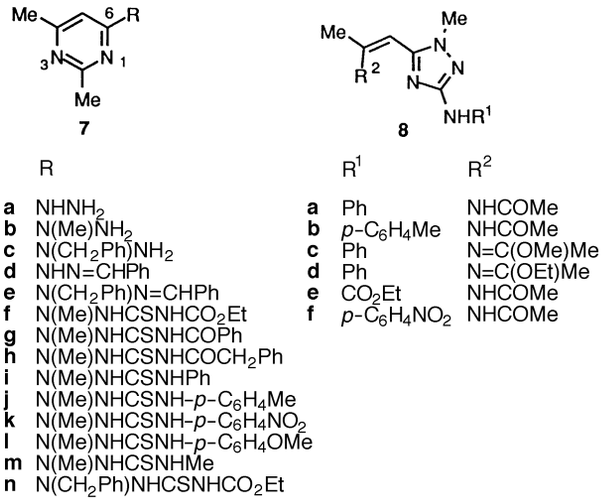
**Scheme 1**

Scheme 2).[6] In the betaine series, recyclisation (*cf.* **10** ⟶ **11**) cannot occur and 5-alkenyl-substituted 1,2,4-triazoles of potential value in synthesis are isolated (see *e.g.* useful preparative transformations of 2-azadienes[7] in the context of compounds **8c,d**).




### 1,2,4-Triazolo[4,3-*a*]pyrazinium betaines

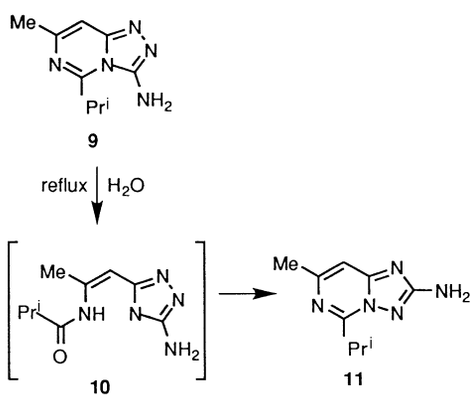
The synthetic route used to prepare aminides in this series **6** followed the procedures described above for condensed pyrimidine analogues (*cf.* **5a**–**h**). Accordingly, hydrazinopyrazines **12b** and **12c** (prepared through the sequence **12a**[8] ⟶ **12d** ⟶ **12e** ⟶ **12c**) were converted through the appropriate thiosemicarbazide derivatives (**12f**–**j**) into 1,2,4-triazolo[4,3-a]pyrazinium 3-aminides **6a**–**e**. The latter were yellow **6b**, red **6a,c,e** or brown solids **6d**, easily isolated and purified to analytical standard without recourse to chromatography.




| | R |
|---|---|
| **a** | $NHNH_2$ |
| **b** | $N(Me)NH_2$ |
| **c** | $N(CH_2Ph)NH_2$ |
| **d** | NHN=CHPh |
| **e** | $N(CH_2Ph)N=CHPh$ |
| **f** | $N(Me)NHCSNHCO_2Et$ |
| **g** | N(Me)NHCSNHCOPh |
| **h** | $N(Me)NHCSNHCOCH_2Ph$ |
| **i** | N(Me)NHCSNHPh |
| **j** | N(Me)NHCSNH-$p$-$C_6H_4Me$ |
| **k** | N(Me)NHCSNH-$p$-$C_6H_4NO_2$ |
| **l** | N(Me)NHCSNH-$p$-$C_6H_4OMe$ |
| **m** | N(Me)NHCSNHMe |
| **n** | $N(CH_2Ph)NHCSNHCO_2Et$ |

| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | Ph | NHCOMe |
| **b** | $p$-$C_6H_4Me$ | NHCOMe |
| **c** | Ph | N=C(OMe)Me |
| **d** | Ph | N=C(OEt)Me |
| **e** | $CO_2Et$ | NHCOMe |
| **f** | $p$-$C_6H_4NO_2$ | NHCOMe |

In contrast to the facile aqueous acidic hydrolysis of 1,2,4-triazolo[4,3-*c*]pyrimidinium-3-aminides **5a**–**h**, the pyrazinium analogues **6a**–**e** proved to be stable under comparable conditions. For example, a solution of the aminide **6a** in 2 M aq. hydrochloric acid changed from purple to yellow after 5 min at room temperature, and the free base could be quantitatively regenerated with aqueous alkali; a hydrochloride **13** could be isolated by passing gaseous hydrogen chloride through a chloroform solution of **6a**. The reactivity of the pyrazinium betaines (*cf.* **6**) is thus parallelled by that of 'neutral' triazolo[4,3-*a*]pyrazines: for example, 3-methyl[1,2,4]triazolo-[4,3-*a*]pyrazine is stable in hot aqueous acid.[9]

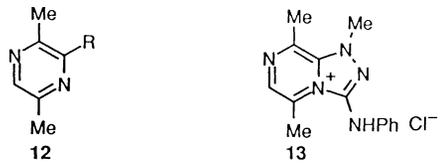



**Scheme 2**

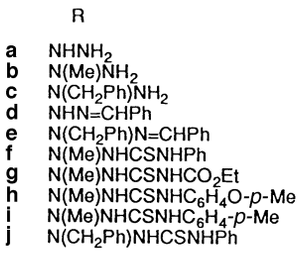
## Theoretical studies

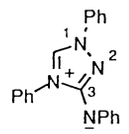
### Methods of calculation

Molecular structures were fully optimised using the PM3[10] method of the MOPAC package[11] at the 'precise' level using the general numbering convention shown in Fig. 1. Solvent effects were introduced into the calculation using the COSMO method[12] which is based on a continuum approach where the solute is embedded in a dielectric continuum of permittivity $\varepsilon$. In these studies, dichloromethane was selected as the solvent wih $\varepsilon = 8.9$.[13] The transition state in passing from **1** to **1A** by an intramolecular hydrogen shift (Scheme 1) was approached from both sides of the reaction using a saddle calculation. This approximate transition state was refined and then characterised by its unique single imaginary frequency. An *ab initio* reference calculation was carried out on **1** using the GAMESS program[14] at the 6-31G level[15] to compare with the semi-empirical results.



12 13



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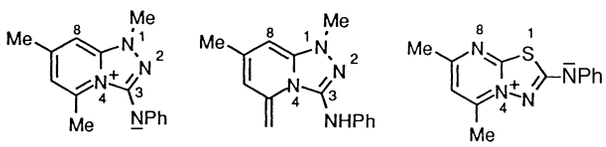
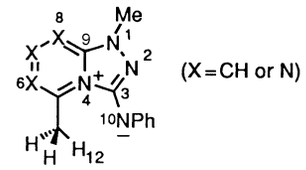


15 15A 16



(X = CH or N)

**Fig. 1** Numbering convention for condensed triazolium betaines listed in Table 2

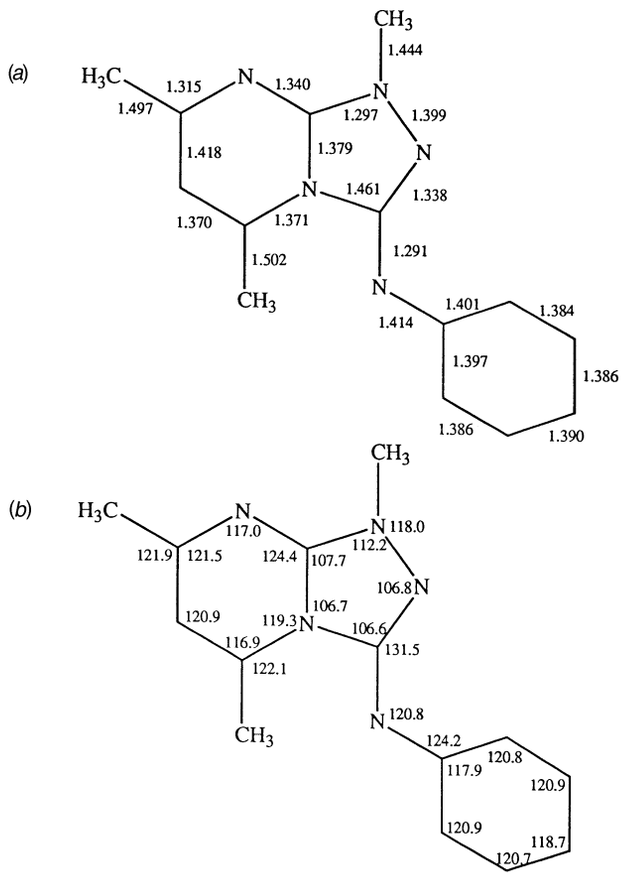



**Fig. 2** Calculated geometry of the aminide **1** obtained at 6-31G level (*a*) bond lengths; (*b*) angles

## Discussion

**Structural aspects.** The triazolium betaine structures selected for study were **1**, **5d**, **6a** and the 1,2,4-triazolo[4,3-*a*]pyridinium betaine **15** described in our earlier work.[2]

While there are a number of experimentally determined structures available in the Cambridge Structural Database[16] which are related to the condensed triazoles discussed here, almost all are organic salts, with the notable exception of 1,4-diphenyl-1,2,4-triazolium-3-(*N*-phenyl)aminide or Nitron[17] **14**. In this structure, there are two molecules in the unit cell which show average bond lengths at the heterocyclic ring which vary from 1.41 at N1–N2, 1.36 at N2–C3, 1.42 at C3–N4, 1.33 at N1–C5, and 1.32 Å at C3–NPh with average angles ranging from 104° at N1–N2–C3, 108° at N2–C3–N4, 109° at C3–N4–C5, and 113° at N2–N1–C5. An *ab initio* reference calculation on the aminide **1** at the 6-31G level with full optimisation of all variables gives a structure which has bond lengths of 1.40 at N1–N2, 1.34 at N2–C3, 1.46 at C3–N4, 1.30 at N1–C9, and 1.29 Å at C3–N10 with angles of 107° at N1–N2–C3, 107° at N2–C3–N4, 107° at C3–N4–C9, and 112° at N2–N1–C9 (Fig. 2). Although the parametrisation of the nitrogen atom in the PM3 method has been criticised,[18] the bond lengths and particularly the angles calculated here appear to show a reasonable correlation with the expected values based on both the experimental data for Nitron and the calculated 6-31G structure for **1**. For example, the PM3 structure for **1** shows calculated bond lengths of 1.41 at N1–N2, 1.45 at C3–N4, and 1.32 Å at C3–N10, with calculated angles of 108° at N1–N2–C3, 107° at N2–C3–N4, 107° at C3–N4–C9, and 111° at N2–N1–C9.

While the PM3 calculations predict planar conformations for the heterocyclic rings of **1**, **5d**, **6a** and **15**, in line with the experimental data for the single heterocyclic ring in Nitron **14** and the *ab initio* results on **1**, the phenyl group attached to the exocyclic nitrogen at the 3-position is twisted from this plane by *ca.* 30° in each case compared with experimental torsion angles of 15° and 6° found for the two molecules in the unit cell of Nitron. The reduced twist in the experimental structure may be a consequence of packing forces in the crystal since the *ab initio* structure for **1** also shows a twist of 28°.

There are no comparable crystallographic data available for the three corresponding tautomeric species **1A**, **5A**, **6A** and **15A**. The heterocyclic rings of these structures are predicted to be essentially planar, but the ring nitrogen at the 1-position now adopts a tetrahedral $sp^3$ conformation so that the attached methyl carbon in **1A** is calculated to be 26° above the ring plane. A similar change in hybridisation occurs at the exocyclic amino nitrogen (at the 3-position), where both the attached hydrogen and phenyl carbon atoms are 33 and 19° below the ring plane, respectively. The $sp^3$ hybridisation at the amino nitrogen is not unexpected, because of the potential clash between the attached hydrogen and one hydrogen on the adjacent methylene carbon at the 5-position of the heterocyclic ring in the alternative trigonal $sp^2$ configuration. Similar results are found for **5A**, **6A** and **15A**.

**Electronic properties.** The dipole moments of **1**, **5d**, **6a** and **15** calculated in dichloromethane are substantial, with values of 8.61, 8.49, 7.26 and 10.4 D respectively (Table 1). However, although these values are large, they compare favourably with the *ab initio* result obtained for **1** of 8.86 D and with the experimental value of 7.2 D found for Nitron **14** in benzene,[19] and reflect the large contribution of the charged resonance form to the overall structure. As might be anticipated, the calculated dipole moments of the tautomers **1A**, **5A**, **6A** and **15A** are considerably less than those of the respective betaines (see Table 1), with the largest change in passing from **15** to **15A** (8.70 D) and the lowest (2.53 D) from **6a** to **6A**.

It is of interest from a theoretical viewpoint to establish the relative importance of canonical forms describing the overall structures of the condensed betaines (*e.g.* **1**), and the relative thermodynamic stabilities of their tautomers (*e.g.* **1A**). It may

**Table 1** Calculated dipole moments and heats of formation for condensed triazolium betaines **1**, **5d**, **6a** and **15** and putative tautomers **1A**, **5A**, **6A** and **15A**

| Structure | $\mu$ | $\Delta H_f$ | Tautomer | $\mu$ | $\Delta H_f$ | $\Delta\mu$ | $\Delta E$ |
|---|---|---|---|---|---|---|---|
| **1** | 8.61 | 93.4 | **1A** | 3.69 | 96.5 | 4.91 | 3.19 |
| **5d** | 8.49 | 92.3 | **5A** | 2.78 | 98.5 | 5.71 | 6.17 |
| **6a** | 7.26 | 96.5 | **6A** | 4.73 | 100.5 | 2.53 | 4.00 |
| **15** | 10.5 | 87.0 | **15A** | 1.69 | 93.9 | 8.70 | 6.89 |

[a] $\mu$ is the dipole moment (D); $\Delta H_f$ is the heat of formation (kcal mol$^{-1}$), and $\Delta\mu$ and $\Delta E$ are the differences in dipole moments and energy (in the same units), respectively, between the tautomers.

**Table 2** Calculated atomic charges in condensed triazolium betaines **1**, **5d**, **6a** and **15** and related tautomers **1A**, **5A**, **6A** and **15A**

| Atom | **1** | **1A** | **5d** | **5A** | **6a** | **6A** | **15** | **15A** |
|---|---|---|---|---|---|---|---|---|
| N1 | 0.436 | 0.140 | 0.444 | 0.121 | 0.492 | 0.082 | 0.384 | 0.076 |
| N2 | −0.560 | −0.353 | −0.564 | −0.370 | −0.538 | −0.371 | −0.554 | −0.364 |
| C3 | 0.082 | −0.020 | 0.084 | −0.016 | 0.065 | −0.014 | 0.070 | −0.013 |
| N4 | 0.303 | 0.231 | 0.269 | 0.223 | 0.360 | 0.229 | 0.345 | 0.241 |
| C5 | 0.045 | −0.020 | 0.065 | −0.014 | −0.077 | −0.014 | −0.037 | −0.018 |
| X6 | −0.286 | −0.267 | −0.237 | −0.272 | −0.172 | −0.039 | −0.207 | 0.214 |
| X7 | 0.135 | 0.039 | 0.067 | 0.129 | −0.089 | −0.106 | 0.039 | 0.006 |
| X8 | −0.199 | −0.305 | −0.207 | −0.349 | 0.016 | −0.147 | −0.177 | −0.241 |
| C9 | −0.167 | −0.027 | −0.162 | −0.046 | −0.265 | −0.156 | −0.168 | −0.111 |
| N10 | −0.308 | 0.148 | −0.295 | 0.151 | −0.313 | 0.138 | −0.320 | 0.144 |
| C11 | −0.121 | −0.284 | −0.095 | −0.294 | −0.101 | −0.216 | −0.088 | −0.319 |

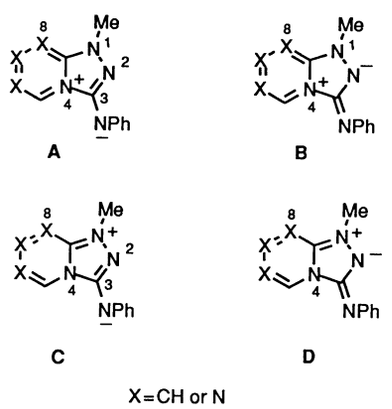



**Fig. 3** Significant canonical structures for condensed triazolium betaines **1**, **5d**, **6a** and **15**

be noted that the acidity of the 5- relative to the 7-$CH_3$ group (*cf*. **1**) is anticipated on the basis of H/D exchange at this site in the $^1$H NMR spectra of analogous condensed triazolium betaines (e.g. **16**).[20] It is notable that the calculated atomic charge at the 6-31G level of H-12 in **1** is +0.30 compared to values of +0.20 for the hydrogens attached to other methyl groups. However, this acidic hydrogen is well removed from the adjacent nitrogen, N-10, by 2.25 Å (Fig. 1).

A detailed analysis of the atomic charges of the nitrogens at the five-membered ring of the triazolium betaines at the PM3 level suggests that there are four major canonical forms which contribute to the large dipole moment (see Table 2 and Fig. 3). Two of these, **A** and **B**, have a positive charge located at N4 which is counteracted by a negative charge at either N10 (**A**) or N2 (**B**), while the others, **C** and **D**, have a positive charge at N1 with the negative charge again at either N10 (**C**) or N2 (**D**). The large negative charge at N2 in each case, which ranges from −0.54 to −0.56 over the series compared with −0.30 to −0.32 for N10, strongly suggests that **B** and **D** make a dominant contribution to the overall structure. Furthermore, an analysis of the charges at N1 and N4, shows that the positive charge at the former is considerably greater than that of the latter for **1**, **5d** and **6a**, suggesting that canonical form **D** is preferred in these cases, though there is little difference between **B** and **D** in the case of **15**.

These conclusions are supported by the PM3 structural data, which in all cases, show double bond character at C3–N10 and N1–C9 with bond lengths of *ca*. 1.32 and 1.35 Å, and single bond character at N1–N2, N2–C3 and N4–C9 with values of *ca*. 1.41, 1.39 and 1.41 Å, respectively. The *ab initio* reference calculation at the 6-31G level is highly supportive with the nominal double bonds at C3–N10 and N1–C9 even shorter at 1.29 and 1.30 Å, respectively (Fig. 2). There seems little doubt, therefore, that canonical structures **D** make an important overall contribution to the resonance hybrid. It is interesting to compare this view with our earlier conclusion on the molecular structure of 1-benzyl-5,7-dimethyl-1*H*-[1,2,4]triazolo[4,3-*a*]-pyrimidinium-3-olate (**1**, R = $CH_2$Ph; $O^-$ for $^-NR^2$) from X-ray crystallographic analysis:[5] namely, that a canonical form isostructural with **C** makes a significant contribution to the overall structure.

Since the charges on the exocyclic aminide nitrogens in the series (**1**, **5d**, **6a** and **15**) are comparable (N-10, Table 2) it was decided to calculate the relative thermodynamic stability of these betaines compared with their respective tautomers (**1A**, **5A**, **6A** and **15A**). A surprising outcome (Table 1) is that the latter are only marginally less stable than the former (3.2–6.9 cal mol$^{-1}$, 1 cal = 4.184 J, see Table 1).

With evidence for the thermodynamic feasibility of the initial step of the proposed rearrangement (Scheme 1) to hand, it was decided to calculate its kinetic basis assuming an intramolecular prototropic shift. The result indicated that the process is energetically demanding: the transition state for the hydrogen transfer is product-like, with $CH_2$–H and H–N distances of 1.56 and 1.25 Å respectively, with a barrier height of 31.5 kcal mol$^{-1}$ relative to **1**. The high activation energy arises, in part, from the strain induced by the transfer process which reduces the angles at N4–C5–$CH_3$ and at N4–C3–NPh from 122.6° and 121.3° in **1** to 115.7° and 117.8°, respectively, in the transition state.

## Conclusions

The target [1,2,4]triazolo[4,3-*c*]pyrimidinium-3-aminides (**5a**–**h**) and [1,2,4]triazolo[4,3-*a*]pyrazinium-3-aminides (**6a**–**e**) are readily synthesised by conventional methods. Unlike analogous [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides **1**, the [4,3-*c*] isomers **5** and the pyrazine derivatives **6** are stable and isolable, independent of whether the exocyclic *N*-substituent

is electron-withdrawing or otherwise; the formation of dimerisation products was not observed. The [1,2,4]triazolo-[4,3-*c*]pyrimidinium betaines **5** are, however, susceptible to nucleophilic attack at the 5-position leading to opening of the pyrimidine ring.

The structure and electronic properties of a series of condensed triazolium betaines **1**, **5d**, **6a** and **15** have been investigated theoretically using the PM3/COSMO method. As would be anticipated, the betaines have relatively high predicted dipole moments which show a good correlation with experimental data for Nitron **14** and with a reference gas phase calculation at the *ab initio* 6-31G level on the structure **1**. An unanticipated feature arises from estimated values of thermodynamic stabilities of the betaines described above, relative to their tautomeric counterparts **1A**, **5A**, **6A** and **15A**; these results suggest that their interconversion is feasible from a thermodynamic viewpoint. However, such a transformation, for **1** ⟶ **1A** at least, is unlikely to occur by a concerted intramolecular mechanism in view of the relatively high calculated barrier height of 31.5 kcal $mol^{-1}$.

The mechanism for formation of dimeric products (**3** and **4**) from [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides remains unclear. The present theoretical study would suggest that the initial step (**1** ⟶ **1A**) in the tentatively suggested route (Scheme 1) would proceed by a non-concerted process. In this context, it is relevant that the dimerisation of [1,2,4]triazolo[4,3-*a*]pyrimidinium salts related to the betaines **1** can be induced by means of an external base.[2] By analogy, an intermolecular mechanism involving sequential protonation (of the aminide nitrogen)/deprotonation (of the C5–Me group) can be envisaged as the initial step in the mechanism of dimerisation of the betaines **1**. We are presently embarked on the synthesis of a wider range of condensed triazolium betaines including [1,2,4]triazolo[4,3-*a*]quinazolinium- and [1,2,4]triazolo[4,3-*a*][1,3,5]triazinium aminides.

## Experimental

Mp values were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 580 and 1600 instruments and calibrated against polystyrene. $^1$H NMR spectra were recorded on Bruker WP80 (80 MHz), or Bruker WP200 (200.13 MHz) spectrometers. $^{13}$C NMR spectra were recorded on a Bruker WP200 (50.32 MHz) spectrometer. Chemical shifts are reported with respect to $SiMe_4$ as reference (positive shifts to high frequency/low field). UV–VIS spectra were recorded on a Shimadzu UV-240 spectrophotometer. Elemental analyses were performed at UMIST, Manchester, UK. Sorbsil C60 40/60 H was used for column chromatography unless otherwise stated, and analytical TLC pre-coated plates were used. *J* values in Hz. THF = tetrahydrofuran.

### Preparation of (2,4-dimethylpyrimidin-6-yl)hydrazine 7a

2,4-Dimethyl-6-chloropyrimidine[3] (11.0 g, 77 mmol) and hydrazine monohydrate (17.35 g, 347 mmol) in methylated spirit (120 $cm^3$) were stirred at room temp. for 1 h. The resulting white precipitate was separated and recrystallised from EtOAc to give the colourless title compound (8.69 g, 82%), mp 183–186 °C (lit.,[4] 186–187 °C). $\nu_{max}$(KBr)/$cm^{-1}$ 3298, 3196 and 1599 (NH). $\delta_H$[$(CD_3)_2SO$] 2.20 (s, 3 H, 4-Me), 2.30 (s, 3 H, 2-Me), 6.35 (s, 1 H, H-5). *m/z* (EI) 138 (100%), 108 (20), 91 (31), 67 (61), 42 (63), 41 (23), 39 (38).

### Preparation of 1-methyl-1-(2,4-dimethylpyrimidin-6-yl)-hydrazine 7b

2,4-Dimethyl-6-chloropyrimidine (45.0 g, 316 mmol), potassium carbonate (61.5 g, 445 mmol) and methylhydrazine (18.15 g, 394 mmol) were heated under reflux in methylated spirit (300 $cm^3$) for 1 h. The product was cooled and filtered and the filtrate was evaporated to give the colourless title compound (38.5 g, 80%), mp 89–90 °C (from hexane) (Found: C, 55.4; H, 8.2; N, 36.6%. $C_7H_{11}N_4$ requires C, 55.2; H, 8.0; N, 36.8%). $\nu_{max}$(KBr)/$cm^{-1}$ 3304 (NH) 3169 (NH), 1594 (NH); $\delta_H(CD_3COCD_3)$ 2.19 (s, 3 H, 4-Me), 2.31 (s, 3 H, 2-Me), 3.28 (s, 3 H, N−Me), 4.45 (br s, 2 H, $NH_2$), 6.75 (s, 1 H, H-5). *m/z* (FAB) 153 (100%) ($M^{\bullet+}$ + 1), 152 (13).

### Preparation of 6-benzylidenehydrazino-2,4-dimethylpyrimidine 7d

A solution of 2,4-dimethyl-6-hydrazinopyrimidine **7a** (10.0 g, 72 mmol) in hot ethanol (200 $cm^3$) was treated with benzaldehyde (11.5 g, 108 mmol) and the mixture was heated under reflux for 2 h. The solution was poured into water (600 $cm^3$) and the resultant precipitate was separated by filtration. This product was purified by washing with light petroleum (bp 60–80 °C) to give the title compound as an amorphous colourless solid (12.8 g, 78%), mp 161–164 °C (from light petroleum bp 60–80 °C) (Found: C, 69.0; H, 6.4; N, 24.5%. $C_{13}H_{14}N_4$ requires C, 69.0; H, 6.2; N, 24.8%). $\nu_{max}$(KBr)/$cm^{-1}$ 3181, 3051, 1596, 1446, 1140; $\delta_H$[$(CD_3)_2SO$] 2.3 (s, 3 H, Me), 2.4 (s, 3 H, Me), 6.9 (s, 1 H, N=CH), 7.35–7.75 (m, 5 H, Ar−H), 8.1 (s, 1 H, H-5), 11.35 (s, 1 H, NH). *m/z* (EI) 227 (2%) ($M^{\bullet+}$), 226 (10), 149 (13), 123 (100), 96 (12), 77 (10).

### Preparation of *N*-benzyl-*N*-(2,4-dimethylpyrimidin-6-yl)-benzaldehyde hydrazone 7e

6-Benzylidenehydrazino-2,4-dimethylpyrimidine **8d** (20.0 g, 88 mmol) in tetrahydrofuran (250 $cm^3$) was added dropwise to a stirred suspension of sodium hydride (2.11 g, 88 mmol) in tetrahydrofuran (250 $cm^3$) during which the temperature rose to *ca.* 30 °C. After 15 min, benzyl bromide (15.05 g, 88 mmol) was added and the solution was heated under reflux for 5 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, and the residual solid was partitioned between water and dichloromethane (total vol 200 $cm^3$). Evaporation of the organic extract and recrystallisation of the residue from light petroleum (bp 60–80 °C) gave the title compound (20.0 g, 72%), mp 129–131 °C (Found: C, 75.7; H, 6.5; N, 17.6%. $C_{20}H_{20}N_4$ requires C, 75.9; H, 6.3; N, 17.7%). $\nu_{max}$(KBr)/$cm^{-1}$ 1584. $\delta_H(CDCl_3)$ 2.5 (s, 3 H, Me), 2.55 (s, 3 H, Me), 5.6 (s, 1 H, $CH_2$), 7.15–7.6 (m, 12 H, Ar−H, H-5 and N=CH). *m/z* (EI) 316 (2%) ($M^{\bullet+}$), 212 (51), 91 (100), 77 (55), 42 (56).

### Preparation of 1-benzyl-1-(2,4-dimethylpyrimidin-6-yl)hydrazine 7c

A solution of *N*-benzyl-*N*-(2,4-dimethylpyrimidin-6-yl)-benzaldehyde hydrazone **7e** (15.0 g, 47 mmol) in 5 M aqueous hydrochloric acid (150 $cm^3$) was heated under reflux for 8 h. Benzaldehyde was removed from the mixture by co-distillation with water. The solution was cooled to room temp., basified with 5 M aqueous sodium hydroxide and then extracted with dichloromethane (2 × 100 $cm^3$). Evaporation of the organic extract gave the title compound as a yellow oil (7.15 g, 66%). No attempt was made to purify this compound to analytical standard and it was used for further transformations. $\delta_H(CDCl_3)$ 2.3 (s, 3 H, Me). 2.5 (s, 3 H, Me), 3.75 (br s, 2 H, $NH_2$) 4.95 (s, 2 H, $CH_2$), 6.7 (s, 1 H, H-5), 7.2–7.4 (m, 5 H, Ar–H). *m/z* (EI) 228.135 91 (50%), $C_{13}H_{16}N_4$ requires 228.137 50 ($M^{\bullet+}$), 137 (100%), 108 (46%), 107 (26%), 91 (99%).

### General method for the preparation of 1-methyl-1(2,4-dimethylpyrimidin-6-yl)thiosemicarbazides 7f–m

A solution of 1-methyl-1-(2,4-dimethylpyrimidin-6-yl)-hydrazine **8b** (1 mol) and the appropriate isothiocyanate derivative (1 mol) were stirred in diethyl ether at room temp. until the reaction was complete (1–24 h) [TLC examination]. The product precipitated to give, for example, colourless 1-methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-ethoxycarbonylthiosemicarbazide **7f** (68%), mp 193–194 °C (from EtOAc) (Found: C, 46.5; H, 6.4;

N, 24.8; S, 11.6%. $C_{11}H_{17}N_5O_2S$ requires C, 46.3; H, 6.7; N, 24.5; S, 11.2%). $\nu_{max}$(KBr)/cm$^{-1}$ 3252 (N–H), 3166 (N–H), 1718 (C=O), 1586 (N–H); $\delta_H(CD_2Cl_2)$ 1.3 (t, 3 H, *J* 7, $OCH_2CH_3$), 2.3 (s, 3 H, 4-Me), 2.5 (s, 3 H, 2-Me), 3.4 (s, 3 H, N–Me), 4.25 (q, 2 H, *J* 7, $OCH_2CH_3$), 6.25 (s, 1 H, H-5), 8.9 (br s, 1 H, NH), 10.3 (br s, 1 H, NH). *m/z* (FAB) 284 (100%) $(M + 1)^+$, 250 (26), 238 (25), 137 (20).

The following colourless compounds were also prepared.

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-benzoylthiosemicarbazide (7g, 80%).** Compound **7g** had mp 175–176 °C (from toluene) (Found: C, 57.3; H, 5.4; N, 22.2; S, 9.9%. $C_{15}H_{17}N_5OS$ requires C, 57.1; H, 5.4; N, 22.2; S, 10.2%). $\nu_{max}$(KBr)/cm$^{-1}$ 3188 (N–H), 3147 (N–H), 1684 (C=O), 1588 (N–H); $\delta_H(CD_3OD)$ 2.25 (s, 3 H, 4-Me) 2.45 (s, 3 H, 2-Me), 3.4 (s, 3 H, N–Me), 6.4 (s, 1 H, H-5), 7.45–7.9 (m, 5 H, Ar–H). *m/z* (EI) 315 (0.29%) ($M^{\cdot+}$), 283 (15), 282 (100), 105 (84), 77 (35).

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-benzyloxycarbonylthiosemicarbazide (7h, 70%).** Compound **7h** had mp 171–173 °C (from toluene) (Found: C, 55.7; H, 5.3; N, 20.5; S, 9.7%. $C_{16}H_{19}N_5O_2S$ requires: C, 56.0; H, 5.0; N, 20.4; S, 9.3%). $\nu_{max}$(KBr)/cm$^{-1}$ 3188 (N–H), 3147 (N–H), 1684 (C=O), 1588 (N–H); $\delta_H(Me_3SO)$ 2.2 (s, 3 H, 4-Me), 2.4 (s, 3 H, 2-Me), 3.3 (s, 3 H, N–Me), 5.2 (s, 2 H, $CH_2$), 6.3 (s, 1 H, H-5), 7.3–7.5 (m, 5 H, Ar–H), 11.45 (br s, 2 H, NH).

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-phenylthiosemicarbazide (7i, 92%).** Compound **7i** had mp 190–192 °C (Found: C, 58.2; H, 6.0; N, 24.5; S, 11.3%. $C_{14}H_{17}N_5S$ requires C, 58.5; H, 5.9; N, 24.4; S, 11.2%). $\nu_{max}$(KBr)/cm$^{-1}$ 3138 (N–H), 1596 (N–H). $\delta_H(CDCl_3)$ 2.4 (s, 3 H, 4-Me), 2.6 (s, 3 H, 2-Me) 3.4 (s, 3 H, N–Me), 6.6 (s, 1 H, H-5), 7.2–7.5 (m, 5 H, Ar–H), 8.05 (br s, 1 H, NH), 8.35 (br s, 1 H NH). *m/z* (EI) 287 (0.2%) ($M^{\cdot+}$), 254 (100), 137 (22), 136 (48), 77 (29).

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-*p*-tolylthiosemicarbazide (7j, 79%).** Compound **7j** had mp 185–186 °C (Found: C, 59.6; H, 6.6; N, 23.4; S, 11.0%. $C_{15}H_{19}N_5S$ requires C, 59.8; H, 6.3; N, 23.3; S, 10.6%. $\nu_{max}$(KBr)/cm$^{-1}$ 3134 and 1588 (N–H). $\delta_H(CDCl_3)$ 2.3 (s, 3 H, 4-Me or Ar–Me), 2.35 (s, 3 H, 4-Me or Ar–Me), 2.5 (s, 3 H, 2-Me), 3.35 (s, 3 H, N–Me), 6.6 (s, 1 H, H-5), 7.15 and 7.35 (dd, 4 H, $A_2B_2$ system of ArMe), 8.15 (br s, 1 H, NH), 8.35 (br s, 1 H, NH). *m/z* (EI) 301 (0.5%) ($M^{\cdot+}$), 268 (100), 137 (35), 136 (54), 108 (28), 91 (28), 67 (31).

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-*p*-nitrophenylthiosemicarbazide (7k, 92%).** Compound **7k** had mp 194–195 °C (decomp.) (Found: C, 50.6; H, 5.0; N, 25.0; S, 10.0%. $C_{13}H_{16}N_6O_2S$ requires: C, 50.6; H, 4.9; N, 25.3; S, 9.6%). $\nu_{max}$(KBr)/cm$^{-1}$ 3153 (N–H), 1587 (N–H). $\delta_H(CDCl_3)$ 2.4 (s, 3 H, 4-Me), 2.6 (s, 3 H, 2-Me), 3.4 (s, 3 H, N–Me), 6.55 (s, 1 H, H-5), 7.9 and 8.2 (dd, 4 H, $A_2B_2$ system of $ArNO_2$). *m/z* (EI) 180 (100%) ($M^{\cdot+}$), 152 (56), 136 (61), 67 (57), 49 (56), 31 (67).

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-*p*-methoxyphenylthiosemicarbazide (7l, 81%).** Compound **7l** had mp 183–184 °C. $\delta_H[(CO_3)_2SO]$ 2.2 (s, 3 H, 4-Me), 2.4 (s, 3 H, 2-Me), 3.2 (s, 3 H, N–Me or Ar–OMe), 3.7 (s, 3 H, N–Me or Ar–OMe), 6.35 (s, 1 H, H-5), 6.85 and 7.3 (dd, 4 H, $A_2B_2$ system of Ar–OMe); *m/z* (EI) 317.131 03 (3%). $C_{15}H_{19}N_5OS$. requires: 317.132 40, [$M^{\cdot+}$], 284 (81), 165 (100), 150 (69), 136 (60), 122 (45), 91 (44).

**1-Methyl-1-(2,4-dimethylpyrimidin-6-yl)-4-methylthiosemicarbazide (7m, 94%).** Compound **7m** had mp 222–223 °C (Found: C, 47.7; H, 7.0; N, 31.2; S, 14.5%. $C_9H_{15}N_5S$ requires: C, 48.0; H, 6.7; N, 31.1; S, 14.2%). $\nu_{max}$(KBr)/cm$^{-1}$ 3164 and 1592 (NH). $\delta_H(CDCl_3)$ 2.35 (s, 3 H, 4-Me), 2.5 (s, 3 H, 2-Me), 3.1 (d, 3 H, *J* 5, 4-NMe), 3.3 (s, 3 H, 1-NMe), 6.45 (s, 1 H, H-5), 6.7 (br s, 1 H, NH), 7.7 (br s, 1 H, NH). *m/z* (EI) 225 (0.2%) ($M^{\cdot+}$), 192 (100), 137 (14), 136 (30), 108 (14), 67 (14).

**1-Benzyl-1-(2,4-dimethylpyrimidin-6-yl)-4-ethoxycarbonylthiosemicarbazide (7n, 74%).** Compound **7n** had mp 170–171 °C (Found: C, 56.6; H, 6.1; N, 19.8; S, 9.2%. $C_{17}H_{21}N_5O_2S$ requires C, 56.8; H, 5.8; N, 19.5; S, 9.2%). $\nu_{max}$(KBr)/cm$^{-1}$ 3414 (N–H), 3214 (N–H), 3005, 1721 (C=O), 1590 (N–H), 1552, 1191, 1044; $\delta_H(CDCl_3)$ 1.3 (t, 3 H, *J* 7, $OCH_2CH_3$), 2.35 (s, 3 H, 4-Me), 2.6 (s, 3 H, 2-Me), 4.2 (q, 2 H, *J* 7, $OCH_2CH_3$), 5.2 (br s, 2 H, $CH_2Ph$), 6.2 (s, 1 H, H-5), 7.3 (s, 5 H, Ar–H), 8.5 (br s, 1 H, NH), 10.9 (br s, 1 H, NH). *m/z* (EI) 360 (1%) ($M^{\cdot+}$), 212 (44), 91 (91).

**General method for the preparation of [1,2,4]triazolo[4,3-*c*]-pyrimidinium-3-aminides 5a–h**

The appropriate thiosemicarbazide derivative (1 equiv.) was stirred with dicyclohexylcarbodiimide (1.5 equiv.) in acetone for 3–7 d. The precipitate was separated by filtration and was either washed with chilled acetone or dissolved in dichloromethane and reprecipitated with light petroleum (bp 40–60 °C). The following compounds were prepared.

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-ethoxycarbonylaminide 5a.** Compound **5a** was a pale-yellow amorphous solid (57%), mp 140 °C (decomp.) (Found: C, 52.9; H, 6.3; N, 27.0%. $C_{11}H_{15}N_5O$ requires C, 52.9; H, 6.0; N, 28.0%). $\nu_{max}$(KBr)/cm$^{-1}$ 3051, 2974, 1644 (C=O), 1600, 1518. $\delta_H(CDCl_3)$ 1.3 (t, 3 H, *J* 7, $CH_2CH_3$), 2.5 (s, 3 H, 7-Me), 3.25 (s, 3 H, 5-Me), 3.85 (s, 3 H, N–Me), 4.1 (q, 2 H, *J* 7, $CH_2CH_3$), 6.9 (s, 1 H, H-8). *m/z* (FAB), 250 (81%) $(M + 1)^+$, 204 (100), 177 (14).

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-benzoyl aminide 5b.** Compound **5b** was a pale-yellow amorphous solid (36%), mp 190–191 °C (decomp.). $\nu_{max}$(KBr)/cm$^{-1}$ 1652 (C=O), 1595, 1579, 1551, 1504. $\delta_H(CDCl_3)$ 2.45 (s, 3 H, 7-Me), 3.4 (s, 3 H, 5-Me), 3.95 (s, 3 H, N–Me), 6.9 (s, 1 H, H-8), 7.35–7.45 (m, 3 H, Ar–H), 8.15–8.5 (m, 2 H, Ar-H). *m/z* (FAB) 282 (100%) $(M + 1)^+$, 281 (21), 204 (20), 105 (43).

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-benzyloxycarbonylaminide 5c.** Compound **5c** was a pale-yellow amorphous solid (39%). mp 161–163 °C (decomp.) (Found: C, 61.4; H, 5.6; N, 22.2%. $C_{16}H_{17}N_5O_2$ requires C, 61.7; H, 5.5; N, 22.5%). $\nu_{max}$(KBr)/cm$^{-1}$ 1644 (C=O), 1594, 1517, 1271, 1120. $\delta_H(CDCl_3)$ 2.45 (s, 3 H, 7-Me), 3.2 (s, 3 H, 5-Me), 3.85 (s, 3 H, N-Me), 5.15 (s, 2 H, $CH_2$), 6.85 (s, 1 H, H-8), 7.15–7.5 (m, 5 H, Ar-H). *m/z* (FAB) 312 (88%) $(M + 1)^+$, 311 (14), 205 (15), 204 (100), 177 (45).

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-phenylaminide 5d.** Compound **5d** was an orange amorphous solid (56%), mp 190–191 °C (decomp.) (Found: C, 66.2; H, 5.8; N, 27.4%. $C_{14}H_{15}N_5$ requires: C, 66.4; H, 5.9; N, 27.7%). $\nu_{max}$(KBr)/cm$^{-1}$ 1655, 1620, 1585, 1520. $\delta_H(CDCl_3)$ 2.4 (s, 3 H, 7-Me), 3.35 (s, 3 H, 5-Me), 3.65 (s, 1 H, N–Me), 6.5 (s, 1 H, H-8), 6.7–6.9 (m, 1 H, Ar–H), 7.1–7.55 (m, 4 H, Ar–H). *m/z* (FAB) 254 (100%) $(M + 1)^+$, 253 (29), 239 (18), 136 (25), 90 (15), 77 (19).

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-*p*-tolylaminide 5e.** Compound **5e** was an orange amorphous solid (52%), mp 184–185 °C (Found: C, 67.4; H, 6.4; N, 26.2%. $C_{15}H_{17}N_5$ requires: C, 67.3; H, 6.5; N, 26.1%). $\nu_{max}$(KBr)/cm$^{-1}$ 1657, 1618, 1595, 1517, 1500. $\delta_H(CDCl_3)$ 2.25 (s, 3 H, 7-Me or Ar–Me), 2.4 (s, 3 H, 7-Me or Ar–Me), 3.3 (s, 3 H, 5-Me), 3.65 (s, 3 H, N–Me), 6.45 (s, 1 H, H-8), 7.05 and 7.35 (dd, 4 H, $A_2B_2$ system of ArMe); *m/z* (FAB) 268 (100%) $(M + 1)^+$, 267 (30), 243 (17), 132 (18), 43 (19).

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-*p*-methoxyphenylaminide 5f.** Compound **5f** was an orange amorphous solid (40%), mp 165–167 °C. $\nu_{max}$(KBr)/cm$^{-1}$ 1655, 1621, 1532, 1500. $\delta_H(CDCl_3)$ 2.4 (s, 3 H, 7-Me) 3.4 (s, 3 H, 2-Me), 3.65 (s, 3 H, N–Me or Ar–OMe) 3.8 (s, 3 H, N–Me or ArOMe), 6.5 (s, 1 H, H-8), 6.85 and 7.4 (dd, 4 H, $A_2B_2$ system of ArOMe). *m/z* (EI) 283.145 21 (8%): $C_{15}H_{17}N_5O$ requires: 283.145 21 ($M^{\cdot+}$), 259 (100), 244 (58), 218 (57), 203 (62).

**1,5,7-Trimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-*p*-nitrophenylaminide 5g.** Compound **5g** was a deep-red amorphous solid (59%), mp 258–259 °C (Found: C, 56.7; H, 4.8; N, 28.1). $C_{14}H_{14}N_6O_2$. requires C, 56.4; H, 4.7; N, 28.2%). $\nu_{max}$(KBr)/cm$^{-1}$ 1651, 1608, 1576, 1510; $\delta_H[(CD_3)_2SO)]$ 2.4 (s, 3 H, 7-Me), 3.2 (s, 3 H, 5-Me), 3.85 (s, 3 H, N–Me), 7.6 (s, 1 H, H-8), 7.4 and 8.0 (dd, 4 H, $A_2B_2$ system of $ArNO_2$). *m/z* (FAB) 299 (100%) $(M + 1)^+$, 149 (24), 89 (17), 81 (15), 71 (17).

**1-Benzyl-5,7-dimethyl[1,2,4]triazolo[4,3-*c*]pyrimidinium-3-ethoxycarbonylaminide 5h.** Compound **7h** formed yellow needles (46%), mp 157–160 °C (Found: C, 62.8; H, 5.6; N, 21.2. $C_{17}H_{19}N_5O_2$ requires: C, 62.8; H, 5.8; N, 21.5%). $\nu_{max}$(KBr)/cm$^{-1}$ 3056, 2964, 1652 (C=O), 1594, 1521. *m/z* (FAB) 326 (100%) $(M + 1)^+$, 325 (18), 281 (17), 280 (29), 137 (25), 91 (59). $\delta_H(CDCl_3)$ 1.3 (t, 3 H, *J* 7, $CH_2CH_3$), 2.4 (s, 3 H, 7-Me), 3.25 (s, 3 H, 5-Me), 4.2 (q, 2 H, *J* 7, $CH_2CH_3$ 5.35 (s, 2 H, $CH_2$Ph), 6.75 (s, 1 H, H-8), 7.3 (s, 5 H, Ar-H).

### Hydrolysis of [1,2,4]triazolo[4,3-*c*]pyrimidinium betaines 5d,e with water

**Compound 5d.** The orange aminide **5d** (0.02 g, 0.073 mmol) was stirred as a suspension in water (5 cm$^3$) for 12 h during which time the mixture became colourless. The precipitate was separated by filtration and dried to give the triazole derivative **8a** in quantitative yield (0.17 g), mp 208–210 °C (Found: C, 61.7; H, 6.2; N, 25.5%. $C_{14}H_{17}N_5O$. requires C, 62.0; H, 6.3; N, 25.8%). $\nu_{max}$(KBr)/cm$^{-1}$ 3414 (N–H), 3278 (N–H), 3154, 1691 (C=O), 1650, 1601, 1572, 1474, 1266. $\delta_H[(CD_3)_2SO]$ 2.1 (s, 3 H, $CH_3CO$), 2.35 [s, 3 H, NHC(*Me*)=], 3.7 (s, 3 H, N–Me), 5.5 [(s, 1 H, -C*H*=C(Me)], 6.7–7.5 (m, 5 H, Ar–H), 9.05 (s, 1 H, NH), 11.4 (s, 1 H, NH). *m/z* (FAB) 272 (88%) $(M + 1)^+$, 271 (100), 230 (47), 229 (27).

**Triazole derivative 8b.** Compound **8b** was prepared in similar fashion (27%), mp 127–129 °C (Found: C, 62.9; H, 6.9; N, 24.3. $C_{15}H_{19}N_5O$ requires C, 63.1; H, 6.7; N, 24.5%). $\nu_{max}$(KBr)/cm$^{-1}$ 3290 (NH), 1690 (C=O), 1650, 1610, 1560, 1530. $\delta_H(CDCl_3)$ 2.1 (s, 3 H, $CH_3CO$ or Ar–Me), 2.2 (s, 3 H, $CH_3CO$ or ArMe), 2.4 [d, 3 H, NHC(*Me*)=], 3.6 (s, 3 H, N–Me), 5.0 [s, 1 H, -C*H*=C(Me)], 6.4 (br s, 1 H, NH), 7.0 and 7.3 (dd, 4 H, $A_2B_2$ system of Ar–Me), 11.35 (br s, 1 H, NH). *m/z* (FAB) 286 (100%) $(M + 1)^+$, 285 (88), 244 (46), 243 (24), 43 (17).

### General procedure for the hydrolysis of [1,2,4]triazolo[4,3-*c*]-pyrimidinium-3-aminides 5a,d,g with aqueous hydrochloric acid

The appropriate aminide (0.10 g,) was suspended in water (5 cm$^3$). Addition of several drops of 5 M HCl(aq.) caused immediate hydrolysis. The product was collected by filtration to afford, for example, the triazole derivative **8a** (0.83 g, 78%) mp 215–217 °C (see above). The following compounds were also prepared.

**Triazole derivative 8e.** Compound **8e** (0.10 g, 93%) had mp 232–234 °C. $\nu_{max}$(KBr)/cm$^{-1}$ 3236 (N–H), 1750 (C=O), 1695 (C=O), 1650, 1600. $\delta_H(CDCl_3)$ 1.3 [t, 3 H, *J* 7, $-OCH_2(CH_3)$], 2.2 (s, 3 H, $CH_3CO$), 2.4 [d, 3 H, *J* 1, NHC(*Me*)=], 3.7 (s, 3 H, NMe), 4.2 (q, 2 H, *J* 7, $OCH_2CH_3$), 5.1 [s, 1 H, *J* 1, -C*H*=C(Me)], 7.3 (br s, 1 H, N–H), 11.4 (br s, 1 H, N–H). *m/z* (EI) 267.130 50. $C_{11}H_{17}N_5O_3$ requires 267.133 14 ($M^{\cdot+}$).

**Triazole derivative 8f**. Compound **8f** (0.048 g, 44%) had mp 244–246 °C (Found: C, 52.9; H, 5.0; N, 26.3. $C_{14}H_{16}N_6O_3$ requires C, 53.2; H, 5.1; N, 26.6%). $\nu_{max}$(KBr)/cm$^{-1}$ 3279 (N–H), 3131 (N–H), 1692 (C=O), 1651, 1603. $\delta_H[(CD_3)_2SO]$ 2.2 (s, 3 H, $CH_3CO$), 3.3 [s, 3 H, *J* 1, NHC(*Me*)=], 3.8 (s, 3 H, N-Me), 5.6 [s, 1 H, *J* 1, -C*H*=C(Me)], 7.7 and 8.2 (dd, 4 H, $A_2B_2$ system of $ArNO_2$), 10.1 (br s, 1 H, N–H), 11.2 (br s, 1 H, N–H). *m/z* (FAB) 317 (100%) $(M+ 1)^+$, 316 (76), 189 (66), 39 (49).

### Reaction of [1,2,4]triazolo[4,3-*c*]pyrimidinium-3-phenylaminide 5d with alcohols

The aminide **5d** (0.10 g, 0.395 mmol) was stirred in methanol (10 cm$^3$) for 45 min during which time the compound dissolved and the solution became colourless. The excess reagent/solvent was evaporated under reduced pressure, and the residual solid was triturated with light petroleum (10 cm$^3$) to provide the colourless triazole derivative **8c** (0.078 g, 71%), mp 128–129 °C (Found: C, 63.0; H, 6.7; N, 24.2. $C_{15}H_{19}N_5O$ requires C, 63.1; H, 6.7; N, 24.5%). $\nu_{max}$(KBr)/cm$^{-1}$ 3275 (NH), 1676, 1603, 1566, 1547, 1505, 1453, 1279. $\delta_H(CDCl_3)$ 1.85 [s, 3 H, $CH_3C(OMe)$], 2.0 [d, 3 H, *J* 1, NC($CH_3$)=CH], 3.7 (s, 3 H, N–Me or OMe), 3.75 (s, 3 H, N–Me or OMe), 5.45 [d, 1 H, *J* 1, C*H*=C(Me)], 6.5 (s, 1 H, NH), 6.8–7.45 (m, 5 H, Ar–H). *m/z* (FAB) 286 (100%) $(M + 1)^+$, 285 (87), 270 (32), 254 (60).

The amide **5d** (0.1 g, 0.395) was treated with ethanol using the procedure described above to give the triazole derivative **8d** (0.094 g, 80%), mp 95–97 °C (Found: C, 43.9; H, 7.0; N, 23.1. $C_{16}H_{21}N_5O$ requires C, 64.2; H, 7.0; N, 23.4%). $\nu_{max}$(KBr)/cm$^{-1}$ 3276 (NH), 1676, 1603, 1565, 1547, 1500, 1270. $\delta_H(CDCl_3)$ 1.3 (t, 3 H, *J* 7, $CH_3CH_2$), 1.8 [s, 3 H, $CH_3C(OEt)$], 2.0 [d, 3 H, *J* < 1, NC($CH_3$)=CH], 3.7 (s, 3 H, N–Me), 4.2 (q, *J* 7, 2 H, $OCH_2CH_3$), 5.45 [q, 1 H, *J* < 1, C*H*=C(Me)], 7.05 (s, 1 H, NH), 6.8–7.5 (m, 5 H, Ar–H). *m/z* (FAB) 300 (35%) $(M + 1)^+$, 77 (100), 74 (83).

### Preparation of 1-methyl-1-(2,5-dimethylpyrazin-6-yl)hydrazine 12b

3-Chloro-2,5-dimethylpyrazine (15.0 g, 100 mmol), potassium carbonate (31.05 g, 250 mmol), methylhydrazine (33.75 g, 750 mmol) and butanol (150 cm$^3$) were heated under reflux for 4 h. The product was cooled and filtered, and the solvent was evaporated by distillation at atmospheric pressure. The residual orange oil solidified on cooling and was digested in diethyl ether. The mixture was filtered and the filtrate was evaporated under reduced pressure. The solid was dissolved in a mixture (1:1) of ethyl acetate and dichloromethane and eluted through a short column of silica gel to afford the title compound as a colourless solid (7.76 g, 51%) mp 46–48 °C (Found: C, 55.5; H, 7.6; N, 36.5. $C_7H_{11}N_4$ requires C, 55.3; H, 7.9; N, 36.8%). $\nu_{max}$(KBr)/cm$^{-1}$ 3300 (NH), 3280 (NH), 1634, 1534. $\delta_H(CDCl_3)$ 2.4 (s, 3 H, CMe), 2.5 (s, 3 H, CMe), 3.0 (s, 3 H, NMe), 4.10 (br s, 2 H, $NH_2$), 7.9 (s, 1 H, H-3). *m/z* (FAB) 153 (100%) $(M + 1)^+$, 152 (77), 151 (18).

### Preparation of 6-benzylidenehydrazino-2,5-dimethylpyrazine 12d

2,4-Dimethyl-6-hydrazinopyrazine **12a** (4 g, 29 mmol) was treated with benzaldehyde (4.6 g, 44 mmol) in ethanol (50 cm$^3$). The solution was heated under reflux for 2.5 h then poured into water (500 cm$^3$) and the precipitate was separated by filtration. The product was recrystallised from light petroleum (bp 60–80 °C) to give the title compound as colourless crystals (3.8 g, 58%), mp 157–159 °C (Found: C, 69.0; H, 6.2; N, 25.0. $C_{13}H_{14}N_4$ requires C, 69.0; H, 6.2; N, 24.7%). $\nu_{max}$(KBr)/cm$^{-1}$ 3222 (N–H), 3056, 1604, 1587, 1542. $\delta_H(CDCl_3)$ 2.45 (s, 3 H, CMe), 2.65 (s, 3 H, CMe), 7.35 (m, 3 H, Ar–H), 7.65 (m, 2 H, Ar–H), 7.85 (s, 1 H, Ar–H or N=CH). 7.9 (s, 1 H, Ar–H or N=CH); *m/z* (FAB) 227 (100%) $(M + 1)^+$, 226 (22), 123 (49).

### Preparation of *N*-benzyl-*N*-(2,5-dimethylpyrazin-6-yl)-benzaldehyde hydrazone 12e

6-Benzylidenehydrazino-2,5-dimethylpyrazine **12d** (1.0 g, 4.4 mmol) in THF (25 cm$^3$) was added dropwise to a stirred suspension of sodium hydride (0.106 g, 4.4 mmol) in THF (25 cm$^3$) for 15 min. Benzyl bromide (0.75 g, 4.4 mmol) was then added and the mixture heated under reflux for 2 h. After cooling to room temp., the mixture was filtered and the filtrate evaporated under reduced pressure. The brown residue was chromatographed on silica using light petroleum (bp 60–80 °C)–ethyl acetate (80:20) as eluent, to afford the title product as yellow crystals (0.92 g, 66%), mp 107–109 °C (Found: C, 76.2; H, 6.4; N, 17.7%. $C_{20}H_{20}N_4$ requires C, 76.9; H, 6.4; N, 17.7%). $\nu_{max}$(KBr)/cm$^{-1}$ 1591, 1563, 1530, 1418, 1144. $\delta_H(CDCl_3)$ 2.35 (s, 3 H, CMe), 2.9 (s, 3 H, (CMe), 5.55 (s, 2 H, $CH_2$), 7.1–7.4 (m, 8H, Ar–H), 7.45 (s, 1 H, N=CH), 7.45–7.55 (m, 2 H, Ar–H), 7.95 (s, 1 H, H-3). *m/z* (FAB) 317 (45%) $(M + 1)^+$, 225 (30), 119 (54), 100 (78), 91 (100).

### Preparation of 1-benzyl-1-(2,5-dimethylpyrazin-6-yl)hydrazine 12c

A solution of *N*-benzyl-*N*-(2,5-dimethylpyrazin-6-yl)benzaldehyde hydrazone **12e** (2.5 g, 8.0 mmol) in 2 M aqueous hydrochloric acid (50 cm$^3$) was heated under reflux for 1 h.

Benzaldehyde was removed from the mixture by co-distillation with water. The solution was cooled to room temp., basified with 2 M aqueous sodium hydroxide, and then extracted with dichloromethane (2 × 25 $cm^3$). Evaporation of the organic extract gave the title compound as a yellow oil (1.1 g, 57%). No attempt was made to purify the compound to analytical standard and it was used for further transformations. $\nu_{max}$(KBr)/$cm^{-1}$ 3328 (NH), 3188 (NH), 3029, 2923, 2849, 1606, 1570, 1533, 1495. $\delta_H$($CDCl_3$) 2.4 (s, 3 H, CMe), 2.6 (s, 3 H, CMe), 3.75 (br s, 2 H, $NH_2$), 7.2–7.4 (m, 5 H, Ar–H), 7.95 (s, 1 H, H-3). *m/z* (EI) 228.137 33 (20%). $C_{14}H_{16}N_4$ requires 228.137 50 ($M^{\bullet+}$), 137 (100), 91 (74).

**General procedure for the preparation of 1-substituted-1-(2,5-dimethylpyrazin-6-yl)thiosemicarbazides 12f–j**

The hydrazine derivative (**12b** or **12c**) (1 equiv.) and the appropriate isothiocyanate derivative (1 equiv.) were stirred in diethyl ether for 24 h at room temp. The resulting precipitate was collected by filtration and recrystallised from light petroleum (bp 60–80 °C)–toluene (1:1). The following compounds were prepared.

**1-Methyl-1-(2,5-dimethylpyrazin-6-yl)-4-phenylthiosemicarbazide 12f.** Compound **12f** formed colourless crystals (69%), mp 148–150 °C (Found: C, 58.3; H, 6.0; N, 24.1; S, 10.7. $C_{14}H_{17}N_5S$ requires C, 58.6; H, 5.9; N, 24.4; S, 11.1%). $\nu_{max}$(KBr)/$cm^{-1}$ 3243 (NH), 3136 (NH), 1593, 1526, 1446. $\delta_H$($CDCl_3$) 2.50 (s, 3 H, CMe), 2.60 (s, 3 H, CMe), 3.10 (s, 3 H, NMe), 7.18–7.67 (m, 5 H, Ar–H), 7.95 (br s, 1 H, NH), 8.15 (s, 1 H, H-3), 8.95 (br s, 1 H, NH). *m/z* (FAB) 288 (87%) $(M + 1)^+$, 254 (100), 147 (29), 109 (28).

**1-Methyl-1-(2,5-dimethylpyrazin-6-yl)-4-ethoxycarbonylthiosemicarbazide 12 g.** Compound **12g** was orange (86%), mp 122–124 °C (Found: C, 46.9; H, 5.8; N, 24.6. $C_{11}H_{17}N_5O_2S$ requires C, 46.7; H, 6.0; N, 24.7%). $\nu_{max}$(KBr)/$cm^{-1}$ 3164 (NH), 3013 (NH), 1708 (C=O), 1539, 1447. $\delta_H$($CDCl_3$) 1.35 (t, 3 H, *J* 8, $CO_2CH_2CH_3$), 2.45 (s, 3 H, 2- or 5-Me), 2.50 (s, 3 H, 2- or 5-Me), 3.25 (s, 3 H, NMe), 4.25 (q, 2 H, *J* 8, $CO_2CH_2CH_3$), 7.95 (br s, 1 H, NH), 8.0 (s, 1 H, H-3), 11.4 (br s, 1 H, NH). *m/z* (FAB), 284 (100%) $(M + 1)^+$, 250 (76), 238 (22).

**1-Methyl-1-(2,5-dimethylpyrazin-6-yl)-4-*p*-methoxyphenylthiosemicarbazide 12 h.** Compound **12h** was colourless (68%), mp 162–164 °C (Found: C, 56.8; H, 6.0; N, 22.1. $C_{15}H_{19}N_5O_5$ requires C, 56.8; H, 6.0; N, 22.1%). $\nu_{max}$(KBr)/$cm^{-1}$ 3329 (NH), 3123 (NH), 2963, 1533, 1449. $\delta_H$($CDCl_3$) 2.50 (s, 3 H, 2- or 5-Me), 2.60 (s, 3 H, 2- or 5-Me), 3.10 (s, 3 H, NMe), 3.80 (s, 3 H, OMe), 6.9 and 7.45 (dd, 4 H, $A_2B_2$ system of $C_6H_4OMe$), 7.8 (br s, 1 H, NH), 8.15 (s, 1 H, H-3), 8.8 (br s, 1 H, NH). *m/z* (FAB) 318 (100%) $(M + 1)^+$, 317 (25), 285 (20), 284 (78), 177 (53).

**1-Methyl-1-(2,5-dimethylpyrazin-6-yl)-4-*p*-tolythiosemicarbazide 12i.** Compound **12i** was colourless (79%), mp 158–160 °C (Found: C, 59.5; H, 6.5; N, 23.2. $C_{15}H_{19}N_5S$ requires C, 59.8; H, 6.3; N, 23.3%). $\nu_{max}$(KBr)/$cm^{-1}$ 3268 (NH), 3146 (NH), 2978, 1527, 1449; $\delta_H$($CDCl_3$) 2.35 (s, 3 H, $C_6H_4Me$), 2.50 (s, 3 H, 2- or 5-Me), 2.60 (s, 3 H, 2- or 5-Me), 3.10 (s, 3 H, NMe), 7.20 and 7.45 (dd, 4 H, $A_2B_2$ system of $C_6H_4Me$), 7.75 (br s, 1 H, NH), 8.15 (s, 1 H, H-3), 8.9 (br s, 1 H, NH). *m/z* (FAB) 302 $(M + 1)^+$.

**1-Benzyl-1-(2,5-dimethylpyrazin-6-yl)-4-phenylthiosemicarbazide 12j.** Compound **12j** formed colourless crystals (70%), mp 145–148 °C (Found: C, 65.9; H, 5.8; N, 19.2. $C_{20}H_{12}N_5S$ requires C, 66.1; H, 5.8 ; N, 19.3%). $\nu_{max}$/$cm^{-1}$ 3312 (NH), 3118 (NH), 2968, 1595, 1543, 1504, 1446, 1265, 1167; $\delta_H$($CDCl_3$) 2.55 (s, 3 H, Me), 2.7 (s, 3 H, Me), 4.25–4.65 (m, 2 H, $CH_2$), 7.15–7.50 (m, 10 H, Ar–H), 8.15 (br s, 1 H, NH), 8.25 (s, 1 H, H-3), 8.65 (br s, 1 H, NH).

**General method for the preparation of 1,2,4-triazolo[4,3-*a*]-pyrazinium-3-aminides 6a–e**

The appropriate thiosemicarbazide (**12f–j**) (1 equiv.) was treated with dicyclohexylcarbodiimide (1.5 equiv.) in acetone for 2 d at room temp. The resultant precipitate was collected by filtration and washed with diethyl ether. The following compounds were prepared.

**1,5,8-Trimethyl-1,2,4-triazolo[4,3-*a*]pyrazinium-3-phenylaminide 6a.** Compound **6a** was a dark-red amorphous solid (75%), mp 204–207 °C (decomp.) (Found: C, 66.1; H, 6.0; N, 27.4. $C_{14}H_{15}N_5$ requires C, 66.4; H, 5.9; N, 27.7%). $\nu_{max}$(KBr)/$cm^{-1}$ 1614, 1575, 1504. $\delta_H$[$(CD_3)_2SO$] 2.75 (s, 3 H, 8-Me), 3.05 (s, 3 H, 5-Me), 4.1 (s, 3 H, N–Me), 6.6 (m, 1 H, Ar–H), 7.1 (m, 2 H, Ar–H), 7.4 (m, 3 H, Ar–H). *m/z* (FAB) 254 (100%) $(M + 1)^+$, 253 (89).

**1,5,8-Trimethyl-1,2,4-triazolo[4,3-*a*]pyrazinium-3-ethoxycarbonylaminide 6b.** Compound **6b** was yellow and fluorescent (63%), mp 212–213 °C (decomp.) (Found: C, 53.0; H, 6.1; N, 27.8. $C_{11}H_{15}N_5O_2$ requires C, 53.0; H, 6.0; N, 28.1%). $\nu_{max}$(KBr)/$cm^{-1}$ 1637 (C=O) 1579, 1503. $\delta_H$($CDCl_3$) 1.3 (t, 3 H, *J* 7, $CO_2CH_2CH_3$), 2.91 (m, 3 H, *J* < 0.7, 8-Me), 3.10 (m, 3 H, *J* < 0.9, 5-Me), 3.47 (q, 2 H, *J* 7, $CO_2CH_2CH_3$), 4.3 (s, 3 H, NMe), 7.52 (m, 1 H *J* < 0.9, H-6). *m/z* (FAB) 250 (100%) $(M + 1)^+$, 204 (63).

**1,5,8-Trimethyl-1,2,4-triazolo[4,3-*a*]pyrazinium-3-*p*-methoxyphenylaminide 6c.** Compound **6c** was a dark-red amorphous solid (78%), mp 198–200 °C (decomp.) (Found: C, 63.5; H, 6.0; N, 24.6. $C_{15}H_{17}N_5O$ requires C, 63.0; H, 6.0; N, 24.7%). $\nu_{max}$(KBr)/$cm^{-1}$ 1612, 1584, 1511. $\delta_H$($CDCl_3$) 2.74 (m, 3 H, *J* < 0.8, 8-Me), 3.11 (m, 3 H, *J* < 0.9, 5-Me), 3.75 (s, 3 H, NMe), 4.10 (s, 3 H, OMe), 7.20 (m, 1 H, *J ca.* 0.9, H-6), 7.35–7.45 (m, 4 H, $A_2B_2$ system of $C_6H_4OMe$). *m/z* (FAB) 284 (100%) $(M + 1)^+$, 283 (62), 119 (24), 100 (48).

**1,5,8-Trimethyl-1,2,4-triazolo[4,3-*a*]pyrazinium-3-*p*-tolylaminide 6d.** Compound **6d** was a brown crystalline solid (91%), mp 208–210 °C (decomp.) (Found: C, 67.1; H, 6.1; N, 25.9. $C_{15}H_{17}N_5$ requires C, 67.4; H, 6.4; N, 26.2%). $\nu_{max}$(KBr)/$cm^{-1}$ 1616, 1588, 1502. $\delta_H$($CDCl_3$) 2.28 (s, 3 H, $C_6H_4Me$), 2.77 (m, 3 H, *J* < 0.8, 8-Me), 3.12 (m, 3 H, *J* < 0.9, 5-Me), 4.1 (s, 3 H, NMe), 7.23 (m, 1 H, *J* < 1, H-6), 7.0–7.4 (m, 4 H, $A_2B_2$ system of $C_6H_4Me$). *m/z* (FAB) 268 (100%) $(M + 1)^+$, 267 (48), 100 (25).

**1-Benzyl-5,8-dimethyl-1,2,4-triazolo[4,3-*a*]pyrazinium-3-phenylaminide 6e.** Compound **6e** was a red amorphous solid (55%), mp 209–210 °C (decomp.). $\nu_{max}$(KBr)/$cm^{-1}$ 1620, 1575, 1503, 1344; $\delta_H$($CDCl_3$) 2.7 (s, 3 H, 8-Me), 3.2 (s, 3 H, 5-Me), 5.6 (s, 2 H, $CH_2$), 6.75–6.85 (m, 1 H, Ar–H), 7.2–7.4 (m, 8 H, Ar–H), 7.5–7.6 (m, 2 H, Ar–H). *m/z* (EI) 329.165 55 (9%). $C_{20}H_{19}N_5$ requires 329.164 05 ($M^{\bullet+}$), 240 (30), 239 (36), 98 (39), 91 (100), 86 (38), 84 (59).

**Preparation of the hydrochloride salt 13 of 1, 5, 8-trimethyl-[1,2,4]-triazolo[4,3-*a*[pyrazinium-3-phenylaminide 6a**

Gaseous hydrogen chloride was bubbled through a suspension of 1,5,8-trimethyl-[1,2,4]-triazolo[4,3-*a*]pyrazinium-3-phenylaminide **6a** (0.80 g) 3.16 mmol) in chloroform (10 $cm^3$) for 5 min. The precipitate changed from red to yellow. The solid was collected by filtration and washed with chloroform to afford the salt **13** as a yellow solid (0.60 g, 66%), mp 150 °C (decomp.). $\delta_H$[$(CD_3)_2SO$] 2.95 (s, 3 H, 8-Me), 3.05 (s, 3 H, 5-Me), 4.45 (s, 3 H, N–Me), 7.05 (m, 1 H, Ar–H), 7.3 (m, 4 H, Ar–H), 8.05 (s, 1 H, H-6); this salt was insufficiently stable to obtain satisfactory data from elemental analysis.

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