Synthesis and Dimerisation of [1,2,4]Triazolo[4,3-*a*]pyrimidinium-3-aminides

Hugh Marley,[a] Kevin J. McCullough,[b] Peter N. Preston,[b] and Stanley H. B. Wright[a]

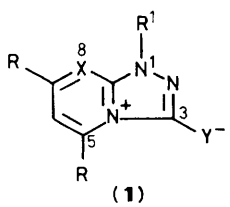
[a] *Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, U.K.*
[b] *Department of Chemistry, Heriot-Watt University, Riccarton, Currie, Edinburgh EH14 4AS, U.K.*

A new method for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridinium-3-aminides (**1a** and **b**) and an analogous [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminide (**1c**) is described; an attempt to extend the procedure to the synthesis of related compounds (**1d—g**) resulted in dimerisation and rearrangement to yield the enamines (**5a—d**).

As part of a study and of the chemistry of mesomeric betaines we have reported the synthesis of [1,2,4]triazolo[4,3-*a*]-pyrimidinium-3-olates and -3-thiolates[1] and novel 1,3-dipolar cycloaddition reactions of [1,2,4]triazolo[1,5-*a*]pyrimidinium-2-olates.[2] We now describe the synthesis† of [1,2,4]triazolo[4,3-*a*]pyridinium-3-aminides and exemplify an extraordinary skeletal rearrangement with dimerisation of certain analogous [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminides.

The hydrazinopyridines (**2a,b**) were converted (PhNCS, EtOH, reflux, 3 h) into the thiosemicarbazides (**2c,d**) which were then cyclised ($C_6H_{11}N{=}C{=}NC_6H_{11}$, CH_2Cl_2, room temp., 72 h) to give the orange-red betaines‡ (**1a**), m.p. 203—205 °C, 62% yield, and (**1b**), m.p. 180—182 °C, 55% yield, the yields being much improved by comparison with existing methods.[3]

This procedure was successfully adapted for the synthesis of an analogous yellow [1,2,4]triazolo[4,3-*a*]pyrimidinium-3-aminide containing an exocyclic ethoxycarbonyl substituent [see (**2e**) → (**2f**), then (**2f**), $C_6H_{11}N{=}C{=}NC_6H_{11}$, CH_2Cl_2, 48 h → (**1c**),‡ m.p. 181 °C (decomp.), 48%]. In contrast, an attempt to prepare an aminide containing an exocyclic phenyl



(**1**)

	X	Y	R	R^1
a	CH	NPh	H	Ph
b	CH	NPh	Me	Me
c	N	NCO_2Et	Me	Me
d	N	NPh	Me	Me
e	N	NMe	Me	Me
f	N	NMe	Me	$CH_2C_6H_4NO_2$-4
g	N	NMe	Me	$CH_2C_6H_3(NO_2)_2$-3,5

† Satisfactory analytical and spectroscopic data were obtained for all new compounds. Compounds (**5b—d**) with a high nitrogen content gave nitrogen analyses which were up to 0.6% lower than calculated values

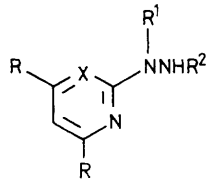
‡ *Spectral data:* (**1b**): i.r. $\nu_{max.}$ (Nujol) 1655, 1610, 1510, 805, 756, and 698 cm^{-1}; ^1H n.m.r. (CD_3OD) δ 2.38 (s, 3H, 7-Me), 3.09 (s, 3H, 5-Me), 3.77 (s, 3H, NMe), 6.49 (s, 1H, H-6), 6.71 (m, 1H, Ar-H), 7.09 (s, 1H, H-8), 7.16 (m, 2H, Ar-H), and 7.38 (m, 2H, Ar-H); *m/z* 252 (100%) [$M^{\cdot+}$], 251 (31), 237 (10), 237 (10), 236 (21), 136 (10), and 137 (7).

(**1c**): i.r. $\nu_{max.}$ (Nujol) 1635 (C=O), 1620, and 1510 cm^{-1}; ^1H n.m.r. (CD_3OD) δ 1.28 (t, 3H, CH_2Me), 2.63 (s, 3H, 7-Me), 3.03 (d, 3H, 5-Me), 4.12 (q, 2H, CH_2Me), and 6.98 (q, 1H, H-6); *m/z* 204 (1%) [$M^{\cdot+} - OC_2H_5$], 203 (4), [$M^{\cdot+} - C_2H_5OH$].

(**5a**): i.r. $\nu_{max.}$ (Nujol) 3405 (NH) and 1605 cm^{-1}; ^1H n.m.r. [$(CD_3)_2SO$] δ 2.02 (s, 3H, allyl Me), 2.13 (s, 3H, Me), 2.22 (s, 3H, Me), 3.47 (s, 6H, NMe), 6.36 (s, 1H, olefinic H), 6.78 (m, 3H, 2 × Ar-H and 1 × Py-H), 6.94 (s, 1H, Py-H), 7.19 (t, 4H, Ar-H), 7.40 (d, 4H, Ar-H), and 9.15 (s, 2H, NH); *m/z* 506 [$M^{\cdot+}$].

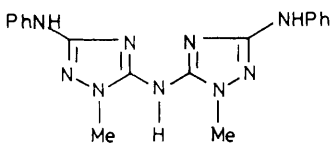
(**3**): i.r. $\nu_{max.}$ (Nujol) 3300, 3150, 1640, 1620, and 735 cm^{-1}; ^1H n.m.r. [$(CD_3)_2SO$–CD_2Cl_2 (1:9)] δ 3.60 (s, 6H, NMe), 6.82 (t, 2H, Ar-H), 7.21 (t, 4H, Ar-H), 7.48 (d, 4H, Ar-H), 8.29 (br. s, 2H, NH), and 9.66 (br. s, 1H, NH); *m/z* 361 [$M^{\cdot+}$].

Spectral data for the ketone (**4**) were in good agreement with those reported[4] for the isomeric 1-(2,6-dimethylpyridin-4-yl)propan-2-one, *e.g.* $\nu_{max.}$ (liq. film) 1710 (C=O), 1610, and 1550 cm^{-1}; ^1H n.m.r. [$(CD_3)_2CO$] δ 2.12 (s, 3H, Me), 2.27 (s, 3H, Me), 2.40 (s, 3H, Me), 3.79 (s, 2H, CH_2), 6.89 (s, 1H, Py-H), and 6.92 (s, 1H, Py-H); *m/z* 163.0985 (14%, $M^{\cdot+}$ requires 163.0997), 121 (100), 106 (10), 91 (6), and 79 (11).

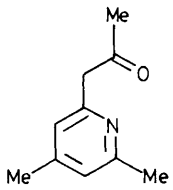


(2)

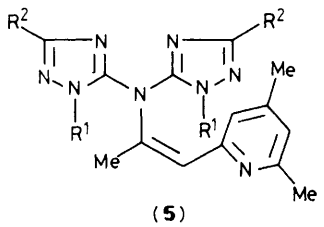
	X	R	R^1	R^2
a	CH	H	Ph	H
b	CH	Me	Me	H
c	CH	H	Ph	CSNHPh
d	CH	Me	Me	CSNHPh
e	N	Me	Me	H
f	N	Me	Me	$CSNHCO_2Et$
g	N	Me	Me	CSNHPh
h	N	Me	Me	CSNHMe
i	N	Me	$CH_2C_6H_4NO_2$-4	CSNHMe
j	N	Me	$CH_2C_6H_3(NO_2)_2$-3,5	CSNHMe



(3)



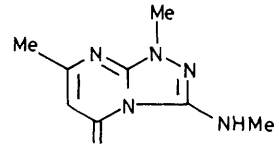
(4)



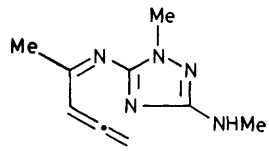
(5)

	R^1	R^2
a	Me	NHPh
b	Me	NHMe
c	p-$O_2NC_6H_4CH_2$	NHMe
d	3,5-$(O_2N)_2C_6H_3CH_2$	NHMe

substituent [from (**2g**)] afforded an uncharacterised red product which was cleanly converted into a stable colourless compound (**5a**) on heating in toluene. Alternatively, conversion [i, MeI, tetrahydrofuran (THF), 24 h; ii, $NaHCO_3$, H_2O, $CHCl_3$] of the thiosemicarbazides (**2g—j**) into the respective methyl thioethers followed by heating in toluene solution gave the thermolysis products (**5a**),‡ m.p. 227—228 °C, 82%; (**5b**), m.p. 190—192 °C, 63%; (**5c**), m.p. 203—205 °C, 60%; and (**5d**), m.p. 128—130 °C, 61%, directly in higher overall yield.



(6)



(7)

Mass spectral data were consistent with dimeric products and the absence of signals characteristic of the pyrimidine ring system in the ^1H n.m.r. spectra‡ indicated that an extensive rearrangement had occured. Acidic hydrolysis [i, 2 M HCl, reflux, 2 h; ii, NH_3 (g), $CHCl_3$] of the dimer formed from (**2g**) gave the amine (**3**),‡ m.p. 191—192 °C, 70% and the ketone (**4**),‡ colourless oil, 90%, suggesting that the enamine (**5a**) was representative of the dimer structure. ^1H N.m.r. spectra of the enamines (**5a—d**) were in full accord with the proposed structures and chemical shifts of the pyridyl substituents were in close agreement with those observed in model compounds.[5] Further evidence for the structures was obtained by single crystal *X*-ray analysis§ of compound (**5d**).[6]

It is notable that compound (**1c**), which bears an electron withdrawing ethoxycarbonyl group on the exocyclic nitrogen atom, is stable. An explanation for the unusual behaviour of the analogues (**1d—g**) may lie in the proximity of a negatively charged nitrogen atom and an acidic methyl group at C-5. We believe that dimer formation is initiated by a protropic shift generating a reactive intermediate, *e.g.* (**1e**) → (**6**) or (**7**), although we have no evidence[7] for this or for other details of the mechanism which is currently under investigation.

Received, 20th November 1987; Com. 1693

References

1 H. Marley, K. J. McCullough, P. N. Preston, and S. H. B. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1988, 351.
2 H. Marley, K. J. McCullough, P. N. Preston, and S. H. B. Wright, *J. Chem. Soc., Chem. Commun.*, 1987, 112.
3 R. J. Grout, T. J. King, and M. W. Partridge, *Chem. Commun.*, 1971, 898.
4 M. Arnaud, A. Pedra, C. Roussel, and J. Metzger, *J. Org. Chem.*, 1979, **44**, 2972.
5 K. T. Potts and H. R. Burton, *J. Org. Chem.*, 1966, **31**, 251.
6 K. J. McCullough, unpublished results.
7 An intermolecular proton abstraction between 1-(diethylamino)prop-1-yne and 2-methylpyrimidinium-4-olates has been proposed to explain product formation: H. Gotthardt and J. Blum, *Chem. Ber.*, 1986, **119**, 3247.

§ The preliminary results for the *X*-ray analysis of compound (**5d**) indicate the general atomic connectivity. The precise positions of the C–N double bonds in the five-membered rings is ambiguous because the atomic positions of pertinent hydrogens have not been located from difference Fourier maps. The geometry in the region of the exocyclic nitrogen atoms provides evidence for exocyclic C–N double bonds. For convenience, structure (**5**) is written in the (substituted)aminotriazole tautomeric form. *X*-Ray data from low temperature measurements are currently being collected, and full details will be given in a full paper.