SHORT PAPER

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Regioselection in 1,3-dipolar cycloadditions of 3-methylpyridine *N*-imide to aromatic carbonitriles. Synthesis of 2-aryl-8-methyl[1,2,4]triazolo [1,5-*a*]pyridines†

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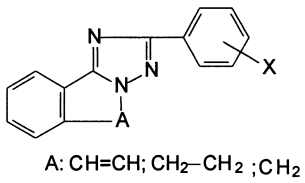
1-Amino-3-methylpyridinium mesitylenesulfonate (**3**) reacts with aromatic nitriles in the presence of potassium hydroxide, undergoing 1,3-dipolar cycloaddition followed by elimination of H_2 to give 2-aryl-8-methyl[1,2,4]triazolo[1,5-*a*]pyridines as the major products, rather than the 6-methyl isomers.

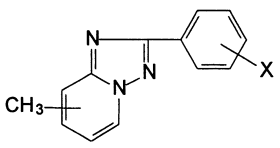
Keywords: 1,3-dipolar cycloaddition, pyridine *N*-imides, fused 1,2,4-triazoles, fused pyridines

2-Aryltriazolo[5,1-*a*]-isoquinolines and -isoindoles (**1**) have been shown to be active as non-hormonal contragestational agents in various animal species after parenteral administration,[1–3] but their very sustained pharmacokinetic profiles and / or their low solubility, even in oily vehicles, have hindered their use in clinical studies.[4,5] In order to study the SAR (structure-activity relationship) of these compounds and to find new contragestational agents, a series of 2-aryl[1,2,4]triazolo[1,5-*a*]pyridines (**2**) has been designed and synthesised by 1,3-dipolar cycloaddition of substituted *N*-aminopyridinium mesitylenesulfonate (**3**) with aromatic nitriles in the presence of potassium hydroxide, as previously described.[6]

Two regioisomers were obtained when *N*-amino-3-methylpyridinium mesitylenesulfonate (**3**) reacted with benzonitrile. We found that the principal product was 8-methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (**6a**) rather than the 6-methyl isomer (**7a**) (ratio = 8:1). The physical data were in agreement with those previously reported[7] for these two structures, and confirmation was obtained from the ^1H and ^{13}C NMR data. Compound **6a** has a triplet ($\delta = 6.89$, $J = 7.0$ Hz) due to H-6, a quaternary carbon at 127.1 ppm due to C-8 and CH at 113.5 ppm due to C-6. Compound **7a** does not show a triplet, but it has a doublet ($\delta = 8.40$, $J = 0.7$) due to H-5, a quaternary carbon at 131.2 ppm due to C-6 and CH at 115.7 ppm due to C-8. So we may conclude that the principal product is **6a**.



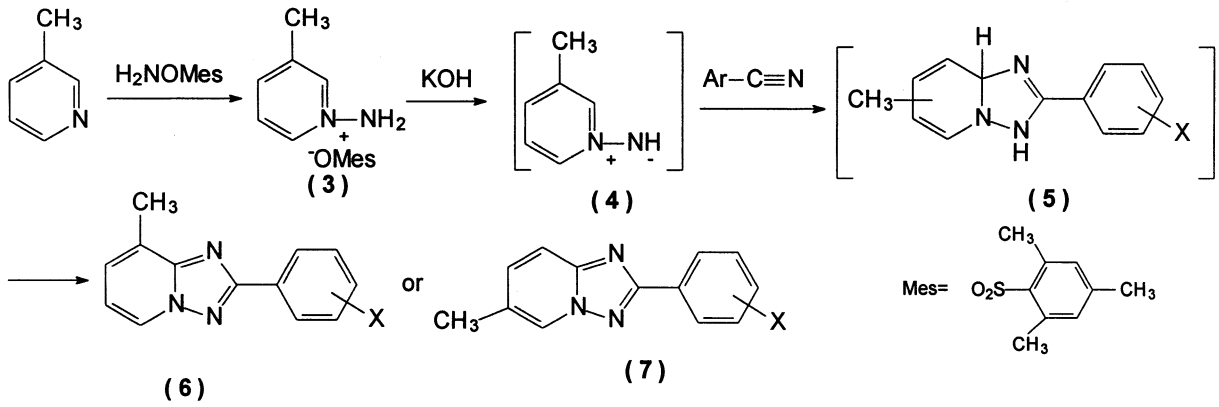
(1)



(2)

In order to investigate the effect of the 3-methyl group upon orientation in the cycloaddition reaction between **3** and aromatic nitriles, a series of aromatic nitriles was reacted with **3** (Scheme 1). The results in Table 1 indicate that all the major products have a triplet ($\delta = 6.85$~6.90) rather than a singlet or a doublet with $J < 3$ Hz. So the predominant products are all the 2-aryl-8-methyl[1,2,4]triazolo[1,5-*a*]pyridines (**6**) rather than the 2-aryl-6-methyl compounds (**7**), even though the position 6 of **3** has lower steric hindrance than the position 2 in the cycloaddition reaction.

As suggested by Huisgen,[8,9] the formation of compounds **6** and **7** must proceed in two stages: a concerted 1,3-dipolar cycloaddition between **4** and the aromatic nitrile, leading to the dihydropyridine intermediate **5**, followed by a dehydrogenation to give the final products (**6** and **7**). Since most 1,3-dipolar cycloadditions are known to be stereospecific and irreversible, it is reasonable to assume that the first step (**4** → **5**) is rate-determining and responsible for determining the orientation. 3-Methylpyridine *N*-imide (**4**) would be expected to produce



(3) (4) (5) (6) (7)

Scheme 1

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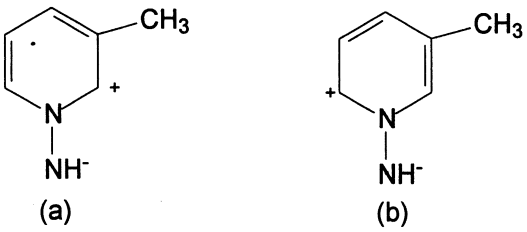
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Data of the products **6b–l**

No.	X	M.p./°C	Yield/%	Formula	^{1}H NMR data (δ, ppm)
6b	4-OCH_2CH_3	128–129	46	$C_{15}H_{15}N_3O$	1.45 (t, *J* = 7.0, 3H, -$OCH_2\underline{CH_3}$), 2.70 (s, 3H, 8-CH_3), 4.11 (q, *J* = 7.0, 2H, -$OC\underline{H_2}CH_3$), 6.89 (t, *J* = 6.9, 1H, 6-H), 7.00, 8.23 (AA′BB′, each 2H, *J* = 8.8, 2 × Ar-2H), 7.26 (dd, *J* = 0.8, *J* = 6.9, 7-H), 8.43 (d, *J* = 6.9, 1H, 5-H)
6c	4-OCH_3	123–125	43	$C_{14}H_{13}N_3O$	2.71 (s, 3H, 8-CH_3), 3.90 (s, 3H, 4′-OCH_3), 6.90 (t, *J* = 6.9, 1H, 6-H), 7.02, 8.25 (AA′BB′, each 2H, *J* = 8.8, 2 × Ar-2H), 7.27 (d, *J* = 6.9, 1H, 7-H), 8.45 (d, *J* = 6.9, 1H, 5-H)
6d	4-Cl	193–195	40	$C_{13}H_{10}ClN_3$	2.70 (s, 3H, 8-CH_3), 6.93 (t, *J* = 6.9, 1H, 6-H), 7.30 (d, *J* = 6.9, 1H, 7-H), 7.46, 8.25 (AA′BB′, each 2H, *J* = 8.6, 2 × Ar-2H), 8.45 (d, *J* = 6.9, 1H, 5-H)
6e	4-$OCH_2C_6H_5$	116–118	40	$C_{20}H_{17}N_3O$	2.69 (s, 3H, 8-CH_3), 5.14 (s, 2H, -OCH_2), 6.89 (d, *J* = 6.9, 1H, 6-H), 7.09, 8.24 (AA′BB′, each 2H, *J* = 8.7, 2 × Ar-2H), 7.26 (brs, 1H, 7-H), 7.34 (m, H, Ar-H), 7.40 (t, *J* = 7.4, *J* = 7.6, 2H, Ar-H), 7.46 (d, *J* = 7.4, Ar-H), 8.43 (d, *J* = 6.80, 1H, 5-H)
6f	3-OCH_3	99–101	41	$C_{14}H_{13}N_3O$	2.70 (s, 3H, 8-CH_3), 3.93 (s, 3H, 3′-OCH_3), 6.90 (t, *J* = 6.9, 1H, 6-H), 7.01 (dd, *J* = 2.4, *J* = 7.9, 1H, Ar-H), 7.26 (dd, *J* = 0.6, *J* = 6.9, 1H, 7-H), 7.40 (t, *J* = 7.9, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.90 (d, *J* = 7.9, 1H, Ar-H), 8.45 (d, *J* = 6.9, 1H, 5-H)
6g	4-$N(CH_3)_2$	190–192	46	$C_{16}H_{16}N_4$	2.69 (s, 3H, 8-CH_3), 3.05 (s, 6H, $N(CH_3)_2$), 6.81, 8.17 (AA′BB′, each 2H, *J* = 8.8, 2 × Ar-2H), 6.85 (t, *J* = 6.9, 1H, 6-H), 7.23 (d, *J* = 6.9, 1H, 7-H), 8.43 (d, *J* = 6.9, 1H, 5-H)
6h	3,4-$(OCH_3)_2$	154–156	50	$C_{15}H_{15}N_3O_2$	2.69 (s, 3H, 8-CH_3), 3.95 (s, 3H, 4′-OCH_3), 4.03 (s, 3H, 3′-OCH_3), 6.87 (t, *J* = 6.9, 1H, 6-H), 6.97 (d, *J* = 8.4, 1H, Ar-H), 7.24 (d, *J* = 6.9, 1H, 7-H), 7.83 (d, *J* = 1.8, 1H, Ar-H), 7.90 (dd, *J*= 1.8, *J* = 8.4, 1H, Ar-H), 8.43 (d, *J* = 6.9, 1H, 5-H)
6i	3-OCH_2O-4	155–157	46	$C_{14}H_{11}N_3O_2$	2.67 (s, 3H, 8-CH_3), 6.03 (s, 2H, -CH_2-), 6.88 (t, *J* = 6.9, 1H, 6-H), 6.92 (d, *J* = 8.1, 1H, Ar-H), 7.25 (m, 1H, 7-H), 7.76 (d, *J* = 1.6, 1H, Ar-H), 7.86 (dd, *J* = 1.6, *J* = 8.1, 1H, Ar-H), 8.42 (d, *J* = 6.9, 1H, 5-H)
6j	3,4,5-$(OCH_3)_3$	127–129	40	$C_{16}H_{17}N_3O_3$	2.72 (s, 3H, 8-CH_3), 3.92 (s, 3H, 4′-OCH_3), 4.01 (s, 6H, 3′- and 5′-OCH_3), 6.88 (t, *J* = 6.9, 1H, 6-H), 7.26 (d, *J* = 6.9, 1H, 7-H), 7.85 (s, 2H, Ar-H), 8.20 (d, *J* = 6.9, 1H, 5-H)
6k	2-OCH_3	123–125	35	$C_{14}H_{13}N_3O$	2.69 (s, 3H, 8-CH_3), 3.96 (s, 3H, OCH_3), 6.88 (t, *J* = 6.6, 1H, 6-H), 7.07 (m, 2H, Ar-H), 7.26 (d, *J* = 6.6, 1H, 7-H), 7.43 (t, *J* = 7.2, 1H, Ar-H), 8.07 (dd, *J* = 1.2, *J* = 7.2, 1H, Ar-H), 8.50 (d, *J* = 6.6, 1H, 5-H)
6l	4-$O(CH_2)_3CH_3$	106–108	42	$C_{17}H_{19}N_3O$	1.02 (t, *J* = 7.5, 3H, CH_3), 1.54 (m, 2H, -$C\underline{H_2}CH_3$), 1.82 (m, 2H, $CH_2C\underline{H_2}$ CH_2CH_3), 2.71 (s, 3H, 8-CH_3), 4.06 (t, *J* = 6.5, 2H, -$OC\underline{H_2}CH_2CH_2CH_3$), 6.89 (t, *J* = 7.0, 1H, 6-H), 7.02, 8.24 (AA′BB′, each 2H, *J* = 8.8, 2 × Ar-2H), 7.27 (d, *J* = 7.0, 1H, 7-H), 8.44 (d, *J* = 7.0, 1H, 5-H)



Scheme 2 Resonance structures of **4**.

two 1,3-dipoles corresponding to the two orientations of addition (Scheme 2). Of the two possible orientations, approach of the nitrile component to the dipole as shown in (a) would be more favoured owing to σ–π hyperconjugation.

Experimental

Proton and carbon-13 magnetic resonance (^{1}H and ^{13}C NMR) spectra were determined in $CDCl_3$ on a Bruker 400 MHz or 500 MHz spectrometer. Chemical shifts are reported in p.p.m. from $SiMe_4$ as the internal standard; *J* values are in Hz. Mass spectral data were obtained by electron ionisation on an HP5989B spectrometer. *N*-Amino-3-methylpyridinium mesitylenesulfonate was prepared by the procedure described in ref. 10.

Preparation of 8-methyl-2-phenyl[1,2,4]triazolo[1,5-a]pyridine (**6a**): A solution of *N*-amino-3-methylpyridinium mesitylenesulfonate (3.08 g, 10 mmol) and benzonitrile (1.03 g, 10 mmol) in ethanol (15 ml) was cooled by ice-water, then 2N KOH (5.2 ml) was added dropwise. After being raised to room temperature, the mixture was stirred for a further 24 h and then concentrated under reduced pressure to remove ethanol. The residual liquid was extracted with $CHCl_3$ (3 × 10ml). The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography to afford the compound **6a** (0.91g, 44%), m.p.: 100–101°C (lit.[7] 97–98°C); ^{1}H NMR: 2.70 (s, 3H, 8-CH_3), 6.90 (t, *J* = 6.9, 1H, 6-H), 7.27 (br, 1H, 7-H), 7.51 (m, 3H, Ar-H), 8.30 (m, 2H, Ar-H), 8.45 (d, *J* = 6.9, 1H, 5-H). ^{13}C NMR: 163.7, 152.3, 131.2, 130.0, 128.7, 128.2, 127.5, 127.1, 125.9, 113.5, 17.1. MS (EI): 209(100%), 105, 104, 103, 92, 79, 78, 77, 76, 65, 53, 52, 41.

Compound **7a**: (0.11g, 5.3%). m.p.: 119–121°C (lit.[7] 120–121 C); ^{1}H NMR: 2.43 (s, 3H, 6-CH_3), 7.37 (dd, *J* = 9.1, *J* = 1.5, 1H, 7-H), 7.49 (m, 3H, Ar-H), 7.68 (d, *J* = 9.0, 1H, 8-H), 8.28 (m, 2H, Ar-H), 8.40 (d, *J* = 0.7). ^{13}C NMR: 164.0, 150.6, 132.6, 131.1, 130.1, 128.9, 127.4, 126.6, 123.9, 115.7, 18.3. MS (EI): 209 (100%), 105, 104, 103, 92, 79, 78, 77, 76, 65, 53, 52, 41.

Compounds **6b–l** were prepared by the procedure described above. The results are reported in Table 1.

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