A New Direct Synthesis of Derivatives of the *s*-Triazolo[1,5-*a*]pyridine Ring System[1]

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The 1,2,4-triazole nucleus has recently been incorporated into a wide variety of therapeutically interesting drug candidates. We now describe a new synthesis of derivatives of the *s*-triazolo[1,5-*a*]pyridine system, which contain the 1,2,4-triazole moiety.

s-Triazolo[1,5-*a*]pyridines have been synthesized by the following methods: (a) from 2-aminopyridine by reaction with dimethylformamide dimethyl acetal, followed by treatment either with hydroxylamine-*O*-sulfonic acid[2] or hydroxylamine and further cyclization by thermal, photochemical, or acidic treatment[3,4]. The reaction of 2-aminopyridines with aliphatic, aromatic, and heteroaromatic nitriles in the presence of aluminium trichloride leads to *N*-(2-pyridyl)-alkyl-(or aryl)-amidines, which undergo ring closure to pyrazolo[1,5-*a*]pyridines[5,6,7,8]. Hydroxylamine-*O*-sulfonic acid reacts with 2-aminopyridine to give 1,2-diaminopyridinium salts which undergo cyclization by reaction with aliphatic and aromatic acids or their chlorides[9,10,11]. (b) *N*-Iminopyridines react with *N*-ethoxycarbonylimidates to give *N*-imidoyliminopyridinium ylids which undergo 1,5-dipolar cyclization followed by aromatization to give pyrazolo[1,5-*a*]pyridines[12,13].

We report a convenient one-step synthesis of 2-substituted 5,7-diphenyl-*s*-triazolo[1,5-*a*]pyridines **3** by reaction of 1-ami-

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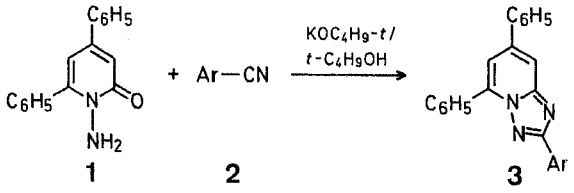
no-4,6-diphenyl-2-pyridone (**1**), readily available from 4,6-diphenyl-2-pyrone and hydrazine hydrate[14], with aromatic and heteroaromatic nitriles **2** under basic conditions.



1 **2** **3**

The best results are obtained when the reaction is carried out in the presence of potassium *t*-butoxide with *t*-butanol as solvent. Attempts with weaker bases such as triethylamine and sodium methoxide were unsuccessful. When treated with one equivalent of potassium *t*-butoxide and one equivalent of nitrile **2** in *t*-butanol under reflux, the *N*-aminoheterocycle **1** is directly converted to the corresponding *s*-triazolo[1,5-*a*]pyridine **3** in good yield. Furthermore, product isolation is easily accomplished by removal of the solvent and recrystallization of the crude *s*-triazolo[1,5-*a*]pyridines. Structural elucidation of **3** was accomplished on the basis of spectral data and microanalysis.

Table. Preparation of 2-Substituted 5,7-Diphenyl-*s*-triazolo[1,5-*a*]pyridines **3**

Product No.	Ar	Reaction time [h]	Yield[a] [%]	m.p.[b] [°C]	Crystallization solvent	Crystal form	Molecular formula[c]	
3a	C_6H_5	36	72	134–136°	C_2H_5OH	Prism	$C_{24}H_{17}N_3$	(347.4)
3b	4-H_3C—C_6H_4	31	74	158–160°	C_2H_5OH	Prism	$C_{25}H_{19}N_3$	(361.5)
3c	4-Cl—C_6H_4	24	79	165–167°	$CHCl_3/C_2H_5OH$ (1:1, v/v)	Prism	$C_{24}H_{16}ClN_3$	(381.8)
3d	4-O_2N—C_6H_4	12	70	244–246°	$CHCl_3/C_2H_5OH$ (1:1, v/v)	Plates	$C_{24}H_{16}N_4O_2$	(392.4)
3e	4-H_3CO—C_6H_4	24	75	133–136°	C_2H_5OH	Prism	$C_{25}H_{19}N_3O$	(377.4)
3f	2-pyridyl	24	64	180–181°	$CHCl_3/C_2H_5OH$ (1:1, v/v)	Needles	$C_{23}H_{16}N_4$	(348.4)
3g	4-pyridyl	24	71	185–186°	C_2H_5OH	Needles	$C_{23}H_{16}N_4$	(348.4)
3h	2-furyl	24	68	151–153°	$CHCl_3/C_2H_5OH$ (1:1, v/v)	Needles	$C_{22}H_{15}N_3O$	(337.4)
3i	2-thienyl	24	70	138–140°	$CHCl_3/C_2H_5OH$ (1:1, v/v)	Needles	$C_{22}H_{15}N_3S$	(353.4)

[a] Recrystallized pure product.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values: C ±0.27, H ±0.23, N ±0.25.

We have also found that compound **1** reacts with ethyl benzimidates under similar conditions to give **3** in moderate yields (40–50%).

We believe that the mechanism of this reaction involves addition of the *N*-amino group to the C≡N-triple bond to give the not isolated intermediate *N*-heteroarylamidine which undergoes cyclocondensation to give **3**.

The method appears to be quite general for the aromatic and heteroaromatic series. Yields are high both when the aromatic ring is substituted by electron-donating and electron-withdrawing groups. However attempts with functionally substituted aliphatic and unsaturated nitriles failed to give **3**.

The principal advantages of the procedure described here are the high yields, the one-step procedure, the convenient work-up of the products, and the availability of starting materials. Principal disadvantages are slow reaction rates and the applicability to aromatic and heteroaromatic nitriles only.

2-Substituted 5,7-Diphenyl-*s*-triazolo[1,5-*a*]pyridines 3; General Procedure:

To a solution of 1-amino-4,6-diphenyl-2-pyridone (**1**; 1.31 g, 5 mmol) in *t*-butanol (50 ml), potassium *t*-butoxide (0.56 g, 5 mmol) and the appropriate aromatic nitrile **2** (5 mmol) are added. The reaction mixture develops a deep red colour which disappears on heating under reflux for 12–36 h (Table). After cooling the solvent is removed under reduced pressure and the resulting crude product recrystallized from the appropriate solvent.

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