A Novel, One-Step Synthesis of [1,2,4] Triazolo[1,5-*a*]-pyridine Derivatives

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A novel, simple, one-step synthesis of previously unknown 2-substituted 4-cyano-5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyridine derivatives was achieved by reacting 1-amino-3-cyano-4,6-dimethyl-2-pyridone with various aliphatic, aromatic and heterocyclic amides.

1,2,4-Triazole derivatives are reported to be useful in a variety of fields, such as, in pharmaceuticals as drugs and in dyestuffs either as dye intermediates or fluorescent whiteners.

A number of methods are known for the synthesis of [1,2,4]triazolo[1,5-*a*]pyridine. The most important ones can be summarized as follows:

Table. Substituted 4-cyano-5,7-dimethyl-[1,2,4]-triazolo[1,5-*a*]pyridines(**3**) Prepared.

Product No.	R	Yield[a] [%]	m.p.[b] [°C] (solvent)	Molecular Formula[c]	IR (nujol)[d] [cm^{-1}]	^{1}H-NMR[e] (DMSO-d_6/TMS) [ppm]	MS/TMS m/e (M^+)	UV (DMF) λmax [nm] Absorption[f]	λ_{max} [nm] Emission[g]	log ε
3a	H	64	> 360 (acetic acid)	$C_9H_8N_4$ (172.1)	2240, 1600, 1460, 1450, 1370, 1260	–	172	327	463	4.13
3b	CH_3	69	> 360 (acetic acid)	$C_{10}H_{10}N_4$ (186.1)	2240, 1590, 1460, 1380, 1270	2.2 (s, 3H); 2.3 (s, 3H); 2.4 (s, 3H); 6.2 (s, 1H)	–	338	429	4.00
3c	C_6H_5	79	270 (acetic acid)	$C_{15}H_{12}N_4$ (248.2)	2240, 1640, 1600, 1440, 1380, 1300	2.2 (s, 3H); 2.3 (s, 3H); 6.3 (s, 1H); 7.2 (s, 5H)	248	347	417	4.04
3d	$CH=CH-C_6H_5$	76	> 360 (acetic acid)	$C_{17}H_{14}N_4$ (274.2)	2240, 1650, 1600, 1450, 1390, 1290	–	274	344	423	4.28
3e	3-Cumarinyl	66	280 (chloroform)	$C_{18}H_{12}N_4O_2$ (316.2)	2240, 1720, 1610, 1460, 1360	–	316	352	439	4.25

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.26, H ±0.23, N ±0.21.
[d] Recorded on a Perkin-Elmer 397 spectrometer.
[e] Recorded at 60 MHz on a Varian EM-360-L spectrometer.
[f] Recorded on Beckman Model 25 spectrophotometer.
[g] Recorded on Aminco Bowman Spectrophotofluorimeter.

(a) 1,2-diaminopyridine derivatives react with a variety of compounds such as carboxylic acids and esters[1–4], 1,3-diketones[3], and acetylene derivatives[5] resulting in s-triazolo[1,5-*a*]pyridines;
(b) 2-*N*-substituted amino pyridines are reported to cyclize[6] using various reagents such as hydroxylamine hydrochloride[7] and hydroxylamine-*O*-sulfonic acid[8] to give triazolopyridine derivatives;
(c) 1-aminopyridinium salts react with various nitriles[9–12] in alkaline condition to give triazolopyridines;
(d) 3-cyanomethyl-1,2,4-triazole derivatives react with various keto methylene compounds[13] to give triazolopyridine derivatives.

We report here a novel, simple, one-step synthesis of hitherto unknown 2-substituted 4-cyano-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyridine derivatives (**3**) by the reaction of 1-amino-3-cyano-4,6-dimethyl-2-pyridone (**1**) with aliphatic, aromatic and heterocyclic carboxamides (**2**) in the presence of anhydrous zinc chloride. Compound **1** can easily be prepared[14] from cyanoacetohydrazide and acetylacetone.

1 2 3a-e

The best results for the annelation reaction were obtained when the reaction was carried out in the presence of anhydrous zinc chloride in refluxing dimethylformamide. Attempts using lower boiling solvents such as ethanol were unsuccessful. Compound **1** reacts with different acid amides (**2**) under the above conditions to give [1,2,4]triazolo[1,5-*a*]pyridines **3** in one step and in good yields. Structural elucidation of **3** was accomplished on the basis of spectral data and microanalysis.

We believe that the mechanism of this reaction involves condensation of N-amino group with the amido keto group of the carboxylic acid amide to give a non-isolable intermediate which undergoes cyclocondensation to give **3**.

The method appears to be quite general for the aliphatic, aromatic and heteroaromatic series. The yields were high with all amides used.

The principal advantages of the procedure described here are that the yields are high, the time of reaction is short, the procedure involves only one facile step, the work up is convenient, and the starting materials are very easily prepared.

2-Substituted 4-Cyano-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyridines (3); General Procedure:

To a solution of 1-amino-3-cyano-4,6-dimethyl-2-pyridone (**1**, 2.45 g, 15 mmol) in dimethylformamide (8 ml), are added anhydrous zinc chloride (0.50 g, 3.7 mmol) and the appropriate carboxamide (15 mmol). The reaction mixture is refluxed for 4–6 hours, until reaction is complete (by TLC). The reaction mixture is allowed to cool to room temperature and then slowly poured over an ice-water mixture (200 ml) with good stirring.

The product is filtered, washed with water, and recrystallized from the appropriate solvent.

One of the authors (RCP) is thankful to the Council of Scientific and Industrial Research, New Delhi for the award of Junior and Senior Research Fellowships

Received: October 1, 1985
(Revised form: February 28, 1986)

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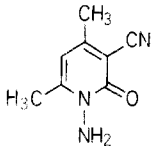
H. Herzog, H.D. Scharf *Synthesis* **1986**, 788. The heading for the experimental procedure on p. 789 (top, right) should be:
Step E: **(1*R*,2*S*,4*S*)-2-benzyloxybornan-3-one (8):**

A.N. Pudovick, I.V. Konovalova, L.A. Burnaeva *Synthesis* **1986**, 793. The text starting in line 2 on page 798 (top, right) should read: leads to 3,3a-dihydro-4*H*-1,2-azaphospholo[5,4-*b*]pyridines **41**[1,63].

R.C. Phadke, D.W. Rangnekar *Synthesis* **1986**, 860. The structure of compound **1** (p. 861) should be:



B. Byrne, K.J. Wengenroth *Synthesis* **1986**, 870. The heading for the first experimental procedure should be:
2-(1-Bromoethyl)-2-ethyl-1,3-dioxolane (1):

S. Torii *Synthesis* **1986**, 873. The heading for the experimental procedure on p. 882 should be:
Electrosynthesis of 1-Benzyl-6,9-dimethyl-2,5-dioxo-8-tosylamino-1,2,3,4,5,6-hexahydro-1-benzazocine (81):

N.G. Bushmakina, A.Y. Misharan *Synthesis* **1986**, 966. The heading for the first experimental procedure should be:
2,2,6,6-Tetramethyl-4-methylsulfonyloxy-1-piperidinyloxy Radical (3):

X. Huang, B.C. Chen *Synthesis* **1986**, 967. The title should be:
Synthesis of Bis(alkylthio)methylene Derivatives of Meldrum's Acid and Barbituric Acid
Throughout the paper the expression "bisalkylthioylide" should be replaced by "bis(alkylthio)methylene".
The heading for the second experimental procedure should be:
5-(1,3-Dithian-2-ylidene)barbituric Acid (6d); Typical Procedure: