Monatshefte für Chemie 126, 1213–1215 (1995)

Monatshefte für Chemie
Chemical Monthly

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

G. Hajós[1,*], G. Timári[1], A. Messmer[1], A. Zagyva[2], I. Miskolczi[2], and J. G. Schantl[3]

[1] Central Research Institute for Chemistry, H-1525 Budapest, Hungary
[2] BIOGAL Pharmaceutical Works, H-4042 Debrecen, Hungary
[3] Institute of Organic Chemistry, University Innsbruck, A-6010 Innsbruck, Austria

Summary. A novel and efficient synthesis of *s*-triazolo[1,5-*a*]pyridines was elaborated by reacting 1,2-diaminopyridinium salts with aldehydes.

Keywords. Ring closure; Triazoles, fused; Dipolar cyclization.

Eine neue Synthese des *s*-Triazolo[1,5-*a*]pyridin-Ringsystems

Zusammenfassung. Eine neue und effektive Synthese von *s*-Triazolo[1,5-*a*]pyridinen durch die Reaktion von 1,2-Diaminopyridiniumsalzen mit Aldehyden wurde ausgearbeitet.

Introduction

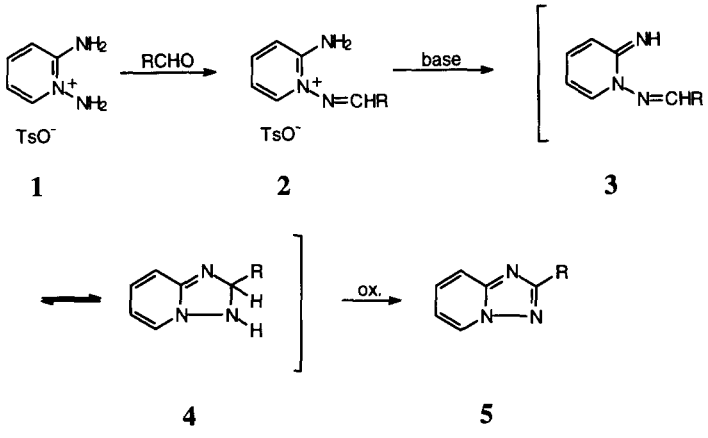
The following important synthetic routes to *s*-triazolo[1,5-*a*]pyridines have been published: (a) reaction of 1,2-diaminopyridinium salts with carboxylic acid derivatives [1–3]; (b) oxidative cyclization of pyridylamidines [4] and pyridylamidoximes [5]; (c) reaction of 1-aminopyridinium salts with various nitriles under alkaline conditions [6]; (d) ring transformation of triazolo[4,3-*a*]pyridines and 2-thioxopyrones [7]; (e) reaction of 1-amino-2-pyridones with amides [8]; and (f) reaction of 3-cyanomethyl-*s*-triazole with various oxo methylene compounds [9]. Although a great variety of *s*-triazolo[1,5-*a*]pyridines are available by these procedures, all of them are fairly limited to certain substituents.

Results and Discussion

We report here a novel and convenient route to the title ring system which can widely be generalized to various substituents on the triazole ring. We found that the 1,2-diaminopyridinium salt **1** [10] readily reacts with aldehydes at room

Dedicated to Prof. *F. Sauter* on the occasion of his 65th birthday

temperature to yield solutions of salt **2**. When this intermediate is treated with aqueous strong base (*e.g.* KOH) product **5** precipitates [12].



1 **2** **3** **4** **5**

	R
a	H
b	C_6H_5
c	4-CN-C_6H_4
d	4-C_5H_4N
e	2-C_4H_3S

Although the synthesis of five membered heteroaromatic rings by reaction of 1,2-diamines with aldehydes is principally known [11], this methodology for the synthesis of systems with bridgehead nitrogen atoms has not been published. This structural feature particularly promotes the ring closure of intermediate **3** ([1, 5] dipolar cyclization) to the dihydro compound **4** which undergoes a spontaneous oxidation to **5**. The first step of the reaction path (*i.e.* the condensation of the N-amino group of **1** with the aldehyde function) was revealed by isolation of the intermediate **2b**. This procedure proved to be generally applicable for aldehydes with aliphatic, aromatic, or heterocyclic residues R. To our knowledge this is the first case for the introduction of a heteroaromatic (*e.g.* pyridyl or thienyl) substituent to the title ring system by only one single and easy step. Studies on the scope and limitations of this new procedure as well as a detailed investigation of the final oxidative step is in progress and will be published elsewhere.

Experimental

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded with a Nicolet 205 FT spectrometer. The NMR spectra were registered on a Brucker WP 200/SY instrument at ambient temperature. *TMS* was used as internal standard.

General procedure for the synthesis of s-triazolo[1,5-a]pyridines (**5**)

A mixture of 1,2-diaminopyridinium tosylate (**1**, 2.8 g, 10 mmol) and the appropriate aldehyde (13 mmol) in methanol (80 ml) was stirred for one hour at room temperature. Aqueous potassium hydroxide solution was then added. A yellow precipitate [12] was formed immediately which turned to a colorless one within a few minutes. The precipitate was filtered off and recrystallized from the appropriate solvent. Elemental analyses of new compounds were in accordance with calculated values.

8-Triazolo[1,5-a]pyridine (**5a**)

5a was prepared by using 36% aqueous formaldehyde solution (1.1 ml, 0.39 g) as a reagent: 0.47 g (40%) of product was obtained. M.p.: 107 °C (*n*-hexane Ref. [2]: 107–8 °C).

2-Phenyl-s-triazolo[1,5-a]pyridine (**5b**)

Yield: 1.32 g (68%); m.p.: 138 °C (benzene; Ref. [2]: 137–9 °C)

2-(4-Cyanophenyl)-s-triazolo[1,5-a]pyridine (**5c**; $C_{13}H_7N_4$)

Yield: 1.12 g (53%); m.p.: 225 °C dec. (EtOH–H_2O); ^{1}H NMR (200 MHz, *DMSO*-d_6): 7.30 (s, 1H, H-6), 7.75 (t, 1H, H-7), 7.95 (d, 1H, H-8), 8.0 and 8.4 (AB, q, 4H, aryl), 9.05 (d, 1H, H-5) ppm.

2-(4-Pyridyl)-s-triazolo[1,5-a]pyridine (**5d**)

Yield: 0.79 g (41%); m.p.: 192 °C (ethanol; Ref. [2]: 192–3 °C)

2-(2-Thienyl)-s-triazolo[1,5-a]pyridine (**5e**; $C_{10}H_7N_3S$)

Yield: 1.06 g (62%); m.p.: 165 °C (ethanol); ^{1}H NMR (200 MHz, *DMSO*-d_6): 7.00 (t, 1H, H-6), 7.15 (t, 1H, H-4′), 7.45 (d, 1H, H-3′), 7.50 (t, 1H, H-7), 7.75 (d, 1H, H-8), 7.90 (d, 1H, H-5′), 8.55 (d, 1H, H-5) ppm.

2-Amino-1-benzaliminopyridinium tosylate (**2a**)

A mixture of 1,2-diaminopyridinium tosylate (**1**, 0.7 g, 2.5 mmol) and benzaldehyde (0.32 g, 3 mmol) in methanol (30 ml) was stirred for one hour at room temperature. Ether was added and the precipitated crystals were filtered off to give 0.63 g of the product (68%). M.p.: 158–159 °C; ^{1}H NMR (200MHz, *DMSO*-d_6): 2.30 (s, 3H, CH_3), 7.05 (t, 1H, H-5), 7.20 (d, 1H, H-3), 7.12 and 7.50 (AB, q, 4H, tosyl), 7.65 and 8.1 (m, 5H, phenyl), 7.95 (t, 1H, H-4), 8.6 (d, 1H, H-6), 9.1 (s, 1H, CH) ppm.

Acknowledgements

Financial support by OTKA 1756, 1757 and E-12240 as well by the Austrian–Hungarian project OMFB A7 is gratefully acknowledged.

References

[1] Potts KT, Burton HR, Bhattacharyya J (1966) J Org Chem **31**: 260
[2] Toshihike O, Massaki H, Vasunobu T, Emike Y (1966) Chem Pharm Bull **14**: 506
[3] Gewald K, Schubert A, Martin G (1975) J Prakt Chem **317**: 561
[4] Berner H, Reinshagen H (1975) Monatsh Chem **106**: 1059
[5] Lin YI, Lang SA (1981) J Org Chem **46**: 3123
[6] Banks RE, Hitchen SM (1982) J Flourine Chem **20**: 373
[7] Molina P, Alajarin M, Soler A (1980) An Quim **76C**: 207
[8] Phadke RC, Rangenkar DW (1986) Synthesis 860
[9] Chuiguk VA, Fedotov KV (1980) Ukr Khim Zh **46**: 1306
[10] Glover EE, Rowbottom KT (1976) J Chem Soc Perk Trans I: 367
[11] e.g. Jerchel D, Kracht M, Krucher K (1954) Liebigs Ann Chem **590**: 232
[12] With the exception of compound **5a** which was isolated by extraction with chloroform

Received March 7, 1995. Accepted March 14, 1995