1,2-Methyl Shift in the Reaction of 4,7-Dihydro-4,5-dimethyl-7-phenyl-(1,2,4)-triazolo[1,5-*a*]pyrimidine with Tosyl Azide

Sergey A. Komykhov, Sergey M. Desenko, Alexander S. Kaganovsky and Valery D. Orlov*

Kharkov State University, Department of Chemistry, UA-310077, Kharkov, Ukraine

Herbert Meier

University of Mainz, Institute of Organic Chemistry, D-55099 Mainz, Germany

Received May 21, 1999

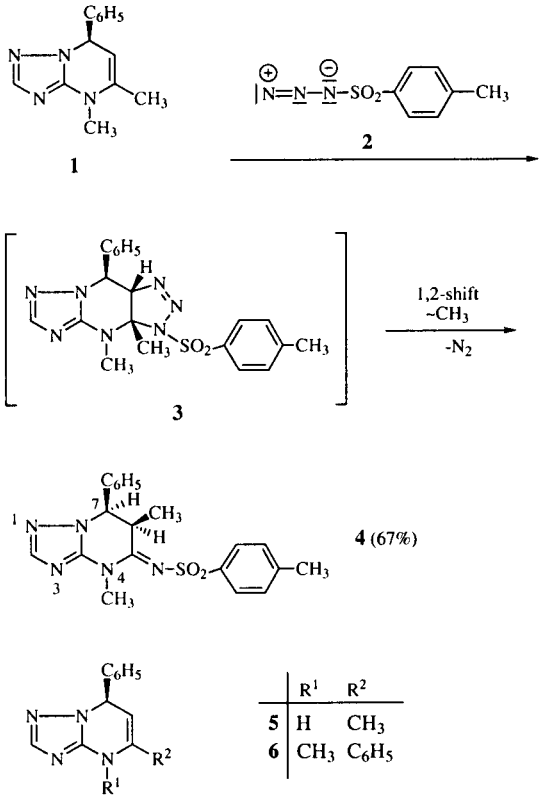
The reaction of the heterocyclic enamine **1** with tosyl azide (**2**) leads to the tosylimino derivative **4** of 1,2,4-triazolo[1,5-a]pyrimidine. The extrusion of nitrogen from the primary adduct **3** is followed by a 1,2-shift of a methyl group. The structure determination of **4** is based on ^1H and ^{13}C nmr spectra including NOE measurements.

J. Heterocyclic Chem., **37**, 195 (2000).

In continuation of our investigations of the chemical properties of 4,7-dihydro derivatives of 1,2,4-triazolo[1,5-*a*]-pyrimidines, a class of compounds with interesting biological and pharmacological properties [1], we studied the capability of some 4,7-dihydrotriazolo[1,5-*a*]pyrimidines (**1**, **5**, **6**) to add sulfonyl azide. It is known that the enamine double bond of 1,4-dihydropyridine can react with a 1,3-dipolar reagent to generate a triazole derivative as a cycloaddition product [2-4]. Moreover, in the reaction of 1,4-dihydropyridine with sulfonyl azides the formation of tetrahydropyridines fused with aziridine rings was communicated [2].

Now, we have established that the reaction of 4,7-dihydro-4,5-dimethyl-7-phenyl-(1,2,4)-triazolo[1,5-*a*]pyrimidine (**1**) with tosyl azide (**2**) in diethyl ether/ethyl acetate leads to the formation of 4,5,6,7-tetrahydro-4,6-dimethyl-7-phenyl-5-tosylimino-(1,2,4)-triazolo[1,5-*a*]pyrimidine (**4**) (Scheme 1).

Scheme 1

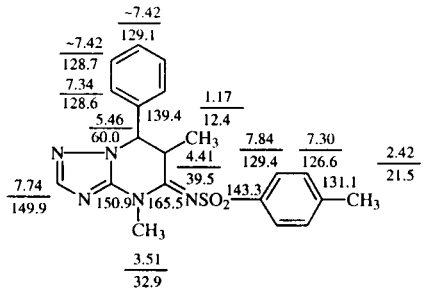


The primary cycloaddition product **3** undergoes nitrogen extrusion and rearrangement with the migration of a methyl group. The attempts to isolate a 1,2,3-triazole or an aziridine derivative were unsuccessful. No reaction was observed between **2** and 4,7-dihydro-5-methyl-7-phenyl-(1,2,4)-triazolo[1,5-*a*]pyrimidine (**5**) or 4,7-dihydro-4-methyl-5,7-diphenyl-(1,2,4)-pyrazolo[1,5-*a*]pyrimidine (**6**). The compounds **5** and **6** remained unchanged under the conditions used for **1**; an experiment at higher temperatures using boiling THF/ethyl acetate (1:1) also was not successful.

The observed 1,2-methyl shift is related to the 1,2-hydrogen shift, which was found in the reaction of 1,2,3,4-tetrahydro-1-methylpyridine with azides [5], and to the ring-contraction in the reaction of 1,2,3,4-tetrahydro-9-methylcarbazole with azides [6,7].

Compound **4** was identified by spectral methods. The ^1H nmr spectrum contained the signals of three methyl groups (two singlets and one doublet) and two signals of neighboring methine protons. (The ABX_3 spin pattern turned into an AB system by irradiation into the signal of the methyl group). Furthermore, a singlet of the proton of the triazole ring and a multiplet for the aromatic protons were found. The ^{13}C nmr spectrum showed 16 signals of carbon atoms. Their assignment (Scheme 2) was based on DEPT (distortionless enhancement by polarization transfer) experiments, a $^1H,^{13}C$ shift correlation and on the data from our previous work [1]. The mass spectrum showed the molecular ion peak at $m/z = 395$.

Scheme 2



The stereochemistry of **4** was determined by means of NOE (nuclear Overhauser effect) measurements. The coupling constant between 6-H and 7-H (4.1 Hz) indicated an axial-equatorial or an equatorial-equatorial interaction of the two protons. Irradiation into the signal of 6-CH_3 showed, in the NOE difference spectrum, an enhancement of the *o*-protons of the phenyl group but no enhancement for 7-H. This result revealed that 6-CH_3 and 7-H are both in axial positions. Thus, the methyl group and the phenyl substituent have a *cis*-configuration with a preferred axial orientation of the methyl group and an equatorial orientation of the phenyl group. Obviously, the azide **2** attacked the double bond of **1** from the side opposite to the phenyl substituent and the methyl group migrated suprafacially. Compound **1** was introduced as racemate; consequently we obtained an enantiomeric mixture of (6*R*,7*R*) - **4** and (6*S*,7*S*) - **4**.

EXPERIMENTAL

The melting point, determined on a Kofler apparatus is uncorrected. The ^1H and ^{13}C nmr spectra were obtained on a Bruker AM 400 in deuteriochloroform with tetramethylsilane as internal standard. The mass spectrum was recorded on a Finnigan M 95 spectrograph operating at 70 eV.

4,5,6,7-Tetrahydro-4,6-dimethyl-7-phenyl-5-tosylimino-(1,2,4)-triazolo[1,5-*a*]pyrimidine (**4**).

Compound **1** [8] (0.20 g, 0.9 mmole) was dissolved in a mixture of 5 ml of diethyl ether and 5 ml of ethyl acetate. A solution of 0.20 g (1.0 mmole) **2** in 5 ml of diethyl ether was added. After 48 hours at room temperature the solution was concentrated and the residue flash-chromatographed on alumina with ethyl acetate to yield **4** (0.24 g, 67%) with mp 182-184° (from ethyl acetate). The ^1H and ^{13}C nmr signals are shown in Scheme 2. The ei ms spectrum shows peaks at *m/z* (%): 395 (17), 155 (31), 144 (35), 118 (14), 117 (60), 116 (37), 115 (22), 104 (15), 97 (17), 92 (28), 91 (100).

Anal. Calcd. for $C_{20}H_{21}N_5O_2S$: C, 60.74; H, 5.35; N, 17.71. Found: C, 60.71; H, 5.40; N, 17.69.

Acknowledgement.

We are grateful to DAAD for financial support.

REFERENCES AND NOTES

[1] S. M. Desenko, S. A. Komykhov, V. D. Orlov, H. Meier, *J. Heterocyclic Chem.*, **35**, 989-990 (1998).

[2] B. K. Warren, E. E. Knaus, *J. Med. Chem.*, **24**, 462-464 (1981); *Chem. Abstr.*, **94**, 174934p (1981).

[3] M. D. Taylor, R. J. Himmelsbach, B. E. Kornberg, J. Quin III, E. Lunney, A. Michel, *J. Org. Chem.*, **54**, 5585-5590 (1989).

[4] G. Adembri, D. Donati, S. Fusi, F. Ponticelli, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2033-2038.

[5] B. K. Warren, E. E. Knaus, *J. Heterocyclic Chem.*, **19**, 1259 (1982).

[6] A. S. Bailey, R. Scattergood, W. A. Warr, *J. Chem. Soc. (C)* 1971, 2479.

[7] See also A. Padwa, 1,3-Dipolar Cycloaddition Chemistry, Vol. 1, p. 617, John Wiley & Sons, New York, NY, 1984.

[8] S. M. Desenko, V. D. Orlov, V. V. Lipson, *Khim. Geterotsikl. Soedin.*, 1990, 1638-1642, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **26**,1362-1366 (1990).