# Easy formation of $S_NH$ products in reactions of indoles and pyrroles with 3-aryl-1,2,4-triazin-5(2*H*)-ones in the presence of tosyl chloride

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The reactions of 3-aryl-1,2,4-triazin-5(2*H*)-ones with indoles and pyrroles in the presence of *p*-toluenesulfonyl chloride afforded 3-aryl-6-hetaryl-1,2,4-triazin-5(2*H*)-ones in high yields. The latter are products of the nucleophilic substitution of hydrogen.

**Key words:** 3-aryl-1,2,4-triazin-5-ones, indoles, pyrroles, tosyl chloride, 3-aryl-6-hetaryl-1,2,4-triazin-5(2*H*)-ones, nucleophilic substitution of hydrogen.

Nucleophilic substitution accompanied by the displacement of hydrogen ($S_NH$) or readily leaving groups ($S_N^{ipso}$), like electrophilic substitution in aromatic compounds, is common to π-deficient heteroaromatic systems.[1,2] Terrier reasoned[2] that $S_NH$ reactions are among the most intensively developing fields of organic chemistry. In these reactions, the attack of a nucleophile occurs at the nonsubstituted C atom of the ring and, hence, there is no need to introduce the leaving group beforehand.

1,2,4-Triazinones exhibit high reactivity in transformations of this type (compared to 1,2,4-triazines). 1,2,4-Triazin-3(2*H*)-ones and 1,2,4-triazin-5(2*H*)-ones can react with aliphatic amines,[3] indoles, and 1-methylpyrrole[4,5] without additional activation to form products of the nucleophilic displacement of hydrogen. The direct nucleophilic displacement of hydrogen in protic salts of 3-aryl-1,2,4-triazin-5(2*H*)-ones, which are prepared *in situ*, takes place in the reactions with dimethylaniline, phenols, and indoles in acetic or trifluoroacetic acids. Aromatization (either spontaneous or proceeding upon bubbling of air through solutions in DMF) of 3-aryl-6-Nu-1,6-dihydro-1,2,4-triazin-5(2*H*)-ones, which were obtained in the initial step ($\sigma^H$ adducts in $S_NH$ reactions), afforded the corresponding 3-aryl-6-Nu-1,2,4-triazin-5(2*H*)-ones.[5,6] The latter compounds are of interest for testing biological activities.[7—9]

High π-deficiency of *N*-acylazinium salts of 3-aryl-1,2,4-triazin-5(2*H*)-ones (**1**) (salts are generated in the *in situ* reactions performed in acetic anhydride) facilitates the addition of arylamines, phenols, indoles, and pyrroles at the nonsubstituted C(6) atom of azines giving rise to stable adducts, *viz.*, 6-Nu-1-acetyl-3-aryl-1,6-dihydro-1,2,4-triazin-5(2*H*)-ones. One of the characteristic features of this transformation typical of most of *N*-acylazinium salts[10] is the fact that the resulting adducts are very stable. Hence, attempts to use conventional procedures for their subsequent aromatization with the aim of preparing the corresponding $S_NH$ products failed.[5,6]

## Results and Discussion

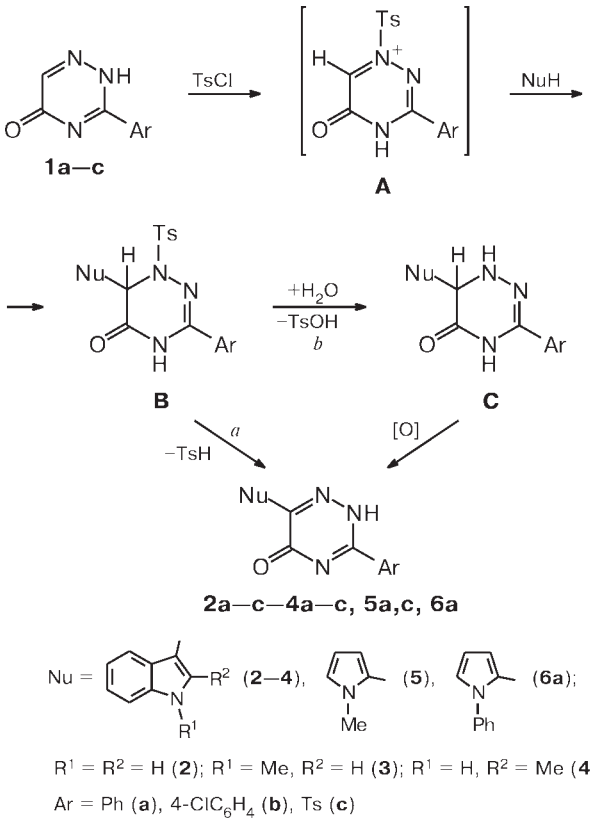
As part of our continuing studies in this field, we found that the reactions of compounds **1** with indoles, *N*-methylpyrrole, and *N*-phenylpyrrole using chlorides of aromatic sulfonic acids as acylating agents gave rise to the corresponding 3-aryl-6-heteryl-1,2,4-triazin-5(2*H*)-ones (**2—6**), which are products of the nucleophilic displacement of hydrogen (Scheme 1). For example, storage of solutions of 1,2,4-triazin-5(2*H*)-ones **1** and the corresponding π-excessive heterocycles in chloroform in the presence of *p*-toluenesulfonyl chloride at room temperature for 24 h afforded compounds **2—6** in 80—90% yields. The spectroscopic characteristics of substituted triazinones **2—4** thus obtained correspond to the assumed structures and are consistent with the published data.[4,5]

The following reaction pathway can be suggested. Activation of 1,2,4-triazin-5(2*H*)-ones **1** through the formation of acylazinium salts **A** is followed by the addition of a nucleophile to give adducts **B**. The reactions of 3-methylthio-1,2,4-triazin-5-one with water and metha-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 957—959, June, 2002.

1066-5285/02/5106-1042 $27.00 

**Scheme 1**




nol proceeded analogously to give products of the addition at the C(6) atom of the heterocycle even at below-zero temperatures.[11,12] Compounds **B** can undergo subsequent transformations into the corresponding $S_NH$ products either directly with elimination of the sulfinic acid molecule (path *a*) or in two steps (path *b*). In the latter case, 6-hetaryl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**C**) are initially generated through hydrolysis with water, which is present in the solvent, followed by oxidation of compounds **C** to produce 3-aryl-6-hetaryl-1,2,4-triazin-5(2*H*)-ones **2—6**.

With the aim of revealing the real pathways of the process, the reactions were examined in an $^1$H-NMR tube (Fig. 1). For this purpose, equimolar amounts of 3-phenyl-1,2,4-triazin-5(2*H*)-one (**1a**) and tosyl chloride were dissolved in argon-saturated $CDCl_3$ containing several drops of DMF-$d_7$. Then one equivalent of *N*-methylpyrrole was added and the mixture was kept under argon at room temperature. After 5 min, the $^1$H NMR spectrum showed the formation of *N*-tosyl-containing product **B**, which was detected from a superposition of the signals of the 1,2,4-triazine, tosyl, and pyrrole fragments as well as from a signal for the H(6) proton at δ 4.78 (see Fig. 1). The subsequent transformation of adduct **B** into compound **C** is evidenced by the upfield shift (δ 4.70) of the signal for the H(6) proton (the positions and the multiplicities of the signals are identical with those published in the literature[4] for 3-aryl-6-Nu-1,6-dihydro-1,2,4-triazin-5(2*H*)-ones). The addition of an oxidant, *viz.*, DMSO-$d_6$ or atmospheric oxygen, to the reaction mixture led to oxidation of intermediates **C** to form products of the nucleophilic displacement of hydrogen as evidenced by the disappearance of the signal for the H(6) proton and the downfield shifts of the signals for the protons of the aromatic fragment. The above-considered data indicate that the reaction in an moist solvent followed the path *b*. The proposed scheme is also supported by the fact that the $^1$H NMR spectrum of the reaction mixture has signals for the aromatic protons of *p*-toluenesulfonic acid as two two-proton doublets at δ 7.13 and 7.70.

Hence, activation of 1,2,4-triazin-5(2*H*)-ones **1** with arenesulfonyl chlorides can serve as a simple one-step procedure for the functionalization of 1,2,4-triazines.

## Experimental

The $^1$H NMR spectra were recorded on a Bruker WH-250 spectrometer (250 MHz) in DMSO with $Me_4Si$ as the internal standard. The mass spectra were obtained on a Varian MAT-311A instrument (70 eV, EI). The melting temperatures were determined on a Boetius stage and were not corrected. The course of the reactions and the purities of the products were monitored by TLC on Silufol UV-254 plates using ethyl acetate as the eluent; visualization was carried out with UV light.

**3-Aryl-6-hetaryl-1,2,4-triazin-5(2*H*)-ones 2—6.** A mixture of 3-aryl-1,2,4-triazin-5(2*H*)-one **1** (1 mmol), indole or pyrrole (1.2 or 3 mmol, respectively), tosyl chloride (0.19 g, 1 mmol), $CHCl_3$ or $CCl_4$ (5 mL), and DMSO (5 mL) was kept at ~20 °C for 24—36. The reaction solution was concentrated to dryness under reduced pressure. The residue was diluted with water (30—50 mL) and the precipitate that formed was filtered off and crystallized from 50% aqueous EtOH.

**3-Aryl-6-indolyl-1,2,4-triazin-5(2*H*)-ones (2—4).** The spectroscopic characteristics and the melting temperatures of compounds **2—4** are identical with those described earlier.[4] The yields (%): **2a**, 88; **2b**, 93; **2c**, 95; **3a**, 90; **3b**, 94; **3c**, 96; **4a**, 90; **4b**, 91; **4c**, 91.

**6-(1-Methylpyrrol-2-yl)-3-phenyl-1,2,4-triazin-5(2*H*)-one (5a)**, the yield was 90%, m.p. 273—275 °C (from MeOH). Found (%): C, 66.90; H, 5.02. $C_{14}H_{12}N_4O$. Calculated (%): C, 66.66; H, 4.79. $^1$H NMR, δ: 3.70 (s, 3 H, N(1′)—Me); 6.66 (br.s, 1 H, H(3′)); 6.80—6.83 (m, 1 H, H(4′)); 7.57—7.61 (m, 3 H, Ar); 7.97 (br.s, 1 H, H(5′)); 8.07—8.10 (m, 2 H, Ar); 13.95 (br.s, 1 H, NH). MS, *m/z* ($I_{rel}$ (%)): 252 $[M]^+$ (100).

**6-(1-Methylpyrrol-2-yl)-3-(4-tolyl)-1,2,4-triazin-5(2*H*)-one (5c)**, the yield was 80%, m.p. >300 °C (from 50% aqueous EtOH). Found (%): C, 67.46; H, 5.41. $C_{15}H_{14}N_4O$. Calculated (%): C, 67.66; H, 5.29. $^1$H NMR, δ: 2.42 (s, 3 H, Me); 3.99 (s, 3 H, N(1′)—Me); 6.13—6.25 (m, 1 H, H(3′)); 7.06 (m, 1 H, H(4′)); 7.39—7.42 (m, 1 H, H(5′)); 7.42 and 8.03 (both d, 2 H each, Ar, $J$ = 8.2 Hz); 14.05 (br.s, 1 H, NH). MS, *m/z* ($I_{rel}$ (%)): 266 $[M]^+$ (100).

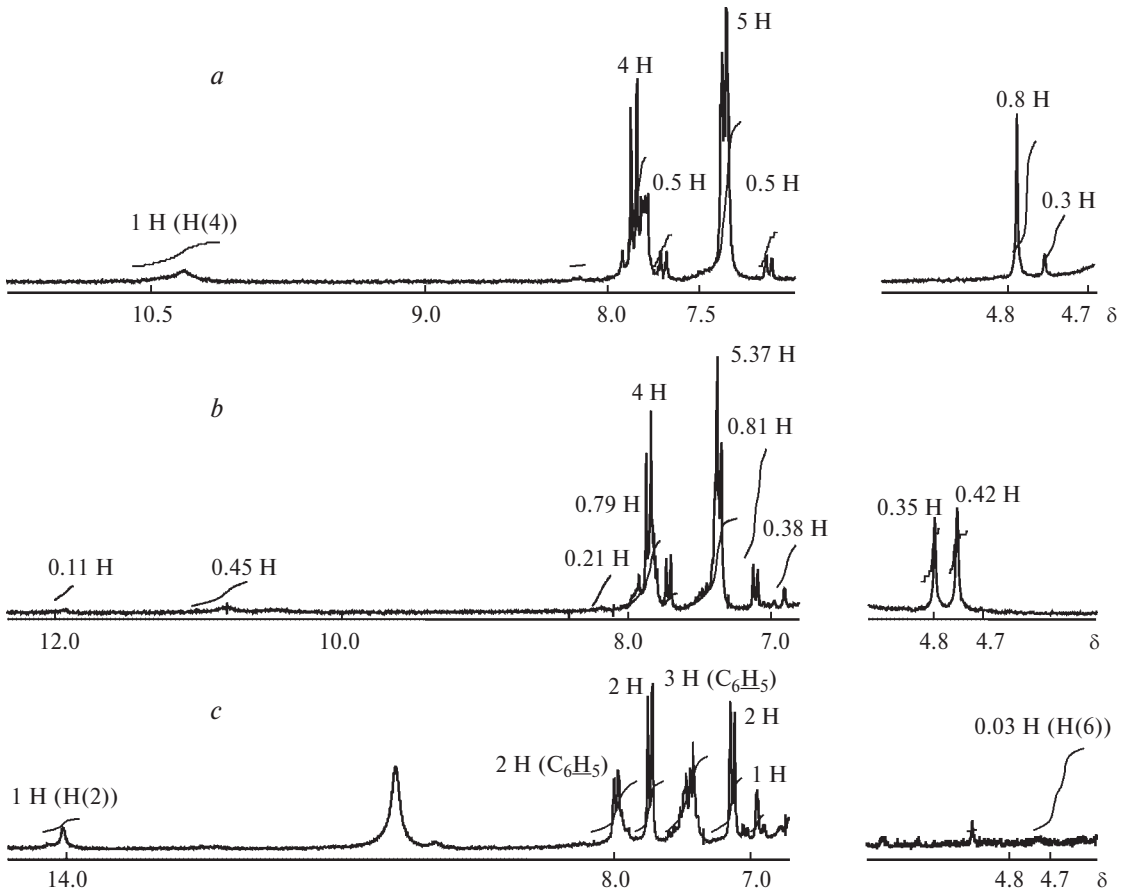



**Fig. 1.** Fragment of the $^1$H NMR spectrum of a solution of 3-phenyl-1,2,4-triazin-5(2*H*)-one (**1a**) in $CDCl_3$ recorded within 5 min (*a*) and 7 h (*b*) after the addition of 1-methylpyrrole and after the addition of the oxidizing agent (*c*).

**3-Phenyl-6-(1-phenylpyrrol-2-yl)-1,2,4-triazin-5(2*H*)-one (6a)**, the yield was 80%, m.p. >300 °C (from MeOH). Found (%): C, 72.90; H, 4.52. $C_{19}H_{14}N_4O$. Calculated (%): C, 72.60; H, 4.49. $^1$H NMR, δ: 6.90 (br.s, 1 H, H(3′)); 7.18—7.29 (m, 2 H, H(5′) + N(1′)—Ar); 7.32—7.60 (m, 7 H, Ar + N(1′)—Ar); 8.13—8.16 (m, 2 H, Ar); 8.46 (br.s, 1 H, H(4′)); 13.95 (br.s, 1 H, NH). MS, *m/z* ($I_{rel}$ (%)): 314 $[M]^+$ (100).

This study was financially supported by the Russian Foundation for Basic Research (Project Nos. 01-03-96443 and 00-15-97390), the US Civilian Research and Development Foundation (CRDF), and the Ministry of Education of the Russian Federation (Grant REC-005).

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*Received June 1, 2001;*
*in revised form December 21, 2001*