C—H-Functionalization of 1,2,4-triazines: 
oxidation and elimination pathways of aromatization of σH-adducts*

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An approach to the synthesis of 1,2,4-triazine thienyl and furyl derivatives through the reaction of aromatic nucleophilic substitution of hydrogen was suggested. Oxidation and cine-elimination pathways of aromatization of the intermediate σH-adducts were considered.

Key words: 1,2,4-triazines, aromatic nucleophilic substitution of hydrogen, thiophenes, furans.

1,2,4-Triazines are one of the most important class of nitrogen-containing heterocycles widely used in medicine, agrichemistry and as ligands for a number of metals.1—5 Triazine derivatives are also known to be used as dyes.6

Triazine derivatives are of huge value in therapy of malaria, epilepsy, cancer, and a number of other diseases.7—12 Besides, triazines are convenient synthetic blocks for the preparation of a wide range of heterocyclic compounds, in particular, pyridine derivatives, by the Diels—Alder reaction.12—14 This shows that 1,2,4-triazine derivatives are of very much interest.

Synthesis of 1,2,4-triazine functional derivatives is based on two principally different approaches. In the first case, functional substituents are introduced into the heterocycle in the step of formation of cyclic system by condensation reaction.1,15 Second approach consists in functionalization of heterocyclic system through the transformation of substituents in the triazine ring,1,15 including application of cross-coupling reactions.16—18

The problem of nucleophilic substitution of hydrogen in 1,2,4-triazines was considered in a number of papers and monographs.19—25 For example, a number of C-nucleophiles were reported to be successfully introduced in the 1,2,4-triazine ring.22,23 In particular, alkylphenols24 and crown-ethers.25 Thus, the dissolution of 1,2,4-triazines in trifluoroacetic or acetic acid results to the formation of protic NH-triazinium salts, which at room temperature easily react with 2,6-dimethylphenol and resorcinol.23 This reaction leads to a reverse formation of C(6)-adducts stable only in strongly acidic solutions (1H NMR spectroscopic data). Attempted isolation of these adducts in the free state failed, but acylation appeared to be one of the successful pathways for their stabilization.23 Another route for modification of 1,2,4-trizine adducts is their oxidation. In a number of cases the adducts can be oxidized by atmospheric oxygen, other cases require oxidants such as DDQ, lead tetraacetate, or potassium hexacyanoferrate.

The purpose of the present work is studies of the reaction of 3-substituted 1,2,4-triazines with furans and thiophenes. We have chosen readily available 3-methylthio-1,2,4-triazine (1) and 3-amino-1,2,4-triazine (2) as the starting compounds.

The reaction of triazines 1 and 2 with a number of thiophenes in the presence of the oxidation mixture K3(Fe(CN)6)—KOH gave good yields of the products of substitution of the hydrogen atom at atom C(5) of the triazine ring (Scheme 1).

It was found that the product of the addition of thiophene to the triazine ring is formed in the first step of the reaction. The composition of the reaction mixtures was analyzed by GLC-MS (Table 1). In a number of cases, σH-adducts turned out to be so stable that they were isolated in the free form. Stability of σH-adducts depends on the character of substituent in the thiophene ring. The larger is the donor effect of such a substituent (for example, phenyl), the more stable is the addition product and, therefore, the higher is the yield of the adduct. Conversely, in the case of thienyl-2-carbaldehyde we isolated neither the corresponding adduct nor the product of nucleophilic aromatic substitution of hydrogen.
The second step consists in the aromatization of the adducts. In this case, the oxidant can be applied to both the reaction mixture (without isolation of the intermediate compound) and to the individual dihydrotriazine (if it is stable). The structures of synthesized compounds were confirmed by a combination of spectroscopic methods, as well as by X-ray diffraction studies using product 5d as an example (Fig. 1).

The reaction of triazine 1 with a 10-fold excess of thiophene (Scheme 2, pathway II) gives adduct 7, however, the GLC-MS data show that the same reaction with 1.5—2-fold excess of thiophene leads to the formation of only monoadduct 3a (Scheme 2, pathway I).

Compounds 3a and 7 have different resistance to oxidants. Compound 7 appears to be comparatively stable to such oxidants as atmospheric oxygen, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and K₃[Fe(CN)₆].

### Table 1. Composition of the reaction mixtures in the reaction of 3-methylthio-1,2,4-triazine with thiophene and furan

<table>
<thead>
<tr>
<th>Ratio triazine/nucleophile</th>
<th>Composition of mixture (%)</th>
</tr>
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<tbody>
<tr>
<td>1a : 2a, 1 : 10</td>
<td>3a (3), 7 (80)</td>
</tr>
<tr>
<td>1a : 2a*, 1 : 10</td>
<td>8 (8), 7 (65)</td>
</tr>
<tr>
<td>1a : 2a, 1 : 2</td>
<td>3a (73), 5a (17)</td>
</tr>
<tr>
<td>1a : 9*, 1 : 2</td>
<td>10 (40), 11 (58)</td>
</tr>
<tr>
<td>1a : 9*, 1 : 10</td>
<td>11 (100)</td>
</tr>
<tr>
<td>12 : 2a*, 1 : 2</td>
<td>6a (84), 13 (13)</td>
</tr>
</tbody>
</table>

* K₃(Fe(CN)₆)/KOH.