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4-AMINO-6-(*tert*-BUTYL)-3-METHYLTHIO-4,5-DIHYDRO-1,2,4-TRIAZIN-5-ONE IN NUCLEOPHILIC SUBSTITUTION REACTIONS WITH CARBOXYLIC ACID HYDRAZIDES

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Keywords: 8-amino-3-aryl-6-(*tert*-butyl)-7,8-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-one, 4-amino-6-(*tert*-butyl)-3-methylthio-4,5-dihydro-1,2,4-triazin-5-one, nucleophilic substitution.

Known methods for synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4]triazine derivatives are based on reaction of 3-hydrazino-4,5-dihydro[1,2,4]triazin-5-one with carboxylic acids [1, 2], orthoformic ester [3], bromocyanine [4], or aromatic isothiocyanates [5].

We showed earlier in [6] that in fusion of 4-hydroxy-6-methyl-2-methylthiopyrimidine with hydrazides of aromatic acids, nucleophilic substitution of the methylthio group is accompanied by spontaneous cyclization to form 3-aryl-5-methyl-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidin-7-one derivatives.

With the aim of further studying nucleophilic substitution of the methylthio group by carboxylic acid hydrazide residues, we carried out fusion of 4-amino-6-(*tert*-butyl)-3-methylthio-4,5-dihydro-1,2,4-triazin-5-one (**1**) with 2-(4-bromophenoxy)acetic acid hydrazide at 150-160°C. We found that it is accompanied by rapid evolution of methanethiol and leads to formation of N^1-[4-amino-6-(*tert*-butyl)-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl]-N^2-[2-(4-bromophenoxy)acetyl]hydrazine (**2**). The presence of a two-proton singlet for the N–NH$_2$ group at 6.11 ppm and two broadened signals from the NH–NH group at 10.2 ppm and 11.9 ppm in the ^{1}H NMR spectrum of compound **2** suggests that the reaction stops at the step of nucleophilic substitution of the methylthio group without further cyclization (Scheme 1).

On the other hand, in fusion of (methylthio)triazine **1** with hydrazides of *p*-chloro(bromo)benzoic acids, nucleophilic substitution of the methylthio group by a hydrazide moiety is accompanied by spontaneous cyclization to form bicyclic compounds **3a,b**. The presence of an amino group in the 4 position in compound **1** allows us to hypothesize two directions for the cyclization, but the presence of a two-proton singlet from the N-amino group in the 6.02-6.06 ppm in the ^{1}H NMR spectra clearly indicates formation of just the 8-amino-6-(*tert*-butyl)-3-aryl-7,8-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-ones **3a,b**.

The ^{1}H NMR spectra were taken in DMSO-d$_6$, internal standard TMS, operating frequency 300 MHz.

N^1-[4-Amino-6-(*tert*-butyl)-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl]-N^2-[2-(4-bromophenoxy)acetyl]-hydrazine (2). A mixture of compound **1** (2.14 g, 0.01 mol) and 2-(4-bromophenoxy)acetic acid hydrazide (2.45 g, 0.01 mol) was heated on an oil bath for 7-8 h at 150-160°C until evolution of methanethiol stopped. After cooling, the reaction mixture was triturated with 2-propanol; the precipitate was filtered out and dried. Yield 2.42 g (59%); mp 254-255°C (DMF). ^{1}H NMR spectrum, δ, ppm: 1.29 (9H, s, C(CH$_3$)$_2$); 4.63 (2H, s, OCH$_2$); 6.11 (2H, s, NH$_2$); 6.97 and 7.46 (4H, two d, C$_6$H$_4$); 10.20 (1H, s, NH); 11.90 (1H, s, NH). Found, %: Br 19.3; N 20.2. $C_{15}H_{19}BrN_6O_3$. Calculated, %: Br 19.5; N 20.4.

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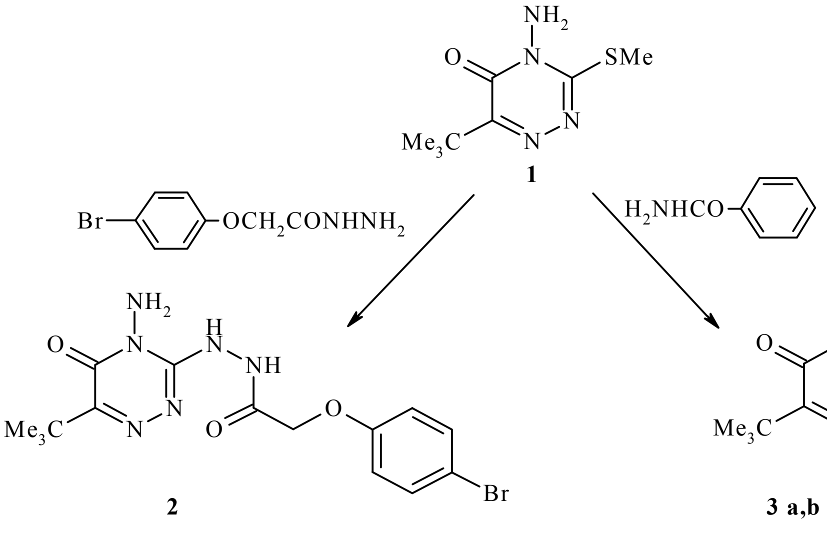
Scheme 1



3 a R = Cl, **b** R = Br

8-Amino-6-(*tert*-butyl)-3-(4-chlorophenyl)-7,8-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-one (3a) was obtained similarly to compound **2a** from equimolar amounts of **1** and 4-chlorobenzoic acid hydrazide. Yield 52%; mp 247-248°C (DMF). ^{1}H NMR spectrum, δ, ppm: 1.42 (9H, s, $C(CH_3)_3$); 6.06 (2H, s, NH_2); 7.66 and 8.18 (4H, two d, C_6H_4). Found, %: Cl 11.5; N 26.2. $C_{14}H_{15}ClN_6O$. Calculated, %: Cl 11.4; N 26.4.

8-Amino-3-(4-bromophenyl)-6-(*tert*-butyl)-7,8-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-one (3b) was obtained similarly to compound **2a** from equimolar amounts of compound **1** and 4-bromobenzoic acid hydrazide. Yield 64%; mp 259°C (DMF). ^{1}H NMR spectrum, δ, ppm: 1.48 (9H, s, $C(CH_3)_3$); 6.02 (2H, s, NH_2); 7.67 and 8.15 (4H, two d, C_6H_4). Found, %: Br 22.1; N 22.8. $C_{14}H_{15}BrN_6O$. Calculated, %: Br 22.0; N 23.1.

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