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Reactions of Diazido Derivatives of *s*-Triazine with *C*-Nucleophiles

Yurii A. Azev,* Inna P. Loginova, Olga L. Guselnikova, Sergei V. Shorshnev, Vladimir L. Rusinov and Oleg N. Chupakhin

Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3432 440458

The reaction of 2,4-diazido-*s*-triazines **1** with an equimolar amount or a two-fold molar excess of ethyl cyanoacetate in the presence of triethylamine in DMF affords the corresponding mono- **2** or diamino derivatives of *s*-triazine **3**; on heating 2,4-diazido-*s*-triazines **1a–d** with a two-fold molar excess of acetoacetone or ethyl acetoacetate in the presence of triethylamine in ethanol the corresponding 1,2,3-triazolo-*s*-triazines **4a–f** are formed.

Organic azides are known to undergo the diazo transfer reaction on treatment with CH-active methylene compounds in the presence of a base. However, they react differently depending on the nature of the reagents used and reaction conditions.[1] Thus, on heating diethyl malonate with *p*-carboxyphenylsulfonylazide in acetonitrile in the presence of triethylamine as a base diazomalonic ester (yield 76%) and *p*-carboxyphenylsulfonylamine were obtained.[2] When the sodium salt of diethyl malonate was allowed to react with *p*-tosyl azide, diazomalonic ester was produced in a poor yield (3%), while

Table 1 Reactions of diazido (**1**) and aminoazido (**2**) *s*-triazines with *C*-nucleophiles.

Compound	CH-active reagent	Molar excess of CH-active reagent	Reaction time/h	Product	Yield (%)	M.p. /°C	IR spectra ν_{N_3}/cm^{-1}
1a	ethyl cyanoacetate	1	24	**2a**	58	230	2156; 2244
		2	24	**3a**	55	240	—
	acetoacetone	2	12	**4a**	31	233	—
	ethyl acetoacetate	2	12	**4d**	42	202	—
1b	ethyl cyanoacetate	1	12	**2b**	30	126	2120; 2220
	acetoacetone	2	12	**4b**	78	182	—
	ethyl acetoacetate	2	12	**4e**	34	>200	—
1c	ethyl cyanoacetate	1	24	**2c**	34	182	2160
		2	24	**3c**	27	230	—
1d	ethyl cyanoacetate	1	24	**2d**	70	250	2160
	acetoacetone	2	12	**4c**	31	276	—
	ethyl acetoacetate	2	12	**4f**	42	285	—
2a	acetoacetone	1	0.5	**4a**	30	233	—
	ethyl acetoacetate	1	9	**4d**	43	202	—
2b	acetoacetone	1	2	**4b**	78	182	—
	ethyl acetoacetate	1	9	**4e**	35	> 200	—
2d	acetoacetone	1	3	**4c**	32	276	—
	ethyl acetoacetate	1	5	**4f**	42	285	—

the corresponding diazomalonoanilide sodium salt was obtained as a major product in 97% yield.[3] The reaction of phenyl azide with ethyl acetoacetate in the presence of sodium ethoxide resulted in rather stable 1-phenyl-5-methyl-1,2,3-triazolocarboxylic acid derivatives.[4] At the same time, no systematic data concerning the reactions with heterocyclic azido derivatives have so far been reported in the literature.

While studying the properties of *s*-triazine azido derivatives we examined their reactions with some CH-active methylene compounds. It turned out that the reaction of compounds **1a–d** with an equimolar amount of ethyl cyanoacetate in the presence of triethylamine in *N,N*-dimethylformamide (DMF) resulted in the formation of the corresponding amino derivatives **2a–d**.† However, when the compounds **1a–c** were allowed to react with a two-fold molar excess of ethyl cyanoacetate the diaminoalkoxy derivatives **3a–c** ‡ were obtained. It is noteworthy that the reaction of diazidoamino derivative **1d** with both equimolar and two-fold excess of ethyl cyanoacetate resulted in the formation of the compound **2d** thus showing that the transfer of the diazo group took place only for one azido function.

Diazido derivatives **1a–d** react with β-dicarbonyl compounds (acetoacetone, ethyl acetoacetate) in a different way yielding triazolo-*s*-triazines **4a–f**§ which were isolated from the reactions of compounds **1a,b,d** with two-fold molar excess of these reagents. The products **4** were also obtained

† A typical procedure for the synthesis of 2-azido-4-amino-*s*-triazines **2a–d**. Ethyl cyanoacetate (2.5 mmol) and triethylamine (2.5 mmol) were added to a solution of the corresponding 2,4-diazido-*s*-triazine **1a–d** (2.5 mmol) in 10 ml DMF and the reaction mixture was kept at room temperature for 24 h. The reaction mixture was then treated with water (1:1) and the precipitate obtained was filtered off. The analytically pure compounds **2a–c** were obtained by recrystallization from absolute ethanol; and compound **2d** from water.

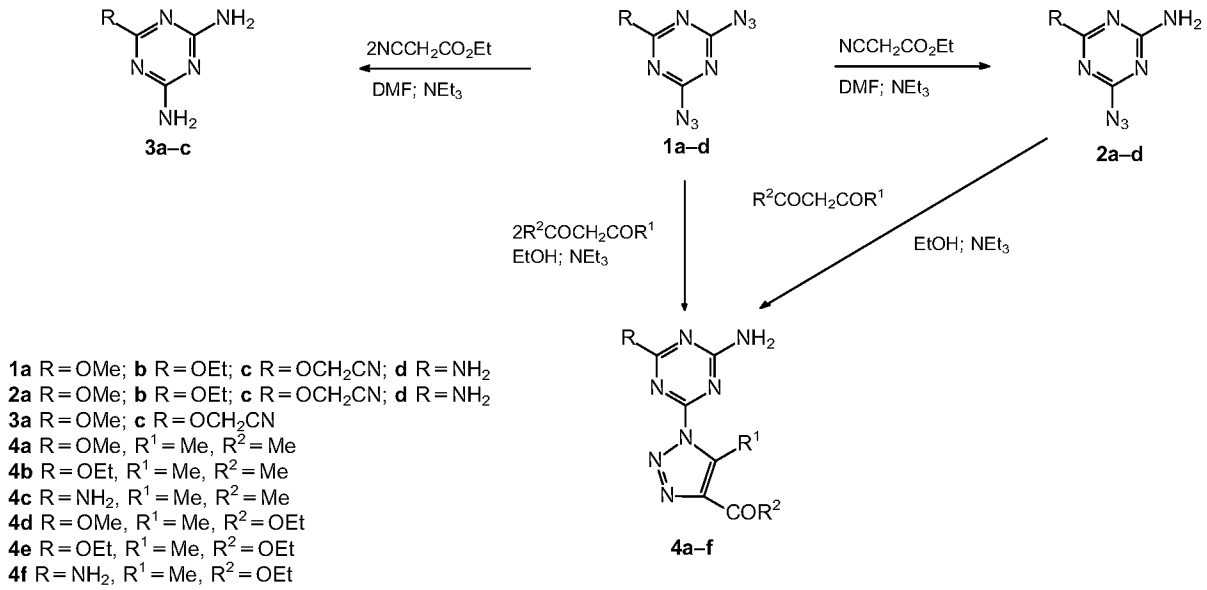
^{1}H NMR ([^{2}H$_6$]DMSO) for **2a**: δ 3.8 (3H, s, OMe), 7.7 (2H, s, NH_2); **2b**: δ 1.3 (3H, t, OCH_2CH_3, *J* 8 Hz), 4.3 (2H, q, OCH_2CH_3, *J* 8 Hz), 7.6 (2H, s, NH_2); **2c**: δ 5.2 (2H, s, OCH_2CN), 7.9 (2H, s, NH_2); ^{13}C NMR ([^{2}H$_6$]DMSO) for **2a**: δ 54.34 (OMe), 168.67 (C-4), 169.94 (C-2), 171.63 (C-6).

‡ A typical procedure for the synthesis of 2,4-diamino-*s*-triazines **3a-c** and **2d**. Ethyl cyanoacetate (6.0 mmol) and triethylamine (6.0 mmol) were added to a solution of the corresponding 2,4-diazido-*s*-triazine **1a–d** (3.0 mmol) in DMF and the mixture was kept at room temperature for 24 h. The precipitate obtained was filtered off. The analytically pure compounds **3a–c** and **2d** were obtained by recrystallisation from water.

^{1}H NMR ([^{2}H$_6$]DMSO) for **3c**: δ 5.0 (2H, s, OCH_2CN), 6.8 (4H, s, $2NH_2$).

§ A typical procedure for the synthesis of triazolo-*s*-triazines **4a–f**. A mixture of the corresponding 2,4-diazido-*s*-triazine **1a,b,d** (6.0 mmol), acetoacetone or ethyl acetoacetate (1.5 ml; 12.0 mmol) and triethylamine (12.0 mmol) was refluxed in ethanol (Table 1). The reaction mixture was then cooled to room temperature and the precipitate obtained was filtered off. The analytically pure compounds **4a–d** were obtained by recrystallization from the following solvents: **4a**: from ethanol; **4b**: from aqueous ethanol (30%); **4c–e**: from aqueous acetic acid (30%); **4f**: from aqueous acetic acid (50%).

^{1}H NMR ([^{2}H$_6$]DMSO) for **4a**: δ 2.7 (3H, s, Me), 2.9 (3H, s, COMe), 3.9 (3H, s, OMe), 8.2 (2H, s, NH_2); **4b**: δ 1.3 (3H, t, OCH_2CH_3, *J* 8 Hz), 2.6 (3H, s, Me), 2.8 (3H, s, COMe), 4.4 (2H, q, CH_2CH_3, *J* 8 Hz), 7.9–8.1 (2H, s, NH_2); **4c**: δ 2.6 (3H, s, –Me), 2.7 (3H, s, COMe), 7.3 (4H, s, NH_2; **4d**: δ 1.4 (3H, t, COOEt, *J* 8 Hz), 2.9 (3H, s, Me), 4.0 (3H, s, OMe), 4.4 (2H, q, –COOEt, *J* 8 Hz), 8.0–8.4 (2H, s, NH_2); **4e**: δ 1.4 (3H, t, COOEt, *J* 8 Hz), 1.6 (3H, t, OEt, *J* 8 Hz), 2.7 (3, s, Me), 4.5 (2H, q, COOEt, *J* 8 Hz), 4.5 (2H, q, OEt, *J* 8 Hz), 6.4, 8.4 (2H, s, NH_2); **4f**: δ 1.3 (3H, t, COOEt, *J* 7.2 Hz), 2.8 (3H, s, Me), 4.2 (2H, q, COOEt, *J* 7.2 Hz), 7.2 (2H, s, NH_2); ^{13}C NMR ([^{2}H$_6$]DMSO) for **4a**: δ 11.03 (Me), 27.93 ($COCH_3$), 54.83 (OMe), 138.98 (C-5′), 143.16 (C-4′), 163.03 (C-2), 168.85 (C-4), 171.63 (C-6), 193.26 ($COCH_3$); **4d**: δ 11.15 (Me), 14.06 ($COCH_2CH_3$), 54.83 (OMe), 60.58 ($COCH_2CH_3$), 136.31 (C-4′), 140.61 (C-5′), 160.79 (*C*OOEt), 162.85 (C-2), 168.67 (C-4), 171.45 (C-6).



1a R = OMe; **b** R = OEt; **c** R = OCH_2CN; **d** R = NH_2
2a R = OMe; **b** R = OEt; **c** R = OCH_2CN; **d** R = NH_2
3a R = OMe; **c** R = OCH_2CN
4a R = OMe, R^1 = Me, R^2 = Me
4b R = OEt, R^1 = Me, R^2 = Me
4c R = NH_2, R^1 = Me, R^2 = Me
4d R = OMe, R^1 = Me, R^2 = OEt
4e R = OEt, R^1 = Me, R^2 = OEt
4f R = NH_2, R^1 = Me, R^2 = OEt

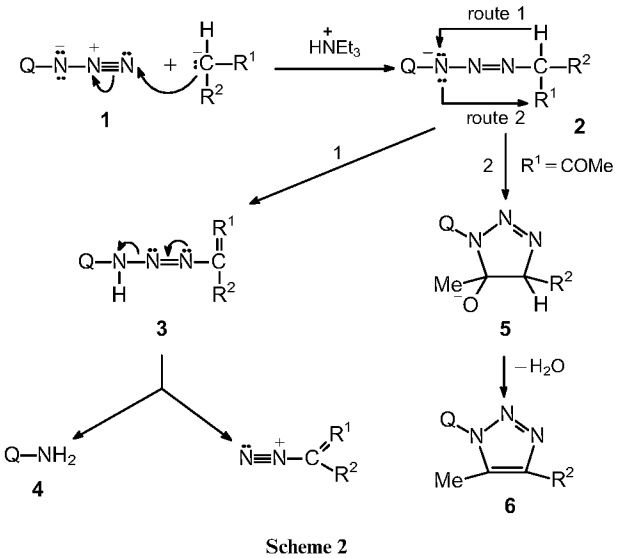
Scheme 1

from azido-amino derivatives **2** under similar conditions.¶

Elemental analyses as well as ^1H, ^{13}C NMR, IR and mass spectrometry data for compounds **2, 3** and **4** are in accordance with the suggested structures. The molecular ion peaks for compounds **2, 3** and **4** determined by mass spectrometry proved to correspond to the calculated values. Absorption bands for the azido group (ν_{N_3}) are available in the IR spectra of all compounds **2** (Table 1).

In the ^{13}C NMR spectrum of compound **2a** measured in [$^2H_6$]DMSO an upfield shift of the carbon $C_{(4)}$ of 2.7 ppm is observed in comparison with that for **1a**. Upfield shifts of the $C_{(2)}$ and $C_{(6)}$ carbon resonances in the ^{13}C NMR spectrum of the compound **2a** are insignificant when compared with those for **1a**. This is due to transformation of one of the azido groups into an amino function at position 4. The triazole ring at $C_{(2)}$ has an even greater shielding effect. That is why in the ^{13}C NMR spectra of compounds **4a** and **4d** upfield shifts of 2.5 and 2.7 ppm for $C_{(4)}$ resonances and 8.4 and 8.5 ppm for $C_{(2)}$ resonances are observed in comparison with those for **1a** (see Fig. 1).

Two plausible mechanisms for the reactions of diazido derivatives with *C*-nucleophiles are presented in Scheme 2. The formation of triazolo-*s*-triazines **6** appears to be a two-step process: at first the diazo transfer transforms one of the azido functions into an amino function (route 1); the cycloaddition reaction of a β-dicarbonyl compound on another azido group then takes place (route 2). The



Scheme 2

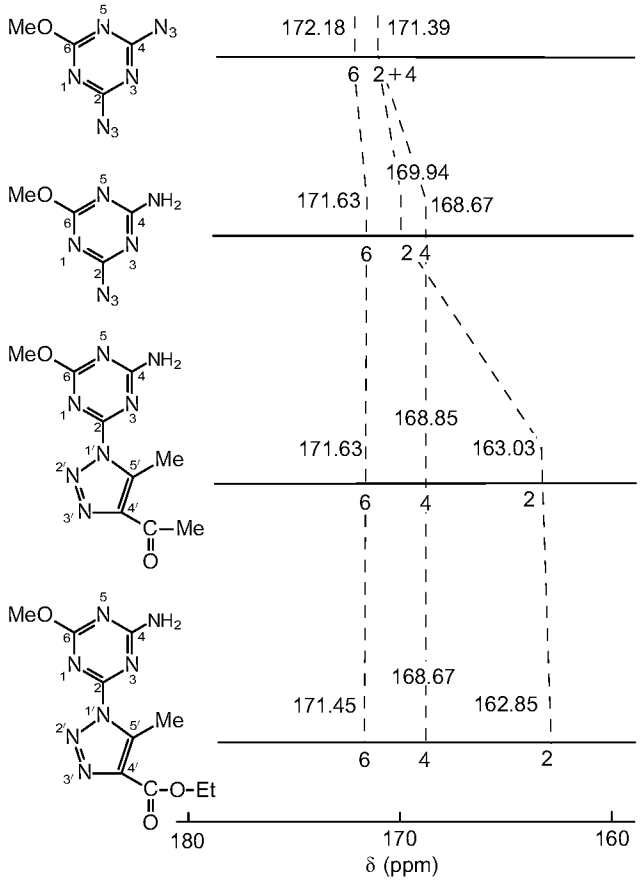


Fig. 1 Chemical shifts for the ^{13}C atoms in the triazine ring of 6-methoxy-*s*-triazines **1a**, **2a**, **4a** and **4d** (in [$^2H_6$]DMSO).

¶ A typical procedure for the synthesis of triazolo-*s*-triazines **4a–f**. A mixture of the corresponding 2-amino-4-azido-*s*-triazine **2a,b,d** (6.0 mmol), acetoacetone or ethyl acetoacetate (6.0 mmol) and triethylamine (6.0 mmol) was refluxed in ethanol (Table 1). The reaction mixture was then cooled to room temperature and the precipitate obtained was filtered off. The analytically pure compounds **4a–f** were obtained by recrystallization from the following solvents: **4a**: from ethanol; **4b**: from aqueous ethanol (30%); **4c–e**: from aqueous acetic acid (30%); **4f**: from aqueous acetic acid (50%).

differences in reactivities between ethyl cyanoacetate and β-dicarbonyl compounds probably depend on the electron and spatial structure of the CH-active fragment in the intermediate adduct. Thus, the diazo transfer for ethyl cyanoacetate is achieved completely through the transfer of a proton.[2–5]

Diazo transfer is apparently the first stage in the reaction of diazido derivatives with β-dicarbonyl compounds resulting in the formation of amino derivatives **4**. The further transformation of amino derivatives **4** by action of β--dicarbonyl compounds depends on intramolecular nucleophilic attack on the carbonyl fragment resulting in the formation of the triazole ring. It is evident that the higher nucleophilicity of the amino-*s*-triazine fragment in comparison with that of the diazido fragment in the intermediate adduct facilitates this nucleophilic reaction.

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