Anomalous One-pot Transformation of 3-Dimethoxymethyl-2-(*N*-cyanoimino)thiazolidine into 6-Unsubstituted 2,4-Diamino-*s*-triazines by the Reaction with Amines

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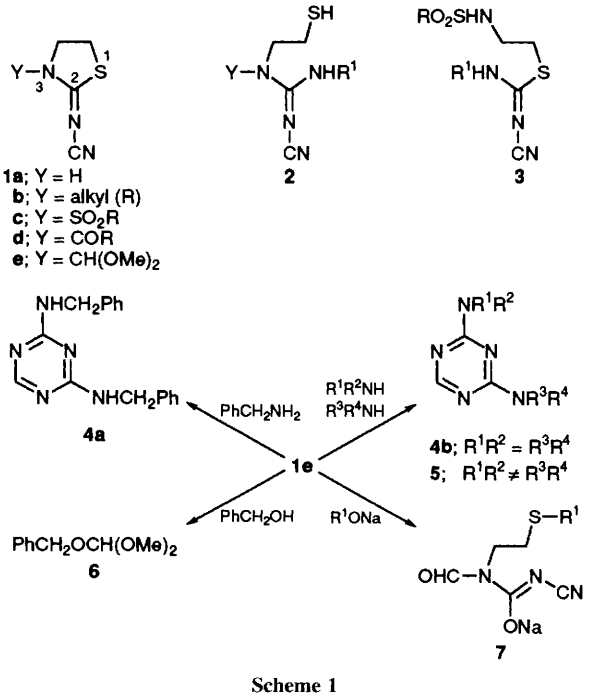
3-Dimethoxymethyl-2-(*N*-cyanoimino)thiazolidine **1e** reacts with secondary amines to afford 2,4-diamino-*s*-triazines **4** unexpectedly, while the triazine **5** bearing different amino groups at 2 and 4 positions is selectively obtained by the reaction with a mixture of two kinds of amines.

The derivatives of 2-(*N*-cyanoimino)thiazolidine (NCT) **1a**[1] exhibit various reactivities according to the substituent of N(3) or the reagents used. For instance, 3-alkyl- or 3-sulfonyl-NCT **1b**, **1c** provided cyanoguanidine **2** or isothiourea derivatives **3** by the reaction with primary amines (R^1NH_2) *via* C(2)–S or C(2)–N(3) bond cleavage.[2] On the other hand, 3-acyl-NCTs **1d** acted as an acylating agent of amines, alcohols and thiols *via* N(3)–CO bond fission.[3] In addition, interesting alkyl migration reactions were observed in the reaction of **1b** and sodium alkoxide,[2] while in the case of the alkyl group at N(3) having acidic hydrogens on the carbon adjacent to N(3), bicyclic heterocycles were available *via* an intramolecular cyclisation.[4] In this paper, we describe an unexpected triazine formation by the reaction of 3-dimethoxymethyl-NCT **1e**,† thereby presenting a new synthetic method for 6-unsubstituted 2,4-diamino-*s*-triazines **4** including the compound **5** bearing different amino groups at 2 and 4 positions.

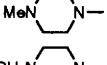
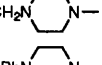
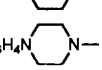
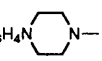
The dimethoxymethyl moiety is an equivalent of formyl group. So, we initially expected a dimethoxymethyl group transfer reaction to the nucleophile similarly to the acyl transfer reaction in **1d** or a ring cleavage reaction affording a cyanoguanidine derivative [**2**: Y = $CH(OMe)_2$] like in the 3-alkyl derivatives **1b**. First, **1e** afforded benzyl formate dimethyl acetal **6**[5] by the reaction with benzyl alcohol in refluxing tetrahydrofuran (THF) in 76% yield together with **1a**. In this reaction, it was found that **1e** acted as the acyl derivative **1d**. On reaction with alkoxide, however, **1e** reacted similarly to the alkyl derivative **1b** resulting in ring cleavage followed by an alkyl transfer reaction, **1e**→**7**.‡ At this point, a similar reactivity to **1b** or **1d** was anticipated in the reaction of **1e** with amines. Contrary to our expectation, the main product in the reaction of **1e** with 3 equiv. of benzylamine in refluxing toluene was found to be a 2,4-dibenzylamino-*s*-triazine **4a** (45% yield), and not a benzyl formamide dimethylacetal nor a cyanoguanidine derivative. The structure of **4a** was confirmed by a known alternative synthesis.[6] Other primary amines afforded only complex mixtures. As shown in Table 1, cyclic secondary amines afforded triazines **4b** in good yield. But in the reaction with acyclic secondary amines, 4-methoxy-2-amino-*s*-triazines **8a** were obtained as a minor product. These results suggest the reaction mechanism given in Scheme 2. The first amine molecule adds to the nitrile carbon and the resultant nitrogen anion **A** reacts intramolecularly with the dimethoxymethyl moiety to cyclise losing one molecule of methanols **A**→**B**. The second amine add to **B** losing the second molecule of methanol, **B**→**C**, followed by C–S bond cleavage, **C**–**D**, and elimination of thiirane (not characterised) and aromatization, **D**→**4**. At the stage of **B**, addition of a small nucleophile (methanol) afforded the methoxy derivative **8a** instead of the bulky secondary amine **E**. When the reaction was performed in the presence of 3 equiv. of ethanol, an ethoxy derivative **8b** was obtained. It was found that the formation of **8a** was attributed to competitive addition of



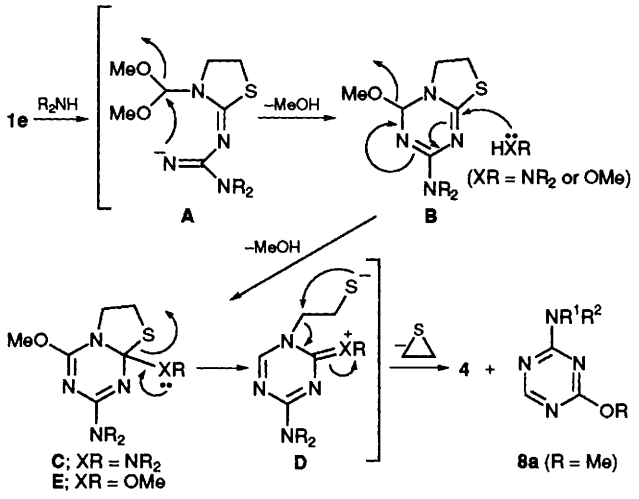
Scheme 1

Table 1 Reaction of 3-dimethoxymethyl-NCT **1e** with secondary amines

$$\mathbf{1e} \xrightarrow[\text{Toluene, reflux}]{R^1R^2NH\ (3\ \text{equiv.})} \mathbf{4b} + \mathbf{8a}\ (R = \text{Me}, \mathbf{b}\ \text{Et})$$

Run	R^1R^2N–	**4b**[a] mp (°C)	**4b**[a] Yield (%)	**8a** Yield (%)
1	Et_2N–	Oil	46	8[b]
2	Bu^n_2N–	Oil	44	14
3	$(PhCH_2)_2N$–	100–101	28	10
4		162.5–165	90	0
5		88–89	72	0
6		98–99	75	0
7		132–132.5	67	0
8		194–195	66	0
9		263–264	67	0
10		195–196	69	0
11		138.5–139	83	0

[a] Satisfactory microanalyses were obtained for all compounds. [b] When the reaction was performed in the presence of 3 equiv. of ethanol, a trace amount of **8b** (R = Et) was obtained together with **4b**.



Scheme 2

Table 2 One-pot synthesis of *s*-triazines **5** bearing different amino groups at 2 and 4 positions.

$$\mathbf{1e} \xrightarrow[\text{Toluene, reflux}]{R^1R^2NH,\ PhCH_2NH_2} \mathbf{4a} + \mathbf{4b} + \mathbf{5}$$

	Equiv. of amine		Yields (%)		
Run	R^1R^2NH[a]	$PhCH_2NH_2$	**4a**	**4b**	**5**
1	1	1	9	16	40
2	2	2	2	25	21
3	3	3	2	12	21
4	1	2	5	26	26
5	1	3	2	29	20
6	2	3	2	19	21
7	3	2	3	10	53
8	2	1	3	6	40
9	3	1	4	8	38

[a] R^1R^2NH is 1-phenylpiperazine.

methanol and acyclic secondary amine. In the reaction with cyclic secondary amines, the suppressed formation of **8a** would be due to their higher nucleophilicity than that of acyclic amines.

Consideration of the reaction mechanism and the different reactivity between primary and secondary amines suggested the one-pot formation of an *s*-triazines **5** having different amino groups in the molecule. Namely, differentiation of the amine which attacks the nitrile or the imino moiety may be possible. The former is the bulkier and more nucleophilic secondary amine attacking the less congested nitrile group and the latter is the less bulky and moderately nucleophilic primary amine adding to the congested imine.§ The reactions of **1e** with a mixture of benzylamine and 1-phenylpiperazine in several ratios were examined (Table 2). In several runs, an *s*-triazine **5**¶ bearing different amino groups was obtained selectively among other expected products **4a** and **4b**.

There are various *s*-triazine derivatives which exhibit interesting biological activities (*e.g.* antileukaemic, cytotoxic, leucotriene antagonist, antiinflammatory, multidrug resistance modulating, and so on).[7] The one-pot process developed here would be useful for the synthesis of various new *s*-triazine derivatives.[8]

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Footnotes

† NCT **1e** was easily synthesized as follows. NCT **1a** was refluxed in triethyl orthoformate for 12 h, then triethyl orthoformate was evaporated off. The residue was recrystalised from benzene–diisopropyl ether to give **1e** (76%), mp 103–104 °C.

‡ Compound **7** was isolated and characterised similarly to the products reported previously in ref. 2, but dimethoxymethyl group was hydrolysed to a formyl group.

§ Normal 3-alkyl-NCT (*e.g.* **1**: Y = methyl or benzyl) does not react with secondary amines.

¶ Physical data for **5**: mp 157–158 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ_H: 3.19 (t, 4H, *J* 5.4 Hz), 3.96 (t, 4H, *J* 5.4 Hz), 4.61 (d, 2H, *J* 5.6 Hz), 5.90 (br, 1H), 6.83–7.00 (m, 3H), 7.20–7.40 (m, 7H), 8.02 (br s, 1H).

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