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The amidine rearrangement in 5-amino-6-aryl-1,2,4-triazine-4-oxides initiated by hydroxylamine†

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Abstract

Addition of hydroxylamine at the 3 position of 6-aryl-5-amino-1,2,4-triazine-4-oxides initiates the amidine rearrangement resulting in 6-aryl-5-hydroxylamine-1,2,4-triazines, as confirmed by an experiment with ^{15}N-labeling. © 2000 Published by Elsevier Science Ltd.

It is known that a nucleophilic attack on 1,2,4-triazine-4-oxides is often accompanied by ring transformation reactions.[1] For instance, on treatment of 6-aryl-1,2,4-triazine-4-oxides with water,[2] amines[3] or CH-active compounds,[4] ring-opening takes place resulting in stable, open-chain products. Ammonia addition at the 5 position of 6-aryl-3-dialkylamino-1,2,4-triazine-4-oxides is followed by a [1,5]sigmatropic hydrogen shift to give intermediate 5-amino-3-dialkylamino-4-hydroxy-3,4-dihydro-1,2,4-triazines followed by ring-opening with cleavage of the C-3–N-4 bond. This ring-opening is a reversible process which allows the cyclic dihydro intermediates to be aromatizated with elimination of the dialkylamino group, thus giving *tele*-substitution products, i.e. 5-amino-1,2,4-triazine-4-oxides.[5] The formation of σ^H-adducts in the reaction of 3-dialkylamino-1,2,4-triazine-4-oxides with the cyanide anion was found to cause a similar [1,5]sigmatropic hydrogen shift-ring-opening, followed by recyclization with incorporation of the C–N-carbon into 3-amino-4-nitrosopyrazoles (according to the ANRORC mechanism).[6]

Herein, we wish to describe a new type of ring transformation for a series of 1,2,4-triazine-4-oxides, i.e. the amidine rearrangement. We have found that a reaction of 6-aryl-5-amino-1,2,4-triazine-4-oxides **1** with hydroxylamine hydrochloride in refluxing DMF for 30 min leads to 6-aryl-5-hydroxylamino-1,2,4-triazines **2** in 70–80% yield. The same products **2** are formed from the reaction of **1** with *O*-methylhydroxylamine. This allows one to conclude that the hydroxylamine has only a catalytic effect on the reaction. Compound **2** was identical to 5-hydroxylamino-6-phenyl-

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† Dedicated to Professor Richard Neidlein on the occasion of his 70th birthday.

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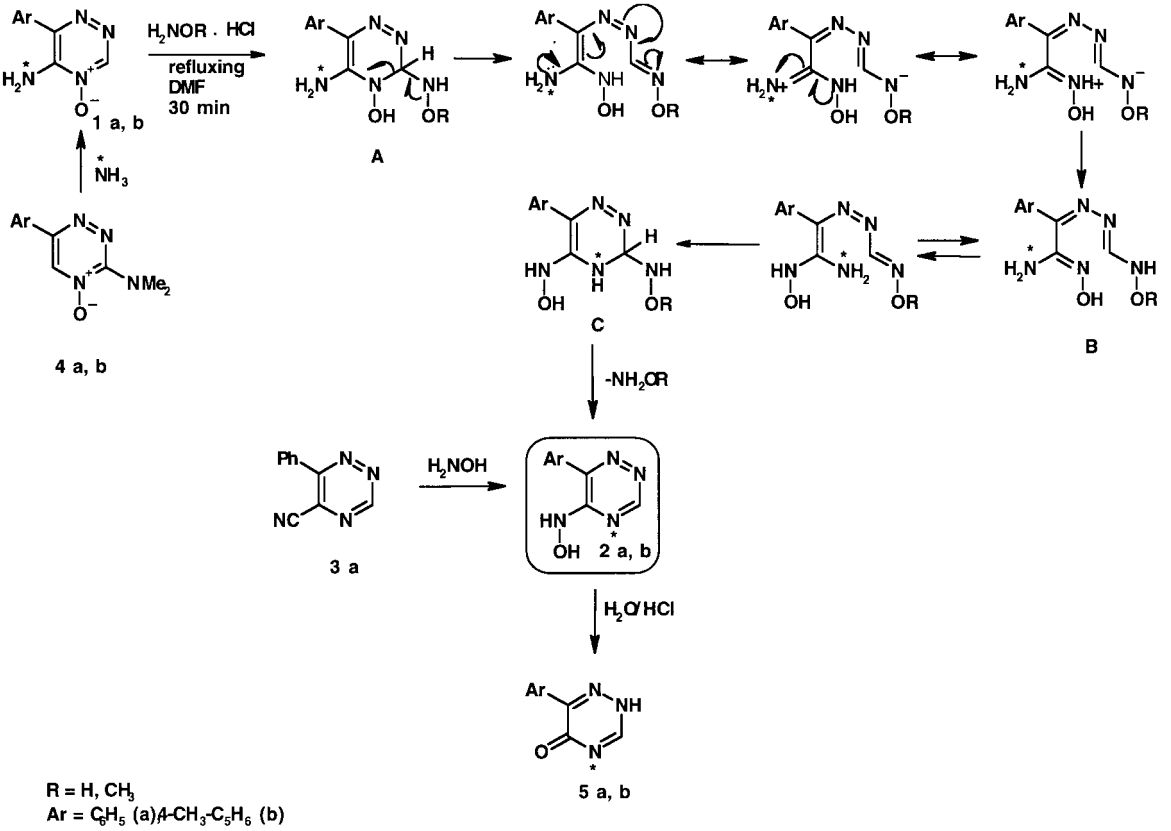
1,2,4-triazine **2** obtained by a straightforward synthesis, i.e. by *ipso*-substitution of the cyano group in 6-aryl-5-cyano-1,2,4-triazine **3** with a slight excess of hydroxylamine in DMF at room temperature (Scheme 1).



Scheme 1.

This reaction is a new example of the Dimroth rearrangement—a kind of degenerate ring transformation which is 'characterized by a "troika" process, involving addition of nucleophile, ring opening, and ring closure (ANRORC)'.[7] It is remarkable that such reactions have never been observed for monocyclic 1,2,4-triazines or their *N*-oxides. In our case, the transformation is initiated by the addition of hydroxylamine at the unsubstituted position 3 of the 1,2,4-triazine ring giving rise to the intermediate σ-adduct **A**. The latter undergoes ring-opening with cleavage of the C-3–N-4 bond, which is usual for adducts of 3-unsubstituted 1,2,4-triazine-4-oxides with nucleophiles and can be characterized as an electrocyclic reaction.[1] Cyclization of the open-chain intermediate **B** by addition of the amino group to the C-3–N double bond and aromatization of the cyclic intermediate **C** with elimination of hydroxylamine leads to **2**.

In order to prove this reaction pathway, we obtained 6-aryl-5-[^{15}N]amino-1,2,4-triazine **1***, containing 84% excess of ^{15}N, by the reaction of 6-aryl-3-dimethylamino-1,2,4-triazine-4-oxide **4** with [^{15}N]ammonia.[5] The reaction of 1,2,4-triazine-4-oxide **1*** with hydroxylamine afforded 5-hydroxylamino-1,2,4-triazine **2***, containing the same excess (84%) as ^{15}N. Hydrolytic deamination of compound **2***, by refluxing in dilute hydrochloric acid, gave 6-aryl-1,2,4-triazine-4(2H)-one **5***

also containing 84% of ^{15}N. These results allowed us to conclude that the nitrogen of the exocyclic amino group of **1** becomes incorporated in the 1,2,4-triazine ring of **2** as the N-4 atom. This fact was also substantiated by the ^{1}H and ^{13}C NMR spectroscopy data for products **2*** and **5***. It shows that this process really is an amidine rearrangement.

Experimental: The melting points are uncorrected. The NMR spectra were taken on a Bruker WM-250, DRX-400 and DRX-500 with TMS as an internal standard.

For **1b**: yield 160 mg (79%); m.p. 265°C (decomp.); ^{1}H NMR (DMSO-d_6, 250 MHz): 2.43 (s, 3H, CH_3), 7.33 (d, 2H, tolyl), 7.58 (d, 2H, tolyl), 7.70 (br.s, 2H, NH_2), 9.10 (s, 1H, H-3); MS *m*/*z* (%): M^+ 202 (100); elemental analysis: found: C = 59.38, H = 4.92, N = 27.65; calcd. for $C_{10}H_{10}N_4O$: C = 59.40, H = 4.98, N = 27.71.

For **1a*** (^{15}N-labeling): yield 158 mg (84%); m.p. 229°C; ^{1}H NMR (DMSO-d_6, 400 MHz): 7.48–7.57 (m, 3H, Ph), 7.68–7.72 (m, 2H, Ph), 7.78 (d, 2H, $^{15}NH_2$, $^{1}J_{NH} = 92$ Hz), 9.12 (s, 1H, H-3); ^{13}C NMR (DMSO-d_6, 100.6 MHz): 128.20 (Ph), 128.46 (Ph), 129.59 (Ph), 132.54 (Ph), 145.27 (C-3), 145.32 (C-6, $^{2}J_{CN} = 1.5$ Hz), 145.33 (C-5, $^{1}J_{CN} = 22$ Hz); MS *m*/*z* (%): M^+ 189 (100).

For **1b*** (^{15}N-labeling): yield 152 mg (75%); m.p. 265°C (decomp.); ^{1}H NMR (DMSO-d_6, 250 MHz): 2.43 (s, 3H, CH_3), 7.33 (d, 2H, tolyl), 7.58 (d, 2H, tolyl), 7.72 (d, 2H, $^{15}NH_2$, $^{1}J_{NH} = 91$ Hz), 9.10 (s, 1H, H-3); MS *m*/*z* (%): M^+ 203 (100).

For **2a**: yield 61 mg (65%): m.p. 217°C; ^{1}H NMR (DMSO-d_6, 250 MHz): 7.3–7.4 (m, 3H, Ph), 7.76 (s, 1H, H-3), 7.85–7.9 (m, 2H, Ph), 9.52 (br.s, 1H, OH), 12.07 (br.s, 1H, NH); MS *m*/*z* (%): M^+ 188 (76); elemental analysis: found: C = 57.40, H = 4.32, N = 29.72; calcd. for $C_9H_8N_4O$: C = 57.44, H = 4.28, N = 29.77.

For **2b**: yield 68 mg (67%): m.p. 220°C; ^{1}H NMR (DMSO-d_6, 250 MHz): 2.37 (s, 3H, CH_3), 7.16 (d, 2H, tolyl), 7.76 (s, 1H, C-3), 7.81 (d, 2H, tolyl), 9.42 (br.s, 1H, OH), 12.12 (br.s, 1H, NH); MS *m*/*z* (%): M^+ 202 (100); elemental analysis: found: C = 59.40, H = 4.92, N = 27.72; calcd. for $C_{10}H_{10}N_4O$: C = 59.40, H = 4.98, N = 27.71.

For **2a***: yield 54 mg (57%): m.p. 217°C; ^{1}H NMR (DMSO-d_6, 400 MHz): 7.34–7.44 (m, 3H, Ph), 7.79 (d, 1H, H-3, $^{2}J_{HCN} = 12$ Hz), 7.86–7.89 (m, 2H, Ph), 9.72 (br.s, 1H, OH), 12.2 (br.s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100, 6 MHz): 127.30 (Ph), 128.30 (Ph), 129.31 (Ph), 133.53 (Ph), 142.18 (C-5), 145.60 (C-6), 147.35 (C-3); MS *m*/*z* (%): M^+ 189 (70).

For **2b***: yield 60 mg (60%): m.p. 220°C; ^{1}H NMR (DMSO-d_6, 250 MHz): 2.37 (s, 3H, CH_3), 7.16 (d, 2H, tolyl), 7.76 (d, 1H, C-3, $^{2}J_{HCN} = 12$ Hz), 7.82 (d, 2H, tolyl), 9.61 (br.s, 1H, OH), 12.08 br.s, 1H, NH); MS *m*/*z* (%): M^+ 202 (79).

Acknowledgements

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