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An unusual aromatisation of dihydropyrimidines facilitated by reduction of the nitro group

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Dedicated to Professor H. Neunhoeffer on the occasion of his 70th birthday

Abstract—An unusual aromatisation of the dihydropyrimidine fragment in 6-nitro-7-substituted-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidines has first been found to occur in parallel with reduction of the nitro group using a number of reducing agents.

According to the up to date concept of nucleophilic substitution in π-deficient aromatics, the displacement of good leaving groups is a two-stage addition–elimination process $S_NAr(AE)$ (Scheme 1, Y = Lg),[1] and the elimination step is not rate-determining, that is, $k_1 < k_2$. Therefore, it is common to consider that greater the electron-deficient character exhibited by an aromatic compound **1**, the more actively it reacts with nucleophiles at the addition step, leading to intermediates **2**, which are easily transformed into substitution products **3**.

This is not the case with the nucleophilic aromatic substitution of hydrogen (S_N^H), the feature of which is that the S_N^H reactions are rather sensitive to the nature of the oxidant, thereby affecting the elimination of hydrogen step (Scheme 1, Y = H). In typical S_N^H reactions, the rates of two concurrent reactions are of the same order $k_1 \approx k_2$; however, some σ^H-adducts **2** (Y = H) undergo aromatisation very easily ($k_1 \ll k_2$), [2,3] while in other cases the addition step leading to very stable σ^H-adducts **2**, is actually the final one ($k_1 \gg k_2$).[4]

While carrying out our studies on reactions of highly electron-deficient nitroazoloazines we came across the problem of aromatisation of σ^H-adducts.[1] Attempts to use conventional oxidative dihydroazoloazine agents failed.

In this Letter, we report a very unusual case of spontaneous aromatisation of σ^H-adducts derived from the reaction of 6-nitrotriazolopyrimidine **4** with a number of nucleophiles, which takes place on treatment of the σ^H-adducts with reducing agents.

Being highly electron-deficient, nitro derivatives of azolopyrimidines can be easily coupled with both anionic and neutral nucleophiles,[1] giving rather stable C7-adducts. In the context of this work we have studied the addition reactions of C-nucleophiles (pyrroles, indoles, CH-active compounds) with 1,2,4-triazolo- (X = CH) **4a** and 1,2,3,4-tetraazolo- (X = N) **4b** pyrimidines. The reactions of **4** and **5** were found to proceed smoothly at reflux giving adducts **6a**–**f** and **7a** in high yields (80–88%).[5] Unlike the more active pyrrole derivatives, thiophene and 2,6-dimethylphenol only reacted with azolopyrimidines in the presence of trifluoroacetic acid.[6] Attempts to carry out oxidative aromatisation of σ^H-adducts **6** and **7** with aerial oxygen, potassium hexacyanoferrate, dichloro-dicyanobenzophenone or triphenylmethyl tetrafluoroborate, failed, while the use of stronger oxidising agents (for instance, potassium permanganate) led to a mixture of unidentified products.

Whilst investigating the reduction of the nitro group in adducts **6** and **7** we found rather unexpectedly, that the reduction process was accompanied by aromatisation of the dihydropyrimidine ring, thus yielding 6-amino-7-substituted-1,2,4-triazolo- (**8a**–**f**) and 6-amino-7-indolil-1,2,3,4-tetraazolo-[1,5-*a*]pyrimidine (**9a**) (Scheme 2).

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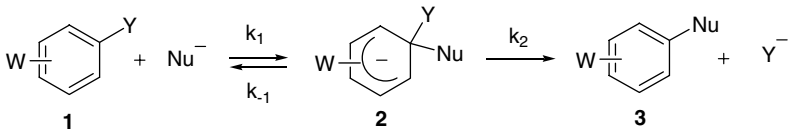
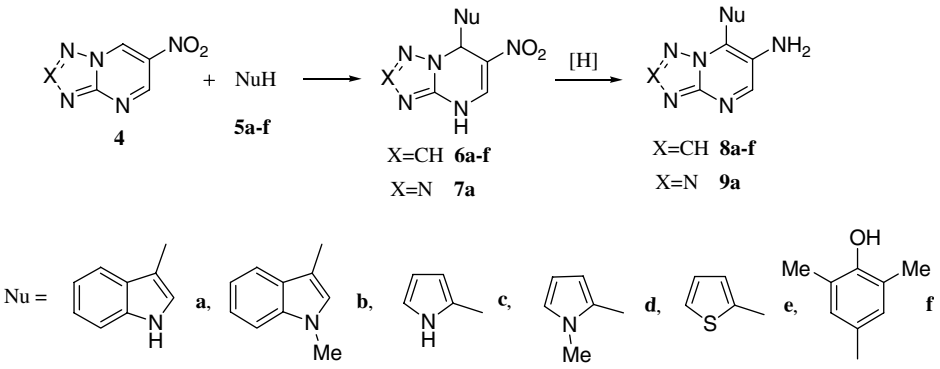


Scheme 1. W = electron-withdrawing group; Y = Lg, H; Lg = good leaving group (Hal, OR, SO_2R, NO_2, etc.).



Scheme 2.

The reactions were facilitated by the action of reducing agents, such as ferrous hydroxide,[7] stannous chloride,[8] sodium dithionite[9] and also hydrogen in the presence of Pd/C catalyst,[10] to give products **8a–f** and **9a** in moderate to excellent yields (Table 1).

In the ^{1}H NMR spectra of compounds **8** and **9** (X = CH) the H-2 and H-5 protons were observed as singlets at $\delta = 8.5$–8.7 and 8.8–8.9 ppm, respectively. Also a broad two-proton signal, corresponding to the amino group resonance, occurred at 3.5–4.0 ppm. The characteristic feature of the ^{1}H NMR spectra of **8a–f**, **9a**, indicating aromatisation of the dihydropyrimidine ring was the disappearance of the H-7 signal present in the ^{1}H NMR spectra of compounds **6a–f** and **7a** at ca. $\delta = 7.32$ ppm.

'Reductive' aromatisation of nitrodihydropyrimidines is not limited to compounds **6** and **7**. Similar processes in which reduction of the nitro group is accompanied by aromatisation of dihydro compounds have been

Table 1. Yields of S_N^H products

Starting material	Product	Reducing agent			
		H_2/Pd (%)	$Na_2S_2O_4$ (%)	$Fe(OH)_2$ (%)	$SnCl_2$ (%)
6a	**8a**	68	90	60	—
6b	**8b**	—	89	64	33
6c	**8c**	—	—	40	—
6d	**8d**	—	70	42	—
6e	**8e**	55	70	64	—
6f	**8f**	45	88	—	—
11a	**12a**	—	—	—	30

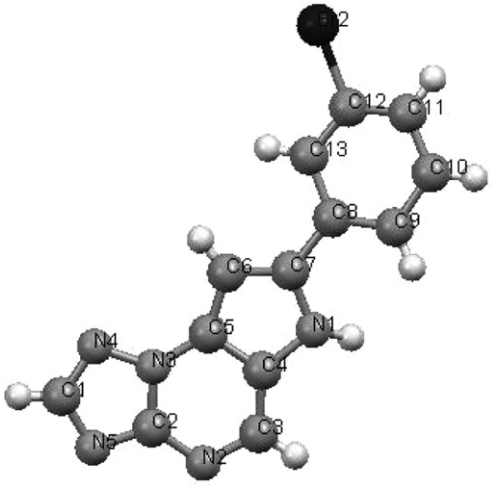
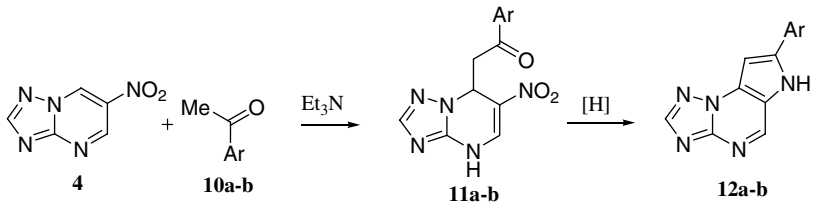
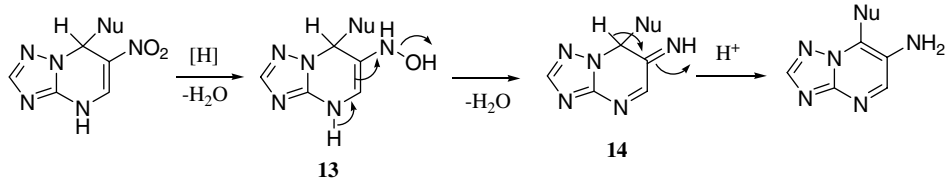


Figure 1. X-ray crystal structure of compound **12b**.



Ar =**a**: Ph, **b**: 3-Br-Ph

Scheme 3.



Scheme 4.

observed to take place in the case of 6-nitro-4,7-dihydro-7-(4-*R*-phenacyl)-1,2,4-triazolo[1,5-*a*]pyrimidines **11a**,**b**. The latter were obtained in 75–85% yields by the addition of acetophenones **10a**,**b** at C-7 of nitroazolopyrimidine **4** under basic conditions (triethylamine).[11] In this case, reduction of the nitro group in carbonyl compounds **11a**,**b** was followed by aromatisation of the dihydropyrimidine ring and intramolecular cyclisation of the intermediate amino compounds into 7-Ar-1,2,4-triazolo[1,5-*a*]pyrrolo[2,3-*e*]-pyrimidines **12a**,**b** (Scheme 3).[12] In the ^{1}H NMR spectra of tricyclic compounds **12** the signal due to H-7 ($\delta = 6.13$–6.10 ppm) was absent on comparison with that of **11**, while the singlet at 7.40 ppm was due to H-8 of the pyrrole ring, in addition to the H-2 and H-5 singlets at 8.52–8.69 ppm and 8.87–9.07 ppm, respectively. The structure of compound **12b** was confirmed unequivocally by X-ray crystallographic analysis (Fig. 1). The mass spectra of compounds **12** displayed strong peaks corresponding to the molecular ions.

To the best of our knowledge, aromatisation of σ^H-adducts derived from nucleophilic addition reactions on π-deficient nitroarenes (hetarenes) have never been interpreted as the process related with reduction of the nitro group in the dihydro intermediates. A similar aromatisation is suggested to occur during reduction of the nitro group in the intermediate adducts derived from nucleophilic addition reactions of O-silylated enones or thiols on nitroaromatics.[13,14] Although we failed to isolate any intermediates, it is clear that the driving force of the presented reactions is the ability of dihydropyrimidines to undergo spontaneous dehydrogenation to gain aromaticity.

It would be reasonable to suggest that the aromatisation proceeds via aerial oxidation; however, reduction of the σ^H-adduct **12b** with stannous chloride in CD_3COOD under an inert gas atmosphere gave the same heteroaromatic system. Therefore, an alternative aromatisation associated with intramolecular processes must occur. Eliminative auto-aromatisation, involving reduction of the nitro group to hydroxylamine **13**, loss of water, and finally, prototropic rearrangement of imine **14** appears to be the most plausible mechanism. Intermolecular oxidation with participation of the starting nitro compound as an oxidant has to be rejected since 70–90% yields of amino compounds **8a,b,d,f** (Table 1) cannot be reached in a disproportionation reaction (see Scheme 4).

The observed phenomenon of unusual auto-aromatisation of σ^H-adducts of the dihydroazine series is of great importance, since it concerns a vast arena of S_N^H reactions, in which the aromatisation on the σ^H-adducts plays a crucial role.[1,2] The S_N^H reactions described above have great synthetic potential, since reduction of the nitro group opens new pathways for modification of σ^H-adducts, while the functional groups present in the structure can participate in further reactions, thus enhancing the so-called functionalisation index of an aromatic substrate.

Crystallographic data (excluding structure factors) for the structures reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 618584. Copies of these data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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5. *Typical procedure for the synthesis of compounds* **6a**–**d** *and* **7a**. A mixture of equimolar quantities of **4** and **5a**–**d** was refluxed for 30 min. The product precipitated after cooling of the reaction mixture and was filtered off, washed with ether and dried in air. Mp, yields: **6a** 279–281 °C,[†] 88%; **6b** 265–266 °C, 84%; **6c** 240 °C, 80%; **6d** 245–246 °C, 82%; **7a** 216–218 °C, 80%.

[†] All melting points are uncorrected and were measured on a Boetius melting point apparatus. All compounds gave satisfactory elemental analyses data.

6. *Typical procedure for the synthesis of compounds* **6e–f**. A mixture of equimolar quantities of **4** and **5e–f** was stirred in trifluoroacetic acid at room temperature for 24 h. The solvent was distilled off under reduced pressure, and the residue was recrystallised from ethanol. The product was filtered off, washed with ether and dried in air. Mp, yields: **6e** 230–232 °C, 70%; **6f** 242–244 °C, 80%.
7. *Typical procedure for the synthesis of compounds* **8a–e** *using ferrous sulfate*. 1 mmol of **6** was dissolved in 5 ml of 20% aqueous ammonia, and an aqueous solution of 7 mmol of ferrous sulfate solution was added with stirring. The reaction mixture was refluxed for 5 min. The product was extracted with methanol (3×10 ml) and filtered. The residue was washed with water and recrystallised from ethanol. Mp, yields: **8a** 288–290 °C, 60%; **8b** 272–273 °C, 64%; **8c** 173–174 °C, 40%; **8d** 80–82 °C, 42%; **8e** 170–172 °C, 64%.
8. *Procedure for the synthesis of compound* **8b** *with stannous chloride*. A solution of stannous chloride dihydrate (3 mmol) in 2 ml of acetic acid and 0.5 ml of concentrated hydrochloric acid was added to a solution of **6** (1 mmol) in 3 ml of acetic acid. The mixture obtained was stirred for 5 min and the precipitate obtained was filtered off. The product was dissolved in ethanol, and hydrogen sulfide was allowed to pass through the solution until the formation of stannous sulfide was complete. The mixture was filtered and concentrated under reduced pressure, the product was separated, washed with ethanol and dried in air. Yield: 33%.
9. *Typical procedure for the synthesis of compounds* **8a,b,d–f** *with sodium dithionite*. A mixture of 1 mmol of **6e** and 6 mmol of sodium dithionite in 5–6 ml of 20% ammonia solution was stirred at 60 °C for 30–40 min. The reaction was concentrated under vacuum and kept for 24 h at room temperature. The precipitated product was separated by filtration, washed with water and recrystallised from ethanol. Yields 70–90% (Table 1).
10. *Typical procedure for the synthesis of compounds* **8a–f** *with* H_2/Pd. A solution of **6** in DMF was treated with hydrogen (15 atm) in the presence of Pd/C at 50 °C for 2 h. The reaction solution was filtered, and the solvent was distilled off under reduced pressure. The residue was recrystallised from ethanol. Yields 45–68%.
11. *Typical procedure for the synthesis of compounds* **11a**,**b**. A mixture of equimolar quantities of **4**,**10a**,**b** and triethylamine in acetonitrile was kept at room temperature for 24 h. The reaction solution was neutralised with concentrated hydrochloric acid. The precipitated product was filtered off and washed with water and acetonitrile. Yields 75–85%.
12. *Typical procedure for the synthesis of* **12a**,**b**. A solution of stannous chloride dihydrate (3 mmol) in 2 ml of acetic acid and 0.5 ml of concentrated hydrochloric acid was added to a solution of **11** (1 mmol) in 3 ml of acetic acid and the reaction mixture was stirred for 5 min. The precipitate was filtered off, dissolved in DMF and purified by thin layer chromatography on alumina oxide with chloroform–ethanol (9:1) as eluent. Mp, yields: **12a** 270–272 °C, 30%; **12b** >300 °C, 34%.

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