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Change of mechanism with a change of substituents for a Zincke reaction

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ABSTRACT

The reaction between *N*-(2,4-dinitrophenyl)-4-(4-pyridyl)pyridinium chloride and 4-aminothiophenol led to an unexpected displacement of the 2,4-dinitrophenyl group, in contrast with the normal Zincke product formed with other nucleophilic 4-substituted anilines. Evidence for a SET process was obtained from EPR spectra of the reaction mixture.

The reaction of *N*-(2,4-dinitrophenyl)pyridinium chloride with amines to form N-substituted pyridinium salts was described for the first time by Theodor Zincke nearly a hundred years ago.[1] The reaction proceeds via an ANRORC (Attack of Nucleophile Ring-Opening Ring-Closure) mechanism, with the initial attack of the pyridinium ring by the nucleophile, followed by ring opening and subsequent ring closure, with the elimination of a molecule of 2,4-dinitroaniline.[2] The reaction thus provides a way of preparing N-substituted nitrogen heterocycles from the corresponding, analogous *N*-(2,4-dinitrophenyl) salts. If secondary amines are employed as nucleophiles in aqueous media, formation of the ring-opened compounds leads to valuable synthetic intermediates (Zincke aldehydes). Thus, Zincke reaction has found widespread applications in organic synthesis. Recent reports employing the reaction include the preparation of *N*,*N*′-diaryl-substituted 4,4′-bipyridinium salts,[3] pyridinium derivatives of amino acids,[4] N-arylated pyridinium salts with reactive groups,[5] 4-aryl bispyridinium salts,[6] new photochromic dyes,[7] and ionic polymers.[8] Zincke aldehydes have been used as intermediates in a variety of applications.[9] The 'normal' Zincke reaction is a formal replacement of the 2,4-dinitrophenyl substituent by an alkyl or aryl group R attached to the primary NH_2 functionality. This may be called the 'endocyclic' pathway to distinguish it from the 'exocyclic' displacement of the 2,4-dinitrophenyl substituent by the nucleophile. This competing process may take place when the pyridinium ring is substituted by electron-releasing groups.[10] However, the reasons for favoring such a process are still not entirely understood. Zincke reactions that are anticipated to occur in a 'normal' way may turn out to follow this competing pathway, leading to unexpected products. A dramatic example of this was the report of a 'normal' Zincke reaction, in the preparation of imidazolium salts with a chiral N-substituent.[11] Reinvestigation of the reaction showed that the formed products were not the reported salts, but resulted from the displacement of the 2,4-dinitrophenyl substituent by the nucleophile and the solvent.[12] As part of our efforts to develop organic spacers acting as self-assembled monolayers for modified electrodes,[13,14] we resorted to the Zincke reaction to prepare N-substituted pyridinium salts **2**.

The preparation of compounds **2** employing this procedure had been described before, for a variety of substituted anilines.[5] We confirmed the formation of a 'normal' Zincke product (**2a**) by the reaction of 4-aminophenol with the pyridinium salt (**1**).[5] However, by following the same procedure with 4-aminothiophenol, we were surprised to obtain 4,4′-bipyridyl and the sulfide (**3**) as the sole products of the reaction (Scheme 1).

X-ray analysis of the obtained orange crystals confirmed its unequivocal formation (Fig. 1).

Attempts to modify the reaction conditions, by employing solvent-free conditions,[15] led to the same products.

By applying the same reaction conditions with 4-methylthioaniline as nucleophile, we obtained the expected Zincke product (**2b**). This observation suggested that the acidic proton present in thiophenol played a decisive role in diverting the course of the reaction.

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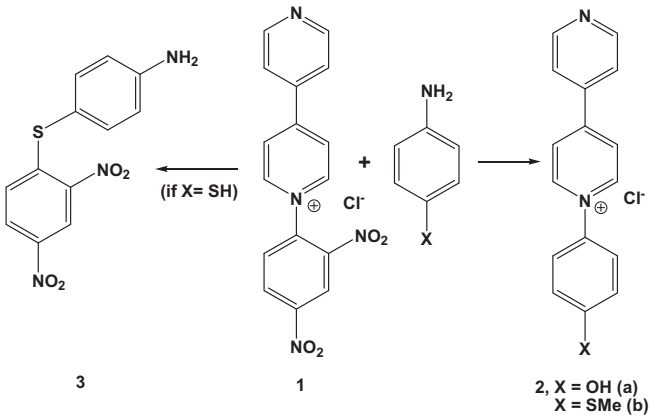


Scheme 1. Reaction of Zincke salt (**1**) with different 4-substituted anilines.

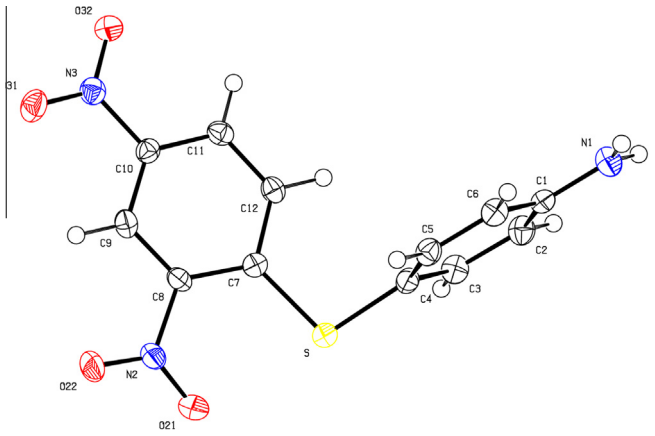
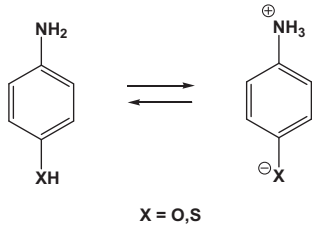


Figure 1. Ortep projection of compound (**3**).

Both 4-amino-phenol and -thiophenol are amphiphilic nucleophiles, resulting from the equilibria below (Scheme 2).

In the case of 4-aminophenol, the reaction products suggest that the amino group behaves as a better, or more efficient nucleophile than the phenolate. The opposite, however, occurs with 4-aminothiophenol, a result which may be explained in terms of the greater nucleophilicity of ArS^- in aromatic nucleophilic substitutions, when compared with ArO^-.[16] This argument might be invoked if the reaction mechanism was in fact an S_NAr process.

Another mechanistic possibility involved a single-electron transfer (SET) process. This process would be easier for the softer, and better reducing agent ArS^-, than for the harder phenolate molecule. In addition, a direct nucleophilic attack by the thiophenolate would have to overcome a significant steric barrier, and would lead to a highly congested Meisenheimer intermediate. Intermolecular charge-transfer from thiophenolates to 2,4-dinitrobenzene has



Scheme 2. Equilibria of 4-amino-phenol and -thiophenol with zwitterionic forms.

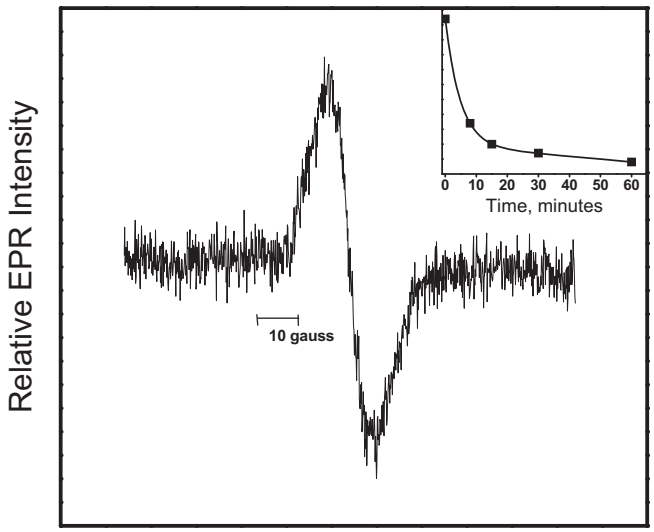
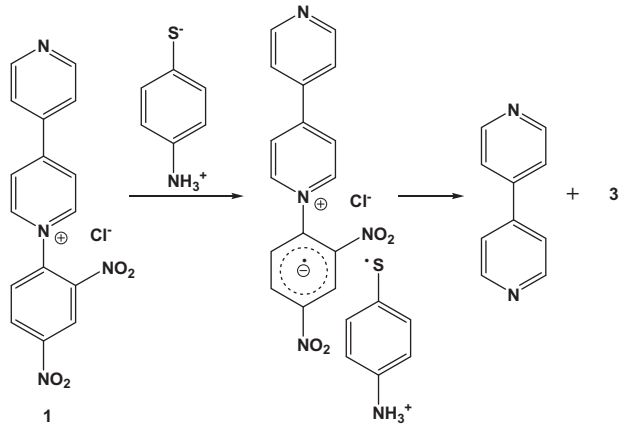


Figure 2. Epr spectrum of the reaction mixture in ethanol (*g* value = 2.00802). In the inset, decay of the recorded signal with time.



Scheme 3. A possible SET mechanism for the reaction.

been described nearly fifty years ago,[17,18] and such a process would have to circumvent a smaller steric hindrance.

In order to decide between the two mechanistic pathways, we recorded epr spectra of an equimolar (25 mM) mixture of **1** and 4-aminothiophenol in ethanol. It was evident from the spectra that a radical intermediate was formed, which collapsed to products within 10–15 min (Fig. 2).

A possible mechanism for the reaction, compatible with the above observation, is shown in Scheme 3. A single-electron transfer from the thiophenolate anion to the *N*-dinitrophenyl ring leads to an intermediate radical pair, which collapses to the observed product by the elimination of 4,4′-dipyridyl.

In conclusion, in the present communication we report the unexpected change of pathways for Zincke salt (**1**) when reacting with different 4-substituted anilines. Instead of the normal nucleophilic attack at the 2-position of the pyridinium ring by the amine, first step of the ANRORC mechanism, a 4-aminothiophenol, in equilibrium with a zwitterionic thiophenolate, transferred one electron to the pyridinium group. The resulting radical pair intermediate rapidly collapsed to 4,4′-dipiridyl and 2,4-dinitro-4′-aminodiphenylsulfide (**3**). The postulated mechanism suggests that other Zincke salts may undergo the same SET process when reacting with aminothiols.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.136.

References and notes

1. Zincke, Th.; Heuser, G.; Moller, W. *Justus Liebigs Ann. Chem.* **1904**, *333*, 296–345.
2. Cheng, W. C.; Kurth, M. J. *Org. Prep. Proc. Int.* **2002**, *34*, 585–608.
3. Bongard, D.; Möller, M.; Rao, S. N.; Corr, D.; Walder, L. *Helv. Chim. Acta* **2005**, *88*, 3200–3209.
4. Nguyen, T. M.; Sanchez-Salvatori, M. R.; Wypych, J.-C.; Marazano, C. *J. Org. Chem.* **2007**, *72*, 5916–5919.
5. Yamaguchi, I.; Higashi, H.; Shigesue, S.; Shingai, S.; Sato, M. *Tetrahedron Lett.* **2007**, *48*, 7778–7781.
6. Papadakis, R.; Tsolomitis, A. *J. Phys. Org. Chem.* **2009**, *22*, 515–521.
7. Mahmoodi, N. O.; Mamaghani, M.; Ghanadzadeh, A.; Arvand, M.; Fesanghari, M. *J. Phys. Org. Chem.* **2010**, *23*, 266–270.
8. Yamaguchi, I.; Minamitani, M. *React. Funct. Polym.* **2012**, *72*, 904–911.
9. Vanderwal, C. D. *J. Org. Chem.* **2011**, *76*, 9555–9567.
10. Kost, A. N.; Gromov, S. P.; Sagitullin, R. S. *Tetrahedron* **1981**, *37*, 3423–3454.
11. Ou, W. H.; Wang, Z. Z. *Green Chem.* **2006**, *8*, 731–734.
12. Pastre, J. C.; Correia, C. R. D.; Génisson, Y. *Green Chem.* **2008**, *10*, 885–889.
13. Ponce, I.; Silva, J. F.; Oñate, R.; Rezende, M. C.; Paez, M.; Pavez, J.; Zagal, J. H. *Electrochem. Commun.* **2011**, *13*, 1182–1185.
14. Ponce, I.; Silva, J. F.; Oñate, R.; Rezende, M. C.; Paez, M.; Zagal, J. H.; Pavez, J.; Mendizabal, F.; Miranda-Rojas, S.; Muñoz-Castro, A.; Arratia-Pérez, R. *J. Phys. Chem. C* **2012**, *116*, 15329–15341.
15. Vianna, G. H. R.; dos Santos, I. C.; de Freitas, R. P.; Gil, L.; Alves, R. B. *Lett. Org. Chem.* **2008**, *5*, 396–398.
16. Smith, M. B.; March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 2001. 5th Ed. p 861.
17. Russel, G. A.; Janzen, E. G.; Strom, E. T. *J. Am. Chem. Soc.* **1964**, *86*, 1807–1814.
18. Ashby, E. C.; Park, W. S.; Goel, A. B.; Su, W. Y. *J. Org. Chem.* **1985**, *50*, 5184–5193.