Tetrahedron Letters, Vol.31, No.51, pp 7499-7500, 1990
Printed in Great Britain

0040-4039/90 \$3.00 + .00
Pergamon Press plc

NEW SYNTHETIC 'TRICKS'. A NOVEL ONE-POT PROCEDURE FOR THE CONVERSION OF PRIMARY NITRO GROUPS INTO ALDEHYDES

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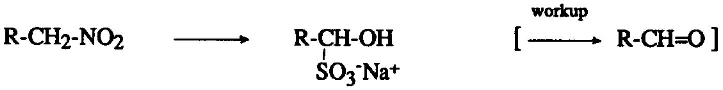
Summary.- Two tin(II) complexes, $Sn(SPh)_3^-$ and $Sn(C_4H_4O_6)_2^{2-}$, besides $NaHSO_3$, are involved in a procedure developed for the rapid transformation at pH 5-6 of $R\text{-}CH_2\text{-}NO_2$ into $R\text{-}CHOH\text{-}SO_3Na$, from which the desired aldehydes have been isolated in 80-91% overall yields. Thus, a new alternative to the Nef reaction is now in hand.

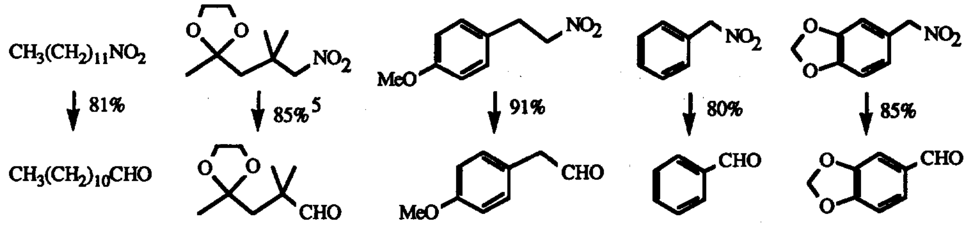
As well known, the Nef type reactions are extremely useful in organic synthesis.[1] Indeed, secondary nitroalkanes may be currently converted to ketones in excellent yields by several methods.[2] Many of them, however, are unsuitable for the transformation of primary nitro groups into aldehydes, as recognised by their authors;[1,2] the problem often lies in the sensitivity of the aldehyde function to either the oxidising, reducing, or hydrolytic conditions required to 'cleave' the corresponding nitronates. After an extensive search among several possibilities, *we have developed a novel version of the Nef reaction that operates under smooth conditions to afford α-hydroxysulphonates (aldehyde-'bisulphite' adducts) and hence aldehydes:*



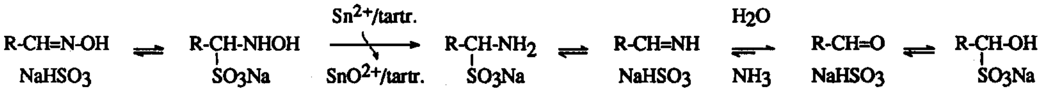
$$R\text{-}CH_2\text{-}NO_2 \longrightarrow \underset{SO_3^-Na^+}{R\text{-}CH\text{-}OH} \quad [\xrightarrow{\text{workup}} R\text{-}CH{=}O\,]$$

After ruling out the nitronate route for the reasons pointed out above, we addressed our efforts to find a mild, controlled reduction cascade. In principle, bearing in mind the tendency of Z-aldoximes—assumed reaction intermediates in many reductions of nitro compounds—to undergo water elimination to give nitriles,[3] either dehydrating species, acids, or heating should be avoided as far as possible. Therefore, operating in an aqueous medium, at almost neutral pH values, not far from room temperature, seemed us the conditions of choice. Since we were interested, of course, in practical one-pot procedures for the nitro-to-formyl conversion, it posed the question of how to hydrolyse aldoximes in an aqueous (reducing) medium without forcing the reaction conditions. We proceeded as follows:

To a stirred solution of $SnCl_2{\cdot}2H_2O$ (1.5 mmol), PhSH (4.5 mmol), and Et_3N (4.5 mmol) in 5 ml of 96% EtOH (or MeOH or $CH_3CN\text{-}H_2O$) at r.t. (pH ≈ 6), nitro compounds shown below (1 mmol) were added. Five-to-ten min later on (when the nitro compound had been converted into the oxime), a solution of $SnCl_2{\cdot}2H_2O$ (1.0-1.2 mmol), L-tartaric acid (5 mmol), and $NaHCO_3$ (5-7 mmol) in 5 ml of H_2O, and a solution of $NaHSO_3$ (5 mmol) in 1 ml of H_2O were introduced; the resulting solution (which showed a buffered pH value of 5-6) was then heated at 40 °C for 1-3 h (until TLC indicated complete disappearance of the corresponding oxime).[4] After cooling, the final mixture was poured into a stirred mixture of 2M HCl and Et_2O (or CH_2Cl_2) at 0 °C and neutralised afterwards with $NaHCO_3$; the two layers were separated and the aqueous one was extracted several times with Et_2O (or CH_2Cl_2); the organic extracts were dried and the solvent evaporated to afford the aldehydes in excellent crude yields (>90%); purification by column chromatography (silica gel, CH_2Cl_2) gave the desired aldehydes in 80-91% yields:



The Sn(II)/tartrate/NaHSO3 mixture is the key to the problem of the oxime cleavage, since in the absence of the Sn(II)/tartrate complexes[6] the reaction of the oxime with NaHSO3 was too slow,[7] and since under our conditions the Sn(II)/tartrate complexes alone did not reduce oximes to imines nor catalyse the oxime hydrolyses. Thus, as a working hypothesis, the steps involved could be summarised as follows:



$$\underset{NaHSO_3}{R\text{-}CH{=}N\text{-}OH} \rightleftharpoons \underset{SO_3Na}{R\text{-}CH\text{-}NHOH} \xrightarrow[SnO^{2+}/tartr.]{Sn^{2+}/tartr.} \underset{SO_3Na}{R\text{-}CH\text{-}NH_2} \rightleftharpoons \underset{NaHSO_3}{R\text{-}CH{=}NH} \underset{NH_3}{\overset{H_2O}{\rightleftharpoons}} \underset{NaHSO_3}{R\text{-}CH{=}O} \rightleftharpoons \underset{SO_3Na}{R\text{-}CH\text{-}OH}$$

Finally, it is worth noting that the process (from nitro groups to α-hydroxysulphonates) also takes place successfully, in similar yields, by mixing at r.t. a 'standard solution' of Sn(II)/PhSH complex (1.5 mmol of $SnCl_2$, 4.5 mmol of PhSH, and 4.5 mmol of Et_3N in 5 ml of EtOH or MeOH) with 'standard solutions' of Sn(II)/tartrate (1.2 mmol of $SnCl_2$, 5.0 mmol of tartaric acid, and 5-7 mmol of $NaHCO_3$ in 5 ml of water) and of $NaHSO_3$ (5 mmol in 1 ml of water), adding 1 mmol of the nitro compound, and heating then the solution at 40 °C for ca. 2 h. The initial pH value (5-6) was self-maintained during the process.

In summary, this combination of tin(II) complexes, in the presence of $NaHSO_3$ (which acts as a peculiar protecting group that prevents reduction of imine and hydroxylamine intermediates to amine), appears to be an extremely mild alternative to the Nef reaction and its oxidative or reductive versions, since functional group incompatibilities inherent in the use of strong basic and/or acid media, as well as of strong oxidants, can be avoided. Additional studies are envisaged to gain insight into some mechanistic details and to improve, if possible, the yields and chemoselectivity of the process.[8]

References and footnotes

1. Classical review: Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. Also see ref. 51 of the following review: Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
2. For very recent, additional references, see: (a) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1989**, *30*, 5329 ($NaClO_2$ oxidation in a CH_2Cl_2/aq. NaOH biphasic system). (b) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361 (MCPBA oxidation of silyl nitronates).
3. See the preceding communication in this issue.
4. As judged by TLC, nitro compounds and oximes do not remain after this treatment; other possible impurities in the final mixtures like nitriles or amines are not observed, either. Apparently the reaction is quantitative (we attribute yields lower than 90% to the loss of material during the workup).
5. Partial hydrolysis of the acetal group has been observed during the workup.
6. For a discussion on the nature of Sn/tartrate complexes, see e.g.: Elbourne, R. G. P.; Buchanan, G. S. *J. Inorg. Nucl. Chem.* **1970**, *32*, 3559.
7. Reduction of aldoximes with sodium hydrogensulphite had been earlier reported (Pines, S. H.; Chemerda, J. M.; Kozlowski, M. A. *J. Org. Chem.* **1966**, *31*, 3446, and ref. therein), but in the absence of Sn(II)/tartrate complexes the reaction is too slow, even in refluxing EtOH. Under our conditions, reduction of oximes with sodium dithionite (Pojer, P. M. *Aust. J. Chem.* **1979**, *32*, 201, and ref. therein) is also too slow; furthermore, sodium dithionite is incompatible with Sn(II)/PhSH complexes. We attempted the acid-catalysed transoximation with aq. formaldehyde and with levulinic acid as well, but it requires gentle heating in the presence of a mineral acid, which is incompatible with many other functional groups potentially present in the molecule.
8. Financial suport from the CICYT (Ministerio de Educación y Ciencia, Grant PB86-0170) is deeply acknowledged.

(Received in UK 18 October 1990)