Pergamon

Tetrahedron Letters, Vol. 36, No. 28, pp. 5075-5078, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00943-4

A New Redox System: Trichloromethylarene - Pyridine Base. On the Mechanism of the Synthesis of N-(4-Pyridyl)pyridinium Dichloride

Leonid I. Belen'kii*, Igor S. Poddubnyi, Mikhail M. Krayushkin

N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913, Moscow, Russian Federation. Fax: +7 095 135 5328

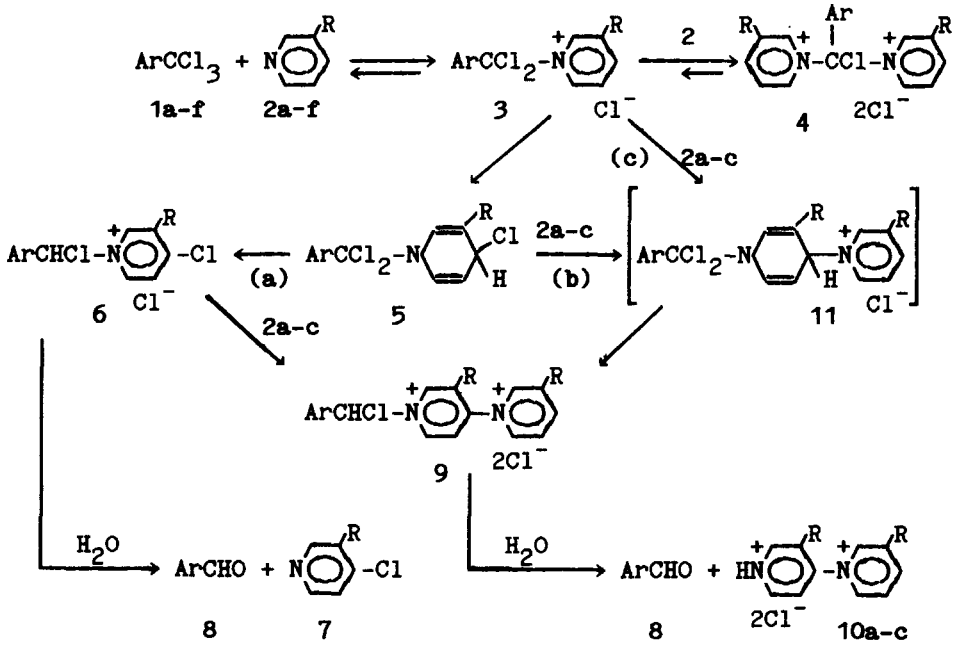
Abstract. A redox reaction of trichloromethylarenes with pyridines results in respective N-(α-chloroarylmethyl)-substituted pyridinium chlorides which give on hydrolysis aromatic aldehydes and 4-chloropyridines or 1,4'-bipyridinium salts.

Recently we have found that in the interaction of trichloromethylarenes $ArCCl_3$ (1) with hydroxylamine or hydrazines in pyridine solution a previously unknown reductive condensation reaction takes place which leads to derivatives of corresponding aldehydes, either oximes and nitriles or aldazines and hydrazones, respectively.[1,2] It was supposed[2] that hydroxylamine or hydrazines are true reducing reagents and the first step of the process (similarly to the reaction carried out using an alcohol as the solvent[3]) is the formation of respective hydroximoyl or hydrazonoyl chlorides which undergo reduction with excess hydroxylamine or hydrazine. However, the results of an additional study[4,5] showed the key role of pyridine in the reduction step.

Now we have studied in detail the reactions of trichlorides 1 (Ar = a Ph, b 2,4-$Me_2C_6H_3$, c 2,4,5-$Me_3C_6H_2$, d 2,4,6-$Me_3C_6H_2$, e 2,3,4,6-Me_4C_6H, f 2,3,5,6-Me_4C_6H, g 2,3,4,5-Me_4C_6H) with pyridine (2a) and those of trichloride 1d with 3-R-pyridines (2, R = b Me, c OH, d $CONH_2$, e COOEt, f Br) which allowed the mechanism of the reductive condensation to be elucidated. Couples formed by trichloromethylarenes 1 with pyridine bases 2 were shown to be potent redox systems. All the transformations are presented by Scheme.

The first step of the reaction is the formation of unstable monopyridinium salts 3. We succeeded in trapping the salt from benzotrichloride 1a and Py as hexachloroantimonate (3a'). It was also possible to prepare an analogous salt (3d') from sterically hindered mesitotrichloride 1d and 4-methylpyridine. In cases of unhindered trichlorides 1a-c salts 3 easily convert to rather stable though hygroscopic bispyridinium salts 4,[6] the equilibrium being shifted to the right. The other and nonreversible transformation of salts 3 is the nucleophilic attack of the position 4 of their pyridine ring by chloride anion to give dihydropyridines 5. This attack is

especially efficient for salts formed by sterically hindered trichlorides 1d-f. 4-Chloro-1,4-dihydronicotinamide hydrochloride[7] observed after the reaction of 1d with nicotinamide among the products of hydrolysis of the reaction mixture can be regarded as an evidence of formation of dihydropyridines 5. The latter undergo redox transformation to give 4-chloropyridinium salts 6, which were identified in reactions of 1d with pyridines 2a,d-f as hydrolysis products, *viz.* 4-chloropyridines 7a,d-f[8] besides mesitoic aldehyde 8d, and in the case of pyridine 2a also as N-(α-chloro-2,4,6-trimethylbenzyl)-4-chloropyridinium hexachloroantimonate (6d').[8]



Scheme

In the reactions of trichloride 1d with pyridines 2a-c and of 1e,f with pyridine 2a, the N-(α-chlorobenzyl)-1,4'-bipyridinium salts 9 were formed (independently of 1d : 2a-c ratio). Salts 9d and 9e formed by 1d,e with Py were isolated as unstable crystalline precipitates, the former being characterized also as hexachloroantimonate 9d'.[12] The structures of salts 9 were also proved by identification of N-(4-pyridyl)pyridinium (1,4'-bipyridinium) dichlorides 10a-c (R = a H, b Me, c OH) and aldehydes 8d-f (Ar = d 2,4,6-$Me_3C_6H_2$, e 2,3,4,6-Me_4C_6H, f 2,3,5,6-Me_4C_6H) obtained on hydrolysis.[13] The formation of salts 6 is practically the only process for pyridines 2d-f. Taking into account that we had no evidence on the formation of intermediates 11 and observed the formation of salt 6d on initial

steps of the reaction between 1d and 2a which gave dichloride 9d as final product, salts 9 seem to be formed *via* 4-chloropyridinium salts 6 (path a) rather than by routes b or c analogous to mechanisms proposed for the formation of N-(4- pyridyl)pyridinium dichloride 10a,[16-18] both routes having the same salt 11 as key intermediate. The reductive transformation of trichlorides 1 can be regarded to some extent as an alternative to the oxidative conversion of monochloromethylarenes to aldehydes by Sommelet reaction, the mechanism of the pyridine base transformation modelling that of N-(4-pyridyl)pyridinium dichloride synthesis. As to the mechanism of the formal hydride ion transfer in dihydropyridines 5 our experiments with Py-d_5 and Py-d_5.HCl[19] have shown that the transfer of a proton and two electrons proceeds similarly to biological processes involving NADH and NADPH.[20]

References and Notes

1. Brokhovetskii D.B., Belen'kii L.I., Krayushkin M.M., *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1989, No. 3, 748. (*Bull. Acad. Sci. USSR. Div. Chem. Sci.*, 1989, 38, 676).

2. Belen'kii L.I., Brokhovetskii D.B., Krayushkin M.M., *Tetrahedron*, 1991, 47, 447.

3. Brokhovetskii D.B., Belen'kii L.I., Krayushkin M.M., *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1990, No. 7, 1692 (*Bull. Acad. Sci. USSR. Div. Chem. Sci.*, 1990, 39, 1538).

4. Belen'kii L.I., Poddubnyi I.S., Krayushkin M.M., *Izv. Akad. Nauk. Ser. Khim.*, 1993, No. 11, 1928 (*Rus. Chem. Bull.*, 1993, 42, 1844).

5. Belen'kii L.I., Poddubnyi I.S., Krayushkin M.M., *Mendeleev Commun.*, 1993, N3, 97.

6. Pyridinium rings of the salts are characterized by the following signals in ^{1}H NMR spectra (δ, $CDCl_3$): for 3d' 8.72 m (2-, 6-H), 7.77 m (3-, 5-H); for 4a-c 8.85-9.20 m (2-, 6-H), 7.96-8.28 m (3-, 5-H), 8.42-8.78 m (4H); for 3a' (in acetone-d_6) 9.67 m (2-, 6-H), 8.52 m (3-, 5-H), 9.06 m (4-H).

7. ^{1}H NMR spectrum (δ, DMSO-d_6 - D_2O): 8.09 br.s (2-H), 6.63 br.d (6-H), 6.16 m (4-H), 5.73 br.d (5-H), J_{56} = 9 Hz.

8. Salt 6d', m.p. 155-157 °C; ^{1}H NMR spectrum (δ, in acetone-d_6): 9.38 m (2-, 6-H), 8.47 m (3-, 5-H), 8.33 s ($CHClN^+$), 7.12 s (H_{Ar}), 2.32 s (3 Me). Found: Cl 46.08, N 2.36, Sb 20.52%. $C_{15}H_{16}Cl_8NSb$. Calculated: Cl 46.07, N 2.28, Sb 19.77%. 4-Chloropyridines were characterized by ^{1}H NMR spectra (δ) in DMSO-d_6 (7a,d) or in $CDCl_3$ (7e,f): 7a 8.52 d (2-, 6-H), 7.40 d (3-, 5-H), (all J = 5.5 Hz); 7d 9.06 s (2-H), 8.52 d (6-H), 7.45 d (3-H), J = 6.8 Hz, 8.10 br. (NH_2); 7e 9.11 s (2-H), 8.75 d (6-H), 7.61 d (3-H), J = 5.4 Hz, 4.52 q (CH_2), 1.51 t (Me), J_{Me-CH_2} = 7 Hz; 7f 8.73 s (2-H), 8.41 d (6-H), 7.40 d (3-H), J = 5.3 Hz. The spect-

rum and n_D^{25} (1.5240) of 7e as well as m.p. 15-17 °C and the spectrum of 7f correlate well with data given in Refs. 9 and 10, 11, respectively.

9. Lhommet G., Sliwa H., Maitte P., *Bull. Soc. chim. France*, 1972, No. 4, 1439.

10. den Hertog H.J., Boelrijk N.A.I.M., *Rec. trav. chim.*- 1951, 70, 578.

11. Yamanaka H., Araki T., Sakamoto T., *Chem. Pharm. Bull.*, 1988, 36, 2246.

12. Salts 9d,e precipitated when reactions of 1d or 1e, respectively, with pyridine 2a were carried out in $CHCl_3$ or CH_2Cl_2 as solvents. Salt 9d, m.p. 148-152 °C, yield 76-96%; ^{1}H NMR spectrum (δ, DMSO-d_6): 9.77 m (2-, 2'-, 6-, 6'-H), 8.97 m (3'-, 5'-H), 8.48 m (3-, 5-H), 8.99 m (4-H), 8.72 s (CHClN$^+$), 7.09 s (3-, 5-H_{Ar}), 2.30 br.s (2-, 4-, 6-Me); ^{13}C NMR spectrum (δ, DMSO-d_6): 147.9 (2'-, 6'-C_{Py}), 124.7 (3'-, 5'-C_{Py}), 154.3 (4'-C_{Py}), 146.2 (2-, 6-C_{Py}), 127.7 (3-, 5-C_{Py}), 144.4 (4-C_{Py}), 79.4 (CHClN$^+$), 127.4 (i-C_{Ar}), 141.7 (o-C_{Ar}), 130.8 (m-C_{Ar}), 137.9 (p-C_{Ar}), 20.7 (o-Me), 19.9 (p-Me). Found: C 60.20, H 5.30, Cl 27.15, N 7.11%. $C_{20}H_{21}Cl_3N_2$. Calculated: C 60.69, H 5.35, Cl 26.88, N 7.08%. Salt 9d', m.p. 206-219 °C, quant. yield; ^{1}H NMR spectrum (δ, acetone-d_6): 10.00 m (2'-, 6'-H), 9.21 m (3'-, 4-, 5'-H), 9.77 m (2-, 6-H), 8.70 m (3-, 5-H), 8.56 s (CHClN$^+$), 7.17 s (3- and 5-H_{Ar}), 2.35 s (2-, 6-Me), 2.33 s (4-Me). Salt 9e, m.p. 162-164 °C, yield 93%; ^{1}H NMR spectrum (δ, DMSO-d_6): 9.79 br. d (2'-, 6'-H), 8.98 br.d (3'-, 5'-H), J = 6 Hz, 9.71 m (2-, 6-H), 8.49 m (3-, 5-H), 9.01 m (4-H), 8.80 s (CHClN$^+$), 7.08 s (H_{Ar}), 2.28 br.s (2-, 6-Me), 2.15 br.s (3-, 4-Me).

13. Identification of compounds 8d and 10a see in Ref. 5. Characteristics of aldehyde 8e, n_D^{20} 1.5554 and salt 10b, m.p. 202-204 °C correlate with the data of Refs. 14, 15. Structures of aldehyde 8f and salt 10c were proved by ^{1}H NMR. For 8f (δ, in DMSO-d_6): 10.46 s (CHO), 7.10 s (4-H), 2.22 s (2-, 6-Me), 2.12 s (3-, 5-Me); for 10c (δ, $CDCl_3$ - DMSO-d_6): 8.86 s (2'-H), 8.74 d (6'-H), 7.94 d (5'-H), J_{56} = 5.7 Hz, 9.35 d (2-H), 8.88 d (6-H), 8.48 dd (4-H), 8.16 dd (5-H), J_{56} = 5.5, J_{45} = 7.0, J_{24} = 2.0 Hz, 9.0 br. (OH + CHClN$^+$).

14. Akkerman O.S., *Rec. trav. chim.*, 1967, 86, 1018.

15. Boduszek B., Wieczorek J.S., *Monatsh. Chem.*, 1980, 111, 1111.

16. Koenigs E., Greiner H., *Ber.*, 1931, 64, 1049.

17. Krönke F., *Angew. Chem.*, 1953, 65, 605.

18. Thomas K., Jerchel D., *Angew. Chem.*, 1958, 70, 719.

19. While from 1d with Py-d_5 aldehyde 8d deuterated (95%) in formyl group was obtained after hydrolysis, preferably non-deuterated (70%) aldehyde 8e was formed from 1e with Py-d_5 - Py-d_5.HCl (1:1).

20. Lehninger A.L., Nelson D.L., Cox M.M., "Principles of Biochemistry", 2nd ed., Worth Publishers, N.Y., 1993, P. 554.

(*Received in UK* 7 *February* 1995; *revised* 24 *May* 1995; *accepted* 26 *May* 1995)