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SOME REACTIONS OF PYRIDINIUM SALTS DERIVED FROM TRICHLORO-METHYLARENES WITH N- AND C-NUCLEOPHILES*

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The reaction of N-(4-pyridyl)pyridinium and 4-chloropyridinium salts obtained from 1-trichloromethyl-2,4,6-trimethylbenzene and pyridine with N-nucleophiles such as piperidine and morpholine and with C-nucleophiles such as N,N-dimethylaniline and indole proceeds through hetarylation and gives the corresponding 4-substituted pyridines. N-(α,α-Dichlorobenzyl)pyridinium and N,N'-(α-chlorobenzylidene)bispyridinium salts obtained from trichloromethylbenzene do not undergo hetarylation.

Keywords: trichloromethylbenzene, 4-substituted pyridines, N- and C-nucleophiles, piperidine, N-(4-pyridyl)pyridinium salts, 4-chloropyridinium salts, N-(α,α-dichlorobenzyl)pyridinium salts, N,N'-(α-chlorobenzylidene)bispyridinium salts, 1-trichloromethyl-2,4,6-trimethylbenzene.

N-(α,α-Dichloromethyl)pyridinium chlorides **3** obtained in the reaction of trichloromethylarenes **1** with pyridines **2** are unstable and undergo further transformations. These salts react with a second pyridine molecule to give bispyridinium salts **4** or 4-pyridinio-1,4-dihydropyridines **5**, while addition of a chloride anion gives 4-chloro-1,4-dihydropyridines **6** [1, 2]. Then, **5** and **6** undergo aromatization with hydrogen transfer from $C_{(4)}$ of the dihydropyridine ring to the benzylic dichloromethylene group to give N-(α-chloroarylmethyl)-4-(pyridinio)pyridinium dichlorides **7** or N-(α-chloroarylmethyl)-4-chloropyridinium chlorides **8**, which are converted upon hydrolysis to pyridylpyridinium salts **9** or 4-chloropyridinium salts **10** and aromatic aldehydes **11**. In the presence of hydroxylamine or hydrazines, these transformations lead to the corresponding aldehydes **11**, which have already been identified as the products of the reductive condensation of trichloromethylarenes with hydroxylamine or hydrazines in pyridine [3-5].

Except for salts **5**, the compounds shown in the reaction scheme below were isolated as such or as derivatives or detected spectroscopically. We should note that bispyridinium salts **4** could be isolated only for trichlorides **1a-c**, which have not more than one methyl group in the *ortho* position, while stable pyridylpyridinium salts **7** were isolated only for 1-trichloromethyl-2,4,6-trimethylbenzene **1d**, 1-trichloromethyl-2,3,4,6-tetramethylbenzene **1e**, and 1-trichloromethyl-2,3,5,6-tetramethylbenzene **1f** with methyl groups occupying both the *o*- and *o′*-positions [2].

* Dedicated to the memory of A. N. Kost on the occasion of the eighty-fifth anniversary of his birth.

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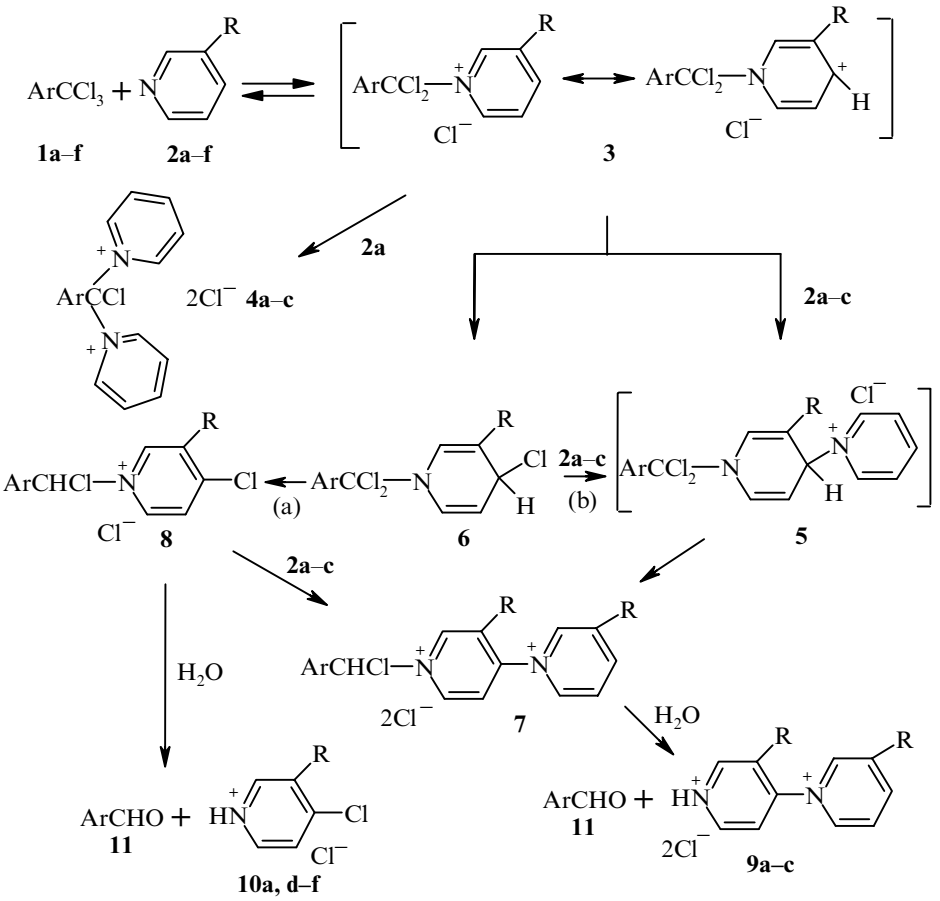
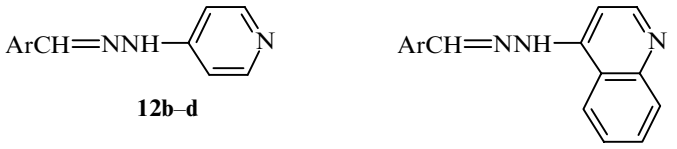


1, 11 a Ar = Ph, **b** Ar = 2,4-$Me_2C_6H_3$, **c** Ar = 2,4,5-$Me_3C_6H_2$, **d** Ar = 2,4,6-$Me_3C_6H_2$,
e Ar = 2,3,4,6-Me_4C_6H, **f** Ar = 2,3,5,6-Me_4C_6H, **4 a** Ar = Ph, **b** Ar = 2,4-$Me_2C_6H_3$,
c Ar = 2,4,5-$Me_3C_6H_2$, **2, 9, 10 a** R = H, **b** R = Me, **c** R = OH, **d** R = $CONH_2$, **e** R = COOEt, **f** R = Br

The structures of monopyridinium salts **3**, bispyridinium salts **4**, 4-pyridylpyridinium salts **7**, and 4-chloropyridinium salts **8** feature several electrophilic sites, which may undergo nucleophilic attack. The action of water or aqueous ethanol on N-(4-pyridyl)pyridinium salts **7** or 4-chloropyridinium salts **8** smoothly leads to aldehydes **11** and salts **9** or **10**, i.e., attack of the hydroxide ion occurs at the benzylic carbon atom with the substitution of pyridinium residue and chlorine atom. A similar type of nucleophilic attack is observed upon the action of hydrazines or hydroxylamine on salt **7** with formation of reductive condensation products.

Another site for nucleophilic attack is found at the $C_{(4)}$ atom of heterocycle in salts **3**, **7**, or **8**. Addition at this position and subsequent replacement of the hydrogen atom, chlorine atom, or pyridinium residue should lead to 4-substituted pyridines. In previous work [5], we found the formation of 4-pyridylhydrazones **12b-d** and 4-quinolylhydrazones of aromatic aldehydes **13** as side-products under the conditions of reductive condensation of trichloromethylarenes **1b-d** with hydrazine.

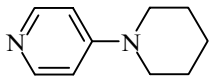


12b–d **13**

Ar = 2,4,6-$Me_3C_6H_2$

In the presence of hydrazine, which is a strong nucleophile, competitive replacement of the chlorine atom at $C_{(4)}$ of chlorodihydropyridines **6** or, more likely, of chloropyridinium salts **8** by hydrazine rather than pyridine may occur, leading to 4-pyridylhydrazine. The reaction of 4-pyridylhydrazine with corresponding aldehydes **11** gives hydrazones **12b-d**. A similar explanation is also holds for the formation of 4-quinolylhydrazine, which is converted to hydrazone **13**. We should recall that the synthesis of 4-pyridylhydrazine from 4-chloropyridine was reported by Mann et al. [6] and is carried out under conditions similar to those for the reductive condensation and in contrast to the vigorous conditions for the synthesis of this hydrazine from N-(4-pyridyl)pyridinium dichloride and hydrazine hydrate [7].

In the present work, we attempted to elucidate the capacity of pyridinium salts **3, 4, 7,** and **8** to react with N- and C-nucleophiles through hetarylation, i.e., at one of the positions of the pyridine ring. The reaction of 1-trichloromethyl-2,4,6-trimethylbenzene **1d** with pyridine and piperidine or morpholine gives 4-piperidino- **14** or 4-morpholinopyridines **15** in 50-60% yield in addition to 2,4,6-trimethylbenzaldehyde.



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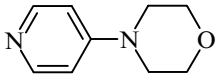

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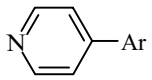
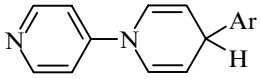
The hetarylation of N,N-dimethylaniline and indole was carried out under similar conditions to give 4-substituted pyridines **16** and **17**. In the case of indole, 4-(3-indolyl)-1-(4-pyridyl)-1,4-dihydropyridine (**18**) was isolated in low yield along with compound **17**. The formation of **18** may be seen as evidence for the intermediacy of N-(α,α-dichloro-2,4,6-trimethylbenzyl)-4-chloro-1,4-dihydropyridine (**6a**) or as the first example of the C-nucleophile addition to a pyridylpyridinium salt. The γ-selectivity of these transformations is likely a consequence both of the steric hindrance of the α-positions in the pyridinium salt by the N-substituent and the relatively "soft" nucleophilic nature of π-excess systems [8].





16 Ar = *p*-$C_6H_4NMe_2$; **18** Ar = 3-indolyl

17 Ar = 3-indolyl

Taking account of the conditions for these reactions, it is difficult to determine which of salts **3, 4, 7**, or **8** is responsible for formation of the hetarylation products. We note that N-acylpyridinium salts are among the most extensively studied and efficient hetarylation reagents [9]. These salts may be seen as analogs of salts **3**. The capacity of pyridylpyridinium salts to react with various nucleophiles is well known and rather commonly used for the synthesis of 4-substituted pyridines [10]. There is also no doubt concerning the capacity of 4-chloropyridines and, especially, corresponding 4-chloropyridinium salts **8** to react with nucleophiles [11].

Our reaction conditions are probably too mild for the analogous exchange of the pyridinium residue in pyridylpyridinium salts **7** and **9** by a hydrazine fragment used in the synthesis of pyridylhydrazines [7]. In order to check the capacity of mono- **3** and bispyridinium salts **4** to undergo hetarylation, we attempted to obtain **14** and **15** using trichloromethylbenzene **1a** instead of 1-trichloromethyl-2,4,6-trimethylbenzene. Trichloride **1a** reacts with pyridine to give salts **4** but cannot form pyridylpyridinium salts **7** and chloropyridinium salts **8** [2]. However, these attempts were unsuccessful and traces of 4-piperidinopyridine **14** were obtained only in one case. The desired products also could not be obtained from rather stable bispyridinium salt **4a**, previously prepared from trichloromethylbenzene and pyridine. There is also evidence to doubt the capacity of unstable monopyridinium salts **3** formed by sterically unhindered trichlorides **1a-c** to undergo hetarylation with nucleophiles, i.e., to react at the $C_{(4)}$ atom of the pyridinium ring since the second pyridine molecule attacks the benzylic carbon atom to give bispyridinium salts **4a-c**.

These findings dictate a reexamination of our scheme for reductive condensation in regard to trichloromethylarenes **1a-c**, which are incapable of forming pyridylpyridinium salts **7** and chloropyridinium salts **8** [1, 2]. Other reductive condensation schemes not requiring formations of salts such as **7** and **8** should be examined in this regard. This is the subject of a separate study.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz in the pulse mode with Fourier transformation. The resonance conditions were stabilized relative to the solvent proton signals. The mass spectra were taken on a Kratos MS-30 mass spectrometer with direct sample inlet into the ion source. The ionization energy was 70 eV and the emission current was 100 μA. The melting points were measured on a Boetius microscopic block and not corrected.

Reaction of 1-Trichloromethyl-2,4,6-trimethylbenzene 1d with Pyridine and Piperidine. A sample of piperidine (1.08 ml, 11 mmol) was added dropwise to a solution of trichloride **1d** (1.3 g, 5.47 mmol) in dry pyridine (0.88 ml, 11 mmol) and dry chloroform (5 ml) and left for 30 days at room temperature. The solvent was evaporated off and the residue was dissolved in ethanol (5 ml) and water (0.3 ml). Then, hydrazine hydrate (0.8 ml, 16.4 mmol) was added with stirring and left for 12 h at about 20°C. The crystalline precipitate was filtered off, washed with water and then ethanol, and dried to give 2,4,6-trimethylbenzaldehyde azine (0.25 g, 31%) identical to the sample described in our previous work [4]. The filtrate was evaporated. The residue was washed with water and extracted with ether. The extract was dried over $MgSO_4$. Ether was evaporated. The residue was sublimed in vacuum at room temperature to give 4-piperidinopyridine **14** (0.43 g, 48%); mp 79-81°C (hexane) (81-82°C [13]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.67 (6H. br, CH_3); 3.31 (4H, br, NCH); 6.62 (2H, d, 3- and 5-H); 8.22 (2H, d, 2- and 6-H); $J_{23} = J_{56} = 5.2$. The spectral parameters were identical to literature data [14].

Reaction of Trichloromethylbenzene 1a with Pyridine and Piperidine. A. A sample of piperidine (5.6 ml, 4.85 g, 57.3 mmol) was added dropwise to a solution of trichloride **1a** (2.7 ml, 3.74 g, 19.1 mmol) in dry pyridine (4.6 ml, 4.52 g, 57.3 mmol) and dry chloroform (5 ml) and the mixture was heated at reflux for 2 h. The solvent was evaporated. The residue was dissolved in ethanol (5 ml) and water (0.3 ml) and then heated at reflux for 0.5 h. A sample of hydrazine (2.8 ml, 57.3 mmol) was added and the mixtures was heated at reflux for about 1 h. The crystalline precipitate was filtered off, washed with ethanol, and dried to give hydrazine hydrochloride (0.38 g); mp 89-90°C. The filtrate was evaporated. The residue was diluted with water and extracted with ether. The extract was dried over $MgSO_4$. Ether was removed to give an oil, which partially crystallized upon standing at low temperature. Filtration gave 4-piperidinopyridine **15** (0.04 g, 4%); mp 79-80°C (hexane).

B. A solution of trichloride **1a** (2.7 ml, 3.74 g, 19.1 mmol) in dry pyridine (4.6 ml) was heated at reflux for 1.5 h. Excess pyridine was distilled from bispyridinium salt **4**. The residue was dissolved in dry chloroform (5 ml). Then, piperidine (3.7 ml, 3.2 g, 38 mmol) was added dropwise and the mixture was heated at reflux. Crystalline piperidine hydrochloride (0.38 g; mp 244-247°C (245-248°C [15])) formed upon cooling was filtered off. The solvent was evaporated and about water (0.5 ml), ethanol (5 ml), and hydrazine hydrate (2.9 ml, 57.3 mmol) were added to the residue. The mixture obtained was heated at reflux for 1.5 h and the solvent was distilled off. The residue was diluted with water (50 ml) and extracted with ether. The extract was dried over $MgSO_4$ and evaporated to give a cherry red oil, which partially crystallized upon standing. Crystallization from ethanol gave 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine (0.14 g, 7%); mp 196-198°C (195-196°C [16]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.68 (2H, br.s, NH); 7.62 (6H, m, *m*- and *p*-H); 8.68 (4H, m, *o*-H).

Reaction of 1-Trichloromethyl-2,4,6-trimethylbenzene 1d with Pyridine and Morpholine. Analogously, the reaction of trichloride **1d** (1.3 g, 5.47 mmol), pyridine (0.88 ml, 11 mmol), and morpholine (0.96 ml, 11 mmol) gave 2,4,6-trimethylbenzaldehyde azine (0.31 g, 39%); mp 170-171°C. Sublimation gave 4-morpholinopyridine **15** (0.51 g, 57%); mp 96-98°C (90-95°C [11]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 3.29 (4H, t, NCH_2, $J = 5$); 3.85 (4H, t, OCH_2); 6.67 (2H, m, 3- and 5-H); 8.29 (2H, m, 2- and 6-H). $M^+ = 164$.

Reaction of 1-Trichloromethyl-2,4,6-trimethylbenzene 1d with Pyridine and N,N-Dimethylaniline. A sample of N,N-dimethylaniline (0.66 g, 5.47 mmol) was added to a solution of trichloride **1d** (1.3 g, 5.47 mmol) in

dry pyridine (0.44 ml, 5.47 mmol) and dry chloroform (5 ml) and maintained for 15 days at room temperature. The solvent was evaporated and the residue was dissolved in a mixture of ethanol (5 ml) and water (0.2 ml). Then, hydrazine hydrate (0.6 ml, 12.3 mmol) was added. The mixture was stirred and left for 12 h at about 20°C. Filtration of the precipitate formed gave aldehyde azine **11d** (0.37 g, 46%); mp 170-172°C. The filtrate was evaporated. The residue was treated with water and extracted with chloroform. The extract was evaporated and the residue was recrystallized from ethanol to give 4-(*p*-dimethylaminophenyl)pyridine **16** (0.32 g, 30%); mp 230-233°C (233-234°C [17]). ^{1}H NMR spectrum ($CHCl_3$), δ, ppm: 3.05 (6H, s, NCH); 6.81 (2H, m, 3'- and 5'-H phenyl); 7.60 (2H, m, 2'- and 6'-H phenyl); 7.50 (2H, m, 3- and 5-H pyridine); 8.58 (2H, m, 2- and 6-H pyridine). M^+ = 198.

Reaction of 1-Trichloromethyl-2,4,6-trimethylbenzene 1d with Pyridine and Indole. By analogy to the previous experiment, the reaction of trichloride **1d** (1.3 g, 5.47 mmol), pyridine (0.88 ml, 10.94 mmol), and indole (0.64 g, 5.47 mmol) in CH_2Cl_2 (5 ml) over 30 days gave aldehyde azine **11d** (0.47 g, 59%); mp 170-172°C. Partial evaporation of the mother liquor gave a precipitate of 4-(3-indolyl-1-(4-pyridyl)-1,4-dihydropyridine **18** (0.71 g, 7%); mp 181-182°C, M^+ = 273. Found, %: C 78.77; H 5.43; N 15.46. $C_{18}H_{15}N_3$. Calculated, %: C 79.10; H 5.53; N 15.37. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 4.52 (1H, br. 4-H dihydropyridine); 5.06 (2H, dd, 3-H and 5-H dihydropyridine); $J_{23} = J_{56} = 8.0$, $J_{34} = J_{45} = 3.7$); 6.93 (1H, m, 5-H indole); 6.98 (2H, d, 2-H and 6-H dihydropyridine); 7.08 (1H, m, 5-H indole); 7.10 (1H, d, 2-H indole, $J_{12} = 2.7$); 7.20 (2H, m, β-H pyridine); 7.37 (1H, d, 7-H indole, $J_{67} = 8.1$); 7.57 (1H, d, 4-H indole, $J_{45} = 8.0$); 8.33 (2H, m, α-H pyridine); 10.92 (1H, br. s, NH). The ^{1}H NMR spectral data are in accord with the data for related 1,4-dihydropyridines [18, 19]. After separation of product **18**, the mother liquor was evaporated, treated with water, and extracted with chloroform. The extract was evaporated and the residue was recrystallized from ethanol to give 4-(3-indolyl)pyridine **17** (0.56 g, 53%); mp 214-217°C (218-219°C [19]), M^+ = 194.

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