ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 12, pp. 1821–1824. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © R.I. Khusnutdinov, A.R. Baiguzina, A.A. Smirnov, R.R. Mukminov, U.M. Dzhemilev, 2007, published in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 12, pp. 1819–1821.

One-Step Synthesis of 3-Dichloromethylpyridine from Pyridine in the Presence of Iron-Containing Catalysts

R. I. Khusnutdinov, A. R. Baiguzina, A. A. Smirnov, R. R. Mukminov, and U. M. Dzhemilev

Institute of Petroleum Chemistry and Catalysis, Russian Academy of Sciences,
pr. Oktyabrya 141, Ufa, 450075 Bashkortostan, Russia
e-mail: ink@anrb.ru

Received October 3, 2006; revised July 27, 2007

Abstract—3-Dichloromethylpyridine was synthesized by reaction of pyridine with the system MeOH–CCl_4–iron catalyst [$FeBr_2$, $Fe_3(CO)_{12}$, or iron(III) naphthenate]. Iron(II) bromide at a $FeBr_2$–pyridine–CCl_4–MeOH ratio of 1 : 100 : 200 : 200 showed the highest catalytic activity.

DOI: 10.1134/S1070428007120147

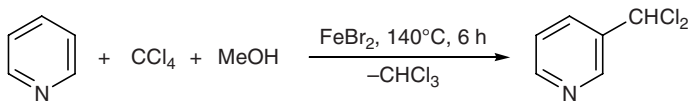
Derivatives of pyridine and α-, β-, and γ-picolines containing one, two, and three halogen atoms are known to exhibit pronounced biological activity and are widely used for the synthesis of herbicides, fungicides, defoliants, nitrification inhibitors, and insecticides [1]. In particular, 3-dichloromethylpyridine (**I**) is a starting material for the preparation of 3-[4-(5-trifluoromethylpyridin-2-yloxy)phenoxy]propionic acid esters possessing strong herbicidal activity [2].

3-Dichloromethylpyridine (**I**) is usually prepared by catalytic chlorination of difficultly accessible 3-methylpyridine (**II**, β-picoline) using concentrated sulfuric acid, glacial acetic acid, and 2,2′-azobis(isobutyronitrile) as radical initiator [3]. 3-Dichloromethylpyridine (**I**) was also synthesized by reaction of 3-methylpyridine with gaseous chlorine in the presence of acids and radical initiators [4]. Gas-phase chlorination of 3-methylpyridine (**II**) with excess chlorine in the presence of carbon tetrachloride at 350°C gave products containing chlorine both in the side methyl group and in the pyridine ring [5]. Rubina et al. [6] made an attempt to synthesize compound **I** by chlorination of 3-methylpyridine with *N*-chlorosuccinimide in the presence of benzoyl peroxide, but the reaction was not selective: as a result, a mixture of three products containing one, two, and three chlorine atoms in the methyl group was obtained. 3-Dichloromethylpyridine can also be prepared in ~38% yield by treatment of pyridine-3-carbaldehyde with PCl_5 in the presence of pyridine [6].

In the present work we used accessible pyridine instead of 3-methylpyridine (**II**) as starting compound for the synthesis of 3-dichloromethylpyridine (**I**). The proposed procedure is based on the reaction of pyridine with the system CCl_4–MeOH in the presence of a catalyst. As the latter we tried iron [$FeBr_2$, $Fe_3(CO)_{12}$, iron(III) naphthenate] and tungsten compounds [$W(CO)_6$], the molar ratio catalyst–pyridine–CCl_4–MeOH being 1 : 100 : 200 : 200 (Scheme 1). The reaction was carried out in a broad temperature range, and the best results were obtained at 140°C (reaction time 6 h). The conversion of pyridine (with no account taken of its consumption for binding liberated hydrogen chloride) was ~40%. No reaction occurred in the absence of methanol or in the presence of a small amount of methanol ($FeBr_2$–MeOH ratio 1 : 10).

3-Dichloromethylpyridine was obtained with a high selectivity (94%) using $Fe_3(CO)_{12}$–$W(CO)_6$ or iron(III) naphthenate as catalyst. However, in these cases the conversion of pyridine was considerably lower, so that

Scheme 1.



I, 35%

Synthesis of 3-dichloromethylpyridine (**I**) by reaction of pyridine with carbon tetrachloride and methanol in the presence of iron-containing catalysts

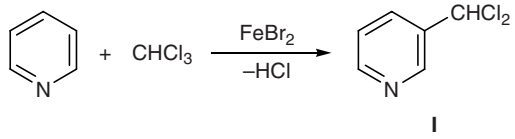
Catalyst	Molar ratio catalyst–pyridine–CCl_4–MeOH	Temperature, °C (time, h)	Conversion of pyridine,[a] %	Yield (overall), %
$Fe_3(CO)_{12}$	1:100:200:200	140 (6)	8	5
$Fe_3(CO)_{12}$–$W(CO)_6$	1:100:200:200	140 (6)	16	15
Iron(III) naphthenate	1:100:200:200	140 (6)	20	19
$FeBr_2$	1:100:200:200	140 (6)	40	35
$FeBr_2$	1:100:200:0	140 (6)	0	0
$FeBr_2$	1:100:200:4	140 (6)	0	0
$FeBr_2$	1:100:200:200	100 (6)	0	0
$FeBr_2$	1:100:200:200	150 (6)	2	0.2
$FeBr_2$	1:100:200:200	140 (3)	5	3

[a] With no account taken of pyridine consumption for binding of hydrogen chloride.

the overall yield of 3-dichloromethylpyridine (**I**) was 15 and 19%, respectively (see table). In all experiments, a large part of the substrate is consumed for binding liberated hydrogen chloride with formation of pyridine hydrochloride. By special experiments with preliminarily prepared pyridine hydrochloride we showed that it is inactive under the above conditions. After neutralization, unreacted pyridine can be used repeatedly.

Taking into account that chloroform is formed during the process, the formation of 3-dichloromethylpyridine (**I**) is likely to involve alkylation of pyridine with $CHCl_3$ in the presence of $FeBr_2$ which is known to be very efficient in Friedel–Crafts reactions (Scheme 2). However, our attempts to effect direct alkylation of pyridine with chloroform were unsuccessful.

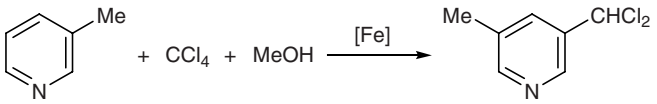
Scheme 2.



I

The presence in the reaction mixture of traces of 3-methylpyridine (**II**) suggests that 3-dichloromethylpyridine (**I**) may be formed along a more complex scheme with participation of methanol and carbon tetrachloride. Presumably, initial alkylation of pyridine with methanol in the presence of $FeBr_2$ gives 3-methylpyridine (**II**) which then undergoes successive chlorination at the methyl group with carbon tetrachloride to afford 3-dichloromethylpyridine (**I**). This assumption was not confirmed experimentally. In the reaction of 3-methylpyridine (**II**) with CCl_4 and MeOH in the presence of $FeBr_2$ we isolated 3-dichloromethyl-5-methylpyridine (**III**) (Scheme 3).

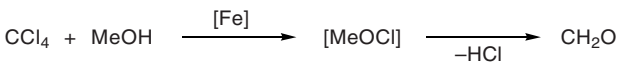
Scheme 3.



II **III**, 32%

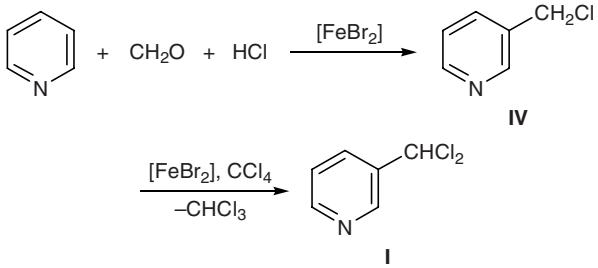
While further searching for a reasonable explanation for the formation of compound **I** we focused on the fact that a part of methanol is oxidized with carbon tetrachloride during the process with formation of formaldehyde and hydrogen chloride according to Scheme 4.

Scheme 4.



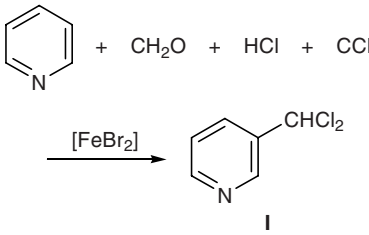
The presence in the reaction mixture of CH_2O, HCl, and $FeBr_2$ promotes chloromethylation of pyridine; therefore, Scheme 5 may be proposed for the formation of compound **I**.

Scheme 5.



This assumption is supported by the following experimental data. First, the reaction of pyridine with formaldehyde in the presence of HCl, CCl_4, and $FeBr_2$ actually gives 3-dichloromethylpyridine (**I**) in 7% yield (Scheme 6).

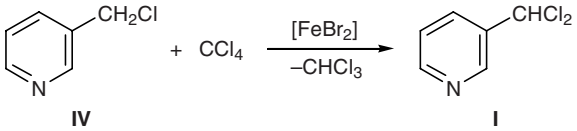
Scheme 6.



I

On the other hand, specially performed chlorination of 3-chloromethylpyridine (**IV**) with CCl_4 in the presence of $FeBr_2$ was successful, and 3-dichloromethylpyridine (**I**) was formed in 10% yield (Scheme 7). We can conclude that the formation of compound **I** with participation of formaldehyde according to Scheme 5 is possible. The relatively poor yield of **I** in control experiments may be attributed to considerable difference in the reaction conditions.

Scheme 7.



IV **I**

According to the GLC data, the conversion of carbon tetrachloride and the amount of $CHCl_3$ derived therefrom were greater by a factor of 3 to 4 than the yield of 3-dichloromethylpyridine (**I**). This may be due to consumption of CCl_4 for both oxidation of methanol and chlorination of intermediate 3-chloromethylpyridine (**IV**). Our attempt to effect further chlorination of 3-dichloromethylpyridine (150°C, 6–12 h) was unsuccessful. Presumably, the system CCl_4–CH_3OH–$FeBr_2$ is a milder chlorinating agent than Cl_2 [1].

EXPERIMENTAL

The IR spectra were recorded in the range from 550 to 3500 cm^{-1} on a UR-20 instrument from samples prepared as KBr pellets or dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ relative to tetramethylsilane on a Jeol FX90Q instrument at 90 and 22.5 MHz, respectively. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT-112S mass spectrometer (ion source temperature 220°C). The reaction mixtures and products were analyzed by gas–liquid chromatography on a Chrom-5 instrument [1.2 or 2 m×3-mm column, stationary phase 5% of SE-30 on Chromaton N-AW-HMDS; carrier gas helium; oven temperature programming from 50 to 280°C at a rate of 8 deg/min].

Commercial catalysts (chemically pure grade) were preliminarily dried under reduced pressure. Carbon tetrachloride, chloroform, methanol, ethanol, pyridine, 3-methylpyridine, and 3-chloromethylpyridine were purified and dehydrated before use.

3-Dichloromethylpyridine (I). *a*. A 17-ml high-pressure microreactor or a 20-ml glass ampule was charged under argon with 0.0216 g (0.1 mmol) of $FeBr_2$, 0.79 g (10 mmol) of pyridine, 3.08 g (20 mmol) of CCl_4, and 0.64 g (20 mmol) of methanol. The reactor was hermetically capped (the ampule was sealed) and heated for 6 h at 140°C. When the reaction was complete, the reactor (ampule) was cooled to room temperature and opened, the mixture was filtered through a layer of silica gel (2 g), and unreacted MeOH, CCl_4, and $CHCl_3$ were distilled off. The residue was neutralized with 10% aqueous sodium carbonate under stirring for 0.5–1 h with a magnetic stirrer and extracted with carbon tetrachloride or diethyl ether. The extract was evaporated, and the residue was distilled under reduced pressure. Yield 0.57 g (35%), bp 90°C (15 mm).

b. The procedure was the same as in *a*. The reaction mixture consisted of 0.0216 g (0.1 mmol) of $FeBr_2$, 1.27 g (10 mmol) of 3-chloromethylpyridine, and 3.08 g (20 mmol) of CCl_4. Yield 0.18 g (10%). IR spectrum, ν, cm^{-1}: 1150, 3600 (OH). ^1H NMR spectrum, δ, ppm: 6.7 s (1H, $CHCl_2$), 7.2–8.9 m (4H, pyridine). ^{13}C NMR spectrum, δ_C, ppm: 147.40 (C^2), 133.88 (C^3), 133.5 (C^4), 134 (C^5), 152 (C^6), 72 (C^7). Mass spectrum, *m*/*z* (I_{rel}, %): 161 $[M]^+$ (22), 38 (2), 39 (2), 51 (3), 63 (7), 64 (3), 65 (7), 73 (4), 78 (7), 90 (5), 91 (5), 99 (12), 101 (5), 106 (4), 125 (5), 126 (100), 127 (7), 128 (34), 129 (3), 161 (22), 162 (2), 163 (17).

3-Dichloromethyl-5-methylpyridine (VI). The procedure was the same as above. The reactor (ampule) was charged with 0.0216 g (0.1 mmol) of $FeBr_2$, 0.93 g (10 mmol) of 3-methylpyridine, 3.08 g (20 mmol) of CCl_4, and 0.64 g (20 mmol) of MeOH. Yield 0.56 g (32%). ^1H NMR spectrum, δ, ppm: 7.2 s (1H, $CHCl_2$), 2.4 s (3H, CH_3), 7.2–8.3 m (3H, pyridine). ^{13}C NMR spectrum, δ_C, ppm: 146.32 (C^2), 137.9 (C^3), 136.9 (C^4), 135.2 (C^5), 149.1 (C^6), 71.4 (C^7), 18.0

(C^8). Mass spectrum, *m*/*z* (I_{rel}, %): 175 $[M]^+$ (17), 39 (11), 51 (10), 65 (10), 77 (15), 78 (8), 79 (4), 92 (8), 93 (4), 104 (26), 105 (11), 106 (15), 140 (100), 141 (12), 142 (29), 176 (2), 177 (12).

This study was performed under financial support by the Ministry of Education and Science of the Russian Federation (project no. NSh 7470.2006.3), by the Federal Science and Innovation Agency (state contract no. 02.442.11.7509), by the Foundation for Support of Russian Science, and by the President of Bashkortostan Republic (grant for young scientists and youth research teams, contract no. 4).

REFERENCES

1. Kovganko, N.V. and Kashkan, Zh.N., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1709.
2. Nishiyama, R., Fujikawa, K., Haga, T., and Hase, K., JPN Patent Appl. no. 55-022617, 1980.
3. Jelich, K., US Patent no. 5116993, 1992.
4. Jelich, K., JPN Patent Appl. no. 11-140053, 1999.
5. Bowden, R. and Seaton, T., UK Patent no. 1599783, 1982; *Ref. Zh., Khim*., 1982, no. 15N163P.
6. Rubina, K.I., Iovel', I.G., Gol'dberg, Yu.Sh., and Shimanskaya, M.V., *Khim. Geterotsikl. Soedin*., 1989, p. 543.