

## Alkylation of Aniline with Methanol in the Presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in Carbon Tetrachloride

R. I. Khusnutdinov, A. R. Bayguzina, and R. I. Aminov

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

Received May 4, 2013

**Abstract**—The reaction of aniline with methanol in the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in carbon tetrachloride leads to the formation of *N*-methyl- and *N,N*-dimethylanilines and 4,4'-methylenebis(*N,N*-dimethylaniline).

**DOI:** 10.1134/S1070428013100072

*N*-Methylaniline is one of the most widely used aniline derivatives. It exhibits antioxidant and anti-knock properties and is used as anti-knock additive to motor fuels. *N,N*-Dimethylaniline is used in industry in the manufacture of polyester resins, dyes (Malachite Green, Methylene Blue), and explosives, as well as in organic synthesis [1].

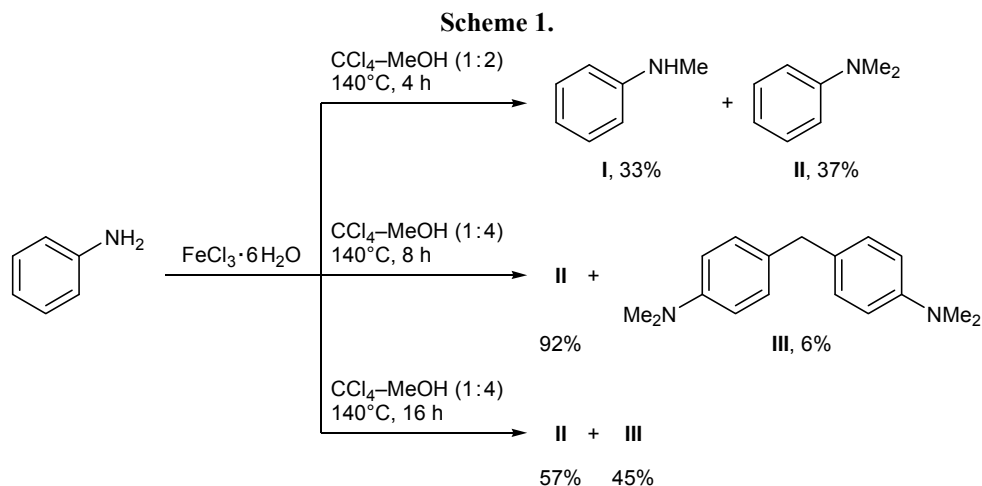
The main procedures for the synthesis of *N*-alkyl aniline derivatives are based on reactions of anilines with aliphatic alcohols, in particular with methanol, by the action of sulfuric acid [2] or copper-containing [3] or ruthenium catalysts [4].

We have now found that *N*-mono- and *N,N*-dimethylanilines can be obtained from aniline and methanol in carbon tetrachloride in the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  as catalyst. By varying the conditions, the reaction can be directed toward *N*-alkylation of aniline

to obtain either a mixture of *N*-mono- and *N,N*-dimethylanilines **I** and **II** or a mixture of compound **II** and 4,4'-methylenebis(*N,N*-dimethylaniline) (**III**). The yields and composition of the products strongly depended on the reaction time and reactant concentration (Scheme 1).

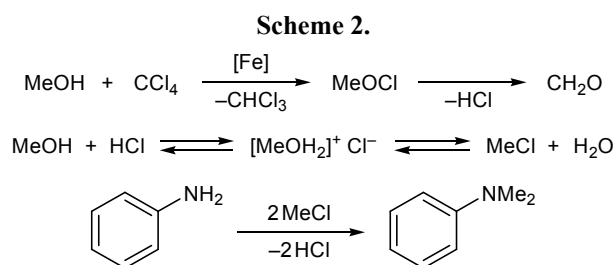
The reaction at 140°C (ratio  $\text{CCl}_4$ –MeOH 1:2) in 4 h gave approximately equal amounts of *N*-mono- and *N,N*-dimethylanilines **I** and **II**. After 8 h, *N,N*-dimethylaniline (**II**) became the major product, and the reaction mixture also contained diarylmethane **III** (yield 6%). The yield of the latter attained 45% after prolonged (16 h) heating in the presence of 4 equiv of methanol.

No *N*-alkylation of aniline with methanol occurred in the absence of carbon tetrachloride, other conditions being equal. With a view to elucidate the role of  $\text{CCl}_4$ ,

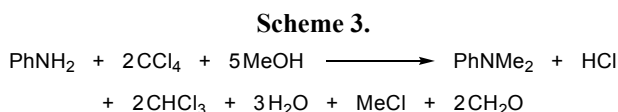


the reaction mixture was analyzed by HPLC/MS, and the presence of chloroform, methyl formate ( $m/z$  60  $[M]^+$ ), and methyl chloride (gas phase,  $m/z$  50  $[M]^+$ ) was revealed.

According to published data, *N*-alkylanilines can be prepared by reaction of aniline with alcohols using iridium and ruthenium complexes as catalysts [5]. *N,N*-Dialkylanilines were synthesized by alkylation of aniline with alkyl halides [6]. Taking into account that the products of the reaction of aniline with methanol in the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  are *N*-mono- and *N,N*-dimethylanilines **I** and **II**, we presumed that the alkylating agent in the reaction under study is methyl chloride which may be generated according to Scheme 2.



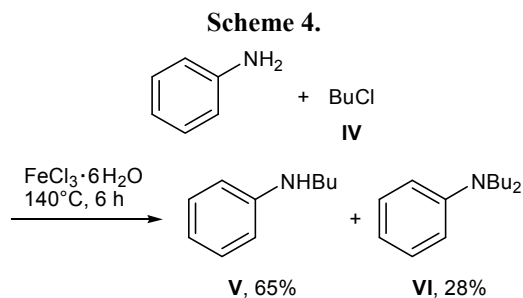
In the first step, methanol is oxidized with carbon tetrachloride under catalysis by  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  to produce formaldehyde through intermediate formation of methyl hypochlorite which decomposes into  $\text{CH}_2\text{O}$  and  $\text{HCl}$  [7]. Hydrogen chloride thus formed reacts with methanol to form methyl chloride [8]. The overall reaction may be represented by Scheme 3.



In 1 h after the reaction started, the concentration of  $\text{HCl}$  was estimated at 163 mg/ml by mercurimetric titration, while it decreased to 1–3 mg/ml by the end of the process as a result of consumption for the formation of methyl chloride which reacted with aniline.

In order to verify the possibility for alkylation of aniline with methyl chloride generated *in situ* (taking into account its high volatility), we carried out model experiments with butyl chloride (**IV**). The reaction of **IV** with aniline in the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  afforded *N*-butyl- and *N,N*-dibutylanilines **V** and **VI** in 65% and 28% yields, respectively (Scheme 4).

Interesting results were obtained in experiments utilizing a mixture of butan-1-ol and 1-chloropropane as alkylating agent ( $[\text{FeCl}_3 \cdot 6\text{H}_2\text{O}]:[\text{PhNH}_2]:[\text{CCl}_4]$ :

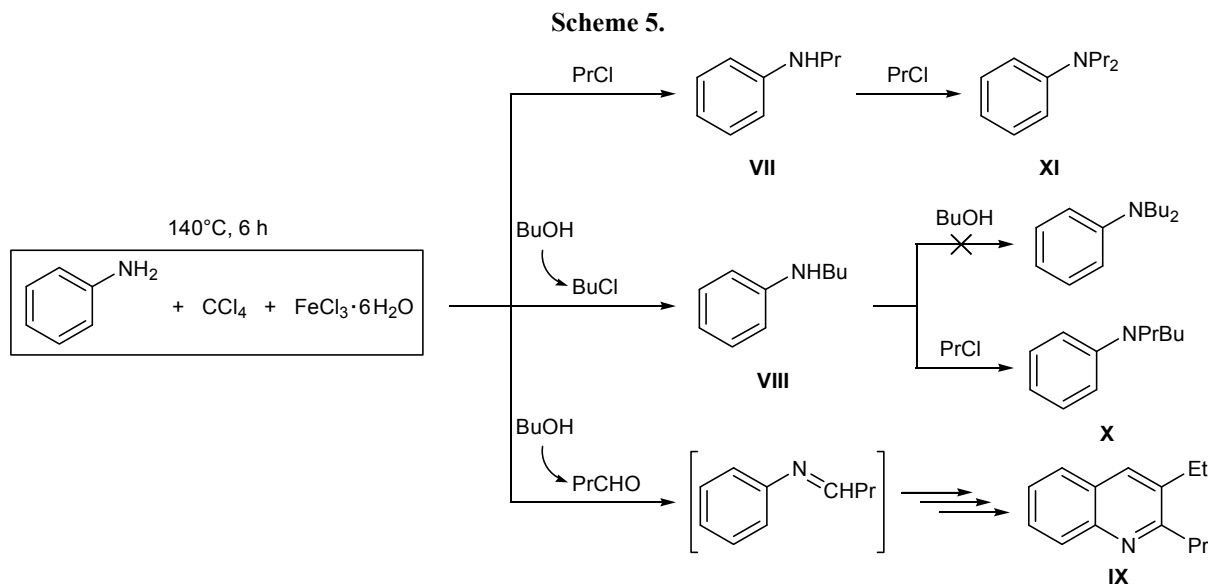


$[\text{BuOH}]:[\text{PrCl}] = 1:100:100:100$ ,  $140^\circ\text{C}$ , 6 h). According to the HPLC/MS data, the product mixture contained 52% of *N*-propylaniline (**VII**), 18% of *N*-butylaniline (**VIII**), 26% of 3-ethyl-2-propylquinoline (**IX**), 3% of *N*-butyl-*N*-propylaniline (**X**), and 1% of *N,N*-dipropylaniline (**XI**), which were identified using NIST/EPA/NIH Mass Spectral Library Version 2008 (Scheme 5). The predominant formation of *N*-propylaniline (**VII**) may be rationalized by facile alkylation of aniline with 1-chloropropane. 2,3-Disubstituted quinoline is likely to be formed via oxidation of butan-1-ol with carbon tetrachloride to butyl hypochlorite and butyraldehyde [7] and condensation of the latter with aniline to produce the corresponding Schiff base  $\text{PhN}=\text{CHPr}$  which undergoes cyclization by the action of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  [9]. These findings confirmed that methyl chloride acts as alkylating agent in the reaction of aniline with methanol.

4,4'-Methylenebis(*N,N*-dimethylaniline) (**III**) also known as Arnolds base is used as indicator in the determination of medicines, narcotics [10], and hypochlorite ions, as well as building block for the synthesis of tetraazacyclophanes and bis(tetraazacyclophanes) which are widely used in pharmaceutical chemistry [11].

Diarylmethane **III** was formed in quantitative yield in the reaction of *N,N*-dimethylaniline (**II**) with excess methanol in  $\text{CCl}_4$  in the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  ( $[\text{Fe}]:\text{MeOH}:\text{CCl}_4 = 1:400:100$ ;  $100^\circ\text{C}$ , 7 h). No reaction occurred in the absence of methanol. A known method of synthesis of compound **III** is based on the condensation of *N,N*-dimethylaniline with  $\text{CH}_2\text{O}$  in the presence of  $\text{HCl}$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{FeCl}_3$ , or  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  [12].

Presumably, in our experiments formaldehyde is also responsible for the formation of **III**. In keeping with published data, in our case generation of formaldehyde *in situ* is possible via catalytic oxidation of methanol with carbon tetrachloride through intermediate methyl hypochlorite (Scheme 2) [7]. The presence of methyl hypochlorite in the reaction mixture was confirmed by iodometric titration; the concentra-



tion of MeOCl increased in parallel with the methanol concentration (0.1 mg/ml at a  $\text{CCl}_4$ -MeOH ratio of 1:2 and 0.3 mg/ml at a  $\text{CCl}_4$ -MeOH ratio of 1:4). However, we failed to detect formaldehyde among gaseous reaction products; nevertheless, its formation was indirectly confirmed by the presence in the reaction mixture of methyl formate as product of its further oxidation.

## EXPERIMENTAL

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400.13 and 100.62 MHz, respectively, using  $\text{CDCl}_3$  as solvent; the chemical shifts were measured relative to tetramethylsilane. The mass spectra were obtained on a Shimadzu GCMS-QP2010Plus instrument (SPB-5 capillary column,  $30\text{ m} \times 0.25\text{ mm}$ ; carrier gas helium; oven temperature programming from 40 to  $300^\circ\text{C}$  at a rate of 8 deg/min; injector temperature  $280^\circ\text{C}$ ; ion source temperature  $200^\circ\text{C}$ ; electron impact, 70 eV). Chromatographic analyses were carried out on Shimadzu GC-9A and GC-2014 instruments (2-m $\times$ 3-mm column packed with 5% of SE-30 on Chromaton N-AW-HMDS; oven temperature programming from 50 to  $270^\circ\text{C}$  at a rate of 8 deg/min; carrier gas helium, flow rate 47 ml/min). Gaseous products were analyzed using a Shimadzu GCMS-QP2010Ultra instrument (Supel-Q PLOT capillary column,  $30\text{ m} \times 0.53\text{ mm}$ ; oven temperature programming from 37 to  $250^\circ\text{C}$  at a rate of 10 deg/min; carrier gas helium, flow rate 3 ml/min; ion source temperature  $200^\circ\text{C}$ ; electron impact, 70 eV).

Commercially available initial reagents were distilled prior to use. The reactions were carried out under continuous stirring in a 10-ml ampule which was placed into a 17-ml stainless steel high-pressure reactor with controlled heating.

***N*-Methylaniline (I).** An ampule was charged under argon with 1 mmol of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , 100 mmol of aniline, 100 mmol of carbon tetrachloride, and 200 mmol of methanol. The ampule was sealed and heated for 4 h at  $140^\circ\text{C}$  under continuous stirring. The ampule was cooled to room temperature and opened, the mixture was treated with 5 ml of 10% aqueous HCl, and the aqueous phase was separated, neutralized with 10% aqueous sodium hydroxide, and extracted with methylene chloride ( $3 \times 5\text{ ml}$ ). The combined extracts were filtered and evaporated, and the residue was distilled under reduced pressure. Yield 33%, light yellow oily liquid, bp  $195$ – $197^\circ\text{C}$ ,  $76$ – $77^\circ\text{C}$  (10 mm),  $n_{\text{D}}^{20} = 1.570$ ; published data [13]: bp  $196^\circ\text{C}$ ,  $n_{\text{D}}^{20} = 1.571$ .

***N,N*-Dimethylaniline (II)** was isolated in a similar way in the reaction of 100 mmol of aniline with 400 mmol of methanol in 100 mmol of carbon tetrachloride in the presence of 1 mmol  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (reaction time 8 h). Yield 92 %, yellow oily liquid, bp  $193$ – $194^\circ\text{C}$ ,  $73$ – $74^\circ\text{C}$  (10 mm),  $n_{\text{D}}^{20} = 1.555$ ; published data [13]: bp  $194^\circ\text{C}$ ,  $n_{\text{D}}^{20} = 1.557$ .

**4,4'-Methylenebis(*N,N*-dimethylaniline) (III)** was synthesized in a similar way by reaction of 100 mmol of *N,N*-dimethylaniline (II) with 100 mmol of carbon tetrachloride and 200 mmol of methanol in the presence of 1 mmol of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (reaction time 8 h). Yield 45%, mp  $89$ – $90^\circ\text{C}$ ; published data [14]: mp  $89$ –

91°C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.92 s (12H,  $\text{CH}_3$ ), 3.86 s (2H,  $\text{CH}_2$ ), 6.84 d (4H,  $m\text{-H}$ ,  $J = 8.2$  Hz), 7.11 d (4H,  $o\text{-H}$ ,  $J = 8.4$  Hz).  $^{13}\text{C}$  NMR spectrum,  $\delta_{\text{C}}$ , ppm: 38.82 ( $\text{CH}_2$ ), 40.97 ( $\text{CH}_3$ ), 113.14 ( $\text{C}^m$ ), 129.45 ( $\text{C}^o$ ), 130.42 ( $\text{C}^i$ ), 149.10 ( $\text{C}^p$ ). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 254 [ $M$ ] $^+$  (100), 253 (68), 210 (30), 134 (24), 126 (17), 118 (16).

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 12-03-00183-a).

#### REFERENCES

1. Stytsenko, V.D., Khyu, T.D., and Vinokurov, V.A., *Kinet. Katal.*, 2005, vol. 46, p. 402.
2. Lebedev, N.N., *Khimiya i tekhnologiya osnovnogo organicheskogo i neftekhimicheskogo sinteza* (Chemistry and Technology of Large-Scale Organic and Petrochemical Synthesis), Moscow: Khimiya, 1975.
3. Golovachev, V.A. and Dogadaev, V.N., Russian Patent no. 2270187, 2004; Mitin, N.A., Slepov, S.K., Merzlyakova, N.V., and Utrobin, A.N., Russian Patent no. 2232749, 2002.
4. Watanabe, Y., Tsuji, Y., Ige, H., Ohsugi, Y., and Ohta, T., *J. Org. Chem.*, 1984, vol. 49, p. 3359; Huh, K.-T., Tsuji, Y., Kobayashi, M., Okuda, F., and Watanabe, Y., *Chem. Lett.*, 1988, vol. 17, p. 449.
5. Naskar, S. and Bhattacharjee, M., *Tetrahedron Lett.*, 2007, vol. 48, p. 3367; Fujita, K., Li, Z., Ozeki, N., and Yamaguchi, R., *Tetrahedron Lett.*, 2003, vol. 44, p. 2687; Watanabe, Y., Morisaki, Y., Kondo, T., and Mitsudo, T., *J. Org. Chem.*, 1996, vol. 61, p. 4214.
6. Mohri, K., Suzuki, K., Usui, M., Isobe, K., and Tsuda, Y., *Chem. Pharm. Bull.*, 1995, vol. 43, p. 159; Hayat, S., Rahman, A., Choudhary, M.I., Khan, K.M., Schumann, W., and Bayer, E., *Tetrahedron*, 2001, vol. 57, p. 9951; Dehmlow, E.V. and Thieser, R., *Tetrahedron Lett.*, 1985, vol. 26, p. 297; Saikia, G. and Iyer, P., *J. Org. Chem.*, 2010, vol. 75, p. 2714.
7. Khusnutdinov, R.I., Shchadneva, N.A., Bayguzina, A.R., Mukminov, R.R., Mayakova, Yu.Yu., Smirnov, A.A., and Dzhemilev, U.M., *Neftekhimiya*, 2008, vol. 48, p. 467.
8. Rozanov, V.N. and Treger, Yu.A., *Kinet. Katal.*, 2011, vol. 52, p. 670.
9. Khusnutdinov, R.I., Bayguzina, A.R., Aminov, R.I., and Dzhemilev, U.M., *Russ. J. Org. Chem.*, 2012, vol. 48, p. 690; Khusnutdinov, R.I., Bayguzina, A.R., and Aminov, R.I., *Izv. Akad. Nauk, Ser. Khim.*, 2013, p. 134.
10. Volf, K. and Pitr, K., *Soud. Lek.*, 1992, vol. 37, p. 62.
11. Lai, C.-F., Odashima, K., and Koga, K., *Chem. Pharm. Bull.*, 1989, vol. 37, p. 2351.
12. Carr, R.H., US Patent no. 7943724, 2011; Li, Z.X., Duan, Z., and Wu, Y.J., *Chin. Chem. Lett.*, 2009, vol. 20, p. 511.
13. Rabinovich, V.A. and Khavin, Z.Ya., *Kratkii khimicheskii spravochnik* (Brief Chemical Handbook), St. Petersburg: Khimiya, 1994, pp. 159, 178.
14. Matsubara, Y., Matsuda, T., Kato, A., Kakedai, Y., and Yamaguchi, Y., *Synth. Commun.*, 2003, vol. 33, p. 1885.