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Electroorganic synthesis of benzathine

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Abstract—Benzathine is prepared in good yields from cyanobenzene by a combination of electrochemical hydrogenation and Kolbe electrolysis using nickel and platinum electrodes in the presence of methanolic sodium methoxide in an undivided cell.

A benzathine salt of penicillin is used in the treatment of viral diseases like syphilis and rheumatic fever.[1–3] In the literature, chemists have synthesized benzathine by a catalytic hydrogenation of N,N^1-dibenzylethylene diamine, by reaction of a benzyl halide and ethylene diamine in the presence of an aqueous solution of caustic soda and also by reacting benzylamine with 1,2-dichloroethane.[4–8] These reactions mostly involve the use of an external supply of hydrogen gas at very high pressure and are thus not recommended because of the possibilities of explosion and fire. The use of noble metal catalysts and the formation of undesirable by-products such as mono-, tri- and tetra-benzylethylenediamines were also major disadvantages of these methods. In view of green chemistry and the developing interest of chemists in electroorganic chemistry, we attempted the synthesis of benzathine by electrochemical methods. Electrochemical hydrogenation and Kolbe electrolysis are used for the synthesis of many organic compounds.[9–14] Schafer and co-workers have published several reviews and papers on Kolbe electrolysis.[15–18]

The advantages of Kolbe electrolysis compared with non-electrochemical radical reactions[19] are the use of simple reaction conditions: a simple undivided cell can be used, methanolic sodium methoxide serves in most cases as the solvent/supporting electrolyte, electrode potential need not be controlled, the cost of the electricity is low, scale-up is comparatively easy, which also makes the reaction attractive for technical use and the starting compounds, carboxylic acids, are readily available in a wide structural variety.

Here, we report a new method for the synthesis of benzathine from the simple molecule cyanobenzene, which involves the combination of electrochemical hydrogenation and Kolbe electrolysis.

Earlier, our group reported the synthesis of amino sulfonamides from cyano sulfonamides by electrochemical hydrogenation involving a nickel cathode and a platinum anode in methanol–sodium methoxide with freshly prepared Raney nickel as catalyst in an undivided cell.[20] Thus benzylamine **2** could be prepared by electrochemical hydrogenation of cyanobenzene **1** in good yield (Scheme 1).[21] The benzylamine was treated with a bromo-ester at room temperature to afford ethyl (benzylamine)acetate **3**, which was refluxed in benzene with benzoyl chloride for 30 min to afford benzoyl protected ethyl-*N*-[benzoyl(benzyl)amino]acetate **4**. Hydrolysis of **4** with 4 N sodium hydroxide yielded the protected acid **5**. Compound **5** on Kolbe electrolysis in an undivided cell, equipped with platinum electrodes in methanol–sodium methoxide by passing 250 mA/cm^2 of electricity until the pH of electrolyte changed to 8, afforded N,N'-dibenzoyl-N,N'-dibenzylethylene diamine **6** along with 9% of the disproportionation product **7**. Finally, **6** on acid hydrolysis afforded benzathine **8** in good yield.

The mechanism of nitrile electroreduction as outlined in Scheme 2 involves in situ electrochemical generation

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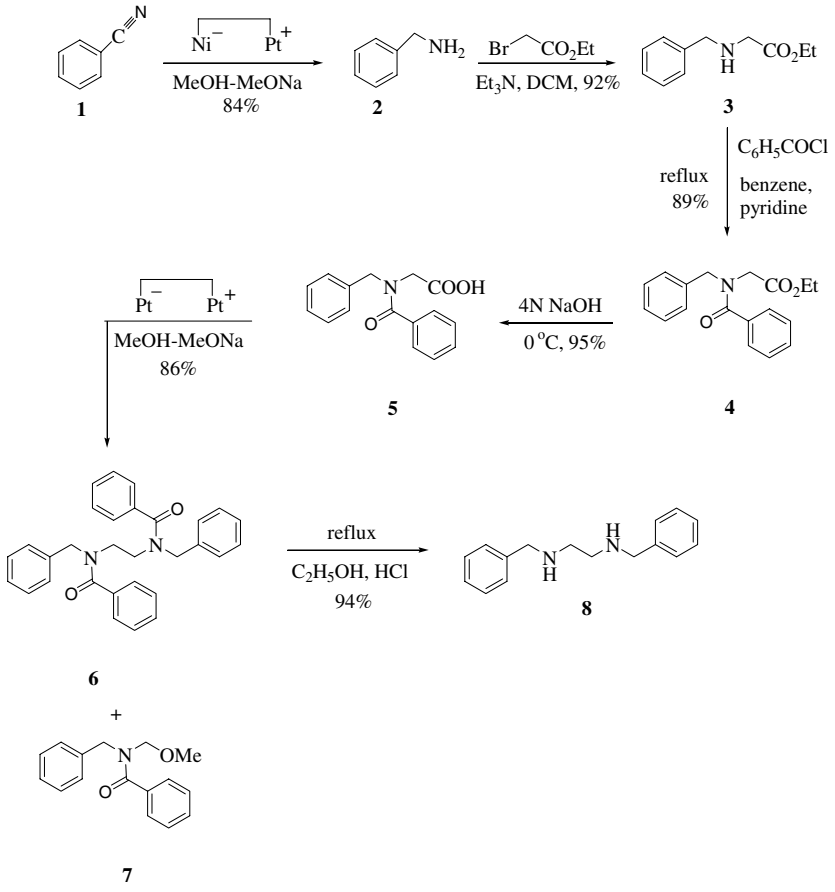
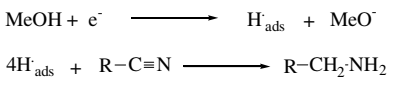


Scheme 1.



Scheme 2.

of hydrogen. The hydrogen ion formed from methanol takes one electron resulting in atomic hydrogen (H·) which is adsorbed on the Raney nickel catalyst, thus no evolution of hydrogen was observed. Finally, the addition of adsorbed atomic hydrogen ($H^{\cdot}_{ads}$) to the nitrile group results in formation of the desired amine.

Tables 1 and 2 show the variation of product yields due to the changes in the reaction temperature and current densities. The conditions which favour the formation of good yields of the product were high temperature and low current density. The reactions at the cathode mainly include hydrogenation and hydrogen evolution, which alters the product yield. The results suggest that elevated temperatures accelerate the reaction of adsorbed hydrogen with the substrate to a greater extent than the adsorbed atomic hydrogen to hydrogen gas reaction. Since the increase of current density increases hydrogen evolution, low current densities are favourable for electrochemical hydrogenation. The improved product yield is again the result of competition between the two reactions.

Compounds having electron-donating groups such as NH_2 α to the carboxylic acid cannot be subjected to radical coupling by Kolbe electrolysis as further oxidation of the intermediate radical predominates due to carbocation stabilization by the amino group. Compounds with remote amino groups (β or ω-position) can be coupled, however, it is appropriate to protect the amino group.[22]

For Kolbe electrolysis, high current densities are needed for the generation of high radical concentrations, which

Table 1. Electrochemical synthesis of benzylamine[a]

Entry	Temperature (°C)	Isolated yield (%) of **2**
1	5	61
2	15	70
3	25	77
4	35	84
5	45	87

[a] Current density is 10 mA/cm^2.

Table 2. Effect of current density on the synthesis of benzylamine[a]

Entry	Current density (mA/cm^2)	Isolated yield (%) of **2**
1	10	77
2	25	73
3	50	66

[a] Temperature is 25 °C.

favour radical coupling. This also leads to fast conversion and a very positive anode potential that promote oxidation of the negatively charged carboxylate and disfavours oxidation of the neutral solvent methanol. Oxidation of carboxylic anion, formation of an alkyl radical and coupling of the two radicals results in the formation of Kolbe dimer **6** from benzoyl-protected adduct [benzoyl(benzyl)amino]acetic acid **5** and in addition to **6**, the disproportionation product *N*-benzyl-*N*-(methoxymethyl)benzamide **7** was formed in 9% by the oxidation of the radical to a carbocation.

In conclusion, benzathine can be prepared via a combination of electrochemical hydrogenation and Kolbe electrolysis in good yields. Electrochemical hydrogenation involves in situ generation of hydrogen, which does not involve high pressure generating equipments. Compounds having electron-donating groups β to a carboxylic group can be successively subjected to Kolbe electrolysis by protection with benzoyl chloride. This electrolysis procedure is an alternative route for the synthesis of benzathine from the simple molecule cyanobenzene and has great potential in green chemistry.

References and notes

1. Fletcher, A. P.; Knappett, C. R. *Br. Med. J.* **1953**, *1*, 188–189.
2. Saxena, A. *Curr. Treat. Options Cardiovasc. Med.* **2002**, *4*, 309–319.
3. Rieder, G.; Rusizoka, M.; Todd, J.; Maboko, L.; Hoelscher, M.; Mmkando, D.; Samky, E.; Lyamuya, E.; Makey, D.; Grosskurth, H.; Hoyes, R. *N. Engl. J. Med.* **2005**, *353*, 1236–1244.
4. Rebenstorf, M. A.; Mich, K. US Patent 2,773,098, 1956; *Chem. Abstr. 51*, P14802d.
5. Jones, W. G. M. GB Patent 762,992, 1956; *Chem. Abstr. 51*, 16534g.
6. Lehmann, B. DE Patent 19,604,102, 1997; *Chem. Abstr. 127*, 135631t.
7. Jones, W. G. M. GB Patent 762,991, 1956, *Chem. Abstr. 51*, 17991d.
8. Ivanovna, A. T.; Nikokevich, D. E.; Evgenevich, D. D.; Evgenevich, E. N. RU Patent 2,237,653, 2004; *Chem. Abstr. 141*, 333941w.
9. Chiba, T.; Okimoto, M.; Nagai, H.; Takuta, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 719–723.
10. Dandge, C. N.; Naik, D. G.; Kapadi, A. H. *Ind. J. Chem.* **1988**, *27*, 854–855.
11. Kubota, T.; Ishii, T.; Minamikawa, H.; Yamaguhi, S.; Tanaka, T. *Chem. Lett.* **1988**, 1987–1990.
12. Sugiya, M.; Nohira, H. *Chem. Lett.* **1998**, 479–480.
13. Bonner, W. A.; Mango, F. D. *J. Org. Chem.* **1964**, *29*, 430–435.
14. Matzeit, A.; Schafer, H. J.; Amatore, C. *Synthesis* **1995**, 1432–1442.
15. Klunenberg, H.; Schafer, H. J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 47–48.
16. Harenbrock, M.; Matzeit, A.; Schafer, H. J. *Liebigs Ann.* **1996**, 55–62.
17. Idelmann, A. W.; Aus dem Kahmen, M.; Schafer, H. J. *Acta Chem. Scand.* **1998**, *52*, 672–682.
18. Goular, M. O. F.; Schafer, H. J. *J. Braz. Chem. Soc.* **1999**, *10*, 153–162.
19. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; pp 36–140.
20. Lateef, S. K.; Krishnamohan, S.; Rameshraju, R.; Jayaramareddy, S. *Helv. Chim. Acta* **2006**, *89*, 1254–1257.
21. *Electrochemical hydrogenation of cyanobenzene*: Electrochemical hydrogenation was carried out in an undivided cell containing a Ni cathode (2×2 cm^2) and a Pt anode (2×2 cm^2) by dissolving 1.03 g (0.01 mol) cyanobenzene **1** in 40 ml of methanol and 0.1 mol of sodium methoxide. To this, 1.0 g of freshly prepared Raney nickel[23] was added and dissolved oxygen was removed by passing N_2 gas through the solution for about 10–15 min. Then, the solution was subjected to electrolysis at a constant current density of 10 mA/cm^2 and at 35 °C temperature until 4 F/mol of electricity had been passed. Next, the solution was transferred to a round-bottomed flask and the solvent was evaporated. The residue was treated with 10% HCl and the aqueous layer was washed with ether. The aqueous solution was made strongly alkaline with sodium hydroxide, extracted with ether (25 ml × 3), dried over Na_2SO_4 and evaporated under reduced pressure to give benzylamine **2** (yield 84%) as a colourless liquid, bp 186–187 °C (lit.[24] 185 °C).
Synthesis of ethyl(benzylamino)acetate (**3**) *from benzyl amine* (**2**): 1.07 g (0.01 mol) of **2** was taken in a round-bottomed flask along with 5 ml of DCM and 2.81 ml of triethylamine. To this mixture, ethyl bromoacetate (1.67 g, 0.01 mol) was added dropwise at room temperature with constant stirring for about 2 h. The solvent was evaporated under vacuum and to this 25 ml of water was added and the aqueous layer was extracted with ether, and the combined organics were dried over sodium sulfate, evaporated and purified by column chromatography (silica gel 60–120 mesh, hexane:ethyl acetate 3:1) to afford compound **3** (yield 92%) as a yellowish liquid, bp 142–143 °C (10 mm Hg) (lit.[25] 140–142 °C at 10 mm Hg).
Synthesis of [benzoyl(benzyl)amino]acetic acid (**5**): To a solution of 1.93 g (0.01 mol) of **3** in 10 ml of dry pyridine and 20 ml of dry benzene (CAUTION: The reaction must be carried out in a well-ventilated fume cupboard and protective gloves should be worn), 1.4 g (0.01 mol) of benzoyl chloride was added dropwise. The mixture was refluxed at 60–70 °C for about 30 min and then poured into 100 ml of water. The benzene layer was separated and the aqueous layer was extracted with benzene (3×10 ml). The combined benzene layers were washed with 5% sodium carbonate solution (15 ml) followed by 10 ml of water and then dried over Na_2SO_4. The benzene layer was removed under vacuum to give ethyl-*N*-[benzoyl(benzyl)-amino]acetate **4** (yield 89%). Compound **4** thus obtained was dissolved in 5 ml of methanol. To this, 4 ml of 4 N NaOH was added at 0 °C and the mixture stirred for 1 h. Methanol was removed under reduced pressure, the solution was acidified with 1 N HCl and then extracted with ethyl acetate, which on removal under vacuum gave compound **5** (yield 95%).
Data for (**4**): pale yellow powder, mp 172–175 °C. IR (KBr): $\nu = 1679, 1746$ cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.26$ (t, 3H, CH_3), 3.50 (s, 2H, Ar–CH_2), 3.84, (s, 2H, –CH_2–CO), 4.16 (m, 2H, –CH_2–CH_3), 7.05–7.62 (m, 10H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 12.91$ (CH_2–CH_3), 51.43 (N–CH_2), 57.69 (Ph–CH_2), 58.33 (CH_2–CH_3), 126.44, 126.91, 127.87, 128.78, 129.45, 131.24, 138.62 (aromatic carbons), 168.36 (Ph–CO), 172.46 (COO). Anal. Calcd for $C_{18}H_{19}NO_3$ (297.34): C, 72.71; H, 6.44. Found: C, 72.69; H, 6.48.
[Benzoyl(benzyl)amino]acetic acid (**5**): colourless powder, mp 258–260 °C. IR (KBr): $\nu = 1689, 1746, 3297$ cm^{-1}. ^{1}H

NMR (300 MHz, $CDCl_3$) $\delta = 4.02$ (s, 2H, N–CH_2–CO), 4.39 (s, 2H, Ph–CH_2–N), 7.04–7.88 (m, 10H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 51.84$ (N–CH_2), 56.91 (Ph–CH_2), 126.14, 126.72, 127.47, 128.56, 129.71, 130.94, 137.11 (aromatic carbons), 168.74 (Ph–CO), 174.93 (COOH). Anal. Calcd For $C_{16}H_{15}NO_3$ (269.30): C, 71.36; H, 5.61. Found: C, 71.40; H, 5.69.

Kolbe electrolysis: Compound **5** (1.35 g (0.005 mol)) was added to an undivided electrolytic cell containing 40 ml methanol equipped with platinum electrodes (2×2 cm^2). The pH was adjusted to slightly alkaline with sodium methoxide and dissolved oxygen was removed by passing N_2 gas through the solution for 10–15 min. The solution was then subjected to electrolysis at 35–40 °C at a constant current density of 250 mA/cm^2 until the pH of the electrolyte had changed to 8. The solution was transferred to a round-bottomed flask and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and transferred to a separating funnel. The organic phase was washed with 10% HCl solution, then saturated sodium bicarbonate (2×25 ml) and brine (2×25 ml). The organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated to give a mixture of *N*,*N*′-dibenzoyl-*N*,*N*′-dibenzylethylenediamine (**6**) (yield 86%) and *N*-benzyl-*N*-(methoxymethyl)benzamide (**7**) (yield 9%), which was purified by column chromatography (silica gel 60–120 mesh, hexane:ethyl acetate 9:1).

Data for (**6**): colourless powder, mp 313–315 °C. IR (KBr): $\nu = 1695$ cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 3.62$ (s, 4H, N–CH_2–), 4.39 (s, 4H, Ph–CH_2–N), 7.01–7.82 (m, 20H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 44.44$ (N–CH_2), 51.92 (Ph–CH_2), 126.35, 126.64, 127.41, 128.39, 129.73, 130.71, 131.46, 136.55 (aromatic carbons), 165.79 (Ph–CO). Anal. Calcd for $C_{30}H_{28}N_2O_2$ (448.56) C, 80.33; H, 6.29. Found: C, 80.30; H, 6.33.

N-benzyl-N-(methoxymethyl)benzamide (**7**): colourless powder, mp 132–135 °C. IR (KBr): $\nu = 1691$ cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 3.58$ (s, 3H, CH_3), 4.32 (s, 2H, Ar–CH_2), 4.96 (s, 2H, CH_2–O–), 7.08–7.58 (m, 10 H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 52.66$ (Ph–CH_3), 52.95 (O–CH_3), 81.26 (N–CH_2), 126.24, 127.12, 128.94, 129.45, 130.11, 131.36, 137.21 (aromatic carbons), 169.45 (Ph–CO). Anal. Calcd for $C_{16}H_{17}NO_2$ (255.32) C,75.27; H, 6.71. Found: C, 75.30; H, 6.65.

Hydrolysis of **6**, *for the synthesis of benzathine* (**8**): Compound **6** (2.24 g (0.005 mol)) was dissolved in 12 ml of ethanol in a 50 ml round-bottomed flask. To this, 4 ml of concentrated HCl was added dropwise and the mixture refluxed for about 40 min and then diluted with 30 ml of water. The reaction mixture was poured into 50 ml of ice water, to this 5% aqueous sodium hydroxide solution was added with vigorous stirring until the solution became slightly alkaline. The mixture was extracted with ether and the organics were dried over Na_2SO_4 and purified by column chromatography (hexane:ethyl acetate 3:1) (yield 94%) pale yellow oily liquid, bp 214–215 °C (12 mm Hg) (lit.[26] 212–213 °C at 12 mm Hg). IR (KBr): $\nu = 3345$ cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 2.62$ (s, 4H, N–CH_2–), 3.75 (s, 4H, Ph–CH_2–N), 4.65 (br s, 2H, NH), 7.18–7.57 (m, 10H, Ar–H). Anal. Calcd for $C_{16}H_{20}N_2$ (240.34) C, 79.96; H, 8.39. Found: C, 79.99; H, 8.36.

22. Haufe, J.; Beck, F. *Chem. Ing. Technol.* **1970**, *42*, 170–172.
23. Mozingo, R. *Org. Synth. Coll.* **1955**, *III*, 181–183.
24. Egli, R. A. *Helv. Chim. Acta* **1970**, *53*, 47–53.
25. Page, B. C. P.; Leach, C. D.; Hayman, M. C.; Hamzah, S. A.; Allin, M. S.; Mckee, V. *Synlett* **2003**, *7*, 1025–1027.
26. Foster, A. E.; Chaberek, S.; Martell, A. E. *J. Am. Chem. Soc.* **1949**, *71*, 3842–3843.