

138. Minoru Sekiya and Keiichi Ito : Reaction of Amide
Homologs. XIV.*¹ N-Monomethylation of
Aromatic Primary Amines.

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In the preceding paper¹⁾ we established that catalytic hydrogenolysis of N-amidomethyl compounds, generally called N-Mannich base, suffers reductive fission at methylene carbon bond connecting to amido nitrogen, affording amide and N-methylated amine in excellent yield. With understanding ease of the preparation of the N-amidomethyl compound from amine, amide, and formaldehyde, this hydrogenolysis has introduced an useful way for N-methylation of amines.

Among the N-methylations of a variety of amines, the N-monomethylation of aromatic primary amine by a convenient, general procedure has long been of interest. We reported in the preceding paper¹⁾ that N-monomethylation of aniline was only performed successfully through the hydrogenolysis of N-(anilinomethyl)phthalimide or -succinimide. As N-amidomethyl compound attached to aromatic primary amine generally forms only as phthalimido and succinimido analogs, in the present paper, we report an extension of the hydrogenolysis of the former analogs to a variety of aromatic primary amines with the modification available for practical purpose and the procedure was proved to be quite versatile for general application.

The modification was made in the way that, without isolation of the N-phthalimidomethyl compound, a solution of aromatic primary amine, phthalimide, and formaldehyde dissolved in ethyl alcohol was preheated and directly subjected to catalytic hydrogenation, for ease of the formation of N-phthalimidomethyl compound was recognized in every case by the test of isolation of the compound from the preheated solution by crystallization or concentration. The general method in brief is in the following. An equimolar mixture of three starting materials dissolved in ethyl alcohol was refluxed for 20 min. and then the whole was hydrogenated over Raney nickel catalyst under high hydrogen pressure at elevated temperature.

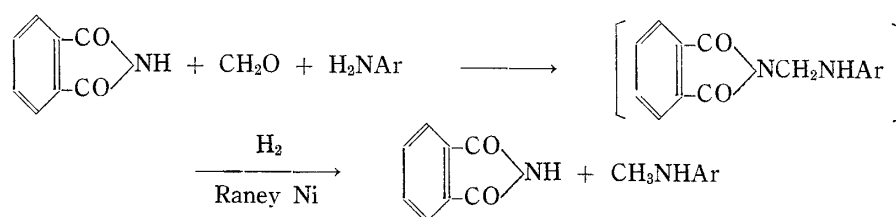


Table I shows the results with a variety of aromatic primary amines indicating excellent yields of the N-methylated amine products in all runs. Good recovery of phthalimide was also shown in every case. As shown in run 8, monomethylations of both amino groups of *p*-phenylenediamine was successfully performed in the same time by this method. Only the procedures for the run 1 and 4 are a bit different from the others. As the starting materials were used *p*-nitro-N,N-dimethylaniline and *p*-nitrophenol respectively, which were prerduced in ethyl alcohol with Raney nickel catalyst under high hydrogen pressure to the corresponding primary amine and then followed

*¹ Part XIII : This Bulletin, 14, 996 (1966).

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1) M. Sekiya, K. Ito : This Bulletin, 14, 996 (1966).

TABLE I. N-Monomethylation of Aromatic Primary Amine

Run	Starting aromatic compound	N-Phthalimido-methyl compound m.p. (°C) ^{b)}	Hydrogenolysis		Product	Yield (%) ^{d)}
			temp. (°C)	time (hr.)		
1	<i>p</i> -(CH ₃) ₂ NC ₆ H ₄ NO ₂ ^{a)}	133~134 ^{a)}	80~85	2.5	<i>p</i> -(CH ₃) ₂ NC ₆ H ₄ NHCH ₃	85
2	<i>p</i> -CH ₃ OC ₆ H ₄ NH ₂	144~145 ²⁾	80~85	1.0	<i>p</i> -CH ₃ OC ₆ H ₄ NHCH ₃	90
3	<i>o</i> -CH ₃ OC ₆ H ₄ NH ₂	112~113 ²⁾	80~85	1.5	<i>o</i> -CH ₃ OC ₆ H ₄ NHCH ₃	91
4	<i>p</i> -HOC ₆ H ₄ NO ₂ ^{a)}	159~160 ³⁾	70~80	1.5	<i>p</i> -HOC ₆ H ₄ NHCH ₃	89
5	<i>p</i> -CH ₃ C ₆ H ₄ NH ₂	174~175 ²⁾	100~105	1.5	<i>p</i> -CH ₃ C ₆ H ₄ NHCH ₃	92
6	<i>o</i> -CH ₃ C ₆ H ₄ NH ₂	137~138 ²⁾	95~100	1.5	<i>o</i> -CH ₃ C ₆ H ₄ NHCH ₃	96
7	C ₆ H ₅ NH ₂	144~145 ²⁾	80~85	3.0	C ₆ H ₅ NHCH ₃	96
8	<i>p</i> -H ₂ NC ₆ H ₄ NH ₂	245~247 (d.) ³⁾	90~95	3.0	<i>p</i> -CH ₃ NHC ₆ H ₄ NHCH ₃	95
9	<i>p</i> -C ₂ H ₅ OCOC ₆ H ₄ NH ₂	176~177 ²⁾	110~120	3.5	<i>p</i> -C ₂ H ₅ OCOC ₆ H ₄ NHCH ₃	92
10	<i>p</i> -HOCOC ₆ H ₄ NH ₂	230~232 (d.) ²⁾	115~125	1.5	<i>p</i> -HOCOC ₆ H ₄ NHCH ₃	84

a) This starting nitro-compound was prereduced to amino-compound by catalytic hydrogenation and the hydrogenation mixture was directly processed as in the other runs.

b) Melting point of the intermediate, N-phthalimidomethyl compound, obtained in a pretest.

c) A new compound, prism from EtOH. Anal. Calcd. for C₁₇H₁₇O₂N₃: C, 69.13; H, 5.80; N, 14.23. Found: C, 68.82; H, 5.79; N, 14.22.

d) Based on product isolation.

by the foregoing general procedure in the same autoclave only by addition of phthalimide and formaldehyde.

We reported in the previous detailed paper¹⁾ that the hydrogenolytic reactivity of N-amidomethyl compound with respect to the amine residue increases in the rising order of the electron density of its amine nitrogen. Consistently with this rationale, the same nature is also qualitatively observed in Table I by comparison of the hydrogenolysis temperatures and times required of the materials. That is, the hydrogenolysis is more facilitated with increase of the basicity of the starting aromatic amine.

The reliability of the method can be said to depend on the successful formation of N-(arylaminoethyl)phthalimide in the first step of the procedure. In view of some experiments the formation appeared to be restrained with the aromatic amine possessing very weak basicity.

In summary, the hydrogenation method is convenient for N-monomethylation of rather basic aromatic amine with certain advantages: excellent yields are obtainable with good recovery of phthalimide; product isolation is simple; and the reagents are readily available.

Experimental

Hydrogenation Procedure—In all the runs except 1 and 4 in Table I, each 0.05 mole of aromatic primary amine, CH₂O as 37% aqueous solution, and phthalimide was added to 90 ml. of EtOH and the whole was refluxed for 20 min. whereupon the formation of N-(arylaminoethyl)phthalimide proceeded (In each run the compound was crystallized in the solution on cool. In a preliminary experiment, the crystals were collected and checked to be the corresponding N-(arylaminoethyl)phthalimide by comparison of the melting point with that reported in the literature^{2,3)} or by elementary analyses.). The whole mixture was transferred into an autoclave with a capacity of 175 ml. and Raney nickel catalyst prepared from 1 g. of 50% alloy was added. Under 80 kg./cm² (at room temperature) the whole was heated and constant shaking was started at the desired temperature interval and continued for further 30 min. after drop of hydrogen pressure was nearly ceased (the period up to this time is written as the hydrogenolysis time in Table I).

2) M. B. Winstead, H. W. Heine: J. Am. Chem. Soc., **77**, 1913 (1955).

3) H. W. Heine, M. B. Winstead, R. P. Blairs: *Ibid.*, **78**, 672 (1956).

Procedure for run 1 and 4, in which nitro-compound was used as starting material, was different from that described above. In the autoclave a solution of 0.05 mole of the nitro-compound dissolved in 90 ml. of EtOH was hydrogenated at 80° over Raney nickel catalyst, prepared from 1 g. of 50% alloy, under high hydrogen pressure (initial hydrogen pressure: 100 kg./cm² at room temperature). Uptake of hydrogen was ceased after 20~30 min. On cool, each 0.05 mole of 37% CH₂O and phthalimide was added to the hydrogenation mixture and then the whole was processed by nearly the same procedure as described in the foregoing.

Product Isolation—In the cooled hydrogenation mixture most of the phthalimide was crystallized, which was filtered together with the catalyst and isolated from the mixture by extraction with hot EtOH. The filtrate was treated as in the following.

In run 2, 3, 5, 6, 7, and 9, in which N-methylated amine products were volatile, the solution was concentrated under reduced pressure and the residue was extracted with ether, when a small amount of phthalimide remained undissolved. After removal of ether from the ethereal solution, distillation of the residue under reduced pressure gave the N-methylated amine product.

In run 1, 4, 8, and 10, in which the products were sensitive in the air or not volatile, the solution was acidified with a slight excess of *N* HCl (run 1, 8, and 10) or *N* H₂SO₄ (run 4) and then concentrated to dryness under reduced pressure. To the residue an adequate amount of H₂O was added and undissolved phthalimide was filtered off. Concentration of the aqueous solution under reduced pressure gave the hydrochloride or the sulfate of the N-methylated amine product.

The followings are the identifications of the amine products.

N,N,N'-Trimethyl-*p*-phenylenediamine—Dihydrochloride: plate from EtOH, m.p. 218~219° (decomp.). *Anal.* Calcd. for C₉H₁₆N₂Cl₂: C, 48.44; H, 7.23; N, 13.79. Found: C, 48.01; H, 7.20; N, 13.63.

N-Methyl-*p*-anisidine—B.p.₁₅ 118~121°, *n*_D¹⁷ 1.5612. Hydrochloride: needle from EtOH, m.p. 119~120°. *Anal.* Calcd. for C₈H₁₂ONCl: C, 55.34; H, 6.97; N, 8.07. Found: C, 55.11; H, 7.18; N, 8.25.

N-Methyl-*o*-anisidine—B.p.₂₀ 122~125°, *n*_D¹⁷ 1.5591. Hydrochloride: prism from EtOH, m.p. 111~112°. *Anal.* Calcd. for C₈H₁₂ONCl: C, 55.34; H, 6.97; N, 8.07. Found: C, 55.56; H, 6.92; N, 7.96.

***p*-Methylaminophenol**—Sulfate: prism from EtOH, m.p. 254~256° (decomp.). *Anal.* Calcd. for C₁₄H₂₀O₈N₂S: C, 48.82; H, 5.85; N, 8.14. Found: C, 48.67; H, 5.86; N, 7.97.

N-Methyl-*p*-toluidine—B.p.₂₄ 111~113°, *n*_D¹⁶ 1.5563. Hydrochloride: leaves from EtOH, m.p. 115~116°. *Anal.* Calcd. for C₈H₁₂NCl: C, 60.94; H, 7.67; N, 8.89. Found: C, 60.89; H, 7.99; N, 8.87.

N-Methyl-*o*-toluidine—B.p.₃₁ 102~104°, *n*_D¹⁵ 1.5655. Hydrochloride: prism from EtOH, m.p. 109~111°. *Anal.* Calcd. for C₈H₁₂NCl: C, 60.94; H, 7.67; N, 8.89. Found: C, 61.12; H, 7.58; N, 9.01.

N-Methylaniline—B.p.₂₁ 91~94°, *n*_D¹⁵ 1.5729. Hydrochloride: needle from EtOH, m.p. 121~122°. *Anal.* Calcd. for C₇H₁₀NCl: C, 58.54; H, 7.02; N, 9.76. Found: C, 58.59; H, 6.97; N, 9.81.

N,N'-Dimethyl-*p*-phenylenediamine—Dihydrochloride: plate from EtOH, m.p. 226~227° (decomp.). *Anal.* Calcd. for C₈H₁₄N₂Cl₂: C, 45.95; H, 6.75; N, 13.40. Found: C, 45.88; H, 6.81; N, 13.42.

Ethyl *p*-Methylaminobenzoate—Prism from petr. ether, m.p. 65~67°. *Anal.* Calcd. for C₁₀H₁₃O₂N: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.61; H, 6.97; N, 8.05.

***p*-Methylaminobenzoic Acid**—Needle from benzene, m.p. 155~157°. *Anal.* Calcd. for C₈H₉O₂N: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.56; H, 5.86; N, 9.41.

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Summary

N-Monomethylation of a variety of aromatic primary amines was successfully carried out through the hydrogenolysis of N-(arylaminoethyl)phthalimides. The method was quite general for rather basic aromatic primary amines, leading to good yield of the N-monomethylated amines.

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