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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Improvement of the Synthesis of 6-Bromo-5-methylimidazo[4,5-*b*]pyridine, a Stabilizer for Color Photography

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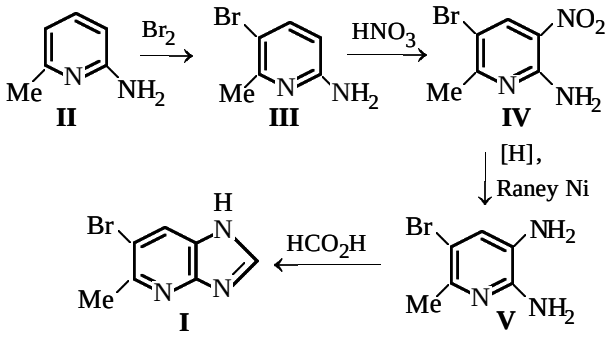
Abstract—Procedures were suggested for preparing 6-bromo-5-methylimidazo[4,5-*b*]pyridine, a stabilizer for TsMF-2 color photographic moment, a component of developing pastes of the photographic kit.

Imidazo[4,5-*b*]pyridine derivatives exhibit unique antifogging properties among color photographic materials [1–8]. A particular mention should be made of 6-bromo-5-methylimidazo[4,5-*b*]pyridine **I**, which is simultaneously a stabilizer of a photographic layer and a component of developing pastes of the Polaroid color photographic kit; it provides high quality of a photographic image.

Data on the synthesis of **I** are available from two patent [1, 2]. The suggested four-step procedure involves bromination of 2-amino-6-methylpyridine **II**, nitration of the resulting 2-amino-5-bromo-6-methylpyridine **III**, reduction of 2-amino-3-nitro-6-methylpyridine **IV** to diamine **V**, and its subsequent cyclization into **I**. According to [1, 9], bromo derivative **III** is prepared by bromination of **II** with bromine in 20% sulfuric acid. An experimental check of the procedures from [1, 9] shows that the yield of **III** after purification is as low as 50–55%. It is known that amino and hydroxy derivatives of nitrogen heterocycles are smoothly halogenated in aqueous solutions or in glacial acetic acid [10, 11]:



Attempted bromination of **II** with an equivalent amount or small excess of bromine in aqueous solution at 20–70°C results in low yields of the reaction product. Bromination of **II** in glacial acetic acid at room temperature gives the product in almost quantitative yield. To bind HBr that is released in the reaction and may prevent the bromination of **II**, an equivalent amount of sodium acetate was added to the reaction mixture. The melting point of the resulting bromopyridine **III**, 73–74°C, somewhat differs from the value reported in the literature (70–71°C [1]).

A GLC analysis of this product revealed the presence of two impurities (10 wt %) along with the main substance **III**. The first impurity was unchanged substrate **II**, and the second, 2-amino-3,5-dibromo-6-methylpyridine **VI**, identified by comparison with an authentic smaple specially prepared by bromination of **II** under the conditions described in [9]. When the bromination of **II** was performed at 10–15°C, the content of unchanged **II** decreased to a minimum, but the content of dibromo derivative **VI** remained virtually the same, 7–8 wt %. By-product **VI** could be eliminated neither by decreasing the amount of bromine taken for the reaction, nor by repeated recrystallization of bromination product **III** from various organic solvents. We found that the concentration of **VI** in the reaction product depends on the rate of adding bromine: The lower the bromine concentration in the reaction mixture, the lower the probability of dehydrobromination. However, we failed to ensure formation of **III** as the only product. To separate **VI**, we took advantage of the fact that monobromo derivative **III** forms with acetic acid a salt readily soluble in water (30 g in 100 g of water at 23°C), whereas 3,5-dibromo derivative **VI** does not form such a salt and is virtual-

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ly insoluble in water. After the bromination completion, the acetic acid was distilled off almost to dryness, and water was added to the residue. By-product **VI** remained in the insoluble residue, and it was filtered off. By alkalization of the filtrate, we isolated virtually pure **III**, without impurity of **VI**.

The nitration of amine **III** under the conditions described in [1, 2] often yielded, instead of the expected nitro compound **IV**, a black precipitate from which we failed to isolate the desired product by recrystallization from solvents in the presence of activated carbon or alumina, or by reprecipitation with alkalis from weakly acidic solutions. In nitration of 2-amino-5-bromopyridine **VII** under the same conditions, a significant amount of 3-nitro-5-bromo-2-pyridone **VIII** is formed along with the desired 3-nitro derivative of **VII** [13].

Nitration of **III** under the similar conditions is also accompanied by deamination. From dark tarry products, we isolated a compound identified as 3-nitro-5-bromo-6-methyl-2-pyridone **IX**.

To avoid formation of **IX** in nitration of **III**, we changed the order of mixing the reactants. Fuming nitric acid was added to a solution of **III** in sulfuric acid not at 55–60 but at 0–5°C, after which the temperature was gradually raised to 55–60°C. By so doing, we considerably reduced the yield of tars. However, after recrystallization of the products from methyl ethyl ketone, we detected **IX** in an amount comparable with that of the target product. By-product **IX** is insoluble in methyl ethyl ketone, alcohol, water, and the majority of aprotic solvents. At decreased nitration temperatures, the amount of **IX** decreased considerably (to 5–10 wt % relative to **IV**).

We examined the influence exerted by the conditions of nitration of **III** on the composition of the reaction products. It is advisable to perform nitration at 0–5°C in concentrated sulfuric acid with 60–63% nitric acid. In isolation of the desired nitro compound **IV**, to avoid formation of tarry impurities, the mixture should be neutralized to pH 2–3 with sodium acetate; in this case, the yield of **IV** is 80–85%. However, even with all these conditions observed, a certain amount of tar is formed; it decreases the melting point of **IV** by 10–20°C. Even a slight excess of nitric acid in nitration of amine **III** causes strong darkening of **IV**. For accurate dosage of nitric acid in nitration, we used instead of amine **IV** its nitrate **X** and added this salt with vigorous stirring at 15°C to concentrated sulfuric acid. Salt **X** is readily formed by mixing a melt of **III** with 60–63% nitric acid in water. Salt **X** can be obtained from crude **III** without its drying. To obtain pure nitro compound **IV** after the transformation of **X** in concentrated sulfuric acid, the acid solution after the nitration was neutralized with sodium acetate. After adding a half of the amount of sodium acetate required for complete neutralization of the reaction mixture, a bright yellow precipirtate of **IV** containing no by-products is formed. Neutralization of the filtrate after the isolation of **IV** to pH 6–7 allows isolation of the precipitate of dibromo derivative **VI**. If salt **X** taken for the nitration is free of amine **VI**, almost quantitative yield of **IV** can be attained, and its purity considerably increases. After recrystallization of **IV** from DMF, its melting point increases by 2–3°C (mp 213°C).

When in nitration of **III** HNO_3 is replaced by a less aggressive and more convenient in handling agent, e.g., KNO_3 in concentrated H_2SO_4, the reaction at 0–10°C yields no nitro compound **IV**, and heating to 40–50°C causes formation of pyridone **IX**. The nitration of **III** in glacial acetic acid also gives negative results.

According to [1, 2], nitro compound **IV** is reduced to diamine **V** with hydrogen in the presence of Raney nickel. Despite a fairly high yield of **V**, ~70%, this procedure is not quite feasible for industrial application, because the catalyst is pyrophoric and hydrogen is dangerously explosive. In the reduction of **IV** with $SnCl_2$ in concentrated HCl according to [12], the yield of **V** does not exceed 60%, and diamine **V** is contaminated with by-products and requires additional purification. Taking into account the fact that structurally related 2-amino-3-nitro-5-chloro(bromo)-6-methylpyridine is smoothly reduced with sodium sulfide in aqueous solution [10], we examined the applicability of this procedure to the reduction of **IV** at 60–100°C. At 60°C, no reduction occurs, and at 100°C the reaction is accompanied by extensive tarring. At 75–80°C, the yield of **V** does not exceed 40%. Experiments on reduction of **IV** with iron in aqueous solution containing a small amount of HCl showed that, when iron dust is added in small portions to a solution of **IV** at 80–90°C, the reduction occurred readily without self-heating and could be controlled. The yield of **V** reached 80% and did not decrease when the reaction time and amount of iron were decreased by half.

The most efficient is the reduction of **IV** with hydrazine hydrate. Refluxing of **IV** with a 15-fold excess of hydrazine hydrate for 5–6 h results in the formation of **V** in 68–70% yield. When the process is performed in a solvent, the consumption of hydrazine hydrate can be decreased by a factor of more than 3. 1-Butanol appeared to be the best solvent for this

purpose, because of high solubility of **IV** and **V** in it and sufficiently high boiling point providing the required reaction temperature. However, the reaction in 1-butanol requires longer time. To accelerate the reduction, we tested the following metals as catalysts: Raney nickel, iron of various brands, powdered aluminum, and zinc dust. The best results were obtained with zinc dust.

By varying the amounts of hydrazine hydrate, 1-butanol, and zinc dust, and also the temperature, we obtained highly pure diamine **V** in 87–90% yield.

When optimizing the synthesis of **I**, we started from the procedure [1, 12] involving heating of diamine **V** in 98–100% formic acid. Our experiments showed that the yield of **I** did not change at the consumption of formic acid decreased by a factor of 3 and the reaction time, by a factor of 2. The by-product was the *N*-formyl derivative of **V**. It seemed appropriate to use as a cyclizing agent pentyl formate suggested previously for the synthesis of a series of imidazo[4,5-*b*]- and -[4,5-*c*]pyridine derivatives [14]. This agent has significant advantages over formic acid: it is less toxic and does not cause scalds and damage mucous membranes of lungs and eyes. Furthermore, the consumption of pentyl formate for preparation of 1 kg of **I** is 5 l, whereas the required amount of formic acid is two times greater. The yield of **I** in refluxing of **V** in pentyl formate is 90–91%.

EXPERIMENTAL

The purity of volatile products was checked in an LKhM-72 analytical chromatograph (2000 × 4-mm column, stationary phase 15% Apiezon on Chromaton N-AW-DMC, carrier gas He, column temperature 220°C). Nonvolatile compounds were analyzed by TLC on Silufol UV-254 plates (eluent ethanol).

2-Amino-5-bromo-6-methylpyridine III. Amine **II** (16.1 g) and anhydrous sodium acetate (12.3 g) were dissolved in 126 ml of glacial acetic acid with stirring at 20–22°C. Then the mixture was cooled to 10–15°C, and a solution of 7.7 ml of bromine in 21 ml of glacial acetic acid was added dropwise at this temperature. After adding the whole amount of bromine, the mixture was stirred at 15°C for 1 h. The solvent was distilled off almost to dryness (~150 ml), and the residue was filtered off, washed with 10 ml of glacial acetic acid, and mixed at 20–25°C with 100 ml of water. The insoluble residue ot **VI** was filtered off, washed with 5 ml of water, and dried in air. Yield of by-product **VI** 2.1 g, mp 142–143°C [5]. The aqueous filtrate was alkalized with 6 ml of 30% NaOH to pH 8, and the colorless precipitate of bromo derivative **III** was filtered off. The product was washed with 5 ml of water, recrystallized from 20% acetic acid, and dried. Yield 25 g (90%), mp 80–82°C. According to [21], mp 71–72°C.

2-Amino-5-bromo-6-methylpyridinium nitrate X. To 16 ml of water heated to 80–85°C we added with stirring 7.6 g of molten 2-aminopyridine **III**. To the resulting emulsion, we added over a period of 5–10 min 3.4 ml of 60% HNO_3. In so doing, base **III** dissolved, and nitrate **X** started to precipitate on cooling the reaction mixture to 60–55°C. After cooling to 10–15°C, the precipitate was filtered off. Yield of **X** 9.7 g (95.5%), mp 170–172°C.

Found, %: C 28.59, H 3.16, N 16.61.
$C_6H_7BrN_2 \cdot HNO_3$.
Calculated, %: C 28.82, H 3.22, N 16.80.

2-Amino-3-nitro-5-bromo-6-methylpyridine IV. Nitrate **X** (21 g) was added in small portions to 45 ml of concentrated sulfuric acid cooled to 10–15°C. The mixture was stirred for 1 h and poured onto 160 g of ice, and 110 g of sodium acetate ($CH_3COONa \cdot 3H_2O$) was added. The light yellow precipitate was filtered off, washed with 10 ml of water and 5 ml of acetone, and dried; 19.5 g (~100%) of nitro compound **IV** was obtained, mp 211–213°C (from DMF); according to [12], mp 210–213°C.

2,3-Diamino-5-bromo-6-methylpyridine V. (*a*) To a mixture of 24 ml of 2-propanol, 6 ml of water, 5.6 g of aminonitropyridine **IV**, and 0.8 ml of concentrated HCl, we added with stirring at 70–75°C 5.6 g of iron carbonyl in portions over a period of 2 h, so that the mixture mildly boiled. Then the mixture was refluxed for 2 h and filtered while hot. The black precipitate on the filter was washed with hot 2-propanol, and the wash solution was combined with the filtrate. The resulting solution was alkalized with 25% aqueous ammonia to pH 8 and refluxed for 0.5 h. The precipitated iron oxides were filtered off, and 2-propanol and then water were distilled off in a water-jet-pump vacuum to ~1/4 of the initial volume. The residue was cooled to 15–20°C, and the precipitate of diamine **V** was filtered off. Yield 4.04 g (80%), mp 135–137°C (from H_2O). According to [12], mp 136–137°C.

(*b*) To a mixture of 5.8 g of **IV**, 50 ml of 1-butanol, and 7 ml of hydrazine hydrate, we added with stirring at 100°C 1.0 g of zinc dust in portions over a period of 2 h. The mixture was refluxed for 3–4 h until the gas evolution ceased. Then the mixture was cooled to 60–70°C and filtered. The gray precipitate

on the filter was washed with 20 ml of hot 1-butanol, and the wash solution was combined with the filtrate. Then 55–60 ml of 1-butanol was distilled off in a water-jet-pump vacuum. The residue was cooled to 15–20°C, and the precipitate of **V** was filtered off. Yield 4.55 g (90%), mp 135–137°C (H_2O).

6-Bromo-5-methylimidazo[4,5-*b*]pyridine I. A mixture of 5 g of **V** and 7 ml of pentyl formate was heated at 170–175°C for 2 h until 0.4–0.5 ml of water was released and then at 170–180°C for 2 h more. Pentyl formate and 1-pentanol were distilled off in a water-jet-pump vacuum (40–50°C, 25–30 mm Hg) to dryness, and the residue was crystallized from ethyl acetate or water–2-propanol (5 : 1). Yield 4.75 g (90.5%), mp 206–207°C. According to [12], mp 204–205°C.

CONCLUSION

Procedures were suggested for preparing 2-amino-5-bromo-6-methylpyridine by bromination of 2-amino-6-methylpyridine in glacial acetic acid in the presence of anhydrous sodium acetate in 90% yield, nitration of the resulting compound in the form of nitrate in concentrated sulfuric acid at 10–15°C (~100% yield), reduction of the product in an acidified alcohol with iron carbonyl (~80% yield) or with hydrazine hydrate and zinc (~87–90% yield), and cyclization of 2,3-diamino-6-methylpyridine in refluxing pentyl formate to 6-bromo-5-methylimidazo[4,5-*b*]pyridine (~90.5% yield), an antifogging compound for color photographic materials.

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REFERENCES

1. US Patent 3473924.
2. US Patent 3629272.
3. US Patent 3687660.
4. French Patent 2134750.
5. Australian Patent 461229.
6. US Patent 4071366.
7. US Patent 4102685.
8. US Patent 4134768.
9. Adams, R. and Schrecker, A.W., *J. Am. Chem. Soc.*, 1949, vol. 71, no. 4, pp. 1186–1195.
10. Israel, M. and Day, A.R., *J. Org. Chem.*, 1959, vol. 24, no. 10, pp. 1455–1460.
11. Weygand–Hilgetag, *Organisch-chemische Experimentierkunst*, Leipzig: Johann Ambrosius Barth, 1964, 3rd ed.
12. Graboues, H. and Day, A.R., *J. Am. Chem. Soc.*, 1957, vol. 79, no. 24, pp. 6421–6426.
13. Abramovich, A.B., *Pyridine and Its Derivatives*, New York, 1974, vol. 14, part 3.
14. USSR Inventor's Certificate no. 717055.