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AN IMPROVED, PRACTICAL, RELIABLE AND SCALABLE SYNTHESIS OF 2,5-DIBROMOPYRIDINE

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ABSTRACT — A convenient and scalable process for preparation of 2,5-dibromopyridine has been developed. Total yield of 83% has been achieved from 2- aminopyridine. The process is convenient and could be easily scaled up. By-product dibromide pyridine is separated and 2-amino-5-bromopyridine is converted by modified Sandmeyer conditions to synthesize 2,5-dibromopyridine from its diazonium salt in presence of bromine instead of conventional copper halide such as CuBr as reagents or catalysts.

KEYWARDS– 2-Aminopyridine, 2-Amino-5-bromopyridine, 2,5-dibromopyridine,

INTRODUCTION:

Polyfunctional pyridines are very useful compounds which have found applications as precursors of pharmacological compounds,[i] in the synthesis of liquid crystals[ii] and polymers,[iii] as well as ligands for different transition metal cations.[iv] The wide range of halopyridines,[v] which are able to undergo metal-halogen exchange with n-BuLi, nucleophilic substitutions and oxidative additions with Pd(0) allowing the introduction of many functional groups to the pyridine ring, means they are of great interest from a synthetic point of view.[vi] Moreover, halo pyridines are themselves important final products as herbicides,[vii] insecticides[viii] and fungicides.[ix] As a consequence of these features the regioselective synthesis of halo pyridines is a matter of great interest. Data published in the literature up to 1970 showed that bromination of activated pyridines must be carried out with bromine in polar protic solvents, such as water or ethanol.[x] Several years later, it was reported the bromination of amino pyridines and N-oxides[xi] with bromine in mixtures of CH_3CN/CH_2Cl_2, while bromination of methoxypyridines [xii] was carried out in acetic acid. In most of these papers, the formation of mixtures of monohalo and dihalo derivatives is reported but their relative proportions as well as their characterisation is omitted.

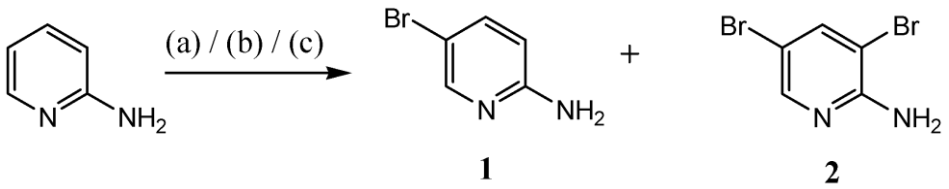
2,5-dibromo pyridine is the important intermediate of organic synthesis, is mainly used in medicine intermediate, organic synthesis, organic solvent, also can be applicable to the aspects such as dye production, pesticide producing and spices. Mears Drive, Zionsville synthesized 2,5-dibromopyridine from 2-hydroxypyridine wherein 2-hydroxypyridine was converted to 5-bromo-2-hydroxypyridine with very low yield of 60% only and it is further

converted to 2,5-dibromopyridine using harsh brominating agent such as PBr_3 with again very low yield of 51% only, hence the overall yield for both the stages round up to ~30%.[xiii]

At present, there are shortcomings such as low yield, long synthetic operational path for 2,5-dibromo pyridines is reported, but there is not much detailed research on its synthesis so far including related by-product identification, their reaction conditions and especially factors for scaling up its production. The objective of the work is to overcome the technical deficiency such as low yield, long operational processes which involves protection deprotection, reusability of solvents and reagents.

In this paper, 2,5-dibromopyridine has been prepared starting from 2-aminopyridine involving bromination with NBS followed by Sandmeyer reaction to synthesize 2,5-dibromopyridine from its diazonium salt in presence of bromine instead of conventional copper halide such as CuBr as reagents or catalysts. The side reaction in bromination produces the major impurity 2-amino-3,5-dibromopyridine which is conveniently removed to obtain pure 2-amino-5-bromopyridine. Moreover, the feasibility of recycling material at both the stages, which was commercially feasible for the large scale, has been verified. With the established optimal condition, the yield of bromination was raised to 90.0% and of the Sandmeyer was 93.0%.

The synthetic route, presented as shown in Scheme-1 started from 2-aminopyridine with bromination using bromine to afford 2- amino-5-bromopyridine.



Scheme-1: Bromination of 2-aminopyridine

Reaction conditions: (a) Bromine, Acetic acid (b) NBS, Acetonitrile (c) DBDMH, Acetonitrile (d) Acetic anhydride, Bromine

Three basic improvements exist in

(1) the major impurity **2** (Scheme-1) of the bromination was isolated and characterized as 2-amino-3,5-dibromopyridine;

(2) the solvent recycling utilization; and

(3) the simple separating method made the process simple.

EXPERIMENTAL

All solvents, reagents and key raw materials such as 2-aminopyridine were commercially available and used without further purification. The proton nuclear magnetic resonance (1 H NMR) spectra were obtained using an AVANCEDMX500 (WB) (Bruker, America) at room temperature using TMS as an internal standard and DMSO-d^6 or $CDCl_3$ as the solvent. GC was performed by using Agilent 7890B systems. The column was HP-5, 30m x 0.32 mm x 0.25µ. Injector temperature 250 °C, detector temperature 255°C, Injection volume 0.2 µL. Moisture analysed using Veego KF analyser and melting points analysed using melting point apparatus of spectralab Checkmelt-1.

GENERAL PROCEDURE:

Typical process for 2-Amino-5-bromopyridine (1)

To a solution of 2-aminopyridine (9.40 kg) in Acetonitrile (50 L) was added slowly NBS (17.7 kg) maintaining the temperature below 20 °C. When the addition of NBS was completed, the mixture was stirred for 1 h. Filter the solid product, which was made alkaline with a solution

of NaOH (5.0 kg) in H_2O (50 L) and cooled (10 °C). The solid was collected by filtration, slurry washed with cold H_2O (10 L), and then washed with heptane (3 × 20 L) to remove the 2-amino-3,5-dibromoaminopyridine, followed by air-drying to constant weight; Yield: 15.7 kg (90%); off-white fine crystals; mp 135–136 °C (Lit. mp 132–135 °C); Rf = 0.4 ($CHCl_3$–EtOAc). IR (KBr): 3452, 3292, 3153, 2924, 2852, 1628, 1587, 1550, 1481, 1387, 1088, 999 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.57 (br s, 2 H, NH_2), 6.41 (d, J = 8.8 Hz, 1 H, H-3), 7.48 (dd, J1 = 8.8 Hz, J2 = 2.4 Hz, 1 H, H-4), 8.09 (d, J = 2.4 Hz, 1 H, H-6). ^{13}C NMR ($CDCl_3$): δ = 108.3, 110.1, 140.2, 148.7, 157.1. MS (EI, 70 eV): m/z (%) = 174 (88, [M (81Br)] +), 172 (100, [M (79Br)] +), 147 (46), 145 (49), 92 (97), 65 (67), 64 (60), 50 (49). Anal. Calcd. for $C_5H_5BrN_2$: C, 34.71; H, 2.91; N, 16.19. Found: C, 34.59; H, 3.01; N, 16.10.

2-Amino-3,5-dibromoaminopyridine (2)

Evaporation of the heptane filtrate from the above workup and further recrystallization of the residue from heptane gave 2-amino-3,5- dibromo aminopyridine as yellow needles; yield 2.25 kg (9 %); mp 105–106 °C (EtOH–H_2O, 3:1) (Lit. mp 104–105 °C); Rf = 0.65 ($CHCl_3$– EtOAc). IR (KBr): 3462, 3280, 3147, 2922, 2852, 1626, 1568, 1466, 1387, 1024 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 5.14 (br s, 2 H, NH_2), 7.75 (d, J = 2.0 Hz, 1 H, H-4), 8.03 (d, J = 2.0 Hz, 1 H, H-6). ^{13}C NMR (CDCl3): δ = 104.6, 107.1, 141.9, 147.6, 154.5. MS (EI, 70 eV): m/z (%) = 254 (51, [M (81Br, 81Br)] +), 252 (100, [M (79Br, 81Br)] +), 250 (59, [M (79Br, 79Br)] +), 173 (22), 171 (22), 144 (15), 92 (65), 65 (32), 64 (31). Anal. Calcd for $C_5H_4Br_2N_2$: C, 23.84; H, 1.60; N, 11.12. Found: C, 23.91; H, 1.43; N, 11.15.

2,5-Dibromopyridine (7)

2-Amino-5-bromopyridine (**1**; 13.0 kg) was added over 10 min to a cold (10 °C) aq. 47% HBr (37 L). Br_2 (11 L) was added, keeping the temperature below 10 °C. Then, a solution of $NaNO_2$ (16.1 kg) in H_2O (19 L) was added dropwise, maintaining the temperature at 0–5 °C. The reaction mixture was stirred for an additional 30 min, then treated with a solution of NaOH (28.0 kg) in H_2O (30 L) at such a rate that the temperature did not exceed 20–25 °C. The mixture was extracted with MTBE (3 × 40 L) and the combined organic layers were dried (Na_2SO_4). The solvent was evaporated under vacuum, the residue was suspended in heptane (10 L), and the solid formed was collected by filtration to afford a pale yellow powder; Yield: 16.5 kg (93%); mp 92–95 °C (Lit. mp 92–97 °C); Rf = 0.55 ($CHCl_3$). IR (KBr): 3411, 3022, 2924, 2852, 1549, 1437, 1356, 1090, 997 cm^{-1}. ^1H NMR (CDCl3): δ = 7.39 (d, J = 8.4 Hz, 1 H, H-3), 7.67 (dd, J1 = 8.4 Hz, J2 = 2.5 Hz, 1 H, H-4), 8.45 (d, J = 2.4 Hz, 1 H, H-6). ^{13}C NMR ($CDCl_3$): δ = 120.1, 129.5, 140.4, 141.2, 151.3.

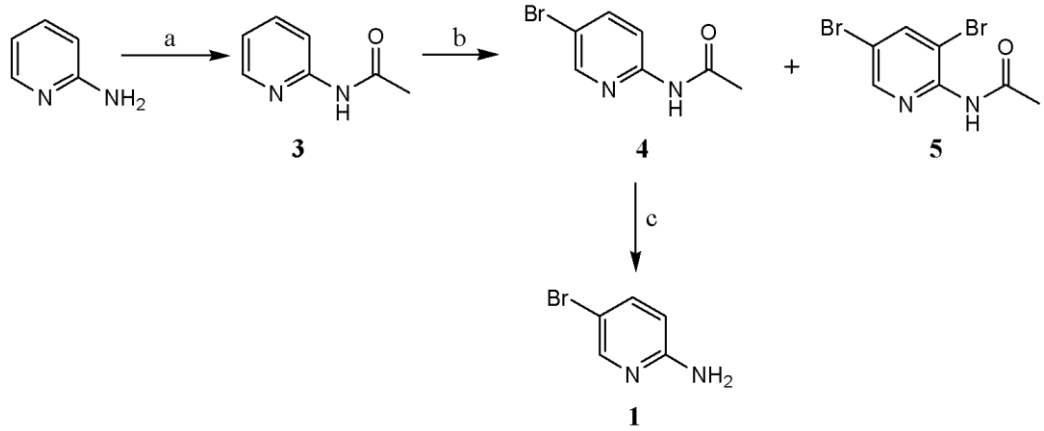
RESULT AND DISSCUSSION

The preparation started from 2-aminopyridine, involving bromination by NBS in the presence of solvent such as Acetone and DMF individually as solvent. Reaction in acetonitrile was found to be best in terms of by-product formation. The great trouble in other two solvents was higher percentage of by-product formation always accompanying with the product in a larger quantity resulting the tedious separation process which is not the case in acetonitrile. For controlling the reaction much better, the by-product was separated and identified as 2-amino-3,5-dibromopyridine **2**. It is elucidated that over-bromination of the substrate happened in bromination. Hence, the amount of the brominating agent plays the key role in the yield of the product, and how to inhibit the by-product emerging becomes important.

To obtain 2-amino-5-bromopyridine as a single predominant product amino group was protected by acetylation using acetyl chloride, acetic anhydride and bulkier propionic anhydride considering to stop the reaction at the mono substitution stage by preventing the formation of di- and or trisubstitution by-products. Acetylation reaction did not go to completion in case of acetyl chloride whereas anhydrides gave complete conversion with

moderate yields. Unfortunately protected amino pyridine still produced protected dibromo impurity **5** as by-product which will be eventually get converted to **2**.

A series of experiments were done looking for an optimal condition not only for the amount of the brominating agent but also involving the other reaction conditions, such as temperature, solvents, brominating agent, molar proportions as shown in Table-1.



Scheme-2: Protection followed by bromination of acetyl protected 2-aminopyridine
Reaction conditions: (a) Acetic anhydride, TEA (b) NBS, Acetonitrile; (c) NaOH, MDC;

The brominated process was initially investigated at relatively low temperature because we hoped the low temperature could prevent formation of dibromo-substituted impurities.

Result showed that the low temperature indeed decreases the content of dibromo by-product, but it is not an inevitable condition and the effect of the temperature on the content of dibromo impurity is irregular. Especially, the low temperature means high energy cost for scale-up production. Feeding time was to effectively control the concentration of brominating agent in the reacting mixture restraining the regional over-bromination. The molar ratio of the substrate and brominating agent has the most significant influence on the yield of 2-amino-5-bromopyridine and content of dibromo impurity. Excess brominating agent could result in over bromination to raise the content of dibromo and the equal ratio of the substrate and brominating agent gives the best yield of the product. 2-amino-3,5-dibromopyridine can be separated from mixture by treating it with nonpolar solvents such as n-hexane, n-heptane, cyclohexane etc.

By-product **2** is also one of the important intermediate widely used in polymer industry, which is used as monomer for sulfonated polypyridines. Dihaloaromatics and dihaloheterocycles can be converted to the corresponding polymers by organometallic dehalogenative polycondensations, and by using the monomers polypyridine bearing sulfo group has been used as a polymer electrolyte for fuel cells[xiv].

Next stage is Sandmeyer reaction of 2-amino-5-bromopyridine (**1**) to obtain 2,5-dibromopyridine (**6**) and this process was not as simple as imagined. Since it was a diazonium reaction, the difficulty of this step is not the impurity formation of multi-substituted compounds, like the previous step, but how to make 2,5-dibromopyridine into the product in a high conversion rate.

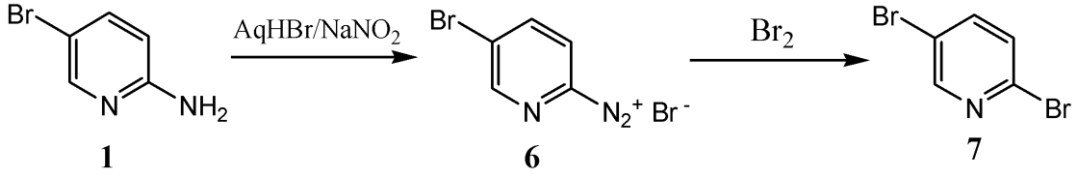
In this step, initially we have followed the typical well known Sandmeyer reaction conditions wherein 2-amino-5-bromopyridine was diazotized using HCl and sodium nitrite at lower temperature and then treated this diazonium salt with copper bromide but reaction doesn't proceed as expected. Large amount of unknown impurities formed along with unconverted starting material.

Table-1: Effect of brominating agent and solvent on bromination of 2-aminopyridine

Sr. No.	Brominating Agent	Solvent	1	2	SM
1	Bromine	Ethanol	54%	40%	-
2	Bromine	Methanol	48%	43%	-
3	NBS	DMF	45%	23%	30%
4	NBS	Acetonitrile	90%	9%	-
5	NBS	Acetone	68%	21%	-
6	Bromine	Acetonitrile	58%	31%	5%
7	Bromine	Acetic Acid	81%	16%	-
8	DBDMH	Acetonitrile	51%	18%	24%

Reaction conditions: 2-aminopyridine (10 mmol) Brominating agent (10 mmol) solvent (5 times) at 25-30^{0}C.
NBS: N-bromosuccinimide & DBDMH: 1,3-Dibromo-5,5-Dimethylhydantoin, SM: starting material

We have further prepared diazonium salt using HBr and sodium nitrite which is treated with CuBr but we end up with same results. The ratio of the amount of CuBr and HBr also studied, unfortunately product formation was very feeble.



1 **6** **7**

Scheme-3: Sandmeyer reaction using bromine instead of CuBr.

Alternatively, we have directed our efforts for Sandmeyer reaction using bromine instead of copper halide reagent and we have achieved excellent outcome, wherein diazonium salt was prepared using 48% aqueous HBr and sodium nitrite which is further treated with bromine, this gives complete conversion of starting material with maximum product formation.

CONCLUSION

A convenient and scalable method for preparation of 2,5-dibromopyridine has been developed. Total yield of ~83% has been achieved from 2- aminopyridine to 2, 5-dibromopyridine. The Sandmeyer reaction carried out using Liq. bromine instead of copper halide. The process is convenient and could be easily scaled up. Convenient process was developed to remove the dibromide by-product from the bromination of 2- aminopyridine which was characterized and identified 2-amino-3,5- dibromopyridine.

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