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An Alternate Route to 2-Amino-3-nitro-5-bromo-4-picoline: Regioselective Pyridine Synthesis via 2-Nitramino-picoline Intermediate

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Abstract:

The 2-nitramino functionality in 2-nitramino-4-picoline was successfully exploited not only as a protecting group but also as a directional handle to afford an efficient, atom-economic, and regioselective synthesis of 2-amino-5-bromo-3-nitro-4-picoline (4), a precursor for a drug candidate in development.

Introduction

As part of our ongoing industry–university collaborative research program, established between Texas A&M University-Kingsville and the Process R&D department at Bristol-Myers Squibb Co., we required an expeditious route to 2-amino-5-bromo-3-nitro-4-picoline (**4**), a precursor for a key intermediate, starting from the readily available 4-picoline (**1**).[1] Only one synthesis of **4** is known.[2] Our initial bench-scale synthesis for the production of **4** involved nitration of 2-amino-4-picoline (**1**), producing a mixture of 3- and 5-nitro isomers in an unfavorable 1:4 ratio. Isolation of the desired minor isomer **3** by tedious steam distillation (or sublimation) followed by bromination produced **4**, albeit in low (<10%) overall yield (Scheme 1).[3]

In short, this process was encumbered by poor yield, unwanted byproducts, and a difficult isolation and was not amenable to pilot plant scale-up.

A hint of a promising solution to this problem was found in an earlier report by Seide et. al. describing the formation of 2-nitramino-pyridine as a discrete intermediate that rearranged to the 3- and 5-nitro isomer during the nitration of 2-amino-pyridine derivatives.[4] Conceivably, by halting the nitration at the intermediate 2-nitraminopicoline stage and exploiting the steric influence of the bulky 2-nitramino functionality, bromine could be selectively introduced to the 5-position. Subsequent rearrangement of the resulting 5-bromo-2-nitramino-pyridine would then produce the desired product provided the integrity of the 2-nitramino functionality remained intact during the entire sequence of operations. These expectations were fully realized, resulting in a simple, efficient, and regioselective synthesis of 2-amino-5-bromo-3-nitro-4-picoline (**4**) whereby the 2-nitramino functionality in the intermediate 2-nitramino-4-picoline (**5**) served a dual role, not only as a masking group but also as a directional handle (Scheme 2).

Results and Discussion

Initially we had sought to modify the traditional nitration chemistry of 2-amino-4-picoline (**1**) in order to optimize the selectivity of the desired 3-nitro isomer **3**. Nitration of 2-amino-4-picoline (**1**) utilizing the established procedure (H_2SO_4 5 g/g of substrate and HNO_3 1.3 g/g of substrate) proceeded via the corresponding 2-nitramino-4-picoline intermediate **5**, which subsequently underwent acid-catalyzed rearrangement at room temperature over 60 h, producing as expected the desired 3- and undesired 5-nitro isomers in a 1:4 ratio. The intermediate formation was complete in 1 h at 0 °C as evidenced by HPLC and MS analysis. High dilution conditions (H_2SO_4 50 g/g of substrate and HNO_3 1.3 g/g of substrate) resulted in improved product selectivity from 1:4 to 1.6:1 in the favor of the regioisomer **3**. The improved ratio under high dilution could be attributed to an intramolecular mechanism, as has been suggested by some mechanistic studies.[5] Additional optimization studies, involving modification of several reaction variables (e.g.,

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(1) Process Chemistry Collaboration, Education Concentrate. *Chem. Eng. News* **2001**, July 23, 41.

(2) For a patented synthesis of 2-amino-5-bromo-3-nitro-4-picoline (1) see: Igarashi et al. U.S. Patent 5,290,943, 1992 [EP0530524]. The synthesis involves protection of the amine function of 2-aminopicoline via N-acetylation followed by bromination of the resulting NH-acetyl derivative. Nitration and aqueous hydrolysis of the acetamido group produced the desired compound.

(3) (a) Partial solubility of the product in water made the isolation even more difficult after the steam distillation. (b) For sublimative isolation of the product, see: Grozinger, K. G.; Fuchs, V.; Hargrave; Maudlin, S.; Vitous, J.; Campbell, S.; Adams, J. *J. Heterocycl. Chem.* **1995**, *32*, 259. (c) Marcello, M. M. P.; Jose da Silva, V. G.; Clive, D. L. J.; Coltart, D. M.; Hof, F. A. *J. Hetereocycl. Chem.* **1999**, *36*, 653. (d) Burton, A. G.; Frampton, R.D.; Johnson, C.D.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans.* **1972**, *2*, 1940.

(4) (a) Seide, O. *Chem. Ber.* **1924**, *57* (791), 1802. (b) Seide, O. *J. Russ. Phys.-Chem. Soc.* **1924**, *50*, 534.

(5) (a) Deady, L. W.; Grimmett, M. R.; Potts, C. H. *Tetrahedron* **1979**, *35*, 2895. (b) White, W. N. *Mechanism of Molecular Migrations*; Thyaagrajan, B. S., Ed.; Wiley-Interscience: New York, 1971, Vol. 3, p 109. (c) Williams, D. L. H. *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Vol. 31, p 433. (d) Thomas, A.; Tomasik, P.; Herman-Matusiak, G. *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **1975**, *23*, 311. (e) Kokocinska, H.; Thomas, A.; Tomasik, P.; Zalewski, R. *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* **1976**, *24*, 535. (f) White, W. N.; Klink, J. R. *J. Org. Chem.* **1970**, *35*, 965.

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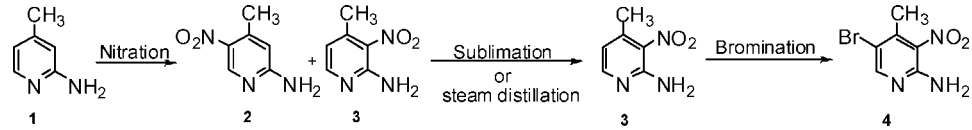
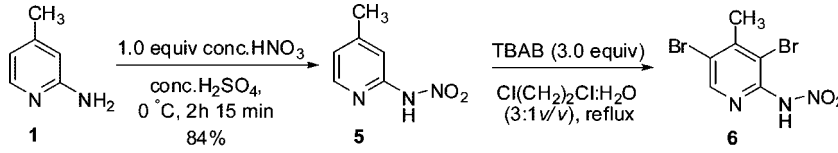
Scheme 1. **Existing route to 2-amino-5-bromo-3-nitro-4-picoline (4)**



Scheme 2. **Exhaustive bromination of 5**



TBAB=Tetrabutylammonium tribromide

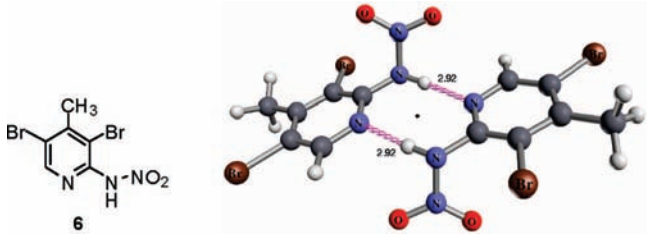


Figure 1. **X-ray structure of two molecules of 3,5-dibromo-2-nitramino-4-picoline (6) H-bonded across a crystallographic inversion center.**

temperature, concentrations, rate of additions, etc.) failed to further improve the selectivity to an acceptable level.[6]

As a result, 2-nitramino-4-picoline (**5**) became a judicious choice as a potential intermediate in our synthetic sequence. 2-Nitramino-4-picoline (**5**) was isolated as a crystalline solid by conducting the nitration for 75 min at 0 °C, followed by quenching the reaction mixture directly into ice–water. We anticipated that the selective introduction of bromine to the desired 5-position would be possible if the 2-nitramino functionality remained intact during the bromination process. To further support the premise that the 2-nitramino functionality can be exploited as an effective protecting group during the bromination process, **5** was subjected to exhaustive bromination with a large excess of tetrabutylammonium tribromide (TBAB), cleanly producing 3,5-dibromo-2-nitramino-4-picoline (**6**) as the sole product. The structure of the product was confirmed by X-ray analysis (Scheme 2, Figure 1).[7]

Once the viability of the 2-nitramino functionality was established, we turned our attention to studying its directional influence in the selective bromination of **5**. The bromination was surveyed employing stoichiometric amounts of various types of brominating agents (Table 1). Typically, bromination of **5** with stoichiometric quantities of brominating agent was uniformly selective, largely resulting in the formation of monobrominated product (major isomer) **7** by HPLC analysis (Scheme 3). In each case the desired product **7** directly crystallized out of the reaction mixture, simplifying the isolation/purification protocol. The 3,5-dibromo byproduct **6**, which was formed in trace amounts under the reaction conditions, remained in the mother liquor as a result of its higher solubility. The orientation effect of the 2-nitramino group could be attributed to the steric bulk of the 2-nitramino functionality directing the incoming electrophile preferentially to the 5-position and away from the sterically congested 3-position. The bromination conditions in Table 1 were successfully employed to prepare the 5-bromo isomer **7**. The bromination with TBAB was performed in dichloromethane/water or dichloroethane/water under biphasic conditions.[8] We have found that the reaction failed to proceed without water.[9]

In the case of bromination with HBr (entry 16), 36 h, the reaction was initiated by the oxidation of HBr to molecular bromine. Bromination of the substrate produced a mole of HBr, which is re-oxidized by H_2O_2 to regenerate Br_2 [$2HBr + H_2O_2 \rightarrow Br_2 + 2H_2O$]. This constitutes a salt-free atom-economic bromination sequence.[11]

Table 1 summarizes the results of the limited optimization studies for the bromination of **5** utilizing various buffer–solvent combinations and bromine sources. Both molecular bromine under buffered conditions as well as TBAB under phase transfer conditions gave satisfactory results leading to the product **7** in good yields (entries 4, 7, 10, and 15). Bromination under buffered conditions revealed interesting observations. With K_2HPO_4 as buffer, decreasing the amount of buffer from 2.5 to 1 equiv produced the optimum yield of **7** (entries 1–4), whereas with NaOAc as buffer, increasing the amount of buffer from 1 to 6 equiv favored **7** (entries 5–10).

(6) 2-Amino-4-picoline (**1**, 1 g) was dissolved in concentrated H_2SO_4 (96%, 20 g) was slowly added to the mixture while maintaining a temperature of 0–5 °C. The reaction mixture was stirred for 15 min at the end of which time, complete disappearance of starting material and formation of the nitramine intermediate was observed by HPLC analysis. The reaction mixture was warmed to 22 °C and stirred for 3 h, at the end of which complete disappearance of the intermediate and the formation of a mixture of 3- and 5-nitro products (1.6:1 ratio) was observed by HPLC analysis. The mixture was neutralized with $NaHCO_3$ maintaining a temperature of 0–5 °C (to pH 8) and steam-distilled to produce 2-amino-3-nitro-4-picoline. Two liters of distillate was collected. The product was isolated via filtration in 35% yields.

(7) Crystallographic data (excluding structure factors) for **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 284780. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk.

(8) For use of TBAB in an organic solvent see: Berthelot, J.; Guette, C.; Essayegh, M.; Desbene, P. L.; Basselier, J. J. *Synth. Commun.* **1986**, *16* (13), 1641.

(9) Deactivating effect of nitramino functionality and partial solubility of **5** in dichloromethane is such that addition of water was necessary to allow insitu generation of molecular bromine resulting from the collapse of tribromide species (into hypobromous acid and molecular bromine).

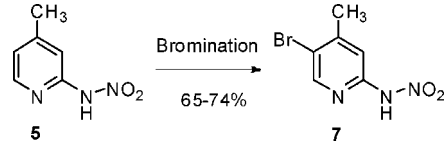
(11) Dunn, A. D.; Currie, A.; Hayes, L. E. *J. Prakt. Chemi.* **1989**, *331* (3), 369.

Table 1. **Bromination studies**

entry	brominating agent [a]	buffer (equiv) – solvent composition (v/v or M) [b]	T (°C)	time (h)	yield **7** (%)[c]
1	Br_2-AcOH (1.65M)	K_2HPO_4 (2.5)- H_2O:AcOH (5:1)	23	12	20
2	Br_2-AcOH (0.5M)	K_2HPO_4 (2.0)- H_2O:AcOH (1.7:1)	23	12	50
3	Br_2-AcOH (0.5M)	K_2HPO_4 (1.0)- H_2O:AcOH (1.7:1)	40	12	65
4	Br_2-AcOH (0.5M)	K_2HPO_4 (1.0) -AcOH (0.2M)	40	12	73[d]
5	Br_2-AcOH (0.85M)	NaOAc (1.0) -AcOH (0.25M)	23	48	50
6	Br_2-AcOH (0.5M)	NaOAc (1.75) -AcOH (0.165M)	23	30	67
7	Br_2-AcOH (0.5M)	NaOAc (6.0) -AcOH (0.18M)	23	30	74[e]
8	Br_2-AcOH (0.85M)	NaOAc (1.75) -AcOH (0.37M)	23	48	65[f]
9	Br_2-AcOH (0.5M)	NaOAc (4.0) -AcOH (0.25M)	23	7	68
10	Br_2-AcOH (0.5M)	NaOAc (6.0) -AcOH (0.25M)	50	2	74
11	NBS [g]	CH_3CN:CH_2Cl_2 (1:1, 0.2M)	23	15	30
12	NBS	CH_3CN (0.2M)	23	15	25
13	NBS	Cl $(CH_2)_2$Cl:CH_3CN (4:1, 0.2M)	23	15	47
14	NBS	CH_3CN (0.65M)	23	20	40
15	TBAB (1.3 equiv) [h]	CH_2Cl_2:H_2O (3:2)	23	48	65
16	HBr-H_2O_2 (1:2 equiv)	NaOAc (6.0), AcOH (0.5M)	45	36	40

[a] Freshly prepared solution (M) or 1.0 equiv of brominating agent used unless otherwise stated. [b] Refers to v/v of solvent or final concentration of substrate in the reaction solvent. [c] Refers to isolated yield. [d] 3 g scale. [e] 10 g scale. [f] 3 g scale reaction on free base of substrate. [g] *N*-Bromosuccinimide.[10] [h] Tetrabutylammonium tribromide.

Scheme 3. **Bromination of 2-nitramino-picoline (5)**



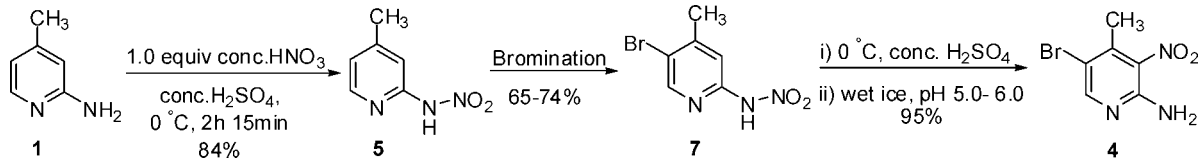
Rearrangement of 5-Bromo-2-nitramino-4-picoline (7) to 4

Having demonstrated the viability of the selective bromination technology to produce 5-bromo-2-nitramino picoline (**7**), we set out to probe the rearrangement of this product. Although preliminary studies by heating in solvents such as toluene or xylene resulted in extensive decomposition, the addition of a catalytic amount of acid (e.g., H_2SO_4 or methanesulfonic acid) dramatically accelerated the rearrangement and reduced impurity formation. This led to the development of optimized reaction conditions of concentrated H_2SO_4 as a solvent at 0 °C. Neutralization of the reaction mixture led to a 95% yield of the product **4**, which was directly carried forward without any further purification (Scheme 4).

We have demonstrated the utility of 2-nitramino picoline (**5**) as a valuable synthetic intermediate in the regioselective and efficient synthesis of 2-amino-5-bromo-3-nitro-4-picoline (**4**). It is also established that the reactivity of 2-amino-4-picoline toward regioselective bromination at C_5 is judiciously modulated by incorporation of the 2-nitramino functionality, which plays an unique role in deactivating and providing the necessary steric influence in masking the C_3 position. Thus, the regiospecific bromination and subsequent intramolecular delivery of the nitro functionality in a selective, atom-economic manner to the C_3 position is unprecedented.[12] We are currently involved in the

(12) During preparation of this manuscript, an example demonstrating utility of nitramine functionality was published: Porcs-Makkay, M.; Mezei, T.; Simig, G. *Org. Process Res. Dev.* **2007**, *11*, 490.

Scheme 4. **Overall synthetic sequence**



delineation of the scope of this process and its application to regioselective pyridine synthesis.

Experimental Section

Preparation of 2-Nitramino-4-picoline (5). To a 500-mL, three-necked flask equipped with a stirrer and an internal thermocouple probe was charged 117 mL of concentrated sulfuric acid (96%, 0.619 mol). The acid was cooled to 0–5 °C, and 25 g (0.231 mol) of 2-amino-4-methyl pyridine (**1**) was added in portions over a period of 1 h with stirring. After 1 h, 15.5 mL (1.0 equiv, 0.231 mol) of concentrated nitric acid (71%) was added dropwise over a period of 75 min while maintaining the reaction mixture between −3 and 0 °C. The reaction mixture was stirred for an additional 1 h and then quenched over 600 g of wet ice in a 1-L beaker.The resulting cold white slurry was stirred at room temperature for an additional 10 min, vacuum filtered, and dried in vacuo (5 mmHg) at 50 °C to a constant weight, affording 29.7 g (84% yield) of 2-nitramino-4-picoline (**5**) as a white solid. **Analytical data:** mp [lit.[4] 220 °C]. ^{1}H NMR (CD_3OD) (δ, ppm): 2.50 (s, 3H), 7.20 (bd, 1H, J = 6.6 Hz, Ar-H), 7.30 (bs, 1H, Ar-H), 8.03 (d, 1H, J = 6.6 Hz, Ar-H). ^{13}C NMR (CD_3OD) (δ, ppm): 21.00, 118.54, 119.91, 135.34, 144.00, 158.46. HRMS calcd for $C_6H_7N_3O_2$ 153.05383, found (M + 1) 154.06166.

Preparation of 5-Bromo-2-nitramino-4-picoline (7). *Method A. Using Br_2-AcOH Sodium Acetate Buffer System.* To a 250-mL, single-necked, round bottomed flask were charged 70 mL of glacial acetic acid and 8.23 g (0.10 mol) of anhydrous sodium acetate. The mixture was stirred at 40 °C until complete dissolution. To this solution was added 3g (19.60 mmol) of 2-nitramino-4-picoline at 40 °C under stirring. After complete addition, the reaction mixture was allowed to cool to room temperature over a period of 15 min. A solution of molecular bromine in acetic acid (3.14 g of 0.5 M solution, 20 mmol, in 40 mL acetic acid) was added over a period of 30 min. The mixture was stirred at room temperature for 30 h. The resulting slurry was vacuum filtered, washed with 5 mL of cold water followed by 2 mL of dichloromethane, and dried (8 inHg, 55 °C) to constant weight to afford 3.75 g (74% yields) of the desired 5-bromo-2-nitramino-4-picoline (**7**) as a white solid.

Method B. Using Potassium Hydrogen Phosphate Buffer System. To a 50-mL, single-necked round bottom flask were charged 65 mL of acetic acid and 4.5 g (0.196 mol) of potassium hydrogen phosphate dibasic trihydrate. The mixture was heated to 40 °C until complete dissolution. To this homogeneous solution was added 3 g (0.196 mol) of 2-nitramino-4-picoline (**5**) at 40 °C, and the stirred reaction mixture was cooled to room temperature. To the stirred mixture was added a solution of molecular bromine in acetic acid (3.14 g of 0.5 M solution, 20 mmol) in 40 mL acetic acid slowly over a period of 30 min at room temperature. After complete addition, the reaction mixture was heated at 40 °C for additional 12 h. The resulting white slurry was cooled to room temperature, filtered, washed with 5 mL of cold water followed by 2 mL of dichloromethane, and dried (8 inHg, 55 °C) to constant weight, yielding 2.87 g (65% yields) of 5-bromo-2-nitramino-4-picoline (**7**) as a white solid.

Method C. Using Tetrabutyl Ammonium Tribromide. To a 50-mL, single-necked round bottom flask was charged 30 mL of dichloromethane and 3.15 g (0.849 mol) of tetrabutylammonium tribromide. Then, 1 g (0.653 mol) of 2-nitramino-4-picoline (**5**) was added under stirring. After 10 min, 20 mL of water was introduced, and the biphasic reaction mixture was stirred vigorously for 48 h. The resulting slurry was filtered, washed with 1 mL of dichloromethane, and dried in vacuo (5 inHg, 50 °C) to give 1.02 g (65% yields) of 5-bromo-2-nitramino-4-picoline (**7**) as a white solid. **Analytical data:** mp 161.7 °C (charring). ^{1}H NMR ($CD_3OD/CDCl_3$) (δ, ppm): 2.39 (s, 3H, -CH_3), 7.63 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H). ^{13}C NMR (DMF-D7) (δ, ppm): 19.46, 116.05, 116.44, 147.22, 147.80, 159.81. HRMS calcd for $C_6H_6BrN_3O_2$ 230.96434, found 231.97217.

Preparation of 2-Amino-5-bromo-3-nitro-4-picoline (4). To a 250-mL, single-necked round-bottomed flask fitted with an internal thermocouple probe was added 72 mL sulfuric acid was added, and the temperature was maintained between 0 and 5 °C with external cooling. 5-Bromo-2-nitramino-4-picoline (**7**) (11.28 g, 0.486 mol) was added over period of 20 min, and the reaction mixture was stirred for an additional 20 min at 0–5 °C. The reaction mixture was cooled to room temperature and stirred for an additional 1 h. The reaction mixture was slowly added to 300 g of wet ice and stirred for additional 30 min. This cold solution was neutralized with 200 mL of 50% sodium hydroxide to pH 5.2. The resulting yellow slurry was filtered, and dried in vacuo (5 inHg, 40 °C) to give 9.53 g (95% yields) of 2-amino-5-bromo-3-nitro-4-picoline (**4**) as a yellow solid. **Analytical data:** mp 132 °C. IR (KBr, cm^{-1}): 1633, 1581, 1538, 1512, 1458, 1377, 1344, 1321, 1244, 869, 779. ^{1}H NMR ($CDCl_3$) (δ, ppm): 2.55 (s, 3H), 5.85 (bs, 2H), 8.25 (s, 1H). ^{13}C NMR ($CDCl_3$) (δ, ppm): 20.81, 112.14, 144.49, 151.91, 153.78 (2C). HRMS: calcd for $C_6H_6BrN_3O_2$ 230.96434, found (M + 1) 231.97217.

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