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The expedient access to bromo-pyridine carbaldehyde scaffolds using *gem*-dibromomethyl intermediates

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Abstract—A simple, efficient, and general two-step synthesis to bromo-pyridine carbaldehyde scaffolds is described. This direct route involves sequential reactions employing the dibromination of bromo-picolines followed by hydrolysis using an aqueous solution of calcium carbonate. Bromo-pyridine carbaldehyde scaffolds **1**–**7** were obtained in good overall yield. Bromo-dibromomethyl-pyridine intermediates have been isolated and characterized.

Pyridine derivatives are one of the most used frameworks for medicines, food flavorings, dyes, agrochemicals, rubber chemicals, and adhesives.[1] In drug discovery, it was well demonstrated that to avoid screening millions of compounds, one might attempt to bias combinatorial chemistry efforts to produce a set of molecules, which contain drug like patterns such as the pyridine heterocyclic ring.[2] From the perspective of structural diversification, we were interested in pyridine scaffolds bearing reactive orthogonal functional groups, with minimal protecting group transformation and synthetic manipulations. For the ease of subsequent derivatization, preferred orthogonal functional groups include halides and aldehydes. Aromatic halides and aldehydes represent very versatile reagents. However, to our knowledge, there is no methodology using the same chemical transformation of appropriate starting materials giving access to diverse regioisomers of bromo-pyridine carbaldehydes. Indeed, it is well described that substitution of the pyridine directs further derivatization, resulting in different specific routes for each regioisomer. Herein, we describe preliminary results concerning the expedient transformation of bromopicolines into gem-dibromomethyl derivatives to access seven bromopyridine carbaldehydes as useful building blocks.

The review of the most frequently used syntheses of bromopyridine carbaldehydes **1**–**7** shows that a common preparation from precursors bearing the same substituents is missing. Access to several regioisomers of bromopyridine carbaldehyde scaffolds has been reported and can be divided into three main methods. A first method consists in a conversion of halopyridines via a halogen–metal exchange reaction. Organolithium,[3] Grignard,[4] and palladium[5] reagents were reported as the most commonly used in the halogen–metal exchange. Such strategy allowed preparing regioisomers **1**–**4** and 5-bromopyridine-3-carbaldehyde. However, modifications such as nature of base, solvent, metal are required for each of the five regioisomers. A second method is the treatment of *ortho*-lithio bromopyridine with dimethylformamide following the procedure of Corey et al.[6] The four regioisomers **2**, **5**, **6**, and 4-bromo- pyridine-3-carbaldehyde, bearing both substituents in *ortho* position, were thus obtained.[7] A third approach consists of an oxidation of bromopicolines into the corresponding acid, ester, hydroxymethyl, or oxime bromo-pyridine derivatives.[8] Then a further specific transformation for each intermediate leads to bromo-pyridine carbaldehydes. An additional example of the third approach, known for benzaldehydes synthesis, is the preparation of dibromo derivatives, which are subsequently transformed into aldehydes. Interestingly, this method has

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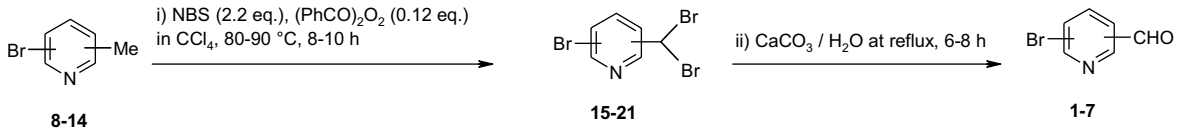
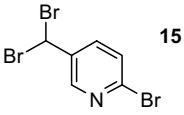
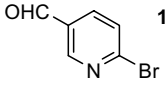
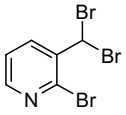
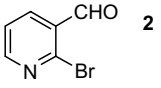
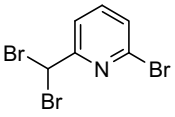
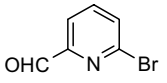
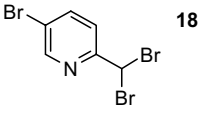
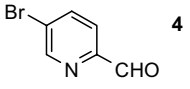
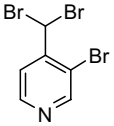
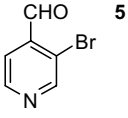
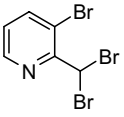
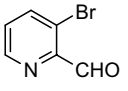
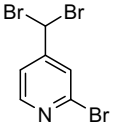
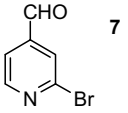
not been exploited for the preparation of bromo-pyridine carbaldehydes.

We wish to report here a concise and practical preparation of seven bromo-pyridine carbaldehydes from the same appropriate bromo-dibromomethyl-pyridine precursors (Scheme in Table 1). We account the straightforward methyl oxidation of bromopicolines into *gem*-dibromomethyl intermediates. Such pyridine precursors showed limited interest so far,[9] so we decided to explore the subsequent hydrolysis into the corresponding aldehydes for the different regioisomers of bromo-pyridines. The scope and generality of this process is illustrated with respect to various bromopicolines and the results are presented in Table 1.

The required starting materials, bromopicolines, were either commercially available, such as 3-bromo-6-picoline **11** or 3-bromo-4-picoline **12**, or readily prepared from the corresponding amino-picoline using a reported protocol analogous to Sandmeyer reaction,[10] as for compounds 2-bromo-5-picoline **8**, 2-bromo-3-picoline **9**, 2-bromo-6-picoline **10**, and 2-bromo-4-picoline **14**, or by bromination of 2-methylpyridine to give 3-bromo-2-picoline **13**.[11] Then the bromopicolines were converted into the corresponding bromo-dibromomethyl-pyridine intermediates using a radical bromination at reflux.[7] Use of 2.0 equiv of *N*-bromosuccinimide was found optimal to complete dibromination. The bromo-dibromomethyl-pyridine compounds **15**–**21** were purified by flash chromatography and stored at room temperature. Intermediates **15**, **17**, and **18** were described earlier.[12] Intermediates **16**, **19**, **20**, and **21** were isolated and characterized for the first time. Exposure of **15**–**20** to a solution of $CaCO_3$ (2.2 equiv) in water (10 vol) at reflux gave the corresponding aldehydes **1**–**6**. Reaction of **21** to a

Table 1. Synthesis of bromo-pyridine carbaldehyde scaffolds **1**–**7**



Entry	Reagent	Bromo-dibromomethyl-pyridine[15]	Product[16]	Yield[a] (%)	
				(i) Bromination	(ii) Hydrolysis
1	2-Bromo-5-picoline **8**[14]	 **15**	 **1**	82	79
2	2-Bromo-3-picoline **9**[14]	 **16**	 **2**	83	83
3	2-Bromo-6-picoline **10**[14]	 **17**	 **3**	88	86
4	3-Bromo-6-picoline **11**	 **18**	 **4**	88	73
5	3-Bromo-4-picoline **12**	 **19**	 **5**	78	77
6	3-Bromo-2-picoline **13**[11]	 **20**	 **6**	76	84
7	2-Bromo-4-picoline **14**[14]	 **21**	 **7**	72[b]	60[c]

[a] Yields of bromination (i), hydrolysis (ii) steps were calculated after purification by flash chromatography or crystallization.
[b] The bromination was carried out for 24 h.
[c] Hydrolysis was carried out in dry DMSO instead of water.

solution of $CaCO_3$ (5.0 equiv) in DMSO (5 vol) at 145 °C yielded the aldehyde **7**. Pyridine carbaldehydes **1**–**7** were isolated in moderate to good yield. This hydrolysis condition was reported earlier for the synthesis of 4-bromobenzaldehyde from the corresponding *gem*-dibromomethyl intermediate but such simple hydrolysis conditions have not been applied to pyridine derivatives.[13]

Optimization of experimental conditions (temperature, solvent) allowed us to obtain regioiomers **1**–**7** in parallel from the corresponding intermediates **15**–**21**. An amount of 2.2 equiv of $CaCO_3$ was found optimal for complete hydrolysis to give the desired carbaldehydes **1**–**6**. A plausible route could involve the formation of bromohydrin intermediate followed by HBr elimination to give the product. Analysis of Table 1 showed that every regioisomer could be synthesized efficiently. Surprisingly, 2-bromo-4-dibromomethylpyridine **21** was the only regioisomer, which exhibited different reactivity in an aqueous solution of $CaCO_3$. In contrast to the close analogue **19**, intermediate **21** exhibited lower solubility. Replacement of $CaCO_3$ by $CsCO_3$ or K_2CO_3 in water did not improve the reaction. The use of DMSO, a well solubilizing polar solvent circumvented this issue and 2-bromopyridine-4-carbaldehyde **7** could be obtained in 60% yield in the presence of 5 equiv of $CaCO_3$. A mixture of solvents, such as a water/dioxane (3/7), led to a better but not total solubility of the reactants and the formation of a complex combination of starting material, compound **7** and 2-bromo-pyridine-4-carboxylic acid derivative were obtained. We presume that the solubility of reagents could be the limiting factor for this transformation and was observed only for regioisomer **21**.

As an example of scale-up production, a 150 g batch of 2-bromo-5-picoline **8** was transformed into 2-bromo-5-dibromomethyl-pyridine in an isolated 70% yield. The further exposure of 201 g of compound **15** to an aqueous solution of $CaCO_3$ gave 6-bromo-pyridine-3-carbaldehyde **1** in 80% yield. This example illustrates the possibility of efficient scale up of bromo-pyridine carbaldehydes synthesis.

In summary, a general and expedient synthesis of bromopyridine carbaldehydes **1**–**7** from the corresponding bromo-*gem*-dibromomethyl intermediates has been developed. No drastic difference in reactivity was observed among the pyridine regioisomers. The simple and ready availability of starting materials distinguishes this preparation from other regioisomer-dependent routes to bromo-pyridine carbaldehydes. Furthermore, we believe that this protocol will improve the access to every regioisomer of bromo-pyridine carbaldehyde scaffolds and analogues, and increase their use especially in combinatorial chemistry for structure–activity relationship studies.

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14. General procedure for bromo-picolines **8**, **9**, **10**, and **14**: at −20 °C, to a mixture of amino-methyl-pyridine (60.0 g, 0.55 mol) in 48% HBr (1 L) was added Br_2 (80 mL, 1.55 mol) dropwise over a period of 20 min. The reaction mixture was stirred for 30 min at −20 °C. Then a solution of $NaNO_2$ (101.0 g, 1.47 mol) in water (200 mL) was added over a period of 30 min. The resulting reaction mixture was stirred for 2 h at the same temperature, then quenched with aqueous NaOH (20%) until pH = 10. The

mixture was extracted with diethyl ether, dried over Na_2SO_4, concentrated, and distilled under reduced pressure to give the desired compounds in 86–91%.

15. General procedure for bromo-dibromomethyl-pyridines **15**–**21**: To a solution of bromo-picoline (25.0 g, 0.145 mol) in CCl_4 (250 mL) was added NBS (51.66 g, 0.29 mol), benzoylperoxide (2.5 g, 0.018 mol) and gradually heated to reflux for 4 h. The reaction mixture was cooled to rt. The succinimide was filtered off and the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography using petroleum ether/EtOAc (9/1).

    2-Bromo-5-dibromomethyl-pyridine **15**:[9b] white solid; yield: 38.0 g (82%); $R_f = 0.8$ (petroleum ether/EtOAc, 9/1), mp 91–92 °C; ^{1}H NMR (DMSO-d_6): δ 7.44 (s, 1H), 7.76 (d, 1H, $J = 9.0$ Hz), 8.03 (d, 1H, $J = 9.0$ Hz), 8.59 (s, 1H).

    2-Bromo-3-dibromomethyl-pyridine **16**: colorless oil; yield: 39.0 g (83%); $R_f = 0.8$ (petroleum ether/EtOAc, 9/1); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.28 (s, 1H), 7.62 (m, 1H), 8.36–8.4 (m, 2H). Anal. Calcd for $C_6H_4Br_3N$: C, 21.85; H, 1.22; N, 4.25. Found: C, 22.06; H, 1.39; N, 4.13.

    2-Bromo-6-dibromomethyl-pyridine **17**:[9b] a white solid; yield: 40.0 g (88%); $R_f = 0.78$ (petroleum ether/EtOAc, 9/1), mp 130–131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32 (s, 1H), 7.65–7.71 (m, 2H), 7.82–7.86 (m, 1H).

    5-Bromo-2-dibromomethyl-pyridine **18** (Int. Appl. 01/72711, 2001): white solid; yield: 40.0 g (88%); mp 56–59 °C; $R_f = 0.78$ (petroleum ether/EtOAc, 9/1); ^{1}H NMR (DMSO-d_6): δ 6.6 (s, 1H), 7.56 (d, 1H, $J = 6.4$ Hz), 7.88 (dd, 1H, $J = 6.4$, 2.4 Hz), 8.46 (d, 1H, 2.4 Hz). Anal. Calcd for $C_6H_4Br_3N$: C, 21.85; H, 1.22; N, 4.25. Found: C, 22.22; H, 1.46; N, 4.15.

    3-Bromo-4-dibromomethyl-pyridine **19**: colorless oil; yield: 36.0 g (78%); $R_f = 0.7$ (petroleum ether/EtOAc, 9/1); ^{1}H NMR (DMSO-d_6) δ 7.1 (s, 1H), 7.62 (d, 1H, $J = 6.4$ Hz), 7.72 (s, 1H), 8.42 (d, 1H, $J = 6.4$ Hz). Anal. Calcd for $C_6H_4Br_3N$: C, 21.85; H, 1.22; N, 4.25. Found: C, 21.92; H, 1.44; N, 4.20.

    3-Bromo-2-dibromomethyl-pyridine **20**: white solid; yield: 2.3 g (76%); mp 48–50 °C; $R_f = 0.75$ (petroleum ether/EtOAc, 9/1); ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1H), 7.30–7.42 (m, 1H), 8.28–8.32 (m, 2H). Anal. Calcd for $C_6H_4Br_3N$: C, 21.85; H, 1.22; N, 4.25. Found: C, 22.07; H, 1.42; N, 4.23.

    2-Bromo-4-dibromomethyl-pyridine **21**: white solid; yield: 33.0 g (72%); $R_f = 0.75$ (petroleum ether/EtOAc, 9/1), mp 65–67 °C; ^{1}H NMR (DMSO-d_6) δ 7.3 (s, 1H), 7.66 (d, 1H, $J = 6.4$ Hz), 7.78 (s, 1H), 8.48 (d, 1H, $J = 6.4$ Hz). Anal. Calcd for $C_6H_4Br_3N$: C, 21.85; H, 1.22; N, 4.25. Found: C, 21.82; H, 1.33; N, 4.19.

16. General procedure for scaffolds **1**–**7**: A mixture of bromo-dibromomethyl-pyridine (20.0 g, 0.062 mol), $CaCO_3$ (13.6 g, 0.136 mol) in water (500 mL) was heated at reflux for 8 h. The reaction mixture was cooled to rt and extracted with EtOAc (2×250 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude compound was purified by crystallization from Petroleum ether/EtOAc (95/5).

    6-Bromo-pyridine-3-carbaldehyde **1**:[9a] white solid; yield: 7.2 g (79%); mp 101–103 °C; $R_f = 0.5$ (petroleum ether/EtOAc, 4/1); IR (neat) ν_{max} 3055, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.88 (d, 1H, $J = 8.1$ Hz), 8.15 (dd, 1H, $J = 8.1$, 2.4 Hz), 8.88 (d, 1H, $J = 1.8$ Hz), 10.08 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6): δ 128.8, 130.7, 138.6, 146.8, 152.3, and 191.5.

    2-Bromo-pyridine-3-carbaldehyde **2**:[3c] white solid; yield: 9.6 g (83%); mp 73–75 °C; $R_f = 0.5$ (petroleum ether/EtOAc, 4/1); IR (KBr pellet) ν_{max} 3025, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.64 (dd, 1H, $J = 6.4$ and 2.8 Hz), 8.18 (m, 1H), 8.63 (m, 1H), 10.17 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 124.2, 130.2, 138.4, 143.9, 154.7, 191.2.

    6-Bromo-pyridine-2-carbaldehyde **3**:[8b] white solid; yield: 9.9 g (86%); mp 76–78 °C; $R_f = 0.5$ (petroleum ether/EtOAc, 4/1); IR (neat) ν_{max} 3040, 1700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.94–8.06 (m, 3H) and 9.88 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 121.4, 132.8, 140.9, 141.8, 153.1, 191.8.

    5-Bromo-pyridine-2-carbaldehyde **4** (Jones, G.; Pitman, M. A.; Lunt, E.; Lythgoe, D. J.; Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *Tetrahedron* **1997**, *53*, 8257–8268): white solid; yield: 8.4 g (73%); mp 95–97 °C; $R_f = 0.5$ (petroleum ether/EtOAc, 4/1); IR (neat) ν_{max} 3055, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, $J = 6.4$ Hz), 8.00–8.04 (m, 1H), 8.85 (s, 1H), 10.03 (s, 1H); ^{13}C NMR($CDCl_3$): δ 122.6, 126.1, 138.3, 139.8, 151.4, 192.2.

    3-Bromo-pyridine-4-carbaldehyde **5**:[7] white solid; yield: 8.9 g (77%); mp 84–86 °C; IR (neat) ν_{max} 3045, 1690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.82 (d, 1H, $J = 6.4$ Hz), 8.10 (d, 1H, $J = 6.4$ Hz) 8.62 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6): 124.2, 129.5, 136.3, 144.4, 151.2, 191.9.

    3-Bromo-pyridine-2-carbaldehyde **6** (Int. Appl. 02/22600, 2002): white solid; yield: 0.98 g (84%); mp 87–89 °C; $R_f = 0.55$ (petroleum ether/EtOAc, 4/1); IR (KBr pellet) ν_{max} 3025, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.41–7.46 (m, 1H), 8.16–8.17 (m, 1H), 8.56–8.57 (m, 1H), 10.33 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 123.3, 130.3, 137.8, 145.2, 154.3, and 190.9.

    2-Bromo-pyridine-4-carbaldehyde **7**:[8b] white solid; yield: 1.44 g (60%); mp 56–57 °C; $R_f = 0.6$ (petroleum ether/EtOAc, 7/3); IR (KBr pellet) ν_{max} 3015, 1700 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.84 (dd, 1H, $J = 5.1$, 1.0 Hz), 8.07 (s, 1H), 8.67 (d, 1H, $J = 5.1$ Hz), 10.02 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 121.3, 127.3, 142.3, 144.3, 152.0, and 191.7.