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A practical synthesis of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid—the key precursor toward imatinib

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ABSTRACT

A simple and efficient in situ synthesis of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid through direct reductive alkylation of 1-methylpiperazine in the presence of triacetoxy sodium borohydride in 95–99% yields is elaborated. The process is easy to scale-up for the large-scale synthesis of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid as the key synthetic intermediate of imatinib. This method was used for the synthesis of benzyl derivatives of heterocyclic amines in 87–90% yields.

4-[(4-Methylpiperazin-1-yl)methyl]benzoic acid is the key intermediate for the synthesis of imatinib, 4-[(4-methyl-1-piperazinylmethyl)-*N*-[4-methyl-3-{[4-(3-pyridinyl)-2-pyrimidi-nyl]amino} phenyl]benzamide mesylate, which is an effective drug for the treatment of chronic myeloid leukemia.[1] Known methods for its synthesis use catalytic reductive amination under hydrogen pressure,[1c,2a] which gives the product in 70% yield. Its synthesis using 4-(bromo- or chloromethyl) benzoic acid derivatives as substrates followed by hydrolysis gives the title product in 58–89% overall yield in two or three steps.[2b–d] Hence the synthesis of imatinib is difficult for large-scale manufacture.

We have investigated the reductive amination of substituted aryl aldehydes with heterocyclic amines with the objective of developing a mild and effective method for the synthesis of tertiary benzyl amines, including 4-[(4-methyl-piperazin-1-yl)methyl]benzoic acid.[3] Herein, we report a new and highly efficient procedure for its preparation.

The reductive amination of carbonyl compounds (or the reductive alkylation of amines) is a very useful method, which provides access to structurally diverse amines.[4] This reaction allows conversion of a carbonyl functionality into an amine by direct reaction of a mixture of the carbonyl compound and the amine with a suitable reducing agent in a single operation without preformation of an intermediate imine or iminium salt.

Many different common reagents for this reduction have been proposed;[4] representatives include various modified borohydride derivatives such as $NaBH_3CN$,[4h] $NaBH(OAc)_3$,[4f] $NaBH_4$–$(MgClO_4)_2$,[4i] $NaBH_4$–$Ti(OPr\text{-}i)_4$,[4j] $NaBH_4$–$ZnCl_2$ (or $NiCl_2$),[4k,l] $NaBH_4$–$H_3PW_{12}O_{40}$.[4e] However, most of these reagents have one drawback or another, for example, toxicity, high cost, or low selectivity. In addition, to the best of our knowledge, the synthesis of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid by reductive alkylation making use of the above-mentioned reagents or with $NaBH_4$ alone has not been reported.

We found that in the presence of sodium borohydride–acetic acid as a reducing system, the reaction of aryl aldehydes with *N*-methylpiperazine (**1**) resulted in the corresponding tertiary benzyl amines in good yields. The desired compounds **4a,b** were obtained under optimized reaction conditions in 90–99% yields (Scheme 1 and Table 1).

The reaction between aldehyde **2** and amine **1** in the presence of acetic acid occurs evidently through aldiminium salt **3** formation followed by reduction to the benzyl amines **4a,b**. The sodium borohydride–acetic acid reducing system forms sodium triacetoxyborohydride in situ and is a very effective reagent for iminium salt reduction. The method was found to tolerate formyl and carboxyl groups, and the formation of by-products was not observed.

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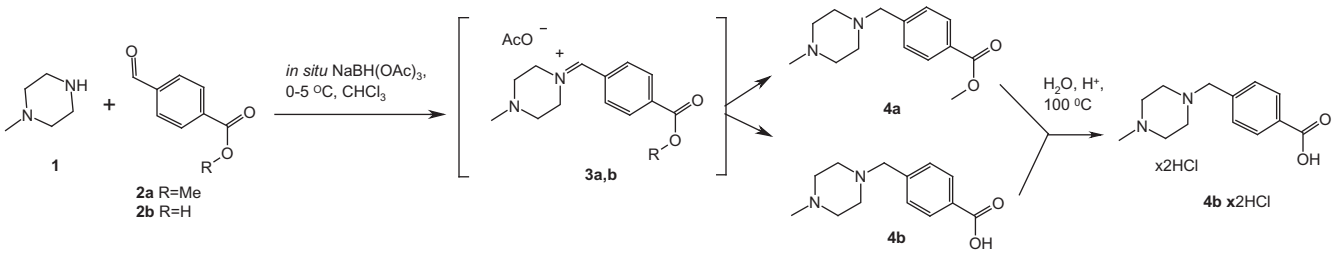


Scheme 1. Reductive alkylation of *N*-methylpiperazine with aryl aldehydes.

Table 1
Preparation of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid by reductive amination in the presence of $NaBH_4$–AcOH as the reducing system

Entry	Substrate	Temp (°C), solvent	Time (h)	Product[b]	Yield[c] (%)
1	**2a**[a]	0–5, $CHCl_3$	12	**4a**[5]	99
2	**2b**[a]	0–5, $CHCl_3$	12	**4b**[6]	90
3	**4a**	100, H_2O	3	**4b** × 2HCl[7]	97[d]

[a] Commercially available.
[b] Products **4** were obtained and characterized as described.[5–7]
[c] Isolated yield.
[d] Total yield of two stages: **2a**→**4a**→**4b** × 2HCl.

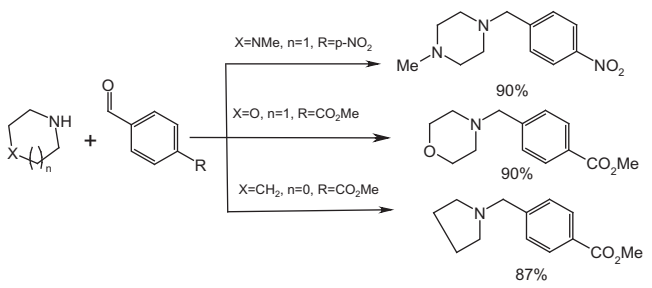
The benzyl amines were isolated by treatment of the reaction solution with base followed by extraction; no further purification was required.

The ^1H NMR, ^{13}C NMR, IR, MS, and elemental analyses were in complete agreement with structures **4a,b**. The highest yield of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid (**4b**) was achieved when it was isolated as the dihydrochloride **4b** × 2HCl by treating the benzylation product with hydrochloric acid or by acid hydrolysis of methyl 4-[(4-methylpiperazin-1-yl)methyl]benzoate (**4a**).[5–7]

As far as we know, our protocol constitutes the first report of the successful use of 4-formylbenzoic acid and its methyl ester in the non-catalytic direct reductive alkylation to prepare 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid, and also is the first example using in situ prepared triacetoxy sodium borohydride. All the previously reported procedures use more complex reagents with less effect.

In light of its simplicity, this method is expected to be suitable for the synthesis of other tertiary amines. Thus we have synthesized tertiary amines including methyl 4-(morpholino-methyl)benzoate, methyl 4-(pyrrolidin-1-ylmethyl)benzoate, and 1-methyl-4-(4-nitrobenzyl)piperazine.[5] These amines were obtained in 87–90% yields, while the same reductive alkylation reaction under the previously described protocol produced these amines in 47–70% yields (Scheme 2).[3a,c,5]

In conclusion, we have described a facile and highly efficient procedure for the in situ synthesis of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid through direct reductive alkylation of 1-methylpiperazine in the presence of triacetoxy sodium borohydride. This synthesis has several advantages, including a simple experimental procedure, use of commercially available starting materials, mild reaction conditions, and high yields of the reaction products. The procedure allows rapid scale-up for the large-scale synthesis of 4-[(4-methylpiperazin-1-yl)-methyl]benzoic acid. It is also suitable for the preparation of other benzyl derivatives of heterocyclic amines.



Scheme 2. Reductive alkylation of heterocyclic amines with aryl aldehydes.

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5. *General procedure for the benzylation of 1-methylpiperazine* (**1**). *Synthesis of methyl 4-[(4-methylpiperazin-1-yl)methyl]benzoate* (**4a**): AcOH (100%) (140 mL, 2.44 mol) was added over 1 h to a flask containing stirred $NaBH_4$ (20.0 g, 0.53 mol) and $CHCl_3$ (220 mL) at 0–5 °C. The resulting mixture was stirred at 0–5 °C for 1.5 h and 1-methylpiperazine (**1**) (28.0 ml, 0.25 mol) and a solution of methyl 4-formylbenzoate (**2a**) (43.4 g, 0.26 mol) in $CHCl_3$ (60 mL) were added. The resulting mixture was stirred at 0–5 °C for 1 h and then for 12 h at rt. the mixture was treated with H_2O (150 mL) and Na_2CO_3 until pH 8.0–9.0. The aqueous phase was extracted with EtOAc (2 × 100 ml) then both organic layers were combined, washed with H_2O (1 × 100 ml), and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvents gave methyl 4-[(4-methylpiperazin-1-yl)methyl]benzoate (**4a**): yellowish oil; yield: 61.6 g, 99%. ^1H NMR (500 MHz, $CDCl_3$): 2.30 (s, 3H, CH_3–N), 2.48 (m, 8H, CH_{pip}), 3.57 (s, 2H, CH_2); 3.92 (s, 3H, CH_3OCO); 7.43 (d, *J* = 8.0 Hz, 2H, H_{ar}), 7.99 (d, *J* = 8.0 Hz, 2H, H_{ar}); ^{13}C NMR (125 MHz, $CDCl_3$): 45.99, 51.90, 53.06, 55.02, 62.52, 128.81, 128.87, 129.46, 143.78, 167.05. IR (film): 3450, 1725, 1275, 755, 620 cm^{-1}. MS (70 eV): *m/z* 248 $[M]^+$ (90%), 149 $[M\text{-}NC_4H_8NCH_3]^+$ (100%), 99 $[NC_4H_8NCH_3]^+$ (80%). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29. Found: C, 67.54; H, 7.98; N, 11.59. Using this protocol methyl 4-(morpholinomethyl)benzoate was obtained in 90% yield, methyl 4-pyrrolidin-1-ylmethyl)benzoate in 87% yield and 1-methyl-4-(4-nitrobenzyl)piperazine in 90% yield; these products had spectral characteristics (^1H NMR, ^{13}C NMR, IR, MS) identical with those described earlier.[3a]
6. *Synthesis of 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid* (**4b**) *and dihydrochloride* (**4b** × 2HCl): According to the general procedure, amine **1** (28.0 g, 0.28 mol) and 4-formylbenzoic acid (**2b**) (45.0 g, 0.30 mol) were reacted for 12 h. The mixture was treated with H_2O and Na_2CO_3 until pH 7.0 and extracted with EtOAc. Evaporation of the aqueous residue under vacuum gave 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid (**4b**): white powder; yield: 61.2 g, 90%; mp. 255 °C; ^1H NMR (500 MHz, D_2O) δ: 2.81 (s, 3H, CH_3-N), 2.5–3.4 (m, 8H, CH_{pip}), 3.72 (s, 2H, CH_2), 7.38 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.88 (d,

J = 8.0 Hz, 2H, H_{Ar}); ^{13}C NMR (125 MHz, D_2O) δ: 42.50, 48.98, 52.35, 60.27, 128.79, 129.70, 135.80, 136.97, 174.71; IR (KBr) ν: 3450, 1643, 1461, 1350, 1296 cm^{-1}; MS (70 eV) m/z: 234 $[M]^+$ (40%), 190 $[M\text{-}CO_2]^+$ (30%), 135 $[HO_2CC_6H_4CH_2]^+$ (100%), 99 $[NC_4H_8NCH_3]^+$ (70%), 44 $[C_2H_6N]^+$ (90%). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.66; H, 7.61; N, 11.90. Found: C, 66.78; H, 7.65; N, 12.10.

Evaporation of the aqueous phase to the one third of the original volume, and refluxing of the residue with 60 mL of concentrated HCl (pH of the mixture must be 1-2) for 3 h and evaporation of H_2O gave 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid dihydrochloride (**4b** × 2HCl): white powder; yield: 81.9 g, 95%; mp. 308–309 °C (lit.[2b] 309–311 °C); ^1H NMR (500 MHz, D_2O) δ: 3.07 (s, 3H, CH_3–N), 3.72 (m, 8H, CH_{pip}), 4.58 (s, 2H, CH_2), 7.65 (d, J = 8.0 Hz, 2H, H_{Ar}) 8.06 (d, J = 8.0 Hz, 2H, H_{Ar}); ^{13}C NMR (125 MHz, D_2O) δ:43.08, 48.56, 50.40, 59.99, 130.66, 131.69, 131.90, 132.87, 169.81; IR (KBr) ν: 3430, 2890, 2650–2400, 1720, 1460, 1248 cm^{-1}; MS (70 eV) m/z: 234 $[M–2HCl]^+$ (60%). Anal. Calcd for $C_{13}H_{20}Cl_2N_2O_2$: C, 50.81; H, 6.51; Cl, 23.13; N, 9.12. Found: C, 50.70; H, 6.35; Cl, 22.89; N, 8.94.

7. *General procedure for acid hydrolysis of methyl 4-[(4-methylpiperazin-1-yl)methyl]-benzoate* (**4a**): a mixture of methyl 4-[(4-methylpiperazin-1-yl)methyl]benzoate (**4a**) (61.6 g, 0.25 mol), H_2O (60 mL) and concentrated HCl (120 mL) was heated to boiling, then the mixture was diluted with 120 mL of hot H_2O and refluxed for 3 h. The hot reaction mixture was treated with activated charcoal, filtered and the H_2O was evaporated. The solid residue was boiled in benzene to remove residual H_2O using a Dean–Stark trap, then filtered and dried to afford 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid dihydrochloride (**4b** × 2HCl): white powder; yield: 75.2 g, 98%; purity (by HPLC): 99.3%.