A New and Efficient Route for the Synthesis of Naturally Occurring Catecholamines

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Dedicated to Professor Enrico Mincione on the occasion of his 70th birthday

Abstract: Catecholamines, sympathomimetic drugs and adrenergic receptor antagonists, have been prepared by a regioselective oxidation of the corresponding 4-hydroxyphenethylamine derivatives by 2-iodoxybenzoic acid (IBX) in homogeneous as well as in heterogeneous conditions and followed by cleavage of the amino protective group. By using polymer-supported IBX, after the first oxidation, the oxidant can be recovered, regenerated, and efficiently reused for several additional times. An efficient, easy and green procedure for the synthesis of *N*-(methoxycarbonyl)dopamine, key component of many pharmaceuticals, has also been reported.

Key words: *N*-(methoxycarbonyl)dopamine, catecholamines, aromatic hydroxylation, 2-iodoxybenzoic acid, polymer-supported IBX

Dopamine (3,4-dihydroxyphenethylamine, **1a**), norepinephrine [noradrenaline, (2-amino-1-(3,4-dihydroxyphenyl)ethanol, **2a**], and epinephrine [adrenaline, 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol, **3a**] (Figure 1) are endogenous catecholamines released by the sympathetic nervous system in response to different stimuli including physical activity, psychological stress, blood loss, and many other normal or disease-related provocations. As the functions mediated or modified by the sympathetic nervous system are diverse, these compounds play an important role in the treatment of many clinical disorders, including hypertension, cardiovascular shock, arrhythmias, asthma, migraine headaches, and anaphylactic reactions.[1]

Generally, for clinical purposes this class of compounds is utilized as hydrochlorides **1b**, **2b**, and **3b** (Figure 1). Dopamine is particularly important in the regulation of the movement. It has a variety of therapeutic uses also as cardiotonic agent in the treatment of acute circulatory insuffiency and hypotension. Norepinephrine is the chemical mediator liberated by mammalian postganglionic adrenergic nerves showing cardiovascular effects. Epinephrine is the primary hormone secreted by the adrenal medulla in mammals. It has many clinical uses for the potent actions on the heart, on vascular and other smooth muscle. It is one of the most powerful vasopressor drugs known exhibiting vascular action on veins, arteries redistributing the blood flow; it acts as cardiac stimulant and has effects on gastrointestinal, uterine, and bronchial muscles.

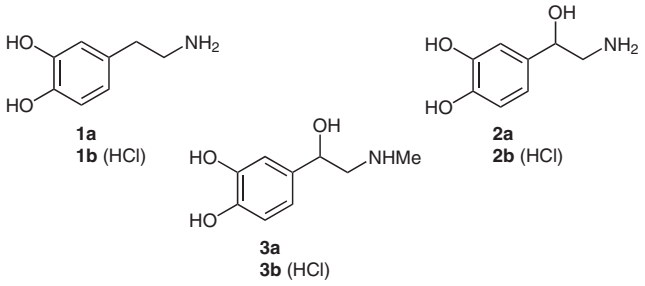

Figure 1

The biosynthesis of dopamine (**1a**) is a two-step procedure from L-tyrosine and it is the immediate metabolic precursor of norepinephrine (**2a**) and epinephrine (**3a**).[2]

Despite their biological and pharmacological importance, few synthesis of these catecholamines have been reported in literature.[3,4]

Recently, our research activity focused on the preparation of bioactive catecholic compounds by oxidative procedure under green chemistry conditions.[5] In the last years, we have published the synthesis of hydroxytyrosol [2-(3,4-dihydroxyphenyl)ethanol] derivatives[6] and lignan and neolignans catecholic derivatives.[7] The key reagent was 2-iodoxybenzoic acid [1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, IBX, Figure 2] able to convert phenols[8] and phenolic methyl aryl ethers[9] into *o*-quinones with high regioselectivity. After the in situ reduction with a water solution of sodium dithionite ($Na_2S_2O_4$), the corresponding catecholic compounds were obtained. More recently, we showed the efficiency of polymer-supported IBX (Figure 2)[10] in the regioselective oxidation of some of these compounds.[11]

In order to develop a new and efficient route for the synthesis of pharmacologically catecholamines, we describe

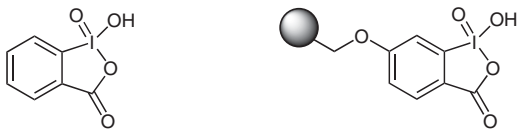

Figure 2

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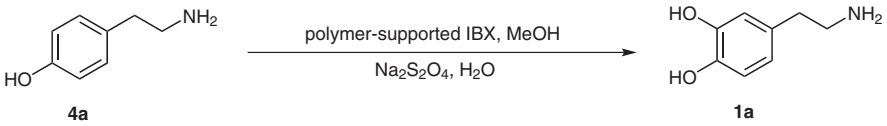


Scheme 1

here the first selective aromatic *ortho*-hydroxylation of 4-hydroxyphenethylamine derivatives by IBX under homogeneous as well as heterogeneous conditions.

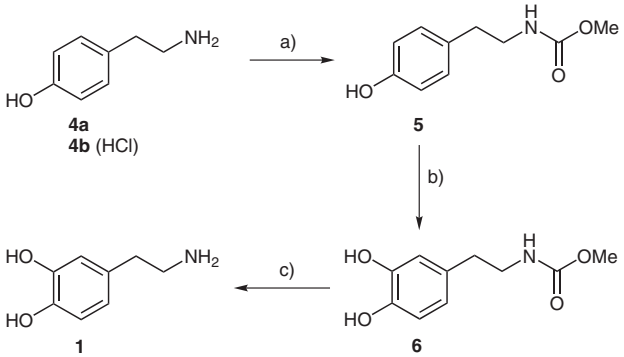
The conversion of tyramine (4-hydroxyphenethylamine, **4a**) into dopamine (**1a**) was our model reaction. Supported by our recent results,[11] we started the study in direct oxidation of tyramine (**4a**) by using polymer-supported IBX in methanol as solvent (Scheme 1).

Tyramine (**4a**, 1.0 mmol) was solubilized in methanol and polymer-supported IBX (loading factor: 1.1, 2.1 mmol) was added. The reaction was kept under magnetic stirring at room temperature and monitored by thin layer chromatography (TLC). After one hour we performed the reductive workup adding water and sodium dithionite (2.0 mmol) but we were not able to isolate dopamine (**1a**), most probably because of its high polarity.

Therefore, we developed the alternative procedure reported in Scheme 2 where the first step (step a) was the chemoselective protection of the amino group of tyramine (**4a**) in order to decrease the hydrophilicity of starting material and to facility the work up after the oxidative/reductive step.

Thanks to our knowledge in the chemoselective functional group protection,[12] we verified the efficiency of dimethyl carbonate (DMC) to convert the amine group of tyramine into its methyl carbamate. In our hands, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 mmol), dimethyl carbonate, used as both reagent and solvent, was able to convert tyramine (**4a**) into *N*-(methoxycarbonyl)tyramine (**5**, >98% yield). We obtained similar result starting from tyramine hydrochloride (**4b**) by using excess DBU (2.1 mmol).

In the following step (step b) both homogeneous and polymer-supported IBX were utilized to perform the oxidation

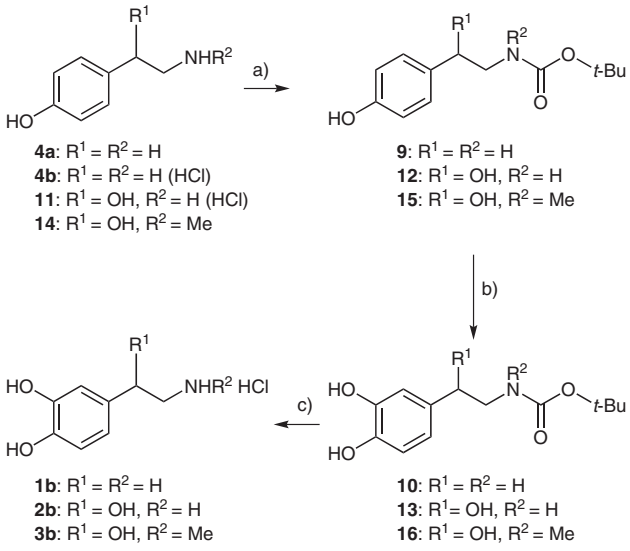


Scheme 2 *Reagents and conditions:* (a) DMC, DBU, reflux, 16 h, 95%; (b) IBX, MeOH, 0 °C or polymer-supported IBX, DMC, r.t.; $Na_2S_2O_4$, H_2O, r.t., 5 min, 90% (c) deprotection.

of *N*-(methoxycarbonyl)tyramine (**5**). Reactions were carried out in methanol or dimethyl carbonate as solvent and checked by TLC. We observed the complete conversion of the substrate either by using homogeneous IBX and polymer-supported IBX. After the in situ reduction with sodium dithionite, the corresponding *N*-(methoxycarbonyl)dopamine (**6**) was isolated in good yields (90%). This result is noteworthy. In fact, this compound is a component of some pharmaceutical formulations useful in the treatment of nerve disorders and cardiovascular diseases,[13] and an active molecule for protecting human cells and tissues from the harmful, aging-accelerating effects of free radicals and reactive oxygen species.[14] Recently, some authors have published the synthesis of a variety of methyl carbamates from amines with (trimethylsilyl)diazomethane ($TMSCHN_2$) under bubbling carbon dioxide in benzene–methanol as reaction media, but according to this procedure, compound **6** was isolated in trace amounts only (6%).[15]

The third step of the procedure depicted in Scheme 2 was the cleavage of the methyl carbamate moiety of **6** to give dopamine (**1**). Unfortunately, a wide number of reagents and different experimental conditions (basic and acidic conditions, hydrides)[16] did not give satisfactory results.

In order to isolate dopamine (**1**), we applied a similar procedure changing the amine protecting group to the *tert*-butoxycarbonyl (Boc), easy to introduce and to remove under mild conditions (Scheme 3).[17] According to the



Scheme 3 Reagents and conditions: (a) $(Boc)_2O$, $NaHCO_3$, MeOH–H_2O (2:1), 2–24 h; (b) IBX, MeOH, 0 °C or polymer-supported IBX, solvent, r.t.; $Na_2S_2O_4$, H_2O, r.t., 5 min, 90% (c) TMSCl, MeOH, r.t., 3 h.

Table 1 Oxidation of Compounds **9**, **12**, and **15**

Entry	Prod.	Conditions	Conv. (%)	Yield[a] (%)
1	**9**	IBX, MeOH, 0 °C, 1 h[b]	>98	95
2	**9**	polymer-supported IBX, DMC, 0.5 h[b]	>98	95
3	**12**	IBX, MeOH, 0 °C, 1 h[b]	>98	92
4	**12**	polymer-supported IBX, THF, r.t., 0.5 h[b]	>98	80
5	**15**	IBX, MeOH, 0 °C, 1 h[b]	>98	90
6	**15**	polymer-supported IBX, THF, r.t., 0.5 h[b]	>98	80

[a] Yields are given for isolated products.
[b] Oxidation with IBX followed by a reductive step with H_2O and $Na_2S_2O_4$.

literature,[18] tyramine (**4a**) and tyramine hydrochloride (**4b**) (1.0 mmol) were converted into *N*-Boc-tyramine **9** in quantitative yield by using di-*tert*-butyl dicarbonate (1.5 mmol), sodium hydrogen carbonate (3.0 mmol) in methanol–water, 2:1 as reaction medium. After the oxidative step with IBX at 0 °C in methanol or dimethyl carbonate and reduction by sodium dithionite, *N*-Boc-dopamine **10** was isolated in satisfactory yields both with homogeneous and heterogeneous IBX (Table 1, entries 1 and 2). Finally, the deprotection of *N*-Boc-dopamine **10** was successfully achieved by using chlorotrimethylsilane in methanol at room temperature for three hours.[19] In this case, the work up consisted in the evaporation of the solvent under reduced pressure and allowed us to isolate dopamine hydrochloride (**1b**) in quantitative yield.

According to the satisfactory overall yield of our multistep procedure, we utilized commercial available (±)-octopamine hydrochloride (**11**) and (±)-synephrine (**14**) as starting materials to prepare (±)-norepinephrine hydrochloride (**2b**) and (±)-epinephrine hydrochloride (**3b**) (Scheme 3). As expected, **11** and **14** were quantitatively converted into the corresponding N-Boc derivatives **12** and **15**, then they were oxidized using polymer-supported IBX to the catecholic compounds **13** and **16** in excellent yields (Table 2, entries 3–6), by using tetrahydrofuran as solvent because of the low solubility in dimethyl carbonate of the substrates. Finally, the deprotection of the *tert*-butoxycarbonyl group with chlorotrimethylsilane gave **2b** and **3b** in quantitative yields.

In order to make this procedure attractive from an industrial economic and environmentally point of view, the efficiency of polymer-supported IBX as oxidant in several cycles of oxidations after its recovery was verified. The model reaction was the oxidation of *N*-Boc-tyramine **9** to *N*-Boc-dopamine **10**. Then, after the disappearance of the substrate, the polymer was removed from the solution containing the final product by filtration. Polymer-supported IBX was regenerated with a solution of tetrabutylammonium oxone and methanesulfonic acid according to the procedure reported in our previous paper.[11] The oxidant was then added to a solution of new substrate in dimethyl carbonate. As shown in Table 2, polymer-supported IBX was used for at least five cycles of oxidation without loss of efficiency to give **10** (Table 2, entries 1–5). We observed a little drop of efficiency at the sixth recycling experiment, the yield decreased from 95% to 88% but no side-chain products were isolated showing that the oxidations proceeded again with high regioselectivity (Table 2, entries 6–10).

Table 2 Experiment of Recycling of Polymer-Supported IBX in the Oxidation of **9**

Entry	Run	Conv. (%)	Yield[a] (%)
1	1	>98	>98
2	2	>98	>98
3	3	>98	>98
4	4	>98	>98
5	5	95	95
6	6	88	88
7	7	75	75
8	8	72	72
9	9	70	70
10	10	70	70

[a] Yields are given for isolated **9**.

In conclusion, we described a new and efficient preparation of pharmacologically bioactive catecholamines with a simple multistep procedure where the key step was the selective aromatic hydroxylation of the corresponding precursors both with homogeneous and heterogeneous IBX. Final products were isolated in excellent overall yields. When the oxidative step was achieved in heterogeneous conditions, the oxidant could be recovered and reused for five oxidation runs without any loss of efficiency and selectivity. A new methodology of chemoselective protection of the amino group of tyramine with dimethyl carbonate and DBU was described. After the oxidative/reductive step, *N*-(methoxycarbonyl)dopamine (**6**), a compound present in pharmaceutical preparations useful in the treatment of nerve disorders and cardiovascular diseases and previously synthesized only in trace, was isolated by us in good yield.

Reagents and solvents were purchased from Aldrich Company (Milan, Italy). All chemicals used were of analytical grade. Homogeneous IBX was prepared in laboratory as described in the literature.[20] Polymer-supported IBX was purchased from Novabiochem (loading factor 1.1 mmol/g). Silica gel 60 F254 plates and silica gel 60 were furnished from Merck. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 200 MHz spectrometer using $CDCl_3$ and CD_3OD as solvents. IR spectra were recorded on a Jasco FT/IR 430 spectrophotometer. GC-MS analysis were performed on a Shimatzu VG 70/250S apparatus equipped with a CP-SIL 8 CB-MS column (25 m, 0.25 mm and 0.25 mm film thickness). The analyses were per-

formed using an isothermal temperature profile of 100 °C for 2 min, followed by a 10 °C/min temperature gradient until 280 °C for 15 min. The injector temperature was 280 °C.

Methyl 4-Hydroxyphenethylcarbamate [*N*-(Methoxycarbonyl)tyramine, 5]

Tyramine (**4a**, 137 mg, 1.0 mmol) was solubilized in DMC (8 mL). Then, DBU (183 mg, 1.2 mmol) was added and the mixture was kept under magnetic stirring at reflux temperature for 16 h. When the substrate had been consumed, the reaction was worked up by cooling to r.t. and the DMC was evaporated under vacuum. The residue was solubilized in EtOAc and washed with 1 M HCl. The organic extracts were treated with sat NaCl soln and dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification of the crude mixture by chromatography (silica gel, hexane–EtOAc, 1:1) gave exclusively **5** as a colorless oil (95% yield). We obtained the same result starting from tyramine **4b** but using an excess of DBU (2.1 mmol). Analytical and spectroscopic data of **5** were identical to those given in the literature.[15]

Protection of the Amino Group with Di-*tert*-butyl Dicarbonate; General Procedure[18]

The amine (1.0 mmol) was solubilized in MeOH–H_2O (2:1, 6 mL). Then $NaHCO_3$ (252 mg, 3.0 mmol) and $(Boc)_2O$ (327 mg, 1.5 mmol) were slowly added. The mixture was kept under magnetic stirring for 2–24 h depending on the substrate. When the substrate had been consumed, MeOH was evaporated under vacuum and the residue was solubilized in EtOAc and washed with 1 M HCl. The organic extracts were treated with sat. NaCl soln and dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification of crude mixture by chromatography (silica gel, hexane–EtOAc, 1:1) gave **9**, **12**, and **15**, which were characterized by analytical and spectroscopic analysis.

***tert*-Butyl 4-Hydroxyphenethylcarbamate [*N*-(*tert*-Butoxycarbonyl)tyramine, 9]**

White solid; yield: >98%; mp 73–74 °C (Lit.[21] 74–75 °C). Analytical and spectroscopic data were according to the literature.[18,21]

***tert*-Butyl 2-Hydroxy-2-(4-hydroxyphenyl)ethylcarbamate [*N*-(*tert*-Butoxycarbonyl)octopamine, 12]**

White solid; yield: 85%; mp 143–144 °C.

IR (KBr): 3402, 3270, 2969, 2931, 1649, 1303, 1074 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.5 Hz, 2 H), 6.62 (d, *J* = 8.5 Hz, 2 H), 4.48 (dd, *J* = 4.2, 7.9 Hz, 1 H), 3.18 (dd, *J* = 4.4, 14.0 Hz, 1 H), 3.02 (dd, *J* = 8.5, 13.9 Hz, 1 H), 1.27 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.8, 156.2, 132.8, 127.0, 115.1, 79.6, 72.6, 49.5, 28.1.

MS (EI, 70 eV): *m*/*z* (%) = 253 (0.5), 197 (4.6), 179 (3.2), 162 (5.5), 135 (13.5), 123 (100).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.56; H, 7.66; N, 5.49.

***tert*-Butyl [2-Hydroxy-2-(4-hydroxyphenyl)ethyl](methyl)carbamate [*N*-(*tert*-Butoxycarbonyl)synephrine, 15]**

White solid; yield: >98%; mp 45–46 °C

IR (KBr): 3444, 1670, 1367, 1230 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$–CD_3OD): δ = 7.04 (d, *J* = 8.0 Hz, 2 H), 6.62 (d, *J* = 8.0 Hz, 2 H), 4.69–4.65 (m, 1 H), 3.79–3.70 (m, 1 H), 3.38–3.19 (m, 1 H), 2.66 (s, 3 H), 1.21 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$–CD_3OD): δ = 157.4, 156.2, 133.2, 127.1, 115.1, 80.1, 72.4, 56.8, 35.7, 28.2.

MS (EI, 70 eV): *m*/*z* (%) = 267 (0.5), 194 (2.9), 145 (11.0), 136 (15.2), 123 (100).

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.00; H, 7.82; N, 5.20.

Oxidation with IBX; General Procedures

(a) Homogeneous conditions: The substrate (1.0 mmol) were dissolved in MeOH (8.0 mL), then IBX (336 mg, 1.2 mmol) was added. The soln was stirred at 0 °C until complete consumption of the substrate. H_2O (8.0 mL) and $Na_2S_2O_4$ (348 mg, 2.0 mmol) were added and the soln was stirred at r.t. for 5 min. After evaporation of the solvent under vacuum, the residue was solubilized with EtOAc and treated with sat. $NaHCO_3$ soln. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with sat. NaCl soln and dried (Na_2SO_4). After evaporation of the solvent, the corresponding catecholic compounds were isolated.

(b) Heterogeneous conditions: The substrate (1.0 mmol) was solubilized in the appropriate solvent (8.0 mL) at r.t. under magnetic stirring and then commercial polymer-supported IBX (954 mg, 2.1 mmol) was added. When the substrate had been completely consumed, the polymer was recovered by simple filtration and the remaining soln was treated with H_2O (8.0 mL) and $Na_2S_2O_4$ (348 mg, 2.0 mmol). After the evaporation of the solvent under reduced pressure, the final products were extracted with EtOAc from the aqueous residue. The combined organic phases were washed with sat. NaCl soln and dried (Na_2SO_4). After evaporation of the solvent, hydroxylated compounds were isolated. Polymer-supported IBX was regenerated by treating the filtered resin with a soln of tetrabutylammonium oxone and MsOH according to the procedure reported by us in a previous paper.[11]

Methyl 3,4-Dihydroxyphenethylcarbamate [*N*-(Methoxycarbonyl)dopamine, 6]

Colorless oil; yield: 98%. Analytical and spectroscopic data were according to the literature.[15]

***tert*-Butyl 3,4-Dihydroxyphenethylcarbamate [*N*-(*tert*-Butoxycarbonyl)dopamine, 10]**

White solid; yield: 90%; mp 136–138 °C.[22] Analytical and spectroscopic data were according to the literature.[22]

***tert*-Butyl 2-(3,4-Dihydroxyphenyl)-2-hydroxyethylcarbamate [*N*-(*tert*-Butoxycarbonyl)norepinephrine, 13]**

White solid; yield: 98%; mp 56–57 °C

IR (KBr): 3430, 2974, 2932, 1681, 1517, 1367, 1286 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$–CD_3OD): δ = 6.69 (d, *J* = 8.0 Hz, 1 H), 6.62–6.45 (m, 2 H), 4.50 (dd, *J* = 4.2, 7.9 Hz, 1 H), 3.24 (dd, *J* = 4.2, 14.0 Hz, 1 H), 3.07 (dd, *J* = 7.8, 13.9 Hz, 1 H), 1.33 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$–CD_3OD): δ = 156.9, 144.3, 144.2, 133.7, 117.8, 115.0, 112.8, 79.8, 72.8, 49.8, 28.2.

MS (EI, 70 eV): *m*/*z* (%) = 270 (94), 252 (100), 214 (13), 196 (51).

Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20; O, 29.71. Found: C, 57.88; H, 7.22; N, 5.25; O, 29.65.

***tert*-Butyl [2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl](methyl)carbamate [*N*-(*tert*-Butoxycarbonyl)epinephrine, 16]**

White solid; yield: 98%; mp 159–160 °C

IR (KBr): 3523, 3288, 2979, 2933, 2877, 1650, 1230 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$–CD_3OD): δ = 6.71 (s, 1 H), 6.61 (d, *J* = 8.1 Hz, 1 H), 6.53–6.49 (m, 1 H), 4.59–4.57 (m, 1 H), 3.21–3.11 (m, 2 H), 2.62 (s, 3 H), 1.24 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$–CD_3OD): δ = 156.2, 144.3, 143.8, 134.5, 117.6, 114.7, 112.8, 79.7, 72.7, 56.9, 35.6, 28.7.

MS (EI, 70 eV): *m*/*z* (%) = 269 (25), 251 (100).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94; O, 28.24. Found: C, 59.40; H, 7.52; N, 4.90; O, 28.18.

Deprotection of *N*-Boc-Amines; General Procedure[19]

The substrate (1.0 mmol) was dissolved in MeOH (20 mL) and TMSCl (217 mg, 2.0 mmol) was added. The mixture was kept at reflux temperature for 3 h. After the evaporation of the solvent under reduced pressure, the amine hydrochloride derivative was isolated in quantitative yields. Spectroscopic and analytical data of **1b**, **2b**, and **3b** were accord with authentic samples.

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