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Selective deprotection of *N-Boc*-imidazoles and pyrazoles by $NaBH_4$ in EtOH

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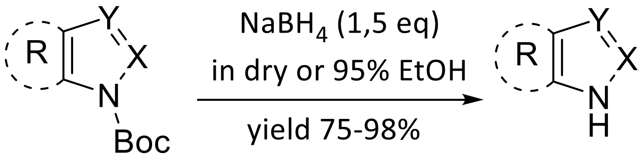
Abstract

Herein, a novel method for the selective *N-Boc* deprotection of imidazoles, benzimidazoles and pyrazoles in good to excellent yield (75-98%), using $NaBH_4$ in EtOH at room temperature is reported. Under these conditions, the primary *Boc*-protected amines and a number of *N-Boc*-protected aromatic heterocycles such as pyrrole and indole remain completely intact.



Imidazole (R=H, X=H, Y=N)
Benzimidazole (R=Ph, X=H, Y=N)
Pyrazole (R=H, Y=H, X=N)

Keywords: *N-tert*-Butoxycarbonyl group; deprotection; imidazole; benzimidazole; pyrazole; indole

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Introduction

The *N-Boc* methodology is widely used in organic synthesis to prepare various functionalized heterocycles as well as in the field of peptide chemistry for the preparation of very interesting bioactive products. The *N*-protected amines being acid labile and inert towards catalytic hydrogenation and basic reagents,[1,2] are compatible with many other protecting groups (*N-Cbz*, *N-Fmoc*, benzylester etc) and therefore ideal partners for orthogonal protective protocols.

Nevertheless, several heterocycles of nitrogen including imidazoles, benzimidazoles, pyrazoles, pyrroles, indoles etc., protected with *N-Boc* group, can also be deprotected under basic conditions. In almost all cases the deprotection is selective only for some heterocycles under certain conditions.

Specifically, the *N-Boc*-imidazole is deprotected with H_2NNH_2 or NH_3/MeOH,[3] the selective cleavage of *Boc* group from *N-Boc* imidazoles and indoles is achieved with Cs_2CO_3, imidazole at 70 °C [4] and *N-Boc*-2-lithiated pyrroles are deprotected with NaOMe/MeOH/THF.[5] Furthermore, deprotection of *N-Boc*-indoles with TBAF in refluxing THF has been reported, [6] while removal of *Boc* protecting group from the aromatic ring of indole as well as the pyrrolidine ring of *S*-proline and of pyroglutamic acid was achieved with $Sn(OTf)_2$ in dry CH_2Cl_2.[7] Thermolytic removal of the *Boc*-protecting group of indoles and pyrroles at 180 °C has also been reported [8] and hydrolysis at 100 °C [9] was used for the deprotection of *N-Boc*-imidazole, benzimidazole, pyrazole, 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-benzo[*d*][1,2,3] triazole as well as other *N*-protected aliphatic amines. Cleavage of the *N-Boc* group of imidazole moiety can be achieved with K_2CO_3 /MeOH [10a, b] under heating, and the same deprotection can be carried out from the heterocycles of indole, indazole, azaindole, indazole, pyrazole, indolone, quinolinone, oxazolone with Na_2CO_3 in refluxing DME. [11] In addition to the aforementioned methods, hydrolytic cleavage of *N-Boc* group from primary aromatic amines, imidazole and benzimidazoles moiety with protic ionic liquids[12] has been reported. Furthermore, the primary *N-Boc* group can be deprotected by excess of *t*-butoxide in slightly wet THF or MeTHF. [13]

During a multistep synthesis of a certain compound, we attempted to reduce a methyl ester with $NaBH_4$ in dry EtOH. Unexpectedly, we obtained deprotection of the *N-Boc*-benzimidazole moiety, present in the substrate structure. Because of this complication, we found it interesting and relevant to investigate the reaction in detail.

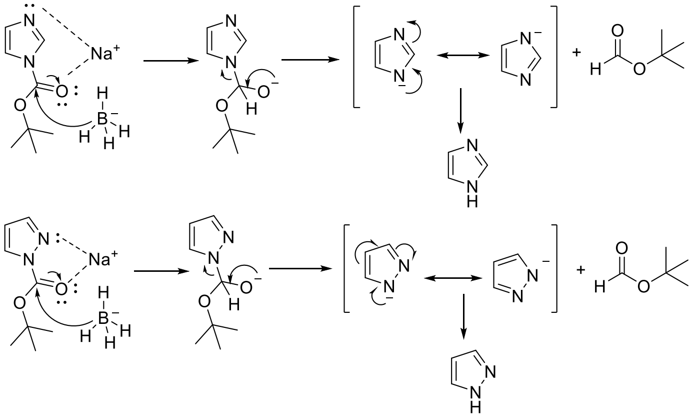
Results and Discussion

In the present study we describe a simple and highly efficient method for the deprotection of *Boc*-protected imidazoles, benzimidazoles and pyrazoles, using $NaBH_4$ in dry or 95% EtOH at rt. The reaction provides the corresponding deprotected heterocycles (Table 1, entries 1, 4, 5, 6, 9, 10) in very good to excellent yield. By using the base NaH (60% in mineral oil) in dry THF, only partial deprotection occurred (Table 1, entry 2), while deprotection was completely impeded by using a suspension of $NaBH_4$ in dry THF (Table 1, entry 3). The benzyl 1*H*-imidazole-1-carboxylate (**6**) (Table 1, entry 8) was fully recovered after 4 h, despite the use of EtOH as solvent. [14] It was also observed that an excess of reagent and prolonged reaction time was necessary for the completion of the reaction of 1-(*tert*-butoxycarbonyl)-1*H*-imidazole-4-carboxylic acid (**2**) bearing a free carboxylic group (Table 1, entry 4), probably because of its acidic character and the consequent reaction with $NaBH_4$. In the case of di-*Boc*-histamine (**3**) (Table 1, entry 5) and of N^{a}, N^{t}-bis(*tert*-butoxycarbonyl)-*L*-histidine (**4**) (Table 1, entry 6), the selective deprotection of N^{im}-*Boc* group was accomplished, and products **15** and **16** were respectively obtained in almost quantitative yield. On the contrary, in the case of the methyl ester of N^{a},

N^t-bis-*Boc*-protected-*L*-histidine (Table 1, entry 7) the reduction of methyl ester was clearly detected by MS after 3 h. Upon completion of the reaction followed by the appropriate purification, *tert*-butyl (*S*)-(1-hydroxy-3-(1*H*-imidazol-4-yl)propan-2-yl)carbamate (**17**) was obtained in 72-77% yield. No reaction was observed in the case of *tert*-butyl 1*H*-pyrrole-1-carboxylate (**9**) (Table 1, entry 11), *tert*-butyl 1*H*-indole-1-carboxylate (**10**) (Table 1, entry 12) or N^α,1-bis(*tert*-butoxycarbonyl)-*L*-tryptophan (**11**) (Table 1, entry 13), using either dry or 95% EtOH. In all the aforementioned cases, the starting compounds were completely recovered after 5 hrs. Finally, the *tert*-butyl 5-methyl-2-oxobenzo[*d*]oxazole-3(2*H*)-carboxylate (**12**) (Table 1, entry 14) also gave the reduction product *tert*-butyl (2-hydroxy-5-methylphenyl) carbamate (**20**).

Mechanism

The proposed mechanism explaining the observed reactivity of $NaBH_4$ on *Boc* protected substrates of imidazole, benzimidazole and pyrazole is presented in Scheme 1. In both cases, the Na^+ can be stabilized by the lone pairs of oxygen and nitrogen forming a type of favored 6-membered and 5-membered ring respectively. The hydride anion from the B-H bond of BH_4^-, attacks like a nucleophile on the carbonyl of *tert*-butoxycarbonyl group, and the tetrahedral intermediate can evolve by considering the *N*-heterocyclic anions as the leaving groups, well stabilized by resonance. The anions in the protic solvent generate the heterocycles, and *tert* butyl formate is also produced.



Scheme 1. Possible mechanism for the cleavage of *Boc*-group from imidazole and pyrazole with $NaBH_4$.

Table 1. Cleavage of *N*-protected heterocycles with $NaBH_4$

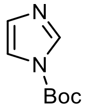
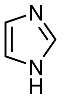
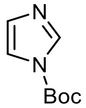
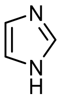
Entry	Substrate	Product	Reaction Time, Yield[a] in 95% EtOH (in dry EtOH)
1	 **1**	 **13**	4h, 95% (3.5h, 98%)
2[b]	 **1**	 **13**	24h, 38%

Table 1. Continued

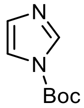
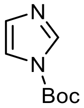
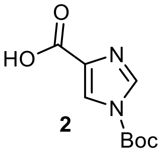
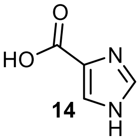
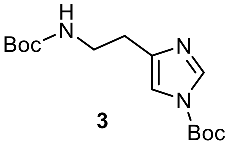
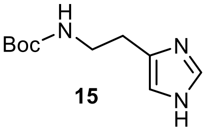
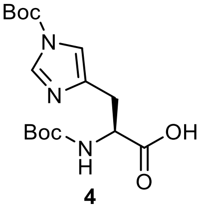
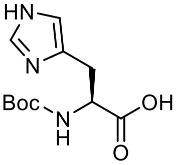
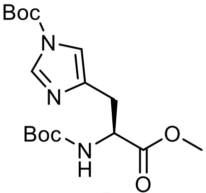
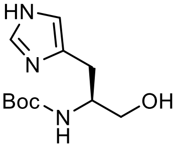
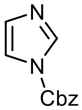
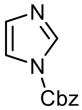
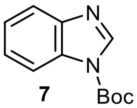
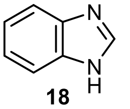
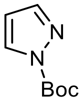
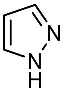
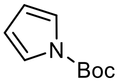
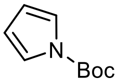
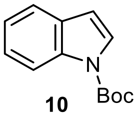
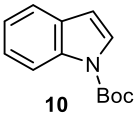
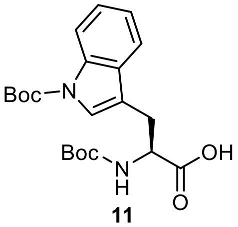
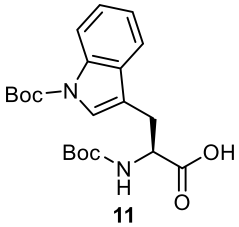
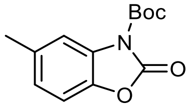
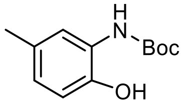
Entry	Substrate	Product	Reaction Time, Yield[a] in 95% EtOH (in dry EtOH)
3[c]	 **1**	 **1**	24h, No reaction
4[d]	 **2**	 **14**	45h, 95% (48h, 90%)
5	 **3**	 **15**	3.5h, 90% (4h, 95%)
6	 **4**	 **16**	7h, 92% (29h, 87%)
7	 **5**	 **17**	6h, 77% (7h, 72%)
8	 **6**	 **6**	4h, No reaction (4h, No reaction)
9	 **7**	 **18**	6h, 93% (5h, 90%)
10	 **8**	 **19**	3.5h, 78% (4h, 75%)
11	 **9**	 **9**	5h, No reaction (5h, No reaction)
12	 **10**	 **10**	5h, No reaction (5h, No reaction)

Table 1. Continued

Entry	Substrate	Product	Reaction Time, Yield[a] in 95% EtOH (in dry EtOH)
13	 **11**	 **11**	5h, No reaction (5h, No reaction)
14	 **12**	 **20**	3h, 95% (3h, 92%)

[a] Yields are given in isolated products; all compounds were either compared with known data in the literature, whereas new compounds (**2, 12, 17**) were fully characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS; [b] Use of 1.5 eq NaH (60% in mineral oil) in dry THF; [c] Dry THF was used as solvent; [d] 3 eq of $NaBH_4$ were used (instead of 1.5 eq).

Conclusions

The selective cleavage of *N-Boc*-protecting group of imidazole, benzimidazole and pyrazole in good to excellent yields can be achieved by using $NaBH_4$ in EtOH (95% or dry). Under the same conditions, other aromatic heterocycles like pyrrole and indole but also the primary *N-Boc*-protected amines remain completely intact. Therefore, this study is highly relevant for researchers engaged in multistep synthesis of substrates containing these entities, such as peptides containing histidine and tryptophan which possess the side chain of imidazole and indole, respectively. Furthermore, if a reduction is attempted with $NaBH_4$, at a later stage in the synthetic process of a compound with a variety of orthogonally protected functional groups, the deprotection of the aforementioned rings can cause undesirable complications. Moreover, this study substantially complements the standard acidic or basic deprotections of *tert*-butyl carbamates already known in literature.

Experimental Section

General. All chemicals and solvents were reagent grade and used without purification. Dry EtOH was purchased from Merck and compounds **11, 13, 14, 18, 19**, pyrrole, indole, histamine, (*S*)-histidine and its methylester were also commercially available. Chromatographic purification of products was accomplished using Merck Silica Gel 60 (70−230 or 230−400 mesh). Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 aluminum plates. TLC spots were visualized with UV light or phosphomolybdic acid in EtOH. Melting points were determined on a Büchi 530 apparatus and are uncorrected. ^{1}H and ^{13}C spectra were recorded on a Varian Mercury (200 and 50 MHz respectively) and for the new compounds (**2, 12, 17**) on a Bruker Avance Neo (400 and 100 MHz respectively) in $CDCl_3$, CD_3OD and DMSO-d$_6$. Specific rotations were measured at 25 °C on a Perkin–Elmer polarimeter using a 10 cm cell. Electron spray ionization (ESI) mass spectra were recorded on a Finnigan, Surveyor MSQ Plus spectrometer. HRMS spectra were recorded on a Bruker Maxis Impact QTOF Spectrometer.

Synthesis of *Boc*-protected substrates 1-12

***tert*-Butyl 1*H*-imidazole-1-carboxylate (1).** To a stirred solution of imidazole (**13**) (681 mg, 10.0 mmol) in MeOH (40 mL), Et_3N (1.40 mL, 1 equiv., 10.0 mmol) and Boc_2O (2.40 g, 1.1 equiv., 11.0 mmol) were added. The reaction mixture was continuously stirred at room temperature overnight, the solvent was evaporated under reduced pressure and the residue, dissolved in AcOEt, was washed with brine, 5% $NaHCO_3$ and H_2O. The organic phase was dried with Na_2SO_4, the solvent was evaporated and purification of the product was achieved by column chromatography eluting with AcOEt-petroleum ether (8:2). The product was isolated as white solid; yield 1.6 g (92%). The analytical data were in accordance to the literature.[15a,b] Mp 46-48 °C ($mp_{(lit)}$[15a] 45-47.5 °C); Rf (AcOEt:PE 8:2) 0.58; ^1H NMR ($CDCl_3$) δ 8.00-7.99 (m, 1H, NCHN), 7.31-7.29 (m, 1H, Ar-H), 6.96-6.95 (m, 1H, Ar-H), 1.54 (s, 9H, $3xCH_3$); ^{13}C NMR ($CDCl_3$) δ 147.05 (CON), [137.01 130.19, 117.07] (Ar), 85.51, 27.83; MS (ESI) *m/z* (%) 169.14 (100) ($[M+H]^+$).

1-(*tert*-Butoxycarbonyl)-1*H*-imidazole-4-carboxylic acid (2). Prepared from 1*H*-imidazole-4-carboxylic acid (**14**) and Boc_2O as described for compound **1** above. The residue of the reaction after the evaporation of MeOH, was acidified with 5% H_2SO_4 at pH~5 and extracted with AcOEt twice. The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvent was evaporated. The product was isolated as white solid; yield 93 %; Rf ($CHCl_3$:MeOH 8:2) 0.45; mp 258-260 °C; ^1H NMR ($CDCl_3$) δ 9.52 (s, 1H, COOH), 8.23 (s, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 1.66 (s, 9H, $3xCH_3$); ^{13}C NMR ($CDCl_3$) δ 164.94, 146.02, 137.50, 134.41, 123.23, 87.42, 27.82; HRMS exact mass calculated for $[M-H]^-$ ($C_9H_{11}N_2O_4$) requires *m/z* 211.0724, found *m/z* 211.0723.

***tert*-Butyl 4-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-imidazole-1-carboxylate** [16] **(3)**. Yield: 89 %; mp 124-126 °C ($mp_{(lit)}$[16] 129.5-130.5 °C); Rf (AcOEt) 0.66; ^1H NMR ($CDCl_3$) δ 7.97 (s, 1H, NCHN), 7.10 (s, 1H, NCHC), 5.05 (br s, 1H, NH), 3.45-3.34 (m, 2H, $NHCH_2$), 2.70 (t, *J* 6.6 Hz, 2H, CH_2), 1.57 (s, 9H, $ImCOOC(CH_3)_3$), 1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ [156.00, 147.05] (NCOO), [141.21, 136.88, 113.76] (Ar), 85.49, 79.12, 39.84, 28.46, 27.94, 26.47; MS (ESI) *m/z* (%) 312.13 (100) ($[M+H]^+$).

N^a,N^t-Bis(tert-butoxycarbonyl)-(*L*)-histidine [17] **(4).** Yield 70 %; $[\alpha]_D$ +19.0 ° (c 2, $CHCl_3$); mp 75-77 °C; Rf ($CHCl_3$:MeOH 8:2) 0.76; ^1H NMR ($CDCl_3$) δ 8.10 (s, 1H, Ar-H, NCHN), 7.16 (s, 1H, Ar-H), 5.61-5.57 (m, 1H, NHC*H*), 4.37 (s, 1H, NH), 3.16-3.13 (m, 2H, $NHCH_2$), 1.59 (s, 9H, $ImCOO(CH_3)_3$), 1.44 (s, 9H, $3xCH_3$); ^{13}C NMR ($CDCl_3$) δ 173.36 (COOH), [155.24, 146.40] (NCOO), [137.07, 136.44, 115.69] (Ar), 86.51, 79.69, 52.84, 45.66, 28.46, 27.91; MS (ESI) *m/z* (%) 354.04 (100) ($[M-H]^-$).

***tert*-Butyl (*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1*H*-imidazole-1-carboxylate** [18a,b] **(5)**. Yield: 50 %; $[\alpha]_D$ +23.47 ° (c 1.21, $CHCl_3$) ($[\alpha]_{D(lit)}$[18a] +19.9 ° (c 1.16, $CHCl_3$)); mp 99.2-100.8 °C ($mp_{(lit)}$[18b] 105-107 °C); Rf (AcOEt:PE 8:2) 0.7; ^1H NMR ($CDCl_3$) δ 7.97 (s, 1H, NCHN), 7.12 (s, 1H, Ar-H), 5.73-5.69 (m, 1H, NHC*H*), 4.54 (s, 1H, NH), 3.72 (s, 3H, $COOCH_3$), 3.04-3.02 (m, 2H, CH_2Im), 1.59 (s, 9H, $ImCOO(CH_3)_3$), 1.43 (s, 9H, $3xCH_3$); ^{13}C NMR ($CDCl_3$) δ 172.17 (*C*OOMe), [155.34, 146.71] (NCOO), [138.50, 136.78, 114.42] (Ar), 85.44, 79.52, 77.36, 53.04, 52.18, 28.18, 27.73; MS (ESI) *m/z* (%) 370.04 (100) ($[M+H]^+$).

Benzyl 1*H*-imidazole-1-carboxylate [19] **(6).** Yield: 97 %, Rf (DCM:MeOH 9:1) 0.61; ^1H NMR ($CDCl_3$) δ 8.14 (s, 1H, NCHN), 7.46-7.31 (m, 6H, Ar-H), 7.04 (s, 1H, Ar-H), 5.39 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 148.59 (CON), [137.14 133.94, 130.65, 129.17, 128.85, 128.74, 117.14] (Ar), 69.83; MS (ESI) *m/z* (%) 203.08 (100) ($[M+H]^+$).

***tert*-Butyl 1*H*-benzo[*d*]imidazole-1-carboxylate** [20] **(7)**. Yield: 59 %; mp 88-90 °C; Rf (AcOEt:PE 8:2) 0.65; ^1H NMR ($CDCl_3$) δ 8.43 (s, 1H, NCHN), 7.99 (d, *J* 7.3 Hz, 1H, Ar-H), 7.78 (dd, J_1 7.00 Hz, J_2 1.63 Hz, 1H, Ar-H), 7.40-7.33 (m, 2H, Ar-H), 1.70 (s, 9H, $3xCH_3$); ^{13}C NMR ($CDCl_3$) δ 148.31 (CON), [144.40, 142.22, 131.67, 125.63, 124.41, 120.81, 114.55] (Ar), 85.68, 28.27; MS (ESI) *m/z* (%) 219.29 (100) ($[M+H]^+$).

***tert*-Butyl 1*H*-pyrazole-1-carboxylate [21] (8).** Yield: 61 %; Rf (AcOEt:PE 2:8) 0.59; ^{1}H NMR (CDCl$_3$) δ 7.97 (d, *J* 2.8 Hz, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 6.26 (dd, J_1 2.80 Hz & J_2 1.60 Hz, 1H, Ar-H), 1.52 (s, 9H, 3xCH$_3$); ^{13}C NMR (CDCl$_3$) δ 147.44 (CON), [143.68, 130.39, 108.41] (Ar), 85.10, 27.70; MS (ESI) *m/z* (%) 169.32 (100) ([M+H]$^+$).

***tert*-Butyl 1*H*-pyrrole-1-carboxylate [22] (9).** Yield: 50 %; Rf (AcOEt:PE 1:1) 0.79; ^{1}H NMR (CDCl$_3$) δ 7.26-7.24 (m ,2H, 2xNCH), 6.23-6.20 (m, 2H, Ar-H), 1.60 (s, 9H, 3xCH$_3$); ^{13}C NMR (CDCl$_3$) δ 148.90 (NCO), [119.94, 111.84] (Ar), 83.45, 27.95; MS (ESI) *m/z* % 168.22 (100) ([M+H]$^+$).

***tert*-Butyl 1*H*-indole-1-carboxylate [23] (10).** Yield: 47 %; Rf (AcOEt:PE 3:7) 0.77; ^{1}H NMR (CDCl$_3$) δ 8.24 (d, *J* 8.20 Hz, 1H, NCH), 7.66 (d, *J* 3.80 Hz, 1H, Ar-H), 7.64-7.59 (m, 1H, Ar-H), 7.42-7.33 (m, 1H, Ar-H), 7.32-7.24 (m, 1H, Ar-H), 6.61 (dd, J_1 3.60 Hz & J_2 0.60 Hz, 1H, Ar-H), 1.72 (s, 9H, 3xCH$_3$); ^{13}C NMR (CDCl$_3$) δ 149.82 (CON), [135.22, 130.61, 125.90, 124.23, 122.67, 120.98, 115.21, 107.33] (Ar), 83.60, 28.21; MS (ESI) *m/z* (%) 218.24 (100) ([M+H]$^+$).

***tert*-Butyl-5-methyl-2-oxobenzo[*d*]oxazole-3(2*H*)-carboxylate (12).** To a stirred solution of 5-methylbenzo[*d*]oxazol-2(3*H*)-one, prepared from 2-amino-4-methylphenol and 1,1′-carbonyldiimidazole (CDI) according to the literature,[24] (200 mg, 1.34 mmol) in acetonitrile (MeCN) (1ml), DMAP (17 mg, 0.1 equiv., 0.134 mmol) and Boc$_2$O (350 mg, 1.2 equiv., 1.61 mmol) were added. The reaction mixture was continuously stirred at room temperature overnight, the solvent was evaporated under reduced pressure and the residue, dissolved in AcOEt, was washed with 5% H$_2$SO$_4$, brine and H$_2$O to neutral pH. The organic phase was dried with Na$_2$SO$_4$, the solvent was evaporated and purification of the product was achieved by column chromatography eluting with AcOEt-petroleum ether (2:8). The product was isolated as white solid; yield 200 mg (95%); mp 88-89 °C; Rf (AcOEt: petroleum ether 2:8) 0.27.

^{1}H NMR (CDCl$_3$) δ 7.54-7.53 (m, 1H, Ar-H), 7.06-7.03 (d, *J* 8.2 Hz, 1H, Ar-H), 7.01-7.00 (ddd, J_1 8.2 Hz, J_2 1.7 Hz, J_3 0.7 Hz, 1H, Ar-H), 2.39 (s, 3H, CH$_3$), 1.67 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$) δ 149.69, 147.80, 139.73, 134.32, 127.41, 125.04, 115.14, 109.46, 86.02, 27.98, 21.61; HRMS exact mass calculated for [M+Na]$^+$ ($C_{13}H_{15}NNaO_4$) requires *m/z* 272.0893, found *m/z* 272.0895.

General procedure of the reaction of the substrates with NaBH$_4$ in dry or 95% EtOH (Table 1)

To a stirring solution of the organic substrate (1 mmol) in dry EtOH or 95% EtOH (3 mL), NaBH$_4$ [57.0 mg, 1.5 eq, 1.5 mmol, (in case of compound **2**, 114.0 mg, 3 eq, 3 mmol)] was added in small portions and the reaction mixture was left stirring at rt. The reaction was followed by TLC (or mass spectroscopy) and upon completion, it was quenched by the dropwise addition of a 3N solution of HCl at 0 °C, until gas production ceased (pH ~7). The organic solvent was evaporated in high *vacuo* and the residue was dissolved in CHCl$_3$ (3 mL) and dried with Na$_2$SO$_4$. After evaporation of the solvent, the product was isolated and appropriately purified.

Imidazole (13) was isolated as white solid. Mp 90-91 °C (mp[25] 89-91 °C); ^{1}H NMR (CDCl$_3$) δ 9.62 (br s, 1H, NH), 7.70 (s, 1H, NCHN), 7.11 (d, *J* 0.84 Hz, 2H, Ar-H); ^{13}C NMR (CDCl$_3$) δ 135.28, 121.92; MS (ESI) *m/z* (%), 69.25 (100) ([M+H]$^+$).

1*H*-Imidazole-4-carboxylic acid (14) was isolated as white solid, and the analytical data were in accordance to the literature.[26] Mp 292-294 ^{o}C (mp$_{(lit)}$[26] 294-295 ^{o}C); Rf (AcOEt) 0.14; ^{1}H NMR (DMSO-*d*6) δ 7.73 (s, 1H, NHC*H*N), 7.62 (s, 1H, Ar-H); ^{13}C NMR (DMSO-*d*6) δ 163.83, 137.59; MS (ESI) *m/z* (%), 111.03 (100) ([M-H]$^-$).

***tert*-Butyl (2-(1*H*-imidazol-4-yl)ethyl)carbamate (15)** Purification of product was achieved by column chromatography eluting with AcOEt. The product was isolated as white solid and the analytical data were in accordance to the literature. [27] Mp 83-85 ^{o}C; Rf (AcOEt) 0.50; ^{1}H NMR (CDCl$_3$) δ 7.67 (s, 1H, Ar-H, NHC*H*N), 7.43 (s, 1H, Ar-H), 6.84 (s, 1H, CHN*H*CH), 5.10 (s, 1H, NH), 3.42-3.43 (m, 2H, NHC*H$_2$*), 2.84-2.78 (m, 2H, CH$_2$), 1.42 (s, 9H, 3xCH$_3$); ^{13}C NMR (CDCl$_3$) δ 156.72 (CON), [134.83, 133.73, 112.45] (Ar), 79.54, 40.30, 28.59, 27.40. MS (ESI) *m/*z (%), 212.21 (100) ([M+H]$^+$).

(*tert*-Butoxycarbonyl)-*L*-histidine (16) was isolated as white solid and the analytical data were in accordance to the literature.[28a,b] Mp 210 °C (mp$_{(lit)}$[28b] 194-195 °C); $[\alpha]_D$ +27° (c 1, MeOH) ($[\alpha]_{D(lit)}$[28b] +26.5 ° (c 1, MeOH)); Rf (CHCl$_3$:MeOH 8:2) 0.34; ^{1}H NMR (MeOH-*d4*) *δ* 8.45 (s, 1H, Ar-H, NC*H*N), 7.18 (s, 1H, Ar-H), 4.24 (m, 1H, C*H*), 3.24-2.94 (m, 2H, C*H$_2$*), 1.40 (s, 9H, 3xCH$_3$); ^{13}C NMR (MeOH-*d4*) δ 178.47 (COOH), 173.75 (CON), [135.47, 133.42, 118.92] (Ar), 81.28, 56.37, 30.49, 29.24; MS (ESI) *m/z* (%) 254.05 (100) ($[M-H]^-$).

***tert*-Butyl (*S*)-(1-hydroxy-3-(1*H*-imidazol-4-yl)propan-2-yl)carbamate (17)** was isolated as white solid. Mp 173-175 °C; $[\alpha]_D$ -67° (c 0.43, MeOH); Rf (AcOEt) 0.29; ^{1}H NMR (MeOH-*d4*) *δ* 8.63 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 3.87-3.83 (m, 1H, BocNH-C*H*-), 3.62-3.53 (m, 2H, -C*H$_2$*OH), 3.01 (dd, J_1 15.0 Hz & J_2 4.4 Hz, 1H, -NH-CH-C*H*H-), 2.79 (dd, J_1 14.9 Hz, J_2 9.7 Hz, 1H, -NH-CH-CH*H*-), 1.40 (s, 9H, 3xCH$_3$); ^{13}C NMR (MeOH-*d4*) *δ* 156.75, 133.58, 131.78, 116.93, 79.06, 63.38, 52.02, 28.53, 27.49; HRMS exact mass calculated for $[M+Na]^+$ ($C_{11}H_{19}N_3NaO_3$) requires *m/z* 264.1319, found *m/z* 264.1316.

Benzimidazole (18) was isolated as white solid, and the analytical data were in accordance to the literature.[29] Mp 170-171 °C (mp$_{(lit)}$[29] 169-170 °C); Rf (AcOEt) 0.44; ^{1}H NMR (MeOH-d4) *δ* 8.14 (s, 1H, NHC*H*N), 7.60 (dd, J_1 6.08 Hz & J_2 3.18 Hz, 2H, Ar-H), 7.25 (dd, J_1 6.10 Hz & J_2 3.16 Hz, 2H, Ar-H), 5.08 (s, 1H, NH); ^{13}C NMR (MeOH-d4) *δ* [142.44, 138.72, 123.75, 116.14] (Ar); MS (ESI) m/z (%) 119.30 (100) ($[M+H]^+$).

Pyrazole (19) was isolated as white solid, and the analytical data were in accordance to the literature.[29] Mp 67-69 °C (mp$_{(lit)}$[29] 68 °C); Rf (AcOEt:PE 2:8) 0.29; ^{1}H NMR (CDCl$_3$) *δ* 11.36 (s, 1H, NH), 7.66 (d, *J* 2.00 Hz, 2H, Ar-H), 6.38 (t, *J* 2.00 Hz, 1H, Ar-H); ^{13}C NMR (CDCl$_3$) δ [133.71, 105.14] (Ar); MS (ESI) m/z (%) 69.46 (100) ($[M+H]^+$).

***tert*-Butyl (2-hydroxy-5-methylphenyl) carbamate (20)** was isolated as white solid, and the analytical data were in accordance to the literature.[30] Mp 96.2 – 97.8 °C (mp$_{(lit)}$[30] 98-99 °C); Rf (CHCl$_3$:MeOH 9:1) 0.67; ^{1}H NMR (CDCl$_3$) *δ* 8.02 (br s, 1H, NH), 7.13 (s,1H, Ar-H), 6.90- 6.84 (m, 1H, Ar-H), 6.80-6.79 (m, 1H, Ar-H), 2.22 (s, 3H, CH$_3$), 1.52 (s, 9H, 3xCH$_3$); ^{13}C NMR (CDCl$_3$) *δ* 154.96 (CON), [144.84, 130.34, 125.90, 125.43, 121.69, 118.26] (Ar), 81.92, 28.38, 20.65; MS (ESI) m/z (%) 241.02 (100) ($[M+NH_4]^+$).

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra and MS of compounds **2**, **12** and **17** are given in the Supplementary Material file associated with this manuscript.

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