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One-Pot Synthesis of Protected Benzylhydrazines from Acetals

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Organic derivatives of hydrazine are used for synthesis of various heterocyclic compounds,[1–4] pharmaceutical substances,[5,6] agricultural chemicals[7,8] and modified peptides.[9] In the structure of aza-peptides at least one amino acid residue is substituted by a hydrazino acid and this modification greatly improves the proteolytic stability of a peptide, which, in turn, makes aza-peptides promising drug candidates.[10–12]

Due to the instability of aza-amino acids (carbazic acids), incorporation of hydrazino acids into the peptide sequences requires protected alkylhydrazines corresponding to the natural amino acids. Major approaches to protected alkylhydrazines include direct alkylation of protected hydrazines,[13–19] reductive alkylation of hydrazines by aldehydes or ketones,[9,10,12–14,20–22] and incorporation of protective groups into commercially available alkylhydrazines.[13,14] To overcome the drawbacks of each of these methods, improvements have been made. For example, efficient alkylation of hydrazine anions was reported.[23,24] In further studies, anions generated from conjugated hydrazones were alkylated by various halogenides and applied to the synthesis of aza-peptides.[25–27] Thereafter the potassium iodide catalyzed direct alkylation of protected hydrazines was studied and reported by our group.[28]

Recently, we developed a convenient one-pot synthesis of protected alkylhydrazines from acetals and ketals that allowed us to avoid deprotection steps and separation of intermediates.[29,30] Encouraged by these results we extended this method to the synthesis of protected benzylic hydrazines, which were previously obtained from protected hydrazines by direct[17] or KI catalyzed alkylation,[28] as well as by reductive alkylation of protected hydrazines with benzaldehyde or substituted benzaldehydes.[10,12,20,22] However, the formed hydrazones are conjugated and their reduction requires $Pd(OH)_2$,[10] or Pd/C catalyzed hydrogenation.[22] In the case of 2-(3,5-dimethoxyphenyl)propan-2-yloxycarbonyl (Ddz) protected hydrazones, $NaBH_3CN$ was successfully applied for reduction of the conjugated -CH = N- bond.[20] Moreover, aromatic aldehydes, such as benzaldehyde, oxidize to carboxylic acids very easily and should be purified prior to use. Storage of these compounds in protected form (usually as the acetal) is thus much more favorable. This, in turn, requires an additional deprotection step.

In the present study a set of five protected hydrazines carrying 9-fluorenylmethyloxycarbonyl (*Fmoc)*, benzyloxycarbonyl (*Cbz)*, benzoyl (*Bz)*, 3-nitrobenzoyl (*3-NO_2Bz*) and 3,4-dimethoxybenzoyl (*3,4-$(OCH_3)_2$Bz)* groups was studied. Benzaldehyde dimethyl

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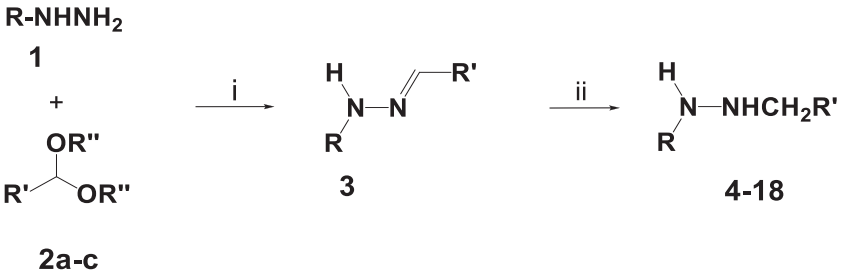
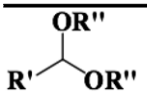


R = Fmoc; Cbz; Bz; 3-NO_2Bz; 3,4-$(OCH_3)_2$Bz; R' = Ph; 2-BrPh; 3-BrPh; R'' = -CH_3; -CH_2CH_3; i) TsOH, EtOH - H_2O, Δ ii) 1. BH_3-THF, THF, rt., EtOH-THF, Δ.

Scheme 1

Table 1
One-Pot Synthesis of Protected Benzylhydrazines from Acetals

			RNHNH$_2$				
	R′	R″	R = Fmoc	R = Cbz	R = Bz	R = 3-NO_2Bz	3,4-$(OCH_3)_2$Bz
2a	Ph	-CH_3	**4**; 92 %	**5**; 65 %	**6**; 93 %	**7**; 61 %	**8**; 92 %
2b	2-BrPh	-CH_2CH_3	**9**; 78 %	**10**; 71 %	**11**; 79 %	**12**; 79 %	**13**; 73 %
2c	3-BrPh	-CH_2CH_3	**14**; 56 %	**15**; 51 %	**16**; 74 %	**17**; 91 %	**18**; 90 %

acetal, 2-bromo- and 3-bromobenzaldehyde diethyl acetals were used as protected carbonyl compounds. All the studied compounds are listed in *Scheme 1* and *Table 1*.

The acetals were reacted with *Fmoc*, *Cbz*, *Bz*, *3-NO_2Bz* and 3,4-$(OCH_3)_2$*Bz* protected hydrazines in refluxing ethanol containing 10% of water (by volume) in the presence of a catalytic amount of *para*-toluenesulfonic acid (TsOH) (0.05 equiv per 1 equiv of protected hydrazine). For the reduction step, the solvent was exchanged to tetrahydrofuran (THF) and the obtained conjugated hydrazone was reduced in the same pot by BH_3-THF complex (3 equiv).

After stirring for three hours the reaction mixture was quenched by the addition of ethanol and refluxed to completely decompose the boron adducts. After evaporation of solvents, the residue was extracted with ethyl acetate and purified by column chromatography on silica gel.

It is important to mention that the described procedure is different from the previously reported methods.[29,30] Firstly, in this method we replaced initially used trifluoroacetic acid (TFA) by TsOH due to the difficult dosing of small amounts of very volatile TFA. Application of solid TsOH conveniently afforded effective acidic catalysis for the condensation of benzaldehyde acetals with protected hydrazines.

Secondly, due to the conjugated nature of the formed hydrazones a 3-fold excess of BH_3-THF complex was applied as a reductant. Although BH_3 complexes with amines and THF were successfully applied for reduction of hydrazones,[31–33] there is no prior information about application of BH_3 for synthesis of protected alkylhydrazines.

Thirdly, application of BH_3 instead of $NaBH_3CN$ avoids the possibility of generating HCN or NaCN. $NaBH_3CN$ reduces iminium salts and imines much faster than carbonyl compounds, which makes it very selective reagent for reductive alkylation. [34] Also, $NaBH_3CN$ tolerates acidic conditions, protic solvents,[34] and allows selective reduction in the presence of amide, ether, nitrile and nitro groups.[35] At the same time, BH_3 complexes are powerful, mild and selective electrophilic reductive agents suitable for reduction of carboxylic acids, aldehydes, ketones, amides, imines and nitriles in the presence of nitro, ester, lactone, carbamate groups and halogen substituents.[36] Aqueous ethanol was unsuitable for the reduction step and this required a solvent exchange, as addition of BH_3-THF into the reaction mixture in ethanol results in rapid decomposition of the reductant. In the new procedure we used azeotropic drying of the crude hydrazone with toluene, followed by vacuum drying. We also noticed that the reduction step proceeded better in commercially available stabilized THF and complete reduction was achieved after 3 hours at room temperature. In experiments where dry and distilled THF was used as solvent a significant amount of hydrazone remained unreacted after 3 hours of reduction.

As it can be seen from the results in *Table 1*, the proposed method works well with protective and functional groups such as Fmoc-, Cbz-, ether-, nitro-, amide as well as aryl bromides. The condensation and reduction steps proceeded without complication and gave products with moderate to excellent yields (51-93%).

In conclusion, we developed a general and convenient one-pot synthesis of protected benzylhydrazines from protected benzaldehydes. The described method allowed efficient condensation of protected hydrazines with protected carbonyl compounds and reduction of the formed conjugated hydrazones in the same pot, without the need for expensive precious metal catalysts and special equipment for hydrogenation.

Experimental Section

All solvents and reagents were purchased from Merck, Sigma-Aldrich or Lach-Ner. NMR spectra were measured on a 700 MHz instrument (Bruker, Germany) in $CDCl_3$ as solvent with tetramethylsilane (TMS) as the internal reference. HR (High resolution) ESI-ICR mass spectra were obtained on a hybrid Varian 910-FT-ICR-MS spectrometer coupled with Varian J-320 3Q mass-spectrometer using acetonitrile as a solvent. IR spectra were determined by using ATR (attenuated total reflectance) measuring technique on a Perkin-Elmer Spectrum BX spectrometer. All the yields are based on the mass of the starting reagents. ***Safety Note***: Since hydrogen is liberated, the procedure should be performed in an efficient hood, and workers should wear appropriate protective equipment.

General Procedure for One-Pot Synthesis of Protected Benzylhydrazines (4-18)

One equiv. of protected hydrazine was dissolved/suspended in EtOH containing 10% water (approx. 5 ml per 1 mmol of protected hydrazine), 1.05 eq of benzaldehyde acetal was added, followed by the addition of 0.05 equiv. of TsOH in an ethanolic solution (10 mg of TsOH per 0.5 ml of EtOH). The obtained reaction mixture was refluxed and monitored by TLC (silica gel) until full conversion of the starting material was observed. Ethyl acetate/light petroleum mixtures or pure ethyl acetate were used as TLC eluents. After completion of the reaction the solvent was removed under reduced pressure, approx. 15 ml of toluene was added to the residue and the solvent was again removed under reduced pressure. The obtained crude hydrazone was dissolved in commercial stabilized THF (approx. 4 ml per 1 mmol of hydrazone), the flask was flushed with

argon and 3 equiv. of 1M BH_3-THF complex was added at room temperature, followed by 3 hours of stirring. The progress of the reaction was checked by TLC and if some unreacted hydrazone was left, stirring was continued for an additional 45 min. After the full conversion of hydrazone EtOH (10 ml) was added to the reaction mixture (***Caution***: Liberation of hydrogen!) and the obtained mixture was refluxed for 1 hour. After cooling to room temperature the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution. The aqueous phase was extracted twice with ethyl acetate, the extracts were washed with saturated NaCl solution, combined with the organic phase, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel by using ethyl acetate/light petroleum 1:1 or 1:2 mixtures or pure ethyl acetate as eluent. For the exact information about the eluent used for monitoring reaction progress and chromatographic purifications, see the R_f value for each compound.

***N*-Fluorenylmethyloxycarbonyl-*N′*-benzylhydrazine** (**4**), 92% yield as a white solid, mp. 140-141 °C, *lit.*[10] 143-145 °C; Rf =0.53 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.00 (s, 2H, CH_2), 4.22 (s, 2H, NH + CH (Fmoc)), 4.45 (d, 2H, J= 6.8 Hz, CH_2(Fmoc)), 6.26 (s, 1H, NH), 7.29-7.33 (m, 7H, Ar(H)), 7.40 (t, 2H, J= 7 Hz, Ar(H)), 7.55 (d, 2H, J= 4.9 Hz, Ar(H)), 7.76 (d, 2H, J= 7.7 Hz, Ar(H)). ^{13}C NMR: δ 47.18, 55.60, 66.91, 120.02, 124.98, 127.07, 127.60, 127.76, 128.50, 129.02, 137.34, 141.33, 143.66, 157.13. IR (cm^{-1}): 3317.9, 3225.7, 3062.9, 1685.7, 1501.0, 1271.5, 1163.2, 1153.0, 735.6, 698.7. HRMS: m/z for $C_{22}H_{21}O_2N_2^{+1}$ $[M+H]^+$: Calcd 345.1598. Found 345.1597.

***N*-Benzyloxycarbonyl-*N′*-benzylhydrazine** (**5**), 65% yield as a white solid, mp. 82-84 °C, *lit.*[37] 50 °C; Rf =0.58 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.93 (s, 2H, CH_2), 4.17 (br s, 1H, NH), 5.08 (s, 2H, CH_2(Cbz)), 6.75 (s, 1H, NH), 7.21-7.30 (m, 10H, Ar(H)). ^{13}C NMR: δ 55.48, 66.95, 127.48, 128.10, 128.19, 128.40, 128.48, 128.94, 136.08, 137.35, 157.20. IR (cm^{-1}): 3255.5, 3033.2, 1720.7, 1514.0, 1453.9, 1280.0, 1229.1, 1145.1, 1023.7, 744.7. HRMS: m/z for $C_{15}H_{17}O_2N_2^{+1}$ $[M+H]^+$: Calcd 257.1285. Found 257.1285.

***N*-Benzoyl-*N′*-benzylhydrazine** (**6**), 93% yield as a white solid, mp. 114-116 °C, *lit.*[38] 115 °C; Rf =0.49 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.09 (s, 2H, CH_2), 5.01 (br s, 1H, NH), 7.31 (t, 1H, J= 7.7 Hz, Ar(H)), 7.36 (t, 2H, J= 7.7 Hz, Ar(H)), 7.40-7.43 (m, 4H, Ar(H)), 7.51 (t, 1H, J= 7.7 Hz, Ar(H)), 7.64 (br s, 1H, NH), 7.69 (dd, 2H, J_1= 8.4 Hz, J_2= 1.4 Hz, Ar(H)). ^{13}C NMR: δ 55.98, 126.81, 127.64, 128.55, 128.67, 129.06, 131.85, 132.79, 137.48, 167.37. IR (cm^{-1}): 3237.3, 3058.8, 1633.0, 1532.4, 1461.8, 1324.3, 729.8, 693.2. HRMS: m/z for $C_{14}H_{15}ON_2^{+1}$ $[M+H]^+$: Calcd 227.1179. Found 227.1178.

Anal. Calcd for $C_{14}H_{14}ON_2$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.34; H, 6.15; N, 12.40.

***N*-(3-Nitro)benzoyl-*N′*-benzylhydrazine** (**7**), 61% yield as a white solid, mp. 79-84 °C;

Rf =0.45 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.04 (s, 2H, CH_2), 5.20 (br s, 1H, NH), 7.22-7.24 (m, 1H, Ar(H)), 7.27 (td, 2H, J_1= 7 Hz, J_2= 2.1 Hz, Ar(H)), 7.31-7.32 (m, 2H, Ar(H)), 7.57 (t, 1H, J= 7.7 Hz, Ar(H)), 8.09 (dt, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 8.29 (ddd, 1H, J_1= 8.4 Hz, J_2= 2.1 Hz, J_3= 0.7 Hz, Ar(H)), 8.58 (s, 1H, Ar(H)), 8.93 (br s, 1H, NH). ^{13}C NMR: δ 55.85, 122.06, 126.36, 127.83, 128.61, 129.06, 129.92, 133.22, 134.31, 137.09, 148.13, 165.09. IR (cm^{-1}): 3223.0, 3070.0, 1632.9, 1528.8, 1350.0, 1051.0, 1025.3, 1005.9, 817.9, 756.3, 717.3, 696.5. HRMS: m/z for $C_{14}H_{14}O_3N_3^{+1}$ $[M+H]^+$: Calcd 272.1030. Found 272.1029.

Anal. Calcd for $C_{14}H_{13}O_3N_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.68; H, 5.06; N, 15.30.

***N*-(3,4-Dimethoxy)benzoyl-*N′*-benzylhydrazine** (**8**), 92% yield as a white solid, mp. 117-120 °C; Rf =0.5 (EtOAc). ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2), 5.20 (br s, 1H, NH), 6.74 (d, 1H, J= 8.4 Hz, Ar(H)), 7.23-7.33 (m, 6H, Ar(H)), 7.39 (d, 1H, J= 2.1 Hz, Ar(H)), 8.80 (s, 1H, NH). ^{13}C NMR: δ 55.83, 55.88, 55.99, 110.34, 110.37, 119.85, 125.26, 127.56, 128.46, 129.08, 137.43, 148.87, 151.89, 167.09. IR (cm^{-1}): 3250.0, 3002.0, 1616.2, 1513.9, 1312.2, 1261.9, 1232.4, 1137.9, 1022.1, 811.6, 772.5, 741.9, 698.3, 666.0. HRMS: m/z for $C_{16}H_{19}O_3N_2{}^{+1}$ $[M+H]^+$: Calcd 287.1390. Found 287.1388.

Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.95; H, 6.19; N, 9.81.

***N*-Fluorenylmethyloxycarbonyl-*N′*-(2-bromo)benzylhydrazine** (**9**), 78% yield as a white solid, mp. 100-103 °C; Rf =0.56 (1:2 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.07 (s + br s, 3H, CH_2 + NH), 4.18 (s, 1H, CH(Fmoc)); 4.43 (s, 2H, CH_2(Fmoc)), 6.41 (s, 1H, NH), 7.10 (td, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 7.21-7-23 (m, 1H, Ar(H)), 7.28 (t, 3H, J= 7 Hz, Ar(H)), 7.37 (t, 2H, J= 7 Hz, Ar(H)), 7.52 (m, 3H, Ar(H)), 7.73 (d, 2H, J= 7 Hz, Ar(H)). ^{13}C NMR: δ 47.15, 55.51, 66.92, 119.98, 124.61, 124.97, 127.05, 127.42, 127.73, 129.18, 131.06, 132.91, 136.64, 141.30, 143.65, 157.10.

IR (cm^{-1}): 3316.0, 3014.2, 1689.9, 1502.6, 1447.5, 1272.1, 1157.2, 1029.2, 755.2, 737.6.

HRMS: m/z for $C_{22}H_{20}O_2N_2Br^{+1}$ $[M+H]^+$: Calcd 423.0703. Found 423.0702.

Anal. Calcd for $C_{22}H_{19}O_2N_2Br$: C, 62.42; H, 4.52; N, 6.62. Found: C, 62.14; H, 4.22; N, 6.42.

***N*-Benzyloxycarbonyl-*N′*-(2-bromo)benzylhydrazine** (**10**), 71% yield as a white solid, mp. 73-75 °C; Rf =0.53 (1:2 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.09 (s, 2H, CH_2), 4.36 (br s, 1H, NH), 5.11 (s, 2H, CH_2(Cbz)), 6.49 (s, 1H, NH), 7.10 (td, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 7.22 (t, 1H, J= 7.7 Hz, Ar(H)), 7.30-7.33 (m, 6H, Ar(H)), 7.52 (d, 1H, J= 7.7 Hz, Ar(H)). ^{13}C NMR: δ 55.49, 67.10, 124.58, 127.42, 128.20, 128.26, 128.52, 129.14, 131.00, 132.88, 136.02, 136.71, 157.15. IR (cm^{-1}): 3324.0, 3034.9, 2924.3, 1690.5, 1515.3, 1470.6, 1273.9, 1149.8, 1049.5, 1027.4, 749.9, 736.2, 694.9. HRMS: m/z for $C_{15}H_{16}O_2N_2Br^{+1}$ $[M+H]^+$: Calcd 335.0390. Found 335.0392.

Anal. Calcd for $C_{15}H_{15}O_2N_2Br$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.57; H, 4.60; N, 8.25.

***N*-Benzoyl-*N′*-(2-bromo)benzylhydrazine** (**11**), 79% yield as a white solid, mp. 117-121 °C; Rf =0.57 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.16 (s, 2H, CH_2), 5.25 (br s, 1H, NH), 7.10 (td, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 7.22 (td, 1H, J_1= 7.7 Hz, J_2= 0.7 Hz, Ar(H)), 7.34 (t, 2H, J= 7 Hz, Ar(H)), 7.39 (dd, 1H, J_1= 7Hz, J_2= 1.4 Hz, Ar(H)), 7.45 (t, 1H, J= 7.7 Hz, Ar(H)), 7.52 (d, 1H, J= 7 Hz, Ar(H)), 7.70 (d, 2H, J= 7 Hz, Ar(H)), 8.45 (s, 1H, NH). ^{13}C NMR: δ 55.63, 124.72, 126.99, 127.47, 128.54, 129.21, 131.03, 131.77, 132.63, 132.89, 136.84, 167.46.

IR (cm^{-1}):3236.1, 3054.8, 1625.8, 1538.4, 1456.7, 1354.7, 1313.5, 747.7, 694.4. HRMS: m/z for $C_{14}H_{14}ON_2Br^{+1}$ $[M+H]^+$: Calcd 305.0284. Found 305.0286.

Anal. Calcd for $C_{14}H_{13}ON_2Br$: C, 55.10; H, 4.29; N, 9.18. Found: C, 54.80; H, 4.27; N, 9.06.

***N*-(3-Nitro)benzoyl-*N′*-(2-bromo)benzylhydrazine** (**12**), 79% yield as a white solid, mp. 138-141 °C; Rf =0.47 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.27 (s, 2H, CH_2), 4.46 (br s, 1H, NH), 7.20 (td, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 7.33 (t, 1H, J= 7.7 Hz, Ar(H)), 7.48 (d, 1H, J= 7 Hz, Ar(H)), 7.60 (d, 1H, J= 7.7 Hz, Ar(H)), 7.66 (t, 1H, J= 7.7 Hz, Ar(H)), 7.90 (br s, 1H, NH), 8.10 (d, 1H, J= 7.7 Hz, Ar(H)), 8.39 (dd, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 8.57 (t, 1H, J= 1.4 Hz, Ar(H)). ^{13}C NMR: δ 55.69, 121.95, 124.86, 126.48, 127.68, 129.58, 130.03, 131.18, 133.01, 133.13, 134.32, 136.38, 148.28, 165.10. IR (cm^{-1}):3245.8, 3042.6, 1667.0, 1520.9, 1471.6, 1349.5, 1310.2, 758.3, 712.9. HRMS: m/z for $C_{14}H_{13}O_3N_3Br^{+1}$ $[M+H]^+$: Calcd 350.0135. Found 350.0135.

Anal. Calcd for $C_{14}H_{12}O_3N_3Br$: C, 48.02; H, 3.45; N, 12.00. Found: C, 47.87; H, 3.48; N, 11.89.

***N*-(3,4-Dimethoxy)benzoyl-*N′*-(2-bromo)benzylhydrazine** (**13**), 73% yield as a white solid, mp. 120-123 °C; Rf =0.62 (EtOAc). ^{1}H NMR (700 MHz, $CDCl_3$):δ 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 5.28 (br s, 1H, NH), 6.76 (d, 1H, J= 8.4 Hz, Ar(H)), 7.10 (td, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 7.22 (td, 1H, J_1= 7 Hz, J_2= 0.7 Hz, Ar(H)), 7.27 (dd, 1H, J_1= 8.4 Hz, J_2= 2.1 Hz, Ar(H)), 7.37-7.40 (m, 2H, Ar(H)), 7.52 (dd, 1H, J_1= 8.4 Hz, J_2= 1.4 Hz, Ar(H)), 8.50 (s, 1H, NH). ^{13}C NMR: δ 55.71, 55.91, 55.93, 110.35, 110.43, 119.79, 124.71, 125.19, 127.45, 129.17, 131.07, 132.86, 136.92, 148.92, 151.95, 167.13. IR (cm^{-1}): 3290.6, 3067.0, 1635.6, 1492.4, 1312.2, 1275.8, 1236.0, 1139.4, 1024.2, 747.3. HRMS: m/z for $C_{16}H_{18}O_3N_2Br^{+1}$ $[M+H]^+$: Calcd 365.0495. Found 365.0494.

Anal. Calcd for $C_{16}H_{17}O_3N_2Br$: C, 52.62; H, 4.69; N, 7.67. Found: C, 52.51; H, 4.68; N, 7.62.

***N*-Fluorenylmethyloxycarbonyl-*N′*-(3-bromo)benzylhydrazine** (**14**), 56% yield as a white solid, mp. 117-121 °C; Rf =0.38 (1:2 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.92 (s, 2H, CH_2), 4.18 (s, 2H, CH(Fmoc) + NH), 4.43 (s, 2H, CH_2(Fmoc)), 6.40 (s, 1H, NH), 7.15 (s, 1H, Ar(H)), 7.19 (s, 1H, Ar(H)), 7.27-7.29 (m, 2H, Ar(H)), 7.38 (t, 3H, J= 7.7 Hz, Ar(H)), 7.48 (s, 1H, Ar(H)), 7.52 (d, 2H, J= 5.6 Hz, Ar(H)), 7.73 (d, 2H, J= 7.7 Hz, Ar(H)). ^{13}C NMR: δ 47.23, 54.95, 67.02, 120.10, 122.61, 125.00, 127.15, 127.57, 127.85, 130.06, 130.69, 131.91, 139.98, 141.39, 143.67, 157.23.

IR (cm^{-1}):3312.2, 1684.4, 1446.2, 1266.4, 1154.2, 756.0, 738.0. HRMS: m/z for $C_{22}H_{20}O_2N_2Br^{+1}$ $[M+H]^+$: Calcd 423.0703. Found 423.0700.

Anal. Calcd for $C_{22}H_{19}O_2N_2Br$: C, 62.42; H, 4.52; N, 6.62. Found: C, 62.81; H, 4.70; N, 6.52.

***N*-Benzyloxycarbonyl-*N′*-(3-bromo)benzylhydrazine** (**15**), 51% yield as a white solid, mp. 87-90 °C; Rf =0.38 (1:2 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.99 (s, 2H, CH_2), 4.24 (br s, 1H, NH), 5.15 (s, 2H, CH_2(Cbz)), 6.54 (br s, 1H, NH), 7.19 (t, 1H, J= 7.7 Hz, Ar(H)), 7.25 (s, 1H, Ar(H)), 7.36-7.38 (m, 5H, Ar(H)), 7.42 (d, 1H, J= 7.7 Hz, Ar(H)), 7.52 (s, 1H, Ar(H)). ^{13}C NMR: δ 54.86, 67.17, 122.53, 127.46, 128.14, 128.32, 128.57, 130.00, 130.61, 131.84, 135.95, 139.87, 157.21. IR (cm^{-1}): 3313.5, 1682.4, 1487.0, 1268.4, 1147.1, 1075.6, 1040.6, 876.2, 780.0, 735.5, 696.7. HRMS: m/z for $C_{15}H_{16}O_2N_2Br^{+1}$ $[M+H]^+$: Calcd 335.0390. Found 335.0389.

Anal. Calcd for $C_{15}H_{15}O_2N_2Br$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.52; H, 4.48; N, 8.15.

***N*-Benzoyl-*N′*-(3-bromo)benzylhydrazine** (**16**), 74% yield as a white solid, mp. 110-113 °C; Rf =0.25 (1:2 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.02

(s, 2H, CH_2), 5.02 (br s, 1H, NH), 7.18 (t, 1H, J= 7.7 Hz, Ar(H)), 7.28 (d, 1H, J= 7.7 Hz, Ar(H)), 7.40 (t, 3H, J= 7.7 Hz, Ar(H)), 7.50 (t, 1H, J= 7 Hz, Ar(H)), 7.55 (s, 1H, Ar(H)), 7.70 (d, 2H, J= 7.7 Hz, Ar(H)), 8.05 (br s, 1H, NH). ^{13}C NMR: δ 55.26, 122.61, 126.93, 127.60, 128.68, 130.09, 130.72, 131.97, 131.98, 132.60, 139.96, 167.63. IR (cm^{-1}): 3273.6, 3062.2, 1662.6, 1531.8, 1464.8, 1311.1, 880.5, 782.1, 691.8. HRMS: m/z for $C_{14}H_{14}ON_2Br^{+1}$ $[M+H]^+$: Calcd 305.0284. Found 305.0284.

Anal. Calcd for $C_{14}H_{13}ON_2Br$: C, 55.10; H, 4.29; N, 9.18. Found: C, 55.05; H, 4.30; N, 9.16.

***N*-(3-Nitro)benzoyl-*N′*-(3-bromo)benzylhydrazine** (**17**), 91% yield as a white solid, mp. 116-119 °C; Rf =0.43 (1:1 EtOAc - light petroleum). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.10 (s, 2H, CH_2), 4.63 (br s, 1H, NH), 7.23 (t, 1H, J= 7.7 Hz, Ar(H)), 7.32 (d, 1H, J= 7 Hz, Ar(H)), 7.44 (d, 1H, J= 8.4 Hz, Ar(H)), 7.58 (s, 1H, Ar(H)), 7.65 (t, 1H, J= 7.7 Hz, Ar(H)), 7.90 (br s, 1H, NH), 8.07 (d, 1H, J= 7.7 Hz, Ar(H)), 8.37 (dd, 1H, J_1= 7.7 Hz, J_2= 1.4 Hz, Ar(H)), 8.55 (s, 1H, Ar(H)). ^{13}C NMR: δ 55.23, 121.95, 122.75, 126.56, 127.57, 130.06, 130.22, 130.99, 131.97, 132.95, 134.22, 139.50, 148.3, 165.27.

IR (cm^{-1}): 3301.7, 1640.8, 1523.2, 1350.6, 1316.1, 877.6, 785.9, 723.8. HRMS: m/z for $C_{14}H_{13}O_3N_3Br^{+1}$ $[M+H]^+$: Calcd 350.0135. Found 350.0135.

Anal. Calcd for $C_{14}H_{12}O_3N_3Br$: C, 48.02; H, 3.45; N, 12.00. Found: C, 47.93; H, 3.44; N, 11.87.

***N*-(3,4-Dimethoxy)benzoyl-*N′*-(3-bromo)benzylhydrazine** (**18**), 90% yield as a white solid, mp. 115-119 °C; Rf =0.58 (EtOAc). ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 5.11 (br s, 1H, NH), 6.77 (d, 1H, J= 8.4 Hz, Ar(H)), 7.13 (t, 1H, J= 7.7 Hz, Ar(H)), 7.24 (d, 1H, J= 7.7 Hz, Ar(H)), 7.28 (dd, 1H, J_1= 8.4 Hz, J_2= 2.1 Hz, Ar(H)), 7.34-7.37 (m, 2H, Ar(H)), 7.51 (s, 1H, Ar(H)), 8.64 (s, 1H, NH). ^{13}C NMR: δ 55.26, 55.90, 55.93, 110.39, 110.40, 119.89, 122.48, 125.09, 127.60, 130.02, 130.58, 131.94, 140.05, 148.91, 152.03, 167.30.

IR (cm^{-1}): 3272.1, 3058.8, 1625.6, 1516.3, 1485.1, 1313.0, 1275.9, 1234.0, 1135.7, 1024.2, 874.5, 775.0, 683.4. HRMS: m/z for $C_{16}H_{18}O_3N_2Br^{+1}$ $[M+H]^+$: Calcd 365.0495. Found 365.0495.

Anal. Calcd for $C_{16}H_{17}O_3N_2Br$: C, 52.62; H, 4.69; N, 7.67. Found: C, 52.34; H, 4.66; N, 7.48.

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