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CHEMISTRY

Synthesis of aza-phenylalanine, aza-tyrosine, and aza-tryptophan precursors via hydrazine alkylation

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Abstract. Aza-amino acid precursors with an aromatic side chain were synthesized using hydrazine alkylation. This synthetic pathway avoided use of hydrogen gas and expensive hydrogenation catalysts. For the optimization of this alkylation reaction various solvents and different reaction conditions were used. Aza-phenylalanine, aza-tyrosine, and aza-tryptophan precursors with different *N*- and side-chain protecting groups were synthesized starting from *N*-protected hydrazines.

Key words: aza-phenylalanine, aza-tyrosine, aza-tryptophan, precursor, hydrazine derivative, monoprotected hydrazine alkylation, protecting group, alkylation, bromination.

Abbreviations
ACN – acetonitrile
AIBN – 2,2′-azobis(2-methylpropionitrile)
Bn – benzyl
Boc – *tert*-butyloxycarbonyl
DCM – dichloromethane
DiPEA – *N*,*N*′-diisopropylethylamine
DMF – *N*,*N*′-dimethylformamide
DMSO – dimethyl sulphoxide
EA – ethyl acetate
ESI-FT-ICR – electrospray ionization Fourier transform ion cyclotron resonance mass spectrometer or mass spectrometry
EtOH – ethanol
Fmoc – 9-fluorenylmethoxycarbonyl
HRMS – high resolution mass spectra
IR – infrared
LRMS – low resolution mass spectra
NBS – *N*-bromosuccinimide
NMP – *N*-methyl-2-pyrrolidone
NMR – nuclear magnetic resonance
PE – petroleum ether
Phe – phenylalanine
rt. – room temperature
TEA – triethylamine
Trp – tryptophan
Tyr – tyrosine
Z (Cbz) – carboxybenzyl

INTRODUCTION

Replacement of the α-carbon atom with nitrogen in the structure of encoded amino acids yields peptide-like compounds with interesting structural, chemical, and biological properties such as non-chiral structure and increased stability towards biodegradation [1–3]. However, these peptidomimetics cannot be synthesized directly from aza-amino acids, as these compounds are not stable. Therefore *N*-protected alkylhydrazines have been used for this synthesis as stable precursors of aza-amino acids (Fig. 1) [1,3].

Several synthetic methods have been proposed and used to prepare these aza-amino acid precursors [1–12]. The most frequently used synthetic route for the preparation of *N*-protected alkyl- and arylhydrazines is

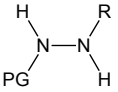

Fig. 1. General structure of the aza-amino acid precursor (PG stands for protecting group and R for alkyl group).

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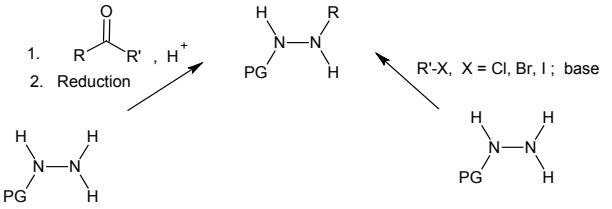


Scheme 1. Two main synthetic routes for the preparation of *N′*-protected *N*-alkyl hydrazine derivatives (PG – protecting group).

reductive hydrazine alkylation (Scheme 1, left side). This method includes hydrazone formation from *N*-protected hydrazine and appropriate aldehyde and its subsequent reduction into alkyl hydrazine. However, this approach has some drawbacks in the case of aromatic aza-amino acid precursors, because reduction of strongly electron deficient hydrazone formed in the reaction of carbazate with benzaldehyde (aza-Phe precursor), *O*-protected 4-hydroxybenzaldehyde (aza-Tyr precursor), and *N*-protected indole-3-aldehyde (aza-Trp precursor) is rather complicated. Certainly, this reduction step can be performed by using a $Pd/C/H_2$ or $Pd(OH)_2/C/H_2$ system [3,10,13]. However, this procedure has a non-selective character [14], requires expensive catalysts, and most importantly, needs a sophisticated hydrogen supply system and special equipment to work with this gas under elevated pressure.

Therefore we decided to use for the preparation of aza-Phe, aza-Tyr, and aza-Trp precursors another known synthetic pathway, which includes direct *N*-alkylation of protected hydrazine with appropriate alkyl halides (Scheme 1, right side). As this alkylation method is not widely applied for the preparation of aza-amino acid precursors it required optimization.

After a systematic study of the reaction conditions this synthetic method was optimized and applied for the preparation of the aromatic aza-amino acid precursors as shown in Schemes 2, 3A, 3B, and 4.

RESULTS AND DISCUSSION

The main goal of the present study was to optimize the hydrazine alkylation reaction. The reaction of benzylation of different carbazates was chosen as the model reaction. Different conditions, solvents, and benzyl halogenides were tested. The obtained results are described in Table 1 and Table 2.

In the case of an equimolar or 2/1 ratio of protected hydrazine and benzyl bromide, relatively poor yields ranging from 13% to 30% were obtained at room temperature. At the same time formation of a significant amount of the dialkylated product was observed. This can be explained by the fact that introduction of alkyl moiety into protected hydrazine increases nucleophilicity of hydrazine, making the monoalkylated compound prone to undergo a second alkylation. In order to suppress polyalkylation, an at least 3-fold excess of hydrazine was used in further experiments.

Besides this, addition of bases such as pyridine or 2,4,6-trimethylpyridine (1–1.3 eq) was found to be useful to increase the yield of the monoalkylated product. It was important to consider that the type of the suitable base was dependent on the properties of the hydrazine

Table 1. Benzylation of $Fmoc\text{-}NHNH_2$

Experimental conditions	Monoalkylated hydrazine yield, %
3 eq of $Fmoc\text{-}NHNH_2$; 0.6 M DMF solution; 1 eq of Bn-Br; 70 °C; 12 h	46
2 eq of $Fmoc\text{-}NHNH_2$; 0.6 M DMF solution; 1.5 eq of DiPEA; 1 eq of Bn-Br; 70 °C; 13 h	– (Fmoc removal occurred)
2 eq of $Fmoc\text{-}NHNH_2$; 0.6 M DMF solution; 1 eq of Bn-Br; rt.; 11 h	26*
2 eq of $Fmoc\text{-}NHNH_2$; 0.1 M DMF solution; 1 eq of benzyl bromide; rt.; 12 h	30**
3 eq of $Fmoc\text{-}NHNH_2$; 0.1 M DMF solution; 1 eq of Bn-Br; 70 °C; 12 h	43
1.5 eq of $Fmoc\text{-}NHNH_2$; 0.1 M ACN solution; 1 eq of Bn-Br; reflux 5 h	36
3 eq of $Fmoc\text{-}NHNH_2$; 0.1 M ACN solution; 1 eq of Bn-Br; reflux 11 h	45***
2 eq of $Fmoc\text{-}NHNH_2$; 0.1 M CH_3OH solution; 1 eq of Bn-Br; reflux 3 h; 12 h at rt.	21
3.5 eq of $Fmoc\text{-}NHNH_2$; 0.1 M CH_3OH solution; 1 eq of Bn-Cl; reflux 4 h	14
4 eq of $Fmoc\text{-}NHNH_2$; 0.1 M EtOH solution; 1 eq of Bn-Br; reflux 11 h	61
3 eq of $Fmoc\text{-}NHNH_2$; 0.1 M ACN solution; 1 eq of 2,4,6-trimethylpyridine; 1 eq of Bn-Br; reflux 6 h	68
4 eq of $Fmoc\text{-}NHNH_2$; 0.1 M ACN solution; 1 eq of 2,4,6-trimethylpyridine; 1 eq of Bn-I; reflux 12 h	74

* Dibenzylated product obtained in 64% yield; ** dibenzylated product obtained in 36% yield; *** dibenzylated product obtained in 40% yield.

Table 2. Benzylation of Boc-$NHNH_2$ and $ZNHNH_2$

Experimental conditions	Monoalkylated hydrazine yield, %
1 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 0.75 M ACN solution; reflux 4 h	13
2 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 0.75 M NMP solution; overnight at rt.	14
3.4 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 2.3 M DMF solution; 70 °C; 5 h	63
3 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 0.1 M DMF solution; 70 °C; 11 h	70
3 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 0.1 M CH_3OH solution; reflux 5 h	11
4 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 0.1 M EtOH solution; reflux 6 h	57
4 eq of Boc-$NHNH_2$; 1 eq of Bn-I; 0.1 M ACN solution; 1.3 eq of 2,4,6-trimethylpyridine; reflux 13 h	75
4 eq of Boc-$NHNH_2$; 1 eq of Bn-Br; 0.1 M ACN solution; 1.3 eq of 2,4,6-trimethylpyridine; reflux 11 h	79
3 eq of $ZNHNH_2$; 1 eq of Bn-Br; 0.1 M ACN solution; reflux 6 h	64

protecting group. For example, tertiary amines such as TEA or DiPEA are compatible with the Boc- and Cbz-protecting group even at elevated temperatures, while in the case of the base-sensitive Fmoc group its scission was observed (Table 1). Weaker bases like pyridine and its derivatives were effective with all the protecting groups.

It was also found that solvent played an important role in the alkylation reaction. In early hydrazine alkylation studies it was found that the use of ethanol as a solvent for hydrazine alkylation reaction helps to increase monoalkylated hydrazine yield [15]. The same conditions were used in later works involving hydrazine alkylation [16]. In the current study it was found that in 96% ethanol the yields of alkylation of Boc-$NHNH_2$ and Fmoc-$NHNH_2$ were 57% and 61%, respectively. At the same time in methanol solution the yield of the monoalkylated product was significantly lower: 21% in the case of Fmoc-$NHNH_2$ (2 eq) and 11% in the case of Boc-$NHNH_2$ (3 eq excess).

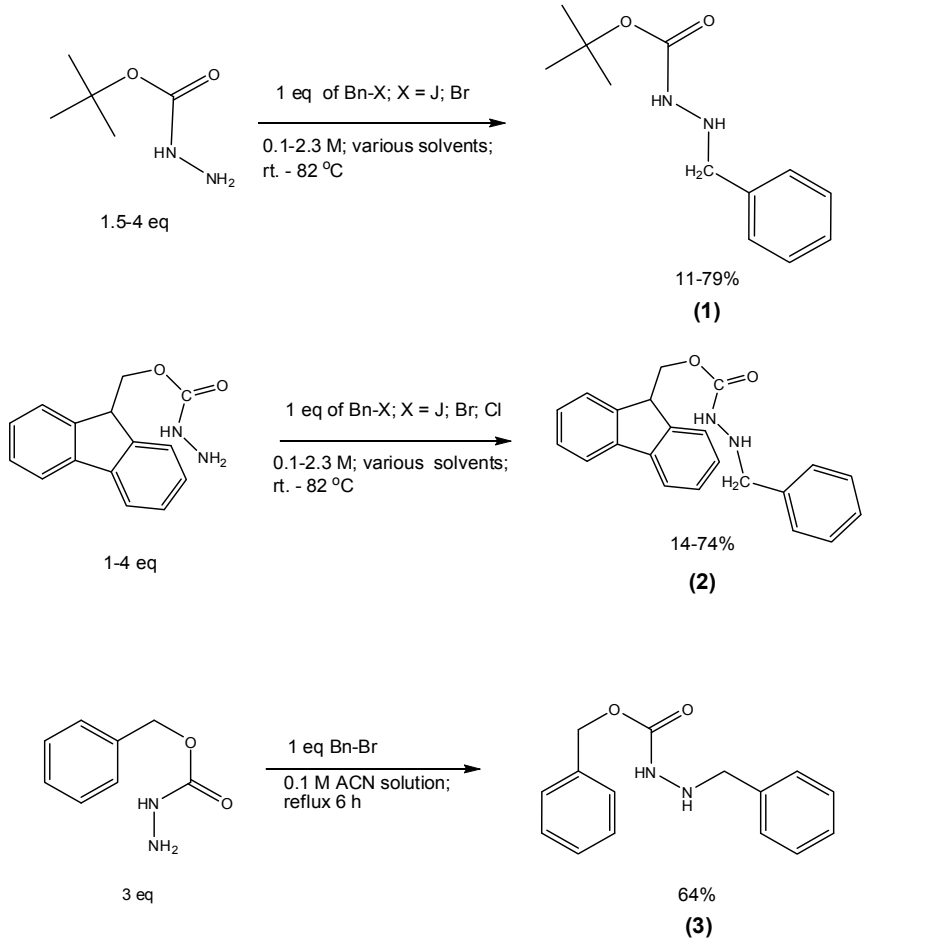
We also tested benzyl chloride as an alkylating reagent for benzylation of *N*-Fmoc-protected hydrazine. In this case the monoalkylated product was obtained in 14% yield in methanol. However, using benzyl iodide as the alkylating agent gave the monoalkylated product with 75% yield in the case of Boc$NHNH_2$ and 74% in the case of Fmoc-$NHNH_2$, which was the highest yield of the synthesis of *N*-Fmoc-*N′*-benzyl hydrazine (Scheme 2, Table 1, Table 2).

The best yields of monoalkylated hydrazine derivatives were obtained using ACN as the solvent (0.1 M solution of starting protected hydrazine) and Bn-Br or Bn-I as the alkylating agent and adding 1–1.3 eq 2,4,6-trimethylpyridine. In this case the yields were 74% (Fmoc-$NHNH_2$), 79% (Boc-$NHNH_2$), and 64% (Z-$NHNH_2$) (Scheme 2, Table 1, Table 2).

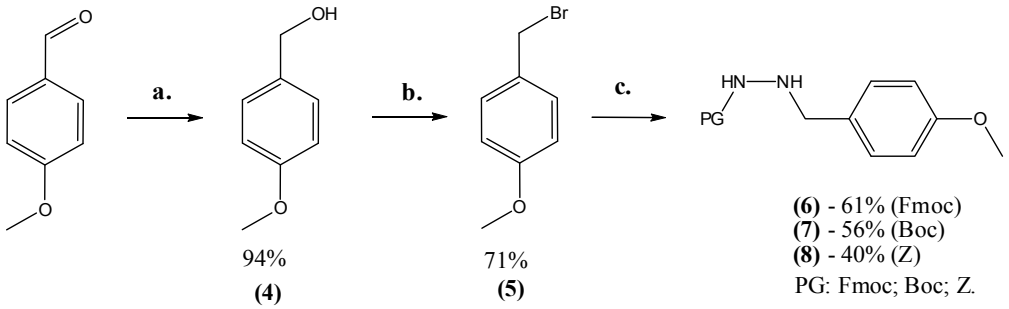
For the preparation of protected aza-Tyr and aza-Trp precursors (Schemes 3A, 3B, and 4) we proceeded from different aldehydes (compounds **9** and **10** in Scheme 3B and **18** in Scheme 4). The functional groups of the side chain of these compounds were protected with different protecting groups that allowed reduction of the aldehyde group with $NaBH_4$ in methanol and production of corresponding alcohols (compounds **4**, **11**, **12**, and **20**). Yields of these syntheses were very good. Syntheses of the corresponding bromides from these alcohols were performed by using PBr_3/DCM in the presence of TEA or a combination of TEA and $NaHCO_3$. Bromides **13** and **14** were unstable and decomposed producing HBr, which in turn cleaved protecting groups and resulted in very complex mixtures. Therefore the bromides were used for the following steps immediately after their preparation.

The obtained bromides were used for the alkylation of monoprotected hydrazine in refluxing ACN solution containing 1 eq of 2,4,6-trimethylpyridine as a base. The yields of monoalkylated hydrazines were in the range of 34–61% (Schemes 3A, 3B, and 4).

We also tested alternative and less harsh methods for the preparation of bromides (compounds **5**, **13**, **14**, and **21**). One of the possibilities was the free-radical bromination of alkyl groups of readily available *p*-cresole and 3-methylindole. Our attempts to obtain 4-(*tert*-butyloxycarbonyloxy)benzyl bromide and *N*-Boc-(3-bromomethyl)indole from Boc-protected *p*-cresole and *N*-Boc-3-methylindole via radical bromination, using NBS/AIBN in refluxing CCl_4 [17], was not successful. As a result of bromination of Boc-protected *p*-cresole the mixtures of different bromides were formed. Experiments with *N*-Boc-3-methylindole resulted in complete degradation of the reaction mixture.

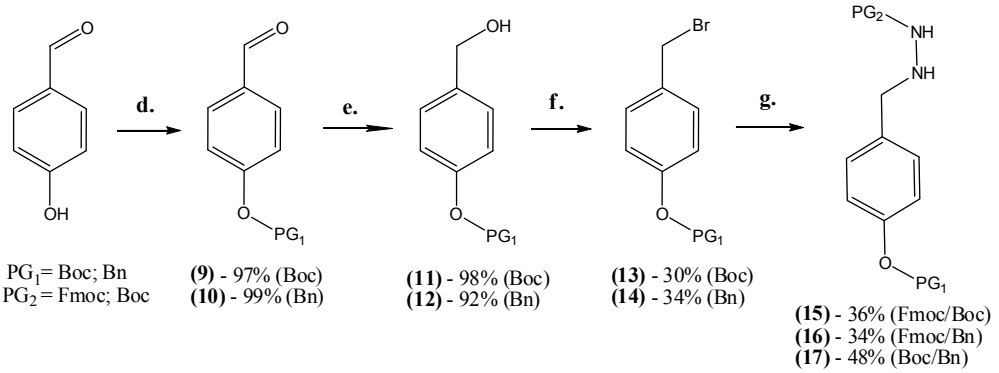


Scheme 2. Synthesis of *N*-protected aza-Phe.



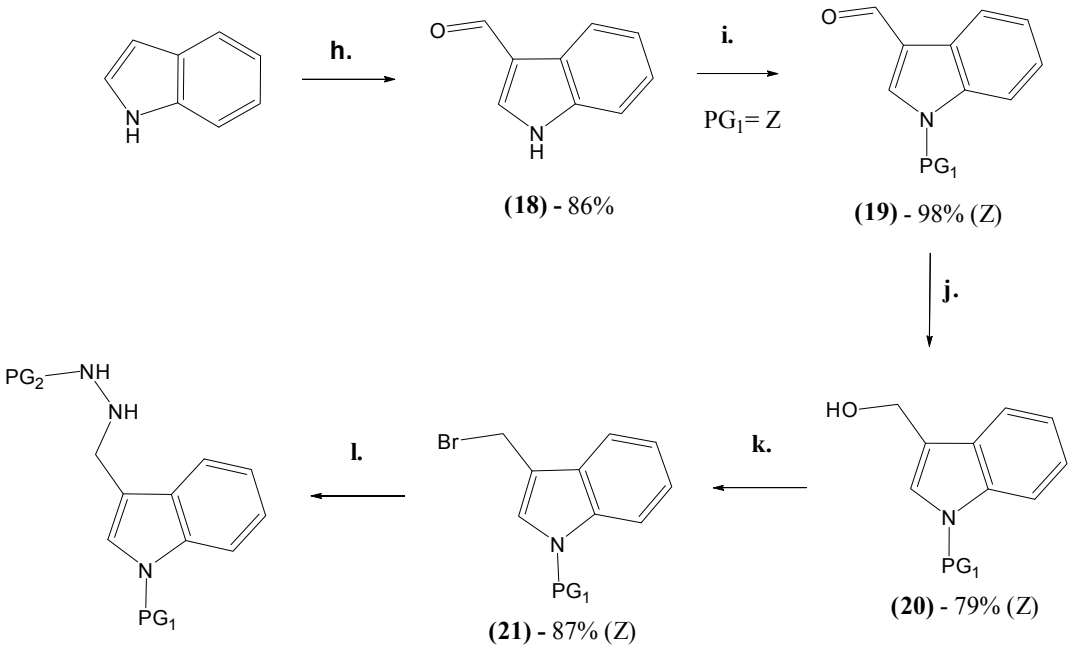
Reaction conditions: **a.** 1 eq of $NaBH_4$, CH_3OH, 2 h; **b.** 0.77 eq of PBr_3, dry DCM, 1 eq of TEA, 0 °C, 1.5 h; **c.** 3 eq of PG-$NHNH_2$, 0.1 M ACN solution, 12 h reflux.

Scheme 3A. Synthesis of *N*-protected aza-Tyr-OCH_3 precursors.



Reaction conditions: **d.** 1.05 eq of Boc_2O, 0.1 eq of DMAP; Or 1.1 eq of BnBr, 3 eq of DiPEA, ACN reflux; **e.** 1 eq of $NaBH_4$, CH_3OH, 0 °C, 2 h; **f.** 0.77 eq of PBr_3, 1 eq of TEA, dry DCM, 0 °C, 2 h; **g.** 3 eq of PG-$NHNH_2$, 1 eq of 2,4,6-trimethylpyridine, 0.1 M ACN sol-on, reflux.

Scheme 3B. Synthesis of *N*-(Fmoc/Boc) aza-Tyr-O(Boc/Bn) precursors.



PG_2= Fmoc; Boc

(22) - 43% (Fmoc/Z)

(23) - 56% (Boc/Z)

Reaction conditions: **h**. DMF, $POCl_3$; **i**. Z-Cl, 1 eq of DiPEA, DCM, 0 °C; **j**. 1 eq of $NaBH_4$, CH_3OH, 0 °C; **k**. 0.5 eq of PBr_3, dry DCM, 0 °C, 1 eq of TEA, $NaHCO_3$; **l**. 4 eq of PG_2-$NHNH_2$, 0.1 M ACN sol-on, 1 eq of N-PG_1-3-bromomethylindole, 1 eq of 2,4,6-trimethylpyridine, reflux 11 h.

Scheme 4. Synthesis of aza-Trp(Z) precursor from indole.

EXPERIMENTAL

General

All solvents and reagents were purchased from Merck, Sigma-Aldrich, or Lach-Ner. NMR spectra were measured on 200 MHz and 700 MHz instruments (Bruker, Germany) in DMSO-d6 or $CDCl_3$ as solvent and using tetramethylsilane as the internal reference. High resolution and low resolution ESI-FT-ICR mass spectra were obtained on a Varian 910-FT-ICR-MS spectrometer using ACN as solvent. IR spectra were determined using the attenuated total reflectance (ATR) measuring technique on a Perkin-Elmer Spectrum BX spectrometer. All yields in multistep syntheses were calculated for each step separately proceeding from the mass of the obtained product.

Syntheses and analytical data on the products

Benzyl iodide was prepared according to the literature method [18] in 76% yield. M.p. 23 °C (lit. m.p. 24 °C [18]). NMR (200 MHz; $CDCl_3$): ^{1}H δ = 4.39 (s, 2H, CH_2I), 7.21–7.34 (m, 5H, Ar(H)). ^{13}C δ = 5.7, 127.7, 128.6, 128.7, 139.2.

9-H-Fluorenyl-9-methyl carbazate was prepared according to the literature method [3]. Fmoc-hydrazine was obtained in 95% yield. M.p. 172 °C (lit. m.p. 171 °C [19]). NMR (200 MHz; DMSO-d_6): ^{1}H δ = 3.8 (s, 2H, NH_2), 4.3 (t, J = 7 Hz, 1H, CH(Fmoc)), 4.5 (d, J = 6.8 Hz, 2H, CH_2), 6.1 (brs, 1H, NH), 7.3–7.9 (m, 8H, Ar(H)). ^{13}C δ = 47.2, 66.3, 120.6, 125.7, 127.6, 128.1, 141.2, 144.4, 158.7.

Preparation of benzyl carbazate: benzyl chloroformate (1 eq) was added dropwise to the mixture of hydrazine hydrate (11 eq) and diethyl ether at 0 °C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with EA, washed with 1 M $NaHCO_3$ solution, water, and brine. The water phase was extracted 3 times with EA; combined extracts were washed with brine. Combined organic phases were dried over anhydrous sodium sulphate and concentrated in vacuum. Benzyl carbazate was obtained in 97% yield. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 3.87 (brs, 2H, NH_2), 5.15 (s, 2H, CH_2), 6.72 (brs, 1H, NH), 7.37 (s, 5H, Ar(H)). ^{13}C δ = 67.2, 128.2, 128.3, 128.5, 136.2, 158.7. IR (cm^{-1}): 3322.2, 3031.6, 1710.7, 1632.9, 1496.4, 1454.1, 1344.6, 1266.7, 1214.5, 1055.6, 1027.9, 913.1, 845.0, 736.0, 695.3. M.p. 64–66 °C (lit. m.p. 69–70 °C [20,21]).

General procedure for the reduction of aldehydes to corresponding alcohols: 1 eq of aldehyde was dissolved in methanol (about 1 g of aldehyde in 20 mL of CH_3OH); the solution was isolated from the atmosphere with Ar and cooled to 0 °C on ice bath. Sodium borohydride (1 eq) was added to the solution and stirred for 1 h. The resulting mixture was quenched with 1 M HCl; methanol was evaporated under reduced pressure. The resulting mixture was diluted with EA, washed with 1 M $NaHCO_3$, ×2 H_2O, and brine. The water phase was extracted 3 times with EA; combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated using a rotatory evaporator. The crude product was used for following reactions without purification.

General procedure for *N*-protected hydrazine alkylation: 3–4 eq of *N*-protected hydrazine was dissolved in ACN (0.1 M solution), heated to reflux; 1 eq of 2,4,6-trimethylpyridine was added. Solution of 1 eq of alkylbromide in ACN (approximately 0.1 g of bromide in 1 mL of ACN) was added dropwise and the reaction mixture was refluxed overnight. ACN was evaporated under reduced pressure; the residue was dissolved in EA, washed with 1 M $NaHCO_3$, ×2 H_2O, and brine. The water phase was extracted 3 times with EA; the combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated using a rotatory evaporator. The crude product was purified on silica gel using EA/PE 1 : 2 mixture as eluent.

During the study of the alkylation reaction various solvents and reaction conditions were used (Table 1 and Table 2).

N-tert-Butyloxycarbonyl-*N′*-benzyl hydrazine [22] **(1)** was prepared according to the general alkylation procedure described above. The compound was obtained in 79% yield. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.45 (s, 9H, ×3 CH_3), 3.95 (s, 2H, CH_2), 4.14 (brs, 1H, NH), 6.57 (brs, 1H, NH), 7.26–7.33 (m, 5H, Ar(H)). ^{13}C δ = 28.4, 55.9, 80.4, 127.4, 128.4, 129.0, 137.8, 156.7. IR (cm^{-1}): 3303.4, 2976.5, 1704.1, 1453.6, 1391.5, 1366.1, 1278.2, 1251.7, 1151.2, 1046.4, 1019, 873.8, 736.1, 697.7. LRMS: calculated $[M + H]^+$ for $C_{12}N_2O_2H_{18}$ *m/z* 223.1, found $[M + H]^+$ *m/z* 223.1.

N-Fluorenylmethyloxycarbonyl-*N′*-benzyl hydrazine [3] **(2)** was prepared according to the general alkylation procedure described above. The compound was obtained in 74% yield. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 3.97 (s, 3H, CH_2 + NH), 4.20 (t, J = 6.2 Hz, 1H, CH (Fmoc)), 4.44 (d, J = 6.8 Hz, 2H, CH_2), 6.37 (brs, 1H, NH), 7.25–7.76 (m, 13H, Ar(H)). ^{13}C δ = 47.4, 55.8, 67.1, 120.1, 125.1, 127.2, 127.7, 127.9, 128.6, 129.1, 137.5, 141.5, 143.8, 157.3. IR (cm^{-1}): 3316.5, 1685.6, 1500.4, 1271.9, 1106.1, 735.8. LRMS: calculated $[M + H]^+$ for $C_{22}N_2O_2H_{20}$ *m/z* 345.2, found $[M + H]^+$ *m/z* 345.1.

N-Benzyloxycarbonyl-*N′*-benzyl hydrazine [23] **(3)** was prepared according to the general alkylation procedure described above. Yield 64%. NMR (700 MHz; $CDCl_3$): ^{1}H δ = 4.04 (s, 2H, CH_2), 4.26 (brs, 1H, NH), 5.20 (s, 2H, CH_2), 6.90 (brs, 1H, NH), 7.40 (d, J = 8.4 Hz, 10H). ^{13}C δ = 55.6, 67.1, 127.5, 128.2, 128.3, 128.5, 129.0, 136.3, 137.5, 157.3. IR (cm^{-1}): 3299.5, 3030.6, 1718.5, 1495.7, 1453.5, 1264.4,

1151.4, 1028.1, 908.2, 848.6, 737.0, 696.3. HRMS: calculated *m/z* for $C_{15}O_2N_2H_{16}$ $[M + H]^+$ 257.12845, found $[M + H]^+$ *m/z* 257.12826.

4-Methoxybenzyl alcohol [24] **(4)** was synthesized using the general procedure of aldehyde reduction with subsequent reaction mixture workup. 4-Methoxybenzyl alcohol was obtained in 94% yield as a transparent liquid. NMR (200 MHz; $CDCl_3$): ^1H δ = 2.53 (brs, 1H, OH), 3.77 (s, 3H, OCH_3), 4.54 (s, 2H, CH_2), 6.85 (d, J = 6.8 Hz, 2H, Ar(H)), 7.24 (d, J = 8.6 Hz, 2H, Ar(H)). ^{13}C NMR ($CDCl_3$): ^{13}C δ = 55.0, 64.3, 113.7, 128.4, 133.3, 158.9. IR (cm^{-1}): 3345.7, 3026.2, 2935.1, 2835.9, 1611.1, 1586.0, 1511.8, 1463.3, 1301.3, 1243.9, 1173.2, 1109.7, 1030.4, 1005.4, 814.7, 752.9, 707.6.

Preparation of 4-methoxybenzyl bromide [25] **(5)** was performed by analogy with the literature method [26] using some modifications: 1 eq of 4-methoxybenzyl alcohol was dissolved in dry DCM (0.5 mL of alcohol in 3 mL DCM). The obtained solution was cooled on ice bath under Ar. 1 eq of TEA was added. 0.77 eq PBr_3 solution in dry DCM (approximately 0.1 g of PBr_3 in 1 mL of dry DCM) was added. The reaction mixture was stirred on ice bath for 3 h, diluted with EA, and washed with 1 M $NaHCO_3$, ×2 H_2O, and saturated NaCl solution. The water phase was extracted 3 times with EA; the combined extracts were washed with brine. The combined organic phases were dried over anhydrous sodium sulphate and concentrated in vacuum. 4-Methoxybenzyl bromide was obtained in 71% yield. The crude product was used in the following reaction without purification. NMR (200 MHz; $CDCl_3$): ^1H δ = 3.76 (s, 3H, O–CH_3), 4.47 (s, 2H, CH_2Br), 6.83 (d, J = 6.8 Hz, 2H, Ar(H)), 7.29 (d, J = 8.6 Hz, 2H, Ar(H)). ^{13}C NMR ($CDCl_3$): δ = 33.9, 55.1, 114.0, 130.0, 130.2, 159.5. IR (cm^{-1}): 3025.4, 2957.7, 2835.8, 1608.2, 1583.5, 1511.8, 1462.0, 1302.3, 1249.4, 1229.6, 1174.6, 1029.9, 830.0, 680.0, 594.0.

N-Fluorenylmethyloxycarbonyl-*N′*-4-methoxybenzyl hydrazine **(6)** was prepared according to the general alkylation procedure described above. The compound was obtained in 61% yield. NMR (700 MHz; $CDCl_3$): ^1H δ = 3.76 (s, 3H, O–CH_3), 3.89 (s, 2H, CH_2), 4.19 (t, J = 7.2 Hz, 2H, CH (Fmoc) + NH), 4.44 (d, J = 7.6 Hz, 2H), 6.47 (brs, 1H, NH), 6.85 (t, J = 8.6 Hz, 2H (Ar)), 7.18–7.41 (m, 6H (Ar)), 7.55 (d, J = 7.4 Hz, 2H(Ar)), 7.74 (d, J = 7 Hz, 2H(Ar)). ^{13}C δ = 47.4, 55.3, 67.1, 114.1, 120.2, 125.2, 127.3, 127.9, 129.6, 130.4, 141.5, 143.9, 157.4, 159.4. IR (cm^{-1}): 3311.6, 2916.1, 1719.1, 1611.2, 1584.8, 1511.6, 1449.6, 1372.4, 1244.6, 1153.4, 1107.7, 1034.4, 814.6, 758.4, 739.6; LRMS: calculated *m/z* for $C_{23}N_2O_3H_{20}$ $[M + H]^+$ 375.17, found $[M + H]^+$ *m/z* 375.1. HRMS: calculated *m/z* for $C_{23}N_2O_3H_{20}$ $[M + H]^+$ 375.17032, found $[M + H]^+$ *m/z* 375.17013.

N-*tert*-Butyloxycarbonyl-*N′*-4-methoxybenzyl hydrazine [10] **(7)** was prepared according to the general alkylation procedure described above. Yield 56%. NMR (200 MHz; $CDCl_3$): ^1H δ = 1.46 (s, 9H, ×3 CH_3), 3.78 (s, 3H, O–CH_3), 3.91 (s, 2H, CH_2), 4.14 (brs, 1H, NH), 6.36 (brs, 1H, NH), 6.85 (d, J = 8.6 Hz, 2H, Ar(H)), 7.26 (d, J = 8.6 Hz, 2H, Ar(H)). ^{13}C NMR ($CDCl_3$): δ = 28.4, 55.3, 80.5, 114.0, 129.7, 130.3, 156.8, 159.2. IR (cm^{-1}): 3314.2, 2975.9, 1709.0, 1612.1, 1512.3, 1457.1, 1366.4, 1278.5, 1247.6, 1154.1, 1035.4, 814.5. LRMS: calculated *m/z* for $C_{13}O_3N_2H_{18}$ $[M + H]^+$ 253.15; found $[M + H]^+$ *m/z* 253.1.

N-Benzyloxycarbonyl-*N′*-methoxybenzyl hydrazine **(8)** was prepared according to the general alkylation procedure described above. The compound was obtained in 40% yield. NMR (200 MHz; $CDCl_3$): ^1H δ = 3.75 (s, 3H, O–CH_3), 3.90 (s, 3H, CH_2 + NH); 5.11 (s, 2H, CH_2(Z)), 6.57 (brs, 1H, NH), 6.81 (d, J = 8.6 Hz, 2H, Ar(H)), 7.21 (d, J = 8.4 Hz, 2H, Ar(H)), 7.34 (s, 5H, Ar(H)). ^{13}C δ = 55.2, 67.0, 113.9, 128.1, 128.2, 128.5, 129.4, 130.2, 136.2, 157.2, 159.1. IR (cm^{-1}): 3267.9, 2933.5, 2834.2, 1715.2, 1610.6, 1585.2, 1510.3, 1453.7, 1301.6, 1240.9, 1173.5, 1149.7, 1031.0, 821.5, 737.7, 695.3. LRMS: calculated *m/z* for $C_{16}O_3N_2H_{18}$ $[M + H]^+$ 287.14, found $[M + H]^+$ *m/z* 287.0. HRMS: calculated *m/z* for $C_{16}O_3N_2H_{18}$ $[M + H]^+$ 287.13902, found $[M + H]^+$ *m/z* 287.13900.

4-(*tert*-Butyloxycarbonyloxy)benzaldehyde [27] **(9)** was prepared according to the method described in [26] with some modifications. Shortly: 1 eq of 4-hydroxybenzaldehyde was suspended in chloroform, 1.05 eq of Boc_2O and 0.1 eq of 4-dimethylaminopyridine were added. Chloroform was evaporated under reduced pressure, residue was dissolved in EA, washed with 1 M $KHSO_4$, 1 M $NaHCO_3$, ×2 H_2O, and brine. The water phase was extracted 3 times with EA, combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated using a rotatory evaporator. 4-(*tert*-Butyloxycarbonyloxy)-benzaldehyde was obtained as a slightly yellowish solid in 97% yield. The crude product was used in the following reaction steps without purification. NMR (200 MHz; $CDCl_3$): ^1H δ = 1.56 (s, 9H, ×3 CH_3), 7.35 (d, J = 8.6 Hz, 2H, Ar(H)), 7.89 (d, J = 7 Hz, 2H), 9.97 (s, 1H, COH). ^{13}C δ = 27.6, 84.3, 121.8, 131.1, 133.9, 150.9, 155.7, 190.7. IR (cm^{-1}): 2934.5, 1755.7, 1700.0, 1600.3, 1370.2, 1271.7, 1256.3, 1217.2, 1138.6, 1012.4, 892.0, 835.5, 778.5.

4-(Benzyloxy)benzaldehyde [28] **(10)** was prepared using the following procedure: 1 eq of 4-hydroxybenzaldehyde was dissolved in ACN and heated to reflux, followed by addition of 3.5 eq of DiPEA and 1.1 eq of benzyl bromide. The reaction mixture was refluxed for 1 h. Volatiles were removed in vacuum and the residue was dissolved in EA. The organic solution was washed with saturated $NaHCO_3$, twice with water, and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. 4-(Benzyloxy)benzaldehyde was obtained in 99% yield. NMR (200 MHz; $CDCl_3$): ^1H δ = 5.08 (s, 2H,

–O–CH_2–), 7.03 (d, J = 8.6 Hz, 2H, Ar(H)), 7.25–7.37 (m, 5H, Ar(H)), 7.78 (d, J = 8.4 Hz, 2H, Ar(H)), 9.82 (s, 1H, COH). ^{13}C δ = 70.2, 115.2, 127.4, 128.2, 128.6, 130.1, 131.8, 136.0, 163.6, 190.7. IR (cm^{-1}): 3056.1, 2829.4, 2745.0, 1685.0, 1598.2, 1573.6, 1508.4, 1461.4, 1452.0, 1425.2, 1394.4, 1320.5, 1300.8, 1257.6, 1213.0, 1162.2, 1110.0, 1077.5, 1018.0, 865.1, 828.9, 788.2, 734.4, 696.0, 653.9, 625.0.

Preparation of 4-(*tert*-butyloxycarbonyloxy)benzyl alcohol [27] **(11)**: the compound was synthesized using the general procedure of aldehyde reduction with subsequent reaction mixture workup. The alcohol was obtained in 98% yield (slightly yellowish solid). NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.57 (s, 9H, ×3 CH_3), 3.08 (brs, 1H, OH), 4.62 (s, 2H, CH_2), 7.12 (d, J = 8.6 Hz, 2H, Ar(H)), 7.30 (d, J = 8.4 Hz, 2H, Ar(H)). ^{13}C δ = 27.8, 64.4, 83.6, 121.3, 128.0, 138.7, 150.5, 152.1. IR (cm^{-1}): 3348.4, 2981.0, 1754.3, 1607.3, 1508.3, 1475.2, 1458.0, 1419.0, 1394.8, 1370.0, 1273.0, 1255.3, 1217.0, 1141.1, 1046.4, 1013.7, 893.1, 832.3, 781.2, 728.6.

(4-(Benzyloxy)phenyl)methanol [29] **(12)** was prepared using the general procedure for the reduction of aldehydes. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 2.01 (s, 1H, OH), 4.55 (s, 2H, –CH_2(OH)), 5.03 (s, 2H, –CH_2–O–), 6.94 (t, J = 6.4 Hz, 2H, Ar(H)), 7.22–7.40 (m, 7H, Ar(H)). ^{13}C δ = 64.9, 70.1, 115.0, 127.4, 128.60, 128.62, 129.3, 133.5, 137.0, 158.4. IR (cm^{-1}): 3322.5, 2921.0, 1609.6, 1511.0, 1454.0, 1381.7, 1298.0, 1240.7, 1172.8, 1111.0, 1001.7, 807.7, 737.1, 694.2.

Preparation of 4-(*tert*-butyloxycarbonyloxy)benzyl bromide [30] **(13)**: the compound was prepared by analogy with the literature method [26] using some modifications: 1 eq of 4-*O*-Boc-benzyl alcohol (0.23 g; 0.00103 mol) was dissolved in 3 mL of dry DCM. The obtained solution was cooled to 0 °C on ice bath under Ar followed by the addition 1 eq of TEA (0.143 mL). Subsequently 0.77 eq of PBr_3 (0.075 mL) solution in dry DCM (3 mL) was added. The reaction mixture was stirred on ice bath for 1 h. Saturated $NaHCO_3$ solution was added to the reaction mixture. The resulting solution was extracted 3 times with chloroform. Combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Volatiles were evaporated under reduced pressure, the oily residue (consisting of unstable 4-(*tert*-butyloxycarbonyloxy)benzyl bromide and some polar impurities) was used for hydrazine alkylation. Crude mixture can be purified on silica gel column using EA/PE 1 : 2 as eluent, which yields about 30% of 4-(*tert*-butyloxycarbonyloxy)benzyl bromide. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.55 (s, 9H, ×3 CH_3), 4.46 (s, 2H, CH_2Br), 7.15 (d, J = 8.6 Hz, 2H, Ar(H)), 7.38 (d, J = 8.6 Hz, 2H, Ar(H)). ^{13}C δ = 27.8, 32.6, 83.7, 121.7, 130.2, 135.3, 151.1, 151.7. IR (cm^{-1}): 2980.6, 1754.0, 1608.9, 1508.3, 1394.5, 1369.7, 1272.0, 1255.4, 1220.5, 1139.9, 1017.5, 893.0, 837.4, 780.0, 718.1, 671.0, 602.9.

4-(Benzyloxy)-1-(bromomethyl)benzene [29] **(14)** was prepared according to the modified literature method [28]. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 4.42 (s, 2H, CH_2Br), 4.96 (s, 2H, CH_2–O), 6.87 (d, J = 8.8 Hz, 2H Ar(H)), 7.22–7.35 (m, 6H, Ar(H)). ^{13}C δ = 33.8, 70.0, 115.1, 127.3, 127.9, 128.5, 130.2, 130.4, 136.7, 158.8.

N-Fluorenyloxycarbonyl-*N′*-(*tert*-butyloxycarbonyloxy)benzyl hydrazine **(15)** was prepared according to the general alkylation procedure. The compound was obtained in 36% yield. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.62 (s, 9H, ×3 CH_3), 4.01 (s, 3H, CH_2 + NH), 4.26 (t, J = 6.6 Hz, 1H, CH (Fmoc)), 4.50 (d, J = 6.8 Hz, 2H, CH_2 (Fmoc)), 6.43 (brs, 1H, NH), 7.20–7.82 (m, 12H, Ar(H)). ^{13}C δ = 27.9, 47.5, 55.2, 67.1, 83.7, 120.2, 121.5, 125.2, 127.3, 128.0, 130.0, 135.2, 141.6, 143.9, 150.8, 152.1, 157.3. IR (cm^{-1}): 3358.3, 2983.4, 1749.4, 1691.6, 1509.3, 1470.3, 1450.5, 1370.1, 1257.4, 1222.1, 1143.8, 1105.9, 1086.2, 1043.7, 1020.0, 982.7, 895.7, 780.1, 755.9, 738.2. LRMS: calculated *m/z* for $C_{27}O_5N_2H_{28}$ $[M + H]^+$ 461.21, found $[M + H]^+$ *m/z* 461.1. HRMS: calculated *m/z* for $C_{27}O_5N_2H_{28}$ $[M + H]^+$ 461.20710, found $[M + H]^+$ *m/z* 461.20688.

N-Fluorenyloxycarbonyl-*N′*-(4-(benzyloxy))benzyl hydrazine **(16)** was prepared according to the general hydrazine alkylation procedure described above. Yield 34%. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 3.51 (brs, 1H, NH), 3.90 (s, 2H, CH_2), 4.20 (t, J = 6.8 Hz, 1H, CH(Fmoc), 4.45 (d, J = 6.6 Hz, 2H (CH_2 (Fmoc)), 5.05 (s, 2H, CH_2–O), 6.37 (brs, 1H, NH), 6.93 (t, J = 8.2 Hz, 2H (Ar(H)), 7.22–7.39 (m, 11H, Ar(H)), 7.55 (d, J = 7 Hz, 2H (Ar(H)), 7.73 (d, J = 7 Hz, 2H, (Ar(H)). ^{13}C δ = 47.3, 55.2, 67.0, 70.1, 115.0, 120.0, 125.0, 127.1, 127.4, 127.8, 128.0, 128.6, 129.7, 130.3, 137.1, 141.4, 143. 7, 157.2, 158.4. HRMS: calculated *m/z* for $C_{29}H_{26}N_2O_3$ $[M + H]^+$ 451.20162, found *m/z* 451.20181.

N-*tert*-Butyloxycarbonyl-*N′*-(4-(benzyloxy))benzyl hydrazine **(17)** was prepared according to the general hydrazine alkylation procedure described above. It was obtained in 48% yield. NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.45 (s, 9H, ×3 CH_3), 3.92 (s, 2H, CH_2), 4.13 (brs, 1H, NH), 5.03 (s, 2H, CH_2–O), 6.51 (brs, 1H, NH), 6.93 (d, J = 6.6 Hz, 2H, Ar(H)), 7.23–7.39 (m, 7H, Ar(H)). ^{13}C δ = 28.3, 55.3, 70.1, 80.8, 114.9, 127.4, 127.9, 128.6, 129.2, 130.4, 137.0, 156.5, 158.5. HRMS: calculated *m/z* for $C_{19}H_{24}N_2O_3Na$ $[M + Na]^+$ 351.16791, found *m/z* 351.16798.

Preparation of indole-3-aldehyde **(18)**: the compound was prepared according to the literature method [31] using 50 times scale down. Indole-3-aldehyde was obtained in 86% yield. M.p. = 194–197 °C (lit. m.p. = 196–197 °C [31]). NMR (d^6-DMSO): ^{1}H δ = 7.31 (t, J = 3.8 Hz, 2H (Ar(H)), 7.59 (s, 1H, Ar(H)), 8.24 (t, J =

5.4 Hz, 1H, Ar(H)), 8.33 (s, 1H, Ar(H)), 10.05 (s, 1H, COH), 11.27 (brs, 1H, NH). ^{13}C δ = 112.5, 118.3, 120.9, 122.2, 123.5, 124.3, 137.2, 138.2, 185.0.

Preparation of (1-benzyloxycarbonyl)indole-3-aldehyde [32] **(19)**: 1 eq (0.42 g; 0.0029 mol) of indole-3-aldehyde was suspended under Ar on ice bath in 4 mL of DCM, 1 eq of DiPEA (V = 0.505 mL) was added followed by dropwise addition of 1 eq of benzyl chloroformate (V = 0.29 mL) at 0 °C. The reaction mixture was stirred for 1.5 h and monitored using TLC (EA/PE 1 : 2); during this time indole-3-aldehyde dissolved forming a yellowish solution. DCM was evaporated using a rotatory evaporator; the residue was dissolved in EA, washed with 1 M $NaHCO_3$, ×2 H_2O, and brine. The water phase was extracted 3 times with EA; combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated using a rotatory evaporator. The crude product was used in the following reaction steps without purification. (1-Benzyloxycarbonyl)-indole-3-aldehyde (yellow solid) was obtained in quantitative yield. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 5.44 (s, 2H, CH_2), 7.23–7.50 (m, 7H, Ar(H)), 8.09–8.25 (m, 3H, Ar(H)), 9.98 (s, 1H, COH). ^{13}C δ = 69.8, 115.1, 122.1, 122.2, 124.8, 126.0, 126.3, 128.7, 128.9, 129.1, 134.3, 135.85, 135.9, 150.0, 185.5. IR (cm^{-1}): 3033.9, 2818.3, 1746.4, 1672.9, 1607.8, 1550.6, 1480.0, 1450.1, 1398.5, 1344.6, 1307.5, 1258.6, 1215.0, 1163.9, 1127.9, 1087.0, 1028.0, 1015.9, 944.3, 909.3, 744.2, 696.3.

(1-Benzyloxycarbonyl-(3-hydroxymethyl))indole [32] **(20)** was synthesized using the general procedure of aldehyde reduction with subsequent reaction mixture workup. The crude product was purified on silica gel column using EA/PE 1 : 2 as eluent. 1-Z-(3-Hydroxymethyl)indole was isolated in 79% yield. NMR ($CDCl_3$): ^{1}H δ = 4.15 (s, 1H, OH), 4.78 (s, 2H, CH_2), 5.38 (s, 2H, CH_2(Z)), 7.31–7.68 (m, 9H, Ar(H)), 8.25 (d, J = 7 Hz, 1H, Ar(H)). ^{13}C δ = 56.3, 68.3, 114.9, 119.1, 121.3, 122.6, 122.7, 124.5, 128.0, 128.3, 128.32, 128.9, 134.8, 135.4, 150.4. IR (cm^{-1}): 3377.8, 2871.3, 1729.9, 1608.1, 1452.0, 1396.1, 1349.6, 1304.6, 1243.7, 1219.7, 1123.2, 1084.0, 1041.9, 1003.1, 909.4, 812.2, 743.1, 696.0, 654.1.

Preparation of (1-benzyloxycarbonyl-(3-bromomethyl))indole [32] **(21)** was performed by analogy with the literature method [24] with some modifications: 1 eq (0.345 g; 0.00122 mol) of ((1-benzyloxycarbonyl)-3-hydroxymethyl) indole was dissolved in 6 mL of dry DCM and cooled down to 0 °C on ice bath under Ar. 1 eq of TEA (0.169 mL) and 5 eq of $NaHCO_3$ (0.512 g) were added followed by dropwise addition with stirring of 0.5 eq PBr_3 (0.057 mL) in a form of solution in 0.5 mL of dry DCM. The reaction mixture was stirred for 2 h. The reaction was monitored using EA/PE 1 : 2 as eluent. After the reaction was complete, saturated $NaHCO_3$ solution was added to the reaction mixture. The resulting solution was extracted 4 times with $CHCl_3$. Combined extracts were washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. $CHCl_3$ was distilled off and the residue was purified on silica gel column using EA/PE 1 : 2 as eluent. (1-Benzyloxycarbonyl-(3-bromomethyl))indole was obtained in 87% yield (crude yield 93%) as a yellowish solid. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 4.69 (s, 2H, CH_2Br), 5.51 (s, 2H, CH_2(Z)), 7.40–7.57 (m, 7H, Ar(H)), 7.74–7.78 (m, 2H, Ar(H)), 8.29 (d, J = 6.6 Hz, 1H). ^{13}C δ = 24.1, 69.0, 115.5, 118.2, 119.5, 123.3, 124.6, 125.4, 128.0, 128.5, 128.6, 128.8, 135.0, 135.9, 150.5. IR (cm^{-1}): 3108.4, 2852.4, 1704.5, 1605.9, 1530.1, 1346.0, 1196.8, 1104.5, 1007.5, 849.5, 814.9, 738.4, 679.0.

N-Fluorenylmethyloxycarbonyl-*N′*-(3-methyl(*N″*-Z-indolyl))hydrazine **(21)** was prepared according to the general alkylation procedure described above. Yield 43%. NMR (700 MHz; $CDCl_3$): ^{1}H δ = 3.61 (brs, 1H, NH), 4.16 (quint, 3H; CH_2 + CH), 4.49 (d, J = 7 Hz, 2H, CH_2 (Fmoc)), 5.38 (s, 2H, CH_2(Z)), 6.27 (brs, 1H, NH), 7.25–7.41 (m), 7.72 (d), 8.18 (d) (18H, Ar(H)). ^{13}C δ = 46.7, 47.4, 67.2, 68.9, 115.4, 117.7, 119.8, 120.1, 123.2, 124.5, 125.1, 127.2, 127.9, 128.6, 128.9, 130.1, 130.4, 135.2, 136.0, 141.5, 143.8, 150.8, 157.3. HRMS: calculated *m*/*z* for $C_{32}N_3O_4H_{27}$ $[M + H]^+$ 518.20743, found $[M + H]^+$ *m*/*z* 518.20717.

N-*tert*-Butyloxycarbonyl-*N′*-(3-methyl(*N″*-Z-indolyl))hydrazine **(22)** was prepared according to the general alkylation procedure desribed above. The compound was obtained in 58% yield. NMR ($CDCl_3$): ^{1}H δ = 1.44 (s, 9H, ×3 CH_3), 3.61 (brs, 1H, NH), 4.11 (s, 2H, CH_2), 5.40 (s, 2H, CH_2(Z)), 6.29 (brs, 1H, NH), 7.24–7.70 (m, 9H, Ar(H)), 8.16 (d, J = 7.2 Hz, 1H, Ar(H)). ^{13}C δ = 28.4, 46.6, 68.7, 80.6, 115.3, 118.0, 119.7, 123.0, 124.2, 124.8, 128.5, 128.7, 128.8, 130.1, 135.2, 135.8, 150.7, 156.8. HRMS: calculated *m*/*z* for $C_{22}H_{25}O4N_3Na + 1$ $[M + Na]^+$ 418.17373, found $[M + Na]^+$ *m*/*z* 418.17373.

CONCLUSIONS

A detailed study of mono-protected hydrazines using benzyl bromide was performed, and the most suitable conditions for these reactions were found. Aza-tyrozine, aza-phenylalanine, and aza-tryptophane precursors with different protecting groups were prepared from various aldehydes via the hydrazine alkylation reaction.

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Asa-fenüülalaniini, asa-türosiini ja asa-trüptofaani prekursorite süntees hüdrasiini alküülimise teel

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Aromaatse külgahelaga asa-aminohapete prekursorid olid sünteesitud, kasutades monokaitstud hüdrasiini alküülimist. See sünteesitee võimaldas vältida vesiniku ja kallite hüdrogeenimise katalüsaatorite kasutamist. Antud reaktsiooni optimeerimiseks olid testitud erinevad solvendid ja reaktsioonitingimused. Asa-fenüülalaniini, asa-türosiini ja asa-trüptofaani prekursorid erinevate *N*- ja külgahela kaitserühmadega olid sünteesitud, lähtudes *N*-kaitstud hüdrasiinidest.