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CHEMISTRY

Potassium iodide catalysis in the alkylation of protected hydrazines

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Abstract. Potassium iodide catalysis was applied for the synthesis of protected benzylhydrazines and hydrazinoacetic acid esters by the alkylation of protected hydrazines. Benzylic halogenides and halogenoacetic acid esters were employed as alkylating agents. In these syntheses the reactive alkyl iodide molecules were generated in situ from less reactive halogenides, which significantly accelerated the alkylation reaction. The effectiveness of potassium iodide catalysis was proved by experiments performed under the same conditions in the absence of this salt.

Key words: alkylation, aza-tyrosine, aza-tryptophan precursors, aza-amino acid precursors, hydrazine derivatives, monoprotected hydrazine alkylation, protecting groups, bromination, potassium iodide catalysis.

Abbreviations

ACN – acetonitrile
Asp – aspartic acid
ATR – attenuated total reflectance
Bn – benzyl
Boc – *tert*-butyloxycarbonyl
Bz – benzoyl
DiPEA – *N*,*N*′-diisopropylethylamine
DMAP – 4-dimethylaminopyridine
DMSO – dimethyl sulphoxide
EA – ethyl acetate
Fmoc – 9-fluorenylmethoxycarbonyl
IR – infrared
Lit. m.p. – melting point from the literature
LRMS – low resolution mass spectra
NBS – *N*-bromosuccinimide
NMR – nuclear magnetic resonance
PE – petroleum ether
PG – protecting group
Phe – phenylalaline
Pro – proline
tBu – tertiary butyl (*tert*-butyl)
TLC – thin layer chromatography
TMS – tetramethylsilane
Tyr – tyrosine
Z – carboxybenzyl

INTRODUCTION

Replacement of natural amino acids with their aza-analogues in peptides yields aza-peptides, a class of peptide-like compounds where the α-C atom of an amino acid is replaced with a nitrogen atom. These peptide analogues have increased biostability [1–4] and therefore these compounds are promising drug candidates serving as inhibitors of HIV-1 [5] and hepatite C protease [6]. However, α-aza-amino acids themselves are not stable compounds and cannot be prepared and isolated due to their spontaneous decarboxylation [7]. Therefore aza-

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amino acids are included into peptides by using protected alkylhydrazines as precursors of α-aza-amino acids.

The most straightforward way for the synthesis of aza-amino acid precursors is direct alkylation of protected hydrazines with alkylhalogenides [8–12]. Compared to the more widely applied reductive alkylation approach, direct alkylation reduces the number of reaction steps and allows omitting the reduction step of hydrazone, formed in the condensation step of a carbonyl compound and hydrazine [8]. This reduction step is technically complicated, especially if a Pd/C catalyst is used at elevated hydrogen pressure [1]. On the other hand, in the case of a direct alkylation reaction, the formation of polyalkylated products should be considered [13]. However, the formation of these side products could be suppressed by using excess of hydrazine and applying an appropriate base and solvent [8,9].

The direct hydrazine alkylation reaction has been used for the preparation of various aza-amino acid precursors [8–12], including the alkylation of Fmoc-$NHNH_2$ by solid phase immobilized 2-bromoacetic acid [14] and on-resin synthesis of aza-Phe residue [15]. Alkylation of di-protected hydrazines by 1,3-dibromopropane was applied for the preparation of aza-Pro precursors carrying orthogonal protecting groups [11,16]. Recently, an effective alkylation of conjugated hydrazone anions by different alkylhalogenides was reported [17–20]. Also, an effective N-alkylation of aza-sulphuryl peptide was reported [21].

Our previous work [9] about synthesis of aza-phenylalanine, aza-tyrosine, and aza-tryptophan precursors, where alkylation of monoprotected hydrazines was used, revealed that application of alkyl chlorides resulted in a very low yield of monoalkylated hydrazine, while higher yields were obtained in the case of alkyl bromides and especially alkyl iodides [9]. However, practical application of these reactions is often complicated, as alkyl iodides are not readily available and often tend to decompose during storage and purification.

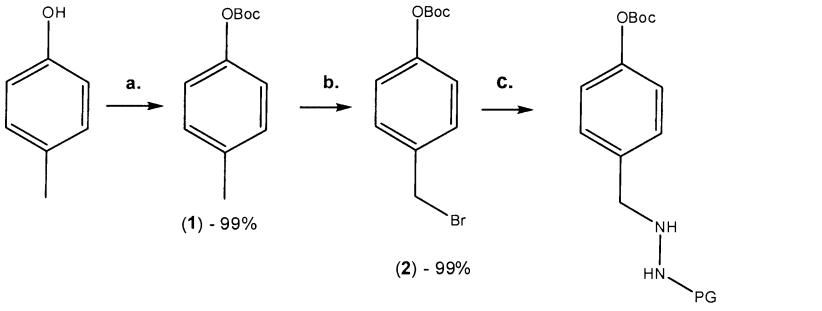
In this study we report the possibility of hydrazine alkylation by generating alkyl iodides from less reactive alkylhalogenides in situ in the presence of catalytic amounts of inorganic iodides such as NaI and KI. Although the iodide catalysed alkylation reaction is known and effectively applied for the synthesis of different organic compounds [22–24], no attention has so far been paid to KI catalysed alkylation of hydrazine and its derivatives. In the reported study we filled this gap.

RESULTS AND DISCUSSION

In this study we observed that a catalytic amount of KI (0.1 eq) promoted the alkylation of different protected hydrazines and provided a possibility of using different alkyl halogenides of rather low reactivity for this reaction. As a result of this catalysis, it was possible to significantly improve the preparation of the precursors for aza-tyrozine, aza-Asp, and aza-phenylalanine.

Firstly, we used the catalytic reaction for the preparation of aza-tyrosine precursor, proceeding from *p*-cresol, which was *O*-protected with a Boc protecting group and thereafter brominated at the methyl group by using the radical halogenation reaction (Scheme 1). The obtained bromide was thereafter used for the bromination of various hydrazines. Yields of these reactions were 49–59% after 5-hour long refluxing (Scheme 1).

Encouraged by the described results, we decided to apply the above-mentioned KI catalysis for the preparation of other protected alkylhydrazines. More specifically, we used benzyl bromide, benzyl chloride, 4-methoxybenzyl chloride, *tert*-butyl bromoacetate, methyl bromoacetate, and ethyl chloroacetate for the alkylation of Fmoc-, Boc-, and Z-protected hydrazines.



(**1**) - 99%

(**2**) - 99%

(**3**) - 57% (PG = Fmoc)
(**4**) - 56% (PG = Boc)
(**5**) - 59% (PG = Z)
(**6**) - 49% (PG = Bz)

Reaction conditions: **a.** 1.05 eq of Boc_2O, $CHCl_3$, 0.05 eq of DMAP; **b.** CCl_4, 1.05 eq of NBS, 0.016 eq of BzOOBz, reflux; **c.** 3 eq of $PGNHNH_2$, 0.1 M solution in ACN, 0.1 eq of KI, 1.5 eq of DiPEA or 2,4,6-trimethylpyridine, reflux.

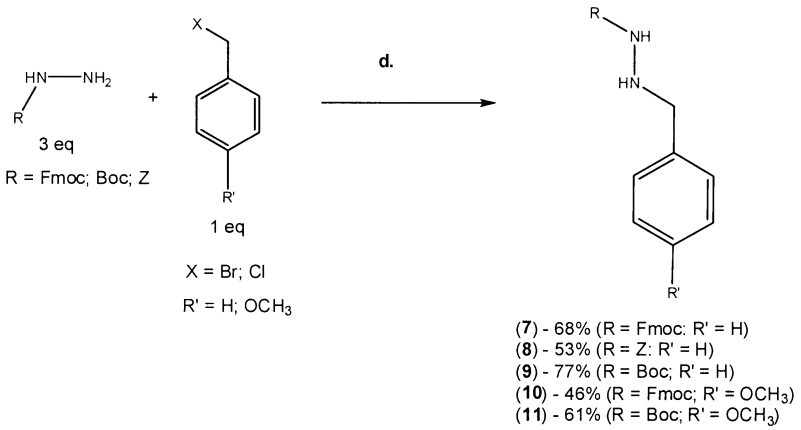
Scheme 1. Preparation of precursors of aza-Tyr(Boc) from *p*-cresol.

In the case of benzylation of hydrazines (Scheme 2) the application of KI catalysis allowed us to react protected hydrazines effectively even with compounds that have a rather low electrophilicity, and nearly equal yields were obtained (Table 1) when Bn bromide and benzyl chloride were used as the alkylating reagents. At the same time the alkylation of protected hydrazines with benzyl chloride in the absence of KI gave only traces of the monoalkylated product during 6-hour refluxing and 21–55% of the desired product after 24 hours (Table 1).

In the reactions with 4-methoxybenzyl chloride (Scheme 2) protected 4-methoxybenzyl hydrazines were obtained in moderate to good yields after 6-hour long reflux, while attempts to use this reaction in the absence of KI gave the products in 13–27% yield after 24-hour long refluxing (Table 1).

In the reactions of protected hydrazines and halogenoacetic acid esters the respective halogenides and protected hydrazines were taken in 1 : 1 ratio, and 1.5 eq of 2,4,6-trimethylpyridine (in combination with Fmoc-$NHNH_2$) or DiPEA (in combination with Boc-$NHNH_2$ or Z-$NHNH_2$) was used as the base. The yields of monoalkylated products (12)–(18) were 54–88% after 24-hour long refluxing (Scheme 3).

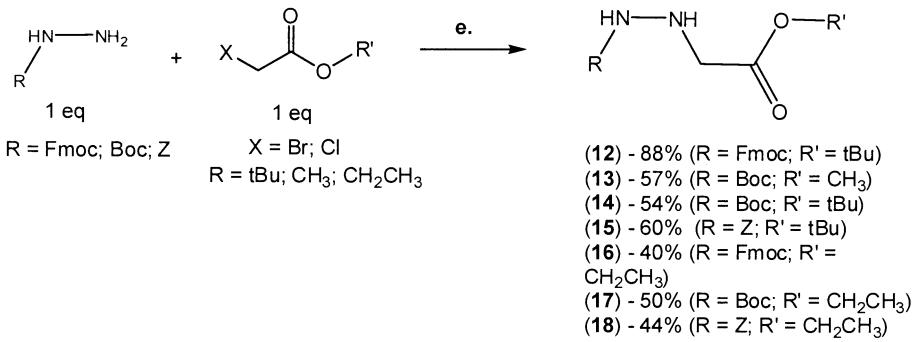
We tested alkylation of protected hydrazines with ethyl chloroacetate in the absence of KI and obtained monoalkyl products with 15–20% yield after 24 hours of refluxing. These experiments together with the results of the alkylation reactions with benzyl chloride and 4-methoxybenzyl chloride clearly show the effectiveness of KI catalysis.



Scheme 2. Potassium iodide catalysed benzylation of protected hydrazines.

Table 1. Benzylation of protected hydrazines. PG-$NHNH_2$ 3 eq; solvent ACN; reflux

PG	Reaction time, h	Alkylating reagent (1 eq)	Base (1.5 eq)	KI, eq	Yield of monoalkylated hydrazine, %
Fmoc	5	Bn-Br	2,4,6-trimethylpyridine	0.1	68
Boc	5	Bn-Br	2,4,6-trimethylpyridine	0.1	71
Boc	5	Bn-Cl	2,4,6-trimethylpyridine	0.1	77
Fmoc	6	Bn-Cl	2,4,6-trimethylpyridine	0.1	49
Z	6	Bn-Cl	DiPEA	0.1	53
Boc	6	Bn-Cl	DiPEA	0.1	65
Boc	24	Bn-Cl	DiPEA	0	55
Fmoc	24	Bn-Cl	2,4,6-trimethylpyridine	0	22
Z	24	Bn-Cl	DiPEA	0	21
Boc	6	4-(OCH_3)-Bn-Cl	DiPEA	0.1	61
Fmoc	6	4-(OCH_3)-Bn-Cl	2,4,6-trimethylpyridine	0.1	46
Boc	24	4-(OCH_3)-Bn-Cl	DiPEA	0	27
Fmoc	24	4-(OCH_3)-Bn-Cl	2,4,6-trimethylpyridine	0	13



Scheme 3. Potassium iodide catalysed alkylation of protected hydrazines with halogenoacetic acid esters.

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 the solvent and using TMS as the internal reference. The LRMS were obtained on an Agilent Series 1100 LC/MSD Trap XCT (Agilent Technologies, Santa Clara, USA) spectrometer using acetonitrile as the solvent. The IR spectra were determined by using the ATR measuring technique on a Perkin-Elmer Spectrum BX spectrometer. The structure of the synthesized compounds was verified by NMR and IR spectroscopy. Purity was checked by means of NMR and TLC. Additional mass spectra analysis was performed. All the yields are given in comparison with the theoretical yield and are calculated proceeding from the mass of the obtained product. All the melting points are uncorrected.

9-H-Fluorenyl-9-methyl carbazate was prepared according to the literature method [1] with slight modifications. Briefly, the slurry of Fmoc-$NHNH_2$ was cooled on ice bath before filtration, ice cold water and toluene were used for washing the product, followed by air drying and drying in vacuum. Fmoc-hydrazine was obtained in 99% yield. M.p. 172 ºC (lit. m.p. 171 ºC [25]). 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 (br s, 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.

Benzyl carbazate was prepared according to the previously reported procedure [9]. NMR (200 MHz; $CDCl_3$): ^{1}H δ = 3.87 (br s, 2H, NH_2), 5.15 (s, 2H, CH_2), 6.72 (br s, 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 ºC (lit. m.p. 69–70 ºC [26]).

General procedure for the preparation of *tert*-butyl 4-methylphenyl carbonate (1): 1 eq of *p*-cresol was dissolved in chloroform followed by the addition of 1.05 eq of Boc_2O and 0.05 eq of DMAP. The reaction mixture was stirred at room temperature for 30 min; diluted with EA; washed with dilute $KHSO_4$ solution, saturated $NaHCO_3$ solution, water, and saturated NaCl solution; and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, giving a transparent oil that crystallized at room temperature. Yield: 98%.

NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.49 (s, 9H, 3 × CH_3), 2.25 (s, 3H, CH_3), 6.98–7.10 (m, 4H, Ar(H)). ^{13}C δ = 20.4, 27.3, 82.5, 120.7, 129.5, 134.8, 148.9, 151.8. IR (cm^{-1}) = 3034.5, 2981.7, 2933.1, 1751.2, 1508.4, 1453.8, 1366.8, 1253.5, 1140.2, 820.5. M.p. = 47–50 ºC (lit. m.p. 48–52 ºC [27]). Rf (EA/PE 1 : 7) = 0.77.

***tert*-Butyloxycarbonyloxy-4-(bromomethyl) benzene (2)** was prepared according to the following procedure: 1 eq of *t*-butyl 4-methylphenyl carbonate (**1**) (0.6 g, 0.00285 mol) was dissolved in 10 mL of dry CCl_4 (distilled from P_2O_5), followed by the addition of 1.05 eq of NBS (539 mg) and 0.016 eq (10 mg) of benzoyl peroxide. The resulting mixture was refluxed for 2 h and cooled to room temperature. The precipitated succinimide was filtered out and washed with 2 mL of dry CCl_4. The filtrate was evaporated to dryness and the obtained white solid was used in the following step without further purification. Yield: 99% [28].

NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.56 (s, 9H, 3 × CH_3), 4.48 (s, 2H, CH_2Br), 7.17 (d, 2H, J = 6.6 Hz, Ar(H)), 7.40 (d, 2H, J = 6.6 Hz, Ar(H)).^{13}C δ = 27.7, 32.6,

83.7, 121.6, 127.8, 130.2, 135.3, 151.1. IR (cm^{-1}) = 3030.0, 2986.0, 1746.9, 1508.6, 1371.2, 1275.8, 1258.0, 1220.2, 1145.2, 895.9, 835.9. Rf (EA/PE 1 : 7) = 0.68.

General procedure for the preparation of compounds (3)–(11): 3 eq of *N*-protected hydrazine was dissolved in ACN (0.1 M solution), 1.5 eq of 2,4,6-trimethylpyridine (for the alkylation of Fmoc-$NHNH_2$ and Bz-$NHNH_2$) or DiPEA (for Boc$NHNH_2$ or Z-$NHNH_2$) and 0.1 eq of KI were added. The reaction mixture was heated to reflux, solution of 1 eq of alkylhalogenide in ACN (approximately 0.1 g of bromide in 1 mL of ACN) was added dropwise and the reaction mixture was refluxed for 5 h. ACN was evaporated under reduced pressure, the residue was dissolved in EA and washed with 1 M $NaHCO_3$, 2 × H_2O, and brine. The water phase was extracted twice 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 an EA/PE 1 : 2 or 1 : 1 mixture as the eluent.

***N*-Fluorenylmethyloxycarbonyl-*N′*-(4-*tert*-butyloxycarbonyloxy)benzyl hydrazine (3):** NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.56 (s, 9H, 3 × CH_3), 3.65 (br s, 1H, NH), 3.96 (s, 2H, CH_2), 4.20 (t, 1H, *J* = 6.4 Hz, CH(Fmoc)), 4.44 (d, 2H, *J* = 6.8 Hz; CH_2(Fmoc)), 6.36 (b rs, 1H, NH), 7.25 (d, 2H, *J* = 8.4 Hz, Ar(H)), 7.10–7.54 (m, 6H, Ar(H)), 7.56 (d, 2H, *J* = 7.2 Hz, Ar(H)), 7.75 (d, 2H, *J* = 6.8 Hz, Ar(H)). ^{13}C δ = 27.7, 47.3, 55.0, 67.0, 83.5, 120.0, 121.3, 125.0, 127.1, 127.8, 129.9, 135.0, 141.4, 143.7, 150.6, 151.9, 157.2. IR (cm^{-1}) = 3355.0, 2985.8, 1747.1, 1694.5, 1510.1, 1449.7, 1472.0, 1267.6, 1259.5, 1144.9, 739.1. LRMS: calculated *m/z* for $C_{27}H_{28}N_2O_5Na$ $[M + Na]^+$: 483.2, found $[M + Na]^+$ *m/z*: 483.2. M.p. = 115–120 ºC. Rf (EA/PE 1 : 2) = 0.29. Yield: 57%.

***N*-*tert*-Butyloxycarbonyl-*N′*-(4-*tert*-butyloxycarbonyloxy)benzyl hydrazine (4):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.46 (s, 9H, 3 × CH_3), 1.56 (s, 9H, 3 × CH_3), 3.97 (s, 2H, CH_2), 4.22 (br s, 1H, NH), 6.08 (br s, 1H, NH), 7.13 (d, 2H, *J* = 7 Hz, Ar(H)), 7.35 (d, 2H, *J* = 8.4 Hz, Ar(H)). ^{13}C δ = 27.8, 28.6, 55.0, 80.5, 83.5, 121.3, 130.0, 135.0, 150.4, 151.9, 156.7. IR (cm^{-1}) = 3286.0, 2980.3, 1754.3, 1715.3, 1509.4, 1369.4, 1276.1, 1220.4, 1142.1, 1017.0, 896.2, 781.9. LRMS: calculated *m/z* for $C_{17}H_{26}N_2O_5Na$ $[M + Na]^+$: 361.2, found $[M + Na]^+$ *m/z*: 361.6. M.p. = 89–92 ºC. Rf (EA/PE 1 : 2) = 0.48. Yield: 56%.

***N*-Benzyloxycarbonyl-*N′*-(4-*tert*-butyloxycarbonyloxy)benzyl hydrazine (5):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.55 (s, 9H, 3 × CH_3), 3.99 (s, 2H, CH_2), 4.27 (br s, 1H, NH), 5.13 (s, 2H, CH_2(Z)), 6.38 (br s, 1H, NH), 7.11 (d, 2H, *J* = 7.7 Hz, Ar(H)), 7.31–7.35 (m, 7H, Ar(H)). ^{13}C δ = 27.7, 54.9, 67.1, 83.6, 121.3, 128.2, 128.3,128.6, 129.9, 135.0, 136.0, 150.5, 151.9, 157.2. IR (cm^{-1}) = 3273.7, 2981.7, 1752.0, 1723.0, 1509.7, 1455.2, 1370.6, 1274.7, 1222.4, 1146.3, 1027.3, 894.0, 781.9. LRMS: calculated *m/z* for $C_{20}H_{24}N_2O_5Na$ $[M + Na]^+$: 395.2, found $[M + Na]^+$ *m/z*: 395.3. M.p. = 75–79 ºC. Rf (EA/PE 1 : 2) = 0.45. Yield: 59%.

***N*-Benzoyl-*N′*-4-(*tert*-butyloxycarbonyloxy)benzyl hydrazine (6):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.56 (s, 9H, 3 × CH_3), 4.03 (s, 2H, CH_2), 5.16 (br s, 1H, NH), 7.12 (d, 2H, *J* = 8.4 Hz, Ar(H)), 7.36–7.40 (m, 4H, Ar(H)), 7.49 (t, 1H, *J* = 7 Hz, Ar(H)), 7.70 (t, 2H, *J* = 7 Hz, Ar(H)), 8.03 (s, 1H, NH). ^{13}C δ = 27.7, 55.2, 83.6, 121.3, 126.9, 128.6, 130.1, 131.9, 132.7, 135.2, 150.5, 151.9, 167.5. IR (cm^{-1}) = 3277.9, 2980.9, 1748.2, 1665.0, 1532.9, 1468.9, 1370.0, 1275.4, 1221.9, 1146.7, 891.0, 824.3, 689.8. LRMS: calculated *m/z* for $C_{19}H_{22}N_2O_4Na$ $[M + Na]^+$: 365.2, found $[M + Na]^+$ *m/z*: 365.3. M.p. = 125–128 ºC. Rf (EA/PE 1 : 1) = 0.37. Yield: 49%.

***N*-Fluorenylmethyloxycarbonyl-*N′*-benzyl hydrazine (7):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 3.84 (br s, 1H, NH), 3.89 (s, 2H, CH_2), 4.21 (t, 1H, *J* = 6.4 Hz, CH (Fmoc)), 4.44 (d, 2H, *J* = 6.8 Hz, CH_2(Fmoc)), 6.35 (br s, 1H, NH), 7.27–7.32 (m, 7H, Ar(H)), 7.39 (t, 2H, *J* = 7.7 Hz, Ar(H)), 7.54 (s, 2H, Ar(H)), 7.75 (d, 2H, *J* = 7 Hz, Ar(H)). ^{13}C δ = 47.2, 55.6, 66.9, 120.0, 125.0, 127.1, 127.6, 127.8, 128.5, 129.0, 137.3, 141.3, 143.7, 157.1. IR (cm^{-1}) = 3316.5, 1685.6, 1500.4, 1271.9, 1106.1, 735.8. LRMS: calculated *m/z* for $C_{22}H_{21}N_2O_2[M + H]^+$: 345.2, found $[M + H]^+$ *m/z*: 345.3. M.p. = 138–140 ºC (lit. m.p. = 143–145 ºC [1]). Rf (EA/PE 1 : 2) = 0.34. Yield: 68%.

***N*-Benzyloxycarbonyl-*N′*-benzyl hydrazine (8):** NMR (200 MHz; $CDCl_3$): ^{1}H δ = 3.92 (s, 2H, CH_2), 4.22 (br s, 1H, NH), 5.08 (s, 2H, CH_2(Z)), 6.73 (br s, 1H, NH), 7.26 (d, 10H, Ar(H)). ^{13}C δ = 55.6, 67.0, 127.5, 128.1, 128.2, 128.4, 128.5, 128.9, 136.1, 137.4, 157.2. IR (cm^{-1}) = 3257.0, 1719.9, 1513.9, 1453.3, 1279.0, 1229.2, 1145.1, 1023.9, 743.9, 693.3. LRMS: calculated *m/z* for $C_{15}H_{17}N_2O_2$ $[M + H]^+$: 257.1, found $[M + H]^+$ *m/z*: 257.1. Rf (EA/PE 1 : 2) = 0.36. Yield: 53% [29].

***N*-*tert*-Butyloxycarbonyl-*N′*-benzyl hydrazine (9):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.46 (s, 9H, 3 × CH_3), 3.97 (s, 3H, CH_2 + NH), 6.30 (br s, 1H, NH), 7.25–7.38 (m, 5H, Ar(H)). ^{13}C δ = 28.4, 55.8, 80.5, 127.5, 128.4, 129.0, 137.7, 156.7. IR (cm^{-1}) = 3306.3, 3030.4, 2979.2, 1704.1, 1453.8, 1392.0, 1367.0, 1278.6, 1252.1, 1151.8, 1020.0, 740.1. LRMS: calculated *m/z* for $C_{12}H_{18}N_2O_2Na$ $[M + Na]^+$: 245.1, found $[M + Na]^+$ *m/z*: 245.2. Rf (EA/PE 1 : 1) = 0.56. Yield: 77% [30].

***N*-Fluorenylmethyloxycarbonyl-*N′*-(4-methoxy)benzyl hydrazine (10):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 3.78 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 4.21 (t, 2H, *J* = 6.5 Hz, CH(Fmoc) + NH), 4.45 (d, 2H, *J* = 6.8 Hz, CH_2(Fmoc)), 6.32 (br s, 1H, NH), 6.85 (d, 2H, *J* = 7 Hz, Ar(H)), 7.24 (d, 2H, *J* = 5.3 Hz, Ar(H)), 7.30 (t, 2H, *J* = 7 Hz, Ar(H)), 7.39 (t, 2H, *J* = 7 Hz, Ar(H)), 7.55 (d, 2H, *J* = 5 Hz, Ar(H)), 7.75 (d, 2H, *J* = 7.7 Hz, Ar(H)). ^{13}C δ = 47.2, 55.0, 55.3, 66.9, 113.9, 120.0, 121.5, 125.0, 127.1, 127.8, 130.3, 141.3, 143.7, 157.2, 159.1. IR (cm^{-1}) = 3321.3, 3018.3, 2948.4, 1687.6, 1612.2, 1512.6, 1451.7, 1276.9, 1245.9, 1159.4, 1034.5, 756.1, 736.7. LRMS: calculated *m/z* for $C_{23}H_{23}N_2O_3$[M + H]$^+$: 375.2, found [M + H]$^+$ *m/z*: 375.3. Rf (EA/PE 1 : 2) = 0.17. Yield: 46%.

***N-tert*-Butyloxycarbonyl-*N′*-(4-methoxy)benzyl hydrazine (11):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.46 (s, 9H, 3 × CH_3), 3.79 (s, 3H, OCH_3), 3.92 (s, 3H, CH_2 + NH), 6.21 (br s, 1H, NH), 6.86 (d, 2H, *J* = 9.1 Hz, Ar(H)), 7.26 (d, 2H, *J* = 8.4 Hz, Ar(H)).^{13}C δ = 28.4, 55.2, 55.3, 80.4, 113.9, 129.6, 130.3, 156.7, 159.0. IR (cm^{-1}) = 3312.2, 2977.0, 1704.4, 1612.7, 1512.4, 1455.7, 1366.6, 1278.2, 1245.9, 1150.8, 1034.1, 806.5. LRMS: calculated *m/z* for $C_{26}H_{40}N_4O_6$[2M]$^+$: 504.3, found [2M]$^+$ *m/z*: 504.9. Rf (EA/PE 1 : 2) = 0.25. Yield: 61% [5].

General procedure for the preparation of compounds (12)–(18): 1 eq of *N*-protected hydrazine was dissolved in ACN (0.1 M solution), 1.5 eq of 2,4,6-trimethylpyridine (for the alkylation of Fmoc-$NHNH_2$) or DiPEA (for BocNHNH$_2$ or Z-$NHNH_2$) and 0.1 eq of KI were added. The reaction mixture was heated to reflux. 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 twice 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 purified on silica gel using an EA/PE 1 : 2 or 1 : 1 mixture as the eluent.

***N*-Fluorenylmethyloxycarbonyl-hydrazinoacetic acid *tert*-butyl ester (12):** NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.46 (s, 9H, 3 × CH_3), 3.52 (s, 2H, CH_2), 4.19 (t, 1H, *J* = 6.8 Hz, CH (Fmoc)), 4.29 (br s, 1H, NH), 4.41 (d, 2H, *J* = 7 Hz, CH_2 (Fmoc)), 6.97 (br s, 1H, NH), 7.24–7.40 (m, 4H, Ar(H)), 7.56 (d, 2H, *J* = 7.2 Hz, Ar(H)), 7.72 (d, 2H, *J* = 7.2 Hz, Ar(H)). ^{13}C δ = 28.1, 47.2, 53.3, 67.1, 81.9, 120.0, 125.0, 127.0, 127.7, 141.3, 143.7, 156.8, 170.5. IR (cm^{-1}) = 3359.1, 2979.5, 1724.9, 1699.4, 1520.0, 1476.6, 1450.5, 1392.1, 1367.1, 1259.6, 1220.0, 1151.2, 1033.1, 755.9, 737.4. LRMS: calculated *m/z* for $C_{21}H_{24}N_2O_4Na$ [M + Na]$^+$: 391.2, found [M + Na]$^+$ *m/z*: 391.3. M.p. = 69–72 °C. Rf (EA/PE 1 : 1) = 0.59. Yield: 88% [1].

***N-tert*-Butylyloxycarbonyl-hydrazinoacetic acid methyl ester (13):** NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.45 (s, 9H, 3 × CH_3), 3.67 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.34 (br s, 1H, NH), 6.68 (br s, 1H, NH). ^{13}C δ = 28.3, 51.8, 57.1, 80.6, 156.3, 170.3. IR (cm^{-1}) = 3409.1, 3308.6, 2979.6, 1755.2, 1703.7, 1480.6, 1368.1, 1278.7, 1250.8, 1150.1, 1021.7. LRMS: calculated *m/z* for $C_8H_{16}N_2O_4Na$ [M + Na]$^+$: 227.1, found [M + Na]$^+$ *m/z*: 227.0. Rf (EA) = 0.61. Yield: 57% [31].

***N-tert*-Butylyloxycarbonyl-hydrazinoacetic acid *tert*-butyl ester (14):** NMR (200 MHz; $CDCl_3$): ^{1}H δ = 1.38 (s, 9H, 3 × CH_3), 1.40 (s, 9H, 3 × CH_3), 3.47 (s, 2H, CH_2), 4.19 (br s, 1H, NH), 6.62 (br s, 1H, NH). ^{13}C δ = 28.1, 28.4, 53.5, 80.3, 81.5, 156.3, 170.4. IR (cm^{-1}) = 3369.5, 2979.7, 2932.2, 1728.9, 1708.7, 1461.3, 1392.4, 1365.7, 1244.1, 1149.4, 754.0. LRMS: calculated *m/z* for $C_{11}H_{22}N_2O_4Na$ [M + Na]$^+$: 269.2, found [M + Na]$^+$ *m/z*: 269.1. Rf (EA/PE 1 : 1) = 0.55. Yield: 54% [32].

***N*-Benzyloxycarbonyl-hydrazinoacetic acid *tert*-butyl ester (15):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.46 (s, 9H, 3 × CH_3), 3.55 (s, 2H, CH_2), 4.21 (br s, 1H, NH), 5.14 (s, 2H, CH_2(Z)), 6.79 (br s, 1H, NH), 7.31–7.36 (m, 5H, Ar(H)). ^{13}C δ = 28.1, 53.4, 67.1, 82.0, 128.2, 128.3, 128.6, 136.0, 156.7, 170.6. IR (cm^{-1}) = 3387.1, 3247.6, 2978.0, 2938.6, 1743.8, 1724.4, 1522.7, 1450.2, 1366.7, 1225.0, 1159.0, 1050.6, 730.3. LRMS: calculated *m/z* for $C_{14}H_{20}N_2O_4Na$ [M+Na]$^+$: 303.1, found [M + Na]$^+$ *m/z*: 303.3. M.p. = 55–57 ºC (lit. m.p. = 61–62 ºC [33]). Rf (EA/PE 1 : 1) = 0.59. Yield: 60% [11,33].

***N*-Fluorenylmethyloxycarbonyl-hydrazinoacetic acid ethyl ester (16):** NMR (700 MHz; $CDCl_3$): ^{1}H δ = 1.29 (t, *J* = 7 Hz, 3H, CH_3), 3.64 (s, 2H, CH_2), 4.22 (q, *J* = 7 Hz, 4H, CH_2 + CH (Fmoc) + NH), 4.44 (d, *J* = 5.6 Hz, 2H, CH_2 (Fmoc)), 6.72 (br s, 1H, NH), 7.31 (d, 2H, *J* = 7 Hz, Ar(H)), 7.40 (t, 2H, *J* = 7.4 Hz, Ar(H)), 7.57 (d, 2H, *J* = 7 Hz, Ar(H)), 7.76 (t, 2H, *J* = 7 Hz, Ar(H)). ^{13}C δ = 14.2, 47.1, 52.7, 61.2, 67.1, 120.0, 125.0, 127.1, 127.8, 141.3, 143.7, 156.7, 171.3. IR (cm^{-1}) = 3334.9, 3229.2, 3071.0, 2924.6, 2854.0, 1741.2, 1707.9, 1479.4, 1449.2, 1375.4, 1252.7, 1200.2, 1156.0, 1024.9, 737.7. LRMS: calculated *m/z* for $C_{38}H_{41}N_4O_8$ [2M + H]$^+$: 681.3, found [2M + H]$^+$ *m/z*: 681.3. Rf (EA/PE 2 : 1) = 0.54. Yield: 40% [34].

***N-tert*-Butylyloxycarbonyl-hydrazinoacetic acid ethyl ester (17):** NMR (700 MHz; $CDCl_3$): ^1H δ = 1.28 (t, 3H, J = 7 Hz, CH_3), 1.46 (s, 9H, 3 × CH_3), 3.65 (s, 2H, CH_2), 4.14 (br s, 1H, NH), 4.21 (q, 2H, *J* = 7 Hz, CH_2), 6.49 (br s, 1H, NH). ^{13}C δ = 14.2, 28.3, 52.9, 61.0, 80.6, 156.2, 171.2. IR (cm^{-1}) = 3320.5, 2979.7, 2933.1, 1735.0, 1715.3, 1456.7, 1392.6, 1367.7, 1251.8, 1203.2, 1153.7, 1022.1. LRMS: calculated *m/z* for $C_9H_{18}N_2O_4Na$ $[M + Na]^+$: 241.1, found $[M + Na]^+$ *m/z*: 241.1. M.p. = – (transparent oil). (lit. m.p. = 22–26 °C [35].) Rf (EA/PE 2 : 1) = 0.57. Yield: 50% [35].

***N*-Benzyloxycarbonyl-hydrazinoacetic acid ethyl ester (18):** NMR (700 MHz; $CDCl_3$): ^1H δ = 1.28 (t, 3H, *J* = 7 Hz, CH_3), 3.66 (s, 2H, CH_2), 4.19 (q, 3H, *J* = 7 Hz, CH_2 + NH), 5.14 (s, 2H, CH_2(Z)), 6.76 (br s, 1H, NH), 7.32–7.36 (m, 5H, Ar(H)). ^{13}C δ = 14.2, 52.8, 61.1, 67.2, 128.2, 128.3, 128.6, 136.0, 156.7, 171.2. IR (cm^{-1}) = 3326.1, 3253.5, 3034.5, 2977.7, 2925.6, 1739.5, 1694.0, 1519.4, 1478.3, 1378.8, 1262.8, 1200.7, 1160.4, 1049.8, 1026.0, 736.3. LRMS: calculated *m/z* for $C_{12}H_{16}N_2O_4Na$ $[M + Na]^+$: 275.1, found $[M + Na]^+$ *m/z*: 275.2. M.p. = 91–94 ºC (lit. m.p. = 94–95 °C [35]). Rf (EA/PE 2 : 1) = 0.55. Yield: 44% [35].

CONCLUSIONS

Potassium iodide catalysis was applied for the alkylation of protected hydrazines. This allowed incorporating less reactive halogenides and performing the alkylation remarkably faster and more effectively than without KI. By using this approach six new Fmoc-, Boc-, and Z-protected hydrazines of interest as precursors for insertion of aza-Tyr and aza-Asp into aza-peptides were prepared.

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Kaaliumjodiidi katalüüs kaitstud hüdrasiinide alküülimises

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Kaitstud bensüülhüdrasiinide ja hüdrasinoetaanhappe estrite sünteesiks kasutati kaaliumjodiidi katalüüsitud hüdrasiini derivaatide reaktsiooni bensüülhalogeniidide ning halogeenetaanhappe estritega. Nende reaktsioonide läbiviimiseks tekitati vähem reaktsioonivõimelistest, aga stabiilsematest halogeniididest reaktsioonivõimelised jodiidi molekulid *in situ* tingimustes, mis kiirendas oluliselt hüdrasiinide alküülimise reaktsiooni. Kaaliumjodiidi katalüütilist rolli selles sünteesis tõestas fakt, et katalüsaatori puudumisel reaktsiooni praktiliselt ei toimunud.