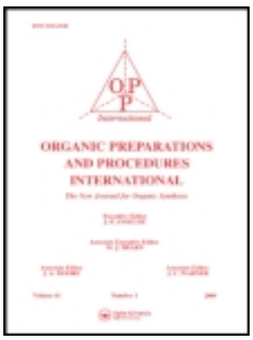

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One-pot Synthesis of Protected Alkylhydrazines from Acetals and Ketals. Scope and Limitations

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Alkylhydrazines are important building blocks in organic synthesis[1–6] and their *N*-protected derivatives are used for the incorporation of α-*aza*-amino acids into peptide sequences to obtain *aza*-peptides.[7] These peptidomimetics, where the α-C atoms of amino acids are replaced by a nitrogen moiety, retain significant structural compatibility with common peptides but have much higher resistance to biodegradation. Therefore *aza*-peptidomimetics have been recognized as promising drug candidates.[8–10] and this concept will certainly be more extensively examined once the difficulties with the efficient synthesis of these *aza*-peptides are overcome. These problems include also preparation of *aza*-amino acid precursors, which are in essence *N*-protected substituted hydrazines.

Since only a few of these hydrazines can be purchased commercially, two main synthetic routes have been devised for the preparation of substituted hydrazines. The most frequently used procedure is the reductive alkylation of hydrazine with the appropriate aldehydes or ketones.[7,8,10–15] The second approach involves the direct alkylation of hydrazine using alkyl halides for example.[11,14,16–19] Evidently, the reductive alkylation is preferred because of its simplicity, availability and relatively low cost of carbonyl compounds; more importantly, it avoids the formation of polyalkylated products. However, if the aldehyde and/or the ketone contain electronegative groups with hetero-atoms and/or unsaturated substituents, they are prone to self-condensation and/or to rapid oxidation to carboxylic acids in the case of aldehydes. This complicates storage and handling of these aldehydes and ketones which are commonly available as acetals or ketals. Although the protecting groups may be removed by hydrolysis,[11] this additional step could be complicated and indeed, in some cases, has hampered application of the reductive alkylation method.[13] To overcome these difficulties, we devised and reported a one-pot synthesis method for the preparation of protected alkylhydrazines directly from acetals and ketals, without prior conversion to aldehydes or ketones, and without the need to isolate the resulting hydrazones.[20] We recently utilized this novel approach for the synthesis of *aza*-methionine precursors from the 2-(methylthio)acetaldehyde dimethyl acetal.[20] Encouraged by these results, we extended this study and explored the limits of this method by using different acetals and ketals as starting materials as listed in the *Scheme* and *Table*.

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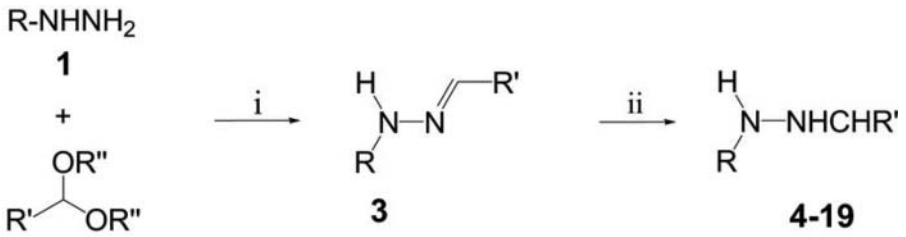
It is important to note that this list includes several compounds that correspond to unstable aldehydes and ketones. *Aza*-amino acid precursors with *Fmoc* (9-fluorenylmethyloxycarbonyl) and *Cbz* (benzyloxycarbonyl) protecting groups were prepared.

Acetals or ketals were treated with *Fmoc* and *Cbz* carbazates at reflux in ethanol, containing 10% (vol.) of water in the presence of a catalytic amount of trifluoroacetic



2a-m

R = Fmoc; Cbz., R' = -CH_2SCH_3; -$(CH_2)_2CN$; -$(CH_2)_2Cl$; -CH_2OBn; -CH_2NHCH_3; -CH_2NH_2; -CH_2NHCbz; -CH_3; -CH_2NHBz; -CH_2NHBoc; -$CH{=}CH_2$; -$(CH_3)_2$; -$(CH_2)_5$-., R" = -CH_3; -CH_2CH_3.

i) TFA, EtOH - H_2O, Δ ii) 1. $NaBH_3CN$, AcOH, EtOH-H_2O, Δ.

Scheme 1

Table 1
Synthesis of Protected Alkylhydrazines from Acetals and Ketals

			$RNHNH_2$	
R' OR" OR"	R′	R″	R = Fmoc	R = Cbz
2a	-CH_2SCH_3	-CH_3	**4**; Yield: 98%	**5**; Yield: 67%
2b	-$(CH_2)_2CN$	-CH_3	**6**; Yield: 62%	**7**; Yield: 76%
2c	-$(CH_2)_2Cl$	-CH_2CH_3	a)	a)
2d	-CH_2OBn	-CH_2CH_3	**8**; Yield 67%	**9**; Yield 65%
2e	-CH_2NHCH_3	-CH_3	(Fmoc scission)	(No reaction)
2f	-CH_2NH_2	-CH_3	(Fmoc scission)	(No reaction)
2g	-CH_2NHCbz	-CH_3	**10**; Yield 70%	**11**; Yield: 63%
2h	-CH_3	-CH_2CH_3	**12**,Yield 74% in THF.<20%in EtOH	**13**, Yield 66 % in THF.<20%in EtOH
2i	-CH_2NHBz	-CH_3	**14**; Yield: 86%	**15**; Yield: 80%
2j	-CH_2NHBoc	-CH_3	b)	b)
2k	-$CH{=}CH_2$	-CH_2CH_3	c)	c)
2l	-$(CH_3)_2$	-CH_3	**16**; Yield: 77%	**17**; Yield: 64%
2m	-$(CH_2)_5$-	-CH_3	**18**; Yield: 72%	**19**; Yield: 87%

a) Formation of alkylated products and subsequent decomposition of the reaction mixture.
b) Only trace amounts of the hydrazone were detected, as *Boc* removal by TFA occurred.
c) Only trace amounts of the hydrazone were formed.

acid (TFA, 0.05 equiv. per equiv. of carbazate) according to our published procedure.[20] Subsequent reduction of the hydrazone was carried out in the same pot (and solution) at 45°C, by addition of three (3) equiv. of $NaBH_3CN$ in tetrahydrofuran (THF) and three (3) equiv. of acetic acid. After cooling to room temperature, the reaction was quenched by acidification with 1.5% HCl in the case of acid-stable *Fmoc* and *Cbz* derivatives. The mixture was then stirred until the evolution of hydrogen gas ceased. Neutralization to pH 8 with saturated aqueous $NaHCO_3$ followed by evaporation to dryness gave a residue that was extracted with ethyl acetate, and the product was purified by chromatography on silica gel.

It is important to mention that the procedure described here is somewhat different from the preparation of *aza*-methionine precursors reported in our previous study[20] wherein the excess acetic acid was first neutralized in the reaction medium after the reduction step by addition of saturated aqueous $NaHCO_3$ followed by reflux of the reaction mixture. The present investigation revealed that this step is not necessary and moreover, basic conditions led to cleavage of the base-sensitive *Fmoc* protecting group thus lowering the yield. Secondly, it was found that decomposition of the boron adducts with cyanoborohydride anion by simple refluxing of the reaction mixture was not an efficient method as decomposition of these adducts occurred very slowly in several cases. To overcome this problem, the reaction mixture was treated with 1.5% hydrochloric acid at room temperature. Although this method worked perfectly with all hydrazines synthesized in this work, it is also important to emphasize that it is suitable only in the case of acid-stable compounds but cannot be used in the case of acid-labile compounds such as *tert*-butyloxycarbonyl (*Boc*) derivatives. In these latter cases, heating the reaction mixture at reflux as was recommended in our previous paper[20] should be used instead of treatment with HCl.

The results listed in *Table 1* indicate that the procedure reported herein is applicable in the case of compounds having sulfide, ether, nitrile, carbamate and amide functional groups or branched and cyclic alkyl groups in substituent R' (*Scheme 1*). As mentioned earlier, the hydrazones should be protected with acid-stable protecting groups such as *Fmoc* and *Cbz* (*Table 1*, compounds **2a, 2b, 2d, 2g, 2h, 2i, 2l** and **2m**). In all these cases, good to excellent yields of the protected monoalkylhydrazines (**4–19**) were obtained. On the other hand, there are functional groups in the R' substituent for which the procedure is not applicable and these entries are indicated by footnotes marked in *Table 1*.

First, in the case of halogenated acetals (**2c**) the mixture of alkylated hydrazines was formed rapidly and this process was followed by complete decomposition of the reaction mixture, irrespective of the nature of the carbazate used and/or protected carbonyl compound. Therefore, it was concluded that halogen-substituted acetals and ketals cannot be used in this procedure, and the same conclusion is most probably true for other acetals whose side-chain containing functional groups capable of acting as alkylating agents.

The second limitation of the present method concerns compounds with unprotected primary and secondary amino groups (**2e, 2f**). In this case, competition between the carbazate and more basic amino group for protons occurred and the reaction did not occur in the absence of an acid catalyst. Attempts to perform this reaction by using 1.1 equiv. of TFA to protonate the amino group were also not effective. Therefore the use of Cbz and Bz (benzoyl) groups to protect the amino groups allowed the synthesis of **10, 11** and **14, 15** (*Table* 1), while the use of *Boc* was not efficient, most likely due to instability of this protecting group in the presence of acid.

Third, experiments with acrolein diethyl acetal (**2k**) resulted in extensive polymerization and only minor amount of the expected hydrazone was obtained. Furthermore, reduction of this conjugated hydrazone did not occur under these reported conditions.

And finally, it was found that reduction of primary aliphatic hydrazones did not go to completion in ethanolic medium and reduction in THF was much more efficient for these compounds. This is illustrated in the case of 1,1-diethoxyethane (**2h**) for which the yield in ethanol was less than 20%. At the same time, the reduction of branched or cyclic alkylhydrazones such as the *N*-protected hydrazones of cyclohexanone and acetone led to good yields in ethanol.

In summary, the proposed one-pot synthesis of protected alkylhydrazines is efficient for acetals and ketals bearing different functional groups, and the hydrazines obtained may be utilized as building blocks for modified *aza*-peptidomimetics and different other biologically active substances. The method described also allows the isolation of the hydrazones (**3**) by simple removal of volatiles from the reaction mixture after the condensation step.

Experimental Section

All solvents and reagents were purchased from Merck, Sigma-Aldrich or Lach-Ner. NMR spectra were measured on a 200 and 700 MHz instrument (Bruker, Germany) in DMSO-d_6 or $CDCl_3$ as solvent and using TMS (tetramethylsilane) 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 solvent. IR spectra were determined by using ATR (Attenuated total reflectance) measuring technique on a Perkin-Elmer Spectrum BX spectrometer. Elemental analyses data were carried out on an Elementar Vario MICRO cube (CHNS or CHN regime). All the yields are based on the mass of the starting reagents.

Synthesis of Mono-protected Alkylhydrazines (4–11 and 14–19)

One equiv. of carbazate was suspended in EtOH containing 10% (by vol.) of water (approx. 5 ml per mmol of the carbazate) and 1.05 equiv. of the acetal or ketal was added, followed by the addition of 0.05 equiv. of TFA. The reaction mixture was heated to reflux and the progress of the reaction was monitored by TLC (thin layer chromatography on silica gel) using ethyl acetate or a mixture of ethyl acetate-light petroleum mixture (for the correct eluent, see characterization data of the compounds). After the reaction was complete, the reaction mixture was cooled to about 45°C and three (3) equiv. of acetic acid was added, followed by the dropwise addition of a THF solution of three (3) equiv. of $NaBH_3CN$ (approx. 1 ml of THF per 1.5 mmol of $NaBH_3CN$). The reaction mixture was stirred at approx. 45°C for 80 min. Subsequently, the reaction mixture was cooled to room temperature, acidified using 0.5 M HCl aqueous solution (6 ml of 0.5 M HCl per 1 mmol of starting carbazate) and stirred until the liberation of hydrogen ceased. The reaction mixture was neutralized (to pH 8) by the dropwise addition of a saturated $NaHCO_3$ solution (4 ml per 1 mmol of carbazate). The volatiles were removed under reduced pressure at approx. 40°C. The residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$, twice with water and finally with saturated aqueous sodium chloride. The combined aqueous washes were extracted twice with ethyl acetate (25 ml per 1 mmol of expected product) and the extracts were washed with saturated aqueous sodium chloride and combined with the organic phase.

After drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel using ethyl acetate-light petroleum (1:1 or 1:2) or ethyl acetate as eluent. For specific information about the eluent used to monitor the progress of the reaction and for purification, see the R_f data for each compound.

Synthesis of Mono-protected Alkylhydrazines (12 and 13)

One equiv. of carbazate was suspended in EtOH containing 10% (by vol.) of water (approx. 5 ml per 1 mmol of the starting carbazate), 1 equiv. of acetal or ketal was added, followed by the addition of 0.05 equiv. of TFA. The reaction mixture was heated to reflux and the progress of the reaction was monitored by TLC using ethyl acetate or ethyl acetate-light petroleum mixture (for the correct eluent, see characterization data of the compounds). After the reaction was complete, the volatiles were removed under reduced pressure and the resulting solid residue was dissolved in THF (approx. 5 ml of THF per 1 mmol of the starting carbazate). Subsequently, three (3) equiv. of acetic acid was added, followed by the dropwise addition of a THF solution of three (3) equiv. of $NaBH_3CN$ (approx. 1 ml of THF per 1.5 equiv. of $NaBH_3CN$). The reaction mixture was stirred at approx. 45°C for 80 min. The reaction mixture was then cooled to room temperature, acidified using 0.5 M HCl solution (6 ml of 0.5 M HCl per 1 mmol of carbazate) and stirred until the liberation of hydrogen ceased. The reaction mixture was neutralized by the dropwise addition of a saturated $NaHCO_3$ solution (4 ml per 1 mmol of the carbazate). The volatiles were removed under reduced pressure at approx. 40°C. The residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$, twice with water and finally with saturated aqueous sodium chloride. The combined aqueous washes were extracted twice with ethyl acetate (25 ml per mmol of product) and the combined extracts were washed with saturated NaCl, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-light petroleum (1:1 or 1:2) or ethyl acetate as eluent. For specific information about the eluent used to monitor the progress of the reaction and for purification, see the R_f data for each compound.

***N*-Fluorenylmethyloxycarbonyl-*N*'-(2-methylthio)ethylhydrazine (4)**, 98% yield as a white solid, mp. 131–135°, *lit.*[20] 132–136°; Rf = 0.12 (1:2 EtOAc-light petroleum).

^{1}H NMR (200 MHz, DMSO-d_6): δ 2.06 (s, 3H, CH_3); 2.53 (t, 2H, J = 6.8 Hz, CH_2); 2.92 (t, 2H, J = 7 Hz, CH_2); 4.25 (t, 1H, J = 6.2 Hz, CH (Fmoc)); 4.36 (d, 2H, J = 6.2 Hz, CH_2 (Fmoc)); 4.70 (br s, 1H, NH); 7.30–7.46 (m, 5H, Ar(H)), 7.71 (d, 2H, J = 7.2 Hz, Ar(H)), 7.88 (q, 2H, J = 6.8 Hz, Ar(H)); 8.77 (br.s, 1H, NH). ^{13}C NMR: δ 15.5; 32.5; 47.5; 50.1; 67.2; 120.2; 125.2; 127.3; 128.0; 141.6; 143.9; 157.5.

IR (cm^{-1}): 3303, 3217, 3099, 2965, 2937,1693,1553, 1261,1147,736.

***N*-Benzyloxycarbonyl-*N*'-(2-methylthio)ethylhydrazine (5)**, 67% yield as a white solid, mp. 63–65°; Rf = 0.17 (1:2 EtOAc-light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07 (s, 3H, CH_3); 2.59 (t, 2H, J = 6.6 Hz, CH_2), 3.05 (t, 2H, J = 6.4 Hz, CH_2); 4.29 (br s, 1H, NH); 5.15 (s, 2H, CH_2 (Cbz)); 6.83 (br s, 1H, NH), 7.32 (s, 5H, Ar(H)). ^{13}C NMR: δ 15.1; 32.2; 49.9; 67.0; 128.1; 128.2; 128.5; 136.1; 157.4. HRMS: m/z for $C_{11}H_{17}N_2O_2S$ $[M+H]^+$. Calcd: 241.10052. Found: 241.10039.

IR (cm^{-1}): 3300, 3243, 3087, 2949, 2915, 1694, 1547, 1251, 1148, 1019, 748.

Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 55.00; H, 6.71; N, 11.66; S, 13.34. Found: C, 55.01; H, 6.65; N, 11.55; S, 13.25.

***N*-Fluorenylmethyloxycarbonyl-*N'*-(3-cyano)propylhydrazine (6)**, 62% yield as a white solid, mp. 134–137°; Rf = 0.73 (EtOAc).

^{1}H NMR (200 MHz, DMSO-d_6): δ 1.66 (quint, 2H, J = 6.4 Hz, CH_2); 2.57 (t, 2H, J = 7.2 Hz); 2.79 (t, 2H; J = 7 Hz; CH_2); 4.25 (t, 1H, J = 6.6 Hz, CH (Fmoc)); 4.39 (d, 2H, J = 6.6 Hz, CH_2 (Fmoc)); 4.76 (br s, 1H, NH); 7.31–7.46 (m, 4H, Ar(H) (Fmoc)); 7.72 (d, 2H, J = 7 Hz, Ar(H) (Fmoc)); 7.89 (d, 2H, J = 7 Hz, Ar(H) (Fmoc)); 8.67 (br s, 1H, NH).

^{13}C NMR: δ 13.7; 23.2; 46.8; 48.8; 65.4; 120.0; 120.6; 125.1; 127.0; 127.6; 140.8; 143.8; 156.9. HRMS: m/z for $C_{19}H_{20}N_3O_2$ $[M+H]^+$. Calcd: 322.15500. Found: 322.15483.

IR (cm^{-1}): 3312, 3229, 3010, 2949, 2933, 2247, 1691, 1488, 1268, 1157, 737.

Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.06; H, 5.96; N, 13.08. Found: C, 70.90; H, 5.94; N, 12.83.

***N*-Benzyloxycarbonyl-*N'*-(3-cyano)propylhydrazine (7)**, 76% yield as a viscous transparent oil; Rf = 0.73 (EtOAc).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74 (quint, 2H, J = 6.8 Hz, CH_2); 2.38 (t, 2H, J = 7 Hz, CH_2); 2.90 (t, 2H, J = 6.4 Hz, CH_2); 3.97 (br s, 1H, NH); 5.01 (s, 2H, CH_2 (Cbz)); 6.81 (br s, 1H, NH); 7.32 (s, 5H, Ar(H)). ^{13}C NMR: δ 14.4; 23.5; 49.7; 67.1; 119.2; 128.1; 128.3; 128.6; 136.1; 157.5. IR (cm^{-1}): 3309, 3030, 2953, 2924, 2245, 1708, 1518, 1453, 1256, 1151, 738.

HRMS: m/z for $C_{12}H_{16}N_3O_2$ $[M+H]^+$. Calcd: 234.12370. Found: 234.12356.

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.82; H, 6.49; N, 18.0. Found: C, 61.83; H, 6.48; N, 17.80.

***N*-Fluorenylmethyloxycarbonyl-*N'*-(2-benzyloxy)ethylhydrazine (8)**, 67% yield as a white solid, mp. 120–122°; Rf = 0.42 (1:1 EtOAc-light petorleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.01 (t, 2H, J = 6 Hz, CH_2); 3.50 (t, 2H, J = 5 Hz; CH_2); 4.17 (t + br s, 2H; J = 6.6 Hz, CH (Fmoc) + NH); 4.42 (d, 2H, J = 6.8 Hz, CH_2 (Fmoc)); 4.51 (s, 2H, CH_2 (Bn)); 6.64 (br s, 1H, NH); 7.19–7.38 (m, 9H, Ar(H)); 7.54 (d, 2H, J = 7.2 Hz, Ar(H)); 7.70 (d, 2H, J = 7.6 Hz; Ar(H)). ^{13}C NMR: δ 47.2; 51.3; 66.9; 68.0; 73.0; 120.0; 125.0; 127.0; 127.6; 127.7; 128.2; 128.4; 138.1; 141.3; 143.8; 157.2. IR (cm^{-1}): 3299, 3068, 2949, 1708, 1552, 1449, 1264, 1101, 736.

HRMS: m/z for $C_{24}H_{25}N_2O_3$ $[M+H]^+$. Calcd: 389.18597. Found: 389.18589.

Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.26; H, 6.33; N, 7.22. Found: C, 74.10; H, 6.16; N, 7.17.

***N*-Benzyloxycarbonyl-*N'*-(2-benzyloxy)ethylhydrazine (9)**, 65% yield as a white solid, mp. 56-59°; Rf = 0.42 (1:1 EtOAc-light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.01 (t, 2H, J = 5 Hz, CH_2); 3.50 (t, 2H, J = 5.6 Hz; CH_2); 4.22 (br s, 1H, NH); 4.44 (s, 2H, CH_2-O); 5.08 (s, 2H, CH_2 (Cbz)); 6.93 (br s, 1H, NH); 7.24 (s, 10H; Ar(H)). ^{13}C NMR: δ 51.2; 66.9; 68.0; 72.9; 127.5; 127.6; 128.06; 128.1; 128.3; 128.4; 136.2; 138.1; 157.2. IR (cm^{-1}): 3319, 3030, 2949, 1685, 1545, 1488, 1265, 1102, 731. HRMS: m/z for $C_{17}H_{21}N_2O_3$ $[M+H]^+$. Calcd: 301.15467. Found: 301.15454.

Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 68.00; H, 6.77; N, 9.33. Found: C, 67.86; H, 6.63; N, 9.32.

***N*-Fluorenylmethyloxycarbonyl-*N'*-(2-N''-benzyloxycarbonyl)ethylhydrazine (10)**, 70% yield as a white solid, mp. 160–162°; Rf = 0.61 (EtOAc).

^{1}H NMR (200 MHz, DMSO-d_6): δ 2.77 (t, 2H, J = 6 Hz, CH_2); 3.11 (t, 2H; J = 6.2 Hz, CH_2); 4.23 (t, 1H, J = 6 Hz; CH (Fmoc)); 4.34 (d, 2H, J = 6.2 Hz, CH_2 (Fmoc));

4.72 (br s, 1H, NH); 5.03 (s, 2H, CH_2 (Cbz)); 7.11 (br s, 1H, NH); 7.29–7.45 (m, 9H, Ar (H)); 7.70 (d, 2H, J = 7 Hz, Ar(H)); 7.89 (d, 2H, J = 7 Hz, Ar(H)); 8.66 (br s, 1H, NH).

^{13}C NMR: δ 38.7; 46.7; 50.4; 65.2; 65.5; 120.0; 125.1; 127.0; 127.4; 127.5; 127.6; 128.2; 137.1; 140.7; 143.7; 156.1; 156.8. IR (cm^{-1}): 3314, 3042, 2949, 1689, 1531, 1253, 737. HRMS: m/z for $C_{25}H_{26}N_3O_4$ $[M+H]^+$. Calcd: 432.19178. Found: 432.19151.

Anal. Calcd for $C_{25}H_{25}N_3O_4$: C, 69.64; H, 5.84; N, 9.75. Found: C, 69.40; H, 5.79; N, 9.62.

***N*-Benzyloxycarbonyl-*N*'-(2-N"-benzyloxycarbonyl)ethylhydrazine (11)**, 63% yield as a white solid, mp. 85–88°; Rf = 0.6 (EtOAc).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.82 (t, 2H, J = 4 Hz; CH_2); 3.19 (t, 2H, J = 4 Hz, CH_2); 4.20 (br s, 1H, NH); 5.05 (s, 4H, 2 x CH_2 (Cbz)); 5.86 (br s, 1H, NH); 7.17 (br s, 1H, NH); 7.26 (s, 10H, Ar(H). ^{13}C NMR: δ 38.4; 51.0; 66.6; 67.0; 128.0; 128.02; 128.04; 128.2; 128.4; 128.5; 136.1; 136.6; 156.9; 157.6. IR (cm^{-1}): 3305, 3032, 2953, 1684, 1539, 1496, 1267, 1133, 737. HRMS: m/z for $C_{18}H_{22}N_3O_4$ $[M+H]^+$. Calcd: 344.16048. Found: 344.16016.

Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.17; N, 12.24. Found: C, 62.81; H, 6.09; N, 12.08.

***N*-Fluorenylmethyloxycarbonyl-*N*'-ethylhydrazine (12)**, 74% yield as a white solid, mp. 152-156°; Rf = 0.31 (1:1 EtOAc/light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (t, 3H, J = 6.5 Hz, CH_3); 2.88 (q, 2H, J = 6.2 Hz, CH_2); 3.77 (br s, 1H, NH); 4.20 (t, 1H, J = 6.2 Hz, CH (Fmoc)); 4.43 (d, 2H, J = 6.3 Hz, CH_2 (Fmoc)); 6.59 (br s, 1H, NH); 7.28–7.39 (m, 4H, Ar(H)); 7.56 (d, 2H, J = 7.4 Hz, Ar(H)); 7.74 (d, 2H, J = 7.5 Hz, Ar(H)). ^{13}C NMR: δ 12.7; 46.3; 47.3; 67.0; 120.0; 125.0; 127.1; 127.8; 141.4; 143.8; 157.3. IR (cm^{-1}): 3290, 3018, 2973, 1699, 1559, 1261, 1146, 734. HRMS: m/z for $C_{17}H_{19}N_2O_2$ $[M+H]^+$. Calcd: 283.14410. Found: 283.14394.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.37; H, 6.43; N, 9.93. Found: C, 72.18; H, 6.41; N, 9.86.

***N*-Benzyloxycarbonyl-*N*'-ethylhydrazine (13)**, 66 % yield as a white solid, mp. 51-53°; Rf = 0.31 (1:1 EtOAc-light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (t, 3H, J = 7.2 Hz, CH_3); 2.88 (q, 2H, J = 7 Hz, CH_2); 3.99 (br s, 1H, NH); 5.12 (s, 2H, CH_2 (Cbz)); 6.80 (br s, 1H, NH); 7.34 (s, 5H, Ar (H)). ^{13}C NMR: δ 12.7; 46.2; 67.0; 128.15; 128.23; 128.5; 136.3; 157.4. IR (cm^{-1}): 3279, 3026, 2969, 1700, 1559, 1258, 1148. HRMS: m/z for $C_{10}H_{15}N_2O_2$ $[M+H]^+$. Calcd: 195.11280. Found: 195.11274.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.89; H, 7.27; N, 14.43. Found: C, 61.88; H, 7.10; N, 14.24.

***N*-Fluorenylmethyloxycarbonyl-*N*'-(2-*N*"-benzoyl)ethylhydrazine (14)**, 86% yield as a white solid, mp. 133–134°; Rf = 0.33 (EtOAc).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.92 (t, 2H, J = 6 Hz, CH_2); 3.45 (t, 2H, 5.8 Hz, CH_2); 3.94 (br s, 1H, NH); 4.16 (t, 1H, J = 6.4 Hz, CH (Fmoc)); 4.43 (d, 2H, J = 6.8 Hz, CH_2 (Fmoc)); 6.39 (br s, 1H, NH); 6.98 (br s, 1H, NH); 7.21–7.56 (m, 9H, Ar(H)); 7.74 (t, 4H, J = 7.8 Hz, Ar(H)). ^{13}C NMR: δ 37.0; 47.2; 51.0; 67.0; 120.1; 125.0; 127.0; 127.1; 127.8; 128.5; 131.4; 134.4; 141.3; 143.6; 157.9; 167.8. IR (cm^{-1}): 3310, 3054, 2957, 1689, 1630, 1533, 1270, 736. HRMS: m/z for $C_{24}H_{24}N_3O_3$ $[M+H]^+$. Calcd: 402.18122. Found: 402.18101.

Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.78; N, 10.47. Found: C, 71.77; H, 5.73; N, 10.22.

***N*-Benzyloxycarbonyl-*N'*-(2-*N''*-benzoyl)ethylhydrazine (15)**, 80% yield as a white solid, mp. 103–106°; Rf = 0.33 (EtOAc).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.91 (t, 2H, J = 5.8 Hz, CH_2); 3.46 (t, 2H, J = 5.6 Hz, CH_2); 4.00 (br s, 1H, NH); 5.08 (s, 2H, CH_2 (Cbz)); 7.29–7.45 (m, 9H, Ar(H)); 7.57 (br s, 1H, NH); 7.79 (d, 2H, J = 6.8 Hz, Ar(H) + NH). ^{13}C NMR: δ 37.2; 51.0; 67.1; 127.1; 128.0; 128.2; 128.4; 128.5; 131.3; 134.4; 136.1; 157.9; 167.9. IR (cm^{-1}): 3317, 3026, 2957, 1688, 1630, 1536, 1488, 1269, 694. HRMS: m/z for $C_{17}H_{20}N_3O_3$ $[M+H]^+$. Calcd: 314.14992. Found: 314.14986.

Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.20; H, 6.12; N, 13.42. Found: C, 64.97; H, 6.10; N, 13.26.

***N*-Fluorenylmethyloxycarbonyl-*N'*-isopropylhydrazine (16)**, 77% yield, mp. 160–162°C, *lit*.[8] 163–164°C; Rf = 0.41 (1:1 EtOAc-light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02 (d, 6H, J = 6 Hz, 2xCH_3); 3.16 (sep, 1H, J = 6.8 Hz, CH(iPr)); 4.21 (t, 1H, J = 6.6 Hz, CH(Fmoc)); 3.85 (br s, 1H, NH); 4.44 (d, 2H, J = 6 Hz, CH_2(Fmoc)); 6.05 (br s, 1H, NH); 7.24–7.42 (m, 4H, Ar(H)); 7.57 (d, 2H, J = 7Hz, Ar(H)); 7.75 (d, 2H, J = 6.8 Hz, Ar(H)). ^{13}C NMR: δ 20.3; 47.2; 51.2; 67.1; 120.1; 125.0; 127.1; 127.8; 141.4; 143.7; 157.8. LRMS: m/z for $C_{18}H_{21}N_2O_2$ $[M+H]^+$. Calcd: 297.1. Found: 297.0. IR (cm^{-1}): 3330, 3066, 2972, 1695, 1491, 1268, 1164, 733.

***N*-Benzyloxycarbonyl-*N'*-isopropylhydrazine (17)**, 64% yield as a white solid, mp. 59–61°C, *lit*.[21] 59–60°; Rf = 0.41 (1:1 EtOAc-light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (d, 6H, J = 6 Hz, 2xCH_3); 3.11 (sep, 1H, J = 6.8 Hz, CH (iPr)); 4.28 (br s, 1H, NH); 5.12 (s, 2H, CH_2 (Cbz)); 6.79 (br s, 1H, NH); 7.33 (s, 5H, Ar(H)). ^{13}C NMR: δ 20.5; 50.8; 52.3; 67.1; 128.1; 128.2; 128.5; 136.2; 157.4.

LRMS: m/z for $C_{11}H_{17}N_2O_2$ $[M+H]^+$. Calcd: 209.1. Found: 209.0.

IR (cm^{-1}): 3325, 3034, 2974, 1688, 1534, 1492, 1273, 1168, 737.

***N*-Fluorenylmethyloxycarbonyl-*N'*-cyclohexylhydrazine (18)**, 72% yield as a white solid, mp. 153–155°; Rf = 0.56 (1:1 EtOAc-light petroleum).

^{1}H NMR (700 MHz, $CDCl_3$): δ 1.10 (d, 2H, J = 14 Hz); 1.18 (d, 1H, J = 14 Hz); 1.27 (t, 2H; J = 7 Hz); 1.62 (d, 1H, J = 14 Hz); 1.75 (d, 2H, J = 14 Hz); 1.83 (d, 2H, J = 14 Hz); 2.84 (s, 1H, N-CH); 3.96 (br s, 1H, NH); 4.25 (t, 1H; J = 7 Hz; CH (Fmoc)); 4.47 (d, 2H, J = 7 Hz, CH_2 (Fmoc)); 6.29 (br s, 1H, NH); 7.28–7.43 (m, 4H, Ar(H)); 7.59 (d, 2H, J = 7 Hz, Ar(H)); 7.78 (d, 2H, J = 7 Hz, Ar(H)). ^{13}C NMR: δ 24.3; 26.0; 31.1; 47.2; 58.4; 66.9; 120.0; 125.0; 127.1; 127.7; 141.3; 143.7; 157.3. IR (cm^{-1}): 3290, 3032, 2929, 1700, 1554, 1446, 1266, 1162, 734. HRMS: m/z for $C_{21}H_{25}N_2O_2$ $[M+H]^+$. Calcd: 337.19105. Found: 337.19097.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 76.86; H, 7.37; N, 8.54. Found: C, 76.65; H, 7.19; N, 8.30.

***N*-Benzyloxycarbonyl-*N'*-cyclohexylhydrazine (19)**, 87% yield as a white solid, mp. 66-69°; Rf = 0.55 (1:1 EtOAc-light petroleum).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (m, 5H); 1.72 (m, 5H); 2.82 (s, 1H, N-CH); 4.72 (br s, 1H, NH); 5.10 (s, 2H, CH_2 (Cbz)); 7.05 (br s, 1H, NH); 7.32 (s, 5H, Ar(H)).

^{13}C NMR: δ 24.4; 26.0; 31.0; 58.5; 67.0; 128.1; 128.2; 128.5; 136.3; 157.6. IR (cm^{-1}): 3281, 3034, 2932, 1705, 1542, 1457, 1256, 1140, 696.

HRMS: m/z for $C_{14}H_{21}N_2O_2$ $[M+H]^+$. Calcd: 249.15975. Found: 249.15994

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.76; H, 8.12; N, 11.29. Found: C, 67.73; H, 7.97; N, 11.25.

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