CHAPTER-4

Synthesis of Acyl Hydrazides from *N*-activated Amides and Hydrazine Hydrate under Metal Free Conditions at Room Temperature

4.1 Introduction

Acyl hydrazides are a very important class of organic compounds which display a wide spectrum of biological activities [1, 2] including antituberculous [3-6], antidepressant [8], anti-inflammatory [9], anticonvulsant [7], antimalarial [10], anticancer [12], antimycobacterial [11], antituberculous [13] anti-HIV activities, etc. Acyl hydrazides are clinically used as antituberculous (Isoniazid and metazid) [14, 15] and antidepressant [16, 17]) (iproniazid and marplan) drugs [1, 20]. Moreover, acyl hydrazides found different applications in the field of herbicides, polymers, chemical preservers, etc. [18].

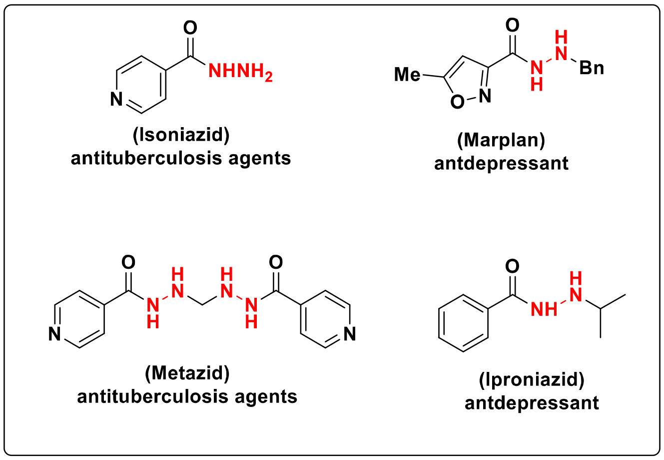
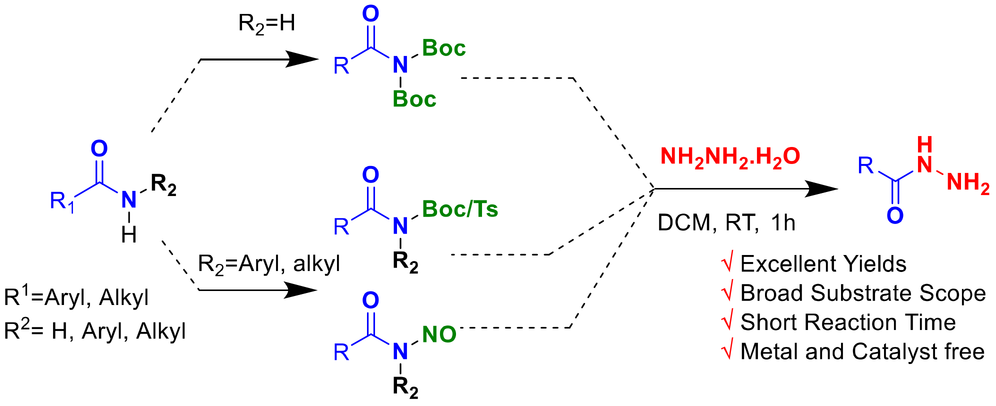


Figure 4.1 structures of some bioactive acyl hydrazides.

On the other hand, acyl hydrazides are valuable synthons and intermediates in organic chemistry. The preparation of synthetically useful functionalities such as thioesters, esters, amides and ketones were demonstrated from acyl hydrazides under mild reaction conditions [19]. Moreover, acyl hydrazides have been exploited in the preparation of various biologically relevant heterocyclic compounds with different ring sizes containing one or more heteroatoms by the cyclization and cycloaddition reactions. Acyl hydrazides have also been used as peptide sub-monomers and ligands [19, 20]. Due to their broad significance in both biology and chemistry, numerous efforts have been made to synthesize acyl hydrazides under mild reaction conditions. Traditional routes rely on the condensation reactions of hydrazine hydrate with different acid derivatives including esters, acyl halides, cyclic anhydrides, etc. Some of these methods suffer from the use of unstable starting materials (e.g. acid chlorides, anhydrides), harsh reaction conditions, longer reactions time, etc. [1]. Alternatively, the reaction of aldehydes with dialkylazodicarboxylate (e.g. DEAD) provides acyl hydrazides [20, 21], however in a protected form. Moreover, most of these reactions require metal catalysts and longer reaction times [22, 23].

Amides are one of the most important functional groups in chemistry and biology [24]. Recently, amides have been utilized as stable precursors for the functional group transformations in organic synthesis via C(O)-N bond cleavage [25]. Considering the high stability, amides are initially converted into activated amides and diversified into different functional groups via transamidations [26], esterifications [27], cross-coupling reactions [25b], etc. However, this approach has not been well explored for the synthesis of acyl hydrazides. Last few years our research group is working on the amide activation reactions and explored transamidation of secondary amides employing *N*-nitroso, and *N*-Cbz amide intermediates, transamidation of *α*–ketoamides using *N*-Boc and *N*-Tosyl *α*–ketoamides, syntheses of aryl ketones from *N*-Bocamides, and reduction of *N*-Boc and *N*-

tosylamides into aldehydes [28]. In continuation of these works, here we report the synthesis of acyl hydrazides from amides at room temperature (**Scheme 4.1**).

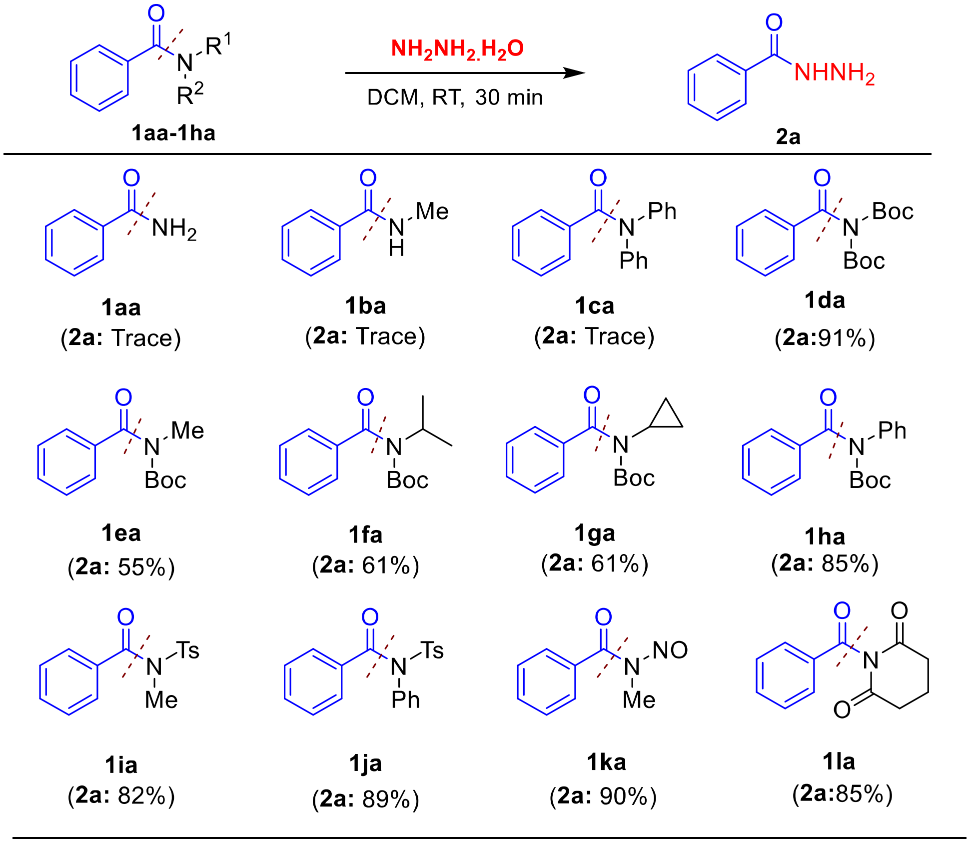


Scheme 4.1 Synthesis of acyl hydrazides from *N*-activated amides.

4.2 Results and discussion

At the outset, different amides were subjected to the transamidation with hydrazine hydrate in dichloromethane at room temperature in the absence of catalysts and additives (**Table 4.1**). Simple amides (non-activated) such as benzamide, *N*-methyl benzamide and *N,N*-diphenyl benzamide did not provide any products. However, to our delight, the activated amides such as *N*-Boc, *N*-tosyl and *N*-nitroso amides (**1da-1ka**) as well as *N*-acyl glutarimide (**1la**) underwent transamidation reactions with hydrazine hydrate and delivered the desired product **2a** in good to excellent yields. In particular, *N,N*-diBoc-benzamide (**1da**), *N*-phenyl-*N*-Boc-benzamide (**1ha**) as well as *N*-tosyl benzamide (**1ia-1ga**) underwent transamidation reaction very efficiently and yielded the desired product **2a** in excellent yields (88-91%).

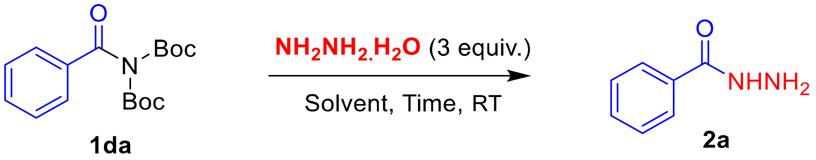
Table 4.1 Reaction of different amides with hydrazine hydrate.[a,b]



[a]Conditions: Substrate (0.5 mmol) and hydrazine monohydrate (0.1 mL, 1.5 mmol) in DCM (3 mL) at RT. [b]Isolated yields.

Further to explore the solvent effect, the reaction of *N,N*-diboc-benzamide (**1ca**) with hydrazine hydrate was carried out in different protic and aprotic solvents including acetonitrile, dioxane, tetrahydrofuran, methanol and toluene (**Table 4.2**). Among these solvents, dichloromethane was found to be the best and provided the desired product in 91% yield (**Table 4.2, entry 6**). Other solvents gave the desired product comparatively in low yields (**Table 4.2, entries 1-5**).

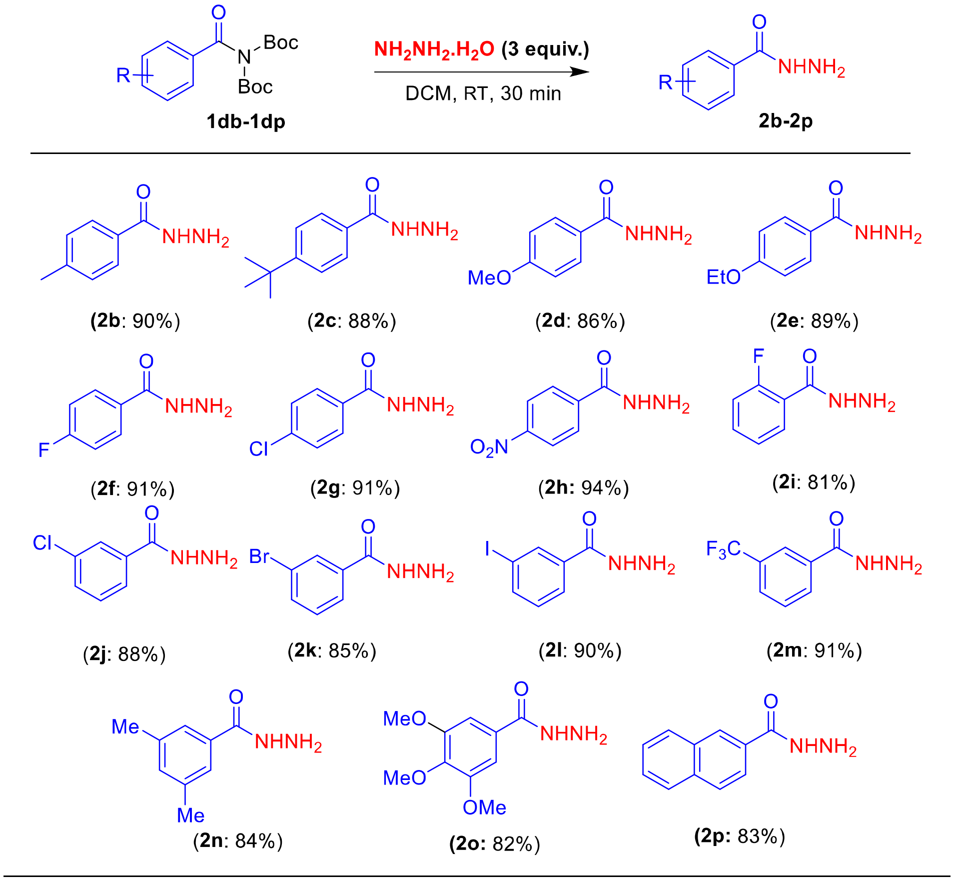
Table 4.2 Reaction of *N,N*-diboc-benzamide(**1da**)with hydrazine hydrate in different solvents.



S.No.	Solvent	Time (min)	Yield (2a) (%)
1	Acetonitrile	30	60
2	Dioxane	30	68
3	Tetrahydrofuran	30	70
4	Toluene	30	45
5	Methanol	30	10
6	**Dichloromethane**	30	**91**

With optimized conditions in our hand, a variety of functionalized *N,N*-diBoc benzamides (**1db-1dp**) were tested for the acyl hydrazide synthesis with hydrazine hydrate (**Table 4.3**). To our delight, the substrates bearing electron-donating groups (e.g., methyl, *tert*-butyl, methoxy, ethoxy) and electron-withdrawing groups (e.g., nitro, halogens, etc.) at the *para*-position underwent transamidation reaction smoothly and provided the corresponding hydrazides(**2b-2h**) in good to excellent yields within 30 minutes. Further, the reaction of *meta*-and sterically hindered *ortho*-substituted amides as well as 2-naphthalene amide were investigated under the optimized reaction conditions. These activated amides were successfully converted into corresponding hydrazides **2i-2p** in 81−91% yields.

Table 4.3 Transamidation of functionalized *N,N*-diboc benzamides with hydrazine hydarate.[a,b]



(**2b**: 90%) (**2c**: 88%) (**2d**: 86%) (**2e**: 89%)

(**2f**: 91%) (**2g**: 91%) (**2h**: 94%) (**2i**: 81%)

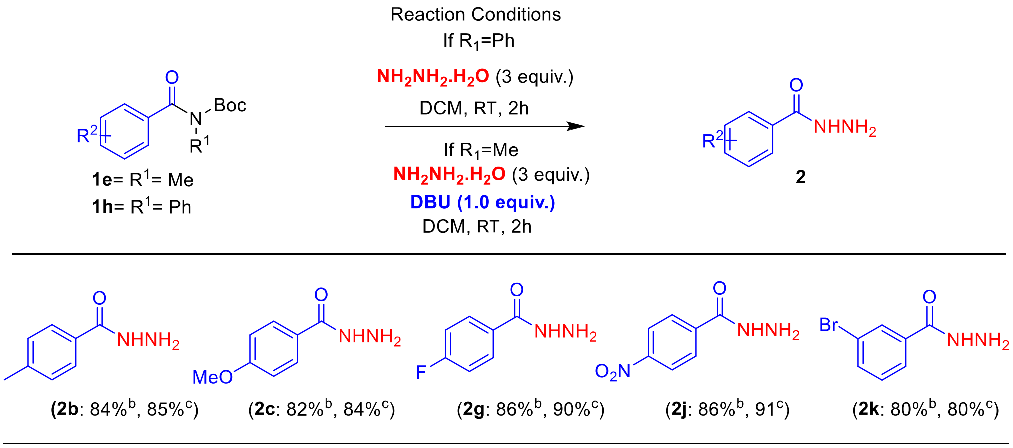
(**2j**: 88%) (**2k**: 85%) (**2l**: 90%) (**2m**: 91%)

(**2n**: 84%) (**2o**: 82%) (**2p**: 83%)

[a]Conditions: *N,N*-diBoc benzamides (0.5 mmol) and hydrazine monohydrate (0.1 mL, 1.5 mmol) in DCM (3 mL) at RT. [b]Isolated yields.

After exploring the scope of various *N,N*-diBoc compounds, we investigated the reactivities of *N*-mono Boc amides for the preparation of acyl hydrazides (**Table 4.4**). It was observed that *N*-phenyl *N*-Boc amides showed similar activity to that of *N,N*-diBoc compounds in the absence of any base or catalysts. On the other hand,low yields were obtained in the case of *N*-alkyl *N*-Boc amides. However, in the presence of a base DBU, various *N*-alkyl *N*-Boc amides were successfully converted into corresponding acyl hydrazides (**2b, 2c, 2g, 2j** and **2k)** in 79-86% yields.

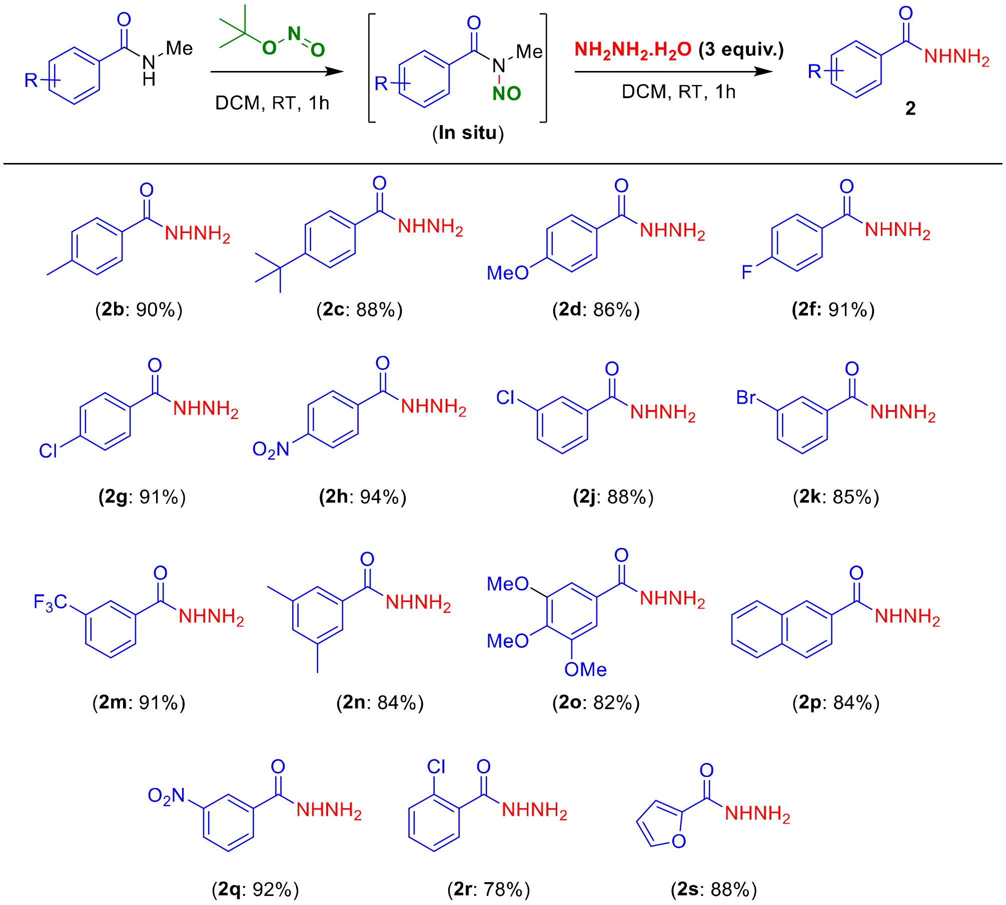
Table 4.4 Transamidation of functionalized *N*-Boc benzamides with hydrazine hydarate.[a,b,c]



[a]Conditions: *N*-methyl *N*-Boc benzamides **1e** (0.5 mmol, 118 mg) or *N*-phenyl*N*-bocbenzamides**1h**(0.5 mmol, 148 mg)and hydrazine monohydrate (0.1 mL, 1.5 mmol) in DCM (3 mL) at RT. [b]Isolated yield from **1e**.[c]Isolated yield from **1h**.

After investigating *N*-Boc amides as precursors for the hydrazide synthesis, we investigated the conversion of secondary amides to acyl hydrazides *viaN*-nitroso intermediate. In this context, various *N*-methyl benzamides were converted into *N*-methyl *N*-nitroso benzamides *in situ* and subjected to the transamidation with hydrazine hydrate under one-pot conditions (**Table 4.5**). To our delight, *N*-methylbenzamide bearing electron-donating groups (e.g.methyl, metoxy, *tert*-butyl) and electron-withdrawing groups (e.g. halogens, trifluoromethane, nitro etc.) at the *para*-and *meta* position underwent transamidation smoothly and provided the amides **2b–2n** in 82–94% yields. On the other hand, *ortho*-substituted 2-chloro-*N*-methylbenzamide also participated in transamidation smoothly and provided the amides 2r in 78% yields. In addition, N-methyl-2-naphthamide and heterocyclic amide such as N-methylfuran-2-carboxamide also showed excellent reactivity with the established method and the desired amides 2p and 2s were obtained in 84-88% yield. This approach does not require any base or catalyst, isolation of activated amide intermediates, etc.

Table 4.5 One-pot conversion of *N*-methylbenzamide with hydrazine hydrate.[a,b]



(**2b**: 90%) (**2c**: 88%) (**2d**: 86%) (**2f**: 91%)

(**2g**: 91%) (**2h**: 94%) (**2j**: 88%) (**2k**: 85%)

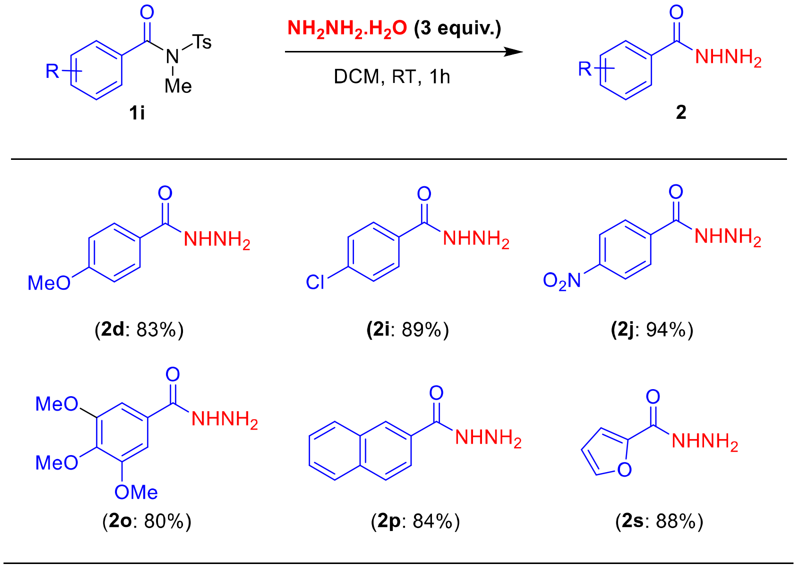
(**2m**: 91%) (**2n**: 84%) (**2o**: 82%) (**2p**: 84%)

(**2q**: 92%) (**2r**: 78%) (**2s**: 88%)

[a] Conditions: *N*-methyl benzamides (1 mmol) and TBN (0.356 mL, 3 equiv.) in DCM (3 mL) at RT for 1h., followed by hydrazine monohydrate (0.2 mL, 3 mmol) RT for 1h. [b] Isolated yields.

Having investigated the scope of *N*-Boc and *N*-nitroso amides, we further examined the reactivities of different *N*-tosylamides with hydrazine hydrate under the optimized conditions (**Table 4.6**). It was pleasant to observe that electron-donating and electron-withdrawing groups functionalized *N*-tosyl *N*-methyl benzamides underwent transamidation efficiently at room temperature in the absence of catalyst and base to provide the desired products **2d, 2i, 2j, 2o, 2p** and **2s** in 80–94% yields(**Table 4.6**) Reaction of different *N*-tosyl amides with hydrazine hydrate.[a,b]

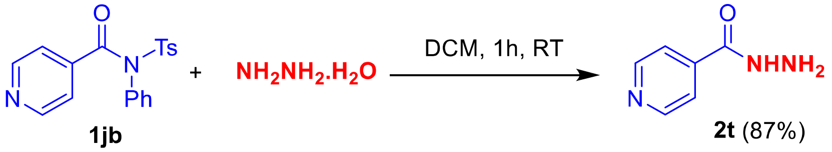
Table 4.6 Transamidation of functionalized *N*-Ts benzamides with hydrazine hydarate.[a,b]



[a]Conditions: *N*-methyl *N*-tosyl benzamides (0.5 mmol) and hydrazine monohydrate (0.1 mL, 1.5 mmol) in DCM (3 mL) at RT. [b]Isolated yields.

After exploring the scope of various amides, we attempted to synthesize anti-tuberculousagentisoniazid (**2t**) using the developed transamidation method. The reaction of *N*-Ts amide **1jb** with hydrazine hydrate gave the desired product **2t** in 87% yield at room temperature (**Scheme 4.2**).

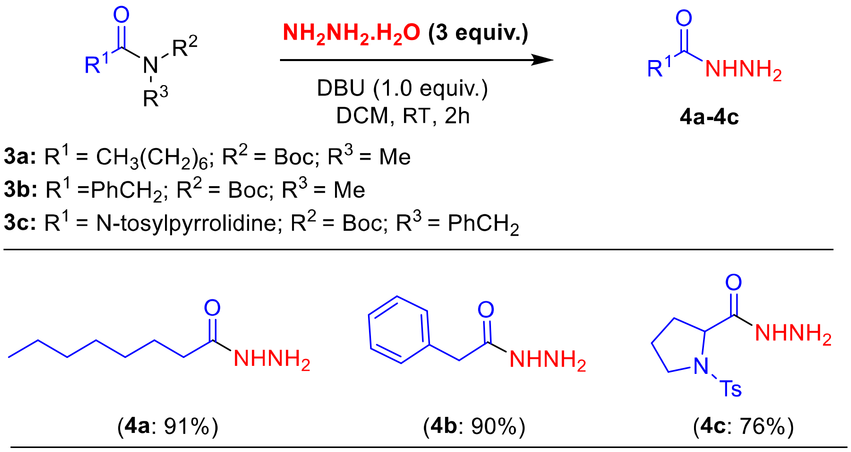
Scheme 4.2 Synthesis of isoniazid.[a,b]



[a]Conditions: *N*-phenyl-*N*-tosylisonicotinamide(0.5 mmol, 175 mg) and hydrazine monohydrate (0.1 mL, 1.5mmol) in DCM (3 mL) at RT. [b]Isolated yield.

After examining the scope of aryl amides, transformation of different alkyl amides into alkyl hydrazides was explored with hydrazine hydrate (**Table 4.7**). To our delight, Boc protected *N*-methyloctanamide (**3a**), *N*-methylphenylacetamide (**3b**), and proline derived tert-butyl benzyl(tosylprolyl)carbamate (**3c**) were efficiently converted to corresponding alkyl hydrazides **4a-4c** in 78-91% yields under the optimized conditions.

Table 4.7 Scope of alkyl amides.[a,b]

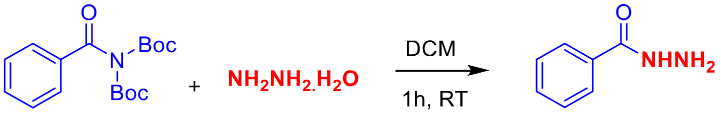


3a: $R^1 = CH_3(CH_2)_6$; R^2 = Boc; R^3 = Me
3b: $R^1 = PhCH_2$; R^2 = Boc; R^3 = Me
3c: R^1 = N-tosylpyrrolidine; R^2 = Boc; $R^3 = PhCH_2$

(**4a**: 91%) (**4b**: 90%) (**4c**: 76%)

[a]Conditions: *N*-methyl*N*-tosyl benzamides (0.5 mmol) and hydrazine monohydrate (0.1 mL, 1.5 mmol) in DCM (3 mL) at RT. [b]Isolated yields.

Finally, to test the practical applicability of the developed method, the coupling reaction was performed in a gram scale (**Scheme 4.3**). The reaction of *N,N*-diBoc benzamide (1.5 g, 4.67 mmol) with hydrazine hydrate provided the desired product (**2a**) in 88% yield.

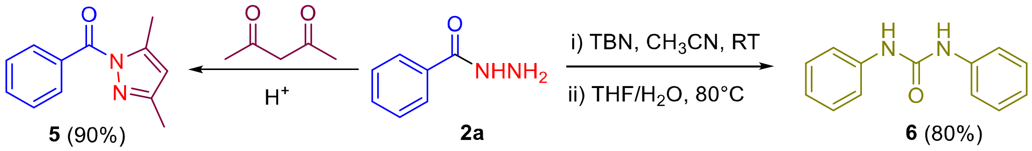


1da
(1.5g,4.67 mmol)

2a
(0.559g, 4.11 mmol)

Scheme 4.3 Gram Scale Reaction.

Further, the synthetic utilities of the acyl hydrazides have been demonstrated as shown in the **Scheme 4.4**. The reaction of benzohydrazide (**2a)** with acetylacetone in acidic medium afforded synthetically relevant (3,5-dimethyl-1*H*-pyrazol-1-yl)(phenyl)methanone (**5**) in 90% yield. On the other hand, benzohydrazide was successfully converted into symmetrical diphenyl urea (**6**) in 80% yield via two-step reaction [29, 30].



Scheme 4.4 Diversification of acyl hydrazides

4.3 Conclusion

In conclusion a mild and practical method for the transformation of *N*-activated amides into acyl hydrazides were demonstrated with hydrazine monohydrate. The reaction proceeds at room temperature and provided the desired products in good to excellent yields under mild reaction conditions. Use of easily accessible and stable starting materials, shorter reaction time and clean conversion are the merits of the developed methodology.

4.4 Experimental Section

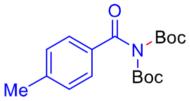
4.4.1 General procedure for the synthesis of starting materials:

(a) Synthesis of primary and secondary amides.

All primary amides (**1aa-1ap**), secondary amides (**1ba-1bs**), **1ca** and **1ja** were prepared using the general literature procedure [31].

(b) General Procedure for the Synthesis of *N,N*-Di-Boc Benzamides [31].

All *N,N*-di-Boc benzamides (**1da-1dp**) were prepared using the general literature procedure [31]. Primary amide (1 mmol, 1.0 equiv.) and DMAP (13 mg, 0.1 mmol) was taken in an oven dried round bottom flask. The mixture was dissolved in dichloromethane (5 mL). Di-*tert*-butyl dicarbonate (Boc_2O) (0.45 mL, ~2.1 mmol) was added to the reaction mixture with vigorous stirring at 0 °C. The resulting reaction mixture was stirred continuously for 12−18 hours at room temperature. Reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under vacuum followed by extraction with EtOAc (3 × 20 mL). The organic layer was washed with H_2O (1 × 20 mL) and brine (1 × 20 mL), dried, and concentrated. The crude product was purified by column chromatography (SiO_2: ethyl acetate/hexane) to obtain the corresponding *N,N*-di-Boc benzamide (1da−1dp). The analytical data is already reported by our group.



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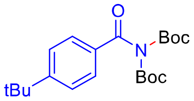

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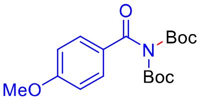

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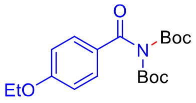

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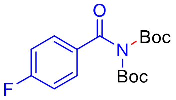

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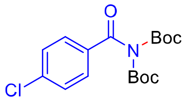

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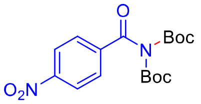

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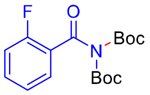

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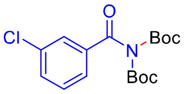

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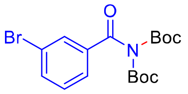

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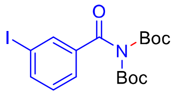

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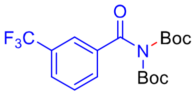

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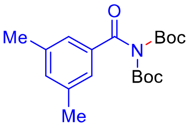

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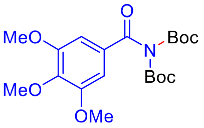

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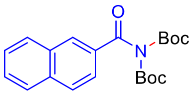
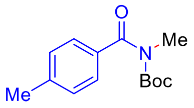


1dp

(c) General Procedure for the synthesis of *N*-Boc Amides [31].

All *N*-Boc amides **1ea-1ef, 1fa, 1ga, 1ha-1hf** and **3a-3c** were prepared using the general literature procedure [31, 32]. A round-bottom flask (100 mL) was charged with a secondary amide (5.0 mmol, 1.0 equiv.) and DMAP (61 mg, 0.5 mmol) dissolved in dichloromethane (10 mL). Di-*tert*-butyldicarbonate (Boc_2O) (1.5 mL, 6.5 mmol) was added slowly and the reaction mixture was allowed to stir for overnight at room temperature. Reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum followed by extraction with EtOAc (3 × 20 mL). The organic layer was washed with H_2O (1× 20 mL) and brine (1 × 20 mL), dried, and concentrated. The crude product was purified by column chromatography (SiO_2: ethyl acetate/hexane) to obtain the corresponding *N*-Boc amide. The analytical data is already reported by our group.



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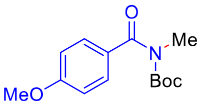

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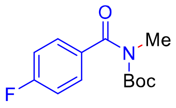

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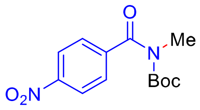

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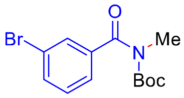

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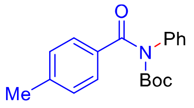

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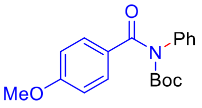

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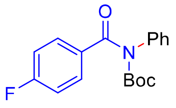

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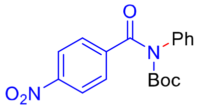
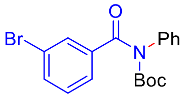
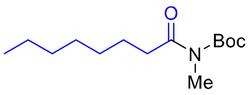


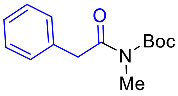
1he



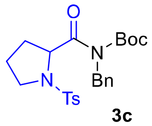
1hf



3a



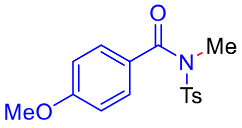
3b



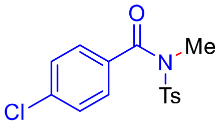
3c

(d) General Procedure for the Synthesis of *N*-Ts Amides [32].

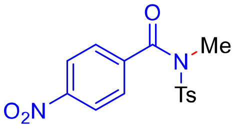
All *N*-Ts amides **1ia-1if** and **1ja** were prepared using the general literature procedure. An oven dried round bottom flask was charged with carboxylic acid (5.0 mmol) in DCM (10 mL) followed by addition of oxalyl chloride (0.6 mL, 6 mmol, 1.2 equiv.) and DMF (two drops) at 0 °C. The reaction mixture was allowed to stir until gas evolution stopped. Reaction was monitored by TLC. After completion, the reaction mixture was concentrated and the crude product (acyl chloride) was used directly for the next step. To a stirred mixture of the sulfonamide (R_1NHTs, 5 mmol, 1.0 equiv.), DMAP (65 mg, 0.5 mmol) and Et_3N (1.4 mL, 10 mmol) in DCM (10 mL) was added a solution of acyl chloride in DCM (5 ml) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and diluted with DCM (20 mL), washed with 5% HCl, brine and H_2O. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography to obtain the corresponding *N*-tosyl carboxylic amides.



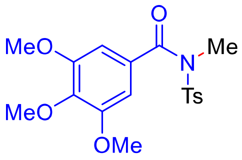
1ia



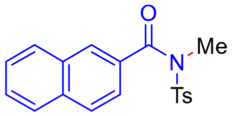
1ib



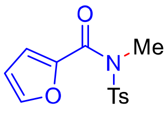
1ic



1id



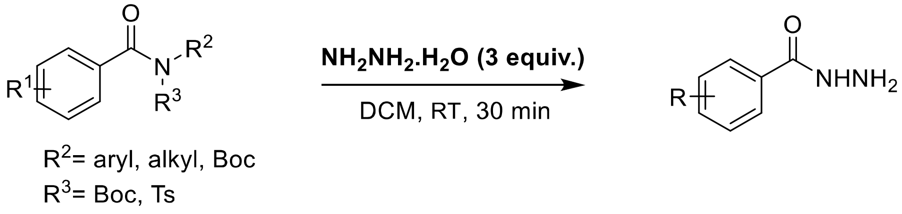
1ie



1if

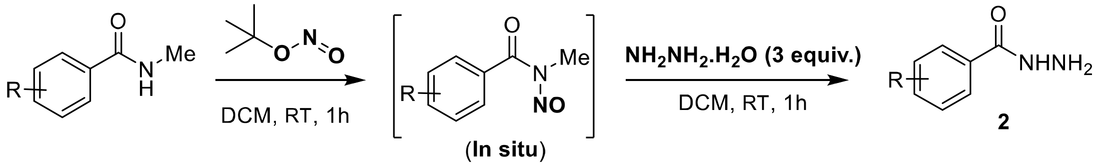
(e) General Procedure for the Synthesis of *N*-Methyl *N*-Nitrosobenzamide (1ka) [31]. *N*-Methylbenzamide (135 mg, 1 mmol) was stirred in dichloromethane (3 mL) for approximately 2 min at room temperature to which *tert*-butyl nitrite (0.179 mL, 1.5 mmol) was added via a syringe and allowed to stir for 1 h at room temperature. After completion, dichloromethane was evaporated and then subjected to silica gel (60−120 mesh) column chromatography purification (SiO_2: ethyl acetate/hexane) to obtain the corresponding *N*-methyl *N*-nitrosobenzamide (1ka).

4.4.2. General procedure for the transamidation of *N*-activated amides.



To a stirred solution of hydrazine monohydrate (1.5 mmol) in DCM (3 mL) was added *N*-Boc/*N*-Ts/*N,N*-diBoc amides **1aa-1la** (0.5 mmol) at room temperature. The resulting mixture was allowed to stir for 30 min. After completion, the reaction mixture was concentrated on vacuum then diluted with H_2O (10 mL) followed by extraction with EtOAc (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (gradient eluent of EtOAc in hexane) to give the desired products **2a-2t** and **4a-4c.**

4.4.3. Procedure for the one-pot synthesis of acyl hydrazides via *N*-nitrosamides



An oven-dried round-bottomed flask was charged with *N*-methyl benzamide (0.5 mmol, 68 mg) in DCM (3 mL) at room temperature to which 3 equiv. of *tert*-butyl nitrite (TBN) was added. The progress of the reaction was monitored by TLC. The resulting mixture was allowed to stir for 1 hour and after the consumption of starting material, hydrazine hydrate (3 equiv.) was added slowly. The reaction mixture was allowed to stir at room temperature for 1 hour. The resulting mixture was diluted with ethyl acetate and washed with 1 M HCl solution and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The resulting crude product was purified by column chromatography (EtOAc/hexane) to obtain the desired products.

4.4.4. General procedure for the synthesis of 5.

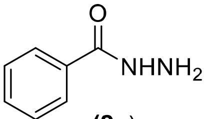
1,3-dicarbonyl compound and an equimolar amount of acyl hydrazide were mixed in a round bottom flask in methanol. To the mixture a drop of concentrated sulfuric acid was added. The mixture was allowed to stir for an hour. After completion, methanol was evaporated and then, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and purified by silica gel column chromatography.

4.4.5. General procedure for the synthesis of 6.

Acyl hydrazide **2a**(1 mmol) was stirred in acetonitrile (5 mL) at room temperature to which 3 equiv. of *tert*-butyl nitrite (TBN) was added. The progress of the reaction was monitored by TLC. After completion, acetonitrile was evaporated and then, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and crude azide was used in next step. The crude acyl azide (1.0 mmol, 1.0 equiv) was dissolved in THF:H_2O (1:1, 5 mL), was stirred at 80 °C for 3 h. The reaction was diluted with EtOAc (20 mL) and the organic layer was washed with water and concentrated under vacuum. The crude product was purified by silica gel column chromatography with ethyl acetate/hexane to afford the desired urea 6.

4.5. Analytical data of the products:

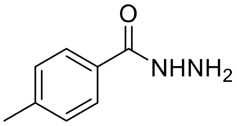
4.5.1. Benzohydrazide (2a)



(2a)

The title compound was obtained as a white solid. M.p. 114-115 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R_f = 0.30; Yield 91% (62 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.96 (s, 1H), 7.75 (dd, J = 5.2, 3.3 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 3.85 (s, 2H).**^{13}C NMR** (125 MHz, $CDCl_3$) δ = 168.6, 132.5, 131.8, 128.6, 126.8.

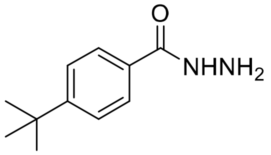
4.5.2. 4-Methylbenzohydrazide (2b)



(2b)

The title compound was obtained as a white solid. M.p. 116 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R$_f$ = 0.32; Yield 90% (68 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.72 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.49 (s, 2H), 2.32 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 165.9, 140.9, 130.5, 128.8, 127.0, 20.9.

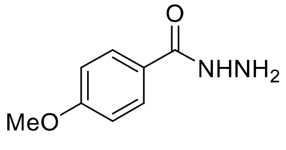
4.5.3. 4-(tert-Butyl)benzohydrazide (2c)



(**2c**)

The title compound was obtained as a white solid. M.p. 124 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R$_f$ = 0.60; Yield 88% (85 mg). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 8.09 (s, 1H), 7.73–7.67 (m, 2H), 7.45–7.40 (m, 2H), 3.88 (s, 2H), 1.30 (s, 9H). **^{13}C NMR** (125 MHz, CDCl$_3$) δ = 168.5, 155.3, 129.6, 126.7, 125.5, 34.8, 31.0.

4.5.4. 4-Methoxybenzohydrazide (2d)

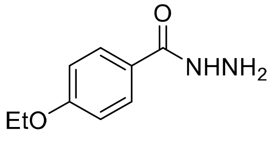


(**2d**)

The title compound was obtained as a white solid. M.p. 137-139 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R$_f$ = 0.60; Yield 86% (78 mg). **^{1}H NMR** (500 MHz, CDCl$_3$) δ =

7.72 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 1.4H).^{13}**C NMR** (125 MHz, $CDCl_3$) *δ* = 168.2, 162.4, 128.6, 124.7, 113.9, 55.3.

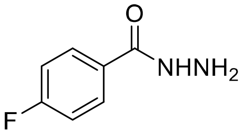
4.5.5. 4-Ethoxybenzohydrazide (2e)



(**2e**)

The title compound was obtained as a sticky solid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R*f* = 0.35; Yield 89% (80 mg). ^{1}**H NMR** (500 MHz, DMSO-D_6) *δ* = 9.63 (s, 1H), 7.83–7.77 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.45 (s, 2H), 4.04 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}**C NMR** (125 MHz, DMSO-D_6) *δ* = 165.7, 160.7, 129.4, 128.7, 125.3, 113.9, 113.7, 63.2, 14.5.

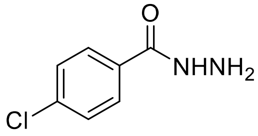
4.5.6. 4-Fluorobenzohydrazide (2f)



(**2f**)

The title compound was obtained as a white solid. M.p. 163−166 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R*f* = 0.26; Yield 91% (71 mg). ^{1}**H NMR** (500 MHz, DMSO-D_6) *δ* = 9.80 (s, 1H), 7.93–7.84 (m, 2H), 7.32–7.20 (m, 2H), 4.50 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 164.9, 164.8, 162.8, 129.8, 129.7, 129.6, 129.5, 129.5, 115.4, 115.3, 115.2, 115.1.

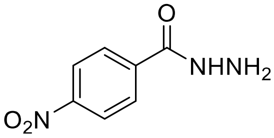
4.5.7. 4-Chlorobenzohydrazide (2g)



(**2g**)

The title compound was obtained as a white solid. M.p. 163-164 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R$_f$ = 0.60; Yield 91% (78 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.86 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.54–7.49 (m, 2H), 4.53 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 164.8, 135.9, 132.0, 128.8, 128.4.

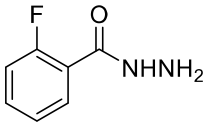
4.5.8. 4-Nitrobenzohydrazide (2h)



(**2h**)

The title compound was obtained as a white solid. M.p. 218 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R$_f$ = 0.26; Yield 94% (85 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 10.13 (s, 1H), 8.33–8.26 (m, 2H), 8.07–8.01 (m, 2H), 4.67 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 163.9, 148.9, 139.0, 128.4, 123.5.

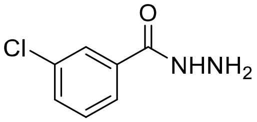
4.5.9. 2-Fluorobenzohydrazide (2i)



(**2i**)

The title compound was obtained as a sticky solid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R*f* = 0.38; Yield 81% (63 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.54 (s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.54–7.47 (m, 1H), 7.27 (dd, *J* = 13.0, 6.2 Hz, 2H), 4.56 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 163.3, 160.1, 158.1, 132.3, 130.0, 129.9, 124.4, 124.4, 123.2, 123.0, 116.1, 116.0.

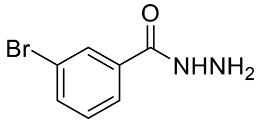
4.5.10. 3-Chlorobenzohydrazide (2j)



(**2j**)

The title compound was obtained as a white solid. M.p. 161 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R*f* = 0.34; Yield 88% (74 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.91 (s, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 4.56 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 164.4, 135.3, 133.2, 131.0, 130.3, 126.8, 125.7.

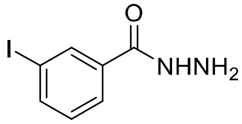
4.5.11. 3-Bromobenzohydrazide (2k)



(**2k**)

The title compound was obtained as a white solid. M.p. 157-159 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R*f* = 0.40; Yield 85% (91 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.90 (s, 1H), 7.99 (t, *J* = 1.7 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.70 (ddd, *J* = 8.0, 1.9, 0.8 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 4.54 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 164.2, 135.4, 133.8, 130.6, 129.7, 126.0, 121.7.

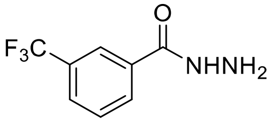
4.5.12. 3-Iodobenzohydrazide (2l)



(**2l**)

The title compound was obtained as a white solid. M.p. 165 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R*f* = 0.44; Yield 90% (118 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.85 (d, *J* = 16.7 Hz, 1H), 8.16 (t, *J* = 1.6 Hz, 1H), 7.89–7.80 (m, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 4.52 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 164.3, 139.6, 135.5, 135.3, 130.5, 126.3, 94.7.

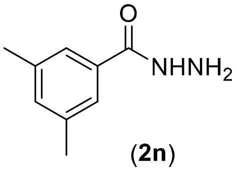
4.5.13. 3-(Trifluoromethyl)benzohydrazide (2m)



(**2m**)

The title compound was obtained as a white solid. M.p. 116-118 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R_f = 0.42; Yield 91% (93 mg). **^{1}H NMR** (500 MHz, DMSO-D_6) δ = 10.06 (s, 1H), 8.25– 8.08 (m, 2H), 7.86 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 4.61 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D_6) δ = 164.3, 134.2, 131.0, 129.7, 129.6, 129.3, 129.1, 127.6, 125.0, 123.6, 122.9.

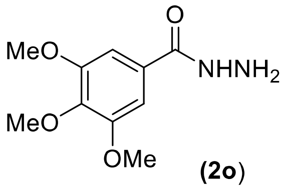
4.5.14. 3,5-Dimethylbenzohydrazide (2n)



(**2n**)

The title compound was obtained as a white solid. M.p. 125 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R_f = 0.36; Yield 84% (69 mg). **^{1}H NMR** (500 MHz, DMSO-D_6) δ = 9.67 (s, 1H), 7.44 (s, 2H), 7.11 (s, 1H), 4.47 (s, 2H), 2.28 (s, 6H). **^{13}C NMR** (125 MHz, DMSO-D_6) δ = 166.2, 137.3, 133.3, 132.3, 124.7, 20.8.

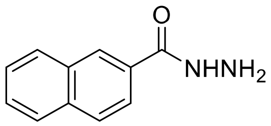
4.5.15. 3,4,5-Trimethoxybenzohydrazide (2o)



(**2o**)

The title compound was obtained as a colourless gum. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R$_f$ = 0.60; Yield 82% (93 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.75 (s, 1H), 7.17 (s, 2H), 3.81 (s, 6H), 3.69 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 165.5, 152.6, 139.8, 128.5, 104.5, 60.1, 56.0.

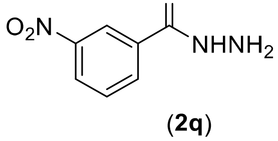
4.5.16. 2-Naphthohydrazide (2p)



(**2p**)

The title compound was obtained as a colourless gum. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R$_f$ = 0.60; Yield 83% (77 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.97 (s, 1H), 8.45 (s, 1H), 8.03–7.91 (m, 4H), 7.63–7.54 (m, 2H), 4.61 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 165.9, 134.0, 132.2, 130.6, 128.8, 127.9, 127.6, 127.5, 127.3, 126.7, 123.8.

4.5.17. 3-Nitrobenzohydrazide (2q)

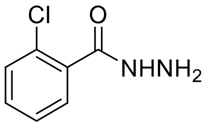


(**2q**)

The title compound was obtained as a yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane:

EtOAc (80:20), R_f = 0.41; Yield 92% (83 mg). **^{1}H NMR** (500 MHz, DMSO-D_6) δ = 10.16 (s, 1H), 8.66–8.58 (m, 1H), 8.33 (dd, J = 8.2, 1.4 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 4.64 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D_6) δ = 163.6, 147.8, 134.7, 133.2, 130.1, 125.7, 121.8.

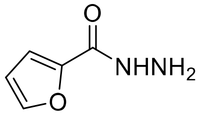
4.5.18. 2-Chlorobenzohydrazide (2r)



(**2r**)

The title compound was obtained as a white solid. M.p. 121 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R_f = 0.45; Yield 78% (67 mg). **^{1}H NMR** (500 MHz, DMSO-D_6) δ = 9.58 (s, 1H), 7.51–7.47 (m, 1H), 7.44 (ddd, J = 8.0, 5.7, 3.4 Hz, 1H), 7.40–7.37 (m, 2H), 4.51 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D_6) δ = 165.7, 135.6, 130.9, 130.3, 129.6, 129.1, 127.0.

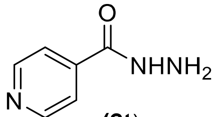
4.5.19. Furan-2-carbohydrazide (2s)



(**2s**)

The title compound was obtained as a white solid. M.p. 78 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R_f = 0.48; Yield 88% (56 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$ δ = 7.98–7.96 (m, 2H), 7.54 (dd, J = 10.6, 4.2 Hz, 1H), 7.44–7.41 (m, 4H), 7.37–7.34 (m, 2H), 7.32–7.29 (m, 1H), 5.62 (s, 1H), 4.27–4.19 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, DMSO-D6) δ = 193.2, 168.8, 135.7, 133.4, 133.00, 129.5, 128.8, 128.7, 128.6, 128.0, 61.7, 60.5, 13.9.

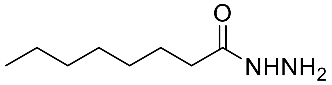
4.5.20. Isonicotinohydrazide (2t)



(2t)

The title compound was obtained as a white solid. M.p. 172 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R$_f$ = 0.28; Yield 87% (60 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 10.11 (s, 1H), 8.78–8.64 (m, 2H), 7.81–7.69 (m, 2H), 4.65 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 163.9, 150.2, 140.3, 121.0.

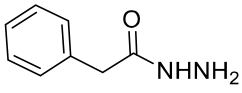
4.5.21. Octanehydrazide (4a)



(**4a**)

The title compound was obtained as a white solid. M.p. 88 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R$_f$ = 0.33; Yield 91% (79 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 8.93 (s, 1H), 4.13 (s, 2H), 1.99 (t, J = 7.5 Hz, 2H), 1.47 (dd, J = 14.2, 7.2 Hz, 2H), 1.30–1.15 (m, 8H), 0.84 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 171.7, 33.4, 31.2, 28.7, 28.5, 25.3, 22.1, 13.9.

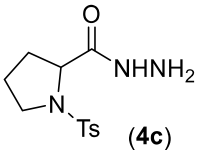
4.5.22. 2-Phenylacetohydrazide (4b)



(**4b**)

The title compound was obtained as a white solid. M.p. 228 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), R$_f$ = 0.50; Yield 90% (68 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ = 9.23 (s, 1H), 7.31–7.23 (m, 4H), 7.23–7.19 (m, 1H), 4.24 (s, 2H), 3.34 (s, 2H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 169.5, 136.2, 128.9, 128.1, 126.3, 40.4.

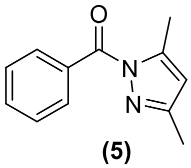
4.5.23. 1-Tosylpyrrolidine-2-carbohydrazide (4c)



(**4c**)

The title compound was obtained as a white solid. M.p. 69.8−71.6 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R$_f$ = 0.60; Yield 76% (108 mg). **^{1}H NMR** (500 MHz, DMSO-D$_6$) δ 9.20 (s, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 4.46–4.12 (m, 2H), 3.98 (dd, J = 8.5, 3.9 Hz, 1H), 3.54–3.27 (m, 2H), 3.17–3.04 (m, 1H), 2.38 (s, 3H), 1.84–1.70 (m, 2H), 1.65–1.55 (m, 1H), 1.48–1.39 (m, 1H). **^{13}C NMR** (125 MHz, DMSO-D$_6$) δ = 170.3, 143.5, 133.9, 129.8, 127.4, 60.2, 49.0, 30.6, 24.1, 21.0.

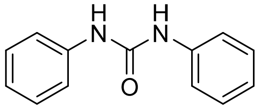
4.5.24. (3,5-Dimethyl-1H-pyrazol-1-yl)(phenyl)methanone (5)



(5)

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R$_f$ = 0.60; Yield 90% (91 mg). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 8.02–7.94 (m, 2H), 7.59–7.53 (m, 1H), 7.49–7.43 (m, 2H), 6.06 (s, 1H), 2.64 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (125 MHz, CDCl$_3$) δ = 168.4, 152.1, 145.0, 133.3, 132.3, 131.3, 127.8, 111.0, 14.2, 13.8.

4.5.25. 1,3-Diphenylurea (6)



(6)

The title compound was obtained as a white solid. M.p. 262 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (20:80), $R_f = 0.20$; Yield 80% (85 mg). **^{1}H NMR** (500 MHz, DMSO-D_6) $\delta = 8.64$ (s, 1H), 7.45 (dd, $J = 8.5$, 1.0 Hz, 2H), 7.32–7.22 (m, 2H), 7.01–6.87 (m, 1H). **^{13}C NMR** (125 MHz, DMSO-D_6) $\delta = 152.5$, 139.7, 128.8, 121.8, 118.2.

4.6 Spectral data of few products:

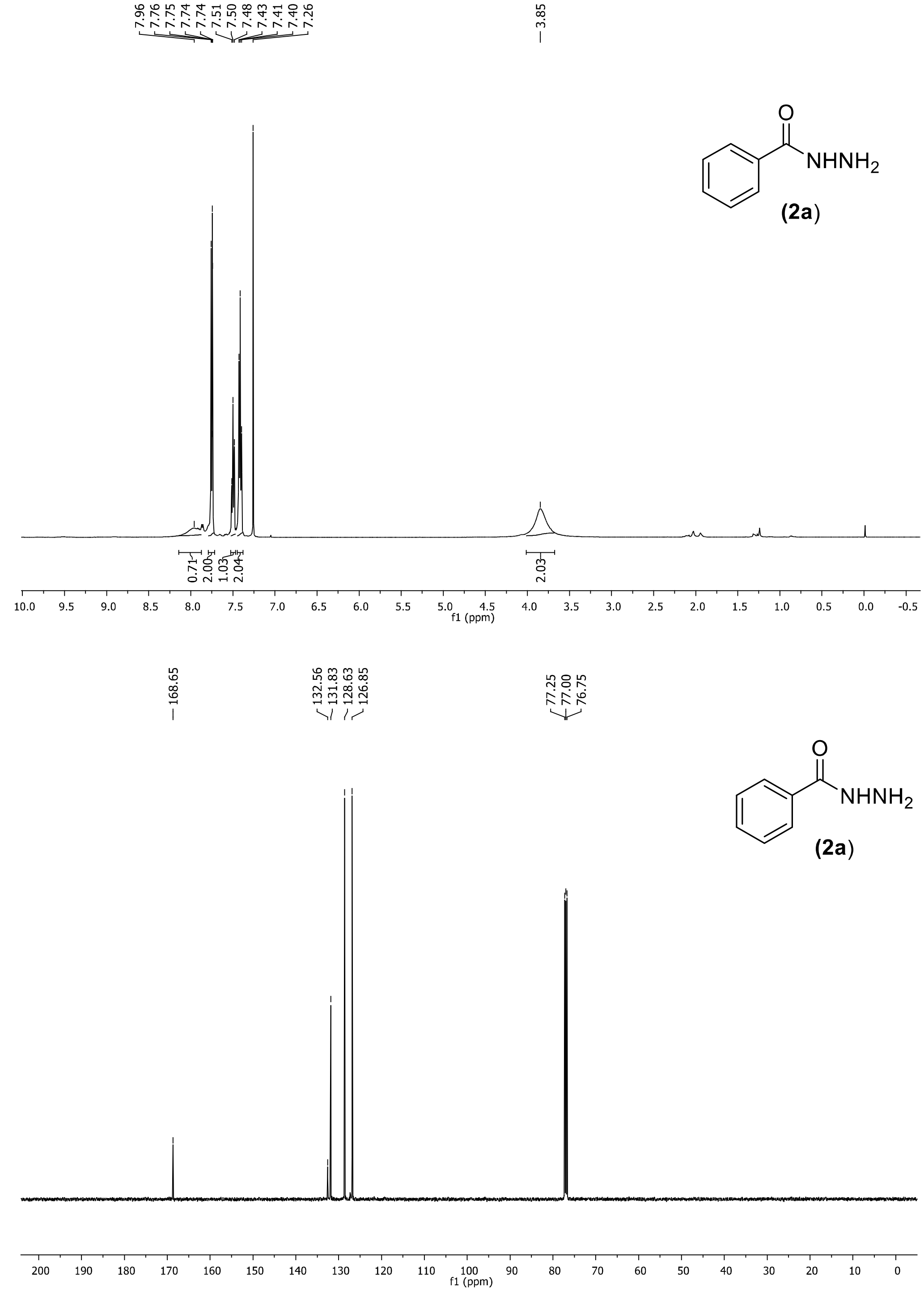


Figure 4.2 ^{1}H and ^{13}C NMR of product **2a** in **$CDCl_3$.**

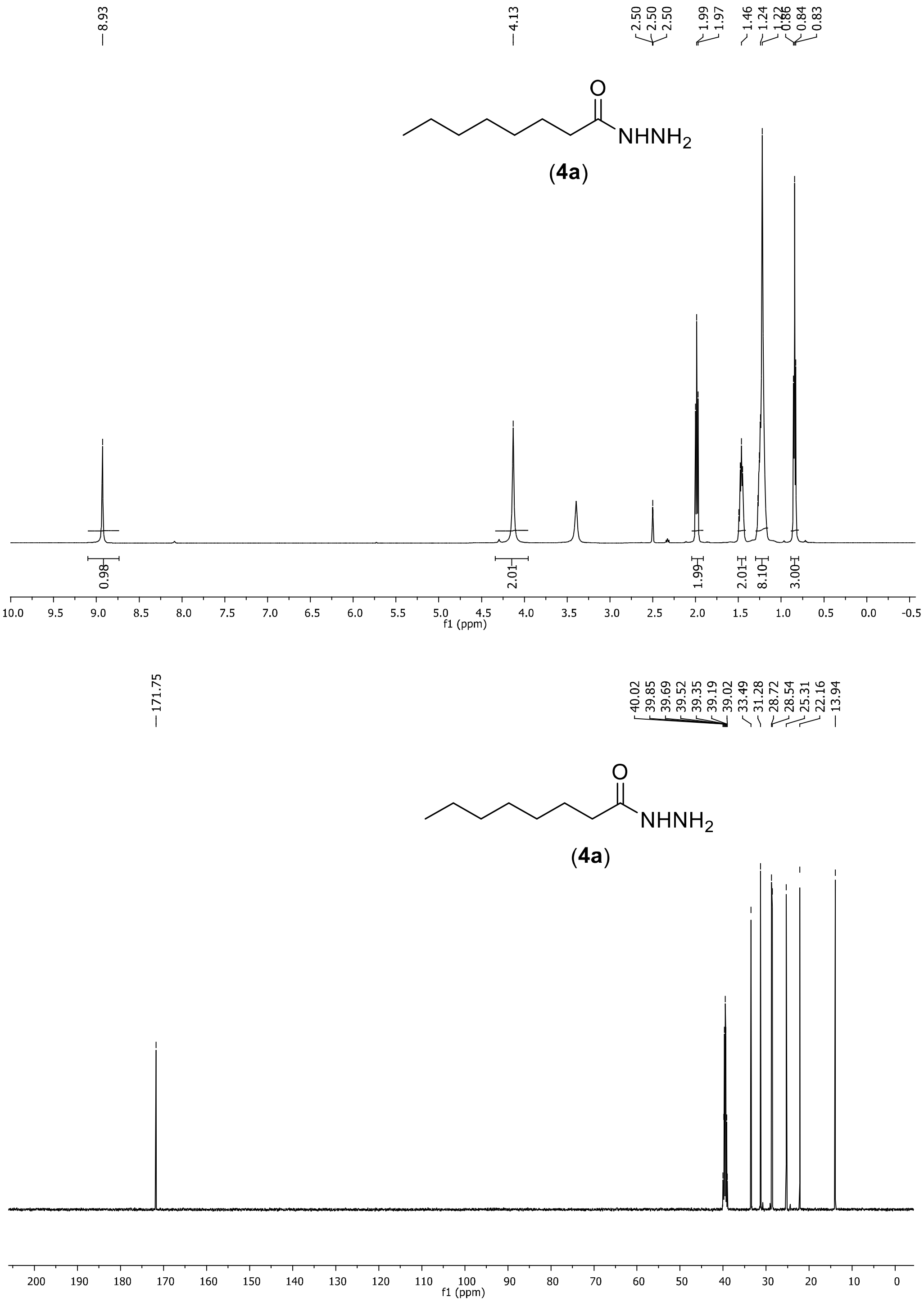


Figure 4.3 ^{1}H and ^{13}C NMR of product **4a** in **DMSO-D6.**

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