Zurich University of Applied Sciences

Departement N

Practical Organic Chemistry

HS12-G15

Synthesis of 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide

and 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide

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Dozent:

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Summary:

The synthesis and, if applicable, structural analysis of 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**4**) and 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**5**) via 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (**3**) are presented in this paper. 2.62 g (9.33 mmol) clean **3** - proven by ^{1}H-NMR - were obtained, resulting in a yield of 87%. Reaction of **3** to **4** via thionyl chloride was carried out and yielded no product, while synthesis in presence of TBTU and triethylamine successfully formed an amide bond. This resulted in 0.3 g (0.75 mmol) **4** with a yield of 53%. The purity and correct structure of **4** was proven by LC-MS, ^{1}H-NMR and ^{13}C-NMR. **5** could not be synthesised because of limited time resources but could easily be prepared according to **4** as no relevant chemical difference is present in the molecules.

Zusammenfassung:

Die Synthese und, insofern anwendbar, strukturellen Analysen von 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**4**) und 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**5**) über 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (**3**) werden in dieser Arbeit präsentiert. 2.62 g (9.33 mmol) - wie mittels ^{1}H-NMR bewiesen wurde - sauberes **3** wurden gewonnen, was einer Ausbeute von 87% entspricht. Die Reaktion von **3** zu **4** über Thionylchlorid wurde ausgeführt, führte jedoch zu keinem verwertbaren Endprodukt, während die Synthese in Gegenwart von TBTU und Triethylamin zur erfolgreichen Ausbildung einer Aminbindung führte. Dies resultierte in 0.3 g (0.75 mmol) **4** mit einer Ausbeute von 53%. Die Reinheit und korrekte Struktur von **4** wurde durch LC-MS, ^{1}H-NMR und ^{13}C-NMR bewiesen. **5** konnte aufgrund der limitierten, verfügbaren Zeit nicht hergestellt werden. Dies sollte jedoch problemlos entsprechend zu **4** möglich sein, da die beiden Moleküle keinerlei essentiellen, chemischen Unterschiede aufweisen.

Contents

1. Assignment of Tasks

1.1. Complete Graphical Reaction Overview

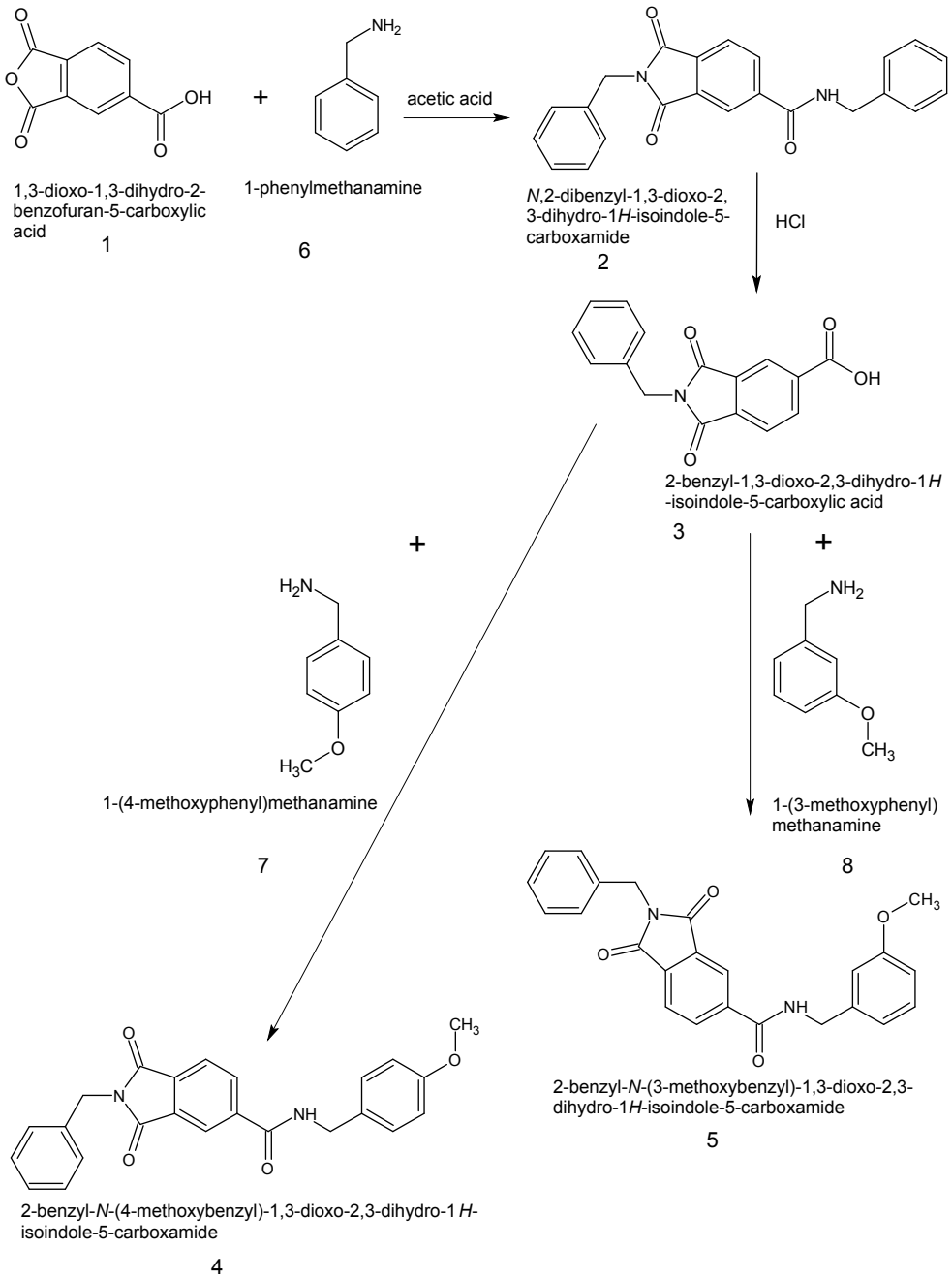
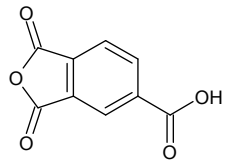
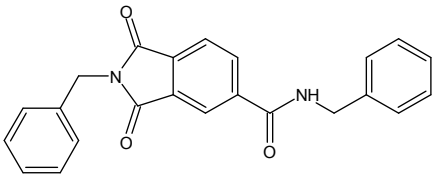
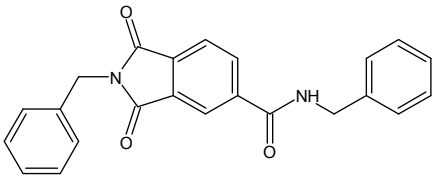
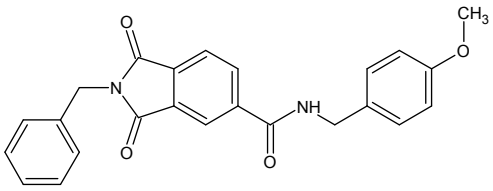
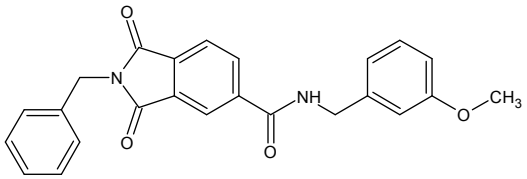
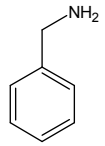
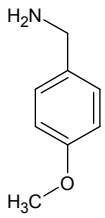
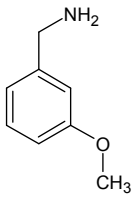


Figure 1.1. – *Complete Overview of Reaction Path*

1.2. Main Compounds

Compound	Compound Number Internal Systematic Number Name
	**1** HS12-G15-1 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid
	**2** HS12-G15-2 N,2-dibenzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide
	**3** HS12-G15-3 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid
	**4** HS12-G15-4 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide
	**5** HS12-G15-5 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide

Compound	Compound Number Internal Systematic Number Name
	**6** 1-phenylmethanamine
	**7** 1-(4-methoxyphenyl)methanamine
	**8** 1-(3-methoxyphenyl)methanamine

1.3. Objective

The objective of the task at hand was to synthesise the above shown compounds **4** (2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide) and **5** (2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide) with high purity. To accomplish the said task, a closer look at the mechanisms of the involved reactions as presented in Chapter 2 on page 8 was to be made and the desired approach to be laid out according to Chapter 3 on page 13. The reactions, carried out according to allotted papers, were to be observed by adequate analytical means, recorded in writing as it has been done in Chapter 4 on page 14 and the thereby synthesised compounds be analysed by means of purity and structural determination.

2. Theoretical Part [1]

2.1. First Step - (1 → 2 → 3)

To allow for a clearer arrangement, the reactions taking place to convert **1** to **2** shall be presented in two separate mechanisms. The former results in **3** directly, while the second shows the additional reaction that results in formation of **2**. Finally, the third shows how possibly formed **2** is transformed into the desired **3**.

2.1.1. Nucleophilic Acyl Substitution - (1 → 3)

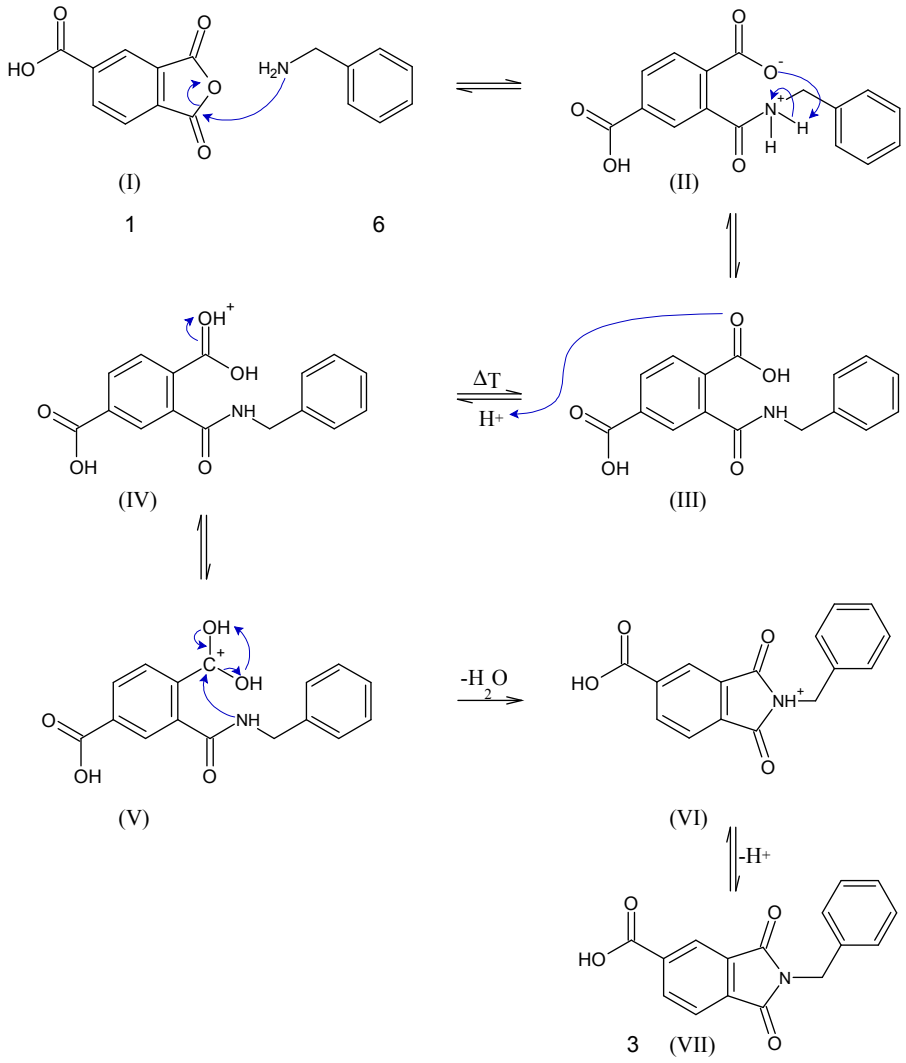


Figure 2.1. – *Nucleophilic Acyl Substitution: Mechanism for the Reaction of 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid (**1**) to 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (**3**)*

According to Figure 2.1 on page 8, one of the carbonyl groups C-atoms is attacked by the nitrogen of **6** under acidic conditions (I), forming (II) and by donation of a hydrogen-atom of the amine group stabilizing to (III). Under additional heating, the formed carboxylic acid is protonated to form the oxonium ion shown in (IV). Following this, water is driven off (V), locating the positive charge on the C-atom while once again forming a carbonyl group and at the same time being attacked by the nitrogen forming the ring as shown in (VI). Lastly, **3** is formed by deprotonation.

2.1.2. Amid Bond by Dehydration - (1 → 2[1])

As mentioned above, Figure 2.2 on page 9 shows the reaction happening parallelly to the former, described in Section 2.1.1 on page 8 resulting in undesired **2**.

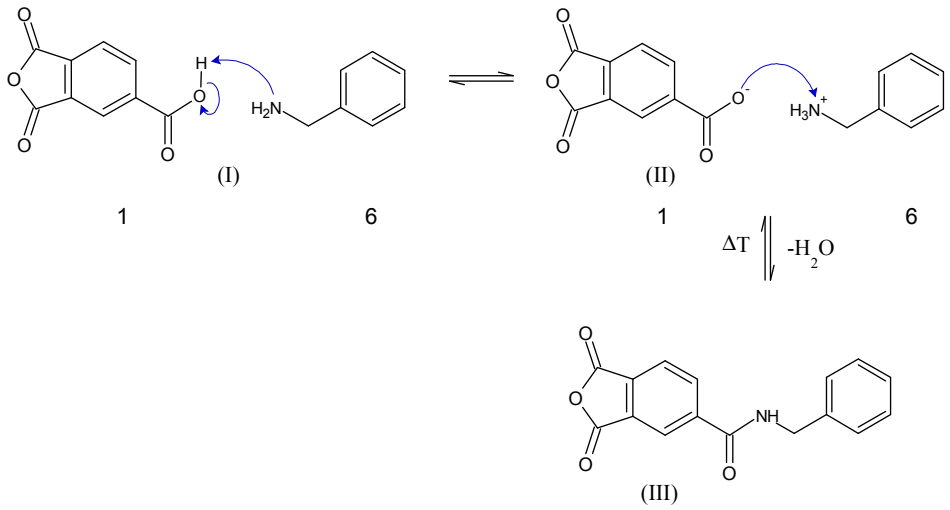


Figure 2.2. – *Amid Bond by Dehydration: Mechanism for the Reaction of 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid (**1**) to N,2-dibenzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**2**)*[1]

Figure 2.2 on page 9 shows the protonation of the amine by the carboxylic acid (I), followed by the formation of a new amid bond (III) by driving off water (II).

2.1.3. Hydrolysis of Amides Under Acidic Conditions - (2 → 3)

To convert potentially accumulated **2** to the desired final product **3** the following reaction is performed. Figure 2.3 on page 10 describes the reverse of Section 2.1.2 on page 9, forming a carboxylic acid and an amine. By protonation (I), the amid bond is activated for hydrolysis (II). The waters hydroxyl group now forms part of the carboxylic acid (IV) while the amine gains the hydrogen ion (III). Steps (V) and (VI) finalise the reaction, resulting in **3**.

2.2. Second Step - (3 → 4 respectively 3 → 5)

The following steps are true for the formation of both **4** and **5** shown by delocalized methoxy groups in Figure 2.5 on page 12 and Figure 2.6 on page 12. Two alternative reaction pathways - Section 2.2.1 on page 10 and Section 2.2.2 on page 10 or Section 2.2.3 on page 10 - are shown.

[1] Additional reaction according to Section 2.1.1 on page 8 anticipated

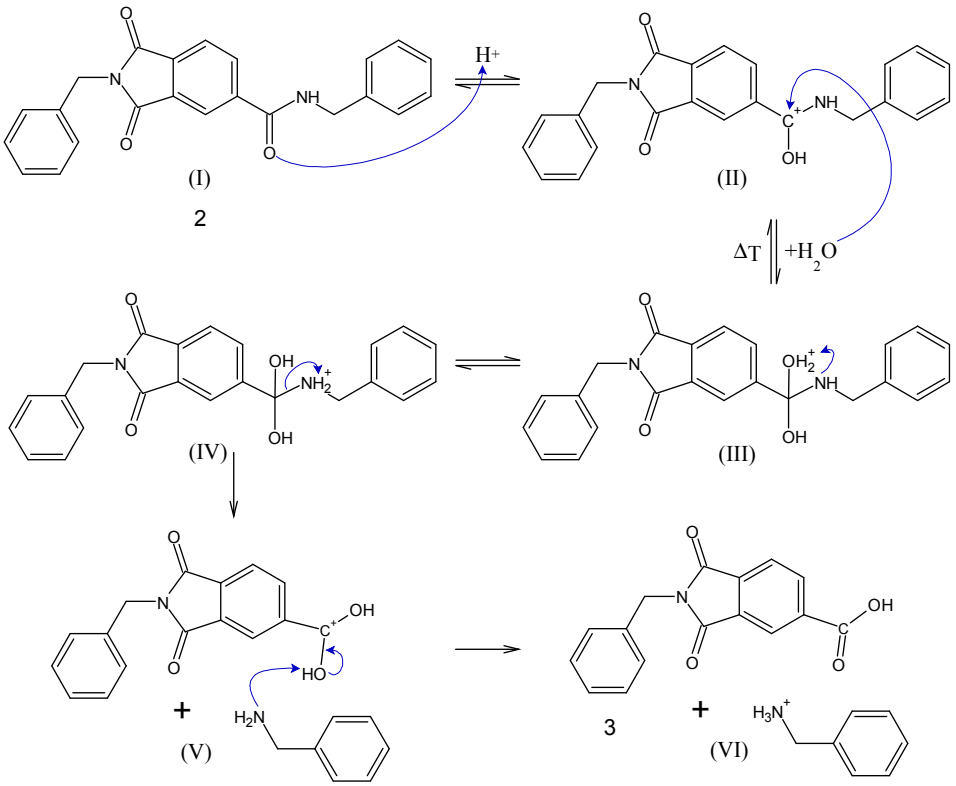


Figure 2.3. – *Hydrolysis of Amides Under Acidic Conditions: Mechanism for the Reaction of N,2-dibenzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**2**) to 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (**3**)*

2.2.1. Acid Chloride Formation - Thionyl Chloride

As shown in Figure 2.4 on page 11, thionyl chloride bonds with the carboxylic acid under abstraction of Cl^- (I) and H^+ (II) forming gaseous hydrogen chloride, leaving the reaction and forming **3-thionyl chloride** (III). Alternatively, the free chloride ion attacks at the C-atom as indicated in (IV) and abstraction of gaseous hydrogen chloride and sulfur dioxide (V), leaving the reaction and thereby driving the reaction toward the acid chloride (VI).

2.2.2. Nucleophilic Addition of Amine under Elimination of Hydrogen Chloride

Figure 2.5 on page 12 shows the nucleophilic addition (I) of **7** respectively **8** to the acid chloride (II). By abstraction of Cl^- (III) and H^+ (IV) gaseous hydrogen chloride is driven off, resulting in the final product **4**, respectively **5**.

2.2.3. Amine Bond by Coupling Reaction Under Basic Conditions

The mentioned Figure 2.6 on page 12 shows an alternative route of synthesis to the above pathway via thionyl chloride. As shown in Figure 2.6 on page 12 the amine is deprotonated by triethylamine while the carboxylic acid looses its hydroxyl group to TBTU, resulting in the coupling of both, yielding the final product **4**, respectively **5**.

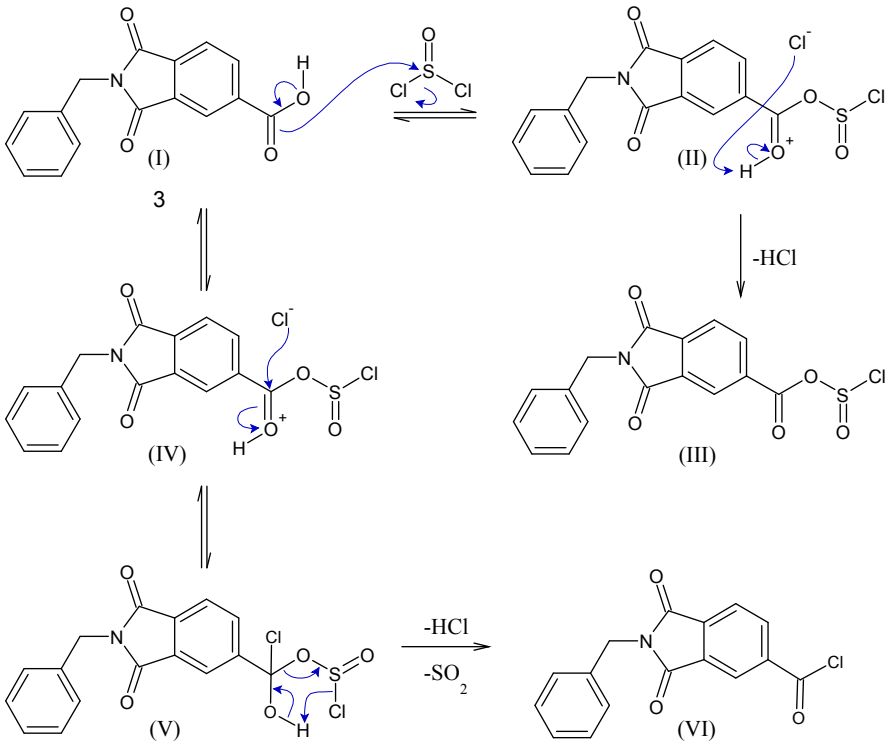


Figure 2.4. – *Acid Chloride Formation: Mechanism for the Reaction of 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (**3**) to the Thionyl Chloride*

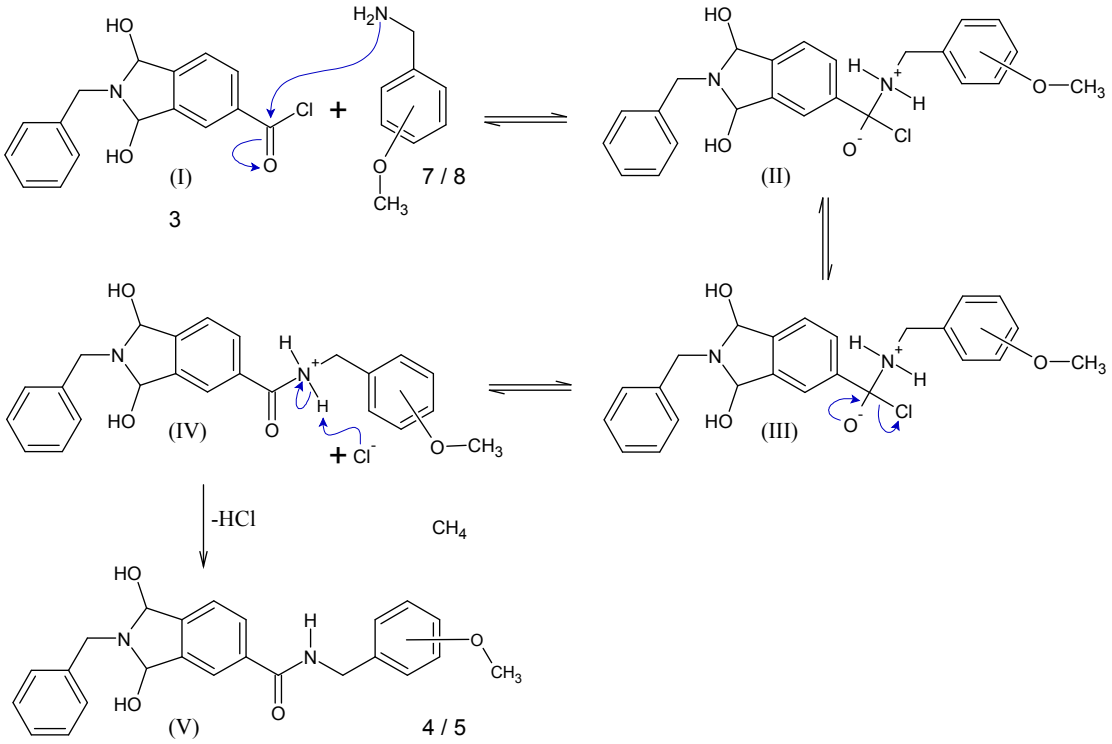


Figure 2.5. – *Nucleophilic Addition of Amine under Elimination of Hydrogen Chloride: Mechanism for the Reaction of the Thionyl Chloride to 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**4**) respectively 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**5**)*

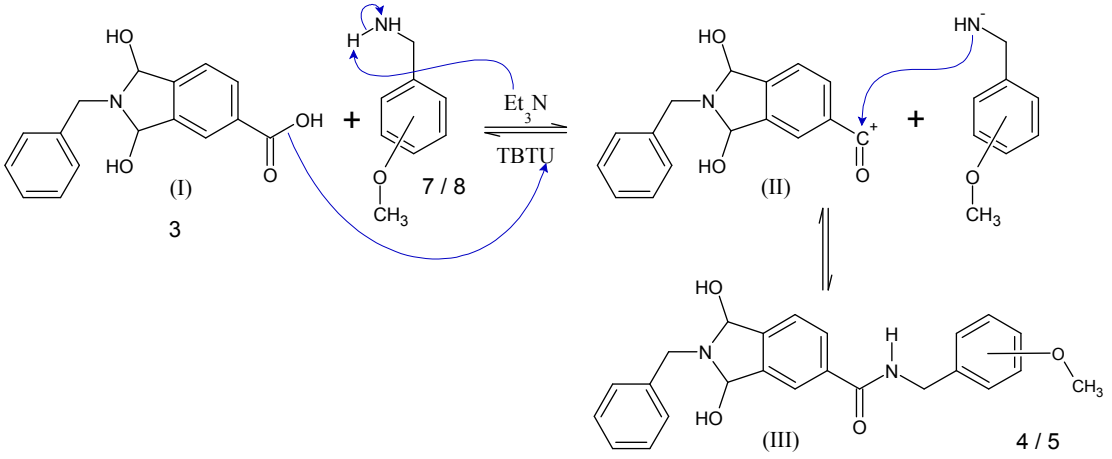


Figure 2.6. – *Amine Bond by Coupling Reaction Under Basic Conditions: Mechanism for the Reaction of **3** to 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**4**) respectively 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (**5**)*

3. Concept and Strategy

3.1. Concept

The assigned task may be divided into three major parts:

- synthesis of **3** via **2**
- synthesis of **4** from **3**
- synthesis of **5** from **3**

As **3** forms the basic intermediate for both **4** and **5**, it first needs te be obtained in adequate mass and quality. Accumulation of **2** is of little interest but shall be given a shot nevertheless.

3.2. Time Management

Upon receipt of the project and overall orientation, the following timetable was set up as basic guideline:

week 1: first day at Laboratory; orientation, information and incorporation; pilot test: synthesis of **3**
week 2: Synthesis of **3**; method enhancements
week 3: reprocessing; pilot test for **4**
week 4: Synthesis of **4**; pilot test for **5**
week 5: reprocessing; Synthesis of **5**
week 6: reprocessing; Analysis
week 7: completion; cleaning, tidy up; reserve

As the first tries at synthesis of **3** via thionyl chloride proved to be futile, an alternative method had to be found. Conclusively, extended trials for **3** were carried out, thus setting back the timetable. For further elaborations, please refer to Chapter 5 on page 15

4. Procedure and Accomplishments

4.1. 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (3)

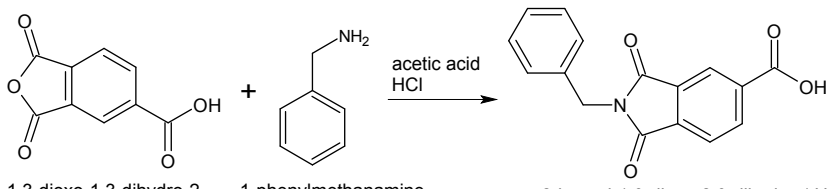


Figure 4.1. – *Schematic of the synthesis of compound **1** to **3***

Synthesis The reaction was made the same as described in [2]. 1.0 eq **1** was suspended in 25 vol acetic acid and 2.0 eq **6** added. The mixture was stirred over 2 hours at reflux. The resulting solution was concentration and the residue solid was solved in 25 vol hot acetic acid and 10% HCl solution was added. The resulting suspension was stirred over 30 min at reflux and the cooled suspension was filtered and dried to give **3**.

4.2. 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide (4)

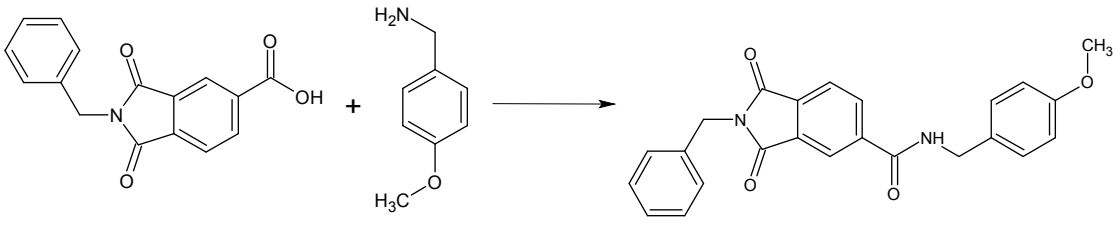


Figure 4.2. – *Schematic of the synthesis of compound **3** to **4***

Synthesis The reaction was made the same as described in [3]. 20 vol DCM, 1.1 eq TBTU and 1.5 eq **7** were stirred for 10 min while the solution became yellowish. 1.0 eq **3** and 3 vol triethylamine was addet to solve the suspension and rise the pH to 9. The solution was extracted with each 3 times 20 vol citric acid, $NaHCO_3$ solution and NaCl solution. The OP was dried with Na_2SO_4, concentrated on the rotary evaporator and the solid crude 1#1 was rectify by flash chromatography (solvent: EA : triethylamine : cyclohexane (49.5 : 1 : 49.5); stationary phase: silica gel, approx. 20 cm) to give **4**.

5. Discussion and Results

5.1. Isolation of 2

As stated in Chapter 3 on page 13, accumulation of **2** is of little practical interest. Nevertheless, it was given a try. Reactions according to Section 2.1.1 on page 8 and Section 2.1.2 on page 9 were carried out as shown in Section 7.5 on page 19. As exemplified in the corresponding section, apparently **2** was not formed to begin with. However, **2** could simply be synthesised by the same means as **4** respectively **5**. The matter was not taken any further as more pressing issues were at hand.

5.2. Synthesis of 3

Synthesis of **3** proved to be simple and stable and posed no obstacles worth mentioning. No additional purification was needed to obtain satisfactorily clean product as proven by ^{1}H-NMR. Via Synthesis as described in Section 7.6 on page 19 and filtering of the product, an acceptable yield of 87% was accomplished.

5.3. Synthesis of 4

5.3.1. Via Acid Chloride (Thionyl Chloride)

The initial synthesis via thionyl chloride seemed promising at first but yielded in no traceable **4** (reaction path to **5** has not been conducted as results for both pathways are comparable). To improve understanding of the reaction, the acid chloride was to be isolated. As not even this basic step could be satisfyingly carried out, the method was dismissed.

5.3.2. By Coupling Reaction Under Basic Conditions

Once the thionyl chloride - pathway had been written of, the synthesis according to [3] was taken as new main route. The initial colouration of the solution as described in Section 4.2 on page 14 was regarded with some suspicion, but seemed to be inevitable and unproblematic. Some product was lost to the aqueous phase during extraction and might be recoverable by concentration and secondary extraction. Conclusively, the yield of about 53% should be improvable but is satisfactory after all.

5.4. Synthesis of 5

After failing the initial trials with thionyl chloride, main focus laid on elaboration of the basic reaction pathway on the example of **4** to be applicable to **5** when proven to be effectively working. However, the timetable allowed for either the purification of crude **4** or synthesis of additional crude **5**. The finalisation of **4** was given priority over obtaining another crude product that would have needed further purification.

6. Future Prospects

6.1. Optimization of Step 1 to 3

Step **1** to **3** has been made as described in [2] and no problems showed up. Only **2** was neither synthesised nor isolated during the reaction. This is not necessary for the process but it might be interesting to isolate the substance as well as to carry out basic analysis and identification or at least to measure a spectra. This step could be realised as the synthesise of **2** from **3** the same way **4** was synthesised.

6.2. Optimization of Step 3 to 4

It is not unclear if all the extractions are really necessary or if some of them might be optional. Less extraction steps might raise the yield of as little as 53%. This might be an option as a flash chromatography is made in the end anyway. With this purification method, salts which have to be extracted, can been separated because of their polarity and the consequential bad elution during chromatography. It is probably also possible to optimize the extractions to omit the flash chromatography.
If possible, the reactant **7** might be purified and the contamination should be identified. This could raise the final yield just as well.

6.3. Optimization of Step 3 to 5

This step was not realised bud should be an easygoing, based of step **3** to **4**. The final molecules **4** and **5** are nearly the same and the meta position of the methoxy group should make no difference for the reaction opposing to the para position.

7. Experimental Part

7.1. Chemicals

The list of chemicals and all essential details are list in C.1.

7.2. Waste Management

All solvents or solutions were thrown in a waste canister. Halogenated compounds were separate collected. The glass equipment was cleaned with acetone and ethanol. Solid waste was stored in a container.

7.3. General Experimental Condition

All syntheses were carried out under a nitrogen or argon atmosphere. If necessary was the cooling water switched on and a reflux condenser used.

Equipment

Table 7.1. – *List of equipment used during the laboratory work*

Equipment	Type
Water cooling system for rotary evaporator condenser	huber Unichiller UC055w-1 spez
Rotary evaporator with vacuum pump and water bath	varying models, Büchi
Vacuum pump for house vacuum	vacuubrand PC8 MD 12C
Vacuum drying cabinet	Heraeus vacutherm
Magnetic stirrer with integrated heat plate	IKA Labortechnik RCT basic
Oil bath temperature controlling system	IKA Labortechnik ETS-D4 fuzzy
Balance	Mettler Toledo PB3002
Analytical balance	Mettler AE 160
Diverse glass equipment	SCHOTT Duran

7.4. Analytical Methods

Thin layer chromatography (TLC)

TLC's were mostly made as a pilot test to find the best conditions for a flash chromatography. The exact conditions for each step are shown in the following sections. The plates were silica gel on aluminium 4 x 8 cm.

Nuclear magnetic resonance spectroscopy (NMR)

For the measurement of the ^{1}H-NMR and ^{13}C-NMR was a 300 MHz nuclear magnetic resonance spectrometer by Bruker used.

Liquid chromatography - mass spectra (LC-MS)

The used mass spectrometer by Agilent was coupled with a liquid chromatograph, 1100 Series by Agilent Technologies. The used eluents and method are described in Table 7.2 on page 18 respectively Table 7.3 on page 18.

HPLC Column	Reverse Phase, Uptisphere Strategy C18-2, 5 μm 4.6 x 250 mm
Wavelength	254 nm or 280 nm, DAD detector
HPLC Apparatus Type	Agilent 1100 Series
MS Apparatus Type	Agilent MSD Trap XCT positive/negative mode switching, Ionization mode APCI
Column temperature	40°C

Table 7.2. – *Eluents as Used in the Method to Obtain Liquid Chromatography - Separated Mass Spectra as Specified in Table 7.3 on page 18*

Eluent type	water /%	methanol /%	acetic acid /%
A	94.8	5	0.2
B	5	94.8	0.2

Table 7.3. – *Method to Obtain Liquid Chromatography - Separated Mass Spectra with Eluents as Specified in Table 7.2 on page 18*

Zeit	Laufmittel		Fliessgeschwindigkeit
/min	/%	type	/ml/min
00:00	100	A	1
10:00	100	B	1
18:00	100	B	1
18:10	100	A	1
20:00	100	A	1

7.5. N,2-dibenzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide

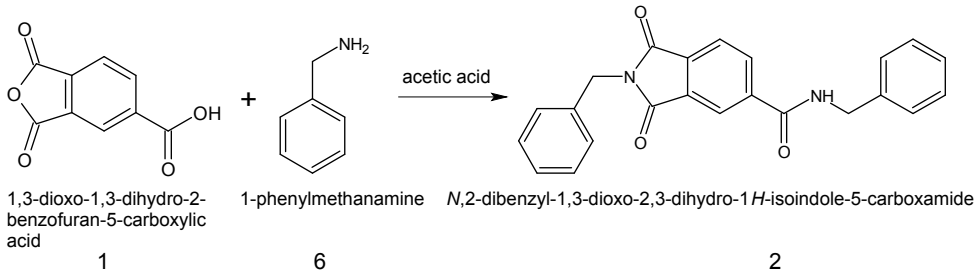


Figure 7.1. – *Schematic of the synthesis of compound **1** to **2***

The synthesis of **2** was tried, but it was found that the amid bound is not composed and **2** was not specific isolated or purified. Step 1 and 2 were combined to a single step to skip the purification of compound **2**. It may be possible to synthesize **2** back from **3** with the same reaction as **4** and **5** will be synthesized.

7.6. 2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

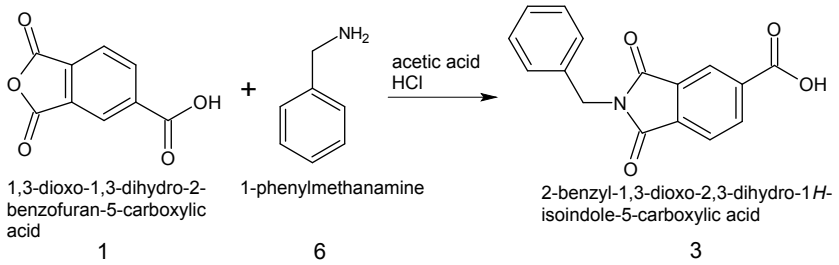


Figure 7.2. – *Synthetic schema of step 1 and 2 form **1** to **3***

Synthesis

2.05 g of **1** (10.7 mmol) was suspended in 50 mL acetic acid in a two neck flask and 2.33 g of **6** (21.3 mmol) was added under light exothermic reaction and solving the suspension. The mixture was stirred over 2 hours at reflux (140 °C). The resulting solution was concentration on the rotary evaporator. The residue solid was solved in 50 mL hot (80 °C) acetic acid in a round-bottom flask and 25 mL 10% HCl solution was added. The resulting suspension was stirred over 30 min at reflux (120 °C). The cooled suspension was filtered through a sinter glass disc büchner funnel, washed with 2 x 5 mL cold acetic acid and dried to give **3** as a white solid (2.62 g; 9.33 mmol; yield: 87%).

TLC

As mobile phase was a mixture of EA, cyclohexane and acetic acid in a ratio of 2 to 1 to 0.3. The substance **3** has a rf value of 0.77, **1** has a rf value of 0.69 and **6** has a rf value of 0.23.

NMR

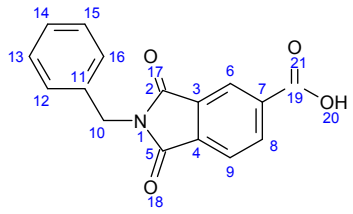
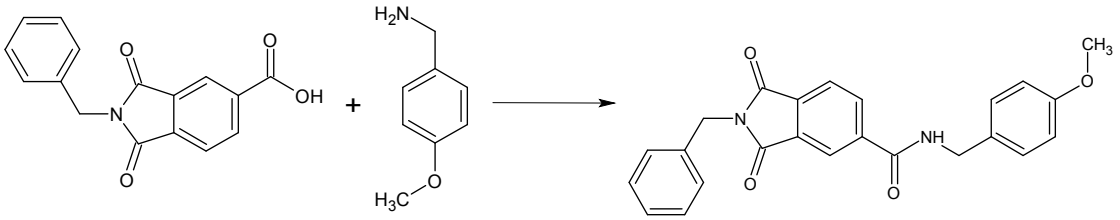


Figure 7.3. – *Arbitrarily numbered molecule* ***3***

^{1}H-NMR (DMSO): δ = 13.71 (s, -COO*H*, 1H), 8.37 (dd, $^{9}J_{H(C8)H(C9)}$ = 7.8 Hz, $^{8}J_{H(C8)H(C6)}$ = 1.4 Hz, C(8)-*H*, 1H), 8.25 (dd, $^{8}J_{H(C6)H(C8)}$ = 1.4 Hz, $^{6}J_{H(C6)H(C9)}$ = 0 Hz, C(6)-*H*, 1H), 8.01 (d, $^{9}J_{H(C9)H(C8)}$ = 7.8 Hz, C(9)-*H*, 1H), 7.34 - 7.25 (m, C(12)-*H*, C(13)-*H*, C(14)-*H*, C(15)-*H*, C(16)-*H*, 5H), 4.80 (s, C(10)-*H*, 2H)

^{13}C-NMR (DMSO): δ = 166.94 (C(2)), 166.91 (C(5)), 165.75 (C(19)), 136.38 (C(3)), 136.30 (C(4)), 135.43 (CH(8)), 134.86 (C(11)), 132.01 (C(7)), 128.54 (2xCH(12, 16)), 127.43 (3xCH(13, 14, 15)), 123.57 (CH(9)), 123.18 (CH(6)), 41.08 (CH_2(10))

7.7. 2-benzyl-N-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide



2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid
3

1-(4-methoxyphenyl) methanamine
7

2-benzyl-*N*-(4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxamide
4

Figure 7.4. – *Synthetic schema of step 3 form* ***3*** *to* ***4***

Synthesis

8 mL DCM, 0.4 g TBTU (1.54 mmol) and 0.3 g **7** (2.1 mmol) were mixed in a 25 mL round-bottom flask and stirred for 10 min while the solution became yellowish. 0.4 g of **3** (1.4 mmol) was added under precipitation of a few solid. 0.3 mL triethylamine was added to solve the suspension and 0.5 mL triethylamine was added to rise the pH up to 9. The solution was extracted in a separatory funnel with each 3 times 8 mL citric acid, $NaHCO_3$ solution and NaCl solution. The OP was dried with Na_2SO_4 and concentrated on the rotary evaporator. The solid crude 1#1 was rectify by flash chromatography (solvent: EA : triethylamine : cyclohexane (49.5 : 1 : 49.5); stationary phase: silica gel, approx. 20 cm) to give **4** as a white solid (0.3 g; 0.75 mmol; yield: 53%).

TLC

As mobile phase was tasted a mixture of EA and triethylamine in a ratio of 99 to 1. This shows good results in the beginning but it was found, that product **4** has the same rf value as **7** (0.79) and the accidentally as product interpreted spot (rf = 5.7) is only a by-product.
Finaly was as mobile phase a mixture of cyclohexane, triethylamine and EA taken in a ratio of 49.5 to 1 to 49.5. The substance **4** has a rf value of 0.53, **7** has a rf value of 0.75 and the by-product has a rf value of 0.69.

NMR

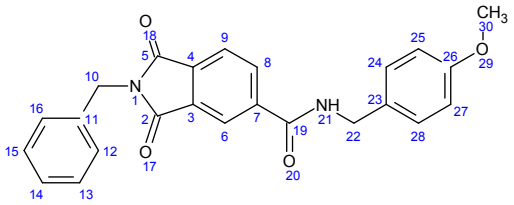


Figure 7.5. – *Arbitrarily numbered molecule* ***4***

^{1}H-NMR (DMSO): δ = 9.37 (t, $^{22}J_{H(N21)H(C22)}$ = 5.7 Hz, -N*H*, 1H), 8.37 (s, C(6)-*H*, 1H), 8.33 (dd, $^{9}J_{H(C8)H(C9)}$ = 7.8 Hz, $^{8}J_{H(C8)H(C6)}$ = 1.4 Hz, C(8)-*H*, 1H), 8.00 (d, $^{9}J_{H(C9)H(C8)}$ = 7.8 Hz, C(9)-*H*, 1H), 7.37 - 7.28 (m, C(12)-*H*, C(13)-*H*, C(14)-*H*, C(15)-*H*, C(16)-*H*, 5H), 7.30 - 7.24 (m, C(28)-*H*, C(24)-*H*, 2H), 6.93 - 6.84 (m, C(27)-*H*, C(25)-*H*, 2H), 4.79 (s, C(10)-*H*, 2H), 4.44 (d, $^{21}J_{H(C22)H(N21)}$ = 5.8 Hz, C(22)-*H*, 2H), 3.73 (s, C(30)-*H*, 3H)

^{13}C-NMR (DMSO): δ = 167.21 (C(5)), 167.14 (C(2)), 164.22 (C(19), 158.27 (C(26)), 139.72 (C(7)), 136.48 (C(4)), 133.75 (CH_2(8)), 133.57 (C(11)), 131.86 (C(3)), 131.04 (C(23)), 128.73 (2xCH(12, 16)), 128.55 (3xCH(13, 14, 15)), 127.35 (4xCH(24, 25, 26, 27)), 123.39 (CH(9)), 121.57 (CH(6)), 113.70 (C(26)), 55.03 (CH_3(30)), 42.37 (CH_2(22)), 41.02 (CH_2(10)),

LC-MS

The mass spectra shows the product as anticipated with 401.0 m/z and the according fragments at 91.3 m/z, 121.2 m/z and 264.0 m/z.

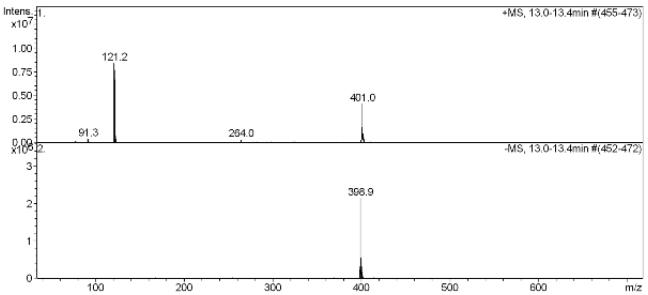
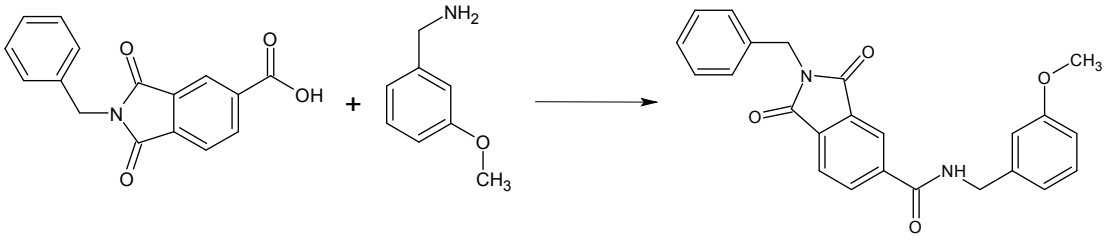


Figure 7.6. – *Mass Spectra of* ***4****, run according to Section 7.4 on page 18, for further details please refer to Appendix B on page 41*

7.8. 2-benzyl-N-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxamide



2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid
3

1-(3-methoxyphenyl) methanamine
8

2-benzyl-*N*-(3-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxamide
5

Figure 7.7. – *Synthetic schema of step 3 form **3** to **5***

4 mL DCM, 0.25 g TBTU (0.78 mmol) and 0.16 g **7** (0.78 mmol) were mixed in a 25 mL round-bottom flask and stirred for 15 min while the solution became yellowish. 0.2 g of **3** (0.7 mmol) was added under precipitation of a few solid. 0.3 mL triethylamine was added and white solid precipitate. 5 mL HCl 1M and 4 mL DCM were added and the suspension was filtrated and dried on the rotary evaporator and a ^{1}H-NMR spectra was measured. The NMR shows only a few percentage of **5** in the solid. The solid was purified with a flash chromatography but as mobile phase was a mixture of EA and cyclohexane in a ratio of 2 to 1 chosen, which shows the same problem as described in 7.7, TLC. The material was not isolated.

Reactants

7.9. 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid

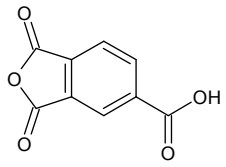


Figure 7.8. – *Compound **1***

A ^{1}H-NMR spectra was made as a reference for step 1 and 2 to see, if any **1** is left in the product. The NMR shows a heavily contaminated spectra. At least 30% of the integrals in the aromatic area are clearly not part of the compound **1**. A flat, wide signal at 3.35 ppm was identified as water, which is explaining the DMSO quintet at 2.5 ppm. A closer look to the molecule **1** shows the functional group anhydride which is insecure in presence of water. **1** is for approximately 30% on hand as hydrated trimellitic acid (benzene-1,2,4-tricarboxylic acid, **9**).

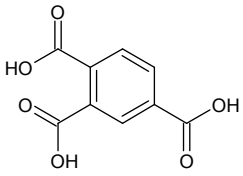


Figure 7.9. – *After hydrating of **1** is a part of it as **9** on hand*

NMR

The mixture of **1** and **9** was measured and both substances were identified with the same spectra. **9** has the same numbering as structure **1**.

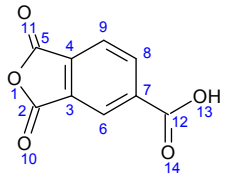


Figure 7.10. – *Arbitrarily numbered molecule **1***

1:	^{1}H-NMR (DMSO): δ = 13.61 (s, -COO*H*, 1H), 8.47 (dd, $^{9}J_{H(C8)H(C9)}$ = 7.8 Hz, $^{8}J_{H(C8)H(C6)}$ = 1.4 Hz, C(8)-*H*, 1H), 8.39 (dd, $^{8}J_{H(C6)H(C8)}$ = 1.4 Hz, $^{6}J_{H(C6)H(C9)}$ = 0.75 Hz, C(6)-*H*, 1H), 8.19 (dd, $^{9}J_{H(C9)H(C8)}$ = 7.8 Hz, $^{6}J_{H(C9)H(C6)}$ = 0.75 Hz, C(9)-*H*, 1H)
9:	^{1}H-NMR (DMSO): δ = 13.61 (s, -COO*H*, 3H), 8.22 (d, $^{8}J_{H(C6)H(C8)}$ = 1.4 Hz, C(6)-*H*, 1H), 8.12 (dd, $^{9}J_{H(C8)H(C9)}$ = 7.8 Hz, $^{8}J_{H(C8)H(C6)}$ = 1.4 Hz, C(8)-*H*, 1H), 7.75 (d, $^{9}J_{H(C9)H(C8)}$ = 7.8 Hz, C(9)-*H*, 1H)

7.10. 1-(4-methoxyphenyl)methanamine

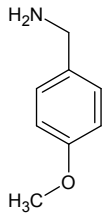


Figure 7.11. – *Compound* **7**

As a purity control of **7** was a ^{1}H-NMR spectra measured. It shows the signals of the compound, which will not be assigned, and approximately 5% of unidentified, probably organic wast. The spectra is shown in Figure A.6 on page 40.

8. Reactionoverview

Step 1 and 2

Reaction Number	Details
HS12-G15-3/4-1/2-1	**Pretest of step 1 according to TIP** • **1.0 eq** (2 mmol; 417 mg) of CAS 552-30-7 was suspended in **25 vol** (10 mL) acetic acid and **2.0 eq** (4 mmol; 0.5 g) benzylamine added • 2h at reflux (140 °C), IPC by TLC • stirred over night at RT → white Susp. • 1h at RT (140 °C) → clear, colourless solution • concentrated • solved in **50 vol** (20 mL) acetic acid 80% and **25 vol** (10 mL) hydrochloric acid 10% and at reflux (120°C) over 30 min • filtrated, washed with conc. acetic acid • crude 2#1 (no yield) • analytic: ^{1}H-NMR (HS12-G15-3.4-1.2-1 crude 2#1), TLC of IPC

Reaction Number	Details
HS12-G15-3/4-1/2-2	**Test to isolate HS12-G15-1** • **1.0 eq** (2 mmol; 426 mg) of CAS 552-30-7 was suspended in **25 vol** (10 mL) acetic acid and **2.0 eq** (4 mmol; 0.5 g) benzylamine added • 2h at reflux (140 °C), IPC by TLC • RM solved in **50 vol** (20 mL) ethyl acetate and 3x with **50 vol** (20 mL) 10% citric acid solution and 2x with **50 vol** (20 mL) 10% $NaHCO_3$ solution extracted. • NaCl solution was added → suspension • ^{1}H-NMR (DMSO): $\delta =$ (HS12-G15-3.4-1-2_crude_uncertain) • solved in H_2O, concentrated, precipitate with hydrochloric acide and filtrated • crude 2#1 (no yield) • analytic: ^{1}H-NMR (HS12-G15-3.4-1.2-2 crude 2#1)
HS12-G15-3/4-1/2-3	**Upscaling for step 3 and 4** • **1.0 eq** (10.67 mmol; 2.05g) of CAS 552-30-7 was suspended in **25 vol** (50 mL) acetic acid and **2.0 eq** (21.34 mmol; 2.33 g) benzylamine added • 2h at reflux (140 °C) • concentrated • solved in **50 vol** (50 mL) acetic acid 80% and **25 vol** (40 mL) hydrochloric acid 10% and at reflux (120°C) over 30 min • filtrated • NaCl solution was added → suspension • crude 1#1 = **2.623g** (4.33 mmol), y = 87% • analytic: ^{1}H-NMR HS12-G15-3/4-1/2-3 crude 1#1

Step 3

Reaction Number	Details
HS12-G15-3-3-1	**first experiment** • **1.0 eq** (0.365 mmol; 0.1 g) HS12-G15-2 stirred in **20 vol** (2 mL) thionyl chloride over 2h at reflux (**85 °C**) • RM split, 1/2 of the volume was remove and a separate reaction was made → see HS12-G15-3-3-1 VV1 • **30 vol** (3 mL) cyclohexane and **2 eq** (0.73 mmol; 0.1 mg) of 4-methoxybenzylamine added • → exothermic, yellow suspension • filtrated, washed with cyclohexane, dried • No yield; educt was isolated; ^{1}H-NMR was made: HS12-G15-3-3-1 crude 1#1
HS12-G15-3-3-1 VV1	**split part** • **30 vol** (3 mL) cyclohexane was added • concentrated • **30 vol** (3 mL) cyclohexane and **2 eq** (0.73 mmol; 0.1 mg) 4-methoxybenzylamine added • → white suspension • filtrated, washed with cyclohexane, dried • No yield; educt was isolated; ^{1}H-NMR was made: HS12-G15-3-3-1 VV1 crude 1#1
HS12-G15-3-3-2	**split part** • **1.0 eq** (0.889 mmol; 0.25 g) HS12-G15-2 stirred in **8 vol** (2 mL) thionyl chloride over 2h at reflux (**85 °C**) • RM split → see HS12-G15-3-3-1 VV1 • **30 vol** (3 mL) cyclohexane and **2 eq** (0.73 mmol; 0.1 mg) of 4-methoxybenzylamine added • → exothermic, yellow suspension • filtrated, washed with cyclohexane, dried • No yield; educt was isolated; ^{1}H-NMR was made: HS12-G15-3-3-2 crude 1#1

Reaction Number	Details
HS12-G15-3-3-3	• **1.0 eq** (0.43 mmol; 0.12 g) HS12-G15-2 stirred in **8 vol** (1 mL) thionyl chloride over 2h at reflux (**85 °C**) • → solution after 30 minutes • the reaction mixture was dried on the rotary evaporator • **2 eq** (0.86 mmol; 0.11 mL) of 4-methoxybenzylamine were placed in **10 vol** (1 mL) THF under a N_2-atmosphere • acid chloride was solved in **4 vol** (0.4 mL) THF and to the solution added. • 10 min stirred • filtrated, washed with THF, dried
HS12-G15-3-3-4	**Last try to synthesize HS12-G15-3 with thionyl chloride** • **1.0 eq** (0.075 mmol; 21 mg) of HS12-G15-2 in **10 vol; 50 eq** (4 mmol; 0.3 mL) thionyl chloride suspended. • heated to reflux (90 °C) over 2h. → clear, colourless solution • stopped; reaction mixture was thown away because the previous ractions didn't shown any good results.
HS12-G15-3-3-5	**Step 3 according to TIP with TBTU** • **1.0 eq** (0.336 mmol; 0.1 g) of HS12-G15-2 in **20 vol** (2 mL) DCM under argon suspended. → white suspension • **3 eq** (1.068 mmol; 0.14 mL) triethylamine and **1.1 eq** (0.39 mmol; 0.126 g) TBTU added • 15 min stirred at RT → yellow, dimmish solution, turning darker • **1.1 eq** (0.39 mmol; 0.05 mL) 4-methoxybenzylamine was addet; pH 9-10; 1h stirred • the reaction solution was washed 3 times with **20 vol** (2mL) 1M HCl solution, 3 times with **20 vol** (2mL) saturated $NaHCO_3$-solution, 3 times with **20 vol** (2mL) brine • the OP was concentrated, resolved in DCM and dried with Na_2SO_4 • analytic: ^{1}H-NMR HS12-G15-3-3-5 crude 1#1 • crude 1#1 was rectify by flash chromatography (solvent: EA : triethylamine (99:1); stationary phase: silica gel, approx. 10 cm) • analytic: ^{1}H-NMR HS12-G15-3-3-5 chrom 1#1 and HS12-G15-3-3-5 chrom 2#1 neu • the NMR shows that the isolated material contains no or just very little of the compound HS12-G15-3

Reaction Number	Details
HS12-G15-3-3-6	**according to TIP with TBTU** • **1.0 eq** (0.356 mmol; 0.1 g) of HS12-G15-2 in **20 vol** (2 mL) DCM under argon suspended. → white suspension • **3 eq** (1.068 mmol; 0.14 mL) triethylamine and **1.1 eq** (0.39 mmol; 0.126 g) TBTU added • 10 min stirred at RT → yellow, dimmish solution, turning darker • **1.1 eq** (0.39 mmol; 0.05 mL) 4-methoxybenzylamine was addet; pH 9-10; 1h stirred • the reaction solution was washed 3 times with **20 vol** (2mL) 1M HCl solution, 3 times with **20 vol** (2mL) saturated $NaHCO_3$-solution, 3 times with **20 vol** (2mL) brine • the OP was concentrated, resolved in DCM and dried with Na_2SO_4 • analytic: ^{1}H-NMR HS12-G15-3-3-6 crude 1#1 • crude 1#1 was rectify by flash chromatography (solvent: EA : triethylamine (99:1); stationary phase: silica gel, approx. 20 cm) • analytic: ^{1}H-NMR HS12-G15-3-3-6 chrom 1#1 and ^{13}C-NMR HS12-G15-3-3-5 chrom 1#1 13C • the NMR shows that the isolated material contains no of the compound HS12-G15-3
HS12-G15-3-3-7	• **1.1 eq** (0.8 mmol; 0.25 g) TBTU and **1.1 eq** (0.8 mmol; 0.1 mL) 4-methoxybenzylamine were solved in **20 vol** (4 ml) DCM • → the solution became dimmish and yellowish • **1.0 eq** (0.7 mmol; 0.2 g) HS12-G15-2 was added → solutoin, yellowish • **3 eq** (2.1 mmol; 0.28 mL) triethylamine was added • stirred over 30 min → clear, yellowish solution • the reaction solution was washed 3 times with **20 vol** (2mL) 1M HCl solution, 3 times with **20 vol** (2mL) saturated $NaHCO_3$-solution, 3 times with **20 vol** (2mL) brine • the OP was concentrated, resolved in DCM and dried with Na_2SO_4 • analytic: ^{1}H-NMR and ^{13}C-NMR HS12-G15-3-3-7 crude 1#1 • crude 1#1 was rectify by flash chromatography (solvent: EA : triethylamine (99:1); stationary phase: silica gel, approx. 20 cm) • analytic: ^{1}H-NMR HS12-G15-3-3-7 chrom 1#1, ^{1}H-NMR HS12-G15-3-3-7 chrom 2#1 and ^{1}H-NMR HS12-G15-3-3-7 nachlauf • the NMR of chrom 2#1 shows that this fraction contains polluted the compound HS12-G15-3

Reaction Number	Details
HS12-G15-3-3-7	**scale up, final reaction** • **1.1 eq** (1.54 mmol; 0.35 g) TBTU and **1.5 eq** (2.1 mmol; 0.3 mL) 4-methoxybenzylamine were solved in **20 vol** (8 ml) DCM • → the solution became dimmish and yellowish • **1.0 eq** (1.4 mmol; 0.4 g) HS12-G15-2 was added → solutoin, yellowish • **3 eq** (4.2 mmol; 0.3 mL) triethylamine was added • stirred over 2h → clear, yellowish solution, pH = ca. 5; **5 eq** (0.5 mL) triethylamine was added to raising the pH to 9-10 • the reaction solution was washed 3 times with **20 vol** (4mL) 5% citric acid solution, 3 times with **20 vol** (4mL) saturated $NaHCO_3$-solution, 3 times with **20 vol** (4mL) brine • the OP was dried with Na_2SO_4 and concentrated. • analytic: ^{1}H-NMR HS12-G15-3-3-8 crude 1#1 • crude 1#1 was rectify by flash chromatography (solvent: EA : triethylamine : cyclohexane (49.5 : 1 : 49.5); stationary phase: silica gel, approx. 20 cm) • chrom 1#1 → whit solid, 0.3 g, yield: 53% • analytic: ^{1}H-NMR HS12-G15-3-3-8 chrom 1#1, ^{13}C-NMR HS12-G15-3-3-8 chrom 1#1 • the NMR of chrom 1#1 shows that this fraction contains nearly clean material of compound HS12-G15-3

Step 4

Reaction Number	Details
HS12-G15-4-4-1	**scale up, last reaction** • **1.1 eq** (0.78 mmol; 0.25 g) TBTU and **1.1 eq** (0.78 mmol; 0.1 mL) 3-methoxybenzylamine were solved in **20 vol** (4 ml) DCM • **1.0 eq** (0.7 mmol; 0.2 g) HS12-G15-2 was added → solutoin, yellowish • **3 eq** (2.1 mmol; 0.3 mL) triethylamine was added • → suspension, pH = 8; • **1.3 vol** (5 mL) 1M HCl solution and **1 vol** (4 mL) DCM added and filtrated • → HS12-G15-4-4-1 crude 1#1 • analytic: ^{1}H-NMR HS12-G15-4-4-1 crude 1#1,

abbreviation	augmentation
TIP	technical information paper
ad	fill to
WS	weighted sample
GC	gas chromatograph/y
scp	single-channel pipette
soln	solution
solv	solvent
RT	room ambient temperature
std	standard
ref	reference solution
RM	reaction mixture
AP	aqueous phase
OP	organic phase
IPC	in-process controls
eq	Equivalent
rf	retention factor
Chemicals	
DCM	dichloromethane
EA	ethyl acetate

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Appendices

A. NMR Spectra

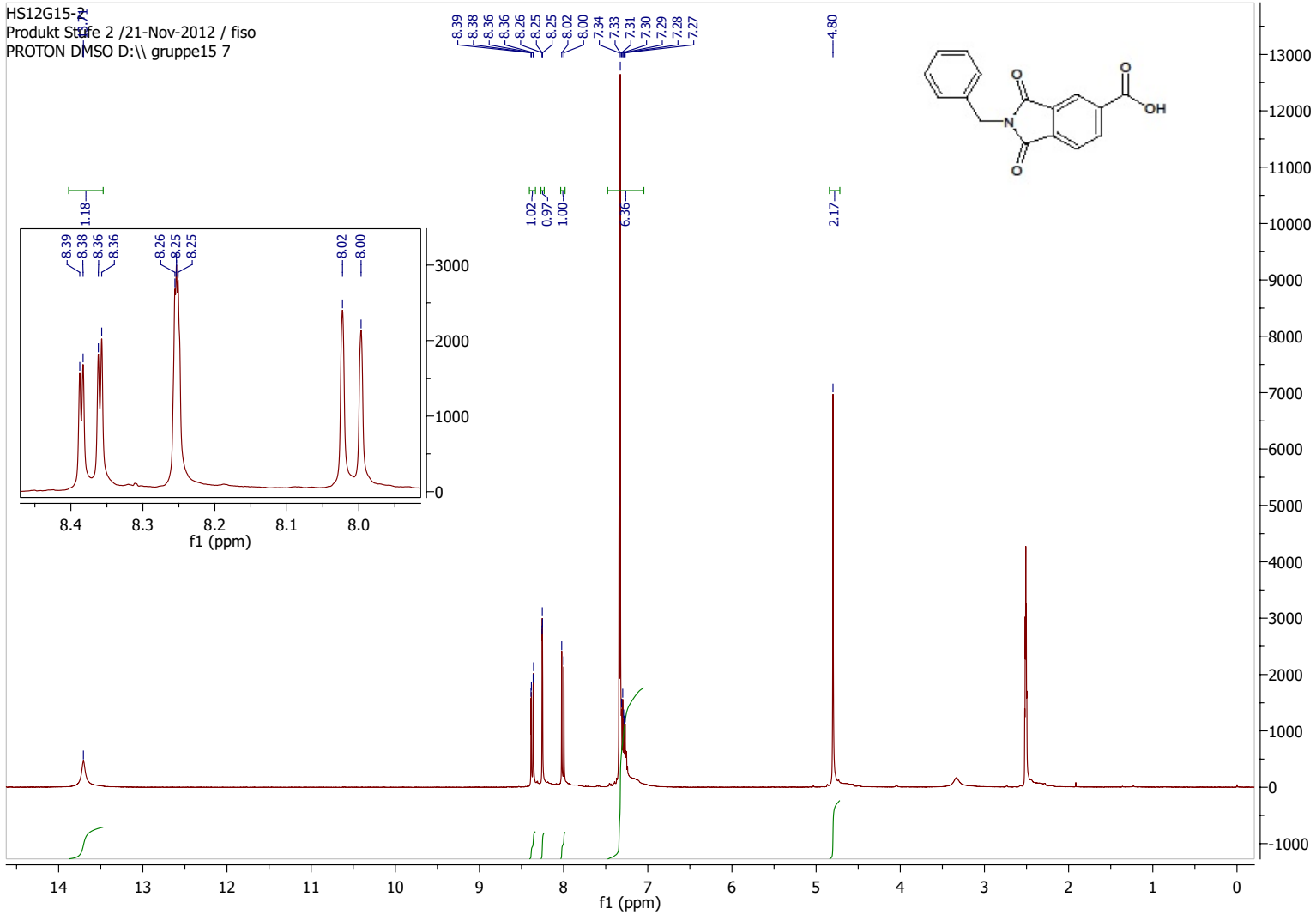

Figure A.1. – ^{1}*H-NMR of the compound* ***3***

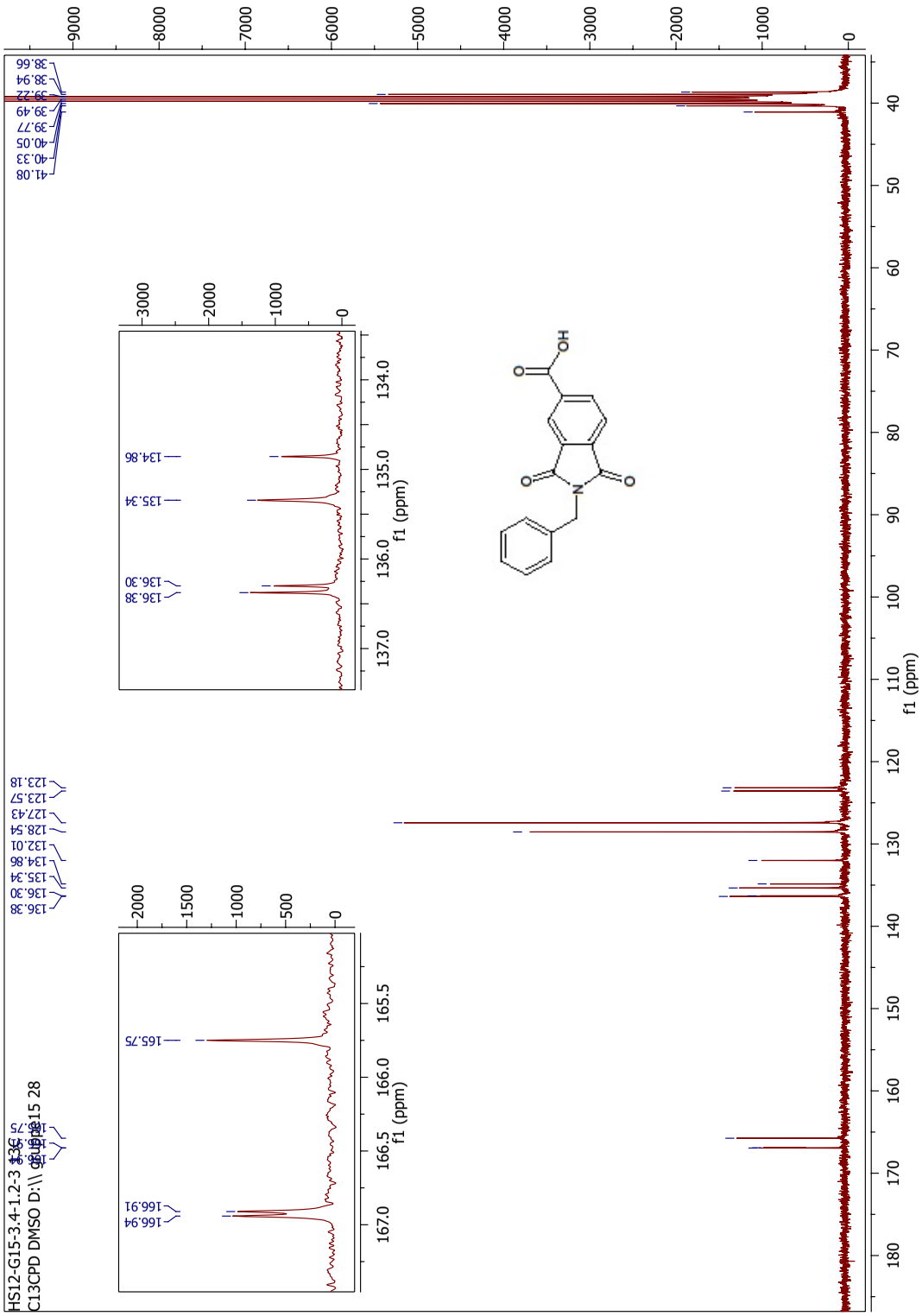

Figure A.2. – ^{13}C-NMR of the compound **3**

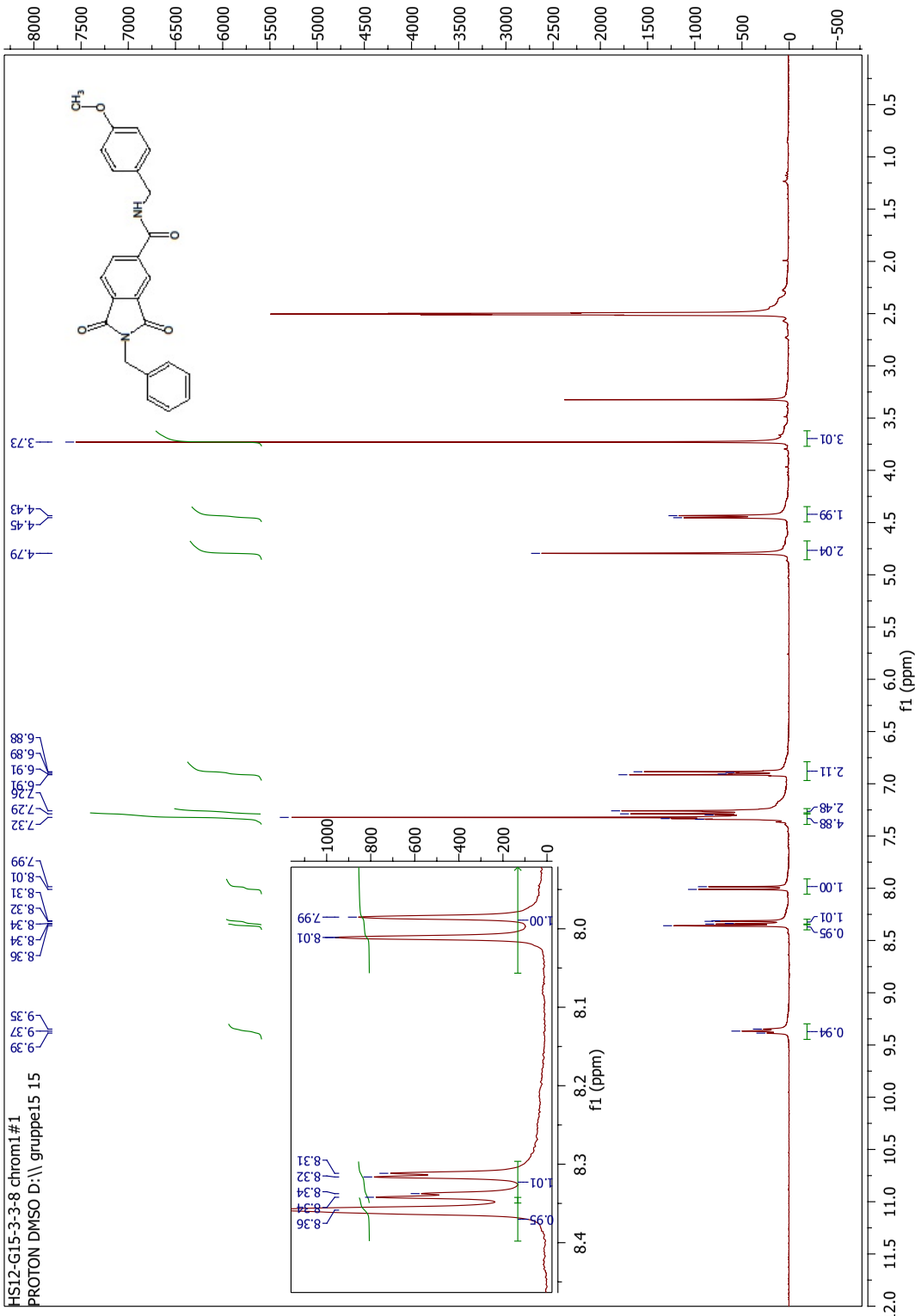

Figure A.3. – ^{1}H-NMR of the compound 4

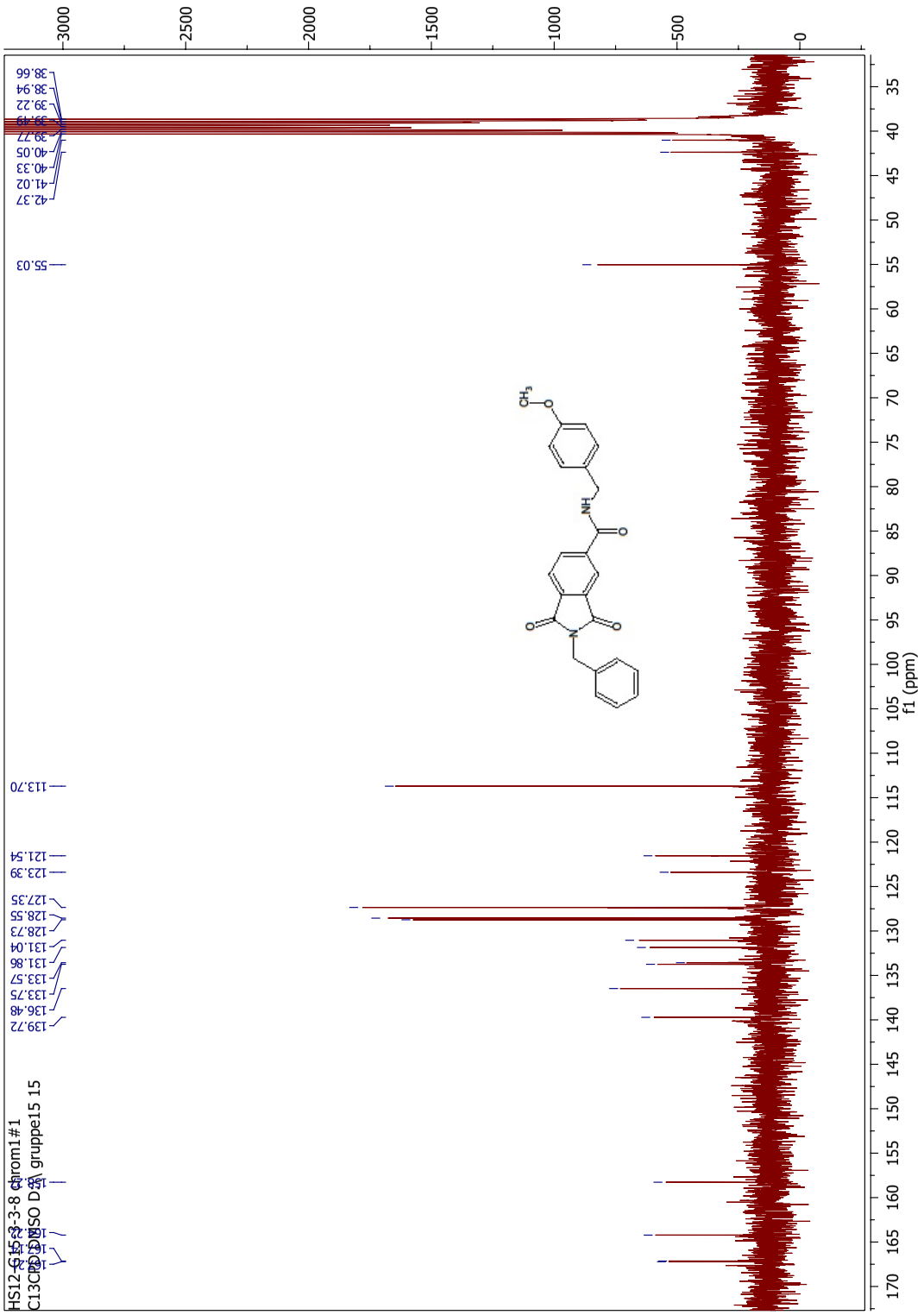

Figure A.4. – ^{13}C-NMR of the compound **4**

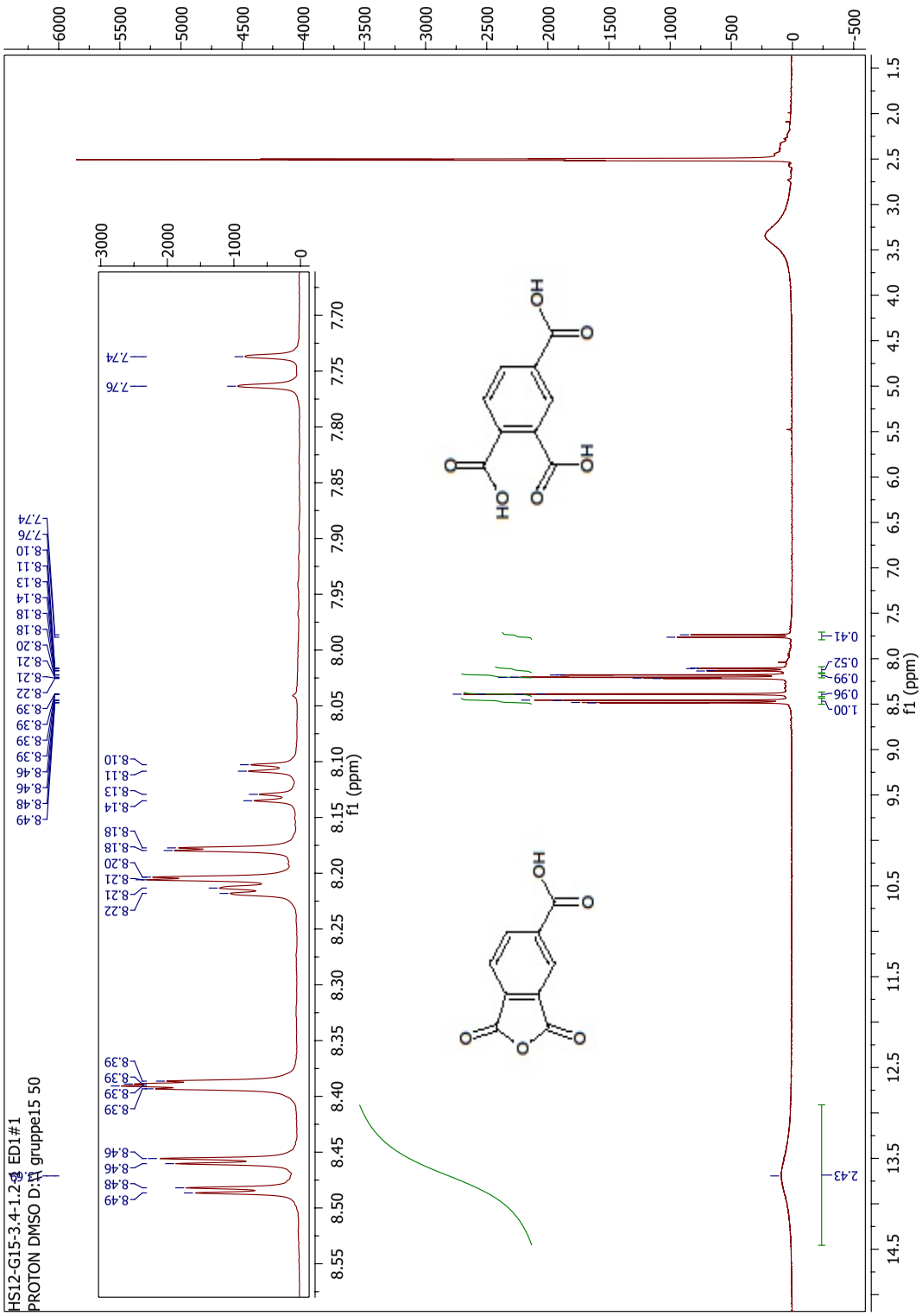

Figure A.5. – ^{1}H-NMR of the compound **1** and **9**

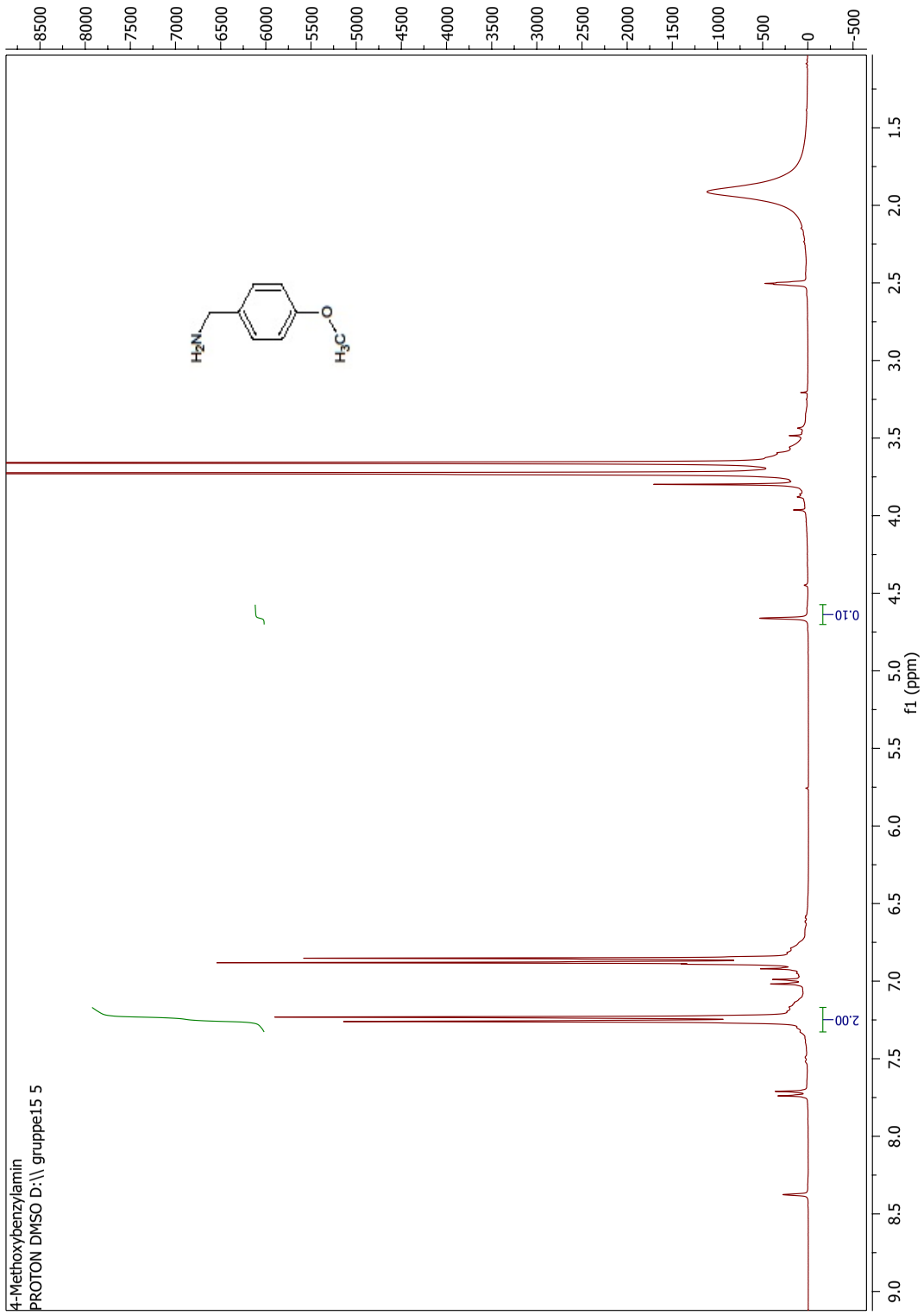

Figure A.6. – ^{1}H-*NMR of the compound* **7**, *contains approx. 5% waste.*

B. Mass Spectra

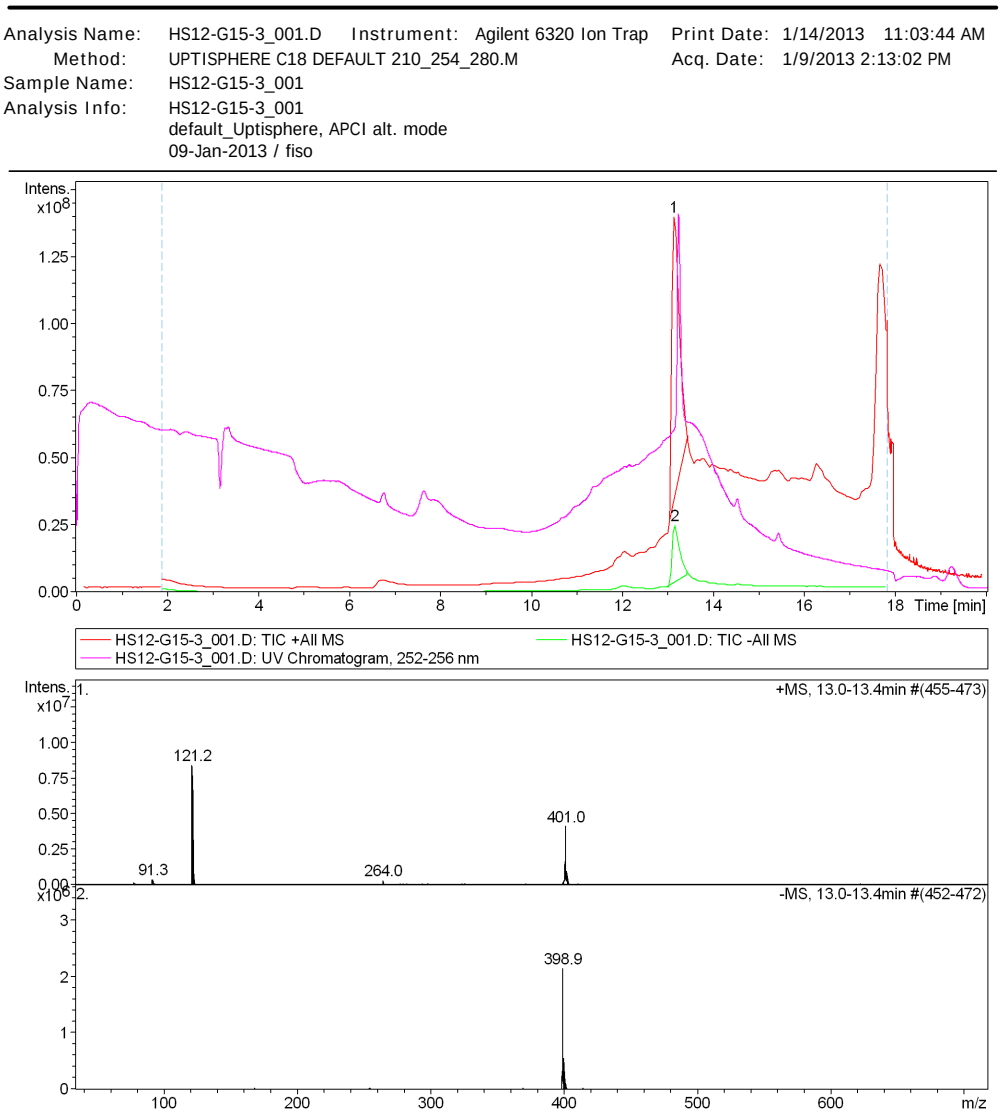

Figure B.1. – *LC-MS of the compound* ***4***

C. Chemicals

Table C.1. – *List of all used chemicals*

Chemical Name	CAS-Nr.	Chemicalformula	Purity	Contractor	GHS
1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid (**1**)	552-30-7	$C_9H_4O_5$	95 %	TCI	
1-phenylmethanamine (**6**)	100-46-9	C_7H_9N	98 %	Fluka	
1-(4-methoxyphenyl)methanamine (**7**)	2393-23-9	$C_8H_{11}NO$	98 %	Alpha Aesar	
1-(3-methoxyphenyl)methanamine (**8**)	225-779-6	$C_8H_{11}NO$	98 %	Alpha Aesar	
Acetic acid	64-19-7	$C_2H_4O_2$	99.8 %	Sigma-Aldrich	
Argon	7440-37-1	Ar	99 %	Pangas	
Brine	7647-14-5	NaCl	conc.	self-made	-
Citric acid soluiton	77-92-9	$C_6H_8O_7$	10 %	self-made	
Cyclohexane	110-82-7	C_6H_{12}	tech	ZHAW canister	
DCM	75-09-2	CH_2Cl	dry	Sigma-Aldrich	
Ethylac acetat	141-78-6	$C_4H_8O_2$	tech	ZHAW canister	
HCl	7647-01-0	HCl	32 %	Sigma-Aldrich	
N,N-Diisopropylethylamine	7087-68-5	$C_8H_{19}N$	99.5 %	Sigma-Aldrich	
Nitrogen	7727-37-9	N_2	tech	ZHAW gas tap	
Sea sand	7631-86-9	SiO_2	p.a.	Merck	-
Silica gel 60 Å	112926-00-8	SiO_2	p.a.	Sigma-Aldrich	-
Sodium bicarbonate	144-55-8	$NaHCO_3$	solution	slef-made	-
TBTU	125700-67-6	$C_{11}H_{16}BF_4N_5O$	-	BACHER	
Tetrahydrofuran	109-99-9	C_4H_8O	99 %	Sigma-Aldrich	
Thionyl chloride	7719-09-7	$SOCl_2$	97 %	Sigma-Aldrich	
Triethylamine	121-44-8	$C_6H_{15}N$	99.5 %	Sigma-Aldrich	
Water deion.	7732-18-5	H_2O	-	tap	-