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Article

DBU as a Catalyst for the Synthesis of Amides via Aminolysis of Methyl Esters

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Benzoato de metila e *p*-clorofenil acetato de metila reagem com benzilamina e pirrolidina levando às correspondentes amidas. Estas reações são mais rápidas na presença de 20 mol% de DBU, fornecendo os produtos com rendimentos levemente superiores. Quando um diéster derivado do ácido L-aspártico foi usado como substrato, a reação com benzilamina e pirrolidina foi quimiosseletiva para o éster metílico, levando às correspondentes amidas em bons rendimentos. Reação do monoéster metílico do ácido aspártico com estas aminas conduziu a amidas com um grupo ácido livre em C1. Anilina, menos básica e menos nucleofílica, não formou os produtos esperados tanto na ausência quanto na presença de DBU. Através do monitoramento da reação por ESI-MS, foi possível interceptar os intermediários-chave catiônicos formados nas reações entre o benzoato de metila e o *p*-clorofenil acetato de metila com a benzilamina, os quais foram caracterizados por ESI-MS/MS.

Methyl benzoate and methyl *p*-chlorophenyl acetate react with neat benzylamine and pyrrolidine to form the corresponding amides. These reactions are faster in the presence of 20 mol% of DBU providing slight better yields. When a diester derived from L-aspartic acid was used as substrate, the reaction with benzylamine and pyrrolidine in the presence of DBU was chemoselective and led to the corresponding amides in good yields. Reaction of aspartic acid monomethyl ester with these amines led to amides having a free carboxy group (at C1). Less nucleophilic and less basic aniline failed to form the expected products in both absence and presence of DBU. By monitoring the course of reaction by ESI-MS, key charged intermediates formed by the reactions of methyl benzoate and methyl *p*-chlorophenyl acetate with benzylamine were intercepted and further characterized by ESI-MS/MS.

Keywords: DBU, catalysis, aminolysis, esters, amides, ESI-MS

Introduction

The amide is one of the most important functional groups in organic molecules. Life depends on this group and its properties since proteins and peptides are essentially polyamides. Many natural and synthetic bioactive molecules are also amides of low molecular weight.[1] The preparation of amides from amines and carboxylic acids or its derivatives is therefore one of the most important and commonly employed reactions in organic synthesis.[1,2]

Amides are usually prepared by transforming carboxylic acids into the corresponding acyl chlorides or by *in situ* activation of the carboxyl group followed by reaction of the resulting intermediates with amines.[3] Aminolysis of esters has also been employed to form amides and has been considered as a model reaction to form peptide bonds.[2,4]

In a molecular modelling study Schaefer III and co-workers[5] showed that the more stable pathway in the aminolysis of ethylformate by ammonia is a self catalyzed

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mechanism in which a second molecule of ammonia is involved in the transition state, facilitating the proton transfer process. The transition state (TS) for this pathway was calculated to be from 7 to17 kcal mol^{-1} more stable than that for the uncatalyzed pathway.[5] The participation of a second molecule of base in the TS of the nucleophilic addition step is also suggested by the second order in amine observed in kinetic studies.[6]

Based on these data, we expected that this reaction could be catalyzed by a strong base, as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[6] DBU catalyze several organic reactions but has not yet been tried as a catalyst in the aminolysis of esters.[5,7]

Herein we report on the use of DBU as an efficient catalyst for the chemoselective aminolysis of methyl esters leading to amides, as tested by the reactions employing esters **1**-**4** and amines **5**-**7** (Figure 1).[8]

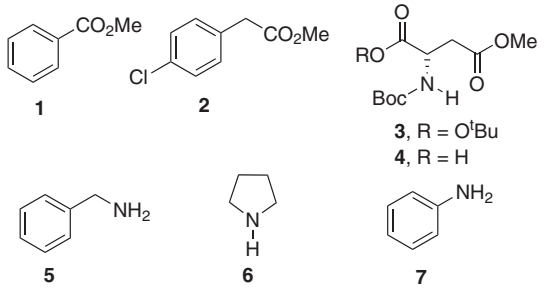
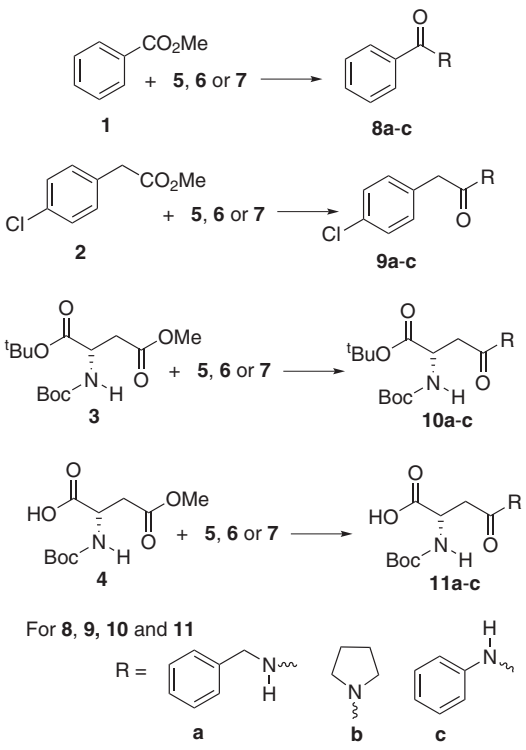


Figure 1. Esters and amines used in this work.

Results and Discussion

Scheme 1 shows the reactions between the selected esters and amines whereas Table 1 summarizes major conditions and yields. We first studied the aminolysis of methyl benzoate (**1**). After 72 h at room temperature, **1** reacted with **5** (10 equiv.) in the absence of solvent yielding **8a** in 42% (Table 1, entry 1). In the presence of catalytic amounts of DBU (20 mol%, entry 2), however, the reaction was relatively faster (48 h) and **8a** was formed in a slightly better yield (51%). The same trend was observed for the reactions of **1** with **6** (entries 3 and 4). For the less nucleophilic and less basic aniline (**7**), no product was observed in the absence of DBU whereas traces of **8c** were determinated in the crude mixture by GC/MS when DBU was employed (entries 5 and 6).

As expected, ester **2** was more reactive than **1** and the corresponding amides **9a** and **9b** were formed in better yields, in both conditions (79-90%), but the reactions were considerably faster in the presence of DBU (entries 7-10). Once again in the reaction with aniline **7**, the corresponding amides were not formed, regardless the use of DBU (entries 11 and 12).



Scheme 1. Aminolysis os esters **1**, **2**, **3** and **4** by amines **5**, **6** and **7**.

We expected that the aminolysis of the diester **3** could occur chemoselectively, exclusively at the less hindered methyl ester group. When **3** was allowed to react with amine **6** in the absence of DBU, the corresponding amide **10b** was obtained in poor yields after 3 days of reaction (entry 15). But in the presence of DBU (entry 16) and after 48 h of reaction, **10b** was chemoselectively formed in a yield as high as 89%. The reaction with amine **5** followed the same trend but, in the presence of DBU **10a** was obtained as a mixture with 20% of the starting material (entries 13 and 14). The use of more prolonged reaction times led to the corresponding diamide (see Supplementary Information). Unfortunately, the reaction with **7** failed to form the desired product in both reaction conditions (entries 17 and 18).

The reactions of the monoester **4** (entries 19-22) with **5** and **6** led chemoselectively to the corresponding amides **11a** and **11b**. The chemical yields were similar but these reactions were faster in the presence of DBU. Using **7** as the nucleophile (entries 23 and 24), no products were formed.

Three pathways have been considered to explain the aminolysis of esters: (*i*) a stepwise mechanism via separated charge intermediates, (*ii*) a stepwise mechanism via neutral intermediates and (*iii*) a concerted mechanism without intermediates.[6] As already mentioned, in a molecular modeling study Schaefer III and co-workers[5] suggest that the more stable pathway in the aminolysis of ethylformate by ammonia is a self catalyzed mechanism in which a

Table 1. Conditions and yields for Scheme 1

entry	ester	amine[a]	amide	DBU[b]	time / h	yield / %
1	**1**	**5**	**8a**	----	72	42
2	**1**	**5**	**8a**	20	48	51
3	**1**	**6**	**8b**	----	72	48
4	**1**	**6**	**8b**	20	48	52
5	**1**	**7**	**8c**	----	72	NR
6	**1**	**7**	**8c**	20	48	traces[c]
7	**2**	**5**	**9a**	----	72	80
8	**2**	**5**	**9a**	20	48	79
9	**2**	**6**	**9b**	----	72	83
10	**2**	**6**	**9b**	20	48	90
11	**2**	**7**	**9c**	----	72	NR
12	**2**	**7**	**9c**	20	48	traces[c]
13	**3**	**5**	**10a**	----	72	20[c]
14	**3**	**5**	**10a**	20	48[d]	80[e]
15	**3**	**6**	**10b**	----	72	34
16	**3**	**6**	**10b**	20	48	89
17	**3**	**7**	**10c**	----	72	NR
18	**3**	**7**	**10c**	20	48	NR
19	**4**	**5**	**11a**	----	72	41
20	**4**	**5**	**11a**	20	48	63
21	**4**	**6**	**11b**	----	72	76
22	**4**	**6**	**11b**	20	48	74
23	**4**	**7**	**11c**	----	72	NR
24	**4**	**7**	**11c**	20	48	NR[e]

[a]Reaction accomplished in the absence of solvent. [b]mol%. [c]Conversion measured by NMR and/or GC/MS in the crude mixture. [d]Formation of a diamide was observed after 4 days of reaction. [e]Partial consumption of starting material and formation of a non-identified product. NR = no reaction.

second molecule of ammonia is involved in the transition state, facilitating the proton transfer process through the formation of a neutral intermediate.

To obtain new data on the reaction mechanism and the catalytic role of DBU, the reactions of **1** and **2** with benzylamine (**5**) were selected as model and monitored via direct infusion ESI-MS and its tandem version (ESI-MS/MS) in the positive ion mode.[9] Samples were diluted in MeOH before recording the MS data in order to transform the putative separated charge oxianion-ammonium intermediates in the corresponding cationic species which were therefore intercepted by ESI-MS.

In the absence of DBU (data not shown), a self-catalyzed reaction would be expected, generating no cationic intermediate. However, the pathway involving separated charge intermediates seems to be a viable mechanism since cations **12aa** and **13aa** of *m/z* 244 and 292, showed in Figure 2A and 2B, respectively, were intercepted after quenching with methanol. Interestingly, cations that would correspond to the participation of a second molecule of $BnNH_2$ in the separated charge intermediates were not detected.

In the presence of DBU cations **12aa** and **13aa** of *m/z* 244 and 292 were also intercepted, suggesting the occurrence of an uncatalyzed pathway. However, the role of DBU as catalyst in these reactions is demonstrated by the interception of cations **14aa** of *m/z* 396 and **15aa** of *m/z* 444 (Figure 2). This finding strongly suggests that DBU stabilizes the transition state of the nucleophilic addition step. The detection of cation *m/z* 260 suggests the possibility of pre-association between DBU and $BnNH_2$.

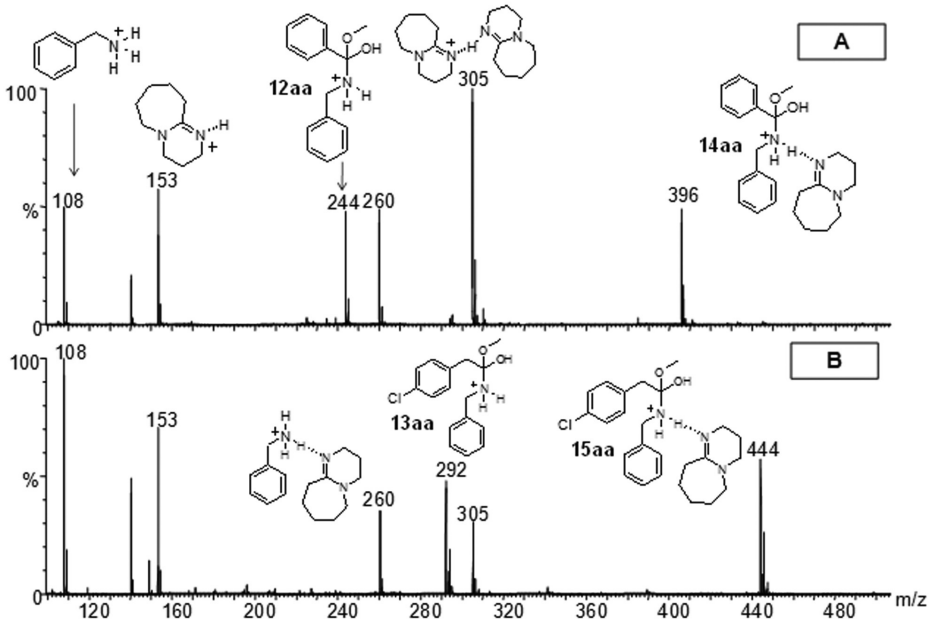
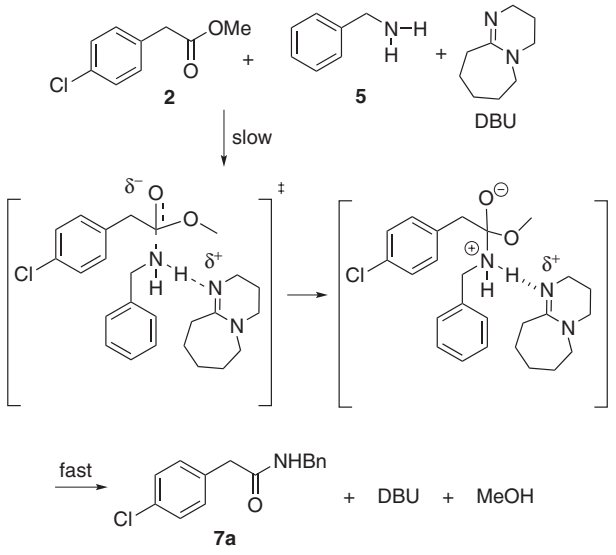


Figure 2. ESI(+)-MS of the aminolysis of **1** (A) and **2** (B) with **5** in the presence of DBU after dilution with MeOH.

Upon ESI-MS/MS (Figures S1 and S2, Supplementary Information), **14aa** and **15aa** were characterized and found to dissociate by losing first DBU to yield respectively **12aa** (*m/z* 244) and **13aa** (*m/z* 292).

Using the aminolysis of **2** by **5** as an example and based on ESI-MS(/MS) data, a mechanistic rationalization is proposed in Scheme 2. DBU acts in the rate determining step by stabilizing the positive charge developed at the nitrogen atom in transition state for the nucleophilic addition of **5** to **2**. A pre-association between **2** and **5** can not be ruled out, since the dimeric specie was intercepted by ESI-MS and theoretical calculations in our laboratory show that it is more nucleophilic than **5** alone. Although primary and secondary amines can participate in a neutral trimolecular transition state acting as a bridge for proton transfer, with DBU this mechanism is impossible and the formation of charge separated intermediate is expected.



Scheme 2. Mechanistic rationalization proposed for the reaction of **2** with **5** in the presence of DBU.

Conclusions

The usefulness of DBU as a catalyst for the aminolysis of esters under soft conditions has been demonstrated. Via ESI-MS(/MS) monitoring, the catalytic role of DBU was probed through the interception and characterization of separated charge intermediates. Methyl esters can be chemoselectivelly transformed into amides in the presence of *t*-butyl esters and free carboxyl group.

Experimental

A mixture of ester **1**, **2**, **3** or **4** (1.0 mmol), amines **5**, **6** or **7** (10.0 mmol) and DBU (0.2 mmol) was stirred at room temperature for 48 h. Ethyl acetate was added (15 mL) and the organic phase was washed with saturated aqueous NH_4Cl solution (4 × 15 mL), dried on Na_2SO_4 and concentrated. When aniline was utilized as nucleophile 5% HCl (2 × 10 mL) was used instead NH_4Cl solution. The analytical data of amides **8a**-**c** and **9a**-**c** were identical to those reported previously.[10] New amides **10a**-**c** and **11a**-**c** were characterized by ^{1}H NMR, ^{13}C NMR and MS.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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Supplementary Information

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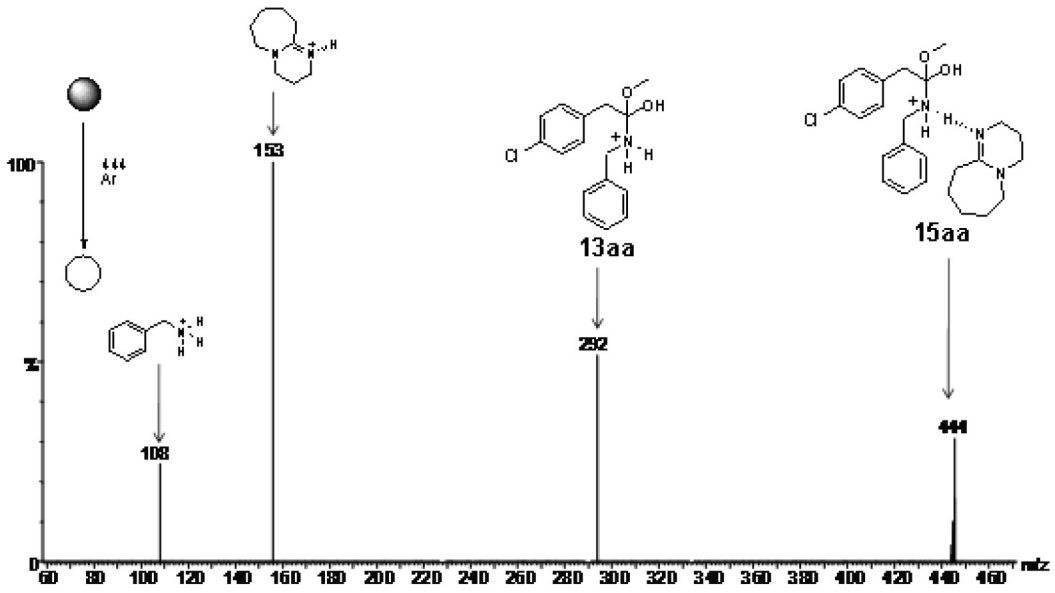

Figure S1. ESI(+)-MS/MS of **15aa** "fished" from the reaction solution of **2** and **5** with DBU.

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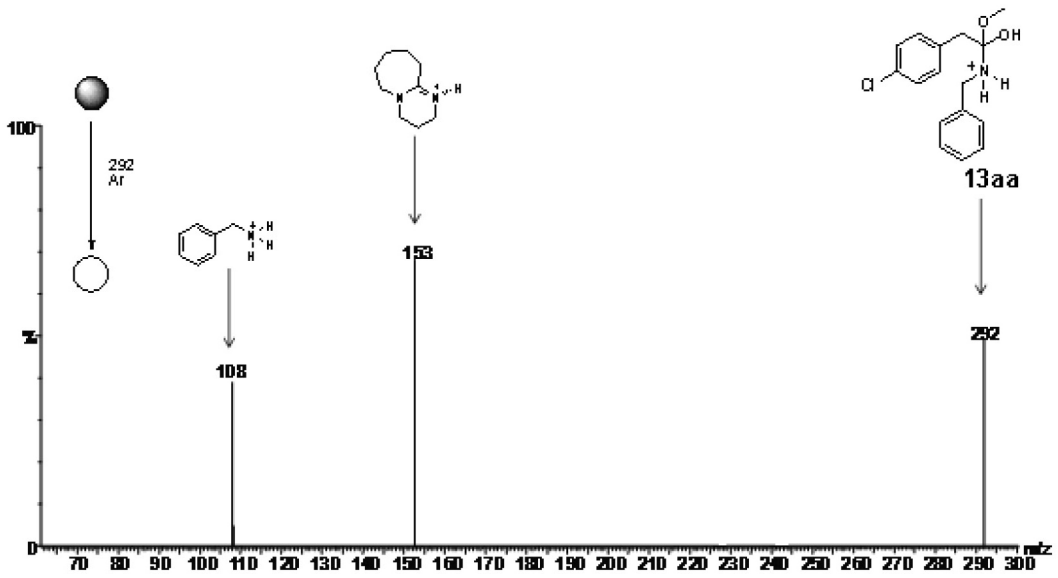

Figure S2. ESI(+)-MS/MS of **13aa** "fished" from the reaction solution of **2** and **5** with DBU.

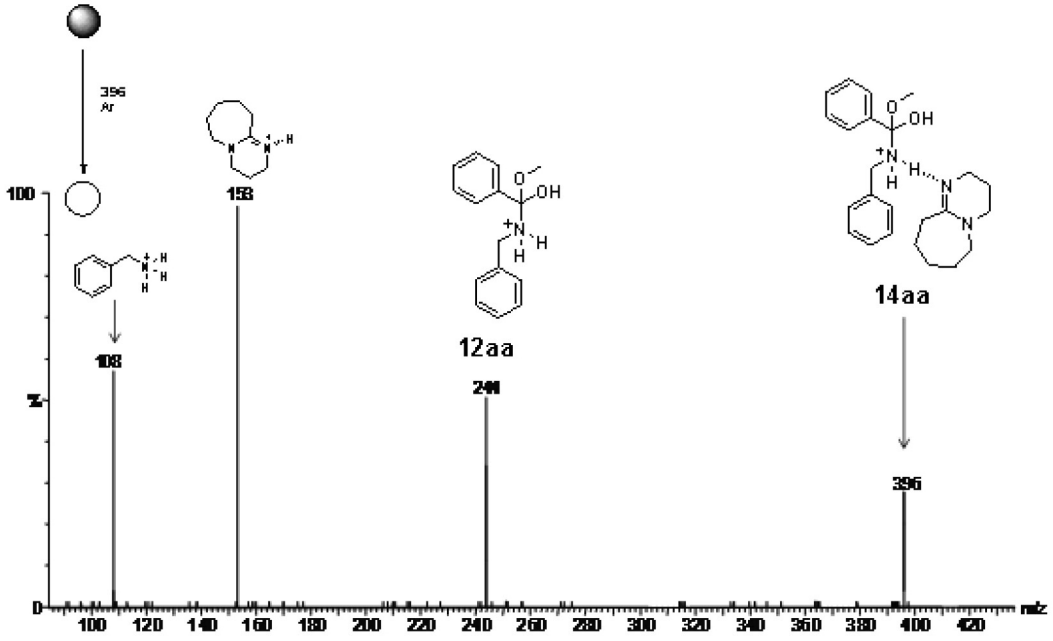

Figure S3. ESI(+)-MS/MS of **14aa** "fished" from the reaction solution of **1** and **5** with DBU.

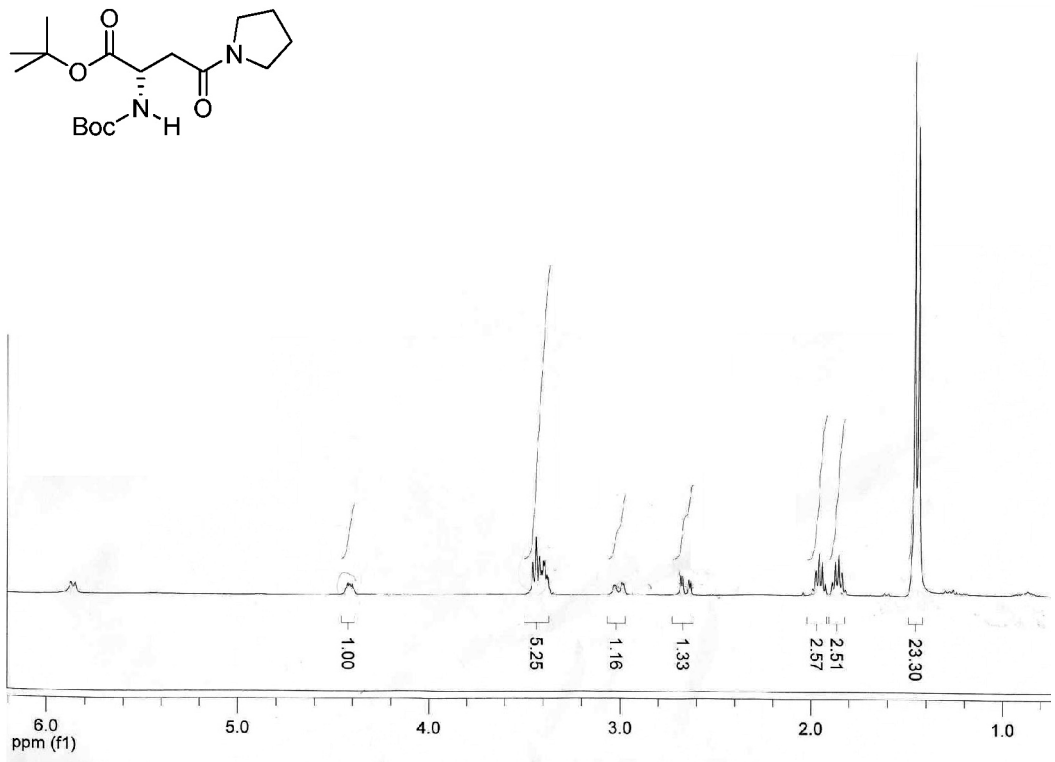

Figure S4. ^{1}H NMR (200 MHz, $CHCl_3$) spectrum of compound **10b**.

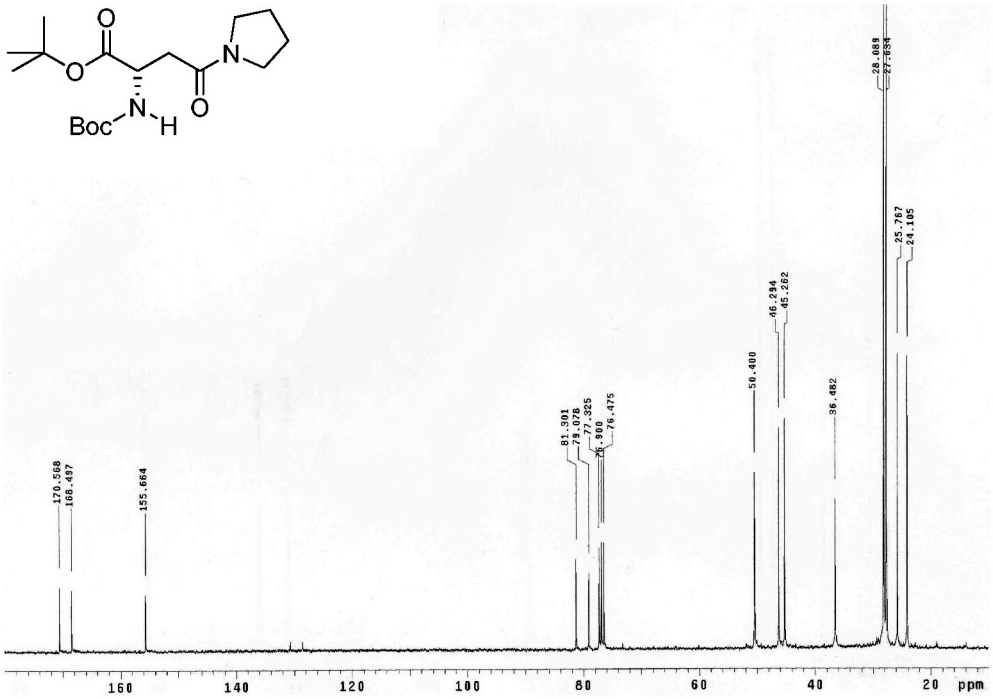

Figure S5. ^{13}C NMR (50 MHz, $CHCl_3$) spectrum of compound **10b**.

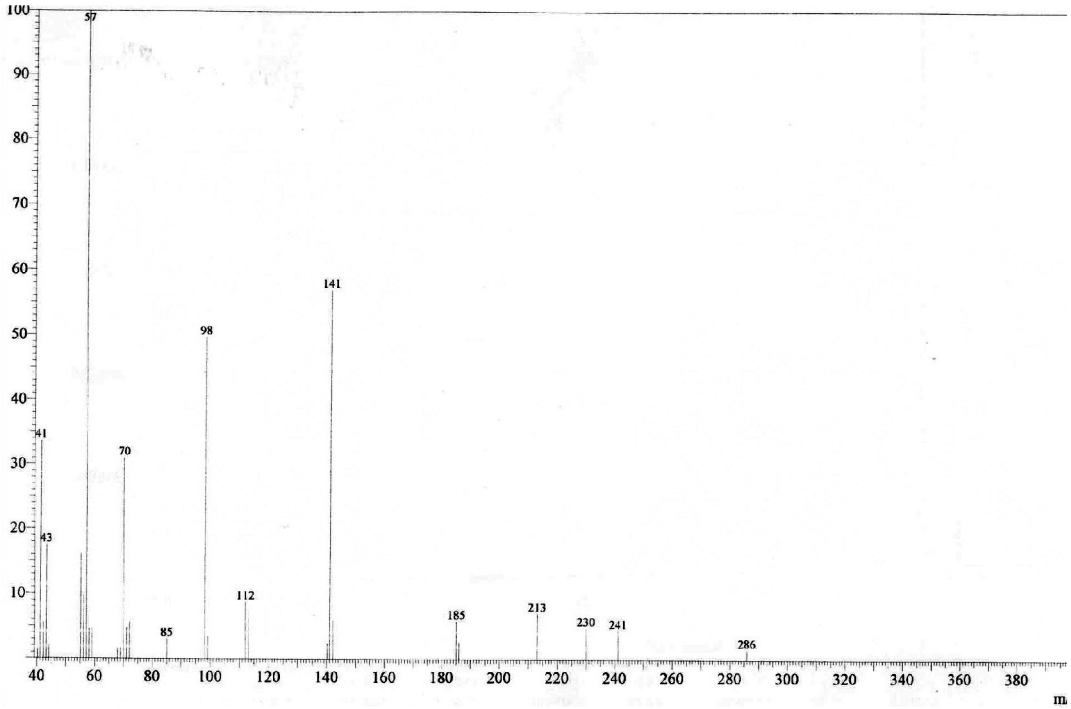

Figure S6. Low resolution mass spectrometry of compound **10b**.

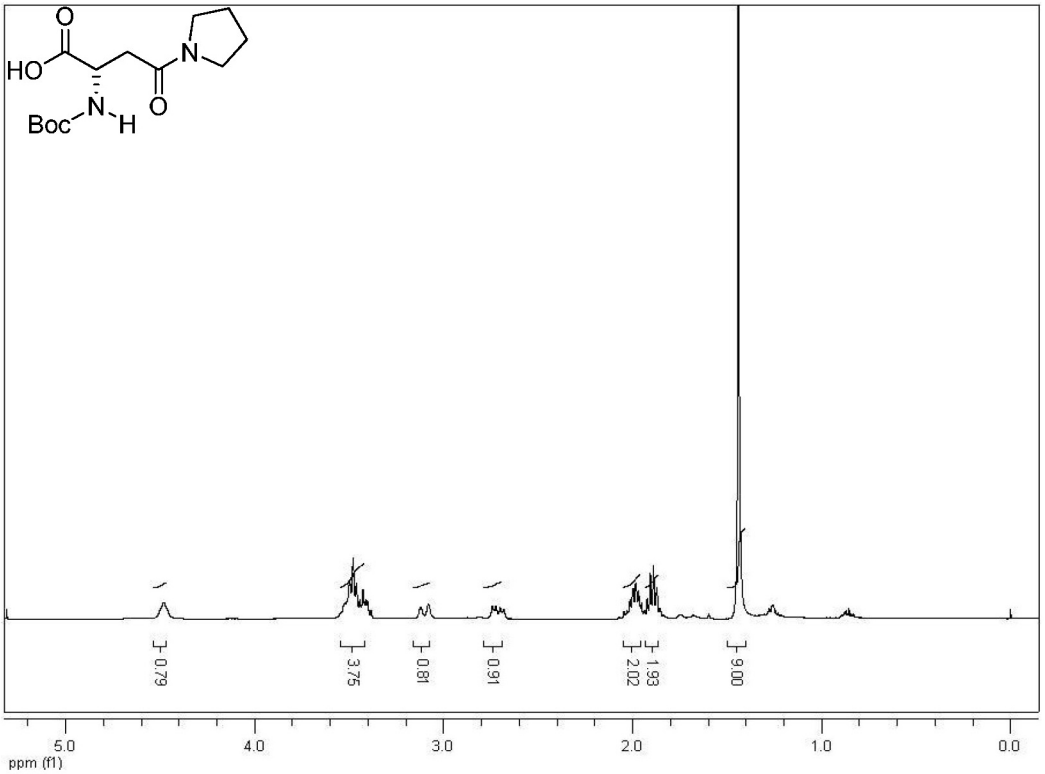

Figure S7. ^{1}H NMR (200 MHz, $CHCl_3$) spectrum of compound **11b**.

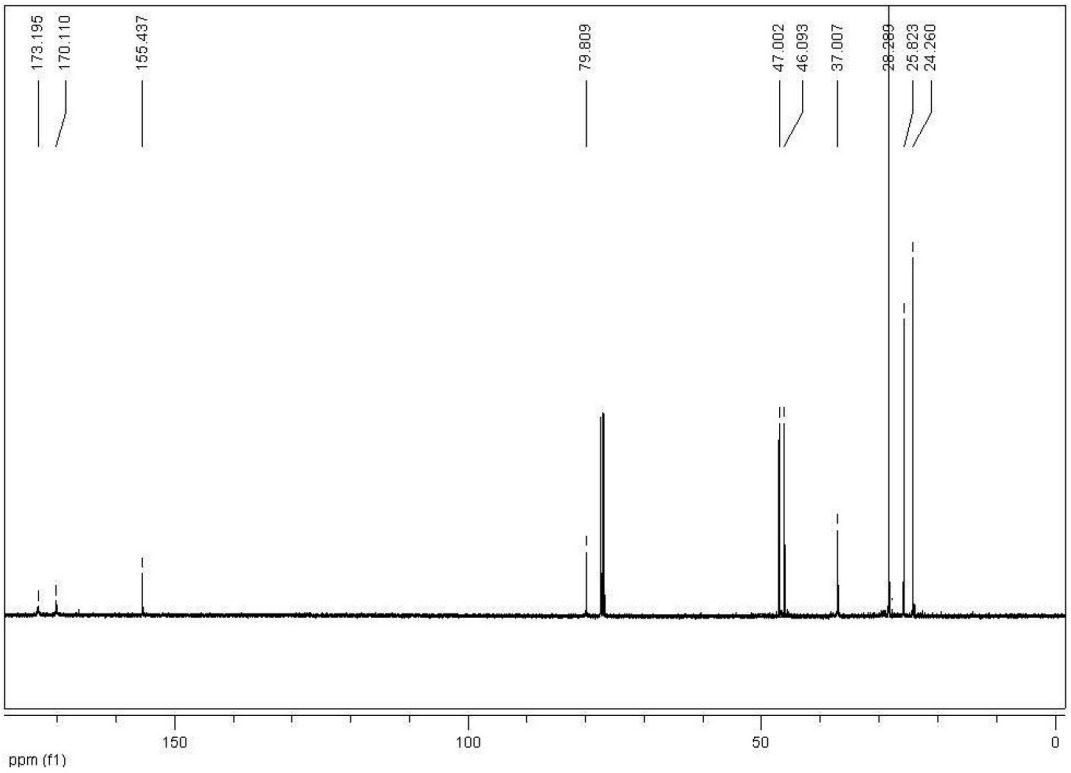

Figure S8. ^{13}C NMR (50 MHz, $CHCl_3$) spectrum of compound **11b**.

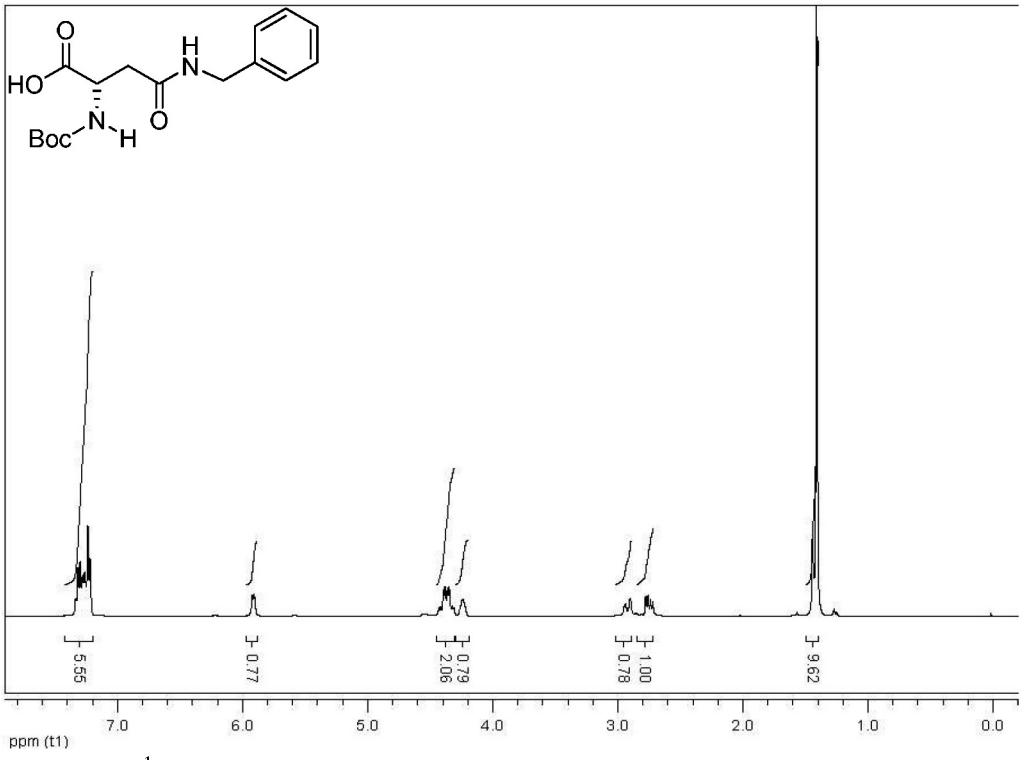

Figure S9. ^{1}H NMR (200 MHz, $CHCl_3$) spectrum of compound **11a**.

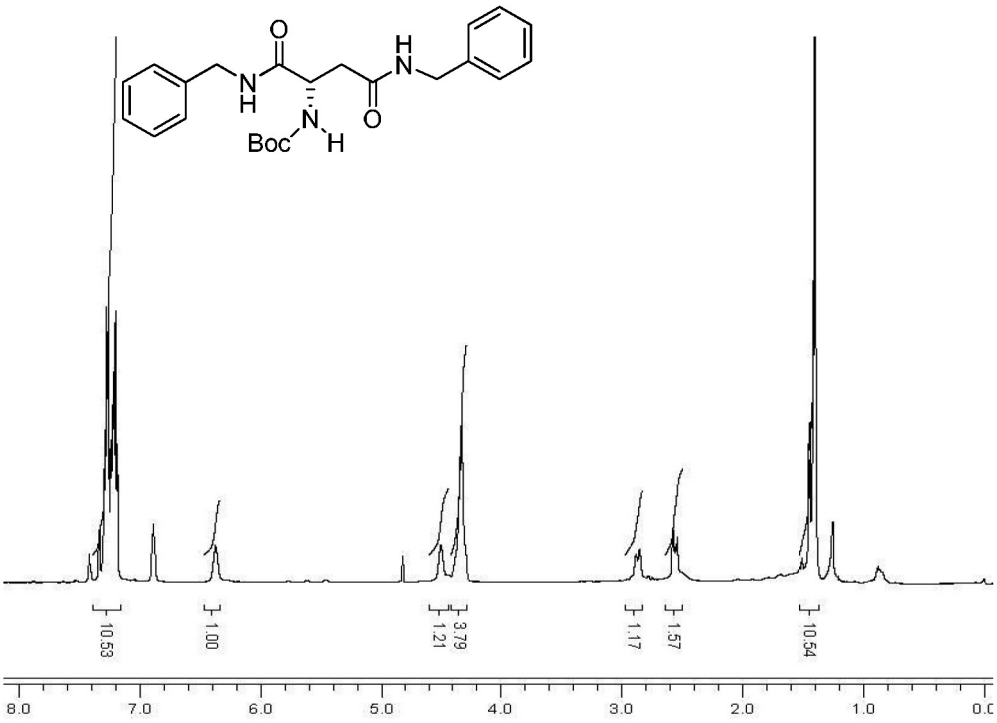

Figure S10. ^{1}H NMR (200 MHz, $CHCl_3$) spectrum of compound derived from addition of benzylamine to ester **3**.