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Continuous-Flow Protocol for the Synthesis of Enantiomerically Pure Intermediates of anti Epilepsy and anti Tuberculosis Active Pharmaceutical Ingredients

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Abstract:

Continuous-flow production of chiral intermediates plays an important role in the development of building blocks for Active Pharmaceutical Ingredients (APIs), being α-amino acids and their derivatives widely applied as building blocks. In this work we developed two different strategies for the synthesis of intermediates used on the synthesis of levetiracetam/brivaracetam and ethambutol. The results obtained show that methionine methyl ester can be continuously converted to the desired ethambutol intermediate by Nickel Raney dessulfurization/reduction strategy

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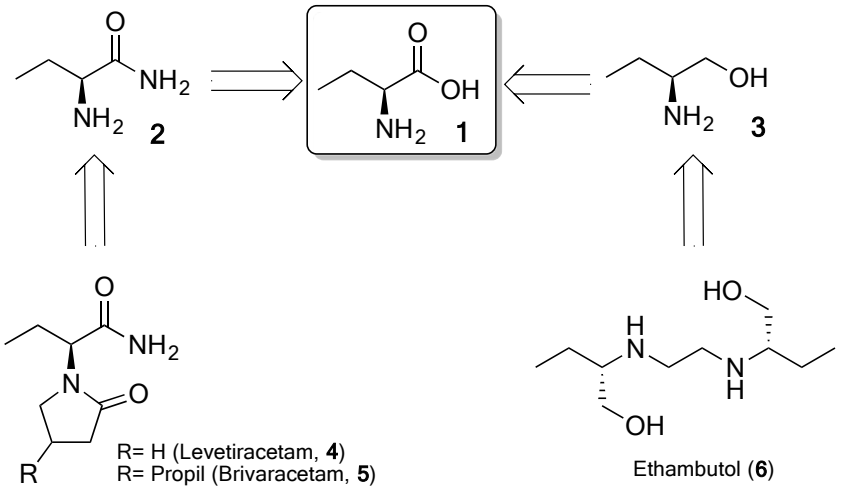
whereas levetiracetam/brivaracetam intermediates could be synthesized by both Nickel Raney (without H_2) and Pd/C – H_2 approach or by photochemical desulfurization.

Introduction

The synthesis of enantiomerically pure compounds plays an important role in the development of building blocks for Active Pharmaceutical Ingredients (APIs), agrochemicals and new materials. Many examples in the literature demonstrate that enantiomeric pairs may exhibit different biological activities such as pharmacodynamics, pharmacokinetics and toxicological or metabolic properties. Therefore, a growing demand for optically pure compounds exists in the pharmaceutical industry.[1] In this context, α-amino acids and their derivatives have been widely applied as building blocks owing to their high abundance, optical purity and low cost.[2] For example, (*S*)-2-amino-butanoic acid (**1**) is a key intermediate in the synthesis of Levetiracetam (**4**) and Brivaracetam (**5**), two antileptic drugs, or Ethambutol (**6**), a medicine used for the treatment of tuberculosis.



Scheme 1. A concise retrosynthetic analysis of Levetiracetam (**4**), Brivaracetam (**5**) and Ethambutol (**6**).

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Several synthetic routes for the preparation of **4** and **5** have already been presented in the literature.[3-24] The most representative methods involve (*S*)-2-amino-butyramide (**2**, Scheme 1) as intermediate.[5,6,9,10,12-14,17-19] On the other hand, the synthetic routes to obtain Ethambutol **6** usually involve (*S*)-2-amino-butan-1-ol (**3**) as the key intermediate (Scheme 1).[21,24]

Preparation of the intermediates **2** and **3** typically involves resolution of the corresponding enantiomers from racemic mixtures by crystallization with L-tartaric acid, which dramatically decreases the overall yield.[22,25,26] Alternatively, asymmetric reactions usually require the use of expensive chiral metal catalysts or sophisticated enzymes to reach the desired yields and enantiomeric excess (Scheme 2).[27-30] Additionally, in some examples, the use of toxic or dangerous reagents such as Cl_2 and $POCl_3$ isneeded.[21]An improved process to produce chiral intermediates **2** and **3** with high purity is therefore highly desirable.

Having in mind the above-mentioned drawbacks, a direct route to the desired enantiomerically pure (*S*)-2-amino-butanoic acid (**1**) by direct desulfurization of L-methionine (**7**) was contemplated. Such an approach was recently developed by our group through a new biocatalyzed cascade reaction where the target compound could be obtained in moderate yields and 98% e.e. [31] Despite being a breakthrough from the viewpoint of biocatalysis, the reaction has low productivity.

Some methods for the desulfurization of disulfides, sulfides or thiols are based on the use of metal catalysts (Ru, Ir, Pd, Raney Nickel) using hydrogen or UV light irradiation.[32-38] Unusual reaction conditions such as hydrogen-oxygen flames[39] or the use of argon-hydrogen plasma jets have also been reported.[40] Therefore, in our continuous work on the development of processes technology which could speed-up or enhance productivity for the synthesis of chiral intermediates,[41-44] we turned our attention towards a chemical desulfurization reaction of methionine and its derivatives based on palladium-catalyzed hydrogenation or treatment with Raney Nickel under continuous-

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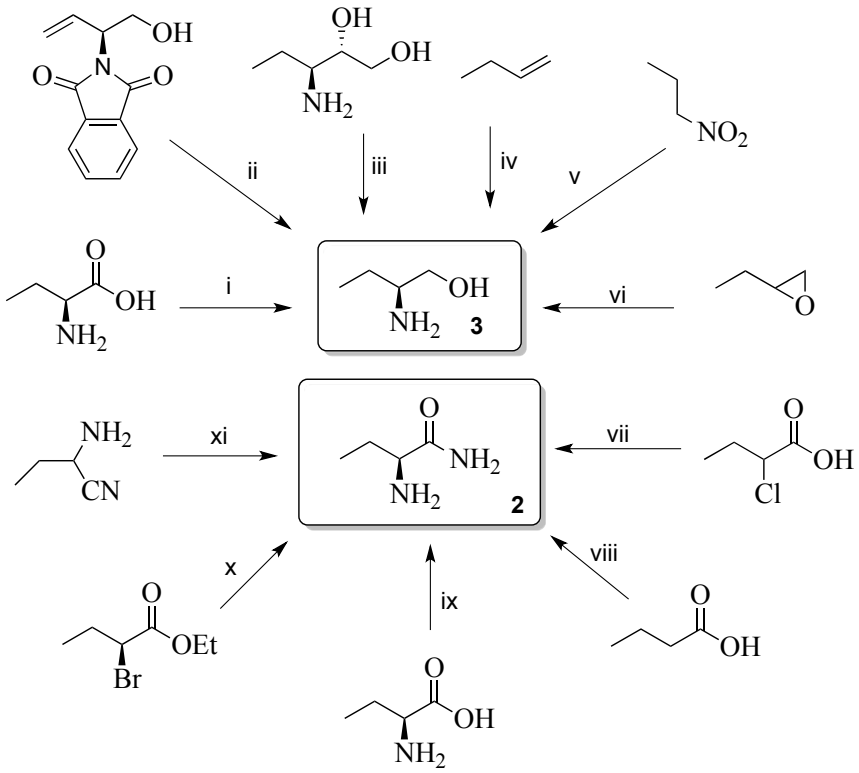
flow conditions. These new approaches significantly enhance the productivity for the synthesis of chiral intermediates (**2**) and (**3**).



i) $SOCl_2$/MeOH, $NaBH_4$, THF/MeOH; ii) H_2, Pd/C, EtOH, ethylenediamine; iii) $NaIO_4$/$NaBH_4$, acetone; iv) CH_3CN/Cl_2, HCl/H_2O, tartaric acid; v) Formaldehyde, Ni-Raney/H2, tartaric acid; vi) BnONa, TsCl/Py, NH_3, HCl, tartaric acid; vii) Cl_2/$POCl_3$, NH_4OH, tartaric acid; viii) Cl_2/$POCl_3$, NH_4Cl/NaOH, tartaric acid; ix)PhCHO/NaOH, NH_3/MeOH; x) NH_3/MeOH, tartaric acid; xi) PhCHO/NaOH, HCl, tartaric acid;

Scheme 2. Synthetic approaches towards the synthesis of Levetiracetam (**4**), Brivaracetam (**5**) and Ethambutol (**6**) key intermediates **2** and **3**.

Results and Discussion

Our desulfurization approach was evaluated for L-methionine (**7**), L-methionine methyl ester (**8**) and L-methionamide (**9**). We have first synthesized L-methionamide (**9**) starting from L-methionine methyl ester hydrochloride (**8**). This transformation took place by treating **8** with ammonia (7N) in methanol at room temperature for 90 h providing a conversion of >97% towards the desired L-

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methionamide (**9**) (90% isolated yield after recrystallization). Using microwave irradiation the reaction time could be shortened to 4 h at 120 °C/8-10bar (97% conversion).

The Raney Nickel desulfurization of L-methionine (**7**) and L-methionamide (**9**) was then studied. According to literature data, [45] the activity of Raney Nickel towards a specific substrate can be adjusted through different catalyst activation procedures that essentially determine the hydrogen content on the final catalyst. Its activity gradually decreases due to loss of this active hydrogen over a period of about 6 months. We decided to prepare our own catalyst from Ni-Al alloy, following an activation procedure previously described.[46] The catalyst was used within one week from its preparation.

The desulfurization reaction of L-methionine (**7**) using Raney Nickel under batch conditions was first described in 1947.[36] The reaction with Raney Nickel afforded the desired aminobutyric acid in only 15% yield. The same procedure was subsequently applied for L- and D-methionine with identical results and enantiomeric excess.[47] The use of Pd/C for the desulfurization of cysteine (thiol) had been previouslydescribed.[35] However, there are no reports on the desulfurization of L-methionine (**7**) (sulfide), and its derivatives.

The results of the reactions both in batch and continuous flow mode are presented in Table 1. Under batch conditions, the use of freshly prepared Raney Nickel is advantageous when compared to the commercial catalyst. On the other hand, under continuous-flow conditions both catalysts performed well yielding the desired product from L-methionine (**7**) and L-methionamide (**9**) in excellent yield and short reaction times.

Table 1. Desulfurization of L-methionine (**7**) and L-methionamide (**9**).

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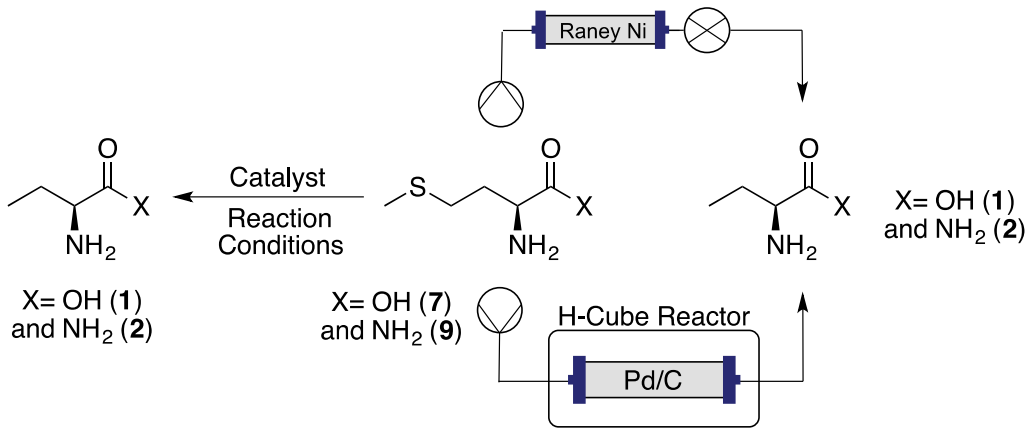

Entry	Conditions		Starting Material	R. T. (min)	Product, Conv. (%)
1	Commercial Raney Ni *	Batch	**7**	240	**1**, 99
2	Fresh Raney Ni **			90	**1**, 99
3	Commercial Raney Ni *	Batch	**9**	240	**2**, 97
4	Fresh Raney Ni **			240	**2**, 97
5	Commercial Raney Ni *	CF	**7**	1	**1**, 99
6	Fresh Raney Ni **			1	**1**, 99
7	H_2, Pd/C			0.2	**1**, 99
8	Commercial Raney Ni *	CF	**9**	1	**2**, 97
9	Fresh Raney Ni **			1	**2**, 97
10	H_2, Pd/C			0.4	**2**, 97

* Aldrich W.R. Grace and Co. Raney® 2800** Raney Nickel freshly prepared (see Supporting Information for further details) Reaction conditions:1)Batch Raney Ni: water, T=80ºC (R=OH) or methanol, T=60ºC (R=NH_2); Flow Raney Ni: 40 mM, water, T=80ºC (R=OH) or 24 mM, methanol, T=60ºC (R=NH_2); Continuous-flow Pd/C: 3mM, water, T=80ºC (R=OH) or 24 mM, methanol, T=60ºC (R=NH_2).

The palladium catalyzed continuous flow reactions required pressures above 40 bar to promote the desulfurization (Entries 7 and 10, Table 1). On the other hand, pressures up to 80 bar were also

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able to desulfurize L-methionine (**7**) yielding a product with excellent enantiomeric excess (See supporting Information).

The main disadvantage of the Raney Nickel catalyzed process is the need of alow substrate/catalyst ratio for achieving the desired conversion and selectivity. The reaction time for the desulfurization of **7** (Entry 1, Table 1) using batch conditions could be reduced from 4 h to 1.5 h (Entry 2, Table 1), with no impact on the conversion, by changing from a commercial source of Raney Nickel to a freshly prepared Raney Ni. In the case of L-methionamide (**9)** no difference was observed between the catalysts studied (Entries 3 and 4, Table 1). When translating to a continuous-flow protocol, no difference can be observed for the catalyst source for the desulfurization of L-methionine (**7**) or L-methionamide (**9**) since the reaction times are extremely short for both Raney Ni catalysts tested (Entries 5, 6, 8 and 9, Table 1). It is important to note that for the reactions catalyzed by Raney Nickel, the addition use of hydrogen gas is not needed. An impressive reduction on reaction time (12 and 24 s depending on the L-methionine derivative) could be observed when using H_2 on the H-Cube reactor loaded with a Pd/C cartridge for the desulfurization reaction. This H_2-Pd/C desulfurization reaction presents a lower substrate/catalyst ratio leading to an increase in productivity when compared to the Raney Nickel process. The disadvantage of this protocol is the half-life of the Pd/C cartridge, which is reduced due to sulfur poisoning (Entries 7 and 10, Table 1). In both cases a certain degree of metal leaching was observed, 130 ppm for Ni and 70 ppm for Pd.

For the substrate L-methionine methyl ester (**8**) some particularities were observed when commercial Raney Nickel (Aldrich W.R. Grace and Co. Raney® 2800) was applied. While under batch conditions (Entry 1, Table 2) a high extent of ester hydrolysis and incomplete desulfurization was observed (L-Methione (**7**)=19%, (*S*)-2-amino-butanoic acid (**1**)=16% and L-Methionine

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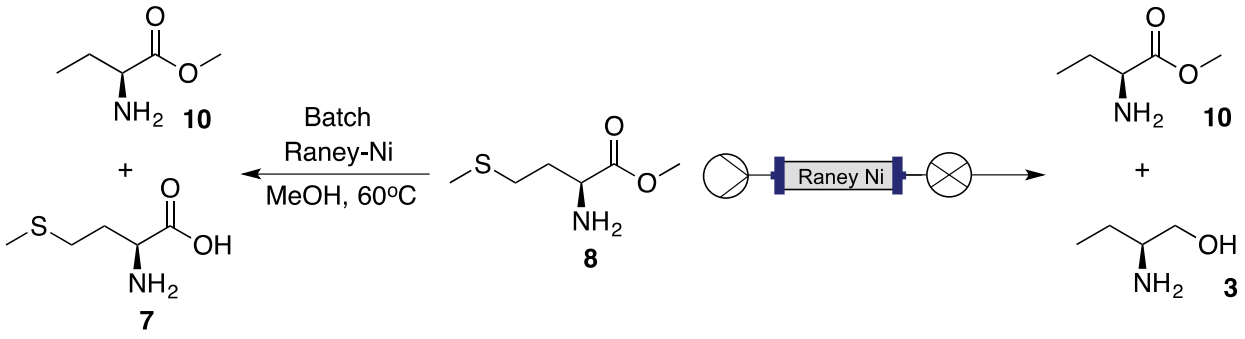
methyl ester (**8**)=18%), under continuous-flow conditions a large amount of *S*-2-amino-butan-1-ol (**3**) formation was noticed (Entry 3, Table 2). On the other hand, when the freshly prepared Raney Nickel was used, the reaction yielded the desired product methyl (*S*)-2-amino-butanoate (**10**) at high conversion both in batch and flow, as can be seen in Table 2 (Entries 2 and 4). The hydrolysis observed could be ascribed to the Lewis acid character of the catalyst or its oxidized counterpart, and the presence of water in the pores of the Raney Nickel catalyst from its preparation. When higher temperatures and prolonged reaction times were applied, a higher amount of hydrolysis was observed.

Table 2.Desulfurization of L-Methionine methyl ester (**8**)



Entry	Conditions		R. T. (min)	Conv. (**10** and **3**, %)
1	Commercial Raney Ni *	Batch	240	82 (**10**, 47)
2	Fresh Raney Ni **		90	**10**, 98
3	Commercial Raney Ni *	CF	1.2	99 (**10**, 52 / **3**, 43)
4	Fresh Raney Ni **		1.2	**10**, 98

* Aldrich W.R. Grace and Co. Raney® 2800** Raney Nickel freshly prepared (see supporting information for further details). Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis. Reaction conditions: 6mM, MeOH, 60ºC.

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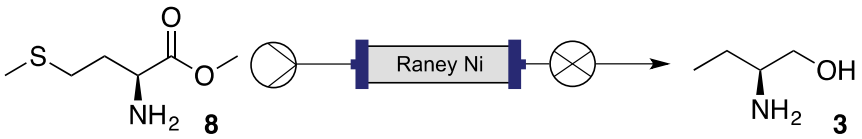
Encouraged by the formation of **3** via ester reduction under continuous flow conditions with freshly prepared Raney Nickel, we decided to further investigate this transformation, as **3** is an important intermediate in the synthesis of Ethambutol. Results are presented on Table 3.

The first attempt to generate *S*-2-amino-butan-1-ol (**3**) from L-methionine methyl ester (**8**) using commercial Raney Nickel (Aldrich W.R. Grace and Co. Raney® 2800) in flow resulted in a large amount of methyl *S*-2-amino-butanoate (**10**). Amino-alcohol (**3**) was obtained in only 43% yield (Entry 1, Table 3). Reducing the concentration of substrate favored the *S*-2-amino-butan-1-ol (**3**) formation (Entry 2, Table 3), while increasing residence time led to 97% of conversion (Entry 5, Table 3).

The best results for the synthesis of *S*-2-amino-butan-1-ol (**3**) were developed starting from L-methionine methyl ester (**8**) and using the commercial Raney Nickel (Aldrich 2800, pH 9) under continuous flow conditions. Freshly prepared Raney Nickel (pH 7) was also capable of producing *S*-2-amino-butan-1-ol (**3**), but at a lesser extent when compared to the commercial catalyst. Analogously, this reaction was tested under batch conditions and the formation of the *S*-2-amino-butan-1-ol (**3**) was not observed.

Table 3: Desulfurization and ester reduction of L-Methionine methyl ester (**8**).



Entry	R. T. (min)	[**8**] (mM)	Conv. (%)
1	1.2	6	43
2	1.2	3	69

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3	2.4	3	74
4	6	3	90
5	12	3	97

Reaction conditions: 6mM, MeOH (R=OH, 20%H_2O), T=50ºC.

It should be noted that the removal the methylthio group from L-methionine (**7**) mediated by Raney Ni had been previously described,[33-36] as well as the reduction of carboxylic esters into their corresponding alcohol, however only in the presence of H_2.[48] On the other hand, performing both transformations in a single step without H_2, as demonstrated in Tables 1 to 3, had not been described so far.

Although metal catalysis gave good results, we were also interested in evaluating the use of light (UV-C) as a desulfurization agent for L-methionine (**7**) and its derivatives. The photo-desulfurization of sulfur-containing amino acids, such as L-cystine and L-methionine (**7**), has been studied under batch conditions in the 1960-1970's with a few published studies.[37,38,49]In these early reports, the photo-desulfurization was performed using high potent lamps or using photosensitizers and/or filters. Despite the advantages of the small dimensions of mesofluidic reactors that can ensure excellent light irradiation of the entire reaction medium, leading to a better radiation homogeneity,[50] the photo-desulfurization of L-methionine (**7**) and its derivatives, especially under flow conditions, has not been exploited previously. The UV irradiation has been predominantly used to enable photochemical transformations because of its high energy content, and for this reason it was chosen to promote the S-C bond dissociation of the substrates.[50]

Photo-desulfurizations of L-methionine (**7**), L-methionamide (**9**) and L-methionine methyl ester (**8**) were evaluated using a UV-C8W lamp (256 nm) under flow conditions. A methanol solution of

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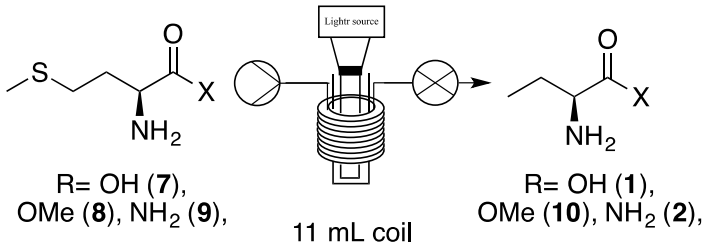
the desired starting material was pumped through the reactor for compounds **8** and **9**. A mixture of methanol/water (1:4) was used for L-methionine (**7**). The reactor consisted of transparent PFA tubing (ID=1,6 mm, 11 mL) coiled around the desired lamp. (See Supporting Information for further details). Temperature was measured during the reaction by an infrared sensor and observed to be at around 50ºC. Other UV-C lamps of 20 and 36 W were also applied leading to poor results, even when the temperature was controlled by different cooling systems. After optimization of starting material concentration (see Supporting Information for further details), residence time was evaluated (Table 4).

Table 4. Photo-desulfurization under continuous-flow conditions.



Entry	Starting Material	R. T.(min)	Conv. (%) *
1	OH (**7**)	60	32 (**1,** 20)
2		120	48 (**1,** 34)
3		180	60 (**1,** 42)
4	OMe (**8**)	60	52 (**10,** 26)
5		120	80 (**10,** 51)
6		180	88 (**10,** 59)
7	NH_2 (**9**)	60	70 (**2,** 45)
8		120	85 (**2,** 65)

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9		180	89 (**2,** 71)

***** Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis. Reaction conditions: 6mM, MeOH (when R=OH, use 20%H_2O), 50ºC, Reactor Volume = 11mL. In all cases it was possible to observe some unknown impurities. Conversion was calculated as a sum of the integration of all peaks present in the chromatogram minus the starting material peak area %;

During the process development, pure water was tested as solvent for **7** (R=OH) and **9** (R=NH_2). Lower selectivity was observed due to formation of high amounts of sulfoxide. When the solvent was changed to methanol, the sulfoxide formation was dramatically reduced. Pure methanol could not be used as solvent for L-methionine (**7**) because of its poor solubility, preventing the desulfurization of this substrate. Best results were achieved for L-methionamide (**9**) in methanol, reaching a selectivity of 70%. Unfortunately, the same result was not observed for L-methionine methyl ester (**8**), even using the same solvent as for L-methionamide(**9**).

Conclusion

In conclusion, we have developed an alternative route for the synthesis of both *S*-2-amino-butyramide (**2**) and *S*-2-amino-butan-1-ol (**3**), key intermediates for the synthesis of levetiracetam/ brivaracetam and ethambutol, starting from cheap reagents such as L-methionine or its derivatives. Ethambutol intermediate *S*-2-amino-butan-1-ol (**3**) could be synthesized on a cascade desulfurization/reduction step by using Raney Nickel in very short reaction times (12 minutes) and high yields (up to 97%). In the case of levetiracetam/brivaracetam intermediate, three different strategies could be applied where the use of Nickel Raney in the absence of H_2 or Pd/C-H_2 could lead to the desired molecule in very short reaction times (1.2 and 0.4 minutes, respectively) and high yields (>98%), as well as the photochemical step where no additives were needed to the desulfurization of methionine derivatives in good yields and moderated selectivities (89% and 71% respectively) in reasonable reaction times (180 minutes).

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