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N-Alkylation of *N*-arylsulfonyl-α-amino acid methyl esters by trialkyloxonium tetrafluoroborates

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ABSTRACT

In this work we present the results obtained for the N-alkylation of a series of *N*-arylsulfonyl-α-amino acid methyl esters bearing different substituents at the 4-position of the sulfonamide aromatic ring. In particular, we compare the reactivity of these species with diazomethane and trimethyloxonium tetrafluoroborate in N-methylation processes. Diazomethylation is unsuccessful for *N*-arylsulfonamide derivatives containing electron-releasing groups on the aromatic ring. In these cases trimethyloxonium tetrafluoroborate is the reagent of choice for the direct and quantitative N-methylation. Further we extend our evaluation to the use of triethyloxonium tetrafluoroborate. This reagent shows to be very efficient in order to prepare *N*-ethyl derivatives of *N*-arylsulfonyl-α-amino acid methyl esters. An experimental protocol similar to that used for N-methylation with trimethyloxonium tetrafluoroborate is applied for the N-ethylation.

1. Introduction

N-Alkyl-α-amino acids are a class of amino acid derivatives. They find application as synthetic building blocks in medicinal chemistry as well as molecular probes in studies related to the structural properties and biological activities of *N*-alkylated peptides and peptidomimetics.[1] These are species largely represented in nature, especially in marine organisms.[2] *N*-Alkyl-α-amino acids are not only biologically active; the substitution of *N*-alkyl-α-amino acids and their β^3 homologs[3] into biologically relevant peptides has led to important insights into the backbone characteristics required for the expression of their bioactivities,[4] allowing the design of analogues with improved biological profiles.[5] *N*-Methyl-α-amino acids are found in nature as free compounds and as structural constituents of various peptides belonging to the cyclosporine,[6] dolastatin,[7] and didemnin families.[8] The incorporation of *N*-methyl and in general of different *N*-alkyl-α-amino acids into peptide chains often improves proteolytic stability, conformational rigidity, lipophilicity, and transport properties.[9]

A wide arsenal of highly chemoselective and efficient methodologies have been sought and reported for the preparation of *N*-alkyl-α-amino acid derivatives.[10] Among them, some procedures directed at the N-methylation of α-amino acids generally describe the treatment of these compounds with strong bases followed by the quenching of the intermediate anionic nucleophiles with the desired alkyl halides, however, sometimes racemization due to the use of strong bases takes place.[10] This two-step procedure works well for the preparation of *N*-methylated derivatives, but it fails when *N*-ethylated products are to be obtained in satisfying overall yields.[11] Alternatively, only a few protocols can be found in the literature for N-ethylation of α-amino acids.[12] N-Chloromethylation of *N*,*O*-protected α-amino acids represents another route to *N*-ethylated species.[13] In this procedure however the use of cuprates is needed to create the reactive anionic intermediates in situ.

One of the most widely employed processes of N-methylation of α-amino acids by alkylation under various conditions is to utilize their *N*-arylsulfonyl protected derivatives. The sulfonamide protection in fact greatly enhances the acidity of the α-NH function,[14] allowing a rapid deprotonation under basic conditions. In the presence of the required alkylating reagent it furnishes the desired *N*-arylsulfonyl-*N*-methyl-α-amino acids. Alternatively, a Mitsunobu protocol could be used to achieve the N-alkylation of *N*-sulfonamide α-amino acid derivatives.[15] In these applications the tosyl residue, a widely used protecting group for the α-amino function of natural and synthetic amino acids,[16] has been employed.[17] The two-step Mitsunobu procedure requires the generation of the nitrogen nucleophile and then the reaction with the alkylating agents. However, the use of strong deprotonating reagents could induce racemization to variable extents. Moreover, tedious chromatographic

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purifications must be applied in order to isolate and purify the final products from the phosphinoxide by-product, especially upon scale-up.

N-Arylsulfonyl groups are also used as pharmacophores, especially when substituted with halogens at the 4-position of the aryl portion.[18] *N*-Arylsulfonyl-α-amino acids are in fact constituents of metalloproteases and carbonic anhydrase inhibitors.[19] Furthermore, *N*-alkyl-sulfonamides have been found to possess a widespread spectrum of bioactivities, including antibacterial, antidiabetic, diuretic, and antithyroid effects.[20] Recently, these compounds have been tested as HIV protease inhibitors in retroviral therapy,[21] and many of them are still under clinical evaluation for their antitumor potential.[22] Thus, the knowledge of the reactive properties of *N*-arylsulfonyl-α-amino acids under different N-alkylation conditions, either for the *N*-methyl or the *N*-ethyl functionalization, is of great importance for the development of new classes of metalloprotease inhibitors.[23] It is also relevant in QSAR studies concerning these particular families of interesting pharmaceuticals.

Various 4-substituted *N*-arylsulfonamides can be *N*-alkylated on solid support by using a modification of the Kenner safety-catch strategy.[24] This approach, however, requires a large excess of alkylating reagents and bases and it is not adequate for large scale preparation. The N-alkylation of *N*-monosubstituted arylsulfonamides containing amino acidic frames has been conducted in ionic liquids by alkyl halides in reactions assisted by strong bases.[25] The Fukuyama–Mitsunobu reaction is another method to realize the chemospecific N-alkylation of secondary arylsulfonamides containing substituents strongly deactivating on the aromatic ring.[15] The use of Lewis acids and ruthenium-catalyzed processes has been reported to be effective in the N-alkylation of *N*-arylsulfonamides.[26] More recently, the use of alcohols in processes assisted by copper(II) species has been proposed at high temperature and in the presence of air.[27]

The synthesis of *N*-methyl and *N*-ethyl-α-amino acids by nucleophilic substitution should generally be represented by a short sequence, applying simple chemical techniques, which can also offer the advantage of a minimal manipulation of the starting materials. From the standpoint of the total synthesis of biologically active natural products, mild, and effective methods for the N-alkylation of α-amino acid derivatives are very appealing and they may represent the most frequently used reactions. In our previously published papers, we have proposed a 'one-pot' procedure based on the use of diazomethane as the methylating reagent in order to obtain *N*-methyl-α-amino acids and their β^3 homologs in a fast and clean way, using *N*-arylsulfonyl derivatives of natural α-amino acids.[28] In those works, the nosyl group has been used to drastically enhance the α-NH function acidity. Although the use of diazomethane presents important improvements in the N-methylation of α-amino acid methyl esters, it is to be used with great caution because of its explosive and toxic nature, especially if preparative scales are entertained. Recently, trimethylsilyldiazomethane has been proposed by our research group as an alternative to diazomethane.[29] Trialkyloxonium salts could play an important role in the preparation of *N*-alkyl-α-amino acids and derivatives. However, the treatment of natural or synthetic α-amino acids with trialkyloxonium species has been confined by the literature in a very few reports. For example, triethyloxonium tetrafluoroborate has been used to promote N-ethylation of Boc- and *Z*-protected α-amino acids.[11] However, in this case it is necessary to bypass the poor reactivity imposed by the low acidity of the NH residue and to produce nucleophilic double anions, which can further be *N*-ethylated. As a consequence, the reported method suffers from the need of a pretreatment of the starting materials with lithium bases. In our previous paper[30] we have proposed triethyloxonium tetrafluoroborate for the direct N-ethylation of *N*-nosyl protected α-amino acid methyl esters.

2. Results and discussion

In the present investigation, and in order to assess the main advantages of the use of trialkyloxonium salts over the existing procedures, we undertook the study of the reactivity of a series of *N*-arylsulfonyl-α-amino acid methyl esters containing differently 4-substituted aromatic rings on the protective group moiety. This aimed at further considering any possibilities in modulating the acidity and nucleophilicity of the α-NH proton, two characteristics required for an efficient N-alkylation process. The increased acidity of the sulfonamide NH functionality can allow the chemoselective N-methylation in a peptide structure.[31] Thus, the reactivity of the NH residue in α-amino acids can sensibly be enhanced or modulated by having a substituted sulfonyl group attached to it. Coordination studies on *N*-tosyl-α-amino acids have also demonstrated that, since the sulfonamide NH residue can become an excellent nucleophile, a sulfonyl group having strong electronic effects is able to exert a modulation of the reactive properties of the NH functionality.[32]

We started our evaluation by subjecting the series of *N*-arylsulfonyl-α-amino acid methyl esters **1a**–**i** to the N-methylation with diazomethane (Scheme 1), according to the synthetic procedure previously used for the process performed on the *N*-nosyl protected derivatives **1a**–**d**.[28a] *N*-Arylsulfonyl-α-amino acid methyl esters **1a**–**i** have been prepared in excellent yields by reacting the corresponding α-amino acid methyl ester hydrochloride with the required arylsulfonyl chloride in the presence of triethylamine and applying a well known general experimental protocol.[30]

1a-i **2a-i**

Scheme 1. Diazomethylation of **1a**–**i** under neutral conditions.

Our first aim was to compare the reactivity of a series of *N*-arylsulfonyl-α-amino acid methyl esters containing electron-withdrawing (F, Cl), and electron-releasing (CH_3, OCH_3) groups at the 4-position of the aromatic portion of the sulfonamide moiety, as opposed to their *N*-nosyl protected analogues.

Diazomethylation under neutral conditions[28] allows a mild, clean, and quantitative N-methylation of *N*-nosyl-α-amino acid methyl esters **1a**–**d**. Thus, we selected L-alanine methyl ester as an ideal molecular model in order to evaluate the influence on the diazomethylation process exerted by the different substituents at the 4-position of the sulfonamide aromatic ring. The electronic effects exerted by the 4-substituents on the reactivity of sulfonamides **1a**–**i** during their N-methylation can easily be recognized from the data showed in Table 1. Diazomethane presents optimal properties for quantitative N-methylation of the α-amino acid derivatives **1a**–**d**, without need of other reagent assistance in a 'one-pot' process. However, it is worth to note that, in the case of the *N*-arylsulfonyl derivatives **1e**–**i** containing 4-substituents, which are different from the NO_2 group (Table 1), this alkylating reagent gives variable overall yields in the corresponding final products **2e**–**i**. Results refer to the yields in isolated products after a maximum reaction time of 40 min. It is important to note that conversion of the starting materials **1a**–**d** is complete after this time, while it is evident that *N*-arylsulfonyl derivatives **1e**–**i** are showed to be much

Table 1
N-Methylation of *N*-arylsulfonyl-α-amino acid methyl esters **1a**–**i**: use of diazomethane

Entry	R^1	R^2	Product	Yields[a] (%)	Yields[b] (%)
1a	NO_2	CH_3	**2a**	100	—
1b	NO_2	$CH(CH_3)_2$	**2b**	100	—
1c	NO_2	$CH(CH_3)CH_2CH_3$	**2c**	100	—
1d	NO_2	CH_2Ph	**2d**	100	—
1e	F	CH_3	**2e**	23	62
1f	Cl	CH_3	**2f**	19	59
1g	CH_3	CH_3	**2g**	12	50
1h	OCH_3	CH_3	**2h**	7	47
1i	H	CH_3	**2i**	15	55

[a] Isolated yields after 40 min.
[b] Isolated yields after 120 h. Entries **1a**–**d** have already been published by the authors.[28a]

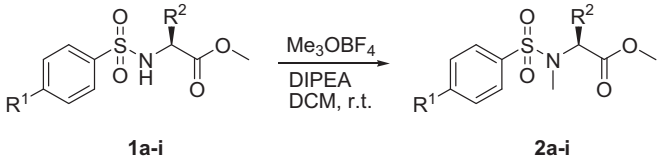
less reactive than the 4-NO_2 substituted analogues. In the case of sulfonamides **1e**–**i** in fact very low yields in isolated products are obtained after 40 min. Moreover the amount of the respective *N*-methylated derivatives does not appreciably increase even after longer times of treatment. Conversions of the less acidic *N*-arylsulfonyl derivatives containing a halogen atom (F, Cl), or electron-releasing groups (CH_3, OCH_3), or featuring no substitution at the 4-position of the aromatic ring, are not complete also after 120 h (Table 1). In the case of **1h**, a 47% overall yield in recovered product is obtained after flash column chromatography. For the other *N*-arylsulfonamides **1e**–**g** and **1i** yields in isolated product **2e**–**g** and **2i** were 62, 59, 50, and 55%, respectively. Note that in the case of the treatment of sulfonamides **1e**–**i** flash column chromatography needed for the recovery and purification of the corresponding *N*-methyl derivatives **2e**–**i**. Furthermore, it should be considered that additions of 10 mL of fresh diazomethane every 6 h were needed in order to obtain **2e**–**i** in fair yields.

From the data collected for the diazomethylation under neutral conditions, it can further be argued that the electronic nature of these various 4-substituents should be the main effect responsible for the observed reactivity order showed by sulfonamides **1a**–**i**. The reactivity of the NH function in the *N*-arylsulfonyl-α-amino acid methyl esters **1a**–**i** appears to be correlated closely with the electronic effects imposed by the nature of each of the different 4-substituents featured by the *N*-arylsulfonyl moiety. The acidity of the sulfonamide NH proton is a crucial factor toward the effectiveness of diazomethylation: the pK_a value 10 of the methylating species[33] requires the presence of strongly electron-withdrawing substituents (such as NO_2) at the 4-position of the sulfonamide aromatic ring, able to drastically enhance the NH acidity, which determines the high reactivity observed for **1a**–**d**. The acidity of the same functionality is sensibly reduced by the 4-substituents exerting an electron-releasing effect, such as CH_3 and OCH_3 in compounds **1g**–**h**. Moderate modulation of the NH reactivity toward diazomethane is, instead, observed in the case of sulfonamides **1e**,**f** bearing a halogen substituent.

The unsatisfying yields observed for the less reactive *N*-arylsulfonamides **1e**–**i**, the need for a repeated addition of large amounts of methylating reagent, its chemical nature, and the slow kinetics of reaction strongly limit the usefulness of diazomethylation.

The failure of diazomethane led us to direct our attention to different and more efficient *N*-alkylating 'one-pot' methodologies. To this aim, we selected trialkyloxonium species. We predicted that the utilization of trialkyloxonium tetrafluoroborates for the N-alkylation of *N*-arylsulfonyl-α-amino acid methyl esters could afford a method general in its applicability, convenient, mild, and which would not require the use of hazardous reagents. As recently proposed by our research group,[30] triethyloxonium tetrafluoroborate can successfully be used for the chemospecific N-ethylation of *N*-nosyl protected α-amino acid methyl esters. Our approach relied upon an in situ 'one-pot' ethylation at the nitrogen atom, avoiding any previous step necessary to generate the required nucleophile. The treatment proceeds smoothly in DCM solution and in the presence of *N*,*N*-diisopropylethylamine (DIPEA). Pure *N*-nosyl-*N*-ethyl derivatives are recovered in excellent to quantitative yields after a simple work-up protocol. The alkylation of the hindered tertiary amine by trialkyloxonium reagents is quite slow,[30] and does not influence the course of reaction. However in our data already published we did not use different *N*-arylsulfonyl groups besides the nosyl for the protection of the NH functionality. On the basis of these preliminary results we thought that trimethyloxonium tetrafluoroborate could be useful also for the N-methylation of *N*-arylsulfonyl-α-amino acid methyl esters containing different substituent groups at the 4-position of the sulfonamide aromatic ring.

Scheme 2 displays the results obtained by reacting the series of compounds **1a**–**i** with trimethyloxonium tetrafluoroborate. The N-methylation was performed in dichloromethane and in the presence of DIPEA, at room temperature. The reaction was found to be fast and chemospecific in all the analyzed cases (Table 2). It also showed a complete conversion of all the sulfonamide precursors **1a**–**i** in a variable time between 15 and 110 min. The corresponding *N*-methylated derivatives **2a**–**i** were recovered by a simple hydrolytic work-up of the reaction mixture. No flash column chromatography was needed in order to purify the final compounds **2a**–**i**, which were isolated in quantitative yields.



Scheme 2. Reaction of **1a**–**i** with trimethyloxonium tetrafluoroborate.

Table 2
N-Methylation of *N*-arylsulfonyl-α-amino acid methyl esters **1a**–**i**: use of trimethyloxonium tetrafluoroborate

Entry	R^1	R^2	Product	Yield[a] (%)	Time[b]
1a	NO_2	CH_3	**2a**	Quantitative	15
1b	NO_2	$CH(CH_3)_2$	**2b**	Quantitative	15
1c	NO_2	$CH(CH_3)CH_2CH_3$	**2c**	Quantitative	15
1d	NO_2	CH_2Ph	**2d**	Quantitative	15
1e	F	CH_3	**2e**	Quantitative	60
1f	Cl	CH_3	**2f**	Quantitative	75
1g	CH_3	CH_3	**2g**	Quantitative	90
1h	OCH_3	CH_3	**2h**	Quantitative	110
1i	H	CH_3	**2i**	Quantitative	90

[a] Isolated products.
[b] Time are expressed in min.

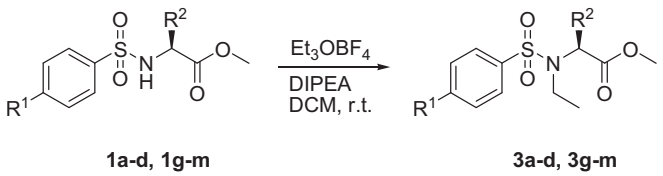
From the data displayed in Table 2, it is once again evident the effect exerted by the strong electron-withdrawing substituent NO_2 in nosyl sulfonamides **1a**–**d**. The sulfonamide proton acidity is drastically influenced by the electronic characteristics of the substituent placed on the aromatic ring, and the enhanced reactivity of the NH functionality determines the fast kinetics observed for the N-methylation process.

Compounds **2a**–**d** are formed in 15 min at room temperature, and reactions proceed with complete consumption of the precursors **1a**–**d**. We used L-alanine methyl ester as a model, similarly to the study performed on the diazomethylation under neutral

conditions, as previously discussed. The presence of a halogen atom at the 4-position of the sulfonamide aromatic ring led to larger reaction times, as verified for sulfonamides **1e**–**f**. Longer reaction times are required in the case of the less acidic sulfonamide derivative **1h** bearing the strong electron-releasing group OCH_3. In all cases the corresponding products were recovered in quantitative yields avoiding chromatographic purification of the crude reaction mixtures. It could be concluded that the chemospecific N-methylation of *N*-arylsulfonyl-α-amino acid methyl esters can straightforwardly be realized by using trimethyloxonium tetrafluoroborate. This represents an effective methylating reagent, which, contrary to diazomethane, can be safely handled and offers great advantages in terms of effectiveness and applicability for the N-methylation of differently reactive *N*-arylsulfonamides.

While diazomethane can easily be prepared in the laboratory scale, diazoethane is less available. Triethyloxonium salts could successfully allow the preparation of *N*-ethyl derivatives of α-amino acids. Hence our work continued with the exploitation of the potentialities of trialkyloxonium salts in obtaining *N*-alkylated derivatives of *N*-arylsulfonyl-α-amino acid methyl esters in which the aromatic ring is substituted with groups other than NO_2. This further test was triggered by our interest in the biological implications that some *N*-ethyl derivatives of α-amino acids and peptides can have.[34] The aim was, again, to propose an easy, mild, efficient, and direct chemospecific N-ethylation, which could minimize synthetic manipulations on the initial amino acid materials.

The *N*-arylsulfonyl-α-amino acid methyl esters **1a**–**d**, **1g**–**m** were subjected to treatment with trialkyloxonium tetrafluoroborate at room temperature, in dichloromethane and in the presence of the base DIPEA (Scheme 3). Sulfonamides **1a**–**d**, containing the strongly electron-withdrawing group NO_2, were smoothly *N*-ethylated, as already reported[30] (Table 3), confirming the effects exerted by that kind of 4-substitution on the enhancement of the acidity of the sulfonamide NH residue. The reactions were complete in 10 min, and the final products **3a**–**d** were recovered in excellent to quantitative yields without the need for flash column chromatography. Relatively lower reactivity was observed for the less acidic *N*-arylsulfonamides **1g**–**i**, for which there was either no substitution or an electron-releasing group placed at the 4-position of the aromatic ring. The reaction proceeded with complete consumption of the respective *N*-arylsulfonamide precursors **1g**–**i** in a time ranging between 85 and 120 min. This allowed the recovery of the corresponding pure *N*-ethylated derivatives **3g**–**i** in excellent yields without flash column chromatography. *N*-Arylsulfonamides **1l**–**m** were, finally, selected in order to assess the possible effects deriving from the steric hindrance caused by the side-chain size of the α-amino acid frame on the N-ethylation process. From the data obtained, it seems that bulkier amino acid side-chains were not interfering with the N-alkylation performed with triethyloxonium tetrafluoroborate. In the latter cases, the kinetics observed for the processes still remained fast (the reaction was completed in 65 and 70 min, for **1l** and **1m**, respectively), and the corresponding *N*-ethylated derivatives **3l**–**m** were recovered pure in excellent yields without the need for flash column chromatography.



Scheme 3. Reaction with triethyloxonium tetrafluoroborate.

Table 3
N-Ethylation of *N*-arylsulfonyl-α-amino acid methyl esters: use of triethyloxonium tetrafluoroborate

Entry	R^1	R^2	Product	Yield[a] (%)	Time[b]
1a	NO_2	CH_3	**3a**	96	10
1b	NO_2	$CH(CH_3)_2$	**3b**	89	10
1c	NO_2	$CH(CH_3)CH_2CH_3$	**3c**	95	10
1d	NO_2	CH_2Ph	**3d**	99	10
1g	CH_3	CH_3	**3g**	91	90
1h	OCH_3	CH_3	**3h**	90	120
1i	H	CH_3	**3i**	93	85
1l	F	$CH(CH_3)_2$	**3l**	94	65
1m	Cl	$CH_2CH(CH_3)_2$	**3m**	93	70

[a] Isolated products.
[b] Time are expressed in min.

3. Conclusion

We exploited the possible use of different methods for the N-alkylation of 4-substituted *N*-arylsulfonyl-α-amino acid methyl esters. Diazomethane and trimethyloxonium tetrafluoroborate showed a significantly different behavior in the N-methylation. For both methylating agents, the reaction seemed to be controlled by the acidity of the sulfonamide NH functionality. Systems characterized by a drastically enhanced acidity of the NH residue, e.g., *N*-nosyl derivatives, can efficiently be *N*-methylated either by trimethyloxonium tetrafluoroborate or diazomethane. The latter showed to be basic enough to generate the conjugated base of the sulfonamide derivatives, allowing diazomethylation under neutral conditions. However, the protocol based on the use of diazomethane fails when the acidity of the sulfonamide NH moiety is sensibly reduced. In the cases of *N*-arylsulfonamides not containing substituents at the 4-position of the aromatic ring, or bearing electron-releasing groups at the same carbon atom, the treatment with diazomethane is ineffective. In these circumstances, the base DIPEA, able to assists the N-methylation when combined with trimethyloxonium tetrafluoroborate, allowed the rapid, clean, and quantitative reaction also in the presence of *N*-arylsulfonyl-α-amino acid methyl esters containing a less acidic NH functionality. The effect of the different types of substituent placed at the 4-position of the *N*-arylsulfonamide moiety is crucial for the NH properties also when *N*-methylated derivatives have to be prepared by using trimethyloxonium tetrafluoroborate. This reagent can successfully replace diazomethane. In fact, trimethyloxonium tetrafluoroborate is more efficient than diazomethane in the N-methylation of less reactive substrates and it is much safer. The data collected about the N-ethylation with triethyloxonium tetrafluoroborate of the same systems further demonstrate the validity of the discussed methodology in providing *N*-ethylated derivatives of *N*-arylsulfonyl-α-amino acid methyl esters.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures and distilled prior to use. Commercially available reagents were purchased from Aldrich Chemical Co. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker Avance 300 spectrometer by using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in hertz (Hz). Reaction mixtures were monitored by TLC using Merck Silica gel 60-F_{254} precoated glass plates, and UV light (254 nm) or 0.2% ninhydrin in ethanol and charring as visualizing agent. Kieselgel 60H without gypsum was used for flash column chromatography. Reactions were performed using flame dried glassware

and under an inert atmosphere (dry N_2). GC–MS analyses were performed by HP-5MS (30 m×0.25 mm, PhMesiloxane capillary column). The mass detector was operated in the electron impact ionization mode (EIMS) with an electron energy of 70 eV. The injection port was heated to 250 °C. The oven temperature program was initially set at 100 °C with a hold of 2 min and ramped to 280 °C at 14 °C/min with a hold of 10 min. Methane gas at a pressure of ca. 2 Torr was used as the CI reagent gas. The DCM solution of diazomethane was prepared from *N*-methyl-*N*-nitrosourea using a classical procedure.[35] The concentration of the diazomethane solution (0.66 M) was obtained by back-titration performed with a standard benzoic acid solution. (Caution: diazomethane is highly toxic. Hence, this reagent must be handled carefully). DCM solutions of diazomethane are stable for long periods if stored on KOH pellets at −20 °C. *N*-Nosyl-α-amino acid methyl esters **1a**–**d**, and *N*-methyl-*N*-nosyl-α-amino acid methyl esters **2a**–**d** were prepared by diazomethylation according to our previously published protocol.[28] Spectral data for **2a**–**d** are already reported.[28a] *N*-Ethyl-*N*-nosyl-α-amino acid methyl esters **3a**–**d** were prepared as reported elsewhere.[30]

4.2. General procedure for the reaction of *N*-arylsulfonyl-α-amino acid methyl esters 1a–i with trimethyloxonium tetrafluoroborate

To a solution of **1a**–**i** (1 mmol), in DCM (20 mL) were added DIPEA (3.5 mmol) and solid trimethyloxonium tetrafluoroborate (2.5 mmol). The reaction mixture was stirred for 15–110 min at room temperature and under an inert atmosphere. The mixture was then quenched with 1 N aqueous HCl until pH 2, and extracted with DCM (3×10 mL). The organic layer was washed with 1 N aqueous NaOH (3×10 mL) and then brine (10 mL). The combined organic layers were dried with Na_2SO_4, and evaporated to dryness under reduced pressure conditions to give the respective *N*-methylated derivatives **2a**–**i** as colorless oils in quantitative yields.

*4.2.1. N-Methyl-N-4-nitrophenylsulfonyl-L-alanine methyl ester (**2a**).* Treatment of a solution of *N*-4-nitrophenylsulfonyl-L-alanine methyl ester (**1a**) (100 mg, 0.347 mmol) in dry DCM (20 mL) with DIPEA (0.212 mL, 1.21 mmol) and trimethyloxonium tetrafluoroborate (128 mg, 0.868 mmol) for 15 min afforded the title compound **2a** (105 mg, quantitative yield).

*4.2.2. N-Methyl-N-4-nitrophenylsulfonyl-L-valine methyl ester (**2b**).* Treatment of a solution of *N*-4-nitrophenylsulfonyl-L-valine methyl ester (**1b**) (100 mg, 0.316 mmol) in dry DCM (20 mL) with DIPEA (0.193 mL, 1.11 mmol) and trimethyloxonium tetrafluoroborate (117 mg, 0.790 mmol) for 15 min afforded the title compound **2b** (104 mg, quantitative yield).

*4.2.3. N-Methyl-N-4-nitrophenylsulfonyl-L-isoleucine methyl ester (**2c**).* Treatment of a solution of *N*-4-nitrophenylsulfonyl-L-isoleucine methyl ester (**1c**) (100 mg, 0.303 mmol) in dry DCM (20 mL) with DIPEA (0.185 mL, 1.10 mmol) and trimethyloxonium tetrafluoroborate (111 mg, 0.75 mmol) for 15 min afforded the title compound **2c** (104 mg, quantitative yield).

*4.2.4. N-Methyl-N-4-nitrophenylsulfonyl-L-phenylalanine methyl ester (**2d**).* Treatment of a solution of *N*-4-nitrophenylsulfonyl-L-phenylalanine methyl ester (**1d**) (100 mg, 0.274 mmol) in dry DCM (20 mL) with DIPEA (0.167 mL, 0.959 mmol) and trimethyloxonium tetrafluoroborate (99 mg, 0.67 mmol) for 15 min afforded the title compound **2d** (103 mg, quantitative yield).

*4.2.5. N-Methyl-N-4-fluorophenylsulfonyl-L-alanine methyl ester (**2e**).* Treatment of a solution of *N*-4-fluorophenylsulfonyl-L-alanine methyl ester **1e** (100 mg, 0.383 mmol) in dry DCM (20 mL) with DIPEA (0.233 mL, 1.34 mmol) and trimethyloxonium tetrafluoroborate (142 mg, 0.958 mmol) for 60 min afforded the title compound **2e** (105 mg, quantitative yield) as a colorless oil; [Found: C, 47.79; H, 5.14; N, 5.11. $C_{11}H_{14}FNO_4S$ requires C, 47.99; H, 5.13; N, 5.09%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, d, *J* 7.3 Hz, CH_3), 2.84 (3H, s, N-CH_3), 3.56 (3H, s, OCH_3), 4.77 (1H, q, *J* 7.3 Hz, α-C*H*), 7.22–7.14 (2H, m, ArH *o*-F), 7.86–7.80 (2H, m, ArH *m*-F) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 29.9, 52.1, 54.6, 116.1 (d, $J_{C,F}$=22.5 Hz), 129.9 (d, $J_{C,F}$=9.0 Hz), 135.3 (d, $J_{C,F}$=3.0 Hz), 165.1 (d, $J_{C,F}$=252.7 Hz), 171.3. MS (CI) (rel int.): *m*/*z* 304 (2, $MC_2H_5^+$), 276 (28, MH^+), 256 (2), 244 (3), 216 (100), 202 (2), 152 (5%).

*4.2.6. N-Methyl-N-4-chlorophenylsulfonyl-L-alanine methyl ester (**2f**).* Treatment of a solution of *N*-4-chlorophenylsulfonyl-L-alanine methyl ester **1f** (100 mg, 0.360 mmol) in dry DCM (20 mL) with DIPEA (0.219 mL, 1.26 mmol) and trimethyloxonium tetrafluoroborate (133 mg, 0.900 mmol) for 75 min afforded the title compound **2f** (105 mg, quantitative yield) as a colorless oil; [Found: C, 45.09; H, 4.85; N, 4.79. $C_{11}H_{14}ClNO_4S$ requires C, 45.28; H, 4.84; N, 4.80%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, d, *J* 7.3 Hz, CH_3), 2.84 (3H, s, NCH_3), 3.56 (3H, s, OCH_3), 4.76 (1H, q, *J* 7.3 Hz, α-C*H*), 7.48 (2H, d, *J* 8.8 Hz, ArH *o*-Cl), 7.75 (2H, d, *J* 8.8 Hz, ArH *m*-Cl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.4, 29.8, 52.2, 54.6, 128.6, 129.0, 137.6, 138.9, 171.1 ppm. MS (EI) (rel int.): *m*/*z* 234 (39), 232 (100), 177 (18), 175 (50), 113 (14), 111 (45), 75 (12%).

*4.2.7. N-Methyl-N-4-methylphenylsulfonyl-L-alanine methyl ester (**2g**).* Treatment of a solution of *N*-4-methylphenylsulfonyl-L-alanine methyl ester **1g** (100 mg, 0.389 mmol) in dry DCM (20 mL) with DIPEA (0.237 mL, 1.36 mmol) and trimethyloxonium tetrafluoroborate (144 mg, 0.973 mmol) for 90 min afforded the title compound **2g** (106 mg, quantitative yield) as a colorless oil; [Found C, 52.90; H, 6.33; N, 5.14. $C_{12}H_{17}NO_4S$ requires C, 53.12; H, 6.32; N, 5.16%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (3H, d, *J* 7.3 Hz, CH_3), 2.42 (3H, s, ArCH_3), 2.83 (3H, s, NCH_3), 3.55 (3H, s, OCH_3), 4.76 (1H, q, *J* 7.3 Hz, α-C*H*), 7.31 (2H, d, *J* 8.3 Hz, Ar*H* *o*-CH_3), 7.68 (2H, d, *J* 8.3 Hz, Ar*H* *m*-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2, 21.3, 29.7, 51.9, 54.4, 127.1, 129.4, 135.9, 143.2, 171.4 ppm. MS (EI) (rel int): *m*/*z* 271 (1), 212 (100), 155 (60), 139 (2), 116 (3), 91 (75), 65(10%).

*4.2.8. N-Methyl-N-4-methoxyphenylsulfonyl-L-alanine methyl ester (**2h**).* Treatment of a solution of *N*-4-methoxyphenylsulfonyl-L-alanine methyl ester **1h** (100 mg, 0.366 mmol) in dry DCM (20 mL) with DIPEA (0.223 mL, 1.28 mmol) and trimethyloxonium tetrafluoroborate (135 mg, 0.915 mmol) for 110 min afforded the title compound **2h** (105 mg, quantitative yield) as a colorless oil; [Found C, 49.97; H, 5.98; N, 4.85. $C_{12}H_{17}NO_5S$ requires C, 50.16; H, 5.96; N, 4.87%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, d, *J* 7.3 Hz, CH_3), 2.82 (3H, s, NCH_3), 3.57 (3H, s, OCH_3), 3.86 (3H, s, ArOCH_3), 4.76 (1H, q, *J* 7.3 Hz, α-C*H*), 6.97 (2H, d, *J* 9.0 Hz, Ar*H* *o*-OCH_3), 7.74 (2H, d, *J* 9.0 Hz, Ar*H* *m*-OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 29.7, 51.3, 54.4, 55.3, 114.0, 129.2, 162.4, 171.5, ppm. MS (EI) (rel int.): *m*/*z*=287 (1), 228 (81), 214 (14), 171 (100), 155 (3), 123 (13), 107 (27), 92 (13), 77 (17%).

*4.2.9. N-Methyl-N-phenylsulfonyl-L-alanine methyl ester (**2i**).* Treatment of a solution of *N*-phenylsulfonyl-L-alanine methyl ester **1i** (100 mg, 0.411 mmol) in dry DCM (20 mL) with DIPEA (0.251 mL, 1.44 mmol) and trimethyloxonium tetrafluoroborate (152 mg, 1.03 mmol) for 90 min afforded the title compound **2i** (106 mg, quantitative yield) as a colorless oil; [Found C, 51.53; H, 5.85; N, 5.43. $C_{11}H_{15}NO_4$ requires C, 51.35; H, 5.88; N, 5.44%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, d, *J* 7.3 Hz, CH_3), 2.79 (3H, s, NCH_3), 3.46 (3H, s, OCH_3), 4.71 (1H, q, *J* 7.2 Hz, α-C*H*), 7.43–7.57 (3H, m, Ar*H*), 7.77–7.72 (2H, m, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$):

δ 15.1, 51.8, 54.4, 126.9, 128.7, 132.3, 138.8, 171.1 ppm; MS (EI) (rel int.): *m*/*z*=198 (80), 184 (4), 156 (28), 141 (52), 118 (33), 91 (28), 77 (100), 65 (3), 41 (37%).

4.3. General procedure for the synthesis of *N*-ethyl-*N*-arylsulfonyl amino acid methyl esters 3g–i, 3l–m

To a solution of **1g–i**, and **1l–m** (1 mmol), in DCM (20 mL) were added DIPEA (3.5 mmol) and solid triethyloxonium tetrafluoroborate (2.5 mmol). The reaction mixture was stirred for 15–120 min at room temperature and under an inert atmosphere. The mixture was then quenched with 1 N aqueous HCl until pH 2, and extracted with DCM (3×10 mL). The organic layer was washed with 1 N aqueous NaOH (3×10 mL) and then once with brine (10 mL). Finally the combined organic layers were dried with Na_2SO_4. Evaporation of the solvent gave the *N*-ethyl derivatives **3g–i** and **3l–m** in 90–94% overall yields.

*4.3.1. N-Ethyl-N-4-methylphenylsulfonyl-L-alanine methyl ester (**3g**).* Treatment of a solution of *N*-4-methylphenylsulfonyl-L-alanine methyl ester **1g** (100 mg, 0.389 mmol) in dry DCM (20 mL) with DIPEA (0.237 mL, 1.36 mmol) and triethyloxonium tetrafluoroborate (185 mg, 0.973 mmol) for 90 min afforded the title compound **3g** (101 mg, 91% yield) as a colorless oil; [Found C, 54.93; H, 6.68; N, 4.90. $C_{13}H_{19}NO_4S$ requires C, 54.72; H, 6.71; N, 4.91%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, t, *J* 6.9 Hz, NCH_2CH_3), 1.41 (3H, d, *J*=7.5 Hz, CH_3), 2.41 (3H, s, $ArCH_3$), 3.21 (1H, m, NCH_2CH_3), 3.34 (1H, m, NCH_2CH_3), 3.53 (3H, s, OCH_3), 4.65 (1H, q, *J* 7.3 Hz, α-CH), 7.27 (2H, d, *J* 8.4 Hz, Ar*H* *o*-CH_3), 7.69 (2H, d, *J* 8.4 Hz, Ar*H* *m*-CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 16.6, 21.5, 40.4, 52.0, 54.9, 127.2, 129.4, 137.3, 143.1, 172.1 ppm; MS (CI) (rel int.): *m*/*z*=314 (7, $MC_2H_5^+$), 286 (45, MH^+), 226 (100), 155 (3%).

*4.3.2. N-Ethyl-N-4-methoxyphenylsulfonyl-L-alanine methyl ester (**3h**).* Treatment of a solution of *N*-4-methoxyphenylsulfonyl-L-alanine methyl ester **1h** (100 mg, 0.366 mmol) in dry DCM (20 mL) with DIPEA (0.223 mL, 1.28 mmol) and triethyloxonium tetrafluoroborate (174 mg, 0.915 mmol) for 120 min afforded the title compound **3h** (100 mg, 90% yield) as a colorless oil; [Found C, 52.01; H, 6.33; N, 4.63. $C_{13}H_{19}NO_5S$ requires C, 51.81; H, 6.35; N, 4.65%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 1.43 (3H, d, *J* 7.3 Hz, CH_3), 3.21 (1H, m, NCH_2CH_3), 3.34 (1H, m, NCH_2CH_3), 3.56 (3H, s, OCH_3), 3.86 (3H, s, $ArOCH_3$), 4.65 (1H, q, *J* 7.3 Hz, α-CH), 6.96 (2H, d, *J* 8.9 Hz, Ar*H* *o*-OCH_3), 7.76 (2H, d, *J* 8.9 Hz, Ar*H* *m*-OCH_3), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 16.6, 40.3, 52.1, 54.7, 55.5, 113.9, 129.3, 162.7, 172.1 ppm. MS (EI) (rel int.): *m*/*z*=301 (1), 242 (100), 171 (95), 155 (2), 123 (9), 107 (18), 92 (7), 77 (9%).

*4.3.3. N-Ethyl-N-phenylsulfonyl-L-alanine methyl ester (**3i**).* Treatment of a solution of *N*-phenylsulfonyl-L-alanine methyl ester **1i** (100 mg, 0.411 mmol) in dry DCM (20 mL) with DIPEA (0.251 mL, 1.44 mmol) and triethyloxonium tetrafluoroborate (196 mg, 1.03 mmol) for 85 min afforded the title compound **3i** (104 mg, 93% yield) as a colorless oil; [Found C, 53.33; H, 6.29; N, 5.17.$C_{12}H_{17}NO_4S$ requires C, 53.12; H, 6.32; N, 5.16%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 1.47 (3H, d, *J* 7.4 Hz, CH_3), 3.25 (1H, m, NCH_2CH_3), 3.40 (1H, m, NCH_2CH_3), 3.54 (3H, s, OCH_3), 4.70 (1H, q, *J* 7.3 Hz, α-CH), 7.50–7.64 (3H, m, Ar*H*), 7.88–7.83 (2H, m, Ar*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 16.6, 40.4, 51.9, 54.9, 127.1, 128.7, 132.4, 140.0, 171.8 ppm; MS (CI) (rel int.): *m*/*z*=300 (3, $MC_2H_5^+$), 272 (28, MH^+), 212 (100), 166 (2%).

*4.3.4. N-Ethyl-N-4-fluorophenylsulfonyl-L-valine methyl ester (**3l**).* Treatment of a solution of *N*-4-fluorophenylsulfonyl-L-valine methyl ester **1l** (100 mg, 0.346 mmol) in dry DCM (20 mL) with DIPEA (0.211 mL, 1.21 mmol) and triethyloxonium tetrafluoroborate (164 mg, 0.865 mmol) for 65 min afforded the title compound **3l** (105 mg, 94% yield) as a colorless oil; [Found C, 52.77; H, 6.37; N, 4.41. $C_{14}H_{20}FNO_4S$ requires C, 52.98; H, 6.35; N, 4.41%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 [3H, d, *J* 6.6 Hz, $CH(CH_3)_2$], 1.05 [3H, d, *J* 6.6 Hz, $CH(CH_3)_2$], 1.22 (3H, t, *J* 7.3 Hz, NCH_2CH_3), 2.09 [1H, m, $CH(CH_3)_2$], 3.45 (3H, s, OCH_3), 3.54–3.40 (2H, m, NCH_2CH_3), 4.05 (1H, d, *J* 10.5 Hz, α-CH), 7.19–7.10 (2H, m, Ar*H* *o*-F), 7.88–7.80 (2H, m, Ar*H* *m*-F), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 19.4, 19.6, 28.7, 40.3, 51.4, 65.7, 115.8 (d, $J_{C,F}$=22.5 Hz), 130.1 (d, $J_{C,F}$=9.0 Hz), 136.2 (d, $J_{C,F}$=3.0 Hz), 164.9 (d, $J_{C,F}$=252.8 Hz), 170.9 ppm. MS (CI) (rel int.): *m*/*z*=346 (9, $MC_2H_5^+$), 318 (19, MH^+), 258 (100), 239 (3), 194 (7), 158 (3%).

*4.3.5. N-Ethyl-N-4-chlorophenylsulfonyl-L-leucine methyl ester (**3m**).* Treatment of a solution of *N*-4-chlorophenylsulfonyl-L-leucine methyl ester **1m** (100 mg, 0.313 mmol) in dry DCM (20 mL) with DIPEA (0.192 mL, 1.10 mmol) and triethyloxonium tetrafluoroborate (149 mg, 0.783 mmol) for 70 min afforded the title compound **3m** (102 mg, 94% yield) as a colorless oil; [Found C, 51.59; H, 6.39; N, 4.04.$C_{15}H_{22}ClNO_4S$ requires C, 51.79; H, 6.37; N, 4.03%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 [3H, d, *J* 6.9 Hz, $CH(CH_3)_2$], 0.97 [3H, d, *J* 6.9 Hz, $CH(CH_3)_2$], 1.20 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 1.70–1.62 (2H, m, $CHCH_2$), 1.75 [1H, m, $CH(CH_3)_2$], 3.40–3.10 (2H, m, NCH_2CH_3), 3.45 (3H, s, OCH_3), 4.55 (1H, dd, *J* 8.8, 5.3 Hz, α-CH), 7.48 (2H, d, *J* 8.1 Hz, Ar*H* *o*-Cl), 7.75 (2H, d, *J* 8.1 Hz, Ar*H* *m*-Cl) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 21.7, 21.8, 23.4, 38.4, 39.8, 50.9, 57.2, 128.3, 127.8, 137.6, 137.9, 170.8 ppm. MS (CI) (rel int.): *m*/*z*=376 (7, $MC_2H_5^+$), 348 (21, MH^+), 288 (100), 208 (5%).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.10.042.

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