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Base-Mediated Coupling Reactions of Benzenesulfonyl Azides with Proline: Synthesis of Proline-Derived Benzenesulfonamides

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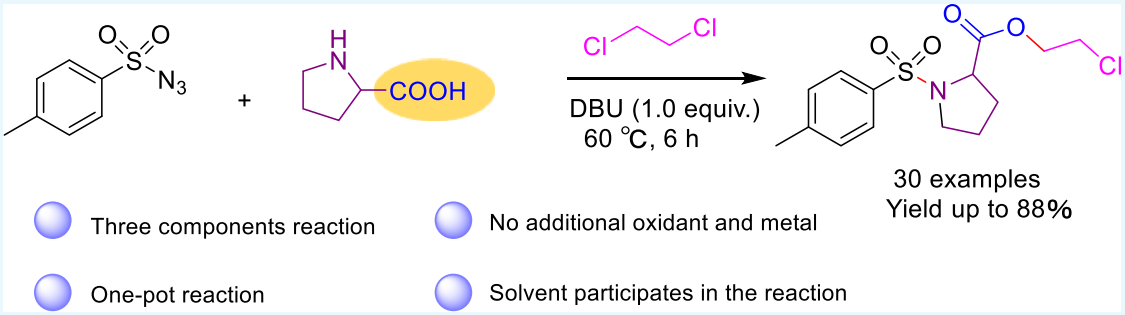

ABSTRACT: Sulfonamides and lipids are widely found in natural products, bioactive substances, and pharmaceuticals. Here, we report *N*-sulfonylation and esterification of carboxylic acids in an environment-friendly one-pot tandem protocol involving 1,2-dichloroethane (DCE). Moreover, 1,8-diazabicyclo (5.4.0) undec-7-ene was necessary for this reaction as a strong base, which drives the reaction to completion. Although DCE is a very low activity reagent, it acts not only as a solvent but also as a reactant in the reaction. The *β*-chloroester contained in the reaction product can be easily dissociated to react with N, S, and O atoms, increasing the possibility for subsequent synthesis.

INTRODUCTION

With the widespread use of sulfonamides and lipids,[1−3] sulfonamides have become the most commonly used antibacterial drugs today, with a wide range of biological and pharmacological activities, including antibacterial, antitumor, and antiviral effects,[4] while carboxylic acid esters also have important uses in the coatings and pharmaceutical industries. Over time, researchers have identified a wide range of indications, such as Alzheimer's disease and other central nervous system disorders, diabetes mellitus, and various cancers.[5] Recently, studies have found that N-substituted sulfonamides are effective against dengue fever and Ebola virus infection, and new carboxyamide derivatives of substituted benzenesulfonamides have antitrypanosomal and anti-inflammatory activities (Figure 1).[6,7]

Over the past decades, great efforts have been made in the preparation of N-functionalized sulfonamides.[8] Among them, one of the most common methods to synthesize sulfonamides is the palladium- or copper-catalyzed cross-coupling reaction of primary sulfonamides with aryl halides,[9] pseudohalides,[10] sodium arylsulfinates,[11] or alkylated ketoesters.[12] Iridium-catalyzed for transfer hydrogenation reduction of *N*-sulfonylimine has recently been developed.[13] Traditionally, sulfonyl azides are rarely used as sulfonyl donors in sulfonation reactions by direct sulfonamylation (Scheme 1a).[14] Subsequently, it was shown that Ugwu's group promoted the

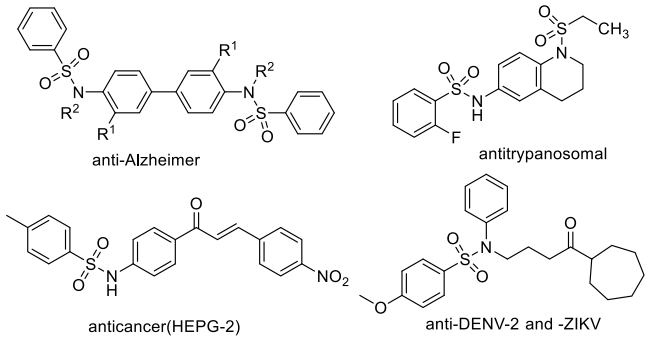

Figure 1. Selected Examples of Biologically Active Sulfonamides.

reaction of L-proline and L-4-hydroxyproline with substituted benzenesulfonyl chloride via bases (Scheme 1b).[6] In addition, Herrera's group used nitrogen-centered radicals for intramolecular C−H amination of unactivated methyl groups and developed a chemoselective procedure to synthesize pyrroli-

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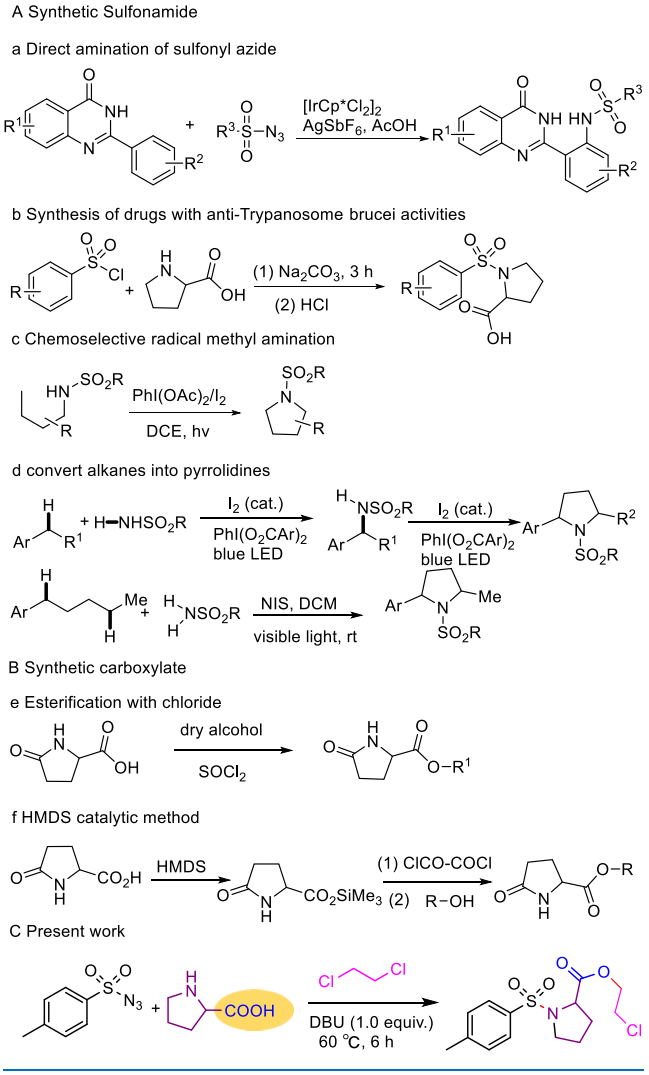
Scheme 1. Previous Reports and Our Design



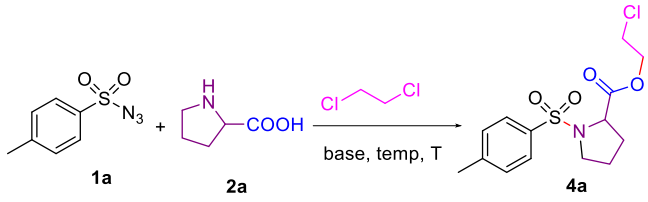
dine under mild conditions (Scheme 1c).[15] Finally, we observed that the pyrrole structure can be obtained directly from alkanes by halogen bond-sequential C_{sp^3}-H amination (Scheme 1d).[16,17]

Being one of the most basic and important central bridging bonds of liquid crystal compounds, the synthesis of ester groups is significant. For a long time now, the synthesis of esters has been mainly performed by using some traditional methods, such as acid-catalyzed, ester exchange, and chloride methods (Scheme 1e).[18] Besides, with the study of various new catalysts and the exploration of organic reaction mechanisms, some novel synthesis methods have emerged. For example, Rigo's group used HMDS to catalyze the synthesis of esters.[19] Moreover, the Mitsunobu reaction was also applied to the synthesis of esters from carboxylic acids.[20] Moreover, here, we use 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU) as a one-pot reagent to complete *N*-sulfonylation and carboxylic acid esterification, which provides a new idea for their synthesis. As we all know that 1,2-dichloroethane (DCE) is an inert reagent and rarely participates in the reaction, herein encouraged by these works and our group's previous application of DCE and continuous efforts on tandem reactions,[21−25] we report a one-step tandem *N*-sulfonylation and esterification involving DCE as both the solvent and reactant, where DBU acts as a strong basic reagent to transfer the proton. This reaction atom is economical, raw materials are readily available, and no hazardous reagents are used, and it is well-tolerated for different functional groups and provides a novel idea of esterification. Furthermore, this is the first report on the synthesis of proline-derived benzenesulfonamides by three components such as sulfonyl azide.

RESULTS AND DISCUSSION

To start with, we selected *p*-toluenesulfonyl azide (**1a**) and proline (**2a**) as model substrates to screen the reaction parameters. The raw materials **1a** (0.2 mmol) and **2a** (0.3 mmol) were treated with DBU (1.0 equiv) in 1,2-dichloroethane (DCE, 2 mL) at a temperature at 60 °C to produce the desired 2-chloroethyl tosylprolinate (**4a**), a kind of yellow liquid, in 88% yield after 6 h. The structure of **4a** was determined by ^{1}H NMR, ^{13}C NMR, HPLC−MS, and NOESY (Table 1, entry 3) for identification. Other known bases

Table 1. Reaction Optimization[a]



entry	base	temp (°C)	time (h)	yield (%)
1	KOH	60	6	trace
2	Cs_2CO_3	60	6	n.r
3	**DBU**	**60**	**6**	**88**
4	$NaHCO_3$	60	6	n.r
5	CH_3COOK	60	6	n.r
6	Et_3N	60	6	trace
7	KO^{t}Bu	60	6	n.r
8	K_2CO_3	60	6	trace
9	pyridine	60	6	n.r
10	DBU	40	6	46
11	DBU	80	6	80
12	DBU	60	2	n.r
13	DBU	60	4	74
14	DBU	60	8	86

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), base (1.0 equiv) and solvent (2.0 mL), in a sealed tube with air atmosphere stirred for 6 h. Isolated yield.

including KOH, Cs_2CO_3, $NaHCO_3$, triethylamine, and so forth were ineffective for the reaction (Table 1, entries 1−8), but the coupling reaction between **1a** and **2a** in the presence of organobasic pyridine also proceeded with poor conversion (Table 1, entry 9). When considering the effect of temperature on the reaction, we noticed a slight decrease in yield when the reaction temperature was lowered to 40 °C or raised to 80 °C (Table 1, entries 10 and 11). Next, the desired product was not obtained when the reaction time was shortened to 2 h (Table 1, entries 12). On the contrary, the yields of **4a** decreased to 74 and 86% when the reaction time was 4 h and extended to 8 h (Table 1, entries 13 and 14).

With the knowledge of the optimal conditions, the range of phenylsulfonyl azides was explored using **2a** as a model reaction partner for the first time. As shown in Table 2, benzenesulfonyl azide derivatives bearing different electron-

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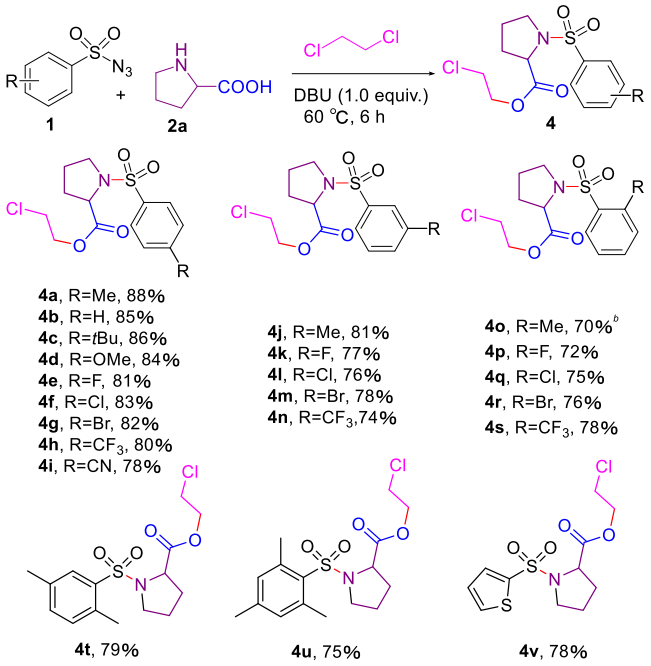
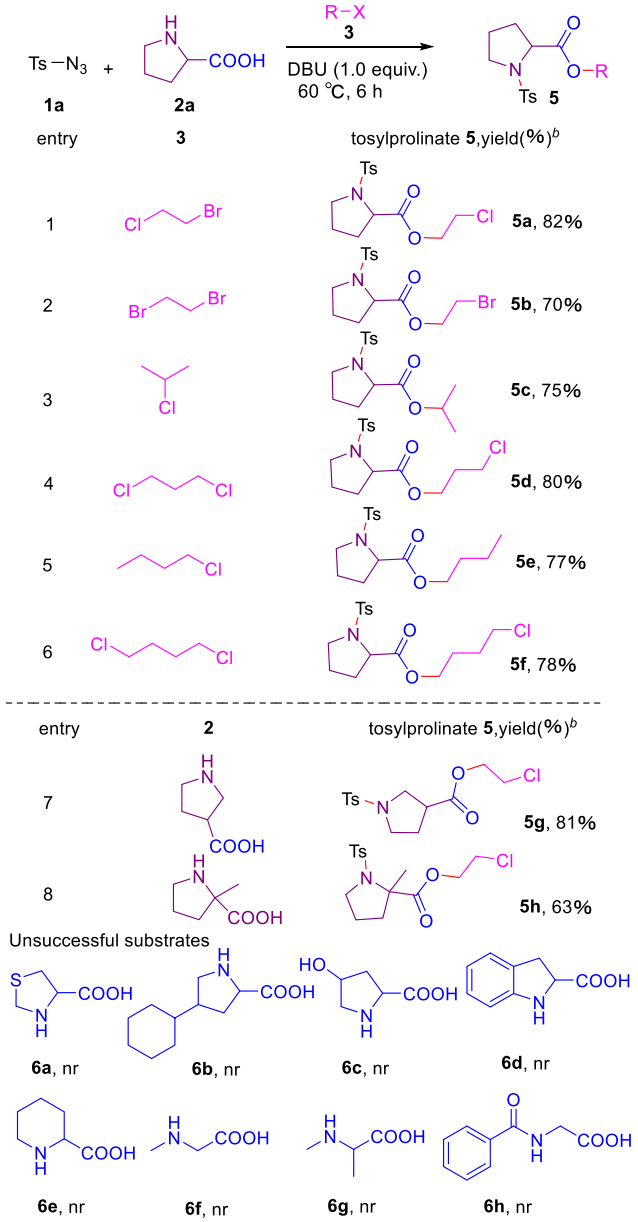
Table 2. Scope for the Synthesis of 4a−4v[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), and DCE (2.0 mL), air, sealed tube, 60 °C, 6 h, isolated yield. [b]24 h.

Table 3. Scope for the Synthesis of 5a−5t[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), and DCE (2.0 mL), air, sealed tube, 60 °C, 6 h. [b]Isolated yield.

donating and electron-withdrawing substituents at the para-position of the benzene ring were suitable for this protocol, providing the corresponding 2-chloroethyl (phenylsulfonyl)-prolinate in moderate to good yields. The reaction of the benzenesulfonyl azide containing electron-donating substituents such as methyl (**4a**), *tert*-butyl (**4c**), and methoxy (**4d**) with **2** smoothly provided the desired product in 84−88% yield. Phenylsulfonyl azides with electron-withdrawing groups such as fluorine (**4e**), chlorine (**4f**), bromine (**4g**), and CF_3 (**4i**) at different positions of the benzene ring were tolerated, providing the corresponding products in moderate to good yields (78−83%). In addition, electron-donating groups were proved to be more favorable for the reaction than electron-withdrawing groups. Moreover, there is excellent tolerance for the neighboring substituents with electron-donating character (**4o**), halogen substituents (**4p**, **4q**, **4r**) and electron-withdrawing character (**4s**). Notably, 2-CH_3 (**4o**) required extended time to reach 70% yield. When meta-substituted benzenesulfonyl azides, such as methyl (**4j**), halogen (**4k**, **4l**, **4m**), and trifluoromethyl (**4n**), were used in the reaction, they showed good compatibility, yielding the corresponding products in about 70−78% yield. Multi-substituted compounds **4t** (2-CH_3, 4-CH_3), **4u** (2-CH_3, 4-CH_3, 6-CH_3) showed slightly lower yields than the compounds with other substituents. Besides, thiophene-2-sulfonyl azide gave 78% yield of **4v**.

According to the above results, the range of substrates varied with the solvent. As shown in Table 3, replacing 1,2-dichloroethane with 1-chloro-2-bromoethane, 1,2-dibromoethane, 2-chloropropane, 1,3-dichloropropane, 1-chlorobutane, and 1,4-dichlorobutane, we could obtain long-chain halogenated tosylprolinate (**5a−5f**) in good yields. However, dichloromethane is not a good solvent for this reaction and the corresponding product was not obtained. To our delight, we used pyrrolidine-3-carboxylic acid and 2-methylpyrrolidine-2-carboxylic acid instead of proline under standard conditions and were able to obtain **5g** and **5h** of product in good yields. Unfortunately, proline derivatives (**6a−6c**), indoline-2-carboxylic acid (**6d**), piperidine-2-carboxylic acid (**6e**), and uncyclized *N*-alkyl *α*-carboxylic acids (**6f−6h**) had been studied under standard conditions, and no products were found.

A gram-scale preparation of **4a** was carried out to demonstrate the practicality of the method. Pleasantly, we were able to obtain the desired product smoothly in 68% yield when in the standard condition (Scheme 2).

To investigate the mechanism of the process, some exploratory experiments were performed. When TEMPO (3.0 equiv) was added, the desired **4a** product was obtained with a slight decrease in yield, indicating the absence of a free radical pathway (Scheme 3a). Furthermore, in order to verify

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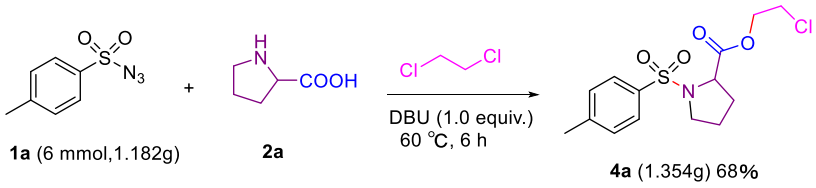
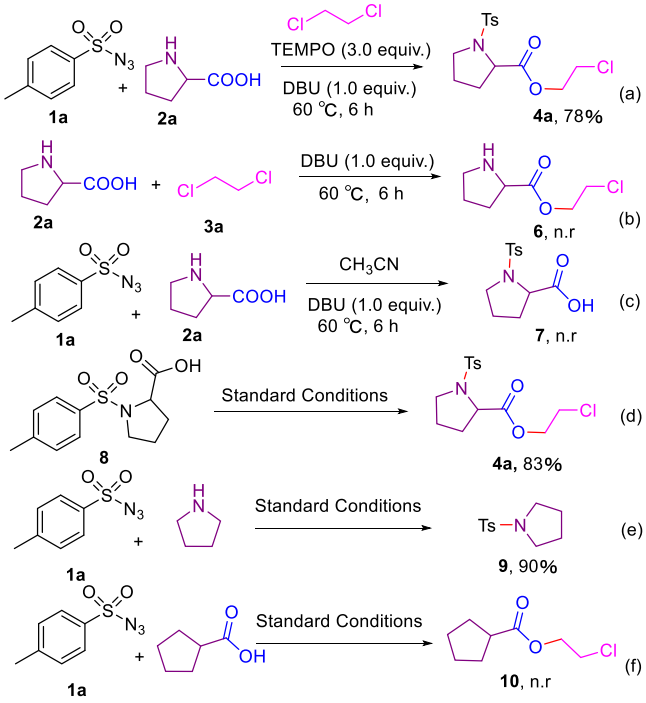
Scheme 2. Scale-Up Experiment



Scheme 3. Mechanistic Studies

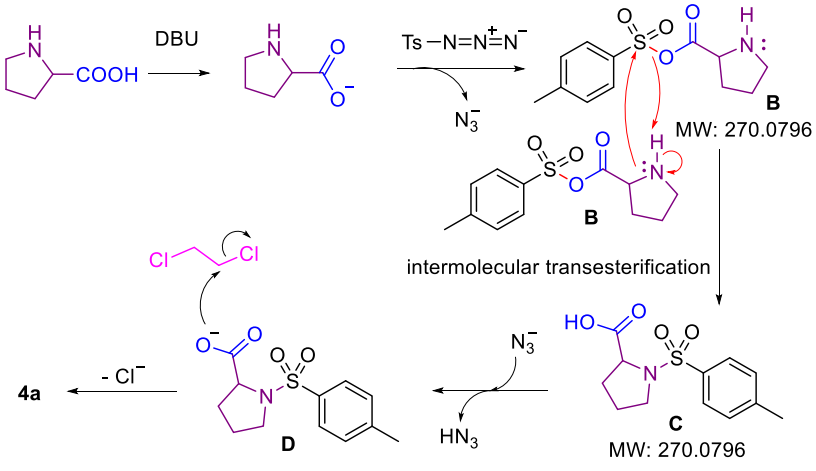


the sequential nature of the reaction, no benzenesulfonyl azide was added in the standard state and it was found that the desired product **6** was not obtained (Scheme 3b), indicating that the presence of benzenesulfonyl azide is essential for the reaction. Finally, we replaced the solvent with acetonitrile, and no ideal product **7** was obtained (Scheme 3c), clearly indicating that DCE plays a key role in the reaction. Additionally, we observed product **4a** when tosylproline **8** was reacted under standard reactions conditions (Scheme 3d). At the same time, about 5 min after the start of the reaction, we detected intermediate **B** and **C** (Scheme 4) from the reaction mixture by HPLC−MS (Supporting Information). In addition, we did a controlled experiment to substitute proline with pyrrolidine and finally succeeded in obtaining product **9** to confirm the correctness of the product (Scheme 3e). To elucidate the connection between the sulfonation of amines and the alkylation of carboxylic acids, we found that the carboxylic acids were not alkylated in the presence of cyclopentane carboxylic acids (Scheme 3f).

Based on the above experimental investigations and some well-documented reports,[14,27] a plausible mechanism is proposed (Scheme 4). First, the base action of DBU, which dehydrogenates the proline ion, leading to the formation of prolinate (**A**), which subsequently forms a known intermediate of 4-methylbenzenesulfonic pyrrolidine-2-carboxylic anhydride (**B**) with benzenesulfonyl azide. Meanwhile, two molecules of intermediate **B** underwent intermolecular ester exchange to form tosylproline **C**. Finally, the target product **4a** was obtained by the esterification reaction of DCE with deprotonated intermediate **D**.

Virtual screening of the products revealed that the products showed good antitumor activity against MCF-7 and SKOV3 cells. Compound **4d** showed a relatively good antitumor activity against MCF-7 cells compared to the positive control drug, as shown in Table S1 with an IC_{50} value of 147.4 ± 0.8 μM comparing to 81.59 ± 9.2 μM of the positive control drug.[26] More detailed experimental results are available in the Supporting Information. Furthermore, because the *O*-chloroethyl of the product has more room for structural modification, it can provide a structural basis for subsequent work, and this study can provide a good foundation for the next step of drug mechanism research and identification.

Scheme 4. Postulated Reaction Mechanism



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Therefore, our laboratory is currently working on the structural modification and modification of the subsequent products.

Herein, we developed an efficient general strategy to provide proline-derived benzenesulfonamides under metal-free conditions. In contrast to benzenesulfonyl azide compounds providing sulfonyl groups, we can obtain the benzenesulfonamide derivatives by reacting with useful amino acids. In this paper, we present a simple, practical, green, and environmentally friendly method to prepare 2-chloroethyl tosylprolinate in moderate to good yields via a one-pot coupling reaction of benzenesulfonyl azides, avoiding the use of transition metal. In addition, the reaction is carried out under convenient handling and has a high tolerance of functional groups.

EXPERIMENTAL SECTION

General Experiment Information. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra (101 MHz) were recorded on the Bruker Ascend 400 spectrometer using $CDCl_3$ and DMSO-d_6 as the solvent. Chemical shifts are given in ppm and coupling constants in Hz. ^{1}H spectra were calibrated in relation to the reference measurement of TMS (0.000 ppm). The following abbreviations were used for ^{1}H NMR spectra to indicate the signal multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet) and combinations of them. Flash chromatography was performed on silica gel 200−300 mesh (purchased from Qingdao Haiyang Chemical, China). MS spectra were recorded on an Agilent 6546 LC/Q-TOF.

*General Procedure for Synthesis of 2-Chloroethyl Tosylprolinate (**4a**).* A mixture of substrate **1a** (39.4 mg, 0.2 mmol), **2** (34.5 mg, 0.3 mmol), in solvent (2.0 mL) was charged in a glass sealed-tube and stirred under air atmosphere at 60 °C for 6 h. When over, the reaction mixture was extracted with saturated aqueous $NaHCO_3$/EA. Then the organic layer was dried with Na_2SO_4, and concentrated to dryness. The crude product was purified by silica gel chromatography (silica gel, PE) to afford the product **4a** as a light-yellow oil with the yield of 88%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84−7.65 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 4.42−4.32 (m, 2H), 4.25 (dd, J = 8.3, 4.3 Hz, 1H), 3.88−3.78 (m, 2H), 3.42−3.37 (m, 1H), 3.15 (dt, J = 9.6, 7.2 Hz, 1H), 2.40 (s, 3H), 2.02−1.88 (m, 2H), 1.87−1.76 (m, 1H), 1.63 (dtt, J = 9.9, 4.9, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.9, 144.1, 134.9, 130.4, 127.7, 65.0, 60.7, 48.8, 42.9, 30.9, 24.6, 21.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}ClNO_4S$, 332.0718; found, 332.0726. The remaining reactions were performed following this typical procedure.

*2-Chloroethyl (Phenylsulfonyl)prolinate (**4b**).* Yellow liquid, 53.9 mg, 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89−7.81 (m, 2H), 7.76−7.68 (m, 1H), 7.64 (dd, J = 8.3, 6.7 Hz, 2H), 4.39−4.31 (m, 2H), 4.28 (dd, J = 8.4, 4.2 Hz, 1H), 3.82 (td, J = 4.6, 1.3 Hz, 2H), 3.45−3.40 (m, 1H), 3.18 (dt, J = 9.7, 7.2 Hz, 1H), 2.05−1.89 (m, 2H), 1.88−1.79 (m, 1H), 1.64 (dddd, J = 12.1, 7.2, 4.7, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 137.8, 133.7, 129.9, 127.6, 65.0, 60.7, 48.8, 42.9, 30.9, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{16}ClNO_4S$, 318.0561; found, 318.0564.

*2-Chloroethyl ((4-(tert-Butyl)phenyl)sulfonyl)prolinate (**4c**).* Colorless solid, 64.1 mg, 86% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81−7.72 (m, 2H), 7.67−7.60 (m, 2H), 4.32 (ddd, J = 6.1, 4.5, 1.9 Hz, 2H), 4.27 (dd, J = 8.6, 4.0 Hz, 1H), 3.85−3.75 (m, 2H), 3.45−3.38 (m, 1H), 3.19 (dt, J = 9.7, 7.2 Hz, 1H), 2.04−1.89 (m, 2H), 1.89−1.82 (m, 1H), 1.67 (dddd, J = 12.0, 7.3, 4.6, 2.5 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 156.6, 135.1, 127.5, 126.7, 65.0, 60.7, 48.8, 42.8, 35.3, 31.2, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{24}ClNO_4S$, 374.1187; found 374.1196.

*2-Chloroethyl ((4-Methoxyphenyl)sulfonyl)prolinate (**4d**).* Colorless liquid, 58.3 mg, 84% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87−7.68 (m, 2H), 7.21−7.04 (m, 2H), 4.44−4.30 (m, 2H), 4.22 (dd, J = 8.4, 4.3 Hz, 1H), 3.86 (s, 3H), 3.85−3.81 (m, 2H), 3.37−3.34 (m, 1H), 3.15 (dt, J = 9.7, 7.1 Hz, 1H), 1.95 (dddd, J = 20.8, 9.9, 5.8, 2.3 Hz, 2H), 1.87−1.77 (m, 1H), 1.70−1.55 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.9, 163.2, 129.9, 129.3, 115.0, 65.0, 60.7, 56.1, 48.8, 42.90, 30.9, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}ClNO_5S$, 348.0667; found 348.0663.

*2-Chloroethyl ((4-Fluorophenyl)sulfonyl)prolinate (**4e**).* Yellow liquid, 54.4 mg, 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99−7.88 (m, 2H), 7.50−7.40 (m, 2H), 4.41−4.33 (m, 2H), 4.31 (dd, J = 8.7, 4.0 Hz, 1H), 3.85−3.80 (m, 2H), 3.44−3.38 (m, 1H), 3.19 (dt, J = 9.5, 7.1 Hz, 1H), 2.07−1.90 (m, 2H), 1.89−1.78 (m, 1H), 1.73−1.62 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 166.4 (d, J_{CF} = 253.5), 163.8, 134.3 (d, J_{CF} = 3.0), 134.3, 130.8 (d, J_{CF} = 9.7), 130.7, 117.2 (d, J_{CF} = 22.6), 116.9, 65.1, 60.7, 48.8, 42.9, 31.0, 24.6. ^{19}F NMR (377 MHz, DMSO): δ −105.83. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}ClFNO_4S$, 336.0467; found, 336.0470.

*2-Chloroethyl ((4-Chlorophenyl)sulfonyl)prolinate (**4f**).* Colorless liquid, 58.4 mg, 83% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91−7.82 (m, 2H), 7.73−7.64 (m, 2H), 4.37−4.33 (m, 2H), 4.33−4.30 (m, 1H), 3.88−3.77 (m, 2H), 3.44−3.38 (m, 1H), 3.19 (dt, J = 9.5, 7.2 Hz, 1H), 2.08−1.90 (m, 2H), 1.90−1.81 (m, 1H), 1.74−1.60 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 138.6, 136.8, 130.0, 129.6, 65.1, 60.7, 48.8, 42.9, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}Cl_2NO_4S$, 352.0172; found, 352.0174.

*2-Chloroethyl ((4-Bromophenyl)sulfonyl)prolinate (**4g**).* Colorless liquid, 64.6 mg, 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 4.37−4.33 (m, 2H), 4.31 (dd, J = 8.7, 3.8 Hz, 1H), 3.88−3.79 (m, 2H), 3.45−3.38 (m, 1H), 3.19 (dt, J = 9.5, 7.1 Hz, 1H), 2.09−1.90 (m, 2H), 1.89−1.79 (m, 1H), 1.69 (dddd, J = 12.0, 7.3, 4.6, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 137.2, 133.0, 129.6, 127.6, 65.1, 60.7, 48.8, 42.9, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}BrClNO_4S$, 395.9667; found, 395.9667.

*2-Chloroethyl ((4-(Trifluoromethyl)phenyl)sulfonyl)-prolinate (**4h**).* Yellow liquid, 61.6 mg, 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14−8.04 (m, 2H), 8.00 (d, J = 8.3 Hz, 2H), 4.39 (dd, J = 8.7, 3.7 Hz, 1H), 4.37−4.29 (m, 2H), 3.82 (td, J = 4.7, 1.4 Hz, 2H), 3.44 (ddd, J = 9.4, 7.4, 4.6 Hz, 1H), 3.24 (dt, J = 9.5, 7.2 Hz, 1H), 2.13−2.01 (m, 1H), 1.99−1.91 (m, 1H), 1.91−1.81 (m, 1H), 1.77−1.65 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.7, 142.0, 133.7 (q, J_{CF} = 32.3), 133.4, 133.1, 132.8, 128.6, 128.0 (q, J_{CF} = 273.9), 127.1 (q, J_{CF} = 3.3), 127.0, 127.0, 127.0, 125.2, 122.5, 119.8, 65.1, 60.8, 48.8, 42.8, 31.0, 24.6. ^{19}F NMR (377 MHz, DMSO): δ −61.80. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{15}ClF_3NO_4S$, 386.0435; found, 386.0438.

*2-Chloroethyl ((4-Cyanophenyl)sulfonyl)prolinate (**4i**).* Colorless liquid, 53.5 mg, 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15−8.07 (m, 2H), 8.07−7.98 (m, 2H), 4.40 (dd, J = 8.7, 3.8 Hz, 1H), 4.38−4.27 (m, 2H), 3.86−3.75 (m, 2H), 3.42 (ddd, J = 9.5, 7.4, 4.6 Hz, 1H), 3.23 (dt, J = 9.6, 7.2

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Hz, 1H), 2.13−1.98 (m, 1H), 2.00−1.86 (m, 1H), 1.92−1.78 (m, 1H), 1.79−1.65 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.7, 142.1, 134.0, 128.4, 118.1, 116.0, 65.1, 60.8, 48.8, 42.9, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{14}H_{15}ClN_2O_4S$, 365.0333; found, 365.0339.

*2-Chloroethyl (m-Tolylsulfonyl)prolinate (**4j**).* Colorless liquid, 53.6 mg, 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69−7.65 (m, 1H), 7.65−7.61 (m, 1H), 7.55−7.48 (m, 2H), 4.38−4.31 (m, 2H), 4.28 (dd, J = 8.4, 4.2 Hz, 1H), 3.87−3.78 (m, 2H), 3.41−3.36 (m, 1H), 3.17 (dt, J = 9.7, 7.2 Hz, 1H), 2.41 (s, 3H), 2.02−1.86 (m, 2H), 1.88−1.77 (m, 1H), 1.69−1.58 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.9, 139.8, 137.7, 134.3, 129.7, 127.7, 124.8, 65.0, 60.7, 48.8, 42.9, 31.0, 24.6, 21.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}ClNO_4S$, 332.0718; found, 332.0726.

*2-Chloroethyl ((3-Fluorophenyl)sulfonyl)prolinate (**4k**).* Colorless liquid, 51.6 mg, 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72−7.70 (m, 2H), 7.68 (dd, J = 3.9, 2.2 Hz, 1H), 7.62−7.55 (m, 1H), 4.41−4.36 (m, 1H), 4.36−4.32 (m, 2H), 3.86−3.80 (m, 2H), 3.41 (ddd, J = 9.6, 7.4, 4.7 Hz, 1H), 3.23 (dt, J = 9.6, 7.2 Hz, 1H), 2.08−1.98 (m, 1H), 1.97−1.89 (m, 1H), 1.89−1.80 (m, 1H), 1.75−1.64 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 163.6 (d, J_{CF} = 249.6), 161.1, 140.1 (d, J_{CF} = 6.7), 140.0, 132.3(d, J_{CF} = 8.1), 132.2, 123.9 (d, J_{CF} = 3.2), 123.9, 121.0 (d, J_{CF} = 21.3), 120.7, 114.8 (d, J_{CF} = 24.3), 114.6, 65.1, 60.8, 48.8, 42.9, 31.0, 24.6. ^{19}F NMR (377 MHz, DMSO): δ −110.13. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{16}FN_3O_2S$, 336.0467; found, 336.0468.

*2-Chloroethyl ((3-Chlorophenyl)sulfonyl)prolinate (**4l**).* Colorless liquid, 53.3 mg, 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (t, J = 1.9 Hz, 1H), 7.83 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.79 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 4.39 (dd, J = 8.7, 3.8 Hz, 1H), 4.36−4.32 (m, 2H), 3.86−3.80 (m, 2H), 3.41 (ddd, J = 9.5, 7.3, 4.7 Hz, 1H), 3.23 (dt, J = 9.5, 7.2 Hz, 1H), 2.08−2.00 (m, 1H), 2.00−1.89 (m, 1H), 1.90−1.81 (m, 1H), 1.78−1.65 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.7, 139.9, 134.6, 133.6, 131.9, 127.1, 126.3, 65.1, 60.7, 48.8, 42.9, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}Cl_2NO_4S$, 352.0172; found, 352.0174.

*2-Chloroethyl ((3-Bromophenyl)sulfonyl)prolinate (**4m**).* Yellow liquid, 61.6 mg, 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (t, J = 1.9 Hz, 1H), 7.93 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.87 (ddd, J = 7.9, 1.8, 1.0 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 4.39 (dd, J = 8.7, 3.8 Hz, 1H), 4.36−4.31 (m, 2H), 3.86−3.80 (m, 2H), 3.43−3.38 (m, 1H), 3.22 (dt, J = 9.5, 7.2 Hz, 1H), 2.10−2.01 (m, 1H), 1.97−1.91 (m, 1H), 1.89−1.80 (m, 1H), 1.76−1.68 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 140.1, 136.5, 132.2, 129.9, 126.7, 122.9, 65.1, 60.7, 48.8, 42.9, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}BrClNO_4S$, 395.9667; found, 395.9666.

*2-Chloroethyl ((3-(Trifluoromethyl)phenyl)sulfonyl)-prolinate (**4n**).* Colorless liquid, 57.0 mg, 74% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21−8.16 (m, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.92−7.87 (m, 1H), 4.45 (dd, J = 8.7, 3.7 Hz, 1H), 4.34 (td, J = 4.7, 1.4 Hz, 2H), 3.82 (td, J = 4.8, 1.4 Hz, 2H), 3.42 (ddd, J = 9.5, 7.4, 4.6 Hz, 1H), 3.25 (dt, J = 9.5, 7.3 Hz, 1H), 2.15−2.01 (m, 1H), 1.99−1.92 (m, 1H), 1.91−1.80 (m, 1H), 1.79−1.69 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.7, 139.5, 131.7, 131.6, 131.0 (q, J_{CF} = 32.8), 130.7, 130.4 (q, J_{CF} = 3.5), 130.4, 130.3, 130.3, 130.0, 127.9 (q, J_{CF} = 273.8), 125.2, 124.1 (q, J_{CF} = 3.7), 124.1, 124.1, 124.0, 122.5, 119.8, 65.1, 60.8, 48.8, 42.9, 31.0, 24.6. ^{19}F NMR (377 MHz, DMSO): δ −61.38. ^{19}F NMR (377 MHz, DMSO): δ −61.38. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{15}ClF_3NO_4S$, 386.0435; found, 386.0437.

*2-Chloroethyl (o-Tolylsulfonyl)prolinate (**4o**).* Yellow liquid, 46.3 mg, 70% yield. ^{1}H NMR (400 MHz, chloroform-d): δ 7.91 (dd, J = 8.2, 1.4 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.26−7.21 (m, 2H), 4.41 (dd, J = 8.8, 3.2 Hz, 1H), 4.14 (dd, J = 6.3, 5.2 Hz, 2H), 3.50 (dd, J = 6.2, 5.2 Hz, 2H), 3.47−3.42 (m, 2H), 2.59 (s, 3H), 2.26−2.16 (m, 1H), 2.09−1.96 (m, 2H), 1.94−1.87 (m, 1H). ^{13}C NMR (101 MHz, chloroform-d): δ 170.7, 137.4, 136.4, 131.9, 131.5, 128.7, 125.0, 63.4, 58.7, 47.4, 40.2, 30.3, 23.7, 19.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}ClNO_4S$, 332.0718; found, 332.0723.

*2-Chloroethyl ((2-Fluorophenyl)sulfonyl)prolinate (**4p**).* Colorless liquid, 48.2 mg, 72% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (td, J = 7.6, 1.8 Hz, 1H), 7.79−7.72 (m, 1H), 7.49 (ddd, J = 10.9, 8.4, 1.1 Hz, 1H), 7.42 (td, J = 7.7, 1.1 Hz, 1H), 4.38 (dd, J = 8.8, 3.4 Hz, 1H), 4.29 (td, J = 4.8, 1.8 Hz, 2H), 3.84−3.75 (m, 2H), 3.49 (ddd, J = 9.5, 7.5, 4.7 Hz, 1H), 3.29 (dt, J = 9.5, 7.2 Hz, 1H), 2.22−2.11 (m, 1H), 2.02−1.96 (m, 1H), 1.95−1.86 (m, 1H), 1.85−1.77 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 159.9 (d, J_{CF} = 253.9), 157.4, 136.4 (d, J_{CF} = 8.8), 136.3, 131.1, 126.5 (d, J_{CF} = 14.9), 126.4, 125.6 (d, J_{CF} = 3.4), 125.5, 118.1 (d, J_{CF} = 21.8), 117.9, 65.0, 60.6 (d, J_{CF} = 2.9), 60.5, 48.6 (d, J_{CF} = 2.0), 48.5, 42.8, 31.0, 24.6. ^{19}F NMR (377 MHz, DMSO): δ −108.95. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}ClFNO_4S$, 336.0467; found, 336.0470.

*2-Chloroethyl ((2-Chlorophenyl)sulfonyl)prolinate (**4q**).* Colorless liquid, 53.3 mg, 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (dd, J = 7.9, 1.5 Hz, 1H), 7.72−7.65 (m, 2H), 7.56 (ddd, J = 7.9, 7.0, 1.7 Hz, 1H), 4.52 (dd, J = 8.8, 3.0 Hz, 1H), 4.30−4.24 (m, 2H), 3.82−3.76 (m, 2H), 3.52 (ddd, J = 9.2, 7.6, 4.6 Hz, 1H), 3.28 (dt, J = 9.2, 7.2 Hz, 1H), 2.31−2.21 (m, 1H), 2.06−2.00 (m, 1H), 1.98−1.80 (m, 2H).^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 136.9, 134.9, 132.6, 131.9, 131.3, 128.3, 65.1, 61.0, 48.6, 42.9, 31.0, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}Cl_2NO_4S$, 352.0172; found, 352.0174.

*2-Chloroethyl ((2-Bromophenyl)sulfonyl)prolinate (**4r**).* Yellow liquid, 60.0 mg, 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (dd, J = 7.6, 2.0 Hz, 1H), 7.88 (dd, J = 7.5, 1.6 Hz, 1H), 7.66−7.48 (m, 2H), 4.59 (dd, J = 8.8, 2.9 Hz, 1H), 4.39−4.17 (m, 2H), 3.94−3.70 (m, 2H), 3.52 (ddd, J = 9.2, 7.7, 4.5 Hz, 1H), 3.25 (dt, J = 9.2, 7.3 Hz, 1H), 2.39−2.20 (m, 1H), 2.09−2.00 (m, 1H), 1.99−1.84 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 138.7, 136.1, 134.8, 132.0, 128.7, 119.9, 65.1, 61.3, 48.5, 42.9, 30.9, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}BrClNO_4S$, 395.9667; found, 395.9667.

*2-Chloroethyl ((2-(Trifluoromethyl)phenyl)sulfonyl)-prolinate (**4s**).* Yellow liquid, 60.0 mg, 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (dd, J = 7.7, 1.5 Hz, 1H), 8.01 (dd, J = 7.5, 1.7 Hz, 1H), 7.94−7.84 (m, 2H), 4.52 (dd, J = 8.8, 2.9 Hz, 1H), 4.33−4.22 (m, 2H), 3.83−3.71 (m, 2H), 3.51 (ddd, J = 9.4, 6.9, 5.1 Hz, 1H), 3.38−3.34 (m, 1H), 2.34 (dq, J = 12.3, 8.6 Hz, 1H), 2.10−2.02 (m, 1H), 2.02−1.92 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 138.5, 134.0, 133.7, 130.7, 129.1 (q, J_{CF} = 6.4), 129.0, 129.0, 128.9, 127.3 (q, J_{CF} = 274.9), 127.1 (q, J_{CF} = 32.7), 126.8, 126.5, 126.1, 124.5, 121.8, 119.1, 65.1, 60.9, 48.9, 42.8, 31.1, 24.6. ^{19}F NMR (377 MHz,

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DMSO): δ −56.15. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{16}F_3N_3O_2S$, 386.0435; found, 386.0439.

*2-Chloroethyl ((2,5-Dimethylphenyl)sulfonyl)prolinate (**4t**).* Colorless liquid, 54.4 mg, 79% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (d, *J* = 1.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 4.34 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.23 (dd, *J* = 6.0, 4.4 Hz, 2H), 3.80−3.68 (m, 2H), 3.43−3.38 (m, 1H), 3.31 (dt, *J* = 9.4, 7.2 Hz, 1H), 2.52 (s, 3H), 2.34 (s, 3H), 2.23 (ddt, *J* = 10.3, 5.1, 2.8 Hz, 1H), 2.04−1.97 (m, 1H), 1.97−1.79 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 137.1, 136.4, 134.7, 134.1, 133.1, 129.6, 64.9, 60.1, 48.6, 42. 8, 31.2, 24.7, 20.8, 20.0. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{20}ClNO_4S$, 346.0874; found, 346.0882.

*2-Chloroethyl (Mesitylsulfonyl)prolinate (**4u**).* Yellow liquid, 53.8 mg, 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.04 (s, 2H), 4.26 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.09 (td, *J* = 5.3, 1.7 Hz, 2H), 3.72−3.63 (m, 2H), 3.38−3.27 (m, 3H), 2.55 (s, 6H), 2.26 (s, 3H), 2.27−2.19 (m, 1H), 2.04−1.97 (m, 1H), 1.97−1.86 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 143.1, 140.2, 132.8, 132.2, 64.8, 59.4, 48.2, 42.6, 31.4, 24.6, 22.8, 20.9. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{22}ClNO_4S$, 360.1031; found, 360.1039.

*2-Chloroethyl (Thiophen-2-ylsulfonyl)prolinate (**4v**).* Colorless liquid, 50.4 mg, 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.75 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.28 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.37 (ddd, *J* = 5.2, 4.4, 1.5 Hz, 2H), 4.22 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.84 (dd, *J* = 5.7, 4.8 Hz, 2H), 3.47 (ddd, *J* = 9.8, 7.0, 4.8 Hz, 1H), 3.21 (dt, *J* = 9.9, 7.1 Hz, 1H), 2.00−1.93 (m, 2H), 1.91−1.82 (m, 1H), 1.69−1.61 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 137.1, 134.2, 133.3, 128.8, 65.1, 61.0, 49.3, 42.9, 31.0, 24.6. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{11}H_{14}ClNO_4S_2$, 324.0126; found, 324.0124.

*2-Chloroethyl Tosylprolinate (**5a**).* Yellow liquid, 54.3 mg, 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76−7.69 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 4.36−4.32 (m, 2H), 4.24 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.83 (dd, *J* = 6.3, 4.3 Hz, 2H), 3.43−3.38 (m, 1H), 3.15 (dt, *J* = 9.7, 7.2 Hz, 1H), 2.40 (s, 3H), 2.02−1.89 (m, 2H), 1.86−1.78 (m, 1H), 1.68−1.57 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.9, 144.1, 134.9, 130.4, 127.7, 65.0, 60.7, 48.8, 42.9, 30.9, 24.6, 21.5. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{18}ClNO_4S$, 332.0718; found, 332.0723.

*2-Bromoethyl Tosylprolinate (**5b**).* Yellow liquid, 52.5 mg, 70% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80−7.63 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 4.49−4.33 (m, 2H), 4.24 (dd, *J* = 8.1, 4.6 Hz, 1H), 3.68 (t, *J* = 5.5 Hz, 2H), 3.47−3.37 (m, 1H), 3.15 (dt, *J* = 9.7, 7.2 Hz, 1H), 2.40 (s, 3H), 2.01−1.89 (m, 2H), 1.88−1.77 (m, 1H), 1.64 (dddd, *J* = 12.0, 7.1, 4.8, 2.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.8, 144.1, 134.9, 130.4, 127.7, 64.8, 60.7, 48.8, 31.1, 31.0, 24.6, 21.5. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{18}BrNO_4S$, 376.0213; found, 376.0220.

*Isopropyl Tosylprolinate (**5c**).* Yellow liquid, 54.3 mg, 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75−7.68 (m, 2H), 7.47−7.39 (m, 2H), 4.99−4.79 (m, 1H), 4.12 (dd, *J* = 8.6, 3.9 Hz, 1H), 3.43−3.36 (m, 1H), 3.14 (dt, *J* = 9.8, 7.0 Hz, 1H), 2.41 (s, 3H), 2.02−1.88 (m, 1H), 1.87−1.74 (m, 2H), 1.60 (dtd, *J* = 11.6, 7.7, 6.8, 4.1 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 144.0, 135.0, 130.4, 127.6, 68.7, 60.9, 48.8, 30.9, 24.6, 21.9, 21.8, 21.5. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{21}NO_4S$, 312.1264; found, 312.1270.

*3-Chloropropyl Tosylprolinate (**5d**).* Colorless liquid, 55.2 mg, 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75−7.71 (m, 2H), 7.47−7.43 (m, 2H), 4.24−4.19 (m, 2H), 4.19−4.17 (m, 1H), 3.72 (t, *J* = 6.5 Hz, 2H), 3.48−3.38 (m, 1H), 3.15 (dt, *J* = 9.8, 7.1 Hz, 1H), 2.41 (s, 3H), 2.05 (p, *J* = 6.3 Hz, 2H), 1.97−1.74 (m, 3H), 1.60 (dddd, *J* = 12.1, 7.2, 5.0, 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.1, 144.1, 134.9, 130.4, 127.6, 62.2, 60.8, 48.9, 42.1, 31.5, 30.9, 24.7, 21.5. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{20}ClNO_4S$, 346.0875; found, 346.0883.

*Butyl Tosylprolinate (**5e**).* Colorless liquid, 50.0 mg, 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76−7.64 (m, 2H), 7.49−7.38 (m, 2H), 4.17 (dd, *J* = 8.5, 3.9 Hz, 1H), 4.06 (ddt, *J* = 10.8, 6.6, 4.3 Hz, 2H), 3.38 (dd, *J* = 5.9, 3.7 Hz, 1H), 3.15 (dt, *J* = 9.7, 7.0 Hz, 1H), 2.40 (s, 3H), 2.01−1.89 (m, 1H), 1.88−1.75 (m, 2H), 1.67−1.58 (m, 1H), 1.58−1.48 (m, 2H), 1.39−1.26 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.2, 144.0, 135.0, 130.4, 127.6, 64.8, 60.8, 48.8, 30.9, 30.5, 24.7, 21.5, 19.0, 14.0. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{23}NO_4S$, 326.1421; found, 326.1431.

*4-Chlorobutyl Tosylprolinate (**5f**).* Colorless liquid, 56.0 mg, 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 7.7 Hz, 2H), 4.19 (dd, *J* = 8.5, 4.1 Hz, 1H), 4.17−4.04 (m, 2H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.43−3.36 (m, 0H), 3.16 (dt, *J* = 9.6, 7.0 Hz, 1H), 2.41 (s, 3H), 2.03−1.90 (m, 1H), 1.93−1.80 (m, 2H), 1.83−1.74 (m, 2H), 1.77−1.67 (m, 2H), 1.66−1.54 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.1, 144.0, 134.9, 130.4, 127.6, 64.5, 60.8, 48.9, 45.4, 30.9, 29.1, 26.0, 24.7, 21.5. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{22}ClNO_4S$, 360.1031; found, 360.1042.

*2-Chloroethyl 1-Tosylpyrrolidine-3-carboxylate (**5g**).* Colorless liquid, 53.8 mg, 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73−7.64 (m, 2H), 7.45 (dd, *J* = 7.3, 1.4 Hz, 2H), 4.29−4.08 (m, 2H), 3.76 (t, *J* = 5.3 Hz, 2H), 3.43−3.35 (m, 2H), 3.24−3.15 (m, 2H), 3.13−3.02 (m, 1H), 2.41 (s, 3H), 2.05−1.93 (m, 1H), 1.89 (ddd, *J* = 12.7, 6.3, 1.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.49, 144.02, 133.24, 130.32, 127.94, 64.78, 49.98, 47.76, 42.85, 42.33, 28.34, 21.46. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{18}ClNO_4S$, 332.0718; found, 332.0716.

*2-Chloroethyl 3-Methyl-1-tosylpyrrolidine-3-carboxylate (**5h**).* Colorless liquid, mg, 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87−7.56 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.29 (dddd, *J* = 72.0, 12.2, 6.5, 4.0 Hz, 2H), 3.87−3.69 (m, 2H), 3.49−3.40 (m, 1H), 3.34−3.27 (m, 1H), 2.39 (s, 3H), 2.18 (dd, *J* = 11.0, 5.2 Hz, 1H), 1.94 (tdd, *J* = 12.7, 5.6, 2.9 Hz, 2H), 1.91−1.84 (m, 1H), 1.50 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 173.55, 143.45, 138.24, 130.12, 127.17, 67.88, 65.14, 49.22, 42.87, 40.67, 23.48, 23.35, 21.44. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{20}ClNO_4S$, 346.0874; found, 346.0871.

*1-Tosylpyrrolidine (**9**).* White solids, 121.8−123.6 °C, 40.5 mg, 90% yield. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.78−7.62 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.29−3.13 (m, 4H), 2.42 (s, 3H), 1.82−1.64 (m, 4H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 143.34, 133.76, 129.62, 127.48, 47.91, 25.14, 21.46.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Huang, Y.; Pi, C.; Tang, Z.; Wu, Y.; Cui, X. Cp*Co(III)-catalyzed C-H amidation of azines with dioxazolones. *Chin. Chem. Lett.* **2020**, *31*, 3237−3240.

(2) Feng, Y.; Liu, Y.; Fu, Q.; Zou, Z.; Shen, J.; Cui, X. Construction of diaminobenzoquinone imines via ferrocene-initiated radical reaction of benzoquinone with amines. *Chin. Chem. Lett.* **2020**, *31*, 733−735.

(3) Fu, R.; Kou, L.; Gao, K.; Zhou, S.; Bao, X. Understanding mechanistic differences between 3-diazoindolin-2-imines and *N*-sulfonyl-1,2,3-triazoles in the Rh_2(II)-catalyzed reactions with nitrosoarenes. *Chin. J. Chem.* **2021**, *39*, 1565−1572.

(4) (a) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. Anticancer and antiviral sulfonamides. *Curr. Med. Chem.* **2003**, *10*, 925−953. (b) Moeker, J.; Peat, T. S.; Bornaghi, L. F.; Vullo, D.; Supuran, C. T.; Poulsen, S.-A. Cyclic secondary sulfonamides: Unusually good inhibitors of cancer-related carbonic anhydrase enzymes. *J. Med. Chem.* **2014**, *57*, 3522−3531. (c) Bag, S.; Tulsan, R.; Sood, A.; Cho, H.; Redjeb, H.; Zhou, W.; LeVine, H.; Török, B.; Török, M. Sulfonamides as multifunctional agents for Alzheimer's disease. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 626−630.

(5) Apaydın, S.; Török, M. Sulfonamide derivatives as multi-target agents for complex diseases. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2042−2050.

(6) Ugwu, D. I.; Okoro, U. C.; Mishra, N. K. Synthesis of proline derived benzenesulfonamides: A potent anti-*Trypanosoma brucei gambiense* agent. *Eur. J. Med. Chem.* **2018**, *154*, 110−116.

(7) Kulman, D. G.; Lama, R.; Li, B.; Su, B. *Evaluation of the selectivity of sulfonamide tubulin inhibitors against human African trypanosomiasis*; Cleveland State University, 2017. Retrieved on 22nd February 22. www.csuohio.edu/sites/default/files/29-%202015.pdf.

(8) Mondal, S.; Malakar, S. Synthesis of sulfonamide and their synthetic and therapeutic applications: Recent advances. *Tetrahedron* **2020**, *76*, 131662.

(9) Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. Mild Pd-catalyzed N-arylation of methanesulfonamide and related nucleophiles: Avoiding potentially genotoxic reagents and byproducts. *Org. Lett.* **2011**, *13*, 2564−2567.

(10) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C. A general method for Palladium-catalyzed reactions of primary sulfonamides with aryl nonaflates. *J. Org. Chem.* **2011**, *76*, 4552−4563.

(11) Jiang, Y.; You, Y.; Dong, W.; Peng, Z.; Zhang, Y.; An, D. Copper-promoted desulfitative N-arylation of sulfonamides and sulfoximines with sodium arylsulfinates. *J. Org. Chem.* **2017**, *82*, 5810−5818.

(12) Liu, T.-L.; Jhou, M.-L.; Hsieh, C.-E.; Lin, C.-J.; Su, H.-H.; Chou, C.-M. Palladium-catalyzed intramolecular allylic amidation via decarboxylative aromatization: Synthesis of N-allyl-N-aryl sulfonamides. *J. Org. Chem.* **2021**, *86*, 9084−9095.

(13) Wen, H.; Luo, N.; Zhu, Q.; Luo, R. Amide Iridium complexes as catalysts for transfer hydrogenation reduction of N-sulfonylimine. *J. Org. Chem.* **2021**, *86*, 3850−3859.

(14) (a) Feng, Y.; Zhang, Z.; Fu, Q.; Yao, Q.; Huang, H.; Shen, J.; Cui, X. Ir-catalyzed regiospecific mono-sulfamidation of arylquinazolinones. *Chin. Chem. Lett.* **2020**, *31*, 58−60. (b) Zhu, S.; Jin, G.; He, P.; Xu, Y.; Huang, Q. Unexpected formation of the novel fluorinated diazenes. *Tetrahedron Lett.* **2003**, *44*, 8717−8719. (c) Liskamp, R. M.; Brouwer, A. J.; Merkx, R.; Dabrowska, K.; Rijkers, D. T. S. Synthesis and applications of *β*-aminoethanesulfonyl azides. *Synthesis* **2006**, *3*, 455−460. (d) Chow, S. Y.; Stevens, M. Y.; Odell, L. R. Sulfonyl azides as precursors in ligand-free palladium-catalyzed synthesis of sulfonyl carbamates and sulfonyl ureas and synthesis of sulfonamides. *J. Org. Chem.* **2016**, *81*, 2681−2691.

(15) Paz, N. R.; Rodríguez-Sosa, D.; Valdés, H.; Marticorena, R.; Melián, D.; Copano, M. B.; González, C. C.; Herrera, A. J. Chemoselective intramolecular functionalization of methyl groups in nonconstrained molecules promoted by N-Iodosulfonamides. *Org. Lett.* **2015**, *17*, 2370−2373.

(16) Bosnidou, A. E.; Muñiz, K. Intermolecular radical C(sp^3)-H amination under Iodine catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 7485−7489.

(17) Wu, F.; Ariyarathna, J. P.; Kaur, N.; Alom, N.-E.; Kennell, M. L.; Bassiouni, O. H.; Li, W. Halogen-bond-induced consecutive Csp^3-H aminations via hydrogen atom transfer relay strategy. *Org. Lett.* **2020**, *22*, 2135−2140.

(18) Gang, F.-l.; Zhu, F.; Li, X.-t.; Wei, J.-l.; Wu, W.-j.; Zhang, J.-w. Synthesis and bioactivities evaluation of $_L$-pyroglutamic acid analogues from natural product lead. *Bioorg. Med. Chem.* **2018**, *26*, 4644−4649.

(19) Rigo, B.; El Ghammarti, S.; Gautret, P.; Couturier, D. Studies on pyrrolidinones. An improved synthesis of pyroglutamoyl chloride. *Synth. Commun.* **1994**, *24*, 2597−2607.

(20) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. A mechanistic study of the Mitsunobu esterification reaction. *J. Am. Chem. Soc.* **1988**, *110*, 6487−6491.

(21) Liu, H.; Pang, Z.; Hao, L.; Sun, J.; Zhang, Z.; Wen, F.; Xia, C. Sulfonylimination of proline with sulfonylazides involving aldehyde-induced decarboxylation coupling. *Org. Lett.* **2021**, *23*, 1234−1238.
(22) Sun, J.; Sun, H.; Hao, L.; Liu, H.; Zhang, Z.; Wen, F.; Li, H.; Duan, G.; You, G.; Xia, C. Metal-free synthesis of pyrrole-imidazole alkaloids via a tandem C-N, C-C coupling protocol. *Adv. Synth. Catal.* **2021**, *363*, 1882−1886.
(23) Hao, L.; Wang, G.; Sun, J.; Xu, J.; Li, H.; Duan, G.; Xia, C.; Zhang, P. From phenylhydrazone to 1*H*-1, 2, 4-triazoles via nitrification, reduction and cyclization. *Adv. Synth. Catal.* **2020**, *362*, 1657−1662.
(24) Hao, L.; Liu, H.; Zhang, Z.; Wen, F.; Xia, C.; Pang, Z. Cascade reaction to 1*H*-pyrazoles from hydrazones via sodium nitrite promoted dual C−C/C−N formation, annulation and aromatization with 1, 2-dichloroethane. *Chin. Chem. Lett.* **2021**, *32*, 2309−2312.
(25) Xia, C.; Wei, Z.; Yang, Y.; Yu, W.; Liao, H.; Shen, C.; Zhang, P. Palladium-catalyzed thioetherification of quinolone derivatives via decarboxylative C−S cross-couplings. *Chem.—Asian J.* **2016**, *11*, 360−366.
(26) Cai, J.; Chen, S.; Zhang, W.; Wei, Y.; Lu, J.; Xing, J.; Dong, Y. Proteomic analysis of differentially expressed proteins in 5-fluorouracil-treated human breast cancer MCF-7 cells. *Clin. Transl. Oncol.* **2014**, *16*, 650−659.
(27) Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. A convenient procedure for esterification of carboxylic acids. *Bull. Chem. Soc.* **1978**, *51*, 2401−2404.

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