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Diastereoselective synthesis of *trans*-trifluoromethyl-β-lactams and α-alkyl-β-trifluoromethyl-β-amino esters

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ABSTRACT

The diastereoselective synthesis of β-lactams was examined from *N*-tosyl-1-chloro-2,2,2-trifluoroethylamine **3** and various nonactivated aliphatic acid chlorides in the presence of a Brønsted base. The mild reaction conditions allowed to get trifluoromethyl-β-lactams in good yields with high trans-diastereo selectivity. In addition, we also demonstrated that ring-opening of β-lactams easily provided α-alkyl-β-trifluoromethyl-β-amino esters.

1. Introduction

Azetidin-2-ones, which are called β-lactams, are part of the structure of several antibiotic families, principally the penicillins, cephalosporins, carbapenems, and the monobactam.[1,2] They biologically act by irreversible acylation of the nucleophilic serine residue at the active site of key enzymes involved in bacterial cell-wall synthesis. More recently, synthetic β-lactams have found applications as inhibitors of other serine proteases, particularly human cytomegalovirus (HCMV) serine protease,[3–5] elastases,[6,7] thrombin,[8] tryptase,[9,10] and chimase.[11] The stereochemistry of β-lactams is very important for their biological activities. For instance, the penicillin and cephalosporin antibiotics possess a *cis*-β-lactam unit, whereas thienamycin, that is, a naturally-occurring carbapenem antibiotic and most of the synthetic inhibitors of other serine proteases have a *trans*-β-lactam moiety. The bactericidal activity of these antibiotics is often hampered by the development of resistance due to the ability of bacteria to produce β-lactamases that hydrolyze the β-lactam ring thus inactivating the antibiotics.[12,13] It is suggested in the literature that introducing an electron-withdrawing fluorinated substituent on the β-lactam ring would have a good effect on antibacterial activity.[14–16] Indeed, the introduction of fluorine atom(s) into a bioactive compound causes minimal steric interaction but it substantially modifies its physicochemical properties. The higher strength of the C–F bond compared to C–H bond avoids undesired metabolic transformations while substituting a methyl group with a trifluoromethyl group increases the lipophilicity. Moreover, due to its high electronegativity, the trifluoromethyl group strongly impacts the neighboring functionalities within the molecule.[17] All these parameters contribute to improve the pharmacokinetic properties of trifluoromethylated molecules that often possess a better therapeutic profile. Consequently, the effective synthesis of stereoselectively defined β-lactams featuring a trifluoromethyl group became a desirable goal for organic and medicinal chemists.[18–20] Intensive research has generated several methods of synthesizing the β-lactam scaffold. β-Lactams are commonly constructed through the Staudinger reaction (ketene–imine cycloaddition, pathway A)[21–24] or by ester enolate–imine cyclocondensation (pathway B), two mechanistically distinct approaches (Fig. 1).[25–31] A less frequently proposed mechanism involves the direct acylation by an acid chloride at the nitrogen atom of an imine followed by a favored [4-*exo*-*tet*] cyclization process (pathway C). This pathway becomes probably operative when the acid chloride is mixed with the imine before the addition of the base.[32–34]

More than 10 year ago Bégué co-workers published the first synthesis of a *cis*-trifluoromethylated β-lactam involving a [2+2] ketene–imine cycloaddition and methyl *syn*-3-trifluoromethyl-isoserinate after opening of the β-lactam cycle.[18,19] Unfortunately, this approach cannot be applied to nonactivated acid chlorides, only α-benzyloxyacetyl chloride reacted with trifluoromethylated imines. As part of our continuing efforts on the development of methods for preparing new trifluoromethylated compounds, we became interested in solving this problem and we now propose the synthesis of new trifluoromethylated β-lactams. In view of the three main pathways to the β-lactam scaffold, which require the same imine as common substrate and three different reaction partners, we surmised that chemical diversity could be provided using a simple

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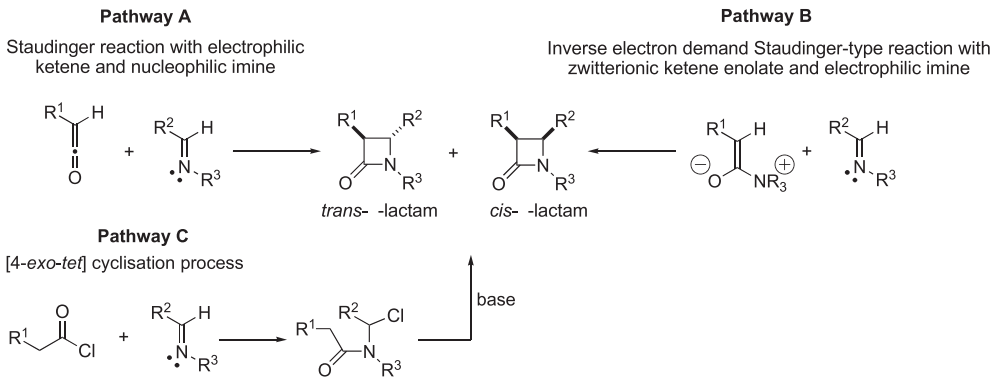
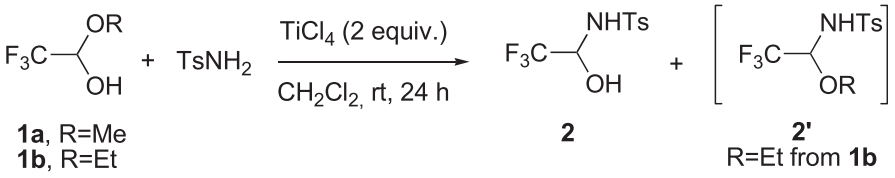


Fig. 1. Synthetic pathways to the β-lactam scaffold.

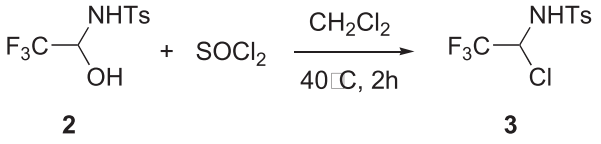
α-chloroamine, instead of the imine, to react with an acid chloride. This is one advantage when considering the very moisture sensitive nature of highly reactive trifluoromethylated imines featuring an electron-withdrawing group (i.e., *N*-tosyltrifluoroacetaldehyde imine) as mentioned by Kumadaki and co-workers[35] We chose the *N*-tosyl-1-chloro-2,2,2-trifluoroethylamine **3** (see Scheme 2) as the trifluoromethylated reactant and various aliphatic acid chlorides for the highly diastereoselective synthesis of *trans*-trifluoromethylated-β-lactams and their ring opening reaction leading to α-alkyl-β-trifluoromethyl-β-amino esters.

2. Results and discussion

Trifluoroacetaldehyde (fluoral) or its hemiacetals are readily available starting materials and suitable for the construction of sophisticated trifluoromethylated molecules.[36] Fluoral hemiacetals are known to react with amines under acidic conditions for generating hemiaminals.[16,35] We modified the conditions reported by Kumadaki from two commercially available fluoral hemiacetals **1a** and **1b** and tosylamine in the presence of a Lewis acid, $TiCl_4$ as dehydrating reagent.[35] The reaction was performed at room temperature for 24 h providing *N*-(1-hydroxy-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **2** in 65% yield from **1a** but only in 25% yield from the ethyl hemiacetal **1b**. In this latter case **2** was accompanied by *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **2′** as the major product isolated in 75% yield (Scheme 1).



Scheme 1. Preparation of hemiaminal **2**.



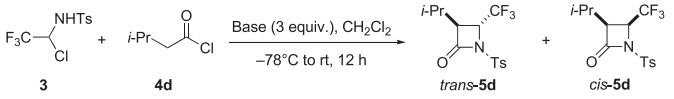
Scheme 2. Preparation of chloroamine **3**.

Next, the hemiaminal **2** smoothly reacted with $SOCl_2$ either in CH_2Cl_2 or without solvent at 40 °C to give the *N*-(1-chloro-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **3** in quantitative yield (Scheme 2). Quite interestingly, chlorination of **2** with PCl_5 furnished a complex mixture and with oxalyl chloride only traces of **3** were obtained. The chloroamine **3**[37] was readily generated but **3** is moisture sensitive and can be easily hydrolyzed to the starting hemiaminal **2**. As a consequence, **3** was obtained after evaporation of the crude mixture, characterized by ^1H and ^{19}F NMR and immediately used in the next reaction step. Preferentially, the one-pot process from hemiaminal **2** to β-lactams (vide infra) was achieved in order to minimize the hydrolysis of **3**.

We initially employed 3-methylbutanoyl chloride **4d** and *N*-(1-chloro-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **3** to set up suitable reaction conditions for the diastereoselective formation of β-lactam **5d**. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and tertiary amines were employed as bases. Base (3 equiv) was required for the overall process to take place. We reduced the amount of base to 2 equiv but the reaction was much slower and the conversion was not complete. The use of dimethylethylamine as the base gave the best results, whereas other bases resulted in a loss of diastereo selection and a strong reduction in yield (Table 1).

The diastereomeric ratios *trans*/*cis* **5d** were determined by ^{19}F NMR on the crude reaction mixtures. Two signals (doublets) for CF_3 group of the diastereomeric β-lactams were recorded at −74 and −69 ppm with relative integration values as shown in Table 1. By ^1H NMR, we also found signals for two diastereomers. The relative trans configuration was assigned on the basis of the $J_{H3\text{-}H4}$ coupling constant values: the $J_{H3\text{-}H4}$ coupling constant of 6 Hz indicates the cis relative configuration, whereas $J_{H3\text{-}H4}$ coupling constant of 2 Hz indicates the trans relative configuration as mentioned in the literature.[38,39] Additionally, the β-lactam *trans*-**5d** was characterized by single-crystal X-ray crystallography, which clearly shows the trans relationship between the CF_3 and the *i*-propyl groups.[40] Previous syntheses of 3-substituted-4-trifluoromethyl-β-lactams were achieved through a Staudinger ketene–imine cycloaddition from a trifluoromethylaldimine and benzyloxyacetyl chloride in the presence of Et_3N. Under these conditions, the *cis*-β-lactams are almost exclusively obtained sometimes accompanied by 5–8% of the *trans*-β-lactams.[19] Because these studies were focussed on the access to *syn*-3-CF_3-isoserinates, used for instance as side-chain of Docetaxel, other 3-substituted-4-trifluoromethyl-β-lactams with alkyl group at C3 were not reported; consequently, all the β-lactams synthesized in

Table 1
Synthesis of β-lactams **5d**: study of reaction parameters



3 4d

Entry	Base	Yield [%][a]	Dr (trans/cis)[b]
1	DBU	0	—
2	Et(*i*-Pr)$_2$N	<5	—
3	Et$_3$N	54	80:20
4	Bu$_3$N	50	75:25
5	Me$_2$EtN	69	98:2

[a] Isolated yields of pure products obtained by flash column chromatography.
[b] Diastereomeric ratio determined by ^{19}F NMR on the crude reaction mixture after work-up.

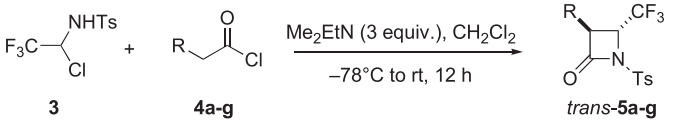
this work are new compounds. Alternatively, the lithium ester enolate–imine cyclocondensation developed by Ojima and co-workers also gave *cis*-β-lactams in most cases. The exclusive formation of the *cis*-β-lactams was rationalized by the selective generation of the *E*-lithium enolate and a Zimmerman–Traxler transition state.[41] However, Guanti and co-workers obtained exclusively a *trans*-β-lactam by cyclocondensation of *N*-(2,2,2-trifluoroethylidene)-4-methoxyaniline with the lithium enolate of *N*,*N*-dibenzyl ethylglycinate. In this case, the *Z*-enolate is favored leading to the *trans*-β-lactam.[16] More recently, 3-substituted-4-trifluoromethyl-β-lactams were synthesized by Reformatsky reaction with α-trifluoromethyl imine yet without discussion on the cis/trans ratios.[42]

In our case study, the precise mechanism and the origin of the excellent diastereoselection are not clear. From a mechanistic point of view, we believe that in our experimental conditions with addition of the acid chloride to the chloroamine **3** when no base is present, a chemical outcome similar to pathway C (see Fig. 1) is reasonable. Indeed, although poorly nucleophilic, the chloroamine **3** could react directly with the acid chloride to form the corresponding adduct.[43] Attempts to isolate the adduct were unsuccessful. A reversible equilibrium between the two reactants and the adduct is likely to happen and displacement of this equilibrium takes place by addition of the base. Then, addition of the tertiary amine causes abstraction of a proton leading to the enolate, which could cyclize via an intramolecular S_N2 reaction. Nevertheless, a standard Staudinger reaction through formation of ketene (pathway A, Fig. 1) or a reaction proceeding through an intermediate zwitterionic ketene enolate that reacts with the electrophilic imine (pathway B, Fig. 1) cannot be completely excluded.

The high diastereomeric ratios in favor of the *trans*-substituted lactams is likely to be obtained from reaction instead of epimerization. Indeed, the diastereomeric ratio of β-lactams **5d** was determined by ^{19}F NMR during the reaction in the presence of triethylamine at various temperatures −78 °C, −20 °C, and 25 °C and gave the same mixture 20:80 of *cis*-β-lactam and *trans*-β-lactam **5d**. Concomitantly, the epimerization of the two diastereomeric β-lactams by the tertiary amine could convert the original diastereomeric mixture of lactams to a thermodynamic equilibrium in which the *trans*-β-lactam could be even more favored. To examine the possibility of C3-epimerization for *cis*-β-lactam to *trans*-β-lactam **5d**, we placed a mixture 20:80 of *cis*-β-lactam and *trans*-β-lactam **5d** under basic conditions with the aid of Et$_3$N as isomerization reagent in CH_2Cl_2. After stirring the mixture at room temperature for 15 h, the pure diastereoisomer *trans*-**5d** was quantitatively obtained. A similar complete isomerization was described by Bégué and co-workers with *t*-BuOK in acetonitrile[44] while Vaccaro and co-workers reported *t*-BuOK epimerization in THF leading to a 1:4 (cis/trans) mixture of β-lactams.[45]

Having established suitable reaction conditions for the synthesis of β-lactam **5d** with high diastereoselectivity, the methodology was applied to a series of nonactivated aliphatic acid chlorides **4a**–**g** (Table 2). Whatever the size of the R group, the reaction provided the β-lactams in very similar yields with high diastereoselectivity, greater than 94:6. However, an improved yield was obtained from 3-phenylpropanoyl chloride **4g**. Although, the diastereomeric ratio was high with R=Me and Et, the diastereoselectivity is almost total with bulkier R groups (Pr, *i*-Pr, Bu, *t*-Bu, CH_2Ph). It is worth noting that diastereomeric mixtures could be purified by careful silica gel column chromatography to afford each diastereomers in analytically pure form. All these β-lactams are new compounds that were fully characterized (see Experimental section).

Table 2
Synthesis of β-lactams **5a**–**g** from various acyl chlorides



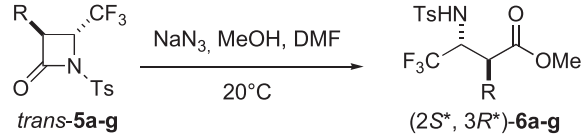
3 4a-g *trans*-5a-g

Entry	Acyl chloride, R	β-lactam[b]	Yield [%][a]	Dr (trans/cis)[b]
1	**4a**, Me	**5a**	68	94:6
2	**4b**, Et	**5b**	67	97:3
3	**4c**, Pr	**5c**	64	99:1
4	**4d**, *i*-Pr	**5d**	69	98:2
5	**4e**, Bu	**5e**	66	96:4
6	**4f**, *t*-Bu	**5f**	63	99:1
7	**4g**, CH_2Ph	**5g**	80	99:1

[a] Isolated yields of pure products obtained by flash column chromatography.
[b] Diastereomeric ratio determined by ^{19}F NMR on the crude reaction mixture after work-up.

Trifluoromethylated β-lactams are useful building blocks for the synthesis of fluorinated β-amino acid derivatives. Thus, having optimized conditions for the synthesis of *trans*-β-lactams **5a**–**g**, if necessary through additional epimerisation step to pure *trans*-β-lactams, we decided to focus our efforts in the opening of the β-lactam cycle. The azide-catalyzed methanolysis is a well established methodology for this purpose. Indeed, the ring opening by methanol was performed in DMF at room temperature providing α-alkyl-β-trifluoromethyl-β-amino esters (2*S**, 3*R**)-**6a**–**g** in good to high yields as single diastereomers (Table 3).[46]

Table 3
Ring opening of β-lactams: synthesis of α-alkyl-β-trifluoromethyl-β-amino esters **6a**–**g**



trans-5a-g (2*S**, 3*R**)-6a-g

Entry	β-lactam, R	Ester	Yield [%][a]
1	**5a**, Me	**6a**	82
2	**5b**, Et	**6b**	79
3	**5c**, Pr	**6c**	97
4	**5d**, *i*-Pr	**6d**	73
5	**5e**, Bu	**6e**	99
6	**5f**, *t*-Bu	**6f**	82
7	**5g**, CH_2Ph	**6g**	86

[a] Isolated yields of pure products obtained by flash column chromatography.

3. Conclusion

We have achieved a convenient highly diastereoselective one-pot synthesis of trifluoromethylated *trans*-β-lactams using *N*-(1-chloro-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **3** and various nonactivated aliphatic acid chlorides. The originality of this

cyclocondensation reaction is the use of the chloroamine **3** as reactant. The methodology is simple and provides rapid access to unprecedented 3-alkyl-4-trifluoromethyl-β-lactams with excellent trans diastereoselectivity. We also obtained α-alkyl-β-trifluoromethyl-β-amino esters by simple ring opening reaction of the β-lactams.[47,48] The present synthetic methodology could find important applications; in particular for the construction of different types of β-peptides and potential biologically active compounds. Further studies concerning the mechanism of the reaction, the deprotection of the tosyl group, the synthesis of amino acids and dipeptides, as well as the development of enantioselective approaches to chiral nonracemic β-lactams are under investigation in our laboratories.[22,30,49,50]

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of dry nitrogen or argon. Solvents were dried according to standard procedures and distilled prior to use. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 200.1, 50.3, and 188.3 MHz, respectively, using $CDCl_3$ and CD_3CN as solvents. The chemical shifts are reported in parts per million relative to $CHCl_3$ (δ=7.25 ppm) and CH_3CN (δ=1.94 ppm) for ^{1}H NMR and to the central $CDCl_3$ resonance (δ 77.0) for ^{13}C NMR. Hexafluorobenzene (C_6F_6) served as internal standard (δ_F=−162.9 ppm) for ^{19}F NMR. Coupling constants (J) are reported in Hertz. Melting points were uncorrected. Flash chromatographies were performed on silica gel (230–400 mesh). Mass spectrometry data are reported in the form of m/z (intensity relative to base peak=100).

4.2. Synthetic procedure for compounds 2 and 3

4.2.1. N-(1-Hydroxy-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide ***2***. To a stirred suspension of *p*-toluenesulfonamide (10 g, 58 mmol) and trifluoroacetaldehyde methyl hemiacetal **1a** (7.6 g, 58 mmol) in 100 ml of dry DCM was added $TiCl_4$ (44.32 g, 232 mmol) at room temperature. The light yellow solution was stirred for 20 h at room temperature. The reaction was quenched by the addition of water (50 ml). The titanium hydroxide was filtered through Celite and the organic phase was separated. The aqueous phase was extracted with DCM (3×20 ml). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was triturated with a small quantity of DCM. The solid was filtered and dried under vacuum to afford 8.16 g of **2**. The mother solution was concentrated under vacuum and purified by column chromatography with 2:1 hexane/ethyl acetate mixture as the eluent to give 2.04 g of the title compound. Total amount of **2** was 10.2 g (65%): white solid; mp 155–156 °C; ^{1}H NMR (CD_3CN): δ 2.42 (s, 3H, C*H*$_3$), 4.98 (d, J=6 Hz, 1H, O*H*), 5.26 (m, 1H, C*H*), 6.82 (d, J_d=10 Hz, 1H, N*H*), 7.39 (d, J_d=8 Hz, 2H, AB-pattern), 7.76 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR (CD_3CN): δ 21.0, 75.5 (q, J_q=36 Hz, *C*–CF$_3$), 117.8, 123.0 (q, J_{C-F}=282 Hz, *C*F$_3$), 127.2, 130.1, 138.8, 144.5; ^{19}F NMR (CD_3CN): δ −80.8 (d, J_d=3.8 Hz C*F*$_3$); MS (EI) m/z: 269 (M^+, 5%), 200 (15%), 171 (25%), 155 ($TolSO_2$, 55%), 91 (Tol, 100%); HRMS-EI, m/z calcd for $C_9H_{10}F_3NO_3S$, 269.03335; found, 269.03344.

4.2.2. N-(1-Chloro-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide ***3***. To a stirred suspension of *N*-(1-hydroxy-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **2** (1 g, 3.72 mmol) in 5 ml of dry DCM was added $SOCl_2$ (5 ml) at room temperature. The reaction mixture was stirred for 2 h at 40 °C. Solvent and excess of $SOCl_2$ were removed under vacuum. The residue was dried for 3 h to afford **3** (quantitative yield) as colorless solid: moisture sensitive; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H, C*H*$_3$), 5.85 (dq, J_d=10 Hz, J_q=4 Hz, 1H, C*H*), 6.16 (d, J_d=10 Hz, 1H, N*H*), 7.36 (d, J_d=8 Hz, 2H, AB-pattern), 7.81 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 22.1, 66.2 (q, J_q=39 Hz, *C*–CF$_3$), 121.6 (q, J_{C-F}=280 Hz, *C*F$_3$), 127.9, 130.5, 136.3, 145.6; ^{19}F NMR ($CDCl_3$): δ −78.3 (d, J_d=3.8 Hz C*F*$_3$); MS (CI) m/z: 251 (M^+−HCl, 36%), 155 ($TolSO_2^+$, 100%).

4.3. General procedure for the synthesis of *N*-tosyl-3-substituted-4-trifluoromethyl-azetidin-2-ones 5

4.3.1. trans-1-Tosyl-3-methyl-4-(trifluoromethyl)azetidin-2-one ***5a***. In an oven-dried, two-neck, 50 ml, round-bottom flask equipped with magnetic stirring bar, a reflux condenser, and an argon inlet were placed **2** (1 g, 3.72 mmol) and $SOCl_2$ (5 ml) in DCM (5 ml). The reaction mixture was stirred for 2 h at 40 °C. Solvent and excess of $SOCl_2$ were removed in vacuum. The residue was dried for 3 h and was dissolved in DCM (8 ml). To the formed solution of **3** was added propionyl chloride **4a** (0.41 g, 0.38 ml, 4.43 mmol) in DCM (1 ml). The solution was cooled to −78 °C and Me_2EtN (0.81 g, 1.2 ml, 11 mmol) was added. After the mixture was stirred at −78 °C for 2 h and then was stirred overnight (the temperature spontaneously was warmed to room temperature). The reaction was complete as monitored by ^{19}F NMR. The solvent was removed in vacuum and residue was treated with EtOAc. The precipitate was filtered, the mother solution was concentrated in vacuum. The crude product was purified by crystallization in cold ethanol (or column chromatography on SiO_2 with hexane/EtOAc=9/1) to give **5a** (0.78 g) as white solid: yield 68%; mp 136–138 °C; ^{1}H NMR ($CDCl_3$): δ 1.41 (d, J_d=8 Hz, 3H, C*H*$_3$), 2.48 (s, 3H, C*H*$_3$), 3.35 (qd, J_d=2 Hz, J_q=8 Hz, 1H, C*H*), 4.15 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.39 (d, J_d=8 Hz, 2H, AB-pattern), 7.89 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 12.69, 22.16, 47.98, 59.5 (q, J_q=36 Hz, *C*–CF$_3$), 123 (q, J_{C-F}=279 Hz, *C*F$_3$), 128.08, 130.52, 135.22, 146.36, 165.29; ^{19}F NMR ($CDCl_3$): δ −74.53 (d, J_d=3.8 Hz C*F*$_3$); MS (ESI, m/z): 330.2 (M^++Na), 696.2; MS (CI, m/z): 307 (M^+, 7%), 232 (31%), 197 (36%), 155 ($TolSO_2^+$, 92%), 91 (Tol^+, 100%); HRMS-EI, m/z calcd for $C_{12}H_{12}F_3NO_3S$, 307.04900; found, 307.04884.

4.3.2. trans-1-Tosyl-3-ethyl-4-(trifluoromethyl)azetidin-2-one ***5b***. Yield 67%; mp 80–82 °C; ^{1}H NMR ($CDCl_3$): δ 1.0 (t, J_t=8 Hz, 3H, C*H*$_3$), 1.8 (m, 2H, CH$_2$), 2.47 (s, 3H, C*H*$_3$), 3.25 (td, J_t=8 Hz, J_d=2 Hz, 1H, C*H*), 4.20 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.38 (d, J_d=8 Hz, 2H, AB-pattern), 7.88 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 11.02, 21.25, 22.15, 54.41, 57.78 (q, J_q=36 Hz, *C*–CF$_3$), 123.54 (q, J_{C-F}=279 Hz, *C*F$_3$), 128.08, 130.5, 135.35, 146.31, 164.81; ^{19}F NMR ($CDCl_3$): δ −74.33 (d, J_d=3.8 Hz C*F*$_3$); MS (EI, m/z): 321 (M^+, 3%), 301 (19%), 232 (30%), 197 (32%), 155 ($TolSO_2^+$, 100%), 91 (Tol^+, 92%); HRMS-EI, m/z calcd for $C_{13}H_{14}F_3NO_3S$, 321.06465; found, 321.06483.

4.3.3. trans-1-Tosyl-3-propyl-4-(trifluoromethyl)azetidin-2-one ***5c***. Yield 64%; mp 61–63 °C; ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J_t=8 Hz, 3H, C*H*$_3$), 1.44 (m, 2H, CH$_2$), 1.76 (m, 2H, C*H*$_2$), 2.48 (s, 3H, C*H*$_3$), 3.30 (td, J_t=8 Hz, J_d=2 Hz, 1H, C*H*), 4.21 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.38 (d, J_d=8 Hz, 2H, AB-pattern), 7.89 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 13.87, 20.05, 22.12, 29.85, 52.92, 58.16 (q, J_q=36 Hz, *C*–CF$_3$), 123.0 (q, J_{C-F}=279 Hz, *C*F$_3$), 128.05, 130.49, 135.32, 146.32, 164.98; ^{19}F NMR ($CDCl_3$): δ −74.33 (d, J_d=3.8 Hz C*F*$_3$); MS (EI, m/z): 336 (M^++H, 10%), 232 (27%), 198 (34%), 155 ($TolSO_2^+$, 100%), 91 (Tol^+, 82%); MS (CI, m/z): 688 ($2M^+$+NH_4, 5%), 353 (M^++NH_4, 100%).

4.3.4. trans-1-Tosyl-3-isopropyl-4-(trifluoromethyl)azetidin-2-one ***5d***. Yield 69%; mp 66–68 °C; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J_d=8 Hz, 3H, C*H*$_3$), 1.4 (d, J_d=8 Hz, 2H, C*H*$_2$), 2.11 (septet, J=8 Hz, 1H, C*H*), 2.46 (s, 3H, C*H*$_3$), 3.10 (dd, J_1=8 Hz, J_2=2 Hz, 1H, C*H*), 4.25 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.38 (d, J_d=8 Hz, 2H, AB-pattern), 7.89 (d, J_d=8 Hz,

2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 19.85, 19.9, 22.15, 27.98, 56.7 (q, J_q=36 Hz, *C*–CF_3), 59.51, 123.6 (q, J_{C-F}=279 Hz, *C*F_3), 128.08, 130.47, 135.46, 146.28, 164.43; ^{19}F NMR ($CDCl_3$): δ −74.06 (d, J_d=3.7 Hz CF_3); MS (EI, *m*/*z*): 335 (M^+, 5%), 198 (28%), 155 ($TolSO_{2+}$, 79%), 118 (37%), 91 (Tol^+, 100%).

4.3.5. trans-1-Tosyl-3-butyl-4-(trifluoromethyl)azetidin-2-one ***5e***. Yield 66%; mp 60–62 °C; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J_t=6 Hz, 3H, CH_3), 1.32 (m, 4H, 2CH_2), 1.75 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 3.29 (td, J_t=6 Hz, J_d=2 Hz, 1H, C*H*), 4.19 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.38 (d, J_d=8 Hz, 2H, AB-pattern), 7.89 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 14.03, 22.12, 22.55, 27.52, 28.65, 53.11, 58.1 (q, J_q=36 Hz, *C*–CF_3), 123.54 (q, J_{C-F}=279 Hz, *C*F_3), 128.06, 130.5, 135.33, 146.32, 165.02; ^{19}F NMR ($CDCl_3$): δ −74.32 (d, J_d=3.7 Hz CF_3); MS (EI, *m*/*z*): 350 (M^++H, 9%), 329 (M^+−HF, 74%), 198 (43%), 155 ($TolSO_{2+}$, 100%), 91 (Tol^+, 91%).

4.3.6. trans-1-Tosyl-3-tert-butyl-4-(trifluoromethyl)azetidin-2-one ***5f***. Yield 63%; mp 107–109 °C; ^{1}H NMR ($CDCl_3$): δ 1.0 (s, 3H, 3CH_3), 2.47 (s, 3H, CH_3), 3.11 (d, J_d=2 Hz, 1H, C*H*), 4.28 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.38 (d, J_d=8 Hz, 2H, AB-pattern), 7.90 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 22.12, 27.04, 32.31, 55.6 (q, J_q=36 Hz, *C*–CF_3), 63.36, 123.7 (q, J_{C-F}=279 Hz, *C*F_3), 128.11, 130.45, 135.55, 146.29, 164.19; ^{19}F NMR ($CDCl_3$): δ −73.84 (d, J_d=3.7 Hz CF_3); MS (EI, *m*/*z*): 350 (M^++H, 14%), 232 (30%), 198 (32%), 155 ($TolSO_{2+}$, 100%), 152 (82%), 91 (Tol^+, 86%); MS (CI, positive, *m*/*z*): 367 (M^++NH_4, 100%), 350 (M^++H, 1%); MS (CI, negative, *m*/*z*): 348 (M^+−H, 7%), 321 (4%), 194 (100%).

4.3.7. trans-1-Tosyl-3-benzyl-4-(trifluoromethyl)azetidin-2-one ***5g***. Yield 80%; mp 138–140 °C; ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.05 (dd, J_1=2 Hz, J_2=6 Hz, 2H, CH_2), 3.61 (td, J_t=6 Hz, J_d=2 Hz, 1H, C*H*), 4.19 (dq, J_d=2 Hz, J_q=4 Hz 1H, C*H*), 7.14 (m, 2H, H_{Ar}), 7.31 (m, 5H, H_{Ar}), 7.78 (d, J_d=8 Hz, 2H, AB-pattern); ^{13}C NMR ($CDCl_3$): δ 22.15, 33.19, 53.98, 56.94 (q, J_q=36 Hz, *C*–CF_3), 123.5 (q, J_{C-F}=279 Hz, *C*F_3), 127.96, 128.04, 129.39, 129.47, 130.52, 135.18, 135.27, 146.24, 164.30; ^{19}F NMR ($CDCl_3$): δ −74.09 (d, J_d=3.8 Hz CF_3); MS (EI, *m*/*z*): 383 (M^+, 27%), 228 (16%), 198 (17%), 186 (89%), 155 ($TolSO_{2+}$, 60%), 117 (38%), 91 (Tol^+, 100%); HRMS-EI, *m*/*z* calcd for $C_{18}H_{16}F_3NO_3S$, 383.08030; found, 383.07976.

4.4. General procedure for the opening of β-lactam cycle by sodium azide

4.4.1. Methyl 4,4,4-trifluoro-2-isopropyl-3-(4-methylphenylsulfonamido) butanoate ***6d***. To a solution of **5d** (0.2 g, 0.596 mmol) in MeOH (3 ml) and DMF (1 ml) was added sodium azide (0.08 g, 1.23 mmol). The reaction mixture was stirred at room temperature for 12 h. The solution was poured into water (10 ml) and extracted with EtOAc (2×15 ml). The organic phases were combined, dried with Na_2SO_4, and concentrated. Chromatography (hexane/EtOAc 3/1) gave 0.16 g (73%) of **6d** as white solid: mp 109–110 °C; ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J=6 Hz, 3H, CH_3), 1.1 (d, J=6 Hz, 3H, CH_3), 2.09 (m, 1H, C*H*), 2.43 (s, 3H, CH_3), 2.47 (dd, J=2.4 Hz, J=10.3 Hz, 1H, C*H*), 3.72 (s, 3H, OCH_3), 4.34 (m, 1H, C*H*), 6.44 (d, J=8 Hz, 1H, NH), 7.3 (d, J=8 Hz, 2H), 7.76 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 20.54, 20.88, 21.86, 28.35, 49.38, 52.56, 54.72 (q, J_{C-F}=31.2 Hz, *C*–CF_3), 124.86 (q, J_{C-F}=283 Hz, *C*F_3), 127.23, 129.89, 138.73, 143.99, 174.75; ^{19}F NMR ($CDCl_3$): δ −75.58 (d, J=7.5 Hz, CF_3); MS (EI, *m*/*z*): 367 (M^+, 16%), 336 (10%), 298 (21%), 270 (7%), 266 (10%), 224 (7%), 212 (17%), 171 (14%), 164 (38%), 155 ($TolSO_{2+}$, 62%), 138 (12%), 115 (78%), 91 (Tol^+, 100%); HRMS-EI, *m*/*z* calcd for $C_{15}H_{20}F_3NO_4S$, 367.10651; found, 367.10719.

4.4.2. Methyl 4,4,4-trifluoro-2-methyl-3-(4-methylphenylsulfonamido) butanoate ***6a***. Yield 82%; mp 83–84 °C; ^{1}H NMR ($CDCl_3$): δ 1.30 (d, J=7.3 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.97 (qd, J=6.8 Hz, J=2.9 Hz, 1H, C*H*), 3.71 (s, 3H, OCH_3), 4.09 (m, 1H, C*H*), 6.35 (d, J=9.3 Hz, 1H, NH), 7.29 (d, J=8.3 Hz, 2H), 7.75 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 15.60, 21.86, 37.25, 52.85, 57.84 (q, J_{C-F}=31.2 Hz, *C*–CF_3), 124.60 (q, J_{C-F}=282.8 Hz, *C*F_3), 127.29, 130.00, 138.50, 144.14, 174.71; ^{19}F NMR ($CDCl_3$): δ −74.54 (d, J=6.9 Hz, CF_3); HRMS-EI, *m*/*z* calcd for $C_{13}H_{16}F_3NO_4S$, 339.07521; found, 339.07526.

4.4.3. Methyl 4,4,4-trifluoro-2-ethyl-3-(4-methylphenylsulfonamido) butanoate ***6b***. Yield 79%; mp 65–67 °C; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J=7.3 Hz, 3H, CH_3), 1.68 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.71 (m, 1H, C*H*), 3.68 (s, 3H, OCH_3), 4.1 (m, 1H, C*H*), 6.42 (d, J=8.8 Hz, 1H, NH), 7.27 (d, J=7.9 Hz, 2H), 7.74 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 11.84, 21.86, 23.88, 43.93, 52.73, 56.25 (q, J_{C-F}=31.3 Hz, *C*–CF_3), 124.21 (q, J_{C-F}=283.2 Hz, *C*F_3), 127.27, 129.93, 138.60, 144.07, 174.70; ^{19}F NMR ($CDCl_3$): δ −74.84 (d, J=8.6 Hz, CF_3); HRMS-EI, *m*/*z* calcd for $C_{14}H_{18}F_3NO_4S$, 353.09086; found, 353.09034.

4.4.4. Methyl 4,4,4-trifluoro-2-propyl-3-(4-methylphenylsulfonamido) butanoate ***6c***. Yield 97%; mp 70–71 °C; ^{1}H NMR ($CDCl_3$): δ 0.82 (t, J=7.3 Hz, 3H, CH_3), 1.1–1.6 (m, 4H, CH_2CH_2), 2.38 (s, 3H, CH_3), 2.80 (m, 1H, C*H*), 3.66 (s, 3H, OCH_3), 4.10 (m, 1H, C*H*), 6.45 (d, J=8.8 Hz, 1H, NH), 7.26 (d, J=8.3 Hz, 2H), 7.73 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.80, 20.47, 21.80, 32.44, 42.00, 52.71, 56.50 (q, J_{C-F}=31.3 Hz, *C*–CF_3), 124.24 (q, J_{C-F}=282.8 Hz, *C*F_3), 127.29, 129.96, 138.62, 144.09, 174.78; ^{19}F NMR ($CDCl_3$): δ −74.94 (d, J=8.6 Hz, CF_3); HRMS-EI, *m*/*z* calcd for $C_{15}H_{20}F_3NO_4S$, 367.10651; found, 367.10670.

4.4.5. Methyl 4,4,4-trifluoro-2-butyl-3-(4-methylphenylsulfonamido) butanoate ***6e***. Yield 99%; mp 77–79 °C; ^{1}H NMR ($CDCl_3$): δ 0.83 (t, J=6.8 Hz, 3H, CH_3), 1.1–1.6 (m, 6H, (CH_2)$_3$), 2.38 (s, 3H, CH_3), 2.76 (m, 1H, C*H*), 3.67 (s, 3H, OCH_3), 4.11 (m, 1H, C*H*), 6.44 (d, J=8.8 Hz, 1H, NH), 7.26 (d, J=8.3 Hz, 2H), 7.74 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.03, 21.81, 22.51, 29.31, 30.18, 42.24, 52.73, 56.52 (q, J_{C-F}=31.0 Hz, *C*–CF_3), 124.31 (q, J_{C-F}=283.2 Hz, *C*F_3), 127.29, 129.96, 138.63, 144.09, 174.81; ^{19}F NMR ($CDCl_3$): δ −75.63 (d, J=8.6 Hz, CF_3); HRMS-EI, *m*/*z* calcd for $C_{16}H_{22}F_3NO_4S$, 381.12216; found, 381.12196.

4.4.6. Methyl 4,4,4-trifluoro-2-tert-butyl-3-(4-methylphenylsulfonamido) butanoate ***6f***. Yield 82%; mp 96–98 °C; ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 9H, (CH_3)$_3$), 2.42 (s, 3H, CH_3), 2.61 (m, 1H, C*H*), 3.73 (s, 3H, OCH_3), 4.48 (m, 1H, C*H*), 6.76 (d, J=6.9 Hz, 1H, NH), 7.28 (d, J=7.3 Hz, 2H), 7.74 (d, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.91, 28.66, 34.20, 50.33, 52.48, 54.09 (q, J_{C-F}=30.4 Hz, *C*–CF_3), 124.27 (q, J_{C-F}=283.8 Hz, *C*F_3), 127.09, 129.75, 139.26, 143.69, 173.96; ^{19}F NMR ($CDCl_3$): δ −75.38 (d, J=6.9 Hz, CF_3); HRMS-EI, *m*/*z* calcd for $C_{16}H_{22}F_3NO_4S$, 381.12216; found, 381.12364.

4.4.7. Methyl 4,4,4-trifluoro-2-benzyl-3-(4-methylphenylsulfonamido) butanoate ***6g***. Yield 86%; mp 107–110 °C; ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 2.9–3.2 (m, 3H, *CHCH*$_2$), 3.57 (s, 3H, OCH_3), 4.1–4.3 (m, 1H, C*H*), 6.52 (d, J=6.9 Hz, 1H, NH), 7.1–7.4 (m, 7H), 7.78 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.94, 36.48, 44.51, 52.79, 56.25 (q, J_{C-F}=31.3 Hz, *C*–CF_3), 124.59 (q, J_{C-F}=283.6 Hz, *C*F_3), 127.36, 127.68, 129.17, 129.40, 130.02, 136.93, 138.61, 144.19, 174.05; ^{19}F NMR ($CDCl_3$): δ −71.08 (d, J=6.9 Hz, CF_3); HRMS-EI, *m*/*z* calcd for $C_{19}H_{20}F_3NO_4S$, 415.10651; found, 415.10700.

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