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Access to novel functionalized trifluoromethyl β-lactams by ring expansion of aziridines†

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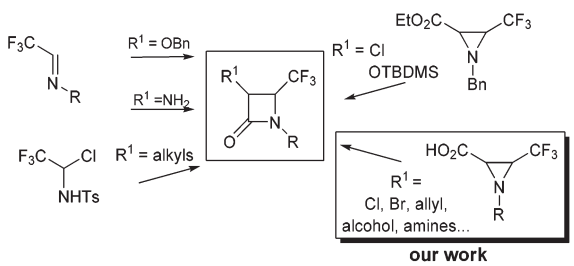
From carboxylic acid trifluoromethyl aziridines, halogeno β-lactams were obtained stereoselectively by ring expansion. Different conditions such as radical, organometallic reactions allowed easy and selective access to CF_3-β-lactams substituted at the C-3 position.

Introduction

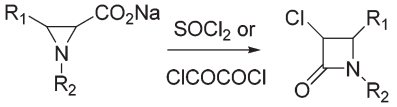
More than 80 years after Fleming's discovery,[1] β-lactams continue to be of major interest not only for their biological properties but also for their usefulness as intermediates in organic synthesis. They represent a major structural part of antibiotic families such as penicillins, cephalosporins, carbapenem and monobactams.[2] Besides their fundamental role in the fight against pathogenic bacteria, β-lactams, and more precisely monobactams, have recently exhibited interesting inhibitory activities on proteases like thrombin,[3] human cytomegalovirus protease,[4] tryptase,[5] human leukocyte elastases[6] and chimases.[7] After the first synthesis of lactams by Staudinger in 1907,[8] many synthetic methods of β-lactams were then developed including rearrangement of heterocyclic compounds, cyclization reactions and carbene insertion reactions.[9] The introduction of the "β-lactam synthon" method by Ojima nearly 20 years ago[10] led to great interest in azetidin-2-one as building blocks and valuable intermediates to access a variety of high-added value products such as peptidomimetics and nitrogen heterocycles.

Introduction of fluorine into a biologically active molecule usually increases its pharmacological properties.[11,12] Although fluorine-containing compounds have been widely used in the field of medicinal chemistry,[13] it is safe to say that 4-CF_3 monobactams diversely functionalized at C-3 are rather rare and scarcely explored. To the best of our knowledge, only few examples described the synthesis of trifluoromethylated rings at the C-4 position and their functionalization at the C-3 position (Scheme 1). From fluorinated imine derivatives[14] and α-chloroamine (*N*-tosyl-1-chloro-2,2,2-trifluoroethylamine),[15] β-lactams were obtained with OBn,[14a] NBn_2 [14b] or alkyl groups at the C-3 position.[14c] Finally, another group used the nucleophilic ring opening of aziridines followed by Grignard-mediated intramolecular cyclisation to obtain the 3-chloro- and 3-(tertbutyltrimethylsilyloxy)-4-trifluoromethyl-β-lactams.[16] However, these approaches did not allow access to a wide range of 4-CF_3 β-lactams functionalized at the C-3 position. Herein, we disclose the synthesis and the functionalization of halogenated CF_3 β-lactams available in one step by ring expansion of aziridines.

Most of the published syntheses using aziridines to produce β-lactams involved ring-opening and closure in two steps[16] and carbonylated reactions.[17] However, a straightforward approach to chloro-β-lactams which has been very less studied is the ring expansion of carboxylic aziridines. Both Clough[18] and Sharma[19] showed the elegant use of non-fluorinated sodium carboxylate aziridine in a one-step rearrangement with thionyl chloride or oxalyl chloride to form 3-chloro-2-azetidinones in moderate yields (Scheme 2).



Scheme 1 Access to trifluoromethylated β-lactams.



Scheme 2 Ring expansion of aziridines.

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Results and discussion

Firstly, both previous conditions were attempted for the ring expansion of the *cis*-CF_3-aziridine carboxylic acid (***cis*-1a**).[20] After saponification of the corresponding ester, the sodium salt of ***cis*-1a** reacted in the presence of the oxalyl chloride and after 24 h in refluxing toluene, led to the β-lactam **2a** in 50% yield as a mixture of diastereomers (*cis*/*trans*: 85/15). Performing the reaction with thionyl chloride and a catalytic amount of NaH (10%) in THF at room temperature for 48 h lowered the yield (40%) and the diastereoselectivity (*cis*/*trans*: 40/60) of the reaction (Scheme 3).

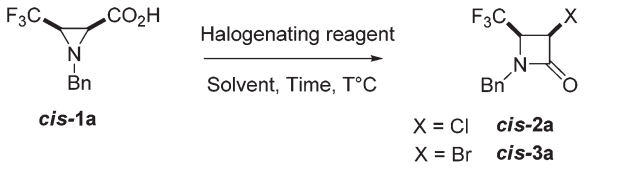
However, after optimization of the reaction conditions, the yields and diastereoselectivities were improved by carrying out the reaction of the carboxylic acid CF_3-aziridines with NaH (1.2 eq.) and thionyl chloride in toluene at 70 °C (Scheme 4).

Aziridines ***cis*-1a** and ***trans*-1a**[16] afforded the corresponding *cis* β-lactam ***cis*-2a** and *trans* β-lactam ***trans*-2a** in 58% and 55% yields respectively. Moreover, the stereoselectivities were excellent. The relative conformations of the products were determined by ^{1}H-NMR according to the coupling constant of *cis* (6 Hz) and *trans* (3 Hz). The mechanism leading to this stereospecificity has been reported to involve a bicyclic ammonium intermediate.[18,19] Given these very encouraging results, we were interested in the use of other halogenated reagents to prepare other halogenated β-lactams (Table 1).

Both phosphorus pentachloride and phosphoryl chloride allowed improving the yield and the diastereoselectivity in the formation of 3-chloro-4-CF_3-β-lactam ***cis*-2a** (entries 1 and 2). The new *cis*-3-bromo-4-CF_3-β-lactam ***cis*-3a** was formed when the reaction was performed with thionyl bromine despite a low yield and a good diastereoselectivity (entry 3). From other brominating agents such as BBr_3 and PBr_3, only traces of the compound were observed. Finally, the expected product ***cis*-3a** was satisfactorily obtained with triphenylphosphine/NBS (entry 6, 70%) and triphenylphosphine dibromide (entry 7, 85%) in excellent yield and diastereoselectivity in less than 30 minutes. Our efforts to introduce the iodine with Ph_3PI_2 or Ph_3P/NIS failed and afforded a mixture of compounds. These optimized conditions were applied to other aziridines having different protective groups (Table 2). The formation of the corresponding bromo-β-lactams ***cis*-3b** and ***cis*-3c** was not disturbed with the *p*-methoxy benzyl and *p*-methoxy phenyl (entries 2 and 3). In contrast, with the diphenyl group, only 38% of 3-bromo-β-lactam ***cis*-3d** was obtained (entry 4). This low yield could be explained by the bromination between the two phenyl rings of the biphenyl which led to the decomposition of the product. Whatever be the protective group, the diastereoselectivity was excellent.

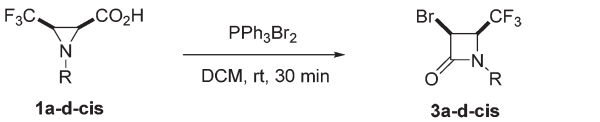
The ring expansion conditions were also effective on the *trans* aziridine ***trans*-1a** to afford stereospecifically the corresponding *trans* 4-Br-3-CF_3 β-lactam ***trans*-3a** in 50% yield (Scheme 5).

Table 1 Ring expansion of aziridines with various halogenating reagents



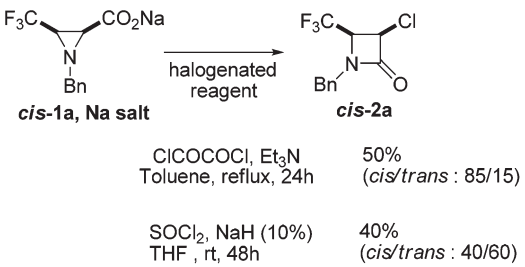
Entry	Reagent	Base	Solvent	Time (h)	*T* (°C)	dr	Yield (%)
1	PCl_5	NaH	Toluene	2	80	100/0	60
2	$POCl_3$	NaH	Toluene	1.5	80	100/0	76
3	$SOBr_2$	NaH	Toluene	1	80	90/10	40
4	BBr_3	—	DCM	1	0	—	Traces
5	PBr_3	—	DCM	24	0	—	Traces
6	PPh_3/NBS	—	DCM	0.5	rt	100/0	70
7	PPh_3Br_2	—	DCM	0.5	rt	100/0	85

Table 2 Formation of 3-bromo 4-CF_3 β-lactams

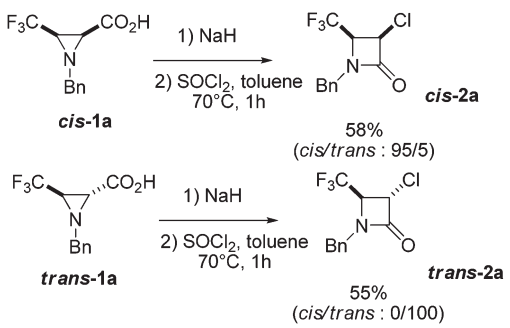


Entry	R	*cis*/*trans*	Product	Yield[a] (%)
1	Bn ***cis*-1a**	100/0	***cis*-3a**	85
2	PMB ***cis*-1b**	100/0	***cis*-3b**	81
3	PMP ***cis*-1c**	100/0	***cis*-3c**	81[b]
4	Ph_2CH ***cis*-1d**	100/0	***cis*-3d**	38

[a] Isolated yield. [b] Ph_3P/NBS was used instead of Ph_3PBr_2.



Scheme 3 Classical reactions.



Scheme 4 Ring expansion of CF_3-aziridines.

The ring expansion conditions were also effective on the *trans* aziridine ***trans*-1a** to afford stereospecifically the corresponding *trans* 4-Br-3-CF_3 β-lactam ***trans*-3a** in 50% yield (Scheme 5).

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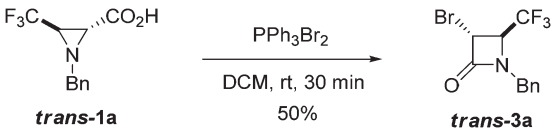
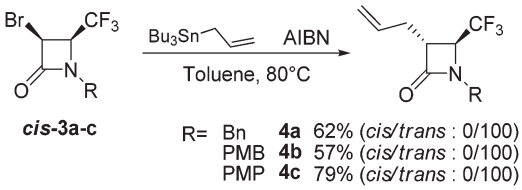


Scheme 5 Ring expansion of the *trans*-CF_3-aziridine **1a**.

With different brominated lactams in hand, we investigated their reactivity under different conditions in order to provide functionalized CF_3 β-lactams. First the substitution of chloride and bromide *cis* and *trans* lactams with a nucleophile such as sodium azide, amines and alcoholates failed totally, and starting materials were recovered unchanged. Fortunately, radical reaction was effective and diastereoselective with allyltin and AIBN[21] to lead exclusively to *trans* 4-allyl-3-CF_3 β-lactams **4a–c**. The radical addition occurred at the opposite side of the CF_3 group (Scheme 6).

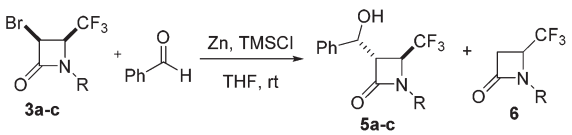
We also studied the reactivity of these 3-bromo-β-lactams with various organometallic reagents. We attempted the Reformatsky reaction in the presence of activated zinc and benzaldehyde (Table 3).

Under these conditions, benzaldehyde was trapped by the organozinc reagents to afford the corresponding 3-functionalized β-lactams **5a–c** as a mixture of diastereomers.[22] However, for each reaction, the side product **6** was always observed in around 20–30% yields.



Scheme 6 Radical reaction.

Table 3 Reformatsky reaction

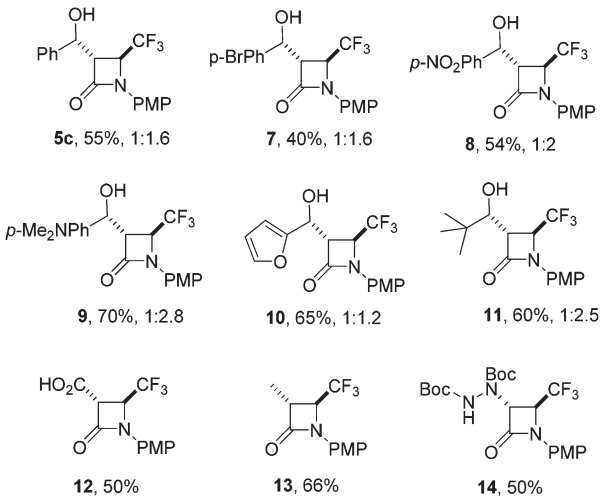


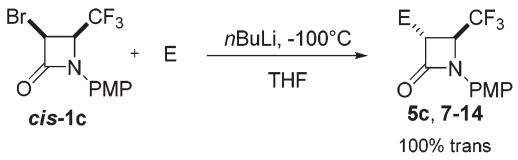
Entry	R	de 5	Yields $5^a/6^b$ (%)
1	Bn, **5a**	1 : 1.7	70/30
2	PMB, **5b**	1 : 1.7	40/20
3	PMP, **5c**	1 : 2.0	60/27

[a] Isolated yield. [b] Determined by ^{19}F NMR.

In order to avoid the formation of the reduced product **6**, we undertook the halogen–metal exchange. After several conditions were studied, here we report the best one: *n*BuLi at −100 °C in THF (Scheme 7).

Condensation with aldehydes provided the corresponding alcohols **5c** and **7–11** in moderate to good yields.[22] Unfortunately, from enolizable substrates, only compound **6** was obtained. However, carbon dioxide and methyl iodide reacted with the enolate intermediate to lead to the β-lactams **12** and **13** in 50% and 66% yields respectively. Nitrogen incorporation could be achieved from the ditertbutyl azodicarboxylate, generating the corresponding hydrazine **14**. The reaction was stereoselective, and addition occurred exclusively from the opposite side of the bulky trifluoromethyl substituent.





Scheme 7 The halogen-metal exchanges.

Conclusions

In conclusion, we achieved a convenient highly diastereoselective one-pot synthesis of 3-halogenated-4-trifluoromethyl *cis* and *trans*-β-lactams by ring expansion of aziridines. We showed that 3-bromo-4-CF_3 β-lactams reacted under various reaction conditions such as radical and nucleophilic reactions. Such novel structures are now available to be exploited for medicinal purposes.

Acknowledgements

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22 The ratio of epimers at the α position of the hydroxy group of **5a–c**, **7–11** is based on ^{19}F NMR. Furthermore no improvement in diastereoselectivity was observed using boron and titanium chelated reagents.

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