Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800275

Link to VoR: http://dx.doi.org/10.1002/adsc.201800275

10.1002/adsc.201800275

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Aluminium Chloride-Mediated Synthesis of 1-Chloro-2,2,2-Trifluoroethylidene-Substituted Pyrrolidones

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. An aluminium chloride-mediated cascade reaction between pyrrolidones and trifluoroacetic anhydride is reported. Functionally diverse 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidones were obtained in moderate to high yields through electrophilic trifluoroacetylation, nucleophilic chlorination, and elimination. This procedure has a wide scope, good functional-group tolerance and the reaction conditions are amenable to scale up. Additionally the obtained 1-chloro-2,2,2-trifluoroethylidene products can be applied to further functionalization as trifluoromethyl-containing building blocks. Some of the title compounds showed fungicidal activity against cucumber downy mildew (CDM).

Keywords: Trifluoromethylation; Pyrrolidones; Aluminium chloride-mediated; Trifluoroacetic anhydride; 2,2,2-Trifluoroethylidene

Introduction

Fluorinated groups-containing drugs and pesticides, frequently synthesized by convenient fluorination and trifluoromethylation methods, have attracted increasing attention in modern bioorganic chemistry.[1] The replacement of hydrogen by fluorine can drastically affect the physical, chemical, and biological properties of pharmaceutical molecules, to enhance their metabolic stability and selectivities. Given the unique physicochemical properties engendered by the trifluoromethyl (CF_3) group, considerable efforts have been directed towards new methodologies for the selective introduction of CF_3 groups into bioactive molecules.[2]

Among a variety of synthetically important trifluoromethylated compounds, molecules containing the C_{vinyl}–CF_3 moiety are known to play important roles in a wide field of science, especially in medicinal chemistry.[3] Therefore, development of efficient methods for the synthesis of these compounds is in great demand. Conventional approaches for the synthesis of C_{vinyl}–CF_3 compounds mainly rely on the coupling of aryl halides with highly volatile reagents, such as 1-iodo-3,3,3-trifluoropropane,[4] (*E*)-trimethyl-(3,3,3-trifluoroprop-1-enyl)silane[5] and 2-(trifluoromethyl)acrylic acid,[6] and the direct trifluoromethylation reaction with unsaturated alkenes,[7] vinyl sulfonates,[8] vinylboron derivatives,[9] vinyl halides,[3b, 10] α,β-unsaturated carboxylic acids,[11] and other methods.[12]

Pyrrolidone structural motifs are frequently found in many biologically active natural products and pharmaceuticals. For example, Aniracetam is a drug with anti-depressive properties used as a mental performance enhancer.[13] Pyrrolidone derivatives are also used as 11-β-hydroxysteroid dehydrogenase inhibitors,[14] or monoamine oxidase B inhibitors[15] (Figure 1). This biological and medicinal importance makes pyrrolidone derivatives desirable compounds for the screening of new biological activities.

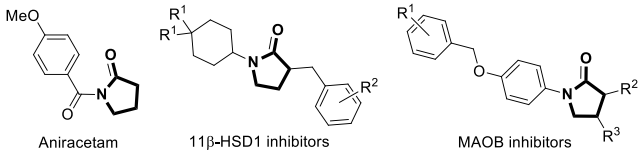
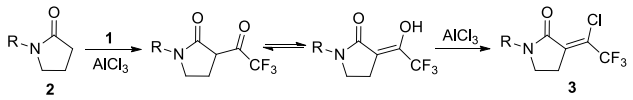


Figure 1. Bioactive 2-pyrrolidone derivatives.

The use of readily available, convenient, and inexpensive trifluoroacetic acid (TFA) and its anhydride (TFAA) as a trifluoromethyl source for trifluoromethylation reactions, would be an attractive approach to the synthesis of trifluoromethylated compounds.[16] In this context, Zhang and co-workers reported a silver-catalyzed radical C–H trifluoromethylation of arenes employing TFA as the trifluoromethylating reagent.[17] Stephenson and co-workers reported an elegant radical trifluoromethylation of arenes and heteroarenes using

TFAA as the trifluoromethylating reagent and pyridine *N*-oxide and photoredox catalysis.[18] Later, Schäfer and co-workers also reported the synthesis of trifluoromethylated imidazo-fused *N*-heterocyles using TFAA as trifluoromethylating reagent.[19]

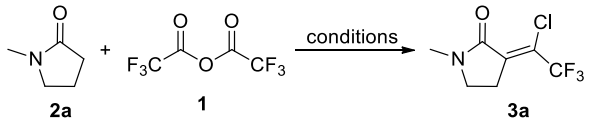
Despite these advancements, to the best of our knowledge, there is no literature precedence on the one-pot synthesis of 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidone compounds using TFAA as 2,2,2-trifluoroethylidene source. Continuing our study on copper-mediated synthesis of trifluoromethylated compounds utilizing TFA or TFAA as trifluoromethylating reagent,[20] we envisioned the feasibility of $AlCl_3$-mediated trifluoroacetylation of 2-pyrrolidone derivatives[21] with TFAA followed by hydroxyl chlorination leading to 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidones (Scheme 1). Herein we disclose the first report of 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidones synthesis from pyrrolidone derivatives *via* $AlCl_3$-mediated trifluoroacetylation and hydroxyl chlorination with TFAA.



Scheme 1. Proposed One-Pot Synthesis of 1-Chloro-2,2,2-Trifluoroethylidene-Substituted Pyrrolidones.

Results and Discussion

Table 1. Optimization of the Reaction Conditions [a)]



Entry	Lewis acid (equiv)	Solvent	T (°C)	Time (h)	Yield (%) [b]	*Z*/*E* [c]
1	$AlCl_3$ (1)	DMF	60	24	78	92:8
2	$CuCl_2$ (1)	DMF	60	24	0	–
3	$ZnCl_2$ (1)	DMF	60	24	0	–
4	$InCl_3$ (1)	DMF	60	24	0	–
5	$FeCl_3$ (1)	DMF	60	24	0	–
6	-	DMF	60	24	0	–
7	$AlCl_3$ (1)	DMSO	60	24	0	–
8	$AlCl_3$ (1)	DCE	60	24	0	–
9	$AlCl_3$ (1)	CH_3CN	60	24	0	–
10	$AlCl_3$ (1)	THF	60	24	<1	–
11	$AlCl_3$ (1.5)	DMF	60	24	96	93:7
12	$AlCl_3$ (1.5)	DMF	30	24	62	94:6
13	$AlCl_3$ (1.5)	DMF	60	12	81	93:7

[a)] Reaction conditions: **1** (0.30 mmol), **2a** (0.10 mmol), solvent (1.2 mL), N_2; [b)] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard; [b] *Z*/*E* ratios were determined by ^{19}F NMR.

To validate the feasibility of our postulation, readily available 1-methyl-2-pyrrolidinone **2a** was chosen as a model substrate to react with TFAA **1** under Lewis acid-catalytic system (Table 1). After screening various reaction parameters, we were pleased to observe 78% NMR yield of the desired pyrrolidone product **3a**, using 1.0 equiv of $AlCl_3$ in DMF at 60 °C for 24 h (entry 1). The structure of **3a** was unequivocally confirmed by single crystal X-ray analysis (Figure 2).[22]

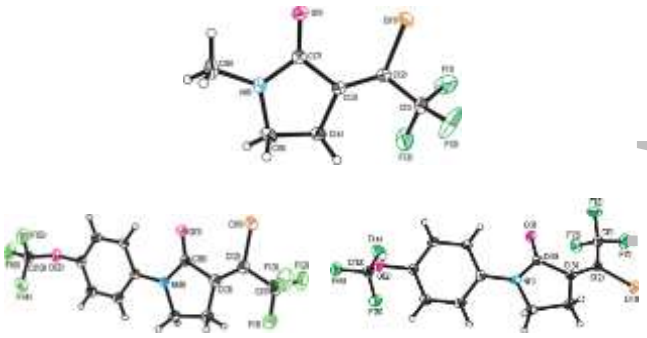


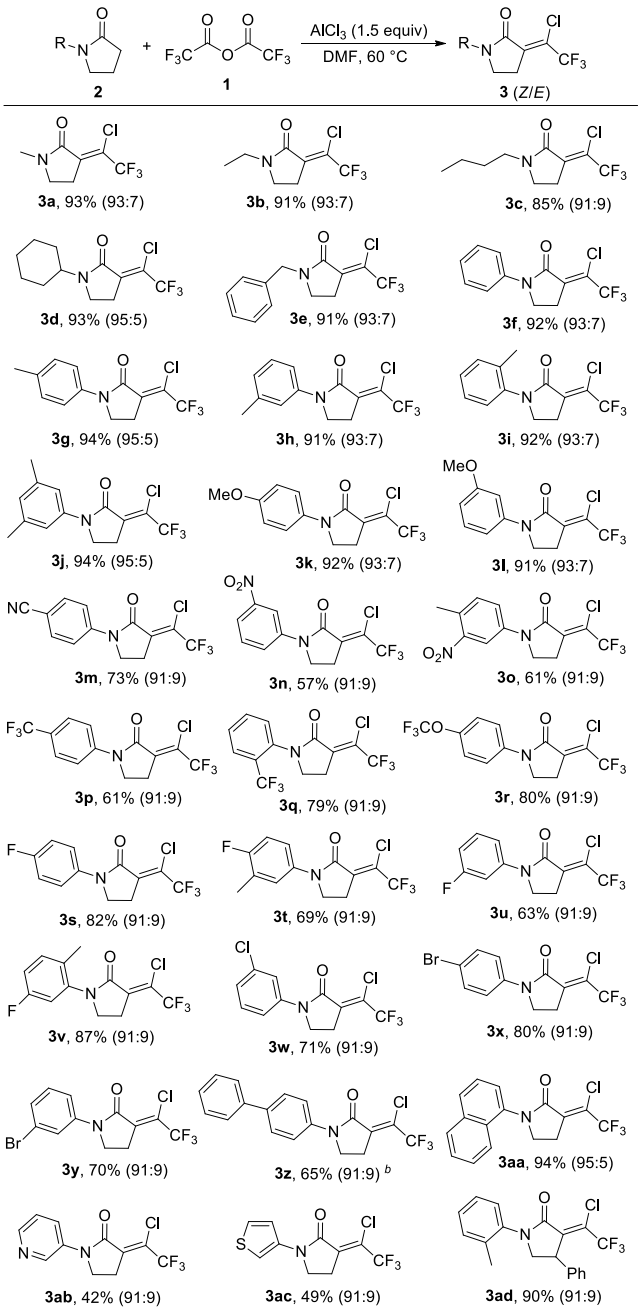
Figure 2. ORTEP diagrams of (*Z*)-**3a** (top), (*Z*)-**3r** (bottom-left), and (*E*)-**3r** (bottom-right).

It is noteworthy that other Lewis acid-catalytic systems such as $CuCl_2$, $ZnCl_2$, $InCl_3$, and $FeCl_3$ were found to be totally ineffective under identical reaction conditions (entries 2-5). Similarly, the reaction did not proceed in the absence of $AlCl_3$ catalyst (entry 6) The utilization of other solvents, such as DMSO, DCE, CH_3CN, or THF, was also inefficient (entries 7-10). Fortunately, increasing the catalyst loading to 1.5 equiv improved the chemical yield dramatically, and the desired product **3a** was obtained in high chemical yield with a high stereoselectivity of the C=C configuration (96%, *Z*/*E*= 93:7; entry 11). When the reaction was conducted at 30 °C, lower yield of **3a** was obtained (62%; entry 12). Moreover, shorter reaction time to 12 h led to a lower yield of product **3a** (81%; entry 13).

Using the optimized reaction conditions, the substrate scope of the reaction was explored using a range of electronically and sterically differentiated 2-pyrrolidone derivatives (Scheme 2). Various alkyl groups such as methyl (**3a**), ethyl (**3b**), *n*-butyl (**3c**), cyclohexyl (**3d**), and benzyl (**3e**) tethered on the pyrrolidone nitrogen were all well compatible, providing good yields of the corresponding products The *N*-phenyl 2-pyrrolidone furnished corresponding product **3f** in high chemical yield (92%). *N*-Aryl 2-pyrrolidone substrates bearing electron-donating (**3g**–**3l**) substituents on the aryl ring were smoothly converted to the corresponding products in 91–94% yields irrespective of the substituent position. However, reactions of *N*-aryl 2-pyrrolidones containing electron-withdrawing (**3m**–**3r**) substituents on the aryl ring furnished the desired products in modest to good yields. Substrates bearing a halide substitution on the *para*- or *meta*-position of the aryl group gave the desired products (**3s**–**3y**) in

63–87% yields. The tolerance of halide groups under these conditions demonstrated the additional synthetic utility of the present method.

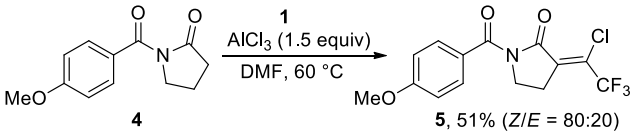
In addition, this strategy was further extended to *N*-biphenyl and 1-naphthyl 2-pyrrolidones to obtain the corresponding products **3z** and **3aa** in 65% and 94% yields, respectively. It was worth noting that heterocyclic derivatives such as *N*-3′-pyridyl (**3ab**) and 3′-thienyl 2-pyrrolidones (**3ac**) were also found to be compatible. Further, when 4-phenyl-1-(*o*-tolyl)pyrrolidin-2-one was used, the corresponding product **3ad** was isolated in 90% yield.



Scheme 2. Scope of the Reaction. [a] Reaction conditions: **1** (1.50 mmol, 3.0 equiv), **2** (0.50 mmol), $AlCl_3$ (0.75 mmol, 1.5 equiv), DMF (4.0 mL), 60 °C, 24 h, N_2; Isolated yields. [b] Performed at 80 °C.

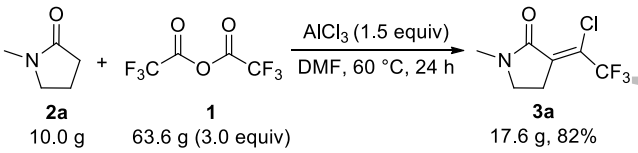
The reaction was found to be stereospecific as the *Z*-isomer was obtained as the major product. The stereochemistry, easily assignable by the ^{19}F NMR (*Z* isomers: -64.6 ± 0.2 ppm; *E* isomers: -57.5 ± 0.5 ppm), is in accordance with the results obtained in closely related molecules.[23] The two *E*- and *Z*-isomers of **3r** could be isolated by flash column chromatography, and the structures of the two isomers were unambiguously confirmed by the single-crystal X-ray analysis (Figure 2).[22]

To further examine the potential of our methodology in late-stage functionalization, we next investigated drug molecules of higher complexity. The reactions of aniracetam (**4**) and **1** proceeded smoothly under similar reaction conditions to afford the corresponding product **5** in 51% yield (Scheme 3). Thus, pharmaceutically relevant molecules can readily be synthesized with this new method.



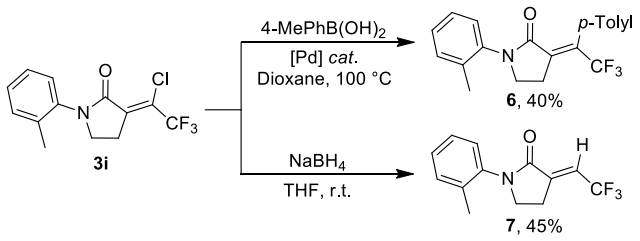
Scheme 3. Synthesis of 1-Chloro-2,2,2-Trifluoroethylidene-Substituted Aniracetam Derivative.

To evaluate the efficiency of this new synthetic strategy, a gram-scale reaction of 1-methylpyrrolidin-2-one (**2a**) with **1** was carried out, and the corresponding product **3a** was given in 82% isolated yield (Scheme 4). This result indicates that the process could potentially be amenable towards scale-up.



Scheme 4. Gram Scale Experiment.

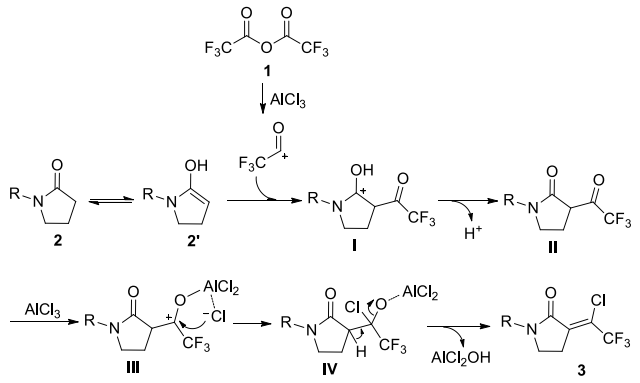
To test the synthetic utility of the present synthetic protocol, the transformation of the 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidone products was performed. As shown in Scheme 5, the reaction of **3i** with *p*-tolylboronic acid under Suzuki cross coupling conditions or with $NaBH_4$ under reductive dechlorination conditions provided the corresponding product **6** and 7 in 40% and 45% isolated yields, respectively. These results demonstrate that the obtained 1-chloro-2,2,2-trifluoroethylidene products can serve as CF_3-containing building blocks.



Scheme 5. Synthetic Utility of **3i**.

To evaluate biological activity of the title compounds, a general screening on their bactericidal activity was performed (See Supporting Information). The biological assays revealed that some of the pyrrolidone products showed potent fungicidal activities against cucumber downy mildew (CDM).

A plausible reaction mechanism is illustrated in Scheme 6. First, $AlCl_3$-promoted electrophilic addition of trifluoroacetyl cation to 2-pyrrolidones gave intermediate **I**, which smoothly underwent deprotonation to afford trifluoroacetylated 2-pyrrolidone derivatives **II**. Subsequently, $AlCl_3$ activated **II** by coordinating with the carbonyl oxygen forming complex **III**. Finally, nucleophilic attack of the chloride anion to the carbon of **III** following with elimination led to the desired product **3**.



Scheme 6. Proposed Mechanism for the Formation of **3**.

Conclusion

In summary, we have developed an efficient and mild approach for the $AlCl_3$-mediated synthesis of various 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidones. This reaction represents an utilization of readily available pyrrolidones and inexpensive trifluoroacetic anhydride for convenient formation C–C and C–Cl bonds in one-pot. Some of the synthesized compounds exhibited bactericidal activity against CDM. A plausible reaction mechanism involving electrophilic trifluoroacetylation, nucleophilic chlorination, and elimination was also proposed. The synthesis of other heterocyclic scaffolds is currently ongoing in our laboratories.

Experimental Section

General Information

^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded using Bruker AVIII 400 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as the external standard and low field is positive. Coupling constants (*J*) are reported in Hertz (Hz). The residual solvent peak was used as an internal reference: ^{1}H NMR (chloroform δ 7.26) and ^{13}C NMR (chloroform δ 77.0). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS were obtained on Waters GCT-TOF at the Shanghai Institute of Organic Chemistry and State Key Discipline Testing Center for Physical Chemistry of Fuzhou University. Reagents were received from commercial sources. Solvents were freshly dried and degassed according to the published procedures prior to use.

General Procedure for $AlCl_3$-mediated synthesis of 1-chloro-2,2,2-trifluoroethylidene-substituted pyrrolidones.

The pyrrolidones derivatives (**2**) (0.50 mmol), trifluoroacetic anhydride (**1**) (1.50 mmol, 3.0 equiv), $AlCl_3$ (100.0 mg, 0.75 mmol, 1.5 equiv), and DMF (4.0 mL) were added to a reaction tube equipped with a stir bar. The mixture was stirred at 60 °C for 24 h. The reaction mixture was diluted with ethyl acetate (30 mL), washed with saturated brine (30 mL), and water (20 mL), dried over $MgSO_4$. The solvent was removed by rotary evaporation and the resulting product **3** was purified by column chromatography over silica gel (*n*-pentanes/ethyl acetate = 1:1).

Acknowledgements

This work was supported by National Natural Science Foundation of China (21772022).

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10.1002/adsc.201800275

FULL PAPER

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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