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One-pot synthesis and theoretical calculation for trifluoromethylated pyrrolizidines by 1,3-dipolar cycloaddition with azomethine ylides and β-trifluoromethyl acrylamides

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ABSTRACT

The reaction with β-trifluoromethyl acrylamide **3e** and azomethine ylides generated from L-proline and several aldehydes provided the corresponding trifluoromethylated pyrrolizidines with excellent diastereoselectivity (>20/1) in all cases and moderate regioselectivity (up to 1/5.9). A DFT calculation was also examined to reveal the origin of these stereoselectivities.

1. Introduction

Pyrrolizidine alkaloids are found in many natural products and have a wide variety of bioactivities [1]. Therefore, structurally diverse pyrrolizidines are attractive targets for organic chemists. Many synthetic strategies were developed over the last few decades with high regio- and stereoselectivity [2]. Unfortunately, most synthetic protocols involve environmentally unfriendly compounds, such as transition metals and the resulting chemical waste from these reactions. However, the intermolecular 1,3-dipolar cycloaddition with olefins and azomethine ylides, decarboxylatively generated from L-proline and aldehydes, alleviates these environmental concerns [3]. All three reagents can be incorporated into the final products by a single one-pot reaction with no extra reagents; moreover, water (H_2O) and carbon dioxide (CO_2) are the only waste products from this reaction (Scheme 1) [4].

Although there are many previous reports on this intriguing synthetic approach toward pyrrolizidines, most studies have encountered problems [5]. First, low chemical yields were often observed. This problem arises from the similar reactivities of carbonyls and olefins as dipolarophiles toward azomethine ylides. As a result of low chemoselectivity, the reaction often results in a large amount of byproducts, such as 1-oxapyrrolizidines [6].

Second, low regio- and/or diastereoselectivity are observed in some reactions because the optimized conditions apply to only a narrow range of substrates [7].

The introduction of fluorinated functional groups into heterocyclic compounds is frequently attempted in drug discovery, and this dramatically alters the pharmacological properties of the parent molecules [8]. The importance of a trifluoromethyl group among several types of fluoroalkyl moieties was observed in many therapeutic medicines [9]. Recently, the stereoselective synthesis of trifluoromethylated pyrrolizidine was reported and expected possible enhancements of biological activity when changing CH_3 to CF_3 [10]. Despite the elegance of their syntheses, these precedent studies did not investigate expanding the range of substrates.

In this article, we focused on the unique electronic and steric properties of trifluoromethylated olefin and report that β-trifluoromethyl acrylamides are good dipolarophiles toward azomethine ylides generated from L-proline and aldehydes [11]. As a result, various 1-trifluoromethylated pyrrolizidines were obtained in moderate yields and had excellent diastereoselectivities. We also examined a DFT calculation to rationalize these selectivities.

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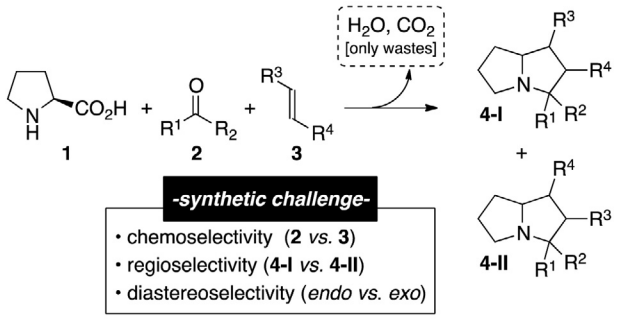


Scheme 1. General reaction scheme of an one-pot, three-component reaction for multi-substituted pyrrolizidines **4-I** and **4-II** by 1,3-dipolar cycloaddition.

2. Results and discussion

2.1. Synthesis

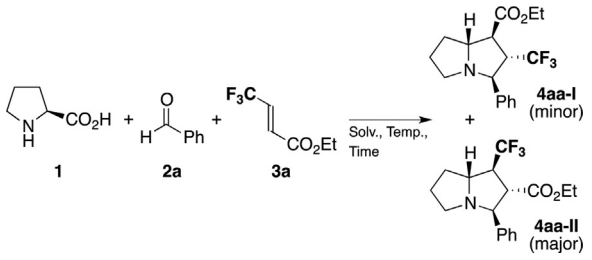
The investigation was started by screening solvents, as shown in Table 1.

In order to suppress the undesired 1-oxapyrrolizidine from the 1,3-dipolar cycloaddition of azomethine ylides and **2a**, an excess of dipolarophile should be applied. However, due to cost considerations and fluorinated reagent availability, the screening was initially carried out with 1 equivalent of ethyl 4,4,4-trifluorocrotonate **3a**. In fact, most solvents mainly resulted in 1-oxapyrrolizidine as the byproduct and a trace amount of target compound **4aa** (Entries 1–4, Table 1). However, polar and non-protic solvents, such as DMF and DMSO, gave promising results and moderate yields of **4aa**. The ^{19}F NMR of these reaction mixtures revealed the modest regioselectivity (**4aa-I**/**4aa-II** = 1/2.0) and excellent diastereoselectivity (>20/1) of each regioisomer (Entry 5–6). Finally, an increased reaction temperature led to drastically shorter reaction times and the ability to use half of the equivalents of L-proline **1** and benzaldehyde **2a** with similar yields and selectivities (Entry 8–9).

Next, the effects of carbonyl functional groups on **3** were examined (Table 2). Excellent diastereoselectivity (>20/1) was maintained in all cases. Switching esters to amides gave higher regioselectivities in spite of the slow reactions, with a ratio up to 1/4.3 using the morpholine amide **3e** (Entry 1–5). Finally, the procedure was modified in order to complete the reaction. Both the slow addition of aldehyde **2a** (Method B) [13] and the separate reagent addition (Method C) led to reaction completion. The desired product **4ae** was obtained in moderate yield and regioselectivity with excellent diastereoselectivity (Entry 6–7). From the viewpoint of convenience, separate addition (Method C) was chosen for the optimal reaction method.

The optimal reaction condition was applied to a wide range of aldehydes (Table 3) and provided excellent diastereoselectivity (>20/1) in all cases. In general, aromatics bearing electron-donating groups gave better yields (up to 82%, Entry 2–5); however, the yields decreased with electron-withdrawing groups (Entry 6–7). Better regioselectivity was attained with 2-methoxybenzaldehyde **2e** (Entry 5) and 1-naphthyladehyde **2 h** (Entry 8). The reaction with the aliphatic aldehyde isovaleraldehyde **2j** did not require an extra addition of reagents to complete the reaction, but it gave a moderate yield with low regioselectivity (Entry 10).

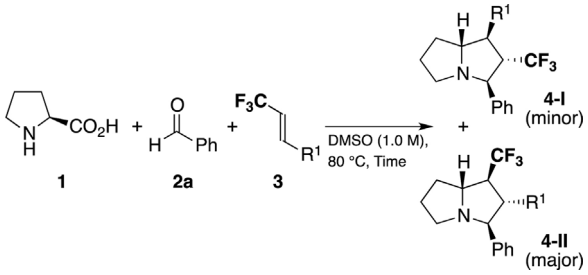
Table 1
Screening for optimum reaction conditions.

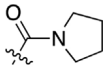
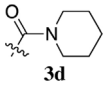
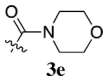


Entry	Equiv of reagents (**1**/**2a**/**3a**)	Solvent (1.0 M)	Temp./°C	Time/h[a]	Yield of **4aa**/%[b, c]
1	4/4/1	Toluene	40	24	trace
2	4/4/1	THF	40	24	trace
3	4/4/1	Dioxane	40	24	trace
4	4/4/1	MeCN	40	24	trace
5	4/4/1	DMF	40	23	41 (1/2.1)
6	4/4/1	DMSO	40	17	49 (1/1.9)
7	4/4/1	i-PrOH	40	24	trace
8	4/4/1	DMSO	80	0.5	61 (1/2.1)
9	2/2/1	DMSO	80	0.5	63 (1/2.0)

[a] The reaction time was determined by monitoring the consumption of the starting material of **3a** by ^{19}F NMR.
[b] The combined isolated yields of **4aa-I** and **4aa-II**.
[c] The values in the parentheses are the ratios of two isomers as determined by ^{19}F NMR of the reaction mixture.

Table 2
The effects of changing R^1 in **3**.



Entry	R^1	Method[a]	Time/h[b]	Yield of **4**/%[c, d, e]
1	CO_2Et **3a**	A	0.5	**4aa**: 63 (1/2.0) [0]
2	CO_2Ph **3b**	A	1	**4ab**: 57 (1/1.9) [3]
3	 **3c**	A	23	**4ac**: 39 (1/4.0) [9]
4	 **3d**	A	19	**4ad**: 41 (1/4.0) [17]
5	 **3e**	A	16	**4ae**: 52 (1/4.3) [12]
6	**3e**	B	58	**4ae**: 67 (1/4.4) [0]
7	**3e**	C	22	**4ae**: 66 (1/4.4) [0]

[a] The details of reaction methods A to C are described in Ref. [12].
[b] The reaction time was determined by monitoring the consumption of the starting material of **2a** and/or **3** by TLC or ^{19}F NMR.
[c] The combined isolated yields of **4-I** and **4-II**.
[d] The values in parentheses are the ratios of two isomers as determined by ^{19}F NMR of the reaction mixture.
[e] The values in brackets are the yields of the remaining starting material **3** as determined by ^{19}F NMR of the reaction mixture.