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Synthesis of trifluoromethylated pyrrolidines via decarboxylative [3+2] cycloaddition of non-stabilized *N*-unsubstituted azomethine ylides

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ABSTRACT

A new method for synthesis of trifluoromethylated and pyrrolidinedione-fused pyrrolidines is developed through a three-component and decarboxylative [3 + 2] cycloaddition of non-stabilized N-unsubstituted azomethine ylides with commercially available trifluoroacetophenones. This efficient and economic synthesis only produces stoichiometric amount of CO_2 and H_2O as byproducts.

1. Introduction

It has been well-recognized that incorporation of fluoro-containing groups such as trifluoromethyl (CF_3) could significantly influence the permeability, bioavailability, binding selectivity and metabolic stability of the parent molecules [1]. Shown in Fig. 1 are some CF_3-bearing compounds which are on the list of top 200 best-selling drugs in 2012 [1e]. A series of methods for nucleophilic, electrophilic, and free radical trifluoromethylation have been developed for the introduction of CF_3 group to sp2 carbons [2]. However, using readily available trifluoromethyled building blocks is still an important approach for making products with a CF_3 group on the sp3 carbons. The construction of pyrrolidine rings is significant for both synthetic and medicinal chemistry considerations because pyrrolidine is a privileged heterocyclic ring for pharmaceutical and agricultural chemicals [3], and also a valuable scaffold for organocatalysts in asymmetric synthesis [4].

1,3-Dipolar cycloadditions of trifluoromethyl azomethine ylides have been reported for the preparation of trifluoromethylated pyrrolidines, but multistep synthesis, requirement of special starting materials, and using metal catalysts could limit the efficiency and the scope of the methods [5]. We have recently introduced a series of one-pot synthesis based on the [3 + 2] cycloaddition of azomethine ylides for making novel and diverse pyrrolidine-containing polycyclic compounds [6]. Introduced in this paper is a one-pot synthesis of trifluoromethyl pyrrolidines through a decarboxylative [3 + 2] cycloaddition using commercially available trifluoroacetophenones as a starting material. Different from the literature methods which utilized N-protected or metal-coordinated azomethine ylides [7] for [3 + 2] cycloadditions, the new method utilized N-unsubstituted azomethine ylides generated from the decarboxlyation for [3 + 2] cycloadditions (Scheme 1).

2. Results and discussion

A model reaction of glycine **2a**, 4-bromo-2,2,2-trifluoroacetophenone **3a**, and N-benzyl maleimide **4a** was carried out to explore the conditions for the proposed three-component reaction. After screening acid and base catalysts including DIPEA, AgOAc, TFA, and AcOH, it was found that a reaction with DIPEA only gave 19% yield of product 1a (Table 1, entry 1), while the reactions with AgOAc or TFA afforded 66% and 80% yield of **1a** (entries 2 and 3), respectively. A reaction without catalyst gave **1a** in 71% (entry 4). Reactions with AcOH under microwave heating afforded moderate yield of 75% and 69% (entries 7 and 8). Obviously acidic conditions are favorable for decarboxylation to form non-stabilized N-protected azomethine ylides for [3 + 2] cycloaddition. Further evaluation of the reaction conditions was carried out by changing the amount of AcOH, using different solvents, and varying the reaction temperature and time (entries 5, 9–12). It was found that using 0.3 equiv of AcOH in EtOH at 110 °C for 12 h resulted the best LC yield of 88% (73% isolated yield). The AcOH played a critical role in facilitating the decarboxylation and stabilizing the azomethine ylides for the [3 + 2] cycloaddition.

The decarboxylative 1,3-dipolar cycloaddition reactions reported in literature involve the generation of non-stabilized N-protected azomethine ylides [8]. To understand the role of the CF_3 group to the

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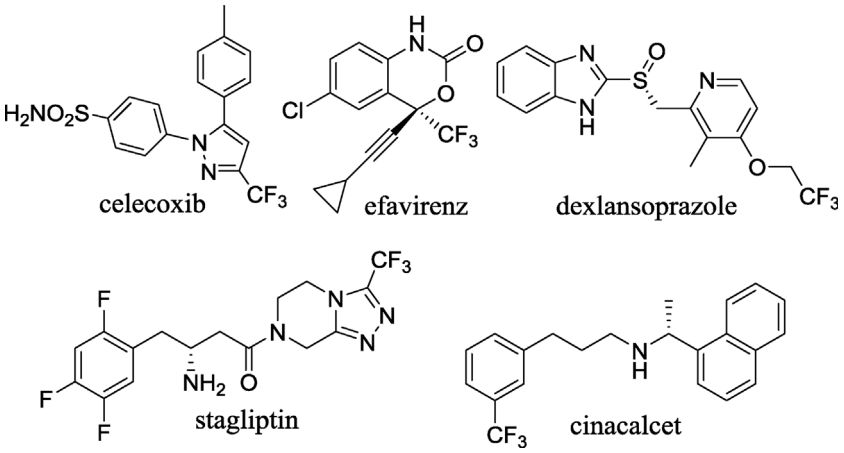
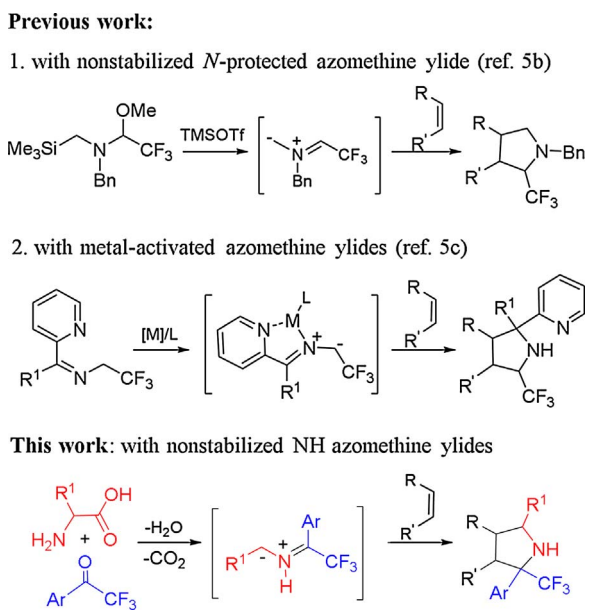


Fig. 1. Representative CF_3-bearing drugs.



Scheme 1. Trifluoromethylated azomethine ylide-based [3 + 2] cycloadditions.

azomethine ylides, we conducted two control reactions using 4-bromoacetophenone and 4-bromobenzaldehyde as starting materials via non-stabilized N-unsubstituted azomethine ylides (Table 2). The yield of **1a** (73%) from the reaction of trifluoromethyl ketone is much higher than the yields of **5** (15%) from methyl ketone or **6** (trace) from an aldehyde. The results indicated that the N-unsubstituted azomethine ylide stabilized by the electronegative CF_3 group could significantly improve the yield for the decarboxylative [3 + 2] cycloaddition. Reactions of CF_3-containing nonaromatic ketone or aldehyde were also conducted, but no expected products **7** and **8** were detected.

With the optimized conditions in hand, we carried out reactions with different amino acid **2**, trifluoroacetophenone **3**, and maleimides **4** for the synthesis of a series of α-trifluoromethyl pyrrolidines 1 with the variation of R^1, R^2 and R^3 groups (Table 3). The isolated yields of products **1a-m** are in the range of 50–77% and dr values from 3:1 to 7:1. But product **1n** was not observed owing to the large steric hindrance of phenyl group. It is known that azomethine ylides could have a W- or a U-shape (Scheme 2) in the formation of trifluoromethylated and pyrrolidinedione-fused pyrrolidines [9]. Using structurally rigid maleimides, the cycloaddition only resulted two diasteroisomers through the suprafacial reactions of W- or U-shaped ylides with maleimides [6a,6b]. The ratio of the diastereomeric products was detected by ^{1}H NMR, while the stereochemistry of the diastereomers was determined by NOE analysis (see SupInf).

3. Conclusions

In summary, a new method for the synthesis of trifluoromethylated and pyrrolidinedione-fused pyrrolidines using commercially available amino acids, trifluoroacetophenones and maleimides is developed. This one-pot decarboxylative [3 + 2] cycloaddition only generates CO_2 gas and H_2O as byproducts. The new method is much more economic and greener than the reported methods.

4. Experimental

4.1. General information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR (400 MHz), ^{13}C NMR spectra (101 MHz) and ^{19}F NMR (376 MHz) were recorded on Agilent NMR spectrometers. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). LC–MS were performed on an Agilent 2100 LC with a 6130 quadrupole MS spectrometers. A C_{18} column (5.0 μm, 6.0 × 50 mm) was used for the separation. The mobile phases were MeOH and H_2O both containing 0.05% CF_3CO_2H. A linear gradient from 25:75 (v/v) MeOH/water to 100% MeOH over 8.0 min at a flow rate of 0.7 mL/min was used as a mobile phase. UV detections were conducted at 210 nm, 254 nm and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). Final products were purified on Angela HP-100 pre-LC system with a Venusil PrepG C_{18} column (10 μm, 120 Å, 21.2 mm x 250 mm).

4.2. General procedure for synthesis of α-trifluoromethyl-substituted pyrrolidines *1*

To a solution of an amino acid **2** (1.5 mmol), trifluoroacetophenones **3** (1.3 mmol), and maleimide **4** (1.0 mmol) in a sealed tube (3.0 mL of ethanol) was added acetic acid (0.3 mmol). After stirred at 110 °C for 12 h. The concentrated reaction mixture was isolated on a semi prep-HPLC with C_{18} column to afford purified product **1**.

4.2.1. Compound *1a*

Colorless oil, 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 4H), 7.40 (dt, J = 8.4, 2.2 Hz, 2H), 7.35–7.27 (m, 3H), 4.77–4.60 (m, 2H), 3.70 (t, J = 6.7 Hz, 1H), 3.56 (t, J = 12.0 Hz, 1H), 3.36 (dt, J = 8.7, 4.3 Hz, 1H), 3.23 (t, J = 9.2 Hz, 1H), 2.57 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.90, 173.36, 135.20, 135.14, 131.91, 129.51, 129.03, 128.66, 128.14, 126.04, 123.53, 123.20, 74.10, 73.82, 54.13, 47.54, 47.14,