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Vinylogous Functionalization of 4-Alkylidene-5-aminopyrazoles with Trifluoromethyl Pyruvates

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Abstract

A valuable vinylogous addition reaction between 4-alkylidene-5-aminopyrazoles and alkyl trifluoropyruvates leading to highly functionalized tertiary alcohols bearing a trifluoromethyl group and a pyrazole ring is presented. The corresponding trifluoromethyl alcohols are obtained in moderate to good yields (up to 80%) and high diastereoselectivity (up to 7:1).

Keywords

Vinylogous reaction; diastereoselectivity; nitrogen heterocycles; alcohols; pyrazoles

Introduction

The transmission of electronic effects through a conjugated π -system known as vinylogy, enables the extension of nucleophilic or electrophilic character of a functional group along a C=C double bond [1]. This effect has been established to be very advantageous to expand the range of reactions of different functional groups that can be coupled efficiently through a conjugated π -system. In this context, the addition reaction of vinylogous nucleophiles to carbonyl compounds is a significant and important reaction for the selective synthesis of homoallylic alcohols in an efficient and sustainable way [2-3]. As carbonyl compounds, alkyl trifluoromethylpyruvates [4-5] are an interesting class of compounds that have been used in addition reactions of different nucleophiles for the synthesis of tertiary trifluoromethyl carbinols. [6-7] In this context, trifluoromethyl carbinols constitute a key structural motif present in a wide range of molecules with important biological activities (Figure 1) [8-10]. On account of the distinctive properties of organofluorine compounds that generally enhance the bioactivity of agrochemical and pharmaceutical substrates.

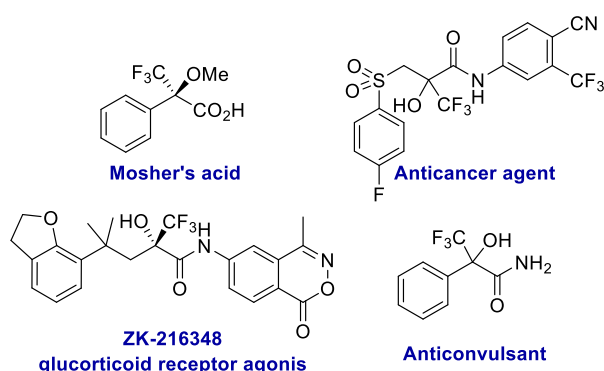


Figure 1: Biologically active compounds featuring a trifluoromethyl carbinol motif.

On the other hand, 5-aminopyrazole [11,12] is a nitrogen heterocycle that has attracted significant interest to pharmaceutical and medicinal chemists due to the presence of

this nitrogen heterocycle in various biologically active compounds, particularly antibacterial and antifungal agents [13,14]. This class of functionalized nitrogen heterocycle is notable for its synthetic versatility, because as it shows different nucleophilic positions, making regioselectivity a synthetic challenge. Numerous studies have reported on the regioselective electrophilic functionalization of this nitrogen heterocycle. [15-25] However the vinylogous functionalization of 5-aminopyrazoles has not been described to the best of our knowledge (Figure 2). As a part of our ongoing interest in the functionalization of 5-aminopyrazoles [26], we decided to study the use of this kind of nitrogen heterocycles as nucleophiles in vinylogous reactions. Therefore, we thought in the use of 4-alkenyl-5-aminopyrazoles as nucleophiles and study its vinylogous addition reaction to electrophiles. Herein, we report the regioselective and diastereoselective functionalization of 5-aminopyrazoles using alkyl trifluoropyruvates [27-29] as electrophiles. It is noteworthy that the development of such vinylogous functionalization of this nitrogen heterocycle with a fluorine containing electrophile may be of interest to pharmaceutical and medicinal chemists.

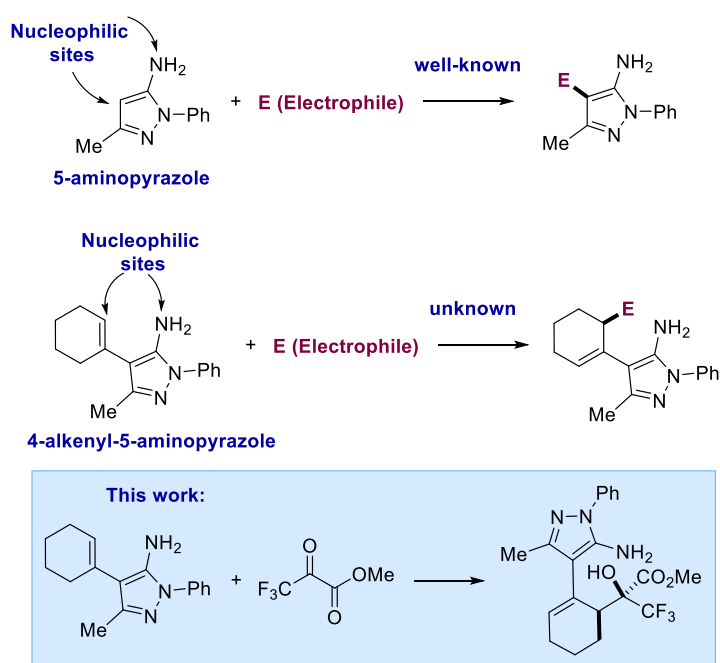
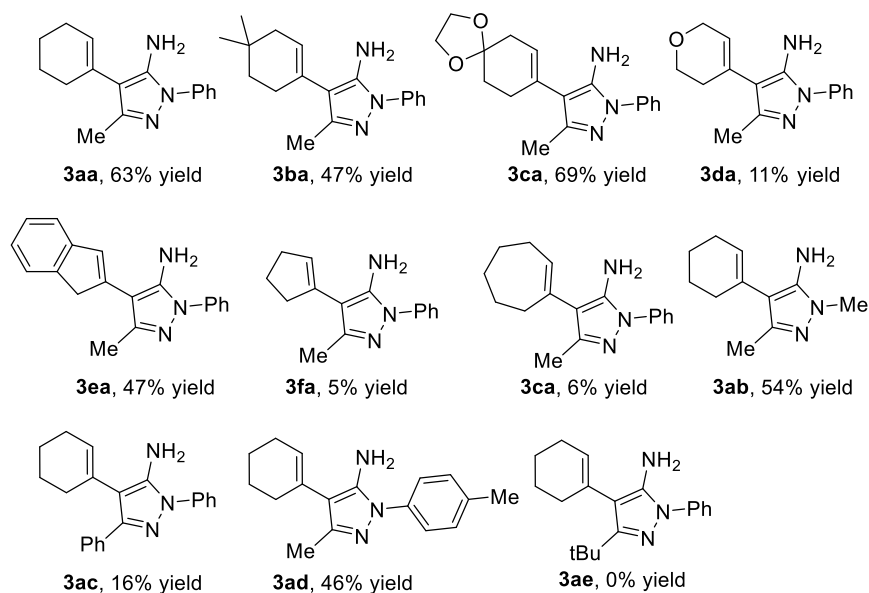
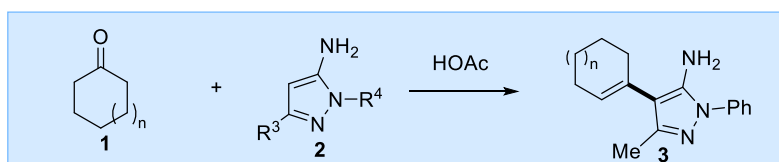


Figure 2: Nucleophilic sites of 5-aminopyrazoles and 4-alkenyl-5-aminopyrazoles. Stereoselective synthesis of trifluoromethyl carbinols through an vinylogous addition reaction of 4-alkenyl-5-aminopyrazoles to alkyl trifluoropyruvates.

Results and Discussion

4-(Alkenyl)-5-aminopyrazoles **3** were selected as starting materials to study the vinylogous functionalization with alkyl trifluoropyruvates. The synthesis of compounds **3** was accomplished by the reaction of cyclic ketones **1** and 5-aminopyrazoles **2** in the presence of acetic acid (Scheme 3) [30,31]. Cyclohexenones (**1a-c**) provided the corresponding products **3aa-ca** in good yields (47-69%). On the other hand, the reaction with tetrahydro-4*H*-pyran-4-one (**1d**) occurred with a significant decrease in yield, dropping to 11%. The yield is also affected by the number of carbons atoms of the starting cyclic ketone (**1**). In the case of structure **3ea**, which involves 2-indanone, the decrease in yield is not very pronounced. However, when cyclopentanone (**1f**) or cycloheptanone (**1e**) are used, the yield drops significantly to 5% and 3%, respectively. Next, maintaining cyclohexanone as a cyclic ketone, a series of compounds **3** were synthesized by modifying the 5-aminopyrazole **2**. Compounds **3ab** and **3ad** were obtained in a comparable yield (54 and 46%) from 1,3-dimethyl-1*H*-pyrazol-5-amine (**2b**) or 3-methyl-1-(*p*-tolyl)-1*H*-pyrazol-5-amine (**2d**). On the other hand, 1,3-diphenyl-1*H*-pyrazol-5-amine (**2c**) provided the corresponding product **3ac** in much lower yield (16%). If a *tert*-butyl group is present in the C-3 position (**2e**), the reaction did not take place, likely due to a considerable increase in steric hindrance.

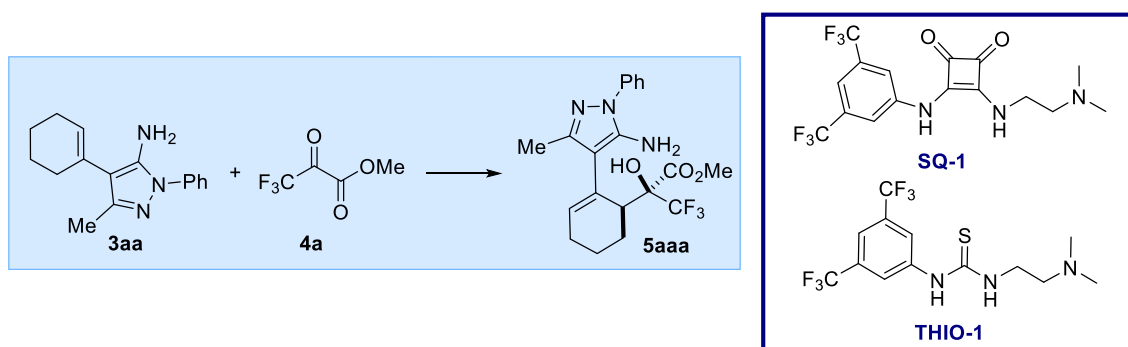


Scheme 3: Synthesis of the starting materials **3**.

Once the starting materials were synthesized, we focused our attention in the optimization of the reaction conditions. We chose the reaction between 4-cyclohexenyl-5-aminopyrazole (**3aa**) and methyl trifluoropyruvate (**4a**) for the optimization studies (Table 1). First, we tried several solvents (dichloromethane, toluene and dichloroethane, entries 1-3) at room temperature, obtaining product **5aaa** in yields around 50% with high diastereoselectivity (up to 6:1) after several days. Increasing the temperature to 50 °C (entries 4-5), reduced the reaction time obtaining similar yields for compound **5aaa**. When the reaction was performed at 70 °C in toluene (entry 6), after 24 hours, full conversion of compound **3aa** was observed, affording the corresponding alcohol **5aaa** in 66% yield and 7:1 dr. Other solvents such as dichloroethane, chloroform or ethyl acetate gave lower yields. Then, we increased the reaction scale to 0.2 mmol obtaining similar results (entry 7). At this point, we decided explore the use of a bifunctional organocatalyst in order to improve the yield. When

squaramide **SQ-1** was used as a catalyst, we observed a similar yield and diastereoselectivity (61 % yield and 7:1 dr, entry 11). By lowering the reaction temperature to 50 °C using the same catalyst (entry 12), the yield of the reaction increased slightly to 73% in 24 hours. Disappointingly, the bifunctional thiourea **THIO-1** gave lower yield and diastereoselectivity at 50 °C (entry 13). Finally, the addition of molecular sieves was evaluated (entries 14 and 15) obtaining in both cases lower yields for the reaction product. On the view of the results of the optimization process, we decided to study the reaction scope using the reaction conditions of entries 10 and 12.

Table 1: Optimization of the reaction conditions^a.



Entry	Solvent	Cat. (5 mol%)	T (°C)	t (h)	Yield 3aa (%) ^b	dr ^c
1	CH ₂ Cl ₂	-	rt	96	52	5:1
2	toluene	-	rt	120	48	6:1
3	ClCH ₂ CH ₂ Cl	-	rt	96	51	6:1
4	toluene	-	50	72	50	5:1
5	ClCH ₂ CH ₂ Cl	-	50	48	55	5:1
6	toluene	-	70	24	66	7:1
7	ClCH ₂ CH ₂ Cl	-	70	24	59	7:1
8	CHCl ₃	-	70	24	46	6:1

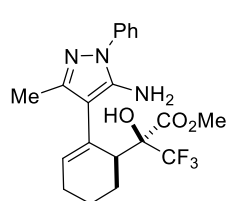
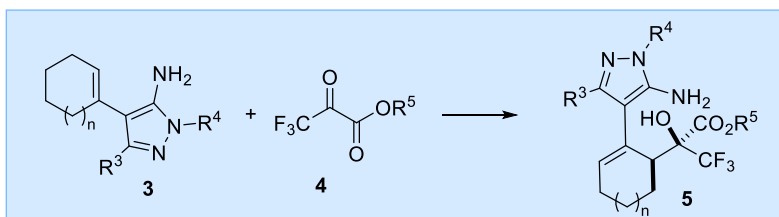
9	EtOAc	-	70	24	26	6:1
10 ^d	toluene	-	70	24	64	7:1
11 ^d	toluene	SQ-1	70	24	61	7:1
12 ^d	toluene	SQ-1	50	24	73	7:1
13 ^d	toluene	THIO-1	50	24	55	4:1
14 ^{d,e}	toluene	-	70	24	44	7:1
15 ^{d,e}	toluene	SQ-1	50	24	61	7:1

^aReaction conditions: **3aa** (0.1 mmol) and **4a** (0.3 mmol) in 1 mL of solvent at T (°C);

^bIsolated yield after column chromatography; ^c Determined by ¹H-NMR of the crude reaction mixture; ^d Reaction conditions: **3aa** (0.2 mmol) and **4a** (0.6 mmol) in 1 mL of solvent at T (°C); ^e 50 mg of molecular sieves 4Å were used.

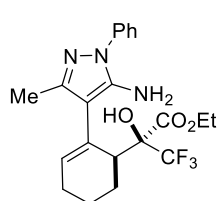
With the optimized reaction conditions in hand, the scope of the vinylogous addition reaction of 4-alkenyl-5-aminopyrazoles **3** to alkyl trifluoropyruvates **4** was studied (Scheme 4). First, we evaluated the influence of the alkyl group in carbonyl compound **4**, where we observed similar results in terms of yield and diastereoselectivity, when methyl or ethyl trifluoropyruvate were used as reactants. Next, we tested the influence of different substituents on the cyclohexenyl ring of the aminopyrazole **3**, observing lower yields for homoallylic alcohols **5baa** and **5caa** in both conditions used. Next, we evaluated the 5-aminopyrazole **3da** prepared from tetrahydro-4*H*-pyran-4-one, interestingly the corresponding trifluoromethyl carbinol **5daa** was afforded, under both reaction conditions, in good yields (66% and 59% yield, respectively) but with a very low diastereoisomeric ratio (near to 1:1). Later, we evaluated the size of the carbocyclic ring, observing a high yield when the 5-aminopyrazole **3ga** prepared from cycloheptanone was used, while 5-aminopyrazole **3fa** bearing a cyclopentenyl ring afforded alcohol **5faa** with lower yield (27-44% yield).

Unfortunately, in the case of the starting material **3ea**, prepared from 2-indanone, the corresponding product was not observed probably due to an increase in steric hindrance. Finally, 4-cyclohexenyl-5-aminopyrazoles bearing different substituents at the *N*-1 or *C*-3 position afforded the corresponding trifluoromethyl carbinols **5aba-5ada** with good diastereoselectivity (4:1 to 7:1) but moderate yields (around 40%).



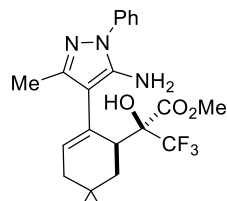
5aaa

Cond. A: 7:1 dr, 64% yield
Cond. B: 7:1 dr, 73% yield



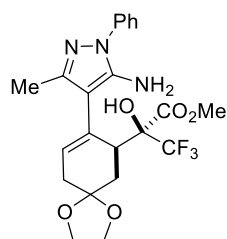
5aab

Cond. A: 6:1 dr, 56% yield
Cond. A: 6:1 dr, 74% yield



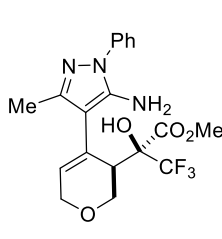
5baa

Cond. A: 6:1 dr, 54% yield
Cond. B: 5:1 dr, 35% yield



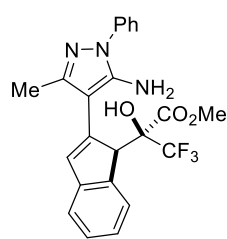
5caa

Cond. A: 7:1 dr, 29% yield
Cond. B: 7:1 dr, 28% yield



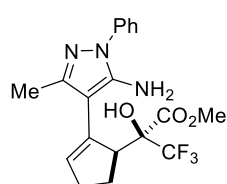
5daa

Cond. A: 1.1:1 dr, 66% yield
Cond. B: 1.8:1 dr, 59% yield



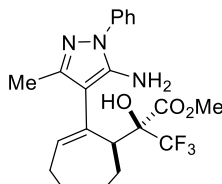
5eaa

Cond. A: 0% yield
Cond. B: 0% yield



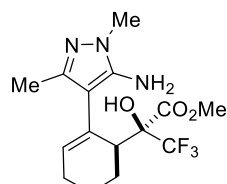
5faa

Cond. A: 6:1 dr, 27% yield
Cond. B: 5:1 dr, 44% yield



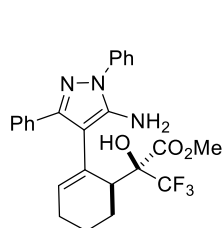
5gaa

Cond. A: 6:1 dr, 80% yield
Cond. B: 6:1 dr, 69% yield



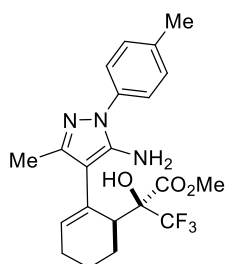
5aba

Cond. A: 4:1 dr, 46% yield
Cond. B: 4:1 dr, 42% yield



5aca

Cond. A: 6:1 dr, 41% yield
Cond. B: 5:1 dr, 37% yield



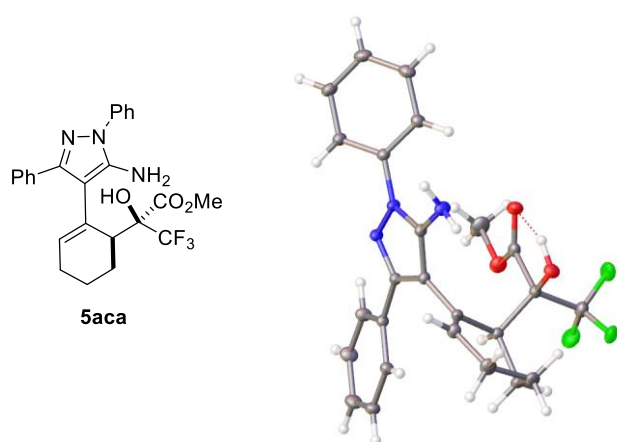
5ada

Cond. A: 7:1 dr, 45% yield
Cond. B: 6:1 dr, 71% yield

Scheme 4: Scope of the reaction. Reaction conditions A: **3** (0.2 mmol) and **4** (0.6 mmol) in 2 mL of toluene at 70°C. Reaction conditions B: **3** (0.2 mmol), **4** (0.6 mmol) and SQ-1 (10 mol%) in 2 mL of toluene at 50 °C. Isolated yield after column

chromatography. Diastereoisomeric ratio (dr) determined by $^1\text{H-NMR}$ of the crude reaction mixture.

The relative configuration of the stereogenic centres in compound **5aca** was determined by X-ray crystallographic analysis (Scheme 5); [32] the relative configurations of the rest of the compounds **5** were assigned on the assumption of a uniform mechanistic pathway.



Scheme 5: X-ray compound **5aca**.

Conclusion

In summary, a regioselective and diastereoselective vinylogous addition reaction of 4-alkenyl-5-aminopyrazoles to alkyl trifluoropyruvate has been studied. Several homoallylic trifluoromethyl carbinols functionalized with a pyrazole moiety were obtained under mild reaction conditions (27-80 % yield). This methodology provides a straightforward access to an unprecedented class of trifluoromethyl carbinol derivatives offering a new synthetic approach to functionalize 5-aminopyrazoles.

Experimental

See Supporting Information File 1 for the Experimental section.

Supporting Information

Supporting Information File 1: Detailed experimental procedures, characterization data, and copies of ^1H -NMR and ^{13}C -NMR spectra.

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32. CCDC 2408111 (**5aca**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.