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Original article

Enantioselective synthesis of functionalized fluorinated dihydropyrano [2,3-c]pyrazoles catalyzed by a simple bifunctional diaminocyclohexane-thiourea

Hong-Fei Zhang, Zheng-Qing Ye, Gang Zhao *

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

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ABSTRACT

Enantioselective synthesis of functionalized fluorinated dihydropyrano[2,3-c]pyrazoles has been achieved *via* a diaminocyclohexane-thiourea catalyzed cascade Michael addition and Thorpe-Ziegler type cyclization in high yields (up to 98%) with moderate to good enantioselectivity (up to 90% *ee*).

1. Introduction

The incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules would affect their lipophilicity and spatial structure, thus emanating unique physical, chemical and biological properties, which can lead to potential applications in materials, medicinal, pharmaceutical and agrochemical sciences [1]. In particular, the replacement of metabolically active hydrogen atoms with fluorine atoms (or CF_3) is commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein–drug interactions [2]. This strategy has been illuminated in the organocatalytic asymmetric synthesis of fluorinated molecules and several important methods have been developed in the last decade [3].

Pyrano[2,3-c]pyrazoles are a large class of heterocyclic compounds possessing many important biological activities, such as analgesic, anti-inflammatory, anti-tumor, insecticidal activities and so on [4]. Since the first reaction for the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene was reported by Junek in 1973 [5a], a large number of efficient synthetic methods to construct dihydropyrano[2,3-c]pyrazole derivatives have been developed [5]. Very recently, Zhao has reported the first organocatalyzed enantioselective method for the synthesis of these compounds using the cinchona alkaloid as the catalyst [6]. However, to the best of our knowledge, no chiral fluorinated dihydropyrano[2,3-c]pyrazoles have been reported up to date [7]. Herein, based on some previous studies in our group [8], we would like to present an efficient catalyst system for the cascade Michael addition–cyclization using diaminocyclohexane-thioureas [9] as a bifunctional catalyst providing a series of novel chiral fluorinated dihydropyrano[2,3-c]pyrazoles.

2. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, with TMS as an internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as an external standard. IR spectra were recorded in cm^{-1}. Melting points were determined on an apparatus, which was not corrected. All solvents were distilled prior to use unless otherwise noted. All reactions sensitive to moisture or oxygen were conducted under an atmosphere of nitrogen or argon.

To a mixture of **1** (0.1 mmol, 1.0 equiv.) and catalyst **3c** (0.01 mmol, 0.1 equiv.) in $CHCl_3$ (2 mL) was added **2** (0.12 mmol, 1.2 equiv.). Then the reaction solution was vigorously stirred at 0 °C and monitored by TLC analysis. After the reaction was complete, the mixture was concentrated and purified by flash column chromatography on silica gel (petroleum ether/EtOAc as

* Corresponding author.
E-mail address: zhaog@mail.sioc.ac.cn (G. Zhao).

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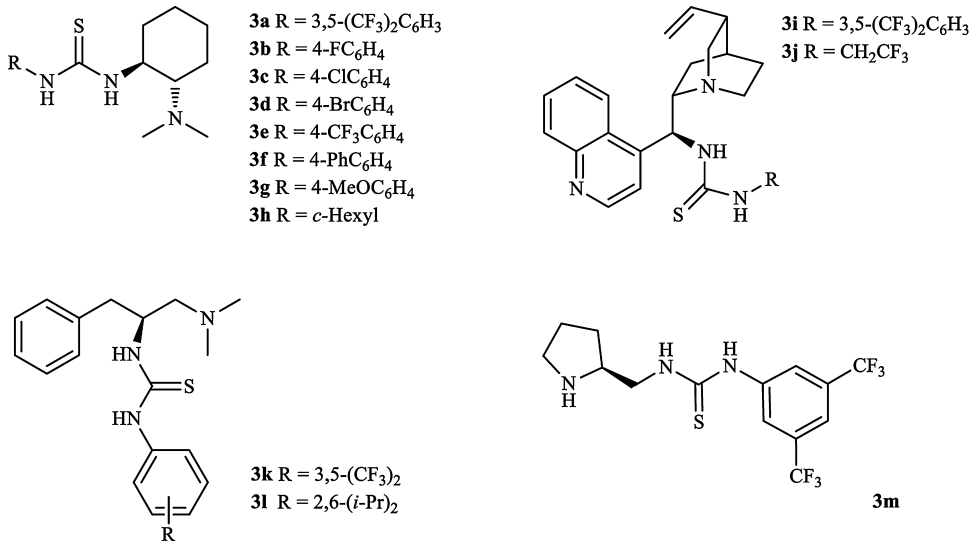


Fig. 1. Thiourea catalysts evaluated in this study.

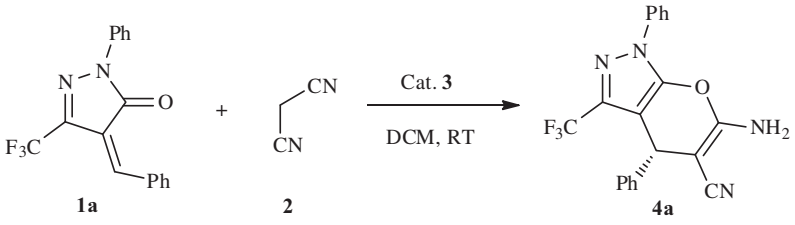
the eluent) to furnish the corresponding product **4**. The data of compounds **4a**–**p** can be found in Supporting information.

3. Results and discussion

Initially, the Takemoto's catalyst **3a** (Fig. 1) was investigated in the model reaction between (*Z*)-4-benzylidene-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (**1a**) and malononitrile (**2**) in dichloromethane (DCM) at room temperature. The reaction gave the desired cyclic product **4a** in an excellent yield; however, a poor enantioselectivity (57% *ee*) was also observed (Table 1, entry 1). In order to enhance the enantioselectivity, several other diaminocyclohexane-thiourea catalysts with weaker H-bond donating ability on the thiourea were screened. As expected, the yields that were more correlative with the tertiary amine altered little with these catalysts but higher enantioselectity could be obtained with catalysts **3b**–**f** (entries 2–7). With the *c*-hexyl substituted catalyst **3h**, a lower *ee* value was obtained (entry 8). Encouraged by the above improvement made with the modified diaminocyclohexane-thiourea catalysts, additional catalysts **3h**–**m** derived from amino acids and the cinchona alkaloid were also synthesized and evaluated in this reaction. We found that the cinchona alkaloid-derived bifunctional thiourea catalysts **3i** and **3j** both gave poor enantioselectivity (entries 9 and 10) probably due to their strong base effect and with the amino acid-based catalysts **3k**, **3l** and **3m**; similar inferior results were also obtained. For all of the reactions, the desired products could be obtained in high yields (>90%) in no more than 50 min.

Then the reactions in various solvents were screened. The results were summarized in Table 2. Generally, the reactions

Table 1
Screening of the catalysts.[a]



Entry	Cat.	Time (min)	Yield (%)[b]	*ee* (%)[c]
1	**3a**	40	95	57
2	**3b**	40	94	71
3	**3c**	30	95	72
4	**3d**	30	94	70
5	**3e**	50	93	70
6	**3f**	40	94	64
7	**3g**	20	93	53
8	**3h**	20	90	46
9	**3i**	50	93	14
10	**3j**	40	92	33
11	**3k**	30	90	5
12	**3l**	40	91	8
13	**3m**	40	90	15

[a] All the reactions were carried out with **1a** (0.1 mmol) and **2** (0.12 mmol) in the presence of **3** (0.01 mmol) in CH_2Cl_2 (2.0 mL) at room temperature.
[b] Yields of isolated products.
[c] Determined by chiral HPLC analysis.