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Recyclable fluorous organocatalysts promoted three-component reactions of pyruvate, aldehyde and amine at room temperature

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ABSTRACT

A new fluorous imine carbothioate has been prepared as an organocatalyst for the synthesis of pyrrol-2-ones via the cyclo-condensation reaction of aldehydes, amines, and pyruvate at room temperature. The fluorous catalyst can be easily recovered from the reaction mixture by simple fluorous solid-phase extraction (F-SPE) and used for next run reaction without further purification.

Introduction

1,5-Dihydro-2*H*-pyrrol-2-ones, particularly their 3-amino-substituted derivatives are found in many natural products.[1–4] As shown in Figure 1, those are selected biologically interesting pyrrol-2-one molecules including lipopeptides microcolin A and B,[5] dithiolopyrrolones,[6] and peptide deformylase inhibitors.[7] Typically, the synthesis of pyrrol-2-ones can be accomplished by condensation of amines, pyrrolidine-2,3-diones,[8] and β,γ-unsaturated α-oxo esters,[3a] or three-component reaction of amines, aldehyde, and pyruvate. H_2SO_4,[3a] thiourea,[3c] phosphoric acid analogs,[3c] SiO_2–$FeCl_3$,[3b] and triethylammonium hydrogen sulfate[3d] have been used as the catalysts for the three-component transformations. As part of our continuous efforts toward the development of metal-free and recyclable fluorous organocatalyst for green chemistry applications,[9,10] we recently reported a series of fluorous thiourea derivates for organic synthesis application.[11]

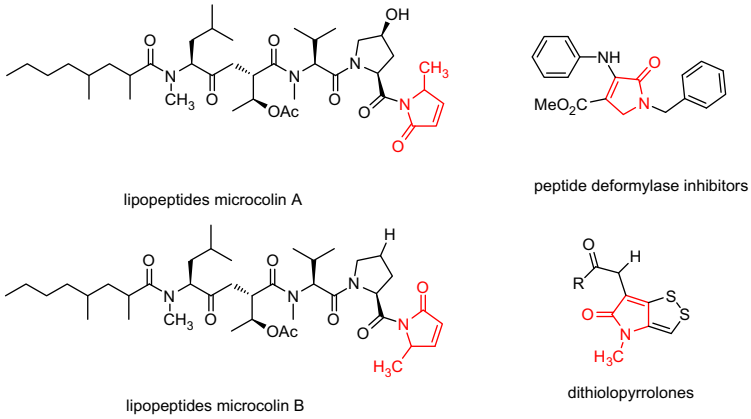

Figure 1. Some selected biologically interesting pyrrol-2-ones.

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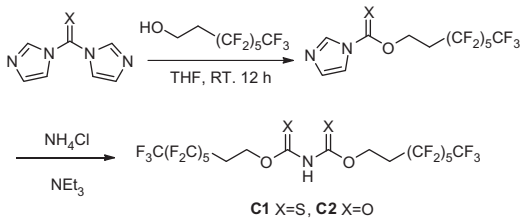


Scheme 1. Preparation of fluorous organocatalysts **C1** and **C2**.

Herein, we report a novel fluorous imine-1,1′-bis(carbothioate) **C1** and fluorous imine-1,1′-dicarboxylate **C2** (Scheme 1) for the synthesis of 1,5-dihydro-2*H*-pyrrol-2-ones. The synthesis was obtained by one-pot multi-component synthesis, which is an atom economic way to prepare molecules with substitution and skeleton diversities;[12] it eliminates waste generated from intermediate purifications; and is a favorable approach for green organic synthesis.[13] The fluorous imine-1,1′-bis(carbothioate) **C1** demonstrated superior catalytic activity and efficiency under room temperature, and could be easily recovered by fluorous solid-phase extraction (F-SPE).

Results and discussions

The organocatalysts fluorous imine-1,1′-bis(carbothioate) **C1** and fluorous imine-1,1′-dicarboxylate **C2** were synthesized using di(1*H*-imidazol-1-yl)methanethione or di(1*H*-imidazol-1-yl)methanone **I** and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol **II** as the starting materials (Scheme 1). The compounds **C1** and **C2** could be easily isolated and purified by fluorous-solid phase extraction (F-SPE) with a cartridge charged with fluorous silica gels.[14] The catalysts are stable in air and soluble in various solvents such as THF, CH_3OH, CH_3Cl, and CH_3CN.

Initially, we selected the reaction of benzaldehyde, aniline, and methyl pyruvate as the model reaction to optimize the reaction conditions (Table 1). Different solvents were screened, and acetonitrile is the best choice in the reaction (entries 4, 6–11). We also tested different catalysts and catalyst **C1** was the best choice (entries 4, 12–14). As revealed in Table 1, the reaction of methyl pyruvate, benzaldehyde, and aniline was very sluggish in the absence of any catalysts, affording only 10% yield after 24 h. The use of 5 mol % **C1** in MeCN gave 90% yield, indicating superior catalytic activity (entries 2–5). For the reaction with **C1**, no significant improvement was observed by increasing reaction time or amount of catalyst (entires 4 and 5).

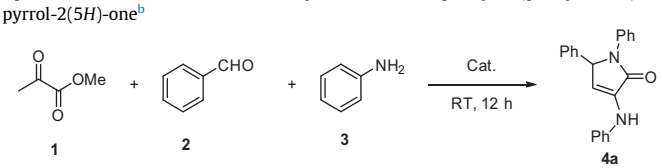
Further investigations indicated that the catalysis of **C1** was highly efficient. Moderate to excellent yields were obtained in the solvents such as MeCN, MeOH, and C_2H_5OH. We also compared **C1** and **C2**′s non-fluorous counterparts (**C1**′ and **C2**′) in the model reaction with their fluorous structures (entries 12–14), and found the non-fluorous version afforded a lower yield (44% vs 90%; 32% vs 48%). The fluorous ponytail helped to recycle the catalysts and probably contributed to generate the H^+ in the reaction with its electron-withdrawing property. A pK_a value detection experiment was used to prove this assumption.[3c] It was found that a correlation between the catalytic activity of the catalyst and its corresponding pK_a is evident, with lower pK_a values, that is, higher acidity, leading to better yields.

Under the optimized conditions, reactions were performed with **C1** to explore the substrate scope with regard to the pyruvates, aldehydes, and amines (Table 2). As expected, the organocatalyst **C1** worked well for this reaction except for those aromatic amines containing electron-withdrawing groups or aliphatic amines (entries 9–11, 13, 14). In all cases, aromatic aldehydes gave higher yields than aliphatic aldehydes. The substituent group of pyruvate showed low effect for this reaction (entries 11-15). Aliphatic aldehydes reacted with aromatic amines smoothly in medium yields (entries 7, 15).

To estimate the efficiency and generality of this methodology, the result obtained by this method was compared with fluorous thiourea and hydrazine, and also with some previously reported cases. It was found that the present method is convincingly superior in terms of reaction time and product yield (Table 3).

The reusability of the catalyst **C1** was tested in the synthesis of 1,5-diphenyl-3-(phenylamino)-1*H*-pyrrol-2(5*H*)-one, as shown in Figure 2. The catalyst was recovered after each run, separated by

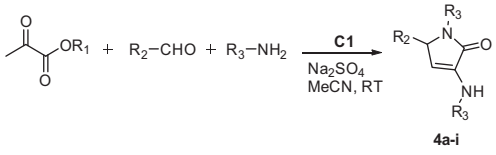
Table 1
Optimized reaction conditions in the synthesis of 1,5-diphenyl-3-(phenylamino)-1*H*-pyrrol-2(5*H*)-one[b]



Entry	Cat. (mol %)	Sol	Yield[a] (%)	pK_a[c]
1	None	MeCN	10	—
2	**C1**(1)	MeCN	46	—
3	**C1**(2)	MeCN	67	—
4	**C1**(5)	MeCN	90	7.12
5	**C1**(10)	MeCN	92	—
6	**C1**(5)	CH_2Cl_2	65	—
7	**C1**(5)	MeOH	85	—
8	**C1**(5)	Toluene	57	—
9	**C1**(5)	$CHCl_3$	61	—
10	**C1**(5)	C_2H_5OH	82	—
11	**C1**(5)	H_2O	8	—
12	**C1**′(5)	MeCN	44	8.15
13	**C2**(5)	MeCN	48	7.84
14	**C2**′(5)	MeCN	32	8.58

[a] Isolated yields based on **2**.
[b] The reactions were carried out on a 1 mmol scale in 3 mL of solvents with a molar ratio of pyruvate/aniline/benzaldehyde/Na_2SO_4 of 2:2:1:3.
[c] Determined in this work with an uncertainty of ±0.1.

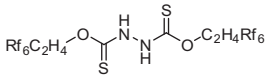
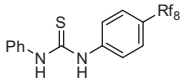
Table 2
Synthesis of 1,5-Dihydro-2H-pyrrol-2-one derivatives using **C1** as catalyst[a]



Entry	R_1	R_2CHO	R_3NH_2	Yield[b] (%)	Product
1	Me	C_6H_5	C_6H_5	90	**4a**
2	Me	C_6H_5	4-$CH_3C_6H_4$	93	**4b**
3	Me	4-ClC_6H_4	4-$CH_3C_6H_4$	87	**4d**
4	Me	4-ClC_6H_4	C_6H_5	85	**4e**
5	Me	4-$OCH_3C_6H_4$	C_6H_5	92	**4i**
6	Me	C_6H_5	4-$CH_3OC_6H_4$	93	**4c**
7	Me	$CH_3(CH_2)_2CH_2$	4-$CH_3OC_6H_4$	53	**4f**
8	Me	4-$NO_2C_6H_4$	C_6H_5	82	**4h**
9	Me	C_6H_5	4-$NO_2C_6H_4$	—	—
10	Me	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	—	—
11	C_2H_5	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	—	—
12	C_2H_5	$CH_3(CH_2)_2CH_2$	4-$CH_3OC_6H_4$	54	**4f**
13	C_2H_5	C_6H_5	Cyclohexyl	—	—
14	C_2H_5	C_6H_5	$CH_3(CH_2)_2CH_2$	—	—
15	C_2H_5	$CH_3(CH_2)_2CH_2$	C_6H_5	41	**4g**

[a] Reaction conditions: The reactions were carried out on a 1 mmol scale in 3 mL of MeCN with a molar ratio of pyruvate/amine/aldehyde/Na_2SO_4 of 2:2:1:3. All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy.
[b] Isolated yield based on aldehyde.

Table 3
Comparison among various catalysts

Entry	Catalyst	Condition	Yield[a] (%)	Refs.
1	Thiourea	Toluene; rt; 18 h	84	3c
2	Phosphoric acid	Toluene; rt; 18 h	84	3c
3	H_2SO_4	CH_2Cl_2; rt; 48 h	73	3a
4		MeCN; rt; 24 h	80	10
5		Toluene; rt; 24 h	88	15
6	**C1**	MeCN; rt; 12 h	93	This work

[a] The yield based on the reaction of benzaldehyde, toluidine, and pyruvate.

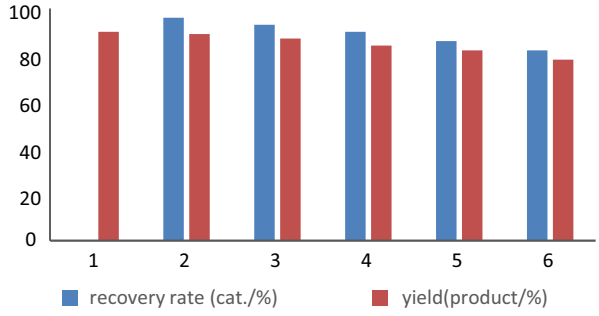


Figure 2. Recovery experiments of the catalyst **C1**.

fluorous-solid phase extraction (F-SPE) easily, tested for its activity in the subsequent run without being added with fresh catalyst. The catalyst was tested for 5 runs. It was seen that the catalyst displayed strong reusability (Fig. 2).

Conclusion

In summary, we have prepared a series of fluorous organocatalysts and successfully applied it for the preparation of pyrrol-2-ones via the cyclo-condensation reaction of aldehydes, amines, and pyruvate. The catalyst showed high catalytic activity and the corresponding products were obtained in moderate to excellent yields. Moreover, the fluorous catalyst could be easily recovered by F-SPE and reused three times without significant loss of activity. The present methodology offers several advantages, such as excellent yields, mild conditions, and simple procedure, making it more efficient.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.058.

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