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Efficient Synthesis of α-Chloroketones Catalyzed by Fluorous Hydrazine-1,2-Bis(Carbothioate) Organocatalyst

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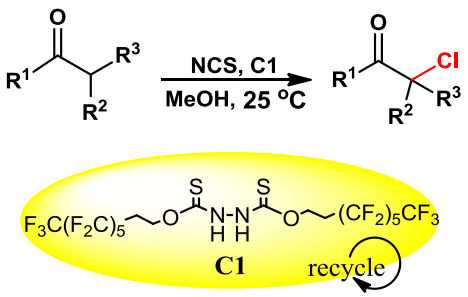
Abstract A novel and recoverable fluorous hydrazine-carbothioate organocatalyst was prepared. It could catalyze α-chlorination of alkyl ketones with *N*-chlorosuccinimide as chlorine source under mild reaction conditions. The reaction afforded the corresponding α-chlorinated carbonyl compounds with excellent yields at rapid reaction speed.

Graphical Abstract



Keywords Fluorous organocatalyst · *N*-chlorosuccinimide · α-Chlorination · Fluorous solid-phase extraction (F-SPE)

1 Introduction

α-Chlorocarbonyl [1–11] compounds have attracted considerable attention from organic and medicinal chemists, primarily because they display a wide range of physiological activities and precursors of biologically active drugs (Scheme 1). Such benefits have created lots of synthetic interest in chlorination catalysis including the innovative use of Lewis acids, amberlyst, transitional metal complexes and inorganic reagents. Currently, there is also much interest in organocatalysts [7, 16–23] due to their low toxicity, operational simplicity, efficiency, and good stereoselectivity compared to traditional metal-based catalysts. Inspired by flourous tag idea, [12–15] herein, our group applied the new fluorous hydrazine-1,2-bis(carbothioate) **C1** and hydrazine-1,2-dicarboxylate **C2** (Scheme 2) to the α-chlorination reaction of alkyl ketones with *N*-chlorosuccinimide (NCS) as chlorine source [24–30]. We found the fluorous hydrazine-1,2-bis(carbothioate) demonstrated superior catalytic activity and efficiency, and the reactions proceeded smoothly at the presence of the organic fluorous catalyst to afford the desired products in excellent yields. Moreover, the fluorous catalyst **C1** could be easily recovered by fluorous solid-phase extraction (F-SPE) without using environmentally harmful perfluorous solvents.

2 Results and Discussion

The fluorous hydrazine-1,2-bis(carbothioate) **C1** and hydrazine-1,2-dicarboxylate **C2** were synthesized as shown in Scheme 3. 2-Perfluorohexyl ethanol **II** was treated with 1,1′-(thio)carbonyl diimidazole **I** at room temperature. Quenching with water and extraction with petroleum ether provided the crude product **III**, after purification in a

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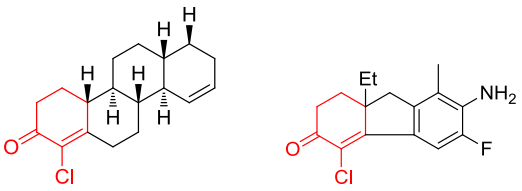
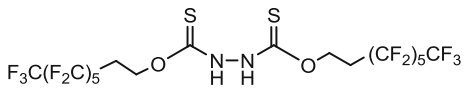
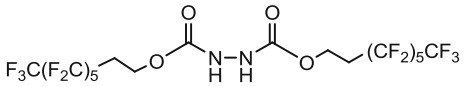


Anti-infective agent Selective estrogen receptor

Scheme 1 Examples of biologically active drugs with α-chlorocarbonyl group



C1



C2

Scheme 2 Fluorous hydrazine-1,2-bis(carbothioate) **C1** and hydrazine-1,2-dicarboxylate **C2**

column, compound **III** reacted with hydrazine monohydrochloride and triethylamine. The fluorous hydrazine (**C1**, **C2**) was isolated as white powder.

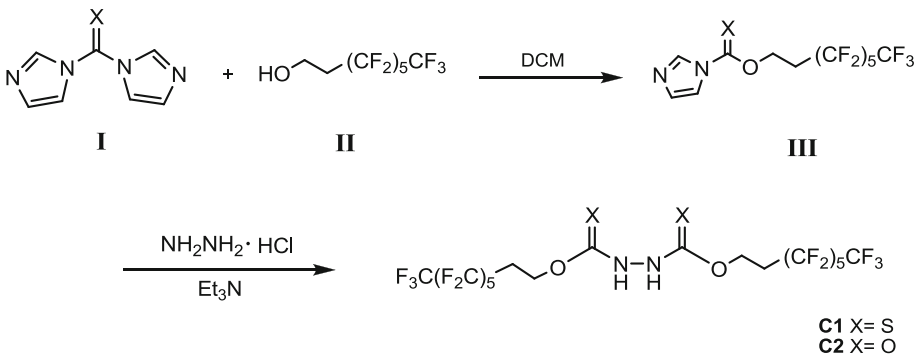
The α-chlorination of 1-indanone **1a** was chosen as model reaction. To optimize the reaction conditions, various parameters including catalyst, solvents and catalyst loadings were investigated. The non-catalyzed α-chlorination of 1-indanone was a slow reaction (Table 1, entry 1). The inclusion of catalyst **C1** gave a dramatic increase in the reaction rate (Table 1, entry 2), and it was a more efficient catalytic structure compared to catalyst **C2** (Table 1, entry 3). When we investigated the catalyst loadings, together considered the economical efficiency, the optimal reaction catalyst loading was set to **C1** 5 mol% (Table 1, entry 3–5). When the usage of NCS was 1.2 mmol, the molecular ratio of **2a**:**3a** was much higher than that of 2.0 mmol. Different solvents such as CH_2Cl_2, EtOAc, MeCN and THF gave moderate to good yields ranging from 62 to 99 % as illustrated in Table 1, entries 7–10. We hoped that the examination of alternative solvents would speed up the reaction, but protic polar methanol proved to be the best solvent. This can be explained by further hydrogen bonding of methanol with fluorous hydrazine-1,2-bis(carbothioate) to give even stronger hydrogen bonds. After an extensive screening of the reaction parameters, the best yield was obtained in MeOH at 25 °C catalyzed by **C1** (5 mol%) (Table 1, entry 4).

The substrate scope of the reaction under the optimal conditions described above was explored next (Table 2). The methoxy derivative **1c** and **1d** were slower than **1b** (Table 2, entry 1–3). The more acidic structures like 1,3-diketones and β-ketoesters were also studied. The chloronations of **1e** and **1f** was very fast and afforded good yields (Table 2, entry 4, 5). The β-ketoester derivatives **1g**, **1h** and **1i** afforded excellent yields within just 10 min (Table 2, entry 6–8). The most reactive ketones **1j** and **1 k** could only afford dichloride in a very short time (Table 2, entry 9 and 10), when we added the loading of NCS, we got pretty good yield of the dichloride compounds.

We also performed the catalyst-recovery experiments using model reaction. After completion of the reaction, the mixture was concentrated and then loaded onto a FluoroFlashs silica gel cartridge for F-SPE. It was found that the catalyst could be recovered in high yield (87–91 %) with excellent purity (99 %). The recycling reactions using the recovered catalyst were conducted 3 times as shown in Scheme 4 and the model reaction could still afford 85 % yield after 3 times recovery of the fluorous catalyst (Scheme 4).

The mechanism of this reaction was not very clear. One explanation was that NCS by means of hydrogen bonding could act as a precursor for the formation of Cl^+, which in turn could behave as a Lewis acid in the reaction medium and accelerate the α-chlorination by adding the quantity of electrophile in the reaction (Fig. 1).

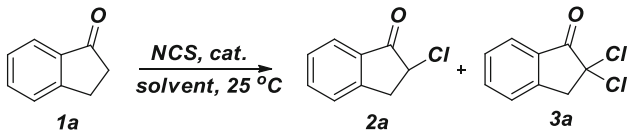
Scheme 3 Preparation of fluorous hydrazine-1,2-bis(carbothioate) **C1** and hydrazine-1,2-dicarboxylate **C2**



I **II** **III**

C1 X= S
C2 X= O

Table 1 α-Chlorination of 1-indanone[a]



Entry	Solvent	Catalyst (mol%)	Time (h)	Yield[b] (%)	Molecular ratio, **2a**:**3a**[c]
1	MeOH	–	96	99	95:5
2	MeOH	**C1** (10)	1	99	92:8
3	MeOH	**C2** (10)	1	48	85:15
4	MeOH	**C1** (5)	1	98	91:9
5	MeOH	**C1** (2)	1	92	90:10
6[d]	MeOH	**C1** (5)	1	97	72:28
7	THF	**C1** (5)	48	62	94:6
8	MeCN	**C1** (5)	24	99	95:5
9	EtOAc	**C1** (5)	8	99	93:7
10	CH_2Cl_2	**C1** (5)	48	67	88:12

[a] **1a** 1 mmol, NCS 1.2 mmol, solvent 3 mL

[b] GC yield based on **1a** (internal standard method)

[c] GC-MS

[d] NCS 2.0 mmol

3 Experimental

3.1 General Remarks

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were characterized with a Bruker Advance RX500 spectrometer. The GC data was recorded on Agilent 7890a. All chemicals were reagent grade and used as purchased without further purifications. All the α-chloroketones products are known compounds and were identified by comparing of their physical and spectra data with those reported in literature.

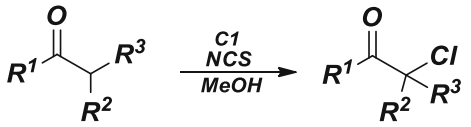
3.2 Procedure for the Preparation of Fluorous Hydrazine-1,2-Bis(Carbothioate) C1

3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanol **II** (3.641 g, 10 mmol) was slowly added to a solution of di(1H-imidazol-1-yl)methanethione **I** (1.958 g, 11 mmol) in dry CH_2Cl_2. After stirring for 12 h at room temperature, the crude reaction mixture was quenched with water and then extracted with petroleum ether (3 × 50 mL). The solvent was removed under reduced pressure and the residue was dried under high vacuum. The crude *O*-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 1H-imidazole-1-carbothioate **III** was taken up in THF (50 mL) and hydrazine monohydrochloride (0.342 g, 5 mmol) and triethylamine (2.529 g, 25 mmol) were added at room temperature. After 7 days, the reaction mixture was quenched with brine (60 mL) and extracted with ether (3 × 40 mL). The organic layers were combined and loaded onto the fluorous silica gel, eluted it with 80 % methanol then with ether to give the fluorous compounds. Purification in standard gel if necessary, gave *O,O*-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl) hydrazine-1,2-bis(carbothioate) **C1** (2.363 g, 56 %) as a white solid; ^{1}H NMR (500 MHz, CD_3OD): δ 4.83–4.76 (m, 4H), 2.78–2.60 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD): δ 194.2 (b), 122.7-111.1 (m), 65.3 (t), 32.8 (b); ^{19}F NMR: δ −82.5 (6F), −114.5 (4F), −122.9 (4F), −123.9 (4F), −124.6 (4F), −127.4 (4F); MS (ESI^+) *m*/*z* 843.00 (M-H).

3.3 Typical Procedure for Fluorous Hydrazine-1,2-Bis(Carbothioate) C1 Catalyzed α-Chlorination of Variety of Ketones

Fluorous hydrazine-1,2-bis(carbothioate) **C1** (0.042 g, 0.05 mmol) with NCS (0.013 g, 1.2 mmol) was added in MeOH (3 mL) was stirred at 25 °C for 10 min. Then ketone **1** (1 mmol) was added and the resulting mixture was stirred at 25 °C for 1 h. After the reaction completed, the mixture was concentrated and then loaded onto a FluoroFlash® silica gel cartridge (5 g), eluted by 80 % methanol at first for non-fluorous components. Then dried over Na_2SO_4 and evaporated for GC analysis. Ether was

Table 2 **C1** catalyzed α-chlorination of variety of ketones[a]



1 2

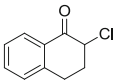
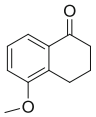
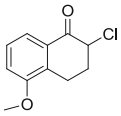
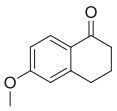
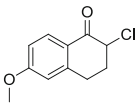
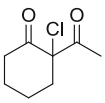
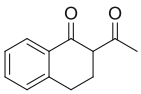
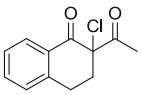
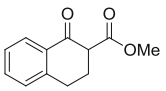
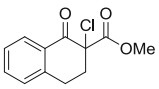
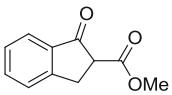
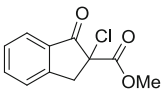
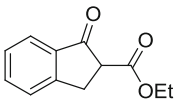
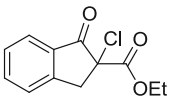
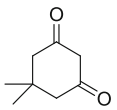
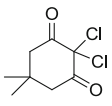
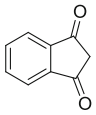
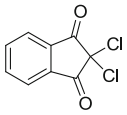
Entry	Ketone	Reaction time (min)	Chloride/yield[c] (%)
1	 **1b**	20	 **2b** **99**
2	 **1c**	40	 **2c** **99**
3	 **1d**	40	 **2d** **99**
4	 **1e**	15	 **2e** **98**
5	 **1f**	5	 **2f** **99**
6	 **1g**	10	 **2g** **99**
7	 **1h**	10	 **2h** **99**
8	 **1i**	10	 **2i** **99**
9	 **1j**	20	 **3j** **41** **80**[b]

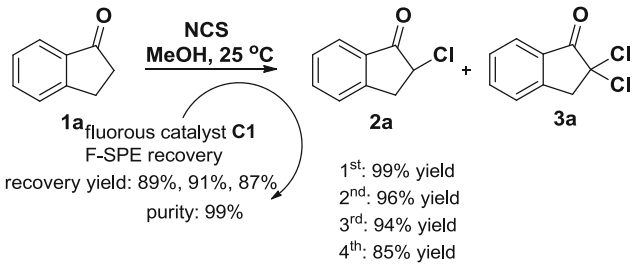
Table 2 continued

Entry	Ketone	Reaction time (min)	Chloride/yield[c] (%)
10	 **1k**	20	 **3k** **44** **82**[b]

[a] Ketone 1 mmol, NCS 1.2 mmol, **C1** 5 mol% solvent 3 mL

[b] NCS 2.0 mmol

[c] GC yield based on **1** (internal standard method)



Scheme 4 Catalyst recycling experiments

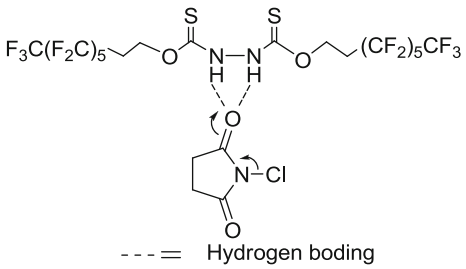


Fig. 1 Speculated key step in the catalytic process

then added onto the fluorous gel column to wash out the fluorous hydrazine-1,2-bis(carbothioate) **C1**. After removal the ether, compound **C1** was dried in vacuo at 40 °C for 8 h and could be directly used in the next run.

4 Conclusions

In summary, a recoverable fluorous hydrazine-1,2-bis(carbothioate) has been developed. Together with NCS, it shows high activity in α-chlorination of ketones. The fluorous organocatalyst could be easily recovered by fluorous solid-phase extraction with excellent purity.

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