

Article

A Recyclable Fluorous Hydrazine-1,2-Bis(Carbothioate) Organocatalyst for the Synthesis of β -Chloroethers with *N*-Chlorosuccinimide

Yi-Wei Zhu *, Yi-Xin Shi and Yu-Qi Yin

School of Biology and Chemical Engineering, Anhui Polytechnic University, 8 Middle Beijing Road, Wuhu 241000, Anhui, China; misshiyx@126.com (Y.-X.S.); blackearl@126.com (Y.-Q.Y.)

* Correspondence: yiwei.zhu@ahpu.edu.cn; Tel.: +86-553-2871-254

Academic Editor: Aurelio G. Csáky

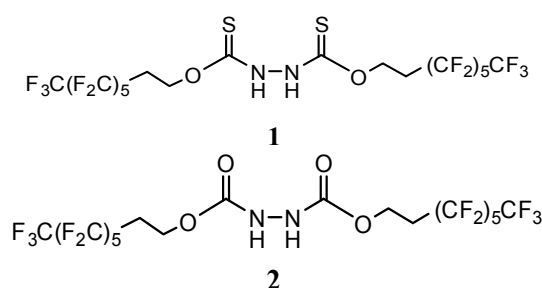
Received: 14 January 2017; Accepted: 15 February 2017; Published: 16 February 2017

Abstract: A novel fluorous hydrazine-1,2-bis(carbothioate) was prepared. It showed good catalytic activity in the synthesis of β -chloroethers with *N*-chlorosuccinimide under mild reaction conditions. This fluorous organocatalyst could be recovered and recycled several times with good purity.

Keywords: organocatalysis; β -chloroethers; recycle; fluorous solid-phase extraction (F-SPE)

1. Introduction

Nowadays there is more and more interest in organocatalysis, due to its low toxicity and good selectivity compared to the traditional metal-based catalysis. Organocatalysis also reflects many requirements of green chemistry. Therefore, many of chemists focus on this field, trying to find some efficient and operationally simple organocatalysts. Many wonderful works were reported and some of them were of great importance. In this paper, we tried to apply the concept of organocatalysis [1–12]. Also, inspired by the fluorous-tagging idea, we prepared recyclable organocatalysts fluorous hydrazine-1,2-bis(carbothioate) **1** and hydrazine-1,2-dicarboxylate **2** (Scheme 1) and then applied them to the synthesis of β -chloroethers under mild reaction conditions [7–9]. The catalytic reaction proceeded smoothly, and with the aid of fluorous silica gel, these fluorous compounds could be recovered easily by fluorous solid-phase extraction (F-SPE) and no environmentally harmful perfluoro-solvents were used [13–22].

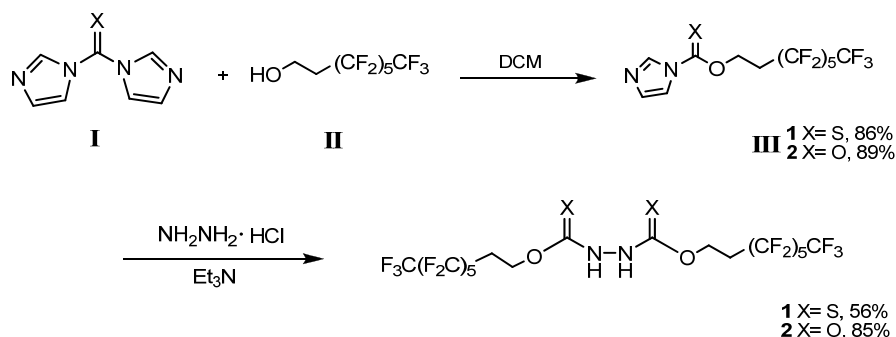


Scheme 1. Fluorous organocatalysts **1** and **2**.

2. Results and Discussion

The synthetic routes for creating the fluorous organocatalysts (**1** and **2**) are illustrated in Scheme 2. First, 1,1'-(thio)carbonyl diimidazole **I** and 2-perfluorohexyl ethanol **II** were mixed and stirred in

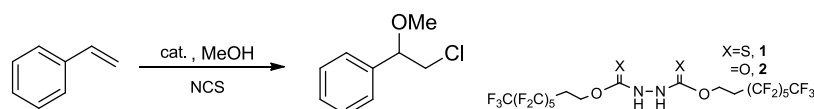
CH_2Cl_2 at room temperature. Then, quenching with H_2O and extraction with petroleum ether afforded crude product **III**, and compound **III** was purified in a silica column, and then reacted with Et_3N and $\text{NH}_2\text{NH}_2 \cdot \text{HCl}$. Fluorous hydrazine-1,2-bis(carbothioate) **1** and hydrazine-1,2-dicarboxylate **2** were isolated as white powders.



Scheme 2. Synthetic route of fluorous hydrazine-1,2-bis(carbothioate) **1** and hydrazine-1,2-dicarboxylate **2**. (DCM: dichloromethane).

The reaction of styrene with NCS (*N*-Chlorosuccinimide) in methanol was selected as the model reaction for further investigation (Table 1). Different catalysts, catalyst loading, reaction times and quantitative ratios of NCS were investigated. It was a slow and low-yield process with no catalyst employed in the model reaction (Table 1, entry 1). We tried the fluorous catalysts **1** and **2** in this catalytic reaction and found catalyst **1** was the more efficient structure for promoting the synthesis compared to **2** as the reaction catalyst (Table 1, entries 6 and 8). Catalyst loading and the quantitative ratios of NCS were also studied (Table 1, entries 2–7), and when economy, reaction speed and reaction yield were all evaluated, entry 6 was considered as the optimal reaction condition for this catalytic reaction.

Table 1. Optimization of the model reaction ^a.



Entry	NCS (mmol)	Catalyst (mol %)	Time (h)	Yield (%)
1	4	-	120	37
2	4	1 (20)	1	88
3	4	1 (10)	1	89
4	4	1 (5)	2	85
5	4	1 (2)	2	82
6	2	1 (5)	2	81
7	1.5	1 (5)	4	68
8	2	2 (5)	48	33

^a The reaction condition: styrene (1 mmol); MeOH (3 mL); 25 °C; NCS (*N*-Chlorosuccinimide).

Next, various alcohols and alkenes were employed in this reaction for observation (Table 2). A lower yield and slower reaction rate was observed when methanol was replaced with ethanol (Table 2, entry 2). When pentan-3-ol, *t*-butanol and phenol were used as substrates in this catalytic reaction, it gave a much slower reaction with only a moderate yield (Table 2, entries 3–5). When the *para* position of styrene was substituted with a methyl or chlorine group, the reaction afforded an excellent yield of product with a slower reaction rate (Table 2, entries 6 and 7). We did not get the correct product when we used 2-chlorostyrene or 3-chlorostyrene. Digeminal-substituted olefin offered a faster reaction with an excellent yield (Table 2, entry 8). Cyclohexene was also investigated, and

it gave a moderate yield. Moreover, the product was completely stereocontrolled (Table 2, entry 9). We also tried aliphatic alkenes (1-octene and 1-decene); however, the yields were too low to detect.

Table 2. Compound **1** catalyzed the synthesis of β -chloroether of variety of olefins and alcohols ^a.

Entry	Olefin	ROH	Reaction Time (h)	Chloride	Yield (%)
1		MeOH	2		81
2		EtOH	6		75
3			48		63
4			48		54
5			24		34
6		MeOH	6		90
7		MeOH	4		89
8		MeOH	0.5		93
9		MeOH	0.5		52

^a Olefin (1 mmol), NCS (2 mmol), **1** (5 mol %) and ROH 3 mL, 25 °C.

We speculated that a possible key step in this synthesis of the β -chloroether reaction with NCS may include hydrogen bonding, as shown in Figure 1. Polar protic solvents or reactants could help to get a strong hydrogen bond network.

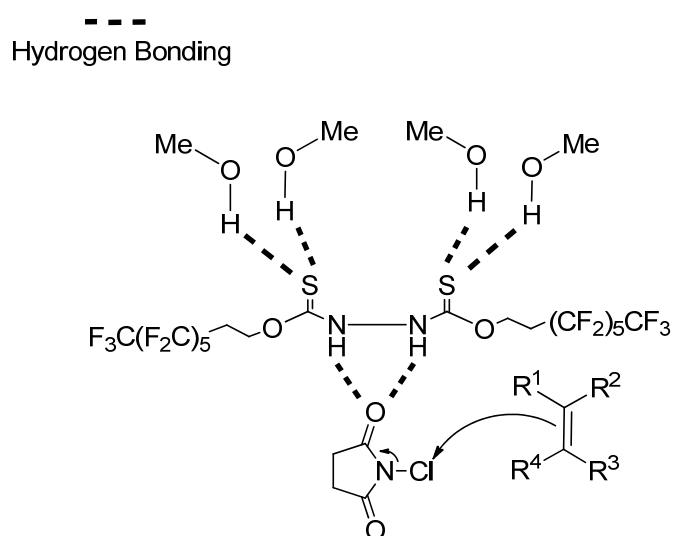


Figure 1. Speculated key step of catalytic process.

We also did catalyst recycling experiments using a model reaction; the fluororous catalyst **1** could be easily recovered up to three times by F-SPE using fluororous silica gel with an excellent catalyst to recover the purity and a good recycling yield (Figure 2).

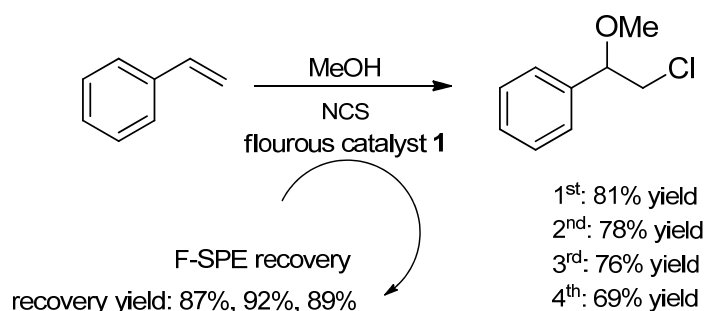


Figure 2. Catalyst recycling experiments.

3. Experimental Section

3.1. General

The Nuclear Magnetic Resonance (NMR) spectra are recorded by spectrometer (Bruker Advance RX500, Bruker, Billerica, MA, USA). And β -chloroether compounds are synthesized and compared to the spectra which are reported by related literature. The substrates and reagents are commercial available and are used without further purification.

3.2. The Synthesis of Fluororous Catalyst **1**

To a solution of compound **I** (1.958 g, 11 mmol) in anhydrous dichloromethane, 3.641 g (10 mmol) **II** was added slowly. The mixture was kept stirring at 25 °C for 12 h, after quenched with water, the mixture was extracted with 50 mL petroleum ether for three times. After removal the solvent and dry the residue. The crude compound **III** was taken up in 50 mL tetrahydrofuran. compound **III** was purified in silica column, then reacted with Et₃N (2.529 g, 25 mmol) and NH₂NH₂·HCl (0.342 g, 5 mmol) at 25 °C for seven days. The fluororous hydrazine-1,2-bis(carbothioate) **1** (2.363 g, 56%) was isolated as white powder: Mass Spectrometer (Electron Spray Ionization⁺) *m/z* 843.00 (M-H); ¹H NMR (500 MHz, CD₃OD): δ 4.83–4.76 (m, 4H), 2.78–2.60 (m, 4H); ¹⁹F NMR: δ -82.5 (6F), -114.5 (4F), -122.9

(4F), -123.9 (4F), -124.6 (4F), -127.4 (4F); ^{13}C NMR (125 MHz, CD_3OD): δ 194.2 (b), 122.7–111.1 (m), 65.3 (t), 32.8 (b).

3.3. The Synthesis of β -Chloroethers Catalyzed by **1** and the Catalyst Recycling Experiment

To a solution of 0.267 g (2 mmol) *N*-chlorosuccinimide and 0.042 g (0.05 mmol) catalyst **1** in 3 mL methanol, 1 mmol olefin was added and kept stirring at room temperature for 0.5–48 h. FluoroFlash[®] silica gel cartridge (5 g) was used for separation. The reaction mixture was loaded onto this silica gel. First, eluted by 80% methanol for non-fluorous components, then concentrated for column chromatography to provide corresponding β -chloroethers products. Diethyl ether was then used to wash out the fluoruous compound **1**. After removal the solvent, the fluoruous catalyst **1** could be used for the next run.

4. Conclusions

In conclusion, we prepared a fluoruous organocatalyst for the β -chloroether reaction with NCS; the fluoruous catalyst exhibited good catalytic activity. This fluoruous organocatalyst could also be easily recycled three times with F-SPE.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/7/2/66/s1, Figures S1–S3, ^1H NMR, ^{13}C NMR and ^{13}C NMR of the fluoruous hydrazine-1,2-bis(carbothioate) **1**.

Acknowledgments: The authors are grateful for the support of the Pre-research Project of Anhui Polytechnic University (2016yyzr06), the Startup Fund from AHPU (2014YQQ011) and the Key Project of the Anhui Provincial Education Department (KJ2014A014).

Author Contributions: Yi-Wei Zhu conceived of and designed the experiments. Yu-Qi Yin performed the experiments. Yu-Qi Yin and Yi-Xin Shi analyzed the experimental data.

Conflicts of Interest: The authors declare that they have no conflict of interest to this work.

References

1. Jimeno, C.; Cao, L.; Renaud, P. Trichloromethanesulfonyl chloride: A chlorinating reagent for aldehydes. *J. Org. Chem.* **2016**, *3*, 1251–1255. [[CrossRef](#)] [[PubMed](#)]
2. Coffey, K.E.; Murphy, G.K. Dichlorination of α -diazo- β -dicarbonyls using (dichloroiodo)benzene. *Synlett* **2015**, *8*, 1003–1007.
3. Coffey, K.E.; Moreira, R.; Abbas, F.Z. Synthesis of 3,3-dichloroindolin-2-ones from isatin-3-hydrazones and (dichloroiodo)benzene. *Org. Biomol. Chem.* **2015**, *3*, 682–685. [[CrossRef](#)] [[PubMed](#)]
4. Faisca, P.; Ana, M.; Barros, M.T.; Pacheco, M. Synthesis and biological evaluation of alpha-hydroxyalkylphosphonates as new antimicrobial agents. *Bioorg. Med. Chem. Lett.* **2014**, *1*, 49–53. [[CrossRef](#)] [[PubMed](#)]
5. Tsuchida, K.; Kochi, T.; Kakiuchi, F. Copper-catalyzed electrochemical chlorination of 1,3-dicarbonyl compounds using hydrochloric acid. *Asian J. Org. Chem.* **2013**, *11*, 935–937. [[CrossRef](#)]
6. Wang, L.; Wang, J.-W.; Cui, A.-J. Regioselective 2,6-dihalogenation of BODIPYs in 1,1,1,3,3,3-hexafluoro-2-propanol and preparation of novel meso-alkyl polymeric BODIPY dyes. *RSC Adv.* **2013**, *24*, 9219–9222. [[CrossRef](#)]
7. Bentley, P.A.; Mel, Y.; Du, J. Thiourea catalysis of NCS in the synthesis of β -chloroethers. *Tetrahedron Lett.* **2008**, *16*, 2653–2655. [[CrossRef](#)]
8. Bentley, P.A.; Mel, Y.; Du, J. Thiourea catalysis of NCS in the synthesis of chlorohydrins. *Tetrahedron Lett.* **2008**, *49*, 1425–1427. [[CrossRef](#)]
9. Mel, Y.; Bentley, P.A.; Du, J. Thiourea catalysis of NCS in the synthesis of α -chloroketones. *Tetrahedron Lett.* **2008**, *49*, 3802–3804.
10. Karmakar, R.; Mal, D. Total synthesis of chlorocyclinone A, a PPAR- γ antagonist. *J. Org. Chem.* **2012**, *22*, 10235–10248. [[CrossRef](#)] [[PubMed](#)]
11. Li, F.; Nie, J.; Wu, J.-W. Stereoselective synthesis of fluorinated 2,3-dihydroquinolin-4(1H)-ones via a one-pot multistep transformation. *J. Org. Chem.* **2012**, *5*, 2398–2406. [[CrossRef](#)] [[PubMed](#)]

12. Cui, H.-F.; Dong, K.-Y.; Nie, J. Lewis acid-catalyzed one-pot sequential reaction for the synthesis of alpha-halogenated beta-keto esters. *Tetrahedron Lett.* **2010**, *17*, 2374–2377. [[CrossRef](#)]
13. Studer, A.; Hadida, S.; Ferritto, R. Fluorous synthesis: A fluorous-phase strategy for improving separation efficiency in organic synthesis. *Science* **1997**, *5301*, 823–826. [[CrossRef](#)]
14. Luo, Z.Y.; Zhang, Q.S.; Oderaotoshi, Y. Fluorous mixture synthesis: A fluorous-tagging strategy for the synthesis and separation of mixtures of organic compounds. *Science* **2001**, *5509*, 1766–1769. [[CrossRef](#)] [[PubMed](#)]
15. Nakamura, H.; Linclau, B.; Curran, D.P. Fluorous triphasic reactions: Transportative deprotection of fluorous silyl ethers with concomitant purification. *J. Am. Chem. Soc.* **2001**, *41*, 10119–10120. [[CrossRef](#)]
16. Curran, D.P. Chemistry—Fluorous tags unstick messy chemical biology problems. *Science* **2008**, *5896*, 1645–1646. [[CrossRef](#)] [[PubMed](#)]
17. Jiang, L.; Qian, J.G.; Yi, W.-B. Direct trifluoromethylthiolation and perfluoroalkylthiolation of C(sp²)-H bonds with CF₃SO₂Na and R_fSO₂Na. *Angew. Chem. Int. Ed.* **2015**, *49*, 14965–14969. [[CrossRef](#)] [[PubMed](#)]
18. Cai, C.; Yi, W.-B.; Zhang, W. Fluorous Lewis acids and phase transfer catalysts. *Mol. Divers.* **2009**, *2*, 209–239. [[CrossRef](#)] [[PubMed](#)]
19. Zhang, W.; Cai, C. New chemical and biological applications of fluorous technologies. *Chem. Commun.* **2008**, *44*, 5686–5694. [[CrossRef](#)] [[PubMed](#)]
20. Zhu, Y.-W.; Qian, J.-L.; Yi, W.-B.; Cai, C. Highly efficient synthesis of polysubstituted 1,2-dihydroquinolines via tandem reaction of α-ketoesters and arylamines catalyzed by fluorous hydrazine-1,2-bis(carbothioate) and NCS. *Tetrahedron Lett.* **2013**, *54*, 638–641. [[CrossRef](#)]
21. Zhu, Y.-W.; Yi, W.-B.; Cai, C. A recyclable fluorous hydrazine-1,2-bis(carbothioate) with NCS as efficient catalysts for acetalization of aldehydes. *New J. Chem.* **2013**, *37*, 890–892. [[CrossRef](#)]
22. Wang, L.; Yi, W.-B.; Cai, C. A green and highly selective oxidation of alcohols by fluorous silica gel-supported gold nanoparticles in aqueous H₂O₂ under base-free conditions. *ChemSusChem* **2010**, *3*, 1280–1284. [[CrossRef](#)] [[PubMed](#)]



© 2017 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).