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Communication

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C–C Bond Cleavage

Detrifluoroacetylation Reaction of Trifluoromethyl-β-diketones: Facile Method for the Synthesis of Succinimide Derivatives and 1,4-Diketones

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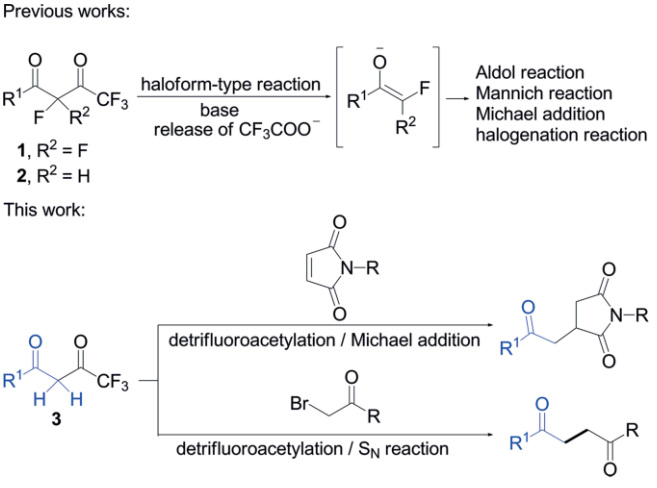
Abstract: Currently, a great deal of research efforts are focused on C–C bond activation for development of novel synthetic methodology. In this paper, a detrifluoroacetylation of trifluoromethyl-β-diketones is described, which allows for the synthesis of succinimides and 1,4-diketones through cascade Michael addition/retro-Claisen reaction and nucleophilic substitution/retro-Claisen reaction. The readily available trifluoromethyl-β-diketones, wide substrate scope, and mild conditions make this method very practical.

Introduction

Organofluorine compounds are of great importance in the pharmaceutical and agrochemical industries, as well as in materials sciences. In the last decades, a great deal of research efforts was focused on the new methodologies for the synthesis of organofluorine compounds. Many C–F bond forming reactions and fluorinated building blocks are available.[1] However, reactions allowing the cleavage of C–F bond or the release of fluorinated moieties had been largely unexplored.[2] Recently, the synthetic utility of 1,1,1,3,3-pentafluoro-2,4-dione **1** and 1,1,1,3-tetrafluoro-2,4-dione **2** was investigated due to their unique reactivity (Scheme 1). These organofluorine compounds are easily accessible from a wide range of available simple ketones and fluorine reagents. As shown in Scheme 1, the synthetic strategy relied on the haloform-type reaction, which led to the C–C bond cleavage and detrifluoroacetylation.[3] New C–C or C–heteroatom bonds were formed simultaneously through Aldol addition, Mannich addition, Michael addition, substitution or halogenation. Although these novel transformations of compounds **1** and **2** have been reported, the direct detrifluoroacetylative reactions of 1,1,1-trifluoromethyl-β-diketone **3** are rare.[4] Compound **3** can be easily prepared by Claisen reaction with various ketones and trifluoroacetates. Therefore, the synthetic methodology based on the application of compound **3** will be attractive. Herein, we present an efficient synthetic approach to succinimide derivatives and 1,4-diketons utilizing trifluoromethyl-β-diketones synthons. The succinimide derivatives are a well-known class of compounds, they serve as important intermediates in organic synthesis, and moreover, they frequently display potent and diverse biological activity.[5]



Scheme 1. The C–C bond cleavage of organofluorine compounds.

Results and Discussion

At the outset, we explored the reaction using 4,4,4-trifluoro-1-phenyl-β-butanedione **3a** and *N*-phenylmaleimide **4a** as model substrates (Table 1). In the presence of NaOH (2.0 equiv.) in CH_2Cl_2 at 60 °C, the desired product **5aa** was obtained in 32 % isolated yield. The reaction afforded **5aa** in low to moderate yields by use of weak bases such as K_2CO_3, $(NH_4)_2CO_3$ and AcONa (Entries 2–4). To our delight, an improved yield of **5aa** was observed using $NaHCO_3$ (Entry 5). We further found that phase-transfer catalyst (PTC) nBu$_4$NI promoted the reaction efficiently and the yield of **5aa** could be enhanced to 85 % (entry 5). Other PTCs such as nBu$_4$NBr and $(n$Bu$_4$N$)_2$SO$_4$ could also catalyze this Michael addition/detrifluoroacetylation reaction to give comparable yields (Entries 7 and 8). However, when the reaction was performed in other solvents including DCE, THF and AcOEt, the decreased yields of **5aa** were observed and the starting materials were reclaimed. (Entries 9–11). In order to obtain high yields and complete consumption of starting mate-

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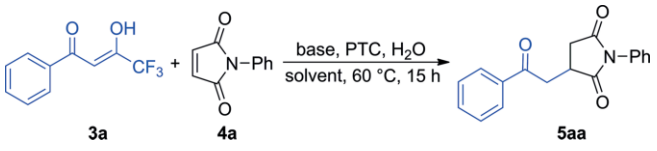
rials, the addition of 10 equiv. of water is necessary. Decreasing or increasing the amounts of water led to the low efficiency (Table 1, Entries 12 and 13).

Table 1. Screening of reaction conditions[a].



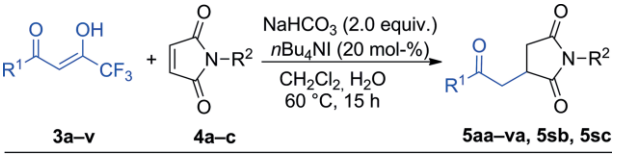
3a 4a 5aa

Entry	Base	PTC	Solvent	Yield
1	NaOH	–	CH_2Cl_2	32
2	K_2CO_3	–	CH_2Cl_2	45
3	$(NH_4)_2CO_3$	–	CH_2Cl_2	29
4	AcONa	–	CH_2Cl_2	49
5	$NaHCO_3$	–	CH_2Cl_2	73
6	$NaHCO_3$	nBu_4NI	CH_2Cl_2	85
7	$NaHCO_3$	nBu_4NBr	CH_2Cl_2	82
8	$NaHCO_3$	$(nBu_4N)_2SO_4$	CH_2Cl_2	80
9	$NaHCO_3$	nBu_4NI	DCE	69
10	$NaHCO_3$	nBu_4NI	THF	51
11	$NaHCO_3$	nBu_4NI	AcOEt	63
12[b]	$NaHCO_3$	nBu_4NI	CH_2Cl_2	60
13[c]	$NaHCO_3$	nBu_4NI	CH_2Cl_2	71

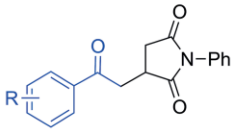
[a] Reaction conditions: **3a** (1.0 mmol), **4a** (0.5 mmol), Base (1.0 mmol), PTC (20 mol-%) and H_2O (5.0 mmol) in 3.0 mL of solvent; isolated yields. [b] H_2O (4.0 mmol). [c] H_2O (6.0 mmol).

With the optimized reaction conditions in hand, the substrate scope of the reaction was evaluated by conversion of various 1,1,1-trifluoromethyl-β-diketones **3** with maleimides **4** (Table 2). The reaction conditions were compatible with a variety of functional groups, including halides, ester, ether, nitro or cyano groups, and gave the corresponding products **5** in 58–98 % yield. It was observed that phenyl containing electron-withdrawing substituents lead to better yields, while the position on the phenyl had no notable influence. The scope was also extended to the heterocycle-substituted 1,1,1-trifluoromethyl-β-diketones, including furan and thiophene, which afforded the desired products **5ra**–**sa** in good to excellent yields (78–98 %). When *N*-methyl and *N*-benzyl maleimides were subjected to the reaction conditions, the desired products were obtained in 92 % and 98 % yield, respectively (Table 2, **5rb** and **5rc**).

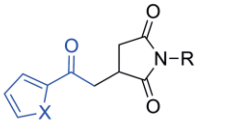
Table 2. Substrate scope of trifluoromethyl-β-diketones and maleimides.[a]



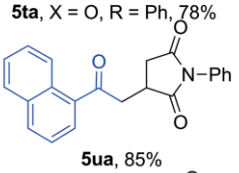
3a–v 4a–c 5aa–va, 5sb, 5sc



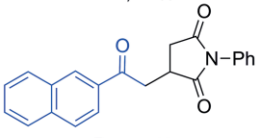
5aa, R = H, 85%
5ba, R = 4-Cl, 78%
5ca, R = 3-Cl, 75%
5da, R = 3,4-di-Cl, 80%
5ea, R = 4-Br, 88%
5fa, R = 4-I, 75%
5ga, R = 4-F, 89%
5ha, R = 4-COEt, 83%
5ia, R = 4-CN, 78%
5ja, R = 3-NO2, 69%
5ka, R = 4-Me, 70%
5la, R = 3-Me, 65%
5ma, R = 3,5-di-Me, 58%
5oa, R = 4-OMe, 63%
5pa, R = 3,4-OCH2O, 60%
5qa, R = 4-BnO, 58%
5ra, R = 3-BnO, 72%



5sa, X = S, R = Ph, 95%
5sb, X = S, R = Me, 92%
5sc, X = S, R = Bn, 98%
5ta, X = O, R = Ph, 78%



5ua, 85%

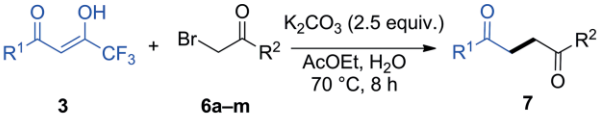


5va, 77%

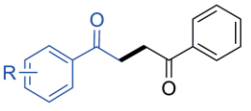
[a] Reaction conditions: **3** (1.0 mmol), **4** (0.5 mmol), $NaHCO_3$ (1.0 mmol), nBu_4NI (20 mol-%) and H_2O (5 mmol) in CH_2Cl_2 (3.0 mL); isolated yields.

1,4-Diketones and their derivatives represent interesting classes of natural and synthetic compounds that display a wide range of biological properties. Moreover, they serve as important intermediates for the synthesis of cyclopentenones, diols, and some heterocycles, such as furans, pyrroles, pyridazine, thiophenes, and pyrrolidines.[6] We next investigated the substitution/detrifluoroacetylation strategy for the synthesis of 1,4-diketones using α-bromo ketones as electrophilic reagents. As shown in Table 3, the cascade reactions of phenacyl bromide **6** with a range of trifluoromethyl-β-diketones **3** took place smoothly by using K_2CO_3 in a combination ethyl acetate and water, affording the desired products **7** in 30–95 % yield. The

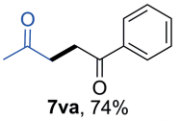
Table 3. Substrate scope of trifluoromethyl-β-diketones and α-bromo ketones[a].



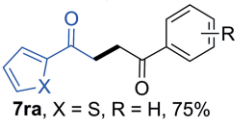
3 6a–m 7



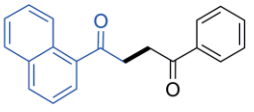
7aa, R = H, 80%
7ba, R = 4-Cl, 76%
7da, R = 3,4-di-Cl, 66%
7fa, R = 4-I, 60%
7ga, R = 4-F, 52%
7ia, R = 4-CN, 37%
7ja, R = 3-NO2, 30%
7ka, R = 4-Me, 83%
7ma, R = 3,5-di-Me, 80%
7na, R = 4-OMe, 93%
7oa, R = 3,4-OCH2O, 85%
7pa, R = 4-BnO, 71%
7wa, R = 3-OMe, 81%
7xa, R = 2-OH, 75%



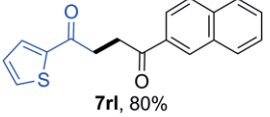
7va, 74%



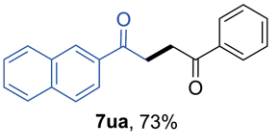
7ra, X = S, R = H, 75%
7rb, X = S, R = 4-Me, 89%
7rc, X = S, R = 4-OMe, 94%
7rd, X = S, R = 4-Ph, 71%
7re, X = S, R = 4-F, 82%
7rf, X = S, R = 3-F, 80%
7rg, X = S, R = 3-Cl, 71%
7rh, X = S, R = 4-Br, 95%
7ri, X = S, R = 3-Br, 73%
7rj, X = S, R = 2-Br, 59%
7rk, X = S, R = 4-CN, 40%
7sa, X = O, R = H, 62%



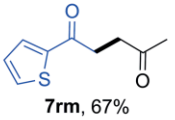
7ta, 56%



7rl, 80%



7ua, 73%

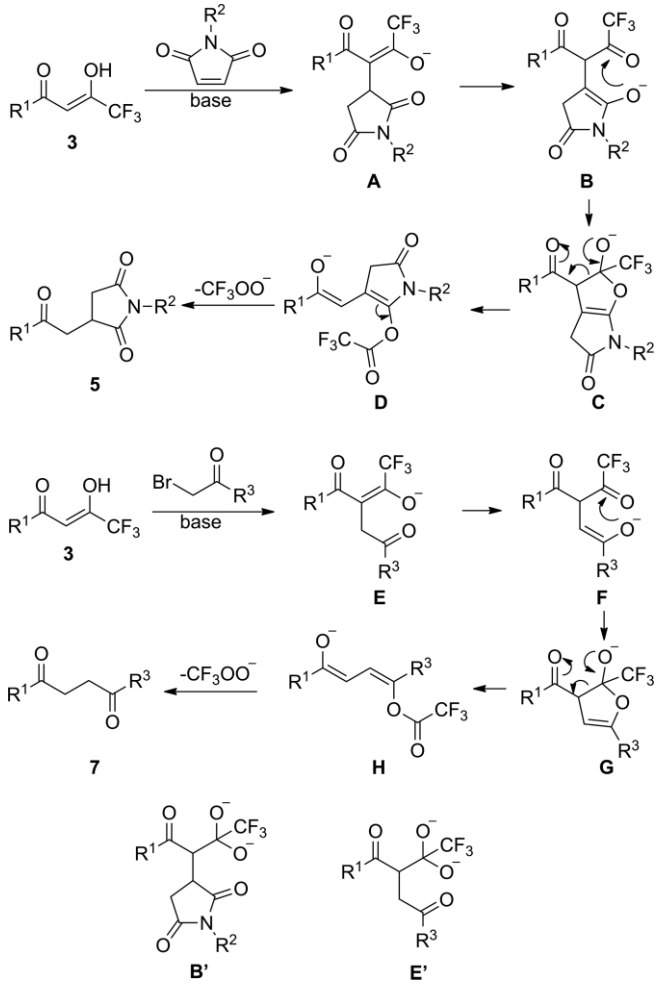


7rm, 67%

[a] Reaction conditions: **3** (2.0 mmol), **6** (0.5 mmol), K_2CO_3 (1.25 mmol) in mixtures of AcOEt (1.8 mL) and H_2O (0.2 mL); isolated yields.

reaction conditions were mild, and 1,1,1-trifluoromethyl-β-diketones containing electron-donating (EDG) and electron-withdrawing aryl groups (EWG) were both tolerated. Compared with EWGs, substrates with EDGs could give the products in better yields. Unfortunately, EWGs such as cyano and nitro only afforded the corresponding products in low yields (Table 3, **7ia** and **7ja**). The substrates bearing a larger aryl substituent such as a naphthyl group was also successfully transformed to the corresponding 1,4-diketones (**7ta** and **7ua**). We were pleased to find that even the aliphatic substrate 1,1,1-trifluoropentane-2,4-dione **6v** was smoothly transformed to 1,4-diketone **7va** in 74 % yield. The substitution/detrifluoroacetylation reactions of various α-bromo ketones with thiophenyl trifluoromethyl-β-diketone **3r** were then investigated. Both aryl and alkyl α-bromo ketones were converted to desired 1,4-diketones in good to excellent yields (**7ra**–**7rl**). It is noteworthy that *para*-bromophenacyl bromide **6h** gave a better result than the *meta*-and *ortho*-bromo isomers (**7ri**–**7rj**). Finally, the substrate scope was extended to readily available bromoacetone **6m**, which gave the desired product **7rm** in 67 % yield.

A plausible mechanism for this transformation is illustrated in Scheme 2. Initially, Michael addition of trifluoromethyl-β-diketone **3** with maleimide produces an enolic adduct **A** under basic conditions. A retro-Claisen reaction takes place from **A** to the final product **5**.[3k,7] First, **A** isomerizes to the enolate **B**, which then undergoes intramolecular addition to the acyl group to give intermediate **C**.[4c] The C–C bond cleavage and isomerization of **C** affords intermediate **D**. Finally, **D** gives product **5** through hydrolysis. Similarly, a cascade substitution/retro-Claisen reaction can account for the pathway of synthesis of 1,4-diketones. Under basic conditions, the direct nucleophilic addition of hydroxyl ion to trifluoroacetyl groups of **A** and **E** to form corresponding intermediates **B′** and **E′** is also possible.



Scheme 2. Proposed reaction mechanisms.

Conclusions

In summary, we have developed a facile method for the synthesis of succinimide derivatives and 1,4-diketones through detrifluoroacetylation reaction of trifluoromethyl-β-diketones. The cascade detrifluoroacetylation/Michael addition and detrifluoroacetylation/substitution are compatible with a variety of functional groups. A retro-Claisen reaction pathway for the C–C bond cleavage is suggested. Other novel applications of trifluoromethyl-β-diketones as synthons in organic synthesis is underway in our laboratory.

Experimental Section

Synthesis of Succinimide Derivatives 5aa: A 50 mL round-bottomed flask with a magneton was charged with trifluoromethyl-β-diketones **3a** (6.0 mmol, 2.0 equiv.) and $NaHCO_3$ (6.0 mmol, 2.0 equiv.) under air at room temperature, and then *N*-phenyl maleimide **4a** (3.0 mmol, 1.0 equiv.), nBu_4NI (20 mol-%), H_2O (5.0 mmol) and in CH_2Cl_2 (10.0 mL) were added. After the mixture was stirred at 60 °C for 15 h, the resulting residue was mixed with silica gel and concentrated. The resulting mixture was purified by silica gel column chromatography on silica gel with petroleum ether/ethyl acetate (15:1) as eluent to give the desired product **5aa** (72 %).

Synthesis of 1,4-Diketones (7aa): To a mixture of **3a** (4.0 mmol, 2 equiv.), K_2CO_3 (2.5 mmol), **6a** (2.0 mmol, 1 equiv.) in a Schlenk tube was added EtOAc (3.6 mL) and H_2O (0.4 mL). The mixture was stirred at 60 °C for 8 h. After cooling to room temperature, the reaction mixture was diluted with HCl aqueous solution (3 %, 20 mL) and extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (15 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether, v/v1:20 to v/v = 1:5) to give product **7aa** (76 %).

Acknowledgments

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Keywords: Synthetic methods · Cleavage reactions · Detrifluoroacetylation · Retro-Claisen reaction · Succinimides · 1,4-Diketones

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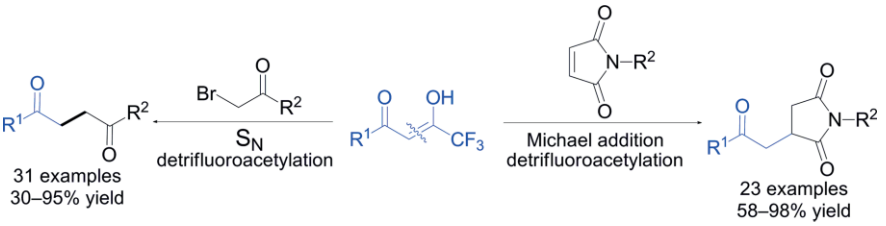
C–C Bond Cleavage



A detrifluoroacetylation of trifluoromethyl-β-diketones has been developed, which allows for the synthesis of succinimides and 1,4-diketones through cascade Michael addition/retro-Claisen reaction and nucleophilic substitution/retro-Claisen reaction.

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