DOI: 10.1002/adsc.201500691

# 1,5-Diketones Synthesis *via* Three-Component Cascade Reaction

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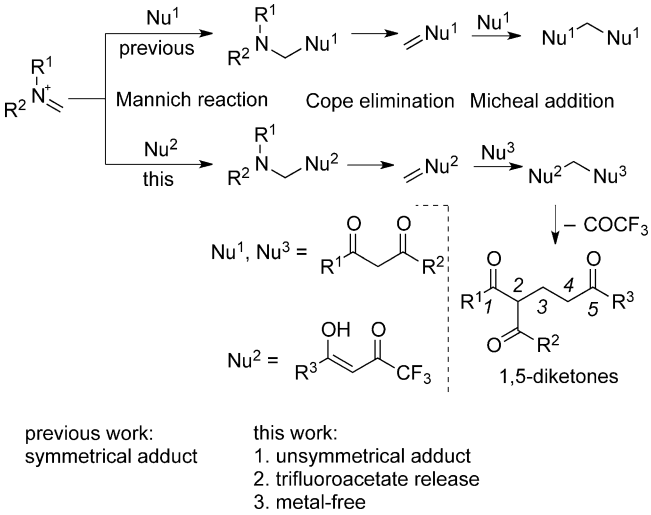
Received: July 20, 2015; Revised: August 17, 2015; Published online: October 13, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500691.

**Abstract:** A mild and efficient cascade synthesis of 1,5-diketones from readily available *N*,*N*-dicyclohexylmethylamine, 1,3-dicarbonyl compounds, and trifluoromethyl β-diketones has been developed. This cascade reaction occurs *via* an oxidation/Mannich reaction/Cope elimination/Michael addition/retro-Claisen reaction sequence, and provides multiple C–C bond formations in one pot. In addition, exquisite chemoselectivity is achieved in the reaction between 1,3-dicarbonyl compounds and trifluoromethyl β-diketones.

**Keywords:** cascade reaction; 1,5-diketones; metal-free conditions; *N*-methylamine; trifluoroacetate release

Starting from the early 1960s, the chemistry of multicomponent cascade or domino reactions has experienced a rapid development.[1] This interest in multicomponent cascade reactions is mainly due to their excellent atom economy and overall efficiency. The major challenge of a cascade reaction is achieving high selectivity, such as chemo-, regio- and stereoselectivity.[1c–e,j] In 2009, Li and co-workers reported an efficient synthesis of methylene-bridged bis-1,3-dicarbonyl compounds *via* iron-catalyzed oxidative reactions of *N*,*N*-dimethylaniline and 1,3-dicarbonyl compounds.[2] A cascade reaction pathway of oxidation/Mannich reaction/Cope elimination/Michael addition has been proposed, in which 1,3-dicarbonyl compound $Nu^1$ first participates in a Mannich reaction as carbon nucleophile and then reacts with a Michael acceptor to afford the methylene-bridged symmetrical adduct (Scheme 1). Very recently, a number of reports have described similar oxidative cascade reactions of *N*-methylamines.[3] Although these processes enable multiple C–C bond formation and C–N bond cleavage, the final products are limited to symmetrical adducts.[2,3] The synthesis of unsymmetrical adducts by this method is still challenging. To realize this goal, the carbon nucleophile $Nu^2$ must be able to react exclusively with an iminium ion in the step of the Mannich reaction and another nucleophile $Nu^3$ must be able to react exclusively with a Michael acceptor in the step of addition. Thus the nucleophiles $Nu^2$ and $Nu^3$ have to be carefully selected to achieve such a chemoselectivity. Recently, trifluoromethyl β-diketones $Nu^2$ were found to be highly reactive nucleophiles, which allowed the easy construction of C–C and C–X bonds *via* the facile release of trifluoroacetate.[4] We envisioned that the use of these substrates would furnish a selective cascade reaction (Scheme 1). Herein, we report a one-pot, three-component cascade reaction that allows the synthesis of methylene-bridged unsymmetrical adducts from *N*-methyl tertiary aliphatic amines, trifluoromethyl β-diketones, and 1,3-dicarbonyl compounds. This reaction



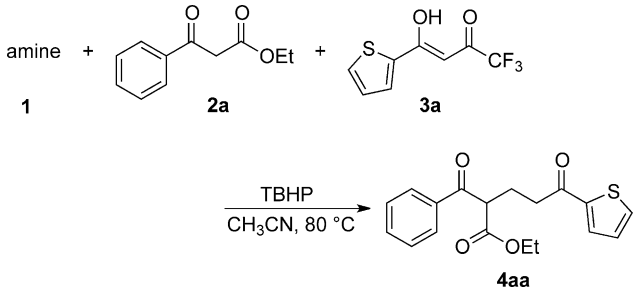

**Scheme 1.** Cascade reaction of *N*-methylamine.

proceeds through an oxidation/Mannich reaction/Cope elimination/Michael addition/retro-Claisen reaction sequence that includes C–N bond cleavage of the amine, C–C bond cleavage of the trifluoromethyl β-diketone, and the chemoselective formation of two C–C bonds. Notably, 1,5-diketones can be readily prepared through this cascade reaction under mild and metal-free conditions. 1,5-Diketone derivatives serve as useful synthetic intermediates for the preparation of cyclopentenes, piperidines, pyridines, hydrazines, ketolactones and many other heterocyclic compounds, which exhibit various potential biological and pharmacological activity. Consequently, the feasible construction of such structures is of great value.[5]

We chose ethyl benzoylacetate **2a** as one nucleophile and 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione **3a** as another nucleophile to evaluate various tertiary amines in the presence of TBHP. In the previous report, *N*,*N*-dimethylanline **1a** was frequently used as carbon partner or carbon source in oxidative coupling reactions.[2,6] However, it only afforded the desired product **4aa** in 20% yield in this transformation (Table 1, entry 1). *N*,*N*-Dimethylbenzylamine **1b** slightly improved the yield of **4aa** to 30% (Table 1, entry 2). The secondary anline *N*-methylaniline **1c** was also investigated, but a messy result was observed and product **4aa** was not detected (Table 1, entry 3). We recently reported that tertiary *N*-ethylamines could be used for oxidative coupling reactions.[7] However, the reactions of *N*,*N*-diisopropylethylamine **1d** and *N*,*N*-dicyclohexylethylamine **1e** could not yield **4aa** (Table 1, entry 4 and 5). Instead, they afforded the symmetrical methylene-bridged bis-1,3-dicarbonyl compounds in very low yields as in our previous report.[7] Interestingly, by using a sterically hindered tertiary amine, *N*,*N*-dicyclohexylmethylamine **1f**, the yield was significant improved to 75% (Table 1, entry 6). Replacing aqueous TBHP with the solution TBHP in *n*-decane led to a lower yield of **4aa** (Table 1, entry 7). It is noteworthy that the symmetrical adduct was not observed when the reaction was performed using *N*-methylamines such as **1a**–**1c** and **1f**.

**Table 1.** Screening studies for various amines.[a]




| Entry | Amine | Yield [%] |
|---|---|---|
| 1 | *N*,*N*-dimethylaniline **1a** | 20 |
| 2 | *N*,*N*-dimethylbenzylamine **1b** | 33 |
| 3 | *N*-methylaniline **1c** | 0 |
| 4 | *N*,*N*-diisopropylethylamine **1d** | 0 |
| 5 | *N*,*N*-dicyclohexylethylamine **1e** | 0 |
| 6 | *N*,*N*-dicyclohexylmethylamine **1f** | 75 |
| 7 | *N*,*N*-dicyclohexylmethylamine **1f** | 62[b] |

[a] Unless otherwise noted, *reaction conditions* were as follows: amine (2.0 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), TBHP (4.0 mmol, 70% aqueous), MeCN (2 mL), 80 °C, 12 h, isolated yield.

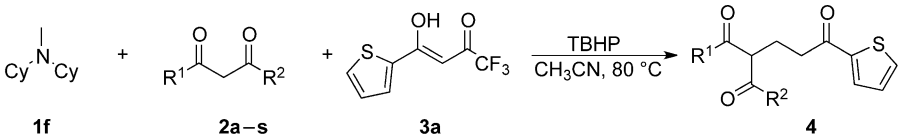
[b] TBHP (5.5 M in *n*-decane)

On the basis of the results achieved with *N*,*N*-dicyclohexylmethylamine **1f** and 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione **3a**, a range of 1,3-dicarbonyl substrates **2** was next examined under the optimal conditions described in Table 1, entry 6. As shown in Table 2, when β-keto esters **2** were substituted with electron-withdrawing groups on the aromatic ring, including halides, nitro and cyano groups, the corresponding products **4ba**–**4ea** were obtained in 35–88% yield (Table 2, **4ba**–**4ea**). Electron-donating groups such as *p*-methyl, *p*-methoxy, *m*-methoxy and methylenedioxy groups were also allowed the formation of **4fa**–**4ia** in moderate to good yields (Table 2, **4fa**–**4ia**, 59–74%). The naphthyl group substituted β-keto esters could also give products in good yields (Table 2, **4ja**, **4ka**). When heterocyclic 1,3-dicarbonyl compounds, such as thiophene, furan and pyrrole 1,3-keto esters were subjected to the conditions, the reactions furnished the corresponding oxidative-coupling products in moderate yields (Table 2, **4la**–**4na**). Besides 1,3-keto esters, we found that 1,3-diphenyl-1,3-propanedione **2o** could also transformed into the target compound **4oa** in 32% yield (Table 2, **4oa**). Moreover, the substrate scope was extended to dialkyl malonates and ethyl acetoacetate, which were converted to the desired products **4pa**–**4sa** in moderate to good yields (Table 2, **4pa–4sa**, 56–77%). These substrates are readily available carbon synthons in organic synthesis. Thus we anticipate that the present cascade reaction will be valuable for the synthesis of complex molecules.

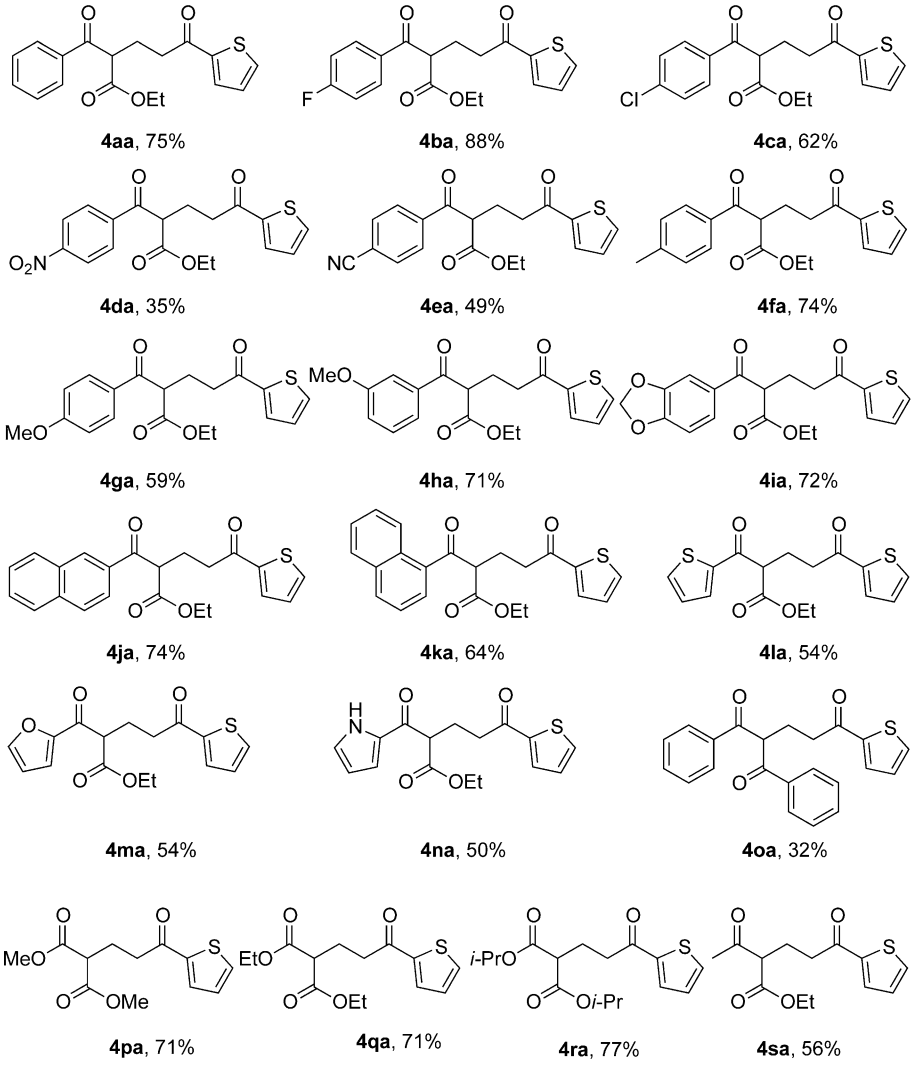
The cascade reaction was also applicable to a variety of trifluoromethyl-1,3-dicarbonyl compounds **3b–n** (Table 3). The aryl halide-substituted substrates gave the desired products **4gb–4ge** in 46–73% yields. When the aromatic ring is substituted with electron-donating groups, such as methoxy, methylenedioxy and benzyloxy groups, the reaction proceeded smoothly to afford the products (Table 3, **4gf–4gj**, **4aj**, 37–84% yield). It is noteworthy that the *para*-methoxy substrate gave a better result than the *meta*- and *ortho*-methoxy isomers (Table 3, **4gf–4gh**). The trifluoromethyl-1,3-dicarbonyl compound bearing a larger aryl substituent such as a naphthyl group was successfully transformed to the corresponding 1,5-diketones

**Table 2.** Substrate scope of various 1,3-dicarbonyl substrates.[a]




**1f** **2a–s** **3a** **4**




**4aa**, 75% **4ba**, 88% **4ca**, 62%

**4da**, 35% **4ea**, 49% **4fa**, 74%

**4ga**, 59% **4ha**, 71% **4ia**, 72%

**4ja**, 74% **4ka**, 64% **4la**, 54%

**4ma**, 54% **4na**, 50% **4oa**, 32%

**4pa**, 71% **4qa**, 71% **4ra**, 77% **4sa**, 56%

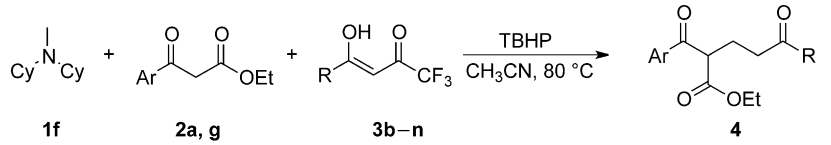
[a] Reactions were carried out with **1f** (2.0 mmol) **2** (0.5 mmol), **3a** (0.5 mmol), and TBHP (4.0 mmol, 70% aqueous) in MeCN (2 mL) at 80 °C for 12 h; yield as indicated.

(Table 3, **4gk**, **4ak**). Furthermore, we were pleased to find that even the aliphatic substrate 1,1,1-trifluoropentane-2,4-dione could be used in our procedure to afford **4gl** in 58% yield (Table 3, **4gl**). However, the nitro substituent on the aromatic ring led to a low yield of 27% (Table 3, **4am**). The furan substituted trifluoromethyl β-diketone was also tolerated in this reaction, and 1,5-diketone **4an** was obtained in 79% yield.

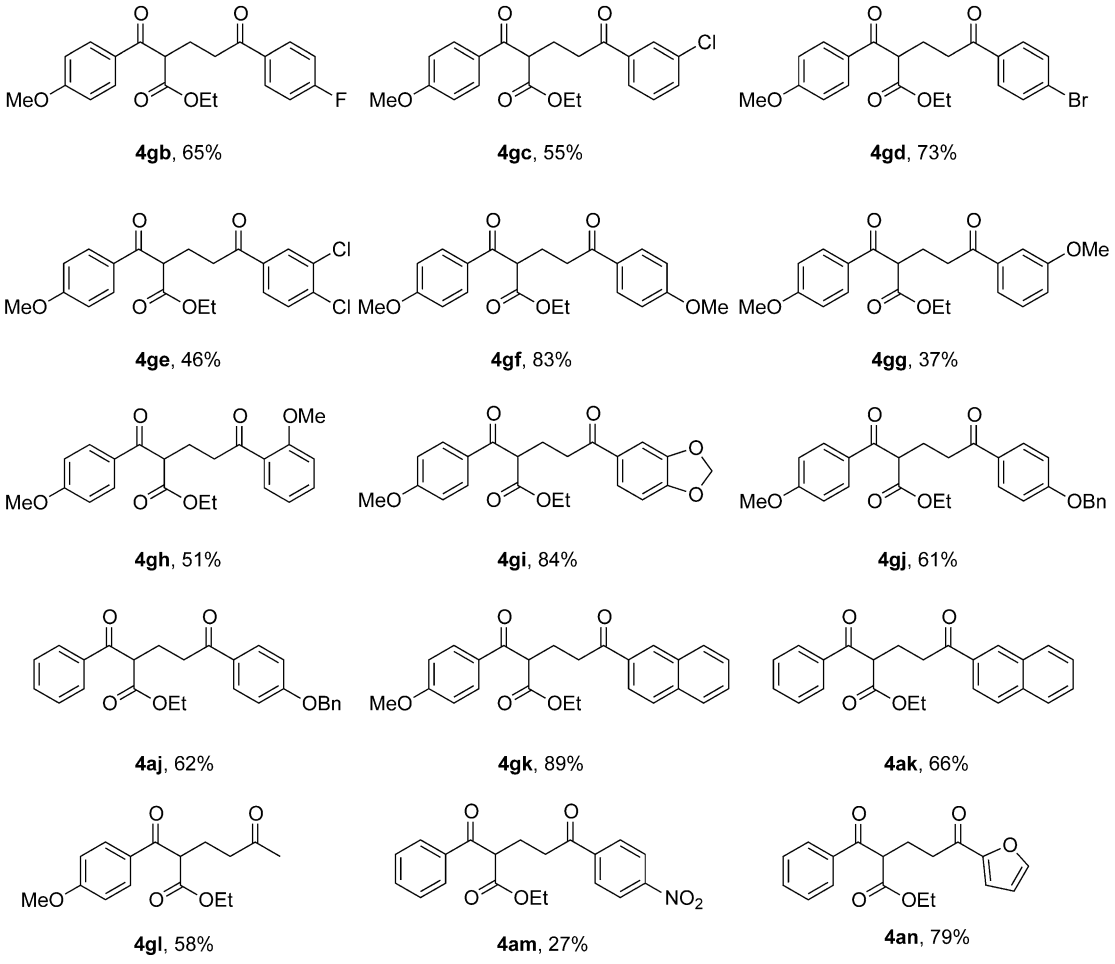
On the basis of earlier studies and our results,[2,4a,d,8] we propose a possible mechanism for the cascade reaction (Scheme 2). The first step is the oxidation of *N*,*N*-dicyclohexylmethylamine **1f** with TBHP affording an iminium ion **A**, which undergoes a Mannich reaction with trifluoromethyl β-diketone to generate a Mannich base **B**. Upon oxidation, Cope elimination of **B** occurs to produce a Michael acceptor **C**. Subsequently, **C** converts to the final product **4** through

**Table 3.** Substrate scope of various trifluoromethyl β-diketones.[a]




**1f** **2a, g** **3b–n** **4**




**4gb**, 65% **4gc**, 55% **4gd**, 73%

**4ge**, 46% **4gf**, 83% **4gg**, 37%

**4gh**, 51% **4gi**, 84% **4gj**, 61%

**4aj**, 62% **4gk**, 89% **4ak**, 66%

**4gl**, 58% **4am**, 27% **4an**, 79%

[a] Reactions were carried out with **1f** (2.0 mmol), β-keto esters substrates **2** (0.5 mmol), trifluoromethyl β-diketones **3** (0.5 mmol), and TBHP (4.0 mmol, 70% aqueous) in MeCN (2 mL) at 80 °C for 12 h; yield as indicated.

a Michael reaction/retro-Claisen reaction sequence.[8] Another alternative pathway, which involves firstly the Knoevenagel condensation between formaldehyde and trifluoromethyl β-diketone, and then a Michael reaction/retro-Claisen reaction, is also possible.

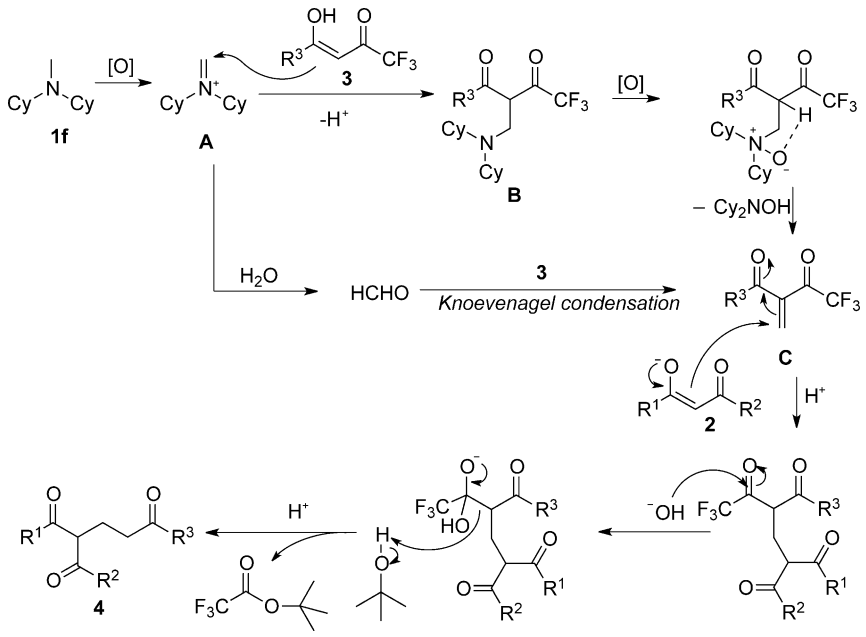
In conclusion, we have developed a mild and efficient cascade reaction for the synthesis of 1,5-diketones employing readily available *N*,*N*-dicyclohexylmethylamine, 1,3-dicarbonyl compounds, and trifluoromethyl β-diketones. In addition, the selective reaction of trifluoromethyl β-diketone and 1,3-dicarbonyl compound is achieved in one pot. Further investigation of this strategy focusing on the construction of other 1,5-diketones and heterocycles is underway in our laboratory.

## Experimental Section

### General Procedure for the Synthesis of 4

A Schlenk tube was charged with 1,3-dicarbonyl compound **2** (0.5 mmol) and trifluoromethyl β-diketone **3** (0.5 mmol) under air at room temperature, then *N*,*N*-dicyclohexylmethylamine **1f** (2.0 mmol) and *tert*-butyl hydroperoxide (TBHP, 4.0 mmol, 70% aqueous solution) were added. The mixture was stirred at 80 °C for 12 h. The resulting reaction




**Scheme 2.** Proposed mechanism for the cascade reaction.

mixture was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:20, v/v) as eluent to give the desired product **4**.

## Acknowledgements

*We gratefully acknowledge the Natural Science Foundation of China (No. 21172120, 21472093),Tianjin Municipal Science and Technology Commission (No. 14 JCYBJC20600) and National University Student Innovation Program (No. 201510055118) for the funding support.*

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