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COMMUNICATION

One-pot synthesis of useful heterocycles in medicinal chemistry using a cascade strategy†

Guiyong Wu,[a] Weiyu Yin,[a] Hong C. Shen*[b] and Yong Huang*[a]

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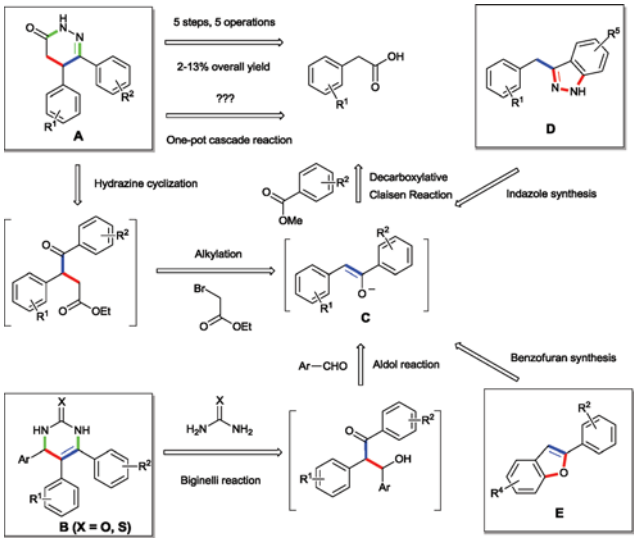
To access useful heterocycles in medicinal chemistry such as pyridazinones, dihydropyrimidinones, and dihydropyrimidinthiones, a "green" mild and highly efficient one-pot triple cascade was developed involving a Claisen–decarboxylation, electrophilic reaction, and subsequent heterocyclization. In addition, indazoles and benzofurans could also be constructed *via* a double cascade. To develop the cascade process, a direct Claisen–decarboxylation reaction was firstly optimized. This reaction can then couple with electrophilic reactions including alkylation, Michael addition or aldol reaction to enable the preparation of various aryl ketones in a one-pot fashion.

Introduction

Efficient construction of molecular complexity *via* multi-component, domino, or cascade reactions has recently drawn significant attention in the organic chemistry community due to its "green" nature. The use of relatively simple starting materials to drastically increase the levels of molecular complexity may be achieved in a single-pot operation by allowing reactive products to continue additional chemical transformations before work-up.[1] A successful process of this kind will generate considerable savings towards solvent, and waste disposal, as well as time consumed during work-ups and purifications. This can often be accomplished by careful substrate and cascade sequence design, as well as delicate reaction condition control. In the context of our medicinal chemistry efforts, we aimed to construct structurally complex scaffolds by merging compatible reactions in a cascade manner, which may provide great opportunities for the development of novel synthetic routes to natural products and drug candidates with remarkable synthetic efficiency. Herein we report our efforts towards developing a cascade strategy to generate heterocycles and aryl ketone analogs of interest in medicinal chemistry involving a Claisen–decarboxylation reaction as the first step.

The first class of targets that drew our attention was the dihydropyrazinone scaffold (**A** in Scheme 1), which were used for the synthesis of a series of acyl-CoA: cholesterol acyltranferase (ACAT) inhibitors. Several compounds containing the pyridazinone core also exhibited arthropodicidal effects[3] or inhibited P38 mitogen activated protein kinase (MAPK).[4] In the literature report, intermediate **A** was prepared from the corresponding substituted phenyl acetic acid over five steps in 2–13% overall yield.[2] To improve the efficiency and yield, we envisioned that a Claisen–decarboxylation–electrophilic substitution–hydrazidation cascade could provide the desired intermediate in one pot *via* ketone enolate **C** as shown in Scheme 1.

Another class of useful compounds in medicinal chemistry is dihydropyrimidinones or dihydropyrimidinthiones (**B** in Scheme 1), which have demonstrated anti-viral, anti-tumor, anti-bacterial, anti-inflammatory, or calcium channel modulating activities.[5] Very recently this class of compounds were also found to be *S*-nitrosoglutathione reductase inhibitors.[6] It is conceivable that the same ketone enolate intermediate **C**, may undergo a three-component Biginelli reaction in the presence of an aldehyde, a urea or thiourea, to yield the corresponding dihydropyrimidinone or dihydrothiopyrimidinone analogues.



Scheme 1 Proposed cascade approaches to heterocycles.

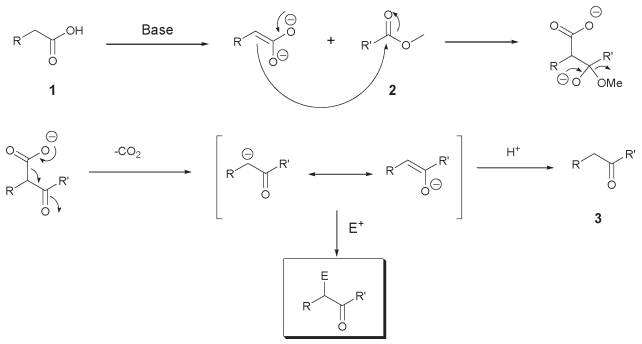
[a]*Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School, Peking University, Shenzhen, 518055, China. E-mail: huangyong@pkusz.edu.cn; Fax: +86 755 26033174; Tel: +86 755 26033586*
[b]*Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Company, Inc.P.O. Box 2000, Rahway, New Jersey 07065-0900, USA. E-mail: hong_shen@merck.com; Fax: +1 732 594 9473; Tel: +1 732 594 1755*

†Electronic supplementary information (ESI) available: Detailed procedures, analytical data, and $^{1}H/^{13}C$ NMR spectra. See DOI: 10.1039/c2gc16457d

Indazoles and benzofurans are abundant in natural products and they possess attractive pharmacological properties.[7,8] For example, close analogues of compound **D** (Scheme 1) were recently reported as potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) against HIV.[9] 2-Aryl benzofurans were reported in >900 patent applications based on the SciFinder search. One series of 2-aryl benzofurans demonstrated utility in treatment of resistant cancers.[10] Rapid synthesis of these structures may significantly impact medicinal chemistry efforts for indazole or benzofuran targets. We envisioned that these heterocycles could also be synthesized in one pot using the Claisen–decarboxylation reaction, coupled with heteroatom cyclization under S_NAr or transition metal-catalyzed reaction conditions (**D** and **E** in Scheme 1, respectively).

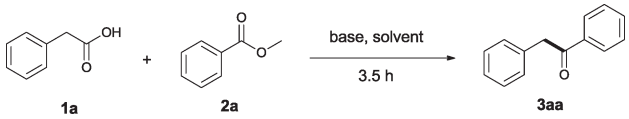
To conduct the cascade reaction, the first step was to achieve a decarboxylative Claisen reaction to provide aryl ketones, a class of important building blocks for both natural products and functional materials.[11] Classical routes to the synthesis of aryl ketones typically rely on oxidation of the corresponding secondary alcohols,[12] Weinreb ketone synthesis,[13] or Friedel–Crafts acylation of aromatic compounds in the presence of a Lewis acid.[14] In recent years, transition metal-catalyzed addition reactions have also provided a useful alternative for the synthesis of aryl ketones from nitriles,[15] or from cross-ketonisation of aryl and alkyl carboxylic acids under thermal conditions.[16]

Claisen condensation has been widely used to prepare various β-keto esters through coupling of two esters under basic conditions.[17] One extension of the Claisen condensation involved the use of acids and benzoyl chlorides showcased in the total synthesis of fredericamycin A.[18] Direct Claisen condensation between an α-carboxylic acid and an ester has been documented in patent literature, but there were no reported systematic optimizations of this reaction to the best of our knowledge.[19]



Scheme 2 The Claisen–decarboxylation cascade.

Table 1 Condition screening for the Claisen–decarboxylation



Entry	Base (eq.)	Solvent	Temp. °C	Conversion (%)[a]
1	NaHMDS (4.0)	THF	0	90
2	KHMDS (4.0)	THF	0	72
3	LiHMDS 4.0)	THF	0	68
4	LDA (4.0)	THF	0	71
5	NaHMDS (3.0)	THF	−78	~20
6	NaHMDS (4.5)	THF	−78	70–93
7	NaHMDS (2.0)	THF	−10	41
8	NaHMDS (3.0)	THF	−10	95
9	NaHMDS (4.0)	THF	−10	99
10	NaHMDS (4.0)	THF	−10	88
11	NaHMDS (4.0)	THF	−30	52

[a] Crude NMR conversion based on integration with the starting materials after aqueous work-up.

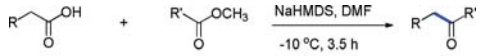
Results and discussions

In view of the versatile utilities of aryl ketones in medicinal chemistry and the development of cascade reactions to form hetereocycles, we decided to optimize the direct Claisen condensation reaction employing carboxylic acids and esters, and then apply the resulting products directly to subsequent functionalizations. Initially, the strategy was conceived as a two-step protocol: firstly a double deprotonation of aryl acetic acid **1** with a strong base generates a highly reactive carboxylate enolate dianion, which can then undergo a Claisen condensation with aryl ester **2** to form a condensation product, followed by decarboxylation upon neutralization/heating to provide the aryl ketone **3** (Scheme 2). To our delight, the initial test showed that the reaction of phenyl acetic acid **1a** with benzoate **2a**, in the presence of 4 equivalents of NaHMDS, led to aryl ketone **3aa** at 0 °C in excellent conversion upon aqueous work-up (entry 1, Table 1). The spontaneous loss of carbon dioxide occurred at −78 °C; quenching the reaction mixture at this temperature gave an excellent yield of the desired decarboxylation product (entry 6, Table 1). It should also be noted that the direct Claisen condensation intermediate prior to decarboxylation was never detected by crude NMR during the reaction or after aqueous work-up.

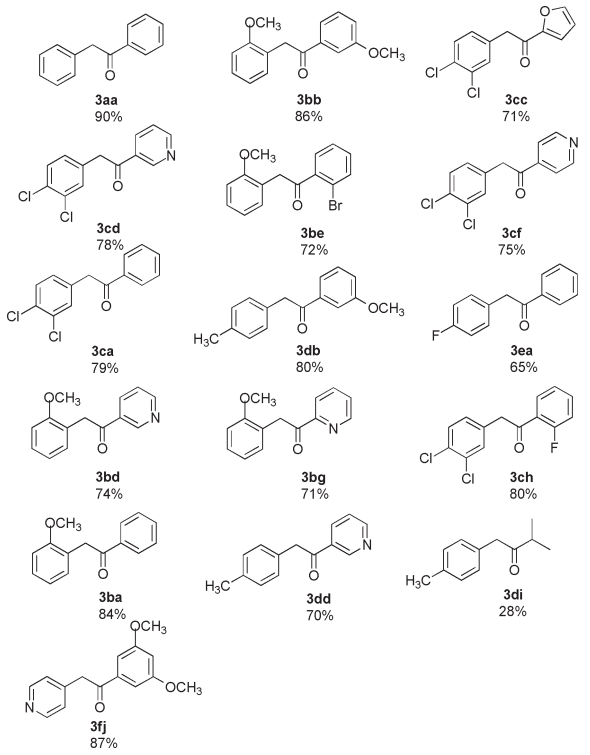
The Claisen–decarboxylation cascade reaction conditions were subsequently optimized by screening bases, solvents, and different temperatures. Bases were first examined and NaHMDS turned out to be optimal for this transformation (entries 1–4, Table 1). The poor solubility of methyl benzoic esters in THF at low temperatures (−78 °C) caused irreproducible yields (entries 5 and 6, Table 1). Thus, DMF and/or a higher reaction temperature (−10 °C) were adopted to enable a more homogeneous reaction mixture, and therefore more consistent results (entries 8–11, Table 1). Importantly, excess base was required to achieve complete conversion (entries 7–9, Table 1), possibly due to incomplete generation of the carboxylate enolate dianion under stoichiometric conditions. As such, the reactions proceeded almost quantitatively in DMF at −10 °C in 3.5 hours (entry 9, Table 1).

Under the optimized conditions, the scope of acids and esters was explored. The Claisen–decarboxylation cascade was quite general for various aryl acetic acids **1a–f** and aryl esters **2a–j** (Table 2); electron-donating, and electron-withdrawing aryl and heteroaryl groups were all suitable substrates, giving the desired aryl or heteroaryl ketones in good yields. The reaction yields using aliphatic esters such as methyl isobutyrate were significantly lower than their aromatic counterparts (Table 2, **3di**). It was assumed that methyl isobutyrate underwent the classical self Claisen condensation to compete with the desired cross

Table 2 The Claisen–decarboxylation cascade of various substrates[ab]



1a-f + 2a-j → 3

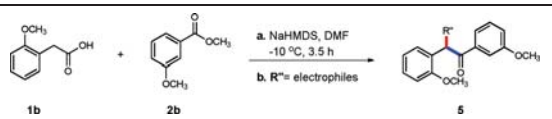


[a] Isolated yields after column chromatography. Reactions were run on a 1.0 mmol scale using an aromatic acetic acid (1.0 eq.), a methyl aromatic ester (1.0 eq.), NaHMDS (2 M in THF) (4.0 eq.) in DMF (3.0 mL) at −10 °C for 3.5 h. [b] Product **3xy** was denoted as derived from the reaction of acid **1x** and ester **2y**.

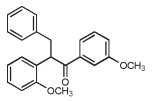
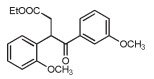
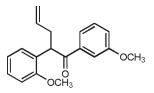
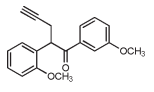
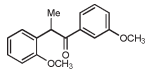
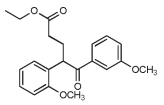
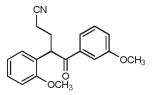
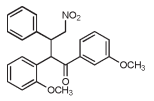
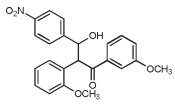
condensation. The rapid *in situ* decarboxylation appeared to be universal. In all cases examined, the initial Claisen products were never observed or isolated.

The initial Claisen–decarboxylation products, namely ketone enolates, could be trapped with various electrophiles *in situ*, as summarized in Table 3. Typically, electrophiles were added in 3.5 hours when the Claisen–decarboxylation process had completed. However, excess amounts of NaHMDS caused decomposition of many electrophiles (*e.g.* polymerization of acrylic nitrile, entry 7, Table 3), as well as other side reactions. The isolated yields for this double cascade were low (≪50%). The yield was later improved by the addition of excess water or alcohols prior to the introduction of electrophiles. The high acidity of the enol form of the Claisen ketone products (p*K*a = 9.9, calculated by using ChemDraw Pro 9.0 ACD version 11.01) suggested that the corresponding enolates should survive the water/alcohol treatment. In addition, the increased solvent media polarity likely contributed to the fast substitution and addition reactions. Reactive alkyl halides, including benzyl bromide, bromoacetate, allyl bromide, propargyl bromide and methyl iodide (entries 1–5, Table 3), were successfully incorporated into the diaryl ketone skeleton. Despite the relatively poor reactivity of these highly

Table 3 The Claisen–decarboxylation–electrophilic reaction cascade for the synthesis of various ketone analogues[a]



1b + 2b → 5

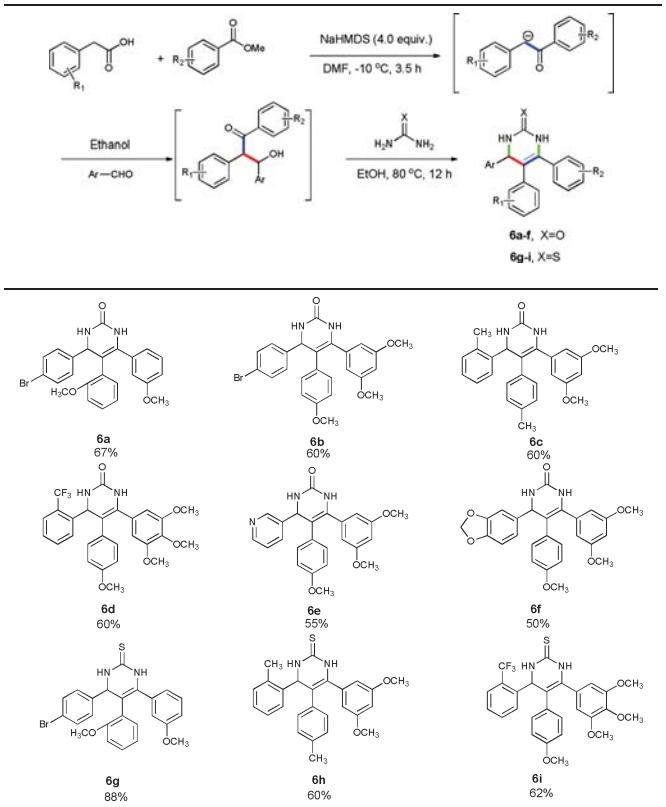
Entry	Electrophile	Product
1	 4a	 5a 77%
2	 4b	 5b 80%
3	 4c	 5c 94%
4	 4d	 5d 79%
5[b]	CH_3I 4e	 5e 99%
6[b]	 4f	 5f 95%
7[b]	 4g	 5g 87%
8[bc]	 4h	 5h 54%
9[d]	 4i	 5i 83%

[a] Isolated yields after column chromatography. Reactions were run on a 0.5 mmol scale using 2-methoxybenzeneacetic acid (1 eq.), methyl 3-methoxybenzoate (1 eq.) and electrophiles (2 eq.). [b] Ethanol was added to quench the excess base prior to the addition of electrophiles. [c] dr = 1 : 2. [d] Ethanol/water was added to quench the excess base prior to the addition of the electrophile.

conjugated enolates, both Michael additions (entries 6–8, Table 3) and aldol reactions (entry 9, Table 3) gave high yields, allowing rapid access of various functionalized aryl ketones.

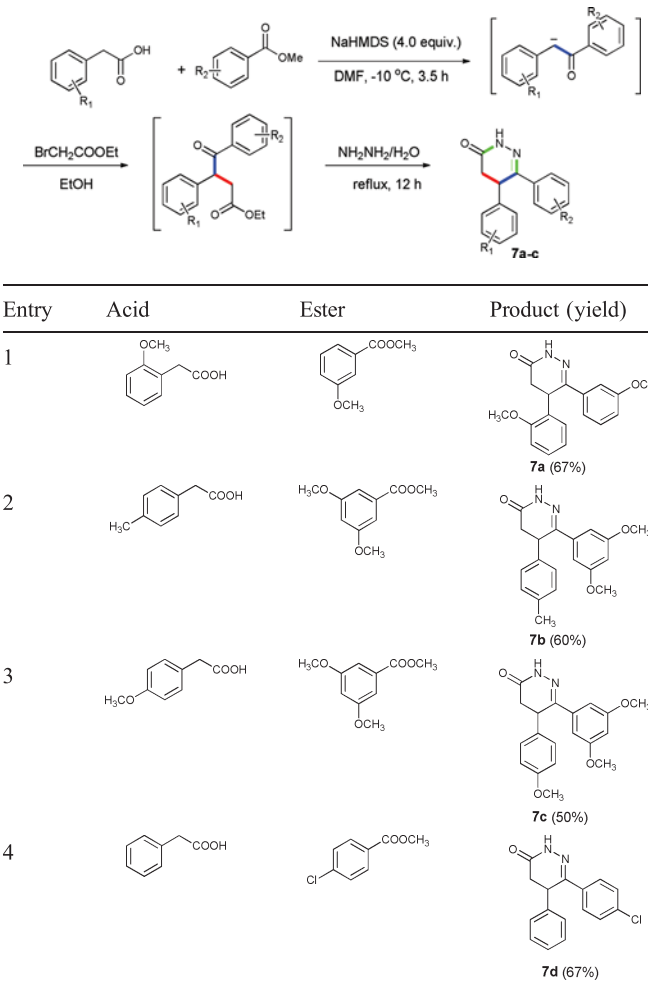
Multi-component condensations[20] (MCCs) can be a powerful tool for medicinal chemists to synthesize novel drug-like

Table 4 One-pot synthesis of dihydropyrimidinones and dihydropyrimidinthiones using a Claisen–decarboxylation–Biginelli cascade[a]



[a] Isolated yields after column chromatography.

Table 5 One-pot synthesis of pyridazinones using a Claisen–decarboxylation–electrophilic substitution–hydrazidation cascade[a]



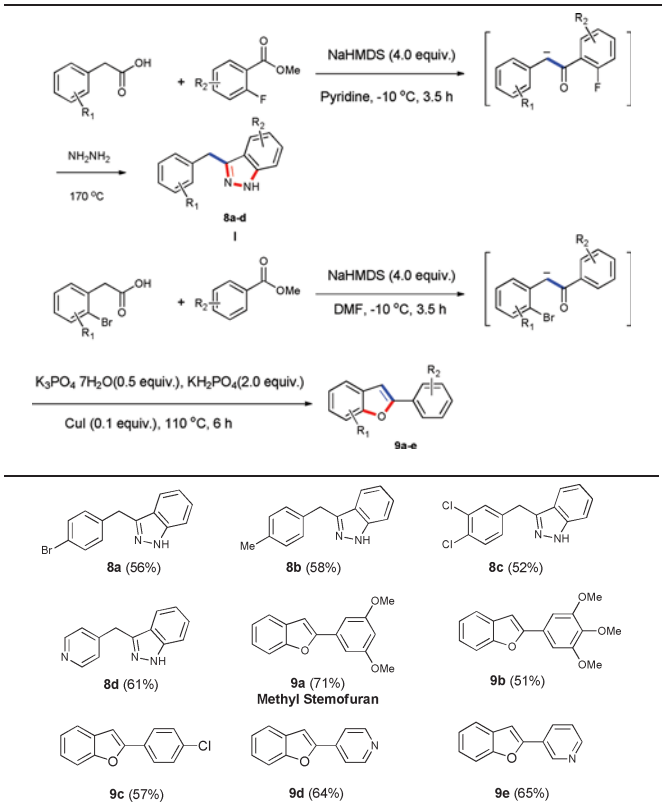
[a] Isolated yields after column chromatography.

scaffolds. In particular, Biginelli reaction, a three-component condensation of an aldehyde, a β-ketoester, and a urea or thiourea, represents one of the most widely used MCCs for the preparation of dihydropyrimidinone or dihydrothiopyrimidinone analogues.[21] As such, we explored the possibility to perform a four-component one-pot tandem reaction sequence, by tethering our Claisen–decarboxylation–aldol double cascade to a one-pot triple cascade in the Biginelli condensation. Indeed, a one-pot protocol for the synthesis of dihydropyrimidinone or dihydropyrimidinthione derivatives was successfully established. The examples were shown in Table 4. They were synthesized directly from commercially available starting materials in 50% to 88% yield. In this cascade reaction, two C–C bonds and two C–N bonds were formed while one C–C and one C–O bond were cleaved.

The triple cascade could also be applied to the synthesis of pyridazinone derivatives (Table 5), the immediate precursors to of the aforementioned ACAT inhibitors,[2] by a one-pot Claisen–decarboxylation–electrophilic substitution–hydrazidation cascade. Compared to the reported five-step procedures which gave a 2–13% overall yield, our synthesis represented a significant improvement in terms of the number of synthetic steps and overall yields achieved. For example, the one-pot protocol allowed for facile access to compound **7d** in 67% yield compared to 2% overall yield from the literature report.[2] As such, our method should enable convenient and thorough SAR studies for this scaffold by strategically replacing three aromatic substitutions on the pyridazinone heterocycle.

By using *ortho*-fluoro aromatic acids, various indazole analogues were also synthesized *via* the one-pot method involving a nucleophilic aromatic substitution (Table 6, **8a–8d**). It was found that a single step indazole cyclization of the corresponding ketone intermediate occurred most efficiently in pyridine. Thus pyridine was attempted to replace DMF as the solvent for the decarboxylation reaction. To our delight, the Claisen–decarboxylation also proceeded smoothly in pyridine, which was followed by the hydrazine ketone cyclization to render the one-pot indazole formation in more than 50% overall yield.[22] In addition, the use of Claisen–decarboxylation/copper-catalyzed cyclization of *ortho*-bromo aryl acetic acids enabled convenient synthesis of 2-aryl and 2-heteroaryl benzofurans in modest to good yields (Table 6, **9a–9e**). The cyclization was conducted in one pot using copper iodide and base after the completion of the decarboxylation.[23] In particular, **9a**, a natural product Stemofuran[24] analogue was obtained in 71% isolated yield. This one-pot protocol was well tolerated on scale-up. The synthesis of methyl

Table 6 One-pot synthesis of indazoles and benzofurans using a Claisen–decarboxylation–heteroatom cyclization cascade[a]



[a] Isolated yields after column chromatography.

stemofuran was scaled up in a multi-gram batch with an isolated yield of 66%.[25] Heterocycles, such as pyridine, were well tolerated for those cascades, which significantly broadened the scope and enhanced the value of these reactions in medicinal chemistry.

Conclusions

In summary, we have established a greener, multiple cascade reaction sequence to construct a wide variety of heterocyclic scaffolds of medicinal chemistry interest. In particular, a triple cascade allowed the one-pot synthesis of various heterocyclic scaffolds in good to high yields. One key step of the sequence is a convenient Claisen–decarboxylation cascade reaction that has enabled the synthesis of various diaryl ketones from easily accessible aryl acetic acids and methyl aryl esters. It was observed that an excess amount of base and a polar solvent such as DMF are preferable for reactions to complete within a reasonable time frame, and to give good and consistent yields. Taking advantage of the resulting enolates, double cascade reactions were achieved by sequential addition of various electrophiles. To avoid the detrimental effects of excess base towards electrophiles, water or alcohol can be added to quench the base before the addition of certain electrophiles. These one-pot multi-cascade reactions were in general very clean and simple flash column chromatography was sufficient to obtain analytically pure products. Compound decomposition during the last cyclization was the primary reason for the somewhat compromised isolated yields. Further extension of this methodology is currently ongoing and will be reported in due course.

Acknowledgements

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