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Novel one-pot synthesis of diverse γ,δ-unsaturated β-ketoesters by thermal cascade reactions of diazodicarbonyl compounds and enol ethers: transformation into substituted 3,5-diketoesters†

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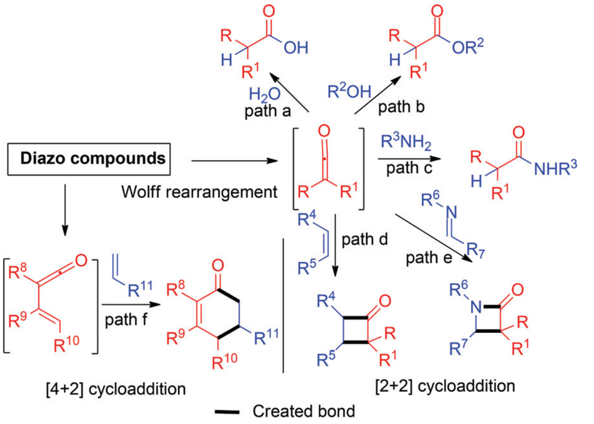
Sequential Wolff rearrangement of α-diazo-β-ketoesters followed by trapping of the ketene intermediates with enol ethers generated a variety of γ,δ-unsaturated β-ketoesters. This method involves a novel thermal cascade reaction and allows the synthesis of γ,δ-unsaturated β-ketoesters with *trans*-stereochemistry under catalyst-free conditions. The synthesized compounds were further transformed into novel 3,5-diketoesters, which were used for the synthesis of naturally occurring 2-pyrone and 1-naphthoic acid ester.

Introduction

Carbon–carbon bond formation is of great importance and a long-standing goal for synthetic chemists.[1] As versatile organic intermediates, ketenes provide an attractive and powerful means of chemical synthesis.[2] Ketenes, though unstable and usually generated *in situ* for trapping,[3] can serve as building blocks for the assembly of various organic materials.[4] In particular, the Wolff rearrangement is widely used for the preparation of reactive ketene intermediates (Scheme 1).[5]



Scheme 1 Reported reactions for the synthesis of various molecules *via* the Wolff rearrangement.

Ketenes have been used for the synthesis of a diverse selection of carboxylic acids, esters, and amides *via* nucleophilic addition on the sp-carbon of ketenes by water, alcohols, or amines (paths a–c).[6] Thermal, photochemical, and Lewis-acid promoted [2 + 2] cycloaddition reactions between ketenes and alkenes or imines give rise to a diverse range of cyclobutanones (path d) and β-lactams (path e).[7] Furthermore, cycloadditions between ketenes and olefins have been used to produce various cyclohexenones through [4 + 2] cycloadditions (path f).[8] However, although numerous [2 + 2] and [4 + 2] cycloaddition reactions between ketene intermediates and alkenes have been reported, no previous report has described the direct generation of unsaturated enones by nucleophilic attack of enol ethers to ketenes derived from diazodicarbonyl compounds.

γ,δ-Unsaturated β-ketoesters are widely used as important intermediates and building blocks in the synthesis of organic and natural products.[9] Multifunctionality in unsaturated ketoesters enables their consumption in the Robinson annulation, in the synthesis of the corresponding enamines, pyrones, and *trans*, *trans*-dienones, and in the preparation of substrates for the Diels–Alder reactions.[10]

The reported general methods for the synthesis of γ,δ-unsaturated β-ketoesters include the dianion reaction between phosphine oxides and ketones,[11] and coupling reaction between the magnesium complex of ethyl hydrogen malonate and acid chlorides.[12] Although several approaches have been reported for the synthesis of γ,δ-unsaturated β-ketoesters, they have a limitation due to the harsh reaction conditions required, low yields, and raw material availability.[13] In particular, there are a few reports on the synthesis of γ,δ-unsaturated β-ketoesters bearing an (*E*)-alkoxy group.[14] Accordingly, there is a demand for a facile one-step synthetic method for the

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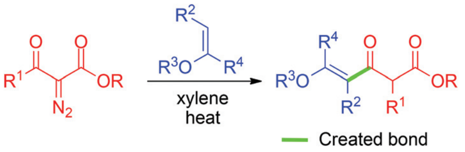


Scheme 2 Novel and efficient synthesis of γ,δ-unsaturated β-ketoesters by the thermal cascade reaction of acyclic diazodicarbonyls and enol ethers.

production of diverse γ,δ-unsaturated β-ketoesters under mild thermal conditions.

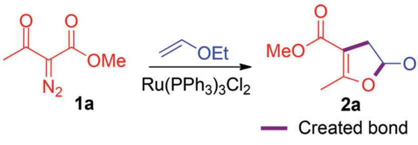
We have developed several methods based on rhodium(II)-catalyzed reactions between cyclic diazodicarbonyl compounds and substrates, such as ketones, isocyanates, nitriles, and halides, to generate a variety of 5-membered heterocycles[15] and α-haloenones.[16] In addition, we recently prepared novel and diverse cyclic β-enaminoamides[17] and indene derivatives[18] *via* the thermal Wolff rearrangement of cyclic diazo compounds.

During our continued studies on the development of new methodologies based on the Wolff rearrangement, we investigated thermal reactions between diazodicarbonyls and several enol ethers. Herein, we describe a novel and efficient one-pot synthesis of a variety of γ,δ-unsaturated β-ketoesters bearing an (*E*)-alkoxy group by thermal Wolff rearrangement of acyclic diazodicarbonyl compounds followed by nucleophilic addition of enol ethers to ketene intermediates (Scheme 2).

Results and discussion

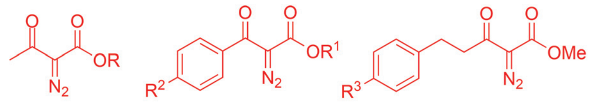
We have recently disclosed a [3 + 2] cycloaddition reaction of ruthenium-carbenoid generated from acyclic diazodicarbonyl **1a** with olefin (Scheme 3).[19] In this case, only dihydrofuran **2a** was produced in high yields and no other product associated with the Wolff rearrangement was obtained.

To investigate thermal reactions between acyclic diazodicarbonyls and enol ethers, three types of acyclic diazodicarbonyl compounds **1a–1i** bearing methyl, aryl, and phenethyl groups at C3 were prepared from the corresponding 1,3-dicarbonyl compounds in 81–98% yield, as previously described (Table 1).[20]



Scheme 3 Reported Ru(II)-catalyzed synthesis of dihydrofuran from acyclic diazodicarbonyls.

Table 1 Synthesized acyclic diazodicarbonyl compounds **1a–1i**

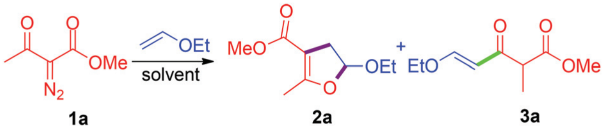


1a R = Me (95%)
1b R = Et (98%)
1c R = allyl (96%)

1d R^1 = Me, R^2 = H (89%)
1e R^1 = R^2 = Me (87%)
1f R^1 = Me, R^2 = OMe (86%)
1g R^1 = Et, R^2 = H (90%)

1h R^3 = Me (84%)
1i R^3 = OMe (81%)

Table 2 Thermal reactions of **1a** with ethyl vinyl ether under several solvents

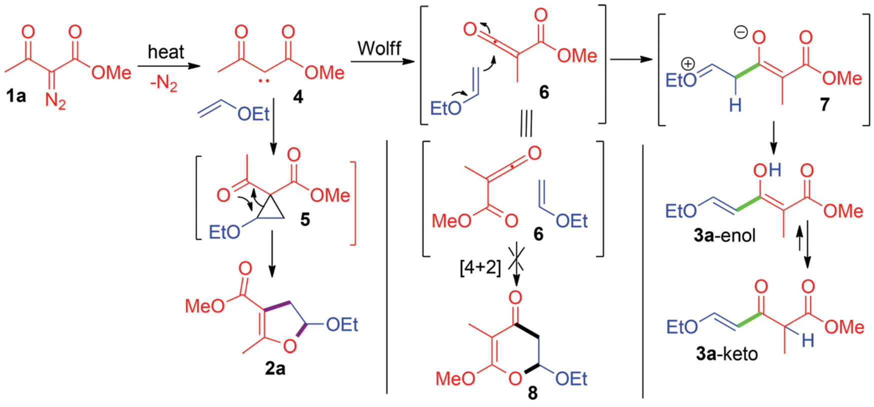


Entry	Solvent	Condition	Yield[a] (%)	
			2a	3a
1	Benzene	Reflux, 24 h	32	21
2	Toluene	Reflux, 24 h	5	51
3	*p*-Xylene	140 °C, 6 h	0	60
4	DMF	120 °C, 12 h	—	—[b]

[a] Isolated yield. [b] Unidentified complex mixtures. ▬ Created bond. ▬ Created bond.

Thermal reactions between acyclic diazodicarbonyl compound **1a** and ethyl vinyl ether were first investigated at different temperatures using different solvents. The results are summarized in Table 2. Treatment of **1a** with ethyl vinyl ether in refluxing benzene for 24 h gave the cycloadduct **2a** (32%) and the coupling product **3a** (21%) with the recovery of 35% of **1a** (entry 1), whereas that in refluxing toluene for 24 h provided products **2a** and **3a** in yields of 5 and 51%, respectively (entry 2). When the temperature was raised to 140 °C using *p*-xylene as a solvent for 6 h, the yield of compound **3a** was increased to 60% and interestingly **2a** was not observed (entry 3). However, reaction of **1a** in polar DMF at 120 °C for 12 h provided complex mixtures (entry 4). The structures of **2a** and **3a** were identified using spectral data. In the ^{1}H NMR of the cycloadduct **2a**, a methine, a methylene, and a methyl proton on the dihydrofuran ring showed peaks at δ 5.51 (1H, dd, *J* = 7.5, 3.0 Hz), 2.98 (1H, dd, *J* = 15.9, 7.5 Hz), 2.69 (1H, dd, *J* = 15.9, 3.0 Hz), and 2.20 (3H, s) ppm, respectively.[19] In CDCl$_3$ solution, compound **3a** exclusively exists in a keto form. In the ^{1}H NMR spectrum of **3a**, a methine proton flanked by two carbonyl groups showed a peak at δ 3.52 ppm as a quartet (*J* = 7.2 Hz) due to a keto form and there was no OH peak associated with an enol form. Its *trans*-stereochemistry was determined by analyzing coupling constants. The two vinylic peaks showed absorptions at δ 7.60 (1H, *J* = 12.3 Hz) and 5.65 (1H, *J* = 12.3 Hz). Further confirmation of the structures of **2a** and **3a** was obtained from ^{13}C NMR spectra. For **2a**, one carbonyl carbon of a conjugated ester on the dihydrofuran ring produced a peak at 166.1 ppm, whereas in **3a** the two carbonyl carbons of the enone and ester groups produced peaks at δ 194.5 and 171.6 ppm, respectively.

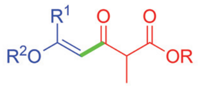
The formation of the dihydrofuran **2a** and the γ,δ-unsaturated β-ketoester **3a** is presumed to be initiated by the thermal



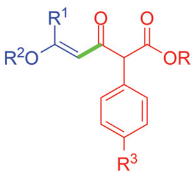
Scheme 4 Proposed mechanisms for formation of **2a** and **3a** from diazodicarbonyl compound **1a**.

decomposition of methyl 2-diazo-3-oxobutanoate (**1a**) to the corresponding carbene intermediate **4** *via* the initial loss of N$_2$ (Scheme 4).[21] Once formed, in refluxing benzene or toluene, carbene **4** would competitively undergo cyclopropanation with ethyl vinyl ether to give **5** or Wolff rearrangement to give ketene **6**. Ring opening of **5** followed by cyclization gives **2a**, whereas nucleophilic addition *via* attack of the vinyl group of the enol ether to ketene **6** afford the zwitterionic adduct **7**. The intermediate **7** would undergo further deprotonation and subsequent protonation to give **3a** as an enol form. During this step, the thermodynamically more stable *trans*-compound would be produced and finally the enol form would adopt the keto form due to a keto–enol tautomerism. Importantly, at high temperature, compound **3a** was only observed by a ketene formation followed by nucleophilic attack of an enol ether. Interestingly, it was reported by Wenkert that reaction of acyclic diazomalonaldehyde in refluxing *n*-butyl vinyl ether provides dihydro-4-pyrone in a good yield.[22] However, in this reaction, any possible adduct **8** *via* [4 + 2] cycloaddition was not formed.

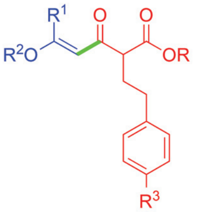
Table 3 Formation of γ,δ-unsaturated β-ketoesters by thermal decomposition of acyclic diazodicarbonyl compounds with enol ethers



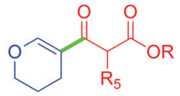
3b R = Me, R^1 = H, R^2 = *n*-Pr
(56%, keto:enol = 100:0)
3c R = Me, R^1 = H, R^2 = *n*-Bu
(45%, keto:enol = 100:0)
3d R = R^1 = R^2 = Me
(66%, keto:enol = 100:0)
3e R = Et, R^1 = H, R^2 = Et
(59%, keto:enol = 100:0)
3f R = Et, R^1 = R^2 = Me
(70%, keto:enol = 100:0)
3g R = allyl, R^1 = R^2 = Me
(76%, keto:enol = 100:0)



3h R = R^1 = R^2 = Me, R^3 = H
(66%, keto:enol = 90:10)
3i R = R^1 = R^2 = R^3 = Me
(70%, keto:enol = 88:12)
3j R = R^1 = R^2 = Me, R^3 = OMe
(69%, keto:enol = 92:8)
3k R = Et, R^1 = R^2 = Me, R^3 = H
(72%, keto:enol = 100:0)



3l R = R^1 = R^2 = R^3 = Me
(68%, keto:enol = 100:0)
3m R = R^1 = R^2 = R^3 = OMe
(61%, keto:enol = 100:0)



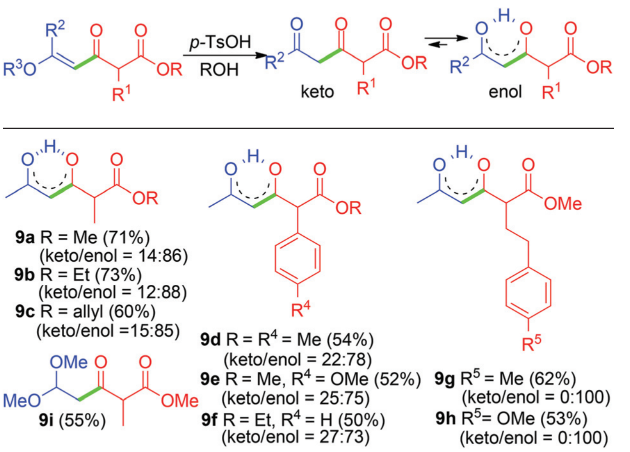
3n R = R^5 = Me
(58%, keto:enol = 100:0)
3o R = Et, R^5 = Ph
(61%, keto:enol = 100:0)

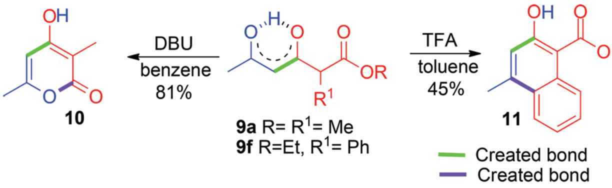
🟩 Created bond

After optimizing the reaction conditions, we explored the scope of thermal cascade reactions by employing three types of acyclic diazodicarbonyl compounds and enol ethers (Table 3). Several cascade reactions through the migration of methyl groups of diazodicarbonyl compounds **1a–1c** were first attempted. Reactions between methyl 2-diazo-3-oxobutanoate (**1a**) and *n*-propyl vinyl ether or *n*-butyl vinyl ether in refluxing *p*-xylene for 6 h provided the desired products **3b** and **3c** in yields of 56 and 45%, respectively. Treatment of **1a** with 2-methoxypropene in refluxing xylene for 6 h gave **3d** in 66% yield. Similarly, thermal reaction between ethyl 2-diazo-3-oxobutanoate (**1b**) or allyl 2-diazo-3-oxobutanoate (**1c**) furnished the desired products **3e–3g** in yields of 59–76%. To investigate the migratory aptitude of aryl groups, additional reactions of diazodicarbonyl compounds **1d–1g** were next carried out. Reactions between methyl 2-diazo-3-oxo-3-phenylpropanoate (**1d**) or methyl 2-diazo-3-oxo-3-arylpropanoates **1e–1f** bearing an electron donating group on the benzene ring and 2-methoxypropene provided the desired products **3h–3j** in yields of 66–70%. Similarly, reaction between ethyl 2-diazo-3-oxo-3-phenylpropanoate (**1g**) and 2-methoxypropene produced compound **3k** in 72% yield. To extend the utility of these cascade reactions, we performed further reactions using diazodicarbonyl compounds **1h–1i** bearing the phenethyl or 4-methoxyphenethyl group. Reactions between methyl 2-diazo-3-oxo-5-phenylpentanoate (**1h**) or methyl 2-diazo-5(4-methoxyphenyl)-3-oxopentanoate (**1i**) and 2-methoxypropene afforded **3l** (68%) and **3m** (61%) through the migration of the phenethyl or 4-methoxyphenethyl group. Interestingly, additional reactions between **1a** or **1g** and 2,3-dihydropyran produced **3n** and **3o** in yields of 58 and 61%, respectively. These results show that the reactions of various diazodicarbonyls bearing methyl, aryl, and phenethyl groups provided the desired products **3b–3o** in moderate yields through the migration of methyl, aryl, and phenethyl groups followed by the addition of vinyl ethers. All products were characterized by spectral analysis and **3b–3g**, **3k**, and **3l–3o** exist exclusively as keto tautomers (in $CDCl_3$ solution).

To examine the potential use of the γ,δ-unsaturated β-ketoesters synthesized by the nucleophilic addition of enol ethers to ketene intermediates, we envisioned that the synthesized enones could be utilized to produce 3,5-diketoesters. Molecules bearing 3,5-diketoesters are found in a variety of biologically active natural polyketides[23] and are important starting materials and building blocks for the synthesis of polyols.[24] Representative synthetic approaches for 3,5-diketoesters include the condensations of 1,3-dicarbonyl dianions with esters, Weinreb amides, chloroacetates, or other acylating agents.[25] In addition, 3,5-diketoesters have also been prepared by the condensation of 1,3-bis(silyl enol ethers) with acid chlorides[26] and by reaction between 1-methoxy-1,3-bis(trimethylsiloxy)-1,3-butadiene and acetyl chloride.[27] Based on these precedents, conversion of the synthesized γ,δ-unsaturated β-ketoesters to 2-substituted 3,5-diketoesters was attempted using *p*-TsOH as a Brønsted acid. Results are summarized in Table 4. Methanol, ethanol, and allyl alcohol were used as solvents to avoid transesterification. Reaction of **3d** in the presence of 1.0 equivalent of *p*-TsOH in refluxing methanol for 10 h afforded **9a** (71%), whereas reactions of **3f** and **3g** in refluxing ethanol or allyl alcohol resulted in **9b** and **9c** at yields of 73 and 60%, respectively. Similarly, when γ,δ-unsaturated β-ketoesters **3i–3k** bearing phenyl or aryl groups were used, compounds **9d–9f** were obtained at yields of 50–54%, whereas when **3l–3m** bearing arylethyl groups at the C2-position were used, the desired products **9g–9h** were isolated at yields of 62 and 53%, respectively. The synthesized compounds **9a–9h** were characterized by spectral analysis and were found to exist predominantly as the enol tautomers. For example, in the ^1H NMR spectrum of **9a**, a methine proton flanked by 1,3-dicarbonyl groups showed a peak at δ 3.34 ppm as a quartet (J = 7.2 Hz) and a vinyl proton on C4 due to an enol form showed a peak at 5.46 ppm as a singlet. The ratio of a keto/enol (= 14 : 86) tautomer was calculated by the integration of a methyl peak on C5. However, reaction of **3a** in the presence of 1.0 equivalent of *p*-TsOH in refluxing methanol for 12 h provided **9i** (55%) through acetal formation from reactive aldehyde.

Table 4 Synthesis of 3,5-diketoesters from the corresponding γ,δ-unsaturated β-ketoesters





Scheme 5

3,5-Diketoesters were also used to synthesize a known natural pyrone and a novel β-naphthol derivative, as shown in Scheme 5. Reaction of **9a** with DBU in refluxing benzene for 1 h provided the naturally occurring methyltriacetic lactone **10** (or USF 2550A; 81%), which was isolated from *Penicillium stipitatum*,[28] *via* condensation and an enolization, and treatment of **9f** with 1.0 equivalent of TFA in refluxing toluene for 12 h gave functionalized 1-naphthoic acid ester **11** *via* an intramolecular Friedel–Crafts reaction at a yield of 45%.

Conclusions

In summary, we describe a novel one-pot approach for the synthesis of γ,δ-unsaturated β-ketoesters based on thermal cascade reactions between α-diazo-β-ketoesters and enol ethers. This catalyst-free reaction allows the synthesis of various *trans*-γ,δ-unsaturated β-ketoesters and could be used to synthesize natural products and pharmaceuticals. Further expansion of the scope of this reaction using other nucleophilic components in the presence of Lewis acid catalysts is in progress.

Acknowledgements

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