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Efficient oxidation-Wittig olefination-Diels–Alder multicomponent reactions of α-hydroxyketones

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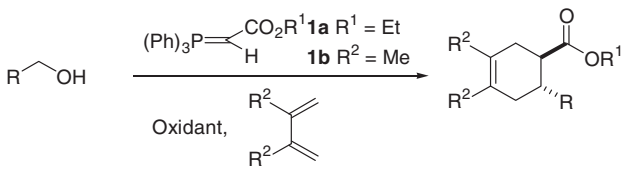
ABSTRACT

α-Hydroxyketones undergo efficient tandem oxidation-Wittig olefination reactions in the presence of an oxidant to produce high yields of γ-ketocrotonate products. On carrying out the oxidation-Wittig olefination reaction in the presence of 2,3-dimethyl-1,3-butadiene, a novel multicomponent reaction sequence provides access to cycloadducts in high yield.

There has been considerable interest in reaction processes that efficiently create complex structures from simple reactants through one-pot operations, which has led to significant advances in the areas of multicomponent processes (MCRs), domino reactions, combinatorial chemistry and sequential/tandem transformations.[1] This interest has primarily been stimulated by the requirement to generate diverse libraries of heterocyclic compounds for drug discovery applications, and a number of innovative approaches have been described.[2] The incorporation of cycloaddition reactions into MCR strategies is a highly attractive proposition for the rapid generation of molecular complexity, as multiple bonds are formed in a single step, and indeed, a number of MCR strategies incorporating intramolecular Diels–Alder reactions have been described, particularly for heterocycle formation.[3] It is surprising that the inclusion of intermolecular Diels–Alder reactions into MCR sequences has attracted less interest,[4] especially given the opportunities for introducing high levels of skeletal and stereochemical complexity. As part of an ongoing programme concerned with the development of efficient routes to heterocyclic natural products,[5] we envisioned that the exploitation of such methodology would provide a potentially rapid and highly flexible route for the construction of a variety of highly functionalised cyclic structures. With this in mind, we explored a MCR strategy in which construction of the dienophile component was achieved employing a tandem oxidation-Wittig olefination strategy, which subsequently underwent Diels–Alder cycloaddition in the presence of a diene (Scheme 1).

A number of groups have reported the successful development of tandem protocols for the direct transformation of alcohols into olefins employing stabilised ylides in the presence of an oxidant.[6] These protocols not only lead to increases in efficiency, but are especially useful when applied to carbonyl compounds that are difficult to isolate due to their instability, toxicity or volatility. Singly activated dienophiles, such as ethyl cinnamate, are easily constructed using this approach, but cycloaddition employing these materials typically require prolonged reaction times at very high temperatures or high pressures in order to achieve acceptable yields.[7] Indeed, in our hands, this dienophile produced no cycloadduct products under a variety of reaction conditions when generated from benzyl alcohol in the presence of manganese dioxide, ylide **1a** and 2,3-dimethyl-1,3-butadiene. We, therefore, considered alternative dienophile candidates, such as γ-ketocrotonates, which being doubly activated, are more reactive in Diels–Alder cycloadditions and so require milder reaction conditions. The inclusion of additional functionality into the dienophile component has the additional benefit that it provides cycloadducts which are highly attractive advanced intermediates for subsequent elaboration into a range of natural products including anthraquinones and hydrindane targets.[7a,8] The synthesis of γ-ketocrotonates from the corresponding α-ketoaldehydes, has been reported to be problematic due the high reactivity of the aldehyde carbonyl group which leads to facile hydration, aerial oxidation or polymerisation reactions.[9] Their synthesis, however, has been described from α-hydroxyketones, such as hydroxyacetophenone **2** and hydroxyacetone **3**, employing a tandem oxidation-Wittig approach.[10]

In order to establish conditions for our proposed MCR, we initially concentrated our efforts on the critical cycloaddition component in order to ensure compatibility with the oxidation-Wittig sequence. Thus, γ-ketocrotonate **4a**, produced from hydroxyaceto-



Scheme 1.

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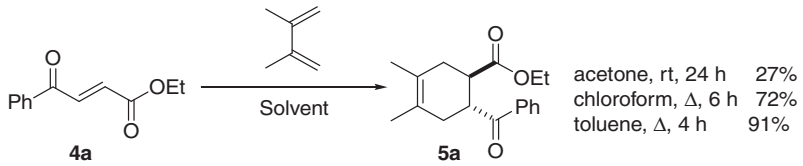


Scheme 2.

phenone **2**,[10] was reacted with 2,3-dimethyl-1,3-butadiene under a variety of reaction conditions (Scheme 2), of which, toluene at reflux proved to be most efficient giving an excellent yield of the cycloadduct **5a**.

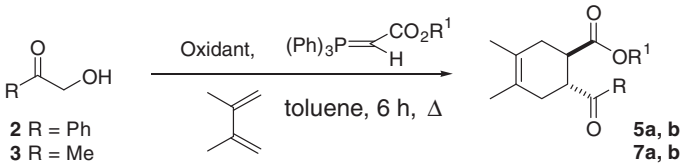
With conditions for the cycloaddition in place, we next studied the MCR of **2** with ylides **1a** and **1b** in the presence of activated MnO_2 and an excess of 2,3-dimethyl-1,3-butadiene, and were delighted to observe that these substrates underwent an efficient oxidation-Wittig olefination-Diels–Alder sequence to produce cycloadducts **5a** and **5b** in high isolated yield (Table 1, entries 1 and 2). The reaction was also achieved in a sequential, one-pot approach, in which the diene component was added to the reaction mixture on completion of the oxidation-Wittig olefination sequence. Disappointingly, however, only poor yields of cycloadduct **7a** were isolated from the reaction of hydroxyacetone **3** and ylide **1a** in the presence of 2,3-dimethyl-1,3-butadiene under these reaction conditions (entry 3).

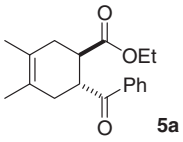
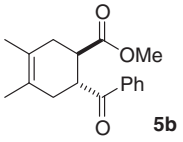
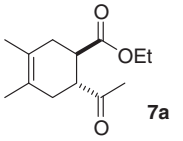
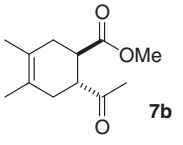
^{1}H NMR analysis of the crude reaction mixtures indicated that these low isolated yields of cycloadduct were explained by poor conversion of **3** under these reaction conditions leading us to consider alternative oxidising agents. We have previously reported that employing less activate grades of MnO_2 can be highly beneficial in MnO_2-mediated tandem oxidation-Wittig sequences producing improved yields, especially where the starting material or product is prone to decomposition.[11] Replacing the activated grade oxidant with MnO_2 of particle sizes <10 μm, however, gave no significant improvement in the formation of **6a** (Table 2, entry 1). We next considered the use of silica-supported pyridinium chlorochromate (PCC), a reagent that has been successfully employed in sequential and tandem oxidation-Wittig sequences.[5b,6h] In light of the fact that there have been no previous examples of its use in tandem processes employing α-hydroxyketones, we first undertook a short study to assess the suitability of this reagent with these substrates (Table 2). We were delighted to observe that, in the presence of excess silica-supported PCC, sodium acetate and ylide **1a**, excellent yields of **6a** were achieved under a range of reaction conditions (Table 2, entries 2–4). Importantly, the tandem oxidation-Wittig olefination sequence proceeded readily when carried out at the elevated temperatures required for efficient cycloaddition reaction (Table 2, entry 4). Application of these modified reaction conditions to the oxidation-Wittig olefination reaction of **2** also proved to be successful, giving **4a** in high isolated yield (Table 2, entry 5).[12]

Finally, we investigated the multicomponent reactions of α-hydroxyketones **2** and **3** under our modified PCC-mediated conditions[13] and were satisfied to observe that both alcohols underwent highly efficient oxidation-Wittig olefination-Diels–Alder sequences to give cycloadducts **5a** and **5b** (Table 1, entries 4 and 5) and **7a** and **7b** (entries 6 and 7) in high isolated yields.[14] This novel sequence allows for the efficient formation of multiple carbon–carbon bonds in a simple, three-component, one-pot operation.

In conclusion, we have demonstrated that α-hydroxyketones undergo efficient tandem oxidation-Wittig olefination reactions in the presence of silica-supported PCC to produce high yields of

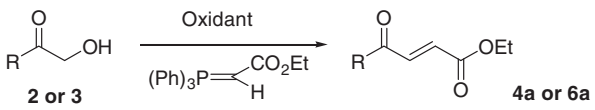
Table 1
Multicomponent oxidation-Wittig olefination-Diels–Alder reactions of α-hydroxyketones



Entry	Alcohol	Ylide	Oxidant	Product[a]	Yield[b] (%)
1	**2**	**1a**	MnO_2	 **5a**	76 80[c]
2	**2**	**1b**	MnO_2	 **5b**	70
3	**3**	**1a**	MnO_2	 **7a**	11
4	**2**	**1a**	PCC	**5a**	82 85[c]
5	**2**	**1b**	PCC	**5b**	77
6	**3**	**1a**	PCC	**7a**	82 71[c]
7	**3**	**1b**	PCC	 **7b**	67

[a] All products gave satisfactory spectroscopic data.
[b] Yields refer to isolated purified yields of isomer shown.
[c] Diene component added on completion of the oxidation-Wittig-olefination reaction.

Table 2
PCC-mediated oxidation of α-hydroxyketones **2** and **3**



Entry	Reaction conditions	Yield[a] (%)
1	**3**/MnO_2 (<10 μm)/toluene/Δ	Trace[b]
2	**3**/PCC-NaOAc/CH_3Cl/Δ4 h	75
3	**3**/PCC-NaOAc/toluene/rt/24 h	78
4	**3**/PCC-NaOAc/toluene/Δ3 h	86
5	**2**/PCC-NaOAc/toluene/Δ3 h	81[c]

[a] Reactions produced ~5% *Z*-isomer.
[b] Determined from ^{1}H NMR analysis of the crude reaction mixture.
[c] Product is **4a**.

γ-ketocrotonate products. On carrying out this oxidation-Wittig olefination sequence in the presence of 2,3-dimethyl-1,3-butadiene, a novel multicomponent reaction protocol can be achieved in which the γ-ketocrotonates, once formed, undergo efficient Diels–Alder reaction giving cycloadducts in high yield. The simplicity and convenience of this MCR protocol, and its efficiency in creating skeletal and stereochemical complexity in a single operation, provides ready access to functionalised cyclic building blocks that can be elaborated into complex structural motifs found in a range of natural products.

Acknowledgements

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12. *Typical procedure for the tandem oxidation/Wittig reaction of hydroxyacetone* ***3*** *using silica-supported PCC/NaOAc*: Hydroxyacetone (143 mg, 1.93 mmol) was added to a solution of silica-supported PCC (830 mg, 3.85 mmol, ground with 2 wt equiv of silica), NaOAc (316 mg, 3.85 mmol) and (carbethoxymethylene)-triphenylphosphorane **1a** (1.68 g, 4.8 mmol) in $CHCl_3$ (15 mL) and stirred at reflux for 4 h. The reaction mixture was then cooled to room temperature and filtered through a Celite pad which was washed with additional $CHCl_3$ (2×10 mL). The combined solvents were then removed to give a yellow oil which was purified by column chromatography (hexane→5% EtOAc/hexane) to give (*E*)-ethyl 4-oxo-2-pentenoate **6a**[15] as a yellow oil (206 mg, 75%); ν_{max} (film)/cm^{-1}, 2985, 1721, 1701, 1290, 1182, 978, 869, 587; ^1H NMR (400 MHz; $CDCl_3$) δ = 6.95 (1H, d, *J* = 16 Hz), 6.55 (1H, d, *J* = 16 Hz), 4.22 (2H, q, *J* = 7 Hz), 2.30 (3H, s), 1.25 (3H, t, *J* = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.0, 165.9, 140.3, 132.0, 61.8, 28.5, 14.5; MS (ES, NH_3) *m/z* 143 $(M+H)^+$, HRMS (ES, NH_3) calcd for $C_7H_{11}O_3$ $(M+H)^+$, 143.0703 $(M+H)^+$, found $(M+H)^+$ 143.0704.
13. The possibility that the Diels–Alder cycloaddition is catalysed by the presence of silica or a metal species derived from PCC or MnO_2 cannot at this time be ruled out. Studies to clarify this point and to assess the potential of Lewis acid catalysis of the cycloaddition step are ongoing. For studies on the beneficial role of silica on Diels–Alder reactions, see: (a) Cunningham, I. D.; Crawley, V. *J. Mol. Catal. A* **2009**, *301*, 47–51; (b) Okamura, H.; Iiji, H.; Hamada, T.; Iwagawa, T.; Furuno, H. *Tetrahedron* **2009**, *65*, 10709–10714; (c) Veselovsky, V. V.; Gybin, A. S.; Lozanova, A. V.; Molseenkov, A. M.; Smit, W. A. *Tetrahedron Lett.* **1998**, *29*, 175–178; For Cr(III) and Mn(II) catalysed Diels–Alder cycloadditions see: (d) Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6043–6046; (e) Phomkeon, K.; Takemoto, T.; Ishima, Y.; Shibatomi, K.; Iwasa, W.; Nishiyama, H. *Tetrahedron* **2008**, *64*, 1813–1822.
14. *Typical procedure for the MCR of* ***3*** *in the presence of silica-supported PCC/NaOAc*: Hydroxyacetone (210 mg, 2.8 mmol) was added to a solution of 2,3-dimethyl-1,3-butadiene (700 mg, 8.2 mmol), silica-supported PCC (1.22 g, 5.7 mmol, ground with 2 wt equiv of silica), NaOAc (465 mg, 5.68 mmol) and (carbethoxymethylene)triphenylphosphorane **1a** (2.47 g, 7.1 mmol) in toluene (15 mL) and stirred at reflux for 6 h. The reaction mixture was then cooled to room temperature and filtered through a Celite pad which was washed with additional toluene (2×10 mL). The combined solvents were removed to give a yellow oil which was purified by column chromatography (hexane→5% EtOAc/hexane) to give ($1R^*,2R^*$)-ethyl 2-acetyl-4,5-dimethylcyclohex-4-enecarboxylate **7a**[16] as a yellow oil (514 mg, 82%); ν_{max} (film)/cm^{-1}; 2913, 1727, 1712, 1231, 1179, 1155, 1032, 616; ^1H NMR (400 MHz; $CDCl_3$) δ = 4.10 (2H, q, *J* = 7 Hz), 2.90 (1H, dt, *J* = 11 and 5 Hz), 2.70 (1H, dt, *J* = 11 and 5 Hz), 2.25–1.80 (4H, m), 2.15 (3H, s), 1.55 (6H, s), 1.15 (3H, t, *J* = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.0, 175.2, 124.3, 123.6, 60.5, 49.0, 41.8, 34.3, 33.8, 29.0, 18.7, 18.6, 14.2; MS (CI, NH_3) *m/z* 225 $(M+H)^+$, HRMS (ES, NH_3) calcd for $C_{13}H_{21}O_3$ 225.1485 $(M+H)^+$, found $(M+H)^+$ 225.1484.
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