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Microwave-assisted, regioselective, Petasis olefination of unsymmetrical oxalates. Formation of pyruvate-based enol ethers and enamines

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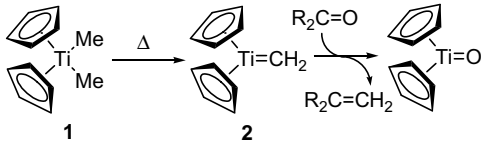
Abstract—The Petasis olefination of unsymmetrical oxalates and oxalate monoesters/monoamides (*tert*-$BuO_2CC(O)X$, where X = OR, NR_2) is highly regioselective and provides pyruvate-based enol ether and enamine derivatives. The olefination step occurs under conventional thermal conditions, but is dramatically improved—shorter reaction times and higher yields—when promoted by microwave irradiation.

The olefination of a carbonyl compound to an alkene is a versatile and important reaction. There are many methods applicable to both ketones and aldehydes, such as the Wittig and Wadsworth–Horner–Emmons reaction, however these protocols are unable to achieve an analogous olefination transformation on carboxylic acid derivatives.[1]

Tebbe et al.[2] discovered that a complex derived from titanocene dichloride and trimethylaluminium also olefinates carbonyl compounds.[3,4] This reagent reacts efficiently with ketones and aldehydes as well as amides, but is less effective with esters and thioesters. Petasis subsequently developed a solution to this latter problem using dimethyl titanocene **1** (the Petasis reagent).[5] This reagent undergoes thermal α-elimination to afford a titanium alkylidene complex (Schrock carbene) **2**,[6] which is the active species in the olefination process (Scheme 1).



Scheme 1.

The Petasis reagent has several advantages over related Ti-based systems being easy to prepare, relatively air and moisture stable, and may be safely synthesised on a large scale.[7] However, less is known about the ability of this reagent to distinguish between related functional groups. Ester discrimination is especially useful and earlier work has demonstrated the ability of this reagent to select between an acetate and a pivalate,[8,9] and a formate will react in preference to a sterically congested ethyl ester.[10] We required pyruvate-based enol ethers (e.g., **4a**), for which current preparative methods are somewhat limited. Alkylation of a pyruvic acid derived enolate (a dianion) does provide access to the *O*-methylated and ethylated enol ethers, but this method requires highly reactive alkylating agents and is not generally applicable.[11] Alternatively, conversion of ethyl pyruvate to the corresponding ketal followed by thermolysis (to induce elimination of ROH) does provide the corresponding enol ether.[12] While effective for simple alcohols, acid sensitive functionalities are not tolerated, and a minimum of 2 equiv of the alcohol component are required initially.

As a result, we have developed a new method for the formation of pyruvate-based enol ethers, which tolerates acid sensitive functionality and requires only 1 equiv of alcohol. This procedure exploits the low reactivity generally shown by the Petasis reagent towards sterically hindered

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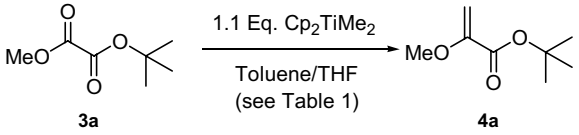
sites, which allows for the ready monoolefination of unsymmetrical oxalates. A similar procedure applied to oxalate monoamides provides the corresponding pyruvate-based enamines.[13]

Methyl *tert*-butyl oxalate **3a** offers a very significant difference in steric demand between the competing ester moieties. Initial experiments used 1.1 equiv of Petasis reagent **1** to favour selective monoolefination and to limit possible side reactions. Petasis reactions on α,β-unsaturated systems are possible[14] and while *tert*-alkyl esters are less reactive, these systems are not inert to related Ti-based reagents. For example, the Tebbe reagent has been reported to react with *tert*-alkyl esters,[15a–c] and the Takai reagent is also known to olefinate *tert*-butyl esters.[15d]

Using 1.1 equiv of **1** (as a solution in THF/toluene), reaction with **3a** proceeded slowly reaching only 43% conversion after 24 h at 65 °C (Scheme 2). Prolonged reaction times and elevated temperatures did drive this process to completion (see Table 1), however this highlighted a potential problem for more hindered and consequently less reactive substrates.

To date, there are no reports of the use of microwaves to accelerate titanium-mediated olefination reactions. However, the microwave-assisted Wittig olefination has been described[16] and recently Wipf has exploited microwave acceleration in the area of hydrozirconation chemistry.[17] Under microwave conditions, olefination of **3a** with **1** (1.1 equiv) proceeded at a dramatically increased rate, and complete conversion of **3a** to **4a** was achieved after only 30 min.[18]

A series of related esters and amides **3b–f** were then subjected to both conventional (thermal) and microwave-assisted olefination reaction conditions identified in Table 1 in order to generate the corresponding enol ethers and enamines **4b–f** (Scheme 3). Under the thermal conditions that allowed for complete conversion of



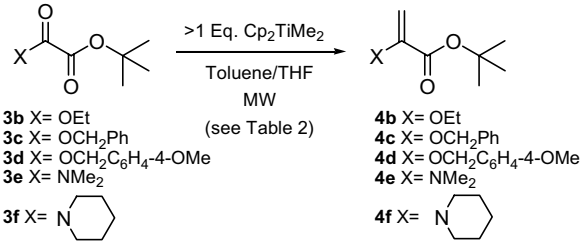
3a **4a**

Scheme 2.

Table 1. Petasis olefination of methyl *tert*-butyl oxalate

Entry	Temperature (°C)	Time	Conversion[a]
1	65	24 h	43
2	75	24 h	71
3	65	48 h	85
4	75	48 h	100
5[b]	150	30 min	100

[a] Conversion of **3a** (and the solution yield of **4a**) was determined by ^{1}H NMR using 4,4′-bis(*tert*-butyl)biphenyl as an internal standard, which was present through the olefination process.
[b] Microwave conditions: 150 W, sealed tube.



Scheme 3.

methyl ester **3a**, these other substrates were significantly less reactive. Only partial conversion of esters **3b–d** was observed after 24 h (using 1.1 equiv of **1**) and amides **3e** and **3f** did not react at all. When microwave-assisted conditions were applied to these less reactive substrates, the extent of conversion and reaction rate were both enhanced significantly. Nevertheless even after prolonged reaction times under these conditions, complete conversions were not possible with decomposition of both starting material and product being observed. This problem was solved by simply increasing the number of equivalents of the Petasis reagent used, with up to 3 equiv of **1** leading to short reaction times and complete consumption of the starting material. An additional consequence of shorter reaction times was reduced levels of decomposition and cleaner reaction mixtures from which generally good yields of products **4b–f** were isolated (Table 2).

Interestingly, no products resulting from further reaction of the *tert*-butyl ester moiety associated with **4** were observed even in the presence of 3 equiv of **1**. This is noteworthy in light of earlier reports on the known reactivity of *tert*-alkyl esters towards Ti-based olefinating agents.[15]

The isolation of enamines **4e**[19] and **4f** derived from amide substrates **3e** and **3f** proved problematic. These products were very sensitive to chromatography (using either base-washed silica gel or neutral alumina) and the preferred method for isolation was bulb-to-bulb distillation directly from the titanium residues. The only

Table 2. Microwave-assisted Petasis olefination of **3b–f**[a]

Substrate	Equiv of **1**[18] (reaction time)	Product	Isolated yield (solution yield)
3b	3 (0.5 h)	**4b**	70 (100)
3c	3 (1 h)	**4c**	80 (100)
3d	1.5 (2 h)	**4d**	82[b]
3e	3 (3 h)	**4e**[19]	20 (100)[c]
3f	3 (1.5 h)	**4f**	52[b]

[a] Microwave-assisted reactions were carried out either in a sealed tube or under 'open vessel' conditions and on a 50 mg scale unless otherwise noted.[20]
[b] These yields correspond to reactions of **3d** and **3f** on a 3.75 mmol scale and experimental details for these preparative scale procedures are described in this paper.[21]
[c] Isolation of **4e** was problematic—see text—and this is reflected in the low isolated yield, although the corresponding solution yield was high.

limitation on this isolation method is that it is inevitably less efficient on small scale,[20] but remains attractive and feasible for larger scale operation.[21]

In conclusion, we have developed a novel and highly selective route to pyruvate-based enol ethers and enamines. A *tert*-butyl residue acts as an effective protecting group for one carboxylate moiety, which is rendered unreactive towards **1**, even under relatively forcing conditions. The Petasis olefination is particularly amenable to microwave assistance, showing a large increase in rate of reaction without loss of selectivity or yield.

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18. Dimethyl titanocene **1** (as a 10% w/w solution in THF/toluene, 0.48 M) was prepared and standardised as described earlier.[7a] All novel compounds were fully characterised with the exception of **4a** which was highly volatile and proved difficult to isolate free of solvent. As a result, only a solution yield of **4a** was determined.
19. Arnold, Z. *Synthesis* **1990**, 39, Enamine **4e** was previously prepared under Lewis acid-mediated conditions, but the sensitive nature of this enamine required the use of $AsCl_3$ (66 mol %) as a very mild Lewis acid. This procedure clearly raises issues associated with toxicity and scale up.
20. Representive microwave conditions using a sealed tube: *tert*-butyl-*N*,*N*-dimethylamino oxalate **3e** (50 mg, 0.265 mmol) and dimethyl titanocene **1** (165 mg, 1.65 mL, 0.795 mmol, 0.48 M in THF/toluene, 3.0 equiv) were heated in a sealed tube at 150 °C (ca. 40 psi, 150 W) using a CEM DISCOVERY Synthesisor for 1.5 h. (After this time, complete conversion of **3e** to **4e** was observed by ^{1}H NMR using 4,4′-bis(*tert*-butyl)biphenyl as an internal standard). To the resulting dark red solution was added hexane (2 cm^3) and the mixture was filtered through Celite and concentrated carefully in vacuo. Subsequent purification of the residue by Kugelrohr distillation apparatus gave **4e** (15 mg, 20%) as a colourless oil. All spectroscopic data were consistent with that reported by Arnold.[19]Representive thermal (nonmicrowave-assisted) conditions: *tert*-butyl-*N*,*N*-dimethylamino oxalate **3e** (50 mg, 0.265 mmol) and dimethyl titanocene **1** (165 mg, 1.65 mL, 0.795 mmol, 0.48 M in THF/toluene, 3.0 equiv) were heated at 75 °C for 24 h. Product **4e** was isolated as described above and in a similar yield.
21. Representive preparative scale reactions under microwave-assisted conditions using an open 50 cm^3 RB flask and a CEM DISCOVERY Synthesisor:
(a) Preparation of enol ether **4d**: 4-methoxybenzyl-*tert*-butyl oxalate **3d** (1 g, 3.75 mmol) was treated with dimethyl titanocene **1** (1.18 g, 11.9 mL, 5.7 mmol, 0.48 M in THF/toluene, 1.5 equiv) under open vessel microwave mediated conditions (2 h, 150 W, 120 °C, atmospheric pressure). The solution was then cooled to room temperature and hexane (20 mL) was added. The resulting precipitate was filtered through a plug of Celite and the filtrate concentrated in vacuo. The resulting dark red residue was then purified by filtration through silica gel (using 9:1 hexane–ethyl acetate) to afford *tert*-butyl-2-(4-methoxybenzyloxy)-2-propenoic acid ester **4d** (0.81 g, 82%) as a colourless oil: R_f 0.55 (8:2 hexane–ethyl acetate); ν_{max} (thin film)/cm^{-1} 2982w (C–H), 1715s (C=O), 1614m, 1514m; δ_H ($CDCl_3$, 400 MHz): 7.32 (2H, d, J = 9.0 Hz, *H*Ar), 7.89 (2H, d, J = 9.0 Hz, *H*Ar), 5.29 (1H, d, J = 2.5 Hz, C=CH_2), 4.77 (2H, s, OCH_2Ar), 4.62 (1H, d, J = 2.5 Hz, C=CH_2), 3.80 (3H, s, OCH_3), 1.53 (9H, s, OC(CH_3)$_3$); δ_C ($CDCl_3$, 100 MHz): 162.2 (*C*=O), 159.4 (CH_2=*C*), 152.2, 129.0, 128.4 and 114.0 (*C*Ar), 94.0 (C=*C*H_2), 81.7 (O*C*(CH$_3$)$_3$), 70.1 (O*C*H_2Ar), 55.3 (O*C*H_3), 28.1 (OC(*C*H_3)$_3$); HRMS (CI) $C_{15}H_{21}O_4$: $[M+H]^+$ requires 265.1440. Found 265.1441.
(b) Preparation of enamine **4f**: Piperidino *tert*-butyl oxalate **3f** (800 mg, 3.75 mmol) was treated with Cp_2TiMe_2 **1** (2.34 g, 23.5 mL, 11.27 mmol, 0.48 M in THF/toluene, 3.0 equiv) under open vessel microwave mediated conditions (3 h, 150 W, 120 °C, atmospheric pressure). The solution was cooled to room temperature and the solvent removed in vacuo. The product was then distilled (using a Kugelrohr distillation apparatus) directly

from the titanium residues to give *tert*-butyl-2-piperidino-2-propenoic acid ester **4f** (0.411 g, 52%) as a colourless oil: ν_{max} (thin film)/cm^{-1} 1718s (C=O), 1599m; δ_H ($CDCl_3$, 400 MHz) 5.03 (1H, s, C=CH_2), 4.47 (1H, s, C=CH_2), 2.82 (4H, t, *J* 5.5, 5.5 Hz, N(CH_2)$_2$), 1.70–1.50 (6H, m, (CH_2)$_3$), 1.52 (9H, s, OC(CH_3)$_3$); δ_C ($CDCl_3$, 100 MHz) 165.4 (*C*=O), 150.6, (CH_2=*C*), 98.5 (*C*H_2=C), 81.3 (O*C*(CH$_3$)$_3$), 50.5 (N(*C*H_2)$_2$), 28.1 (OC(*C*H_3)$_3$), 25.7 and 24.3 (*C*H_2)$_3$. Anal. Calcd for $C_{12}H_{21}NO_2$ requires C, 68.21; H, 10.02; N, 6.63. Found: C, 68.02; H, 10.20; N, 6.35.