

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

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Received 20 September 2004; revised 1 November 2004; accepted 9 November 2004

Available online 30 November 2004

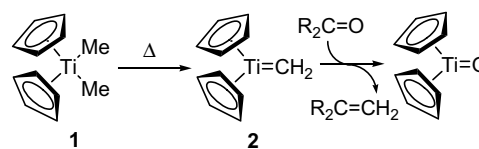
Abstract—The Petasis olefination of unsymmetrical oxalates and oxalate monoesters/monoamides (*tert*-BuO₂CC(O)X, where X = OR, NR₂) is highly regioselective and provides pyruvate-based enol ether and enamine derivatives. The olefination step occurs under conventional thermal conditions, but is dramatically improved—shorter reaction times and higher yields—when promoted by microwave irradiation.

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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).

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 ear-



Scheme 1.

lier 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

Keywords: Petasis reagent; Olefination; Pyruvates; Enamines; Enol ethers.

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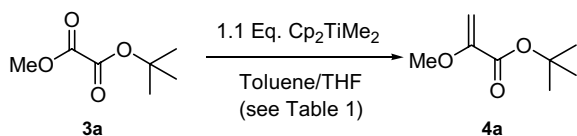
sites, which allows for the ready monoolefination of unsymmetrical oxalates. A similar procedure applied to oxalate monoamides provides the corresponding pyruvate-based enamines.¹³

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 possible¹⁴ 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 described¹⁶ 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



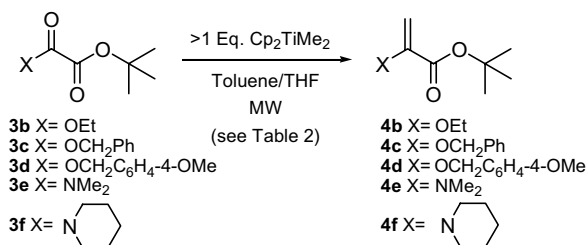
Scheme 2.

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 ¹H 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.

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