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METHYLENATIONS OF HETEROATOM-SUBSTITUTED CARBONYLS WITH DIMETHYL TITANOCENE

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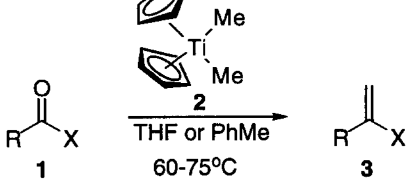
Abstract: Reaction of dimethyl titanocene with a variety of heteroatom-substituted carbonyl compounds, including: silylesters, anhydrides, carbonates, amides, imides, thioesters, selenoesters and acyl silanes gives the corresponding heteroatom-substituted alkenes.

We have recently reported that dimethyl titanocene (**2**), easily prepared from titanocene dichloride and methyllithium, is a convenient reagent for the methylenation of carbonyl compounds, including aldehydes, ketones, esters and lactones.[1] This process was also demonstrated with other dialkyl titanocenes[2] and has already found several synthetic applications by us[3] and others.[4] Herein we report additional studies involving the reaction of **2** with a variety of hetero-substituted carbonyl compounds (**1c-j**). The ability of this reagent to methylenate these types of carbonyls allows a facile entry to various synthetically useful hetero-substituted olefins (**3**).[5]

(1)

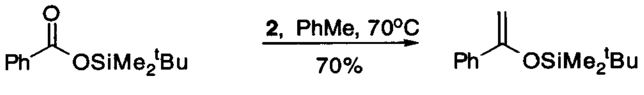


a, X = H
b, X = R', Ar
c, X = OR'
d, X = OSi^tBuMe_2
e, X = OCOR'
f, X = NR_2'
g, X = N(R')COR
h, X = SR'
i, X = SeR'
j, X = $SiMe_3$

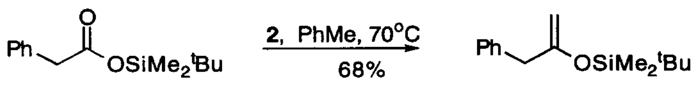
These reactions proceed by a simple heating at 60-75°C of a mixture of **2** and the carbonyl substrate in THF or toluene. Upon completion of the reaction the crude product can be isolated by evaporation of the solvent, precipitation of the byproduct titanocene oxide with the addition of pentane, filtration, and solvent evaporation. Since aqueous work-up is not needed, this process is suitable for the preparation of highly labile products.

Thus, silyl esters are converted to silyl enol ethers (eqs. 2, 3). This method allows the preparation of derivatives that are difficult to prepare via a regioselective ketone enolization (eq. 3).

(2)

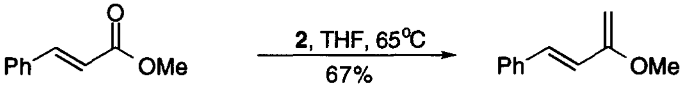


(3)



Various other ester and lactone derivatives are also smoothly methylenated, including α,β-unsaturated esters (eqs. 4, 5), spirobislactones (eq. 6) and vinylogous lactones (eq. 7). Anhydrides give the mono- or bis-methylenated product depending on the amount of reagent used (eq. 8).[6] Both types of products, however, are somewhat labile and their isolation is often difficult. Carbonates can be methylenated to give ketene acetals[7] (eqs. 9, 10), which are among the most labile derivatives prepared with this process and are isolated by distillation.

(4)



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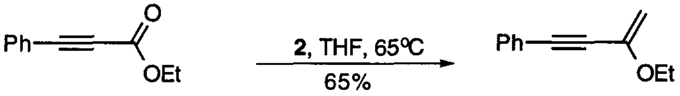

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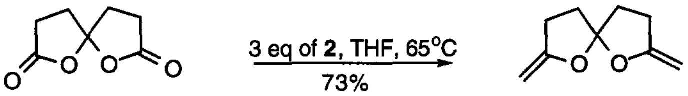

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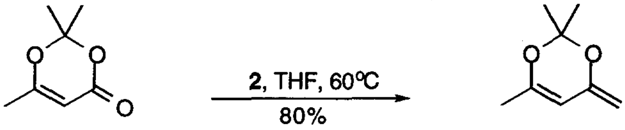

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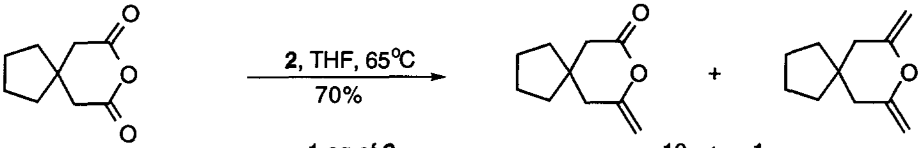
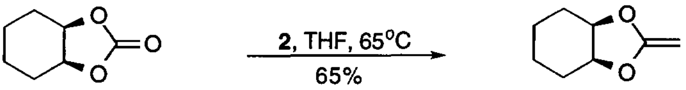


1 eq of **2**	10	:	1
2 eq of **2**	2	:	1
4 eq of **2**	0	:	1

(9)



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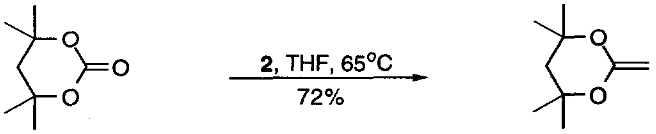
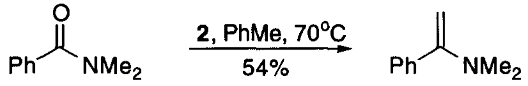


Although the reaction of **2** with amides and lactams is somewhat slower than reactions with other carbonyls, this synthetically valuable olefination process does take place (eqs. 11, 12, 13). Although the NMR spectra of the crude mixtures often confirms the formation of the expected enamine products, the complete separation of these highly polar and labile derivatives from the titanium by-products by precipitation, distillation or chromatography is usually difficult. The enamine products, however, can be used directly in further reactions without prior purification (eq. 13).

(11)



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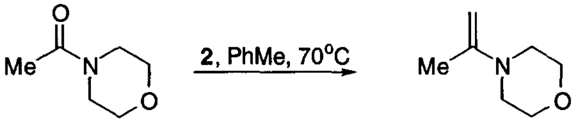
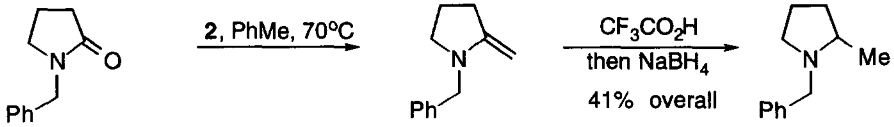
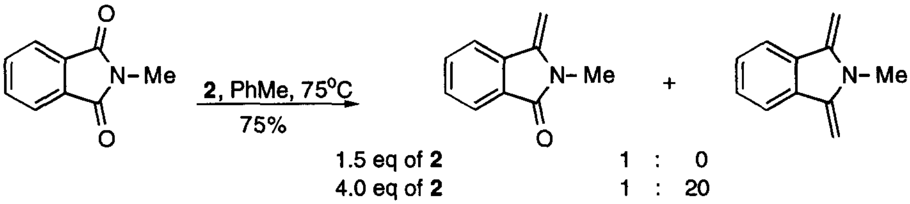


(13)



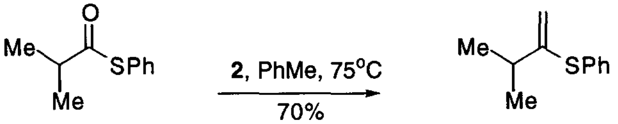
Similarly to anhydrides, imides give mono- and/or bis- methylenated products (eq. 14).

(14)



In a similar manner, thioesters give alkenyl sulfides (eq. 15), selenoesters form alkenyl selenides (eq. 16) , while acyl silanes are converted to alkenyl silanes (eq. 17).

(15)



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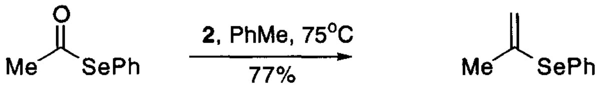

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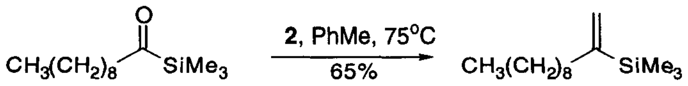

In summary, we have shown that our mild and experimentally convenient methylenation process can be extended to several hetero-substituted carbonyls. In combination with a variety of subsequent transformations of the resulting olefins, this process makes possible the conversion of many readily available carbonyl compounds to various homologated products.

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