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A one-pot procedure for methylenating carbonyl compounds using the Nysted reagent and titanocene dichloride

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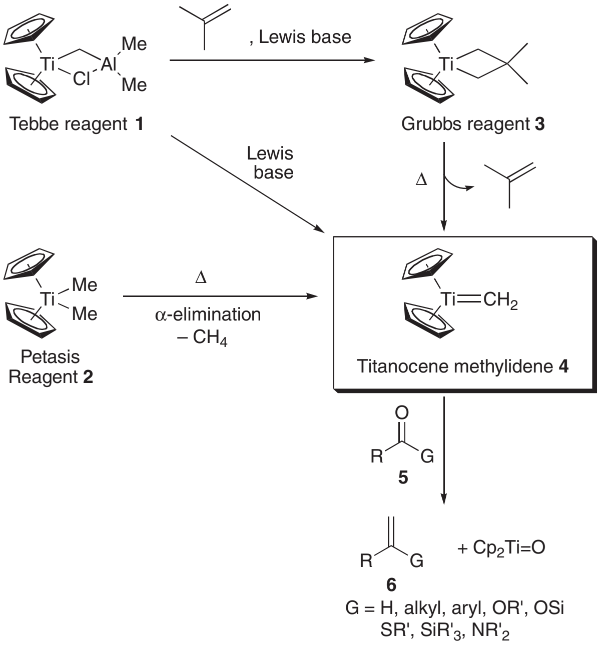
ABSTRACT

The combination of the Nysted reagent and titanocene dichloride methylenates aldehydes and ketones to give alkenes, and in a microwave-assisted process, esters and lactones give enol ethers. The methylenating agent in this one-pot procedure is presumed to be titanocene methylidene, which is the same reactive intermediate as that generated from Tebbe, Petasis and Grubbs reagents, each of which have to be prepared before use.

The Tebbe reagent[1] **1** and Petasis reagent[2] **2** are widely used for the methylenation of carbonyl compounds **5** to give alkenes **6** (Scheme 1).[3] They are non-basic reagents that can be used for the methylenation of aldehydes and ketones when a Wittig reagent would promote epimerisation of chiral centres or retro-Michael reactions, or would fail to react due to steric hindrance. Most importantly, they will convert carboxylic acid derivatives directly into hetero-substituted alkenes,[3,4] rather than inducing the nucleophilic substitution observed with Wittig reagents. Although, it is too reactive to be isolated, titanocene methylidene **4** is believed to be the reactive intermediate and the formation of Grubbs reagent **3** from the Tebbe reagent and 2-methylpropene,[5] and thermal regeneration of the titanocene methylidene **4** supports this, as does the isolation of related Schrock carbenes.[6] Both the Tebbe reagent **1** and the Petasis reagent **2** are prepared from titanocene dichloride,[7–9] and though both are available commercially as solutions in toluene, they are extremely expensive, and the Tebbe reagent in particular can be unsatisfactory when not freshly prepared. It would be more satisfactory if titanocene methylidene **4** (or an equivalent titanium-containing 1,1-bimetallic[3]) could be generated in situ in a one-pot procedure from titanocene dichloride without the use of reactive methyllithium or methylmagnesium halide.

The reagent **8** patented by Nysted in 1975 is believed to have the structure shown,[10] and is commercially available as a suspension in THF. We reasoned that the combination of titanocene dichloride (**7**) and the Nysted reagent **8** would give titanocene



Scheme 1.

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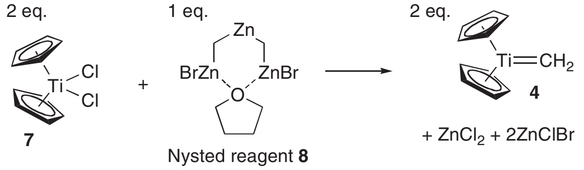
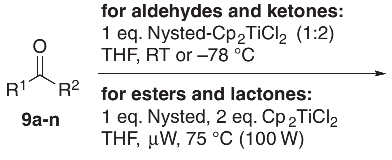


Scheme 2.

methylidene **4** directly (Scheme 2). The Nysted reagent **8** has been used with titanium tetrachloride, trichloride or dichloride to methylenate aldehydes and ketones,[11–13] a reaction that also works with Lewis acids such as boron trifluoride,[12,14] but has never been used in combination with titanocene dichloride, or to achieve methylenation of carboxylic acid derivatives. Our approach could be viewed as a simplified access to the reagent system, derived from $CH_2(ZnI)_2$ and titanocene dichloride, used by Eisch and Piotrowski to methylenate two ketones.[15]

Our methylenation was optimized by varying the ratio of Nysted reagent **8** to titanocene dichloride (**7**), the number of equivalents of the new reagent relative to the carbonyl compound, its mode of preparation, and the reaction temperature. The expected 1:2 ratio of Nysted reagent **8** to titanocene dichloride (**7**) proved most effective and heating was required to generate the reagent. Although, 1 mol of Nysted reagent **8** should give rise to 2 mol of titanium carbenoid **4** in this way (Scheme 2), it proved best to use equimolar quantities of the carbonyl compound and the Nysted reagent **8**. Similarly, 2 equiv of Petasis reagent **2** are often used in methylenation reactions because the reagent reacts with the titanocene oxide side product.[9]

A range of carbonyl compounds **9a–n** were methylenated using the new reagent (Scheme 3, Figs. 1 and 2). When methylenating aldehydes and ketones, the reagent was generated by heating the Nysted reagent **8** and titanocene dichloride (**7**) together in THF until a red solution was formed and then reactions were carried out at a lower temperature.[16,17] The electron-rich benzaldehyde and acetophenone derivatives **9a,b** reacted smoothly at room temperature. In accordance with the nucleophilic nature of the reagent, the electron-poor derivatives **9c**,**d** reacted much more rapidly and required low temperature to avoid over-reaction, beginning at −78 °C and allowing to warm for the short time shown. The α,β-unsaturated aldehyde **9e** and benzophenone **9f** presented no problem and the branched aldehyde **9g** and cyclic ketone **9h** were successfully methylenated, though the yields were modest.



Scheme 3.

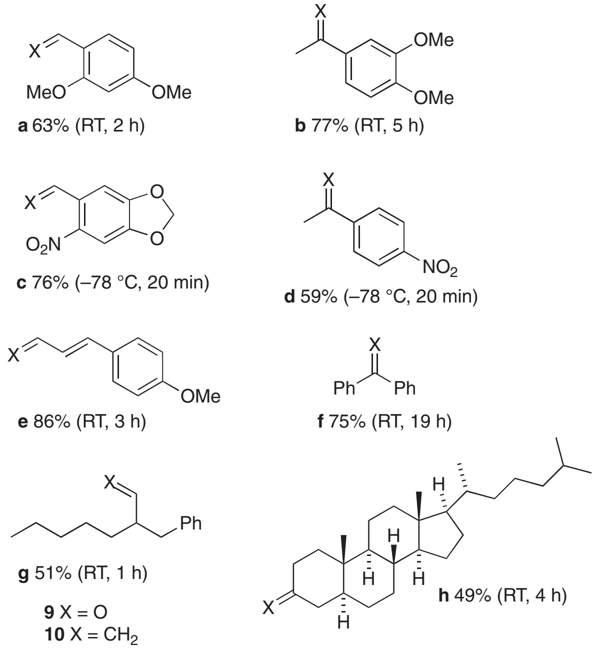


Figure 1. Aldehydes and ketones **9a–h** methylenated with isolated yields of product alkenes **10a–h** and conditions in parentheses.

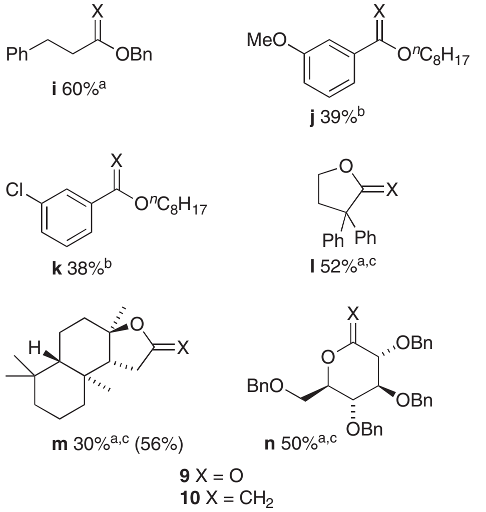


Figure 2. Esters **9i–k** and lactones **9l–n** methylenated and yields of enol ethers **10i–n** produced using (a) a 1:1:2 mol ratio of ester/lactone, Nysted reagent and titanocene dichloride; (b) a 1:2:4 mol ratio of ester/lactone, Nysted reagent and titanocene dichloride; (c) with 1 equiv of ethyl pivalate. All reactions were carried out at 75 °C in a microwave (100 W) for 22 min.

Reactions with carboxylic acid derivatives required higher temperature and so pre-generation of the reagent was not necessary: all components were simply mixed and heated together.[18,19] Methylenations were best achieved using microwave irradiation (100 W), which gave complete conversion in 22 min at 75 °C; conventional heating required longer reaction times and led to decomposition. Similar advantages to microwave heating have been observed with the Petasis reagent.[20] Alkanoate ester **9i** worked well, isolated yields were lower for enol ether **10j,k** derived benzoate derivatives and more equivalents of the reagent were required. Methylenation of lactones **9l–n** was successful with 1 equiv of the reagent, but ethyl pivalate had to be included as a sacrificial sterically-hindered ester[9,21] to avoid products resulting from the reaction between the product enol ether and the titanocene methylidene (the same type of reaction that is exploited to form the Grubbs reagent **3**[5]). All the enol ethers were acid-sensitive, so purification on neutral alumina was necessary; indeed the enol ether **10m** derived from (+)-sclareolide was so sensitive that hydrolysis was carried out with HCl in THF–water and the yield for the corresponding ketone is reported in parentheses.

In summary, we have introduced a new one-pot procedure for the methylenation of carbonyl compounds by in situ generation of titanocene methylidene or a related 1,1-bimetallic complex from the commercially available Nysted reagent **8**. Methylenation of esters and lactones involves simply mixing the reagents and heating them under microwave irradiation for less than half an hour. The brevity, simplicity and relatively low temperature of this one-pot procedure should mean that it competes effectively with the popular Petasis and Tebbe reagents **1** and **2**, which must be preformed prior to use.

Acknowledgements

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16. *Typical procedure*: titanocene dichloride (2 mmol) was suspended in dry THF (5 mL) under argon and the Nysted reagent added (1 mmol, 20 wt % in THF). This was heated to 40 °C for 30 min until a very dark red solution formed and was then cooled to the appropriate temperature for reaction (rt or −78 °C). A solution of the aldehyde or ketone **9a–h** (2 mmol) in dry THF (3 mL) was then added. The mixture was stirred until no starting material remained (see Fig. 1 for reaction time) and then quenched by pouring into satd aq $NaHCO_3$ (50 mL), and extracted with Et_2O (3 × 50 mL). The organic extracts were combined then washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (SiO_2, Pet. ether–Et_2O) afforded the alkene **10a–h**.
17. The analytical data are in agreement with the literature for alkenes **10a**,[22] **b**,[23] **d**,[24] **e**,[25] **f**,[26] and **h**.[27] Alkene **10c** was isolated as yellow needles: R_f [SiO_2, Et_2O–Pet. ether (1:1)] 0.48. δ_H (400 MHz, $CDCl_3$) 5.45 (1H, d, J = 10.9 Hz, $=CH^AH^B$), 5.65 (1H, d, J = 17.2 Hz, $=CH^AH^B$), 6.15 (2H, s, CH_2O_2), 7.02 (1H, s, 4-H), 7.23 (1H, dd, J = 17.2, 10.9 Hz, ArCH=), 7.52 (1H, s, 7-H); δ_C (100 MHz, $CDCl_3$) 102.6 (CH_2), 104.9 (CH), 106.8 (CH), 117.5 (CH_2), 130.4 (C), 132.8 (CH), 141.5 (C), 147.1 (C), 151.5 (C); IR (cm^{-1}) 3090 (Ar-H), 2925 (Ar-H), 1602 (C=C), 1499 (NO_2), 1329 (NO_2); LRMS (CI^+) 194 [$(M+H)^+$, 100%], 164 (17); HRMS: 194.0457, $C_9H_8NO_4$ requires $(M+H)^+$ 194.0453; mp 59–63 °C. Compound **10g** was isolated as an oil: R_f [SiO_2, Et_2O–Pet. ether (1:1)] 0.66. δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, J = 6.8 Hz, CH_3), 1.16–1.44 (8H, m, 4 × CH_2), 2.22–2.32 (1H, m, 2′-H), 2.60 (1H, dd, J = 13.4, 7.6 Hz, 1′-CH^AH^B), 2.65 (1H, dd, J = 13.5, 6.7 Hz, 1′-CH^AH^B), 4.85 (1H, ddd, J = 17.0, 2.0, 0.8 Hz, $=CH^CH^D$), 4.92 (1H, ddd, J = 10.3, 2.0, 0.3 Hz, $=CH^CH^D$), 5.53–5.59 (1H, m, =CH), 7.11–7.19 (3H, m, ArH), 7.23–7.30 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 23.8 (CH_2), 31.9 (CH_2), 34.1 (CH_2), 41.8 (CH_2), 45.7 (CH), 114.4 (CH_2), 125.7 (CH), 128.0 (CH), 129.3 (CH), 140.7 (C), 142.6 (CH); IR (cm^{-1}) 3150 (Ar-H), 2926 (C–H), 1641 (C=C); LRMS (EI^+): 202 [$M^{+\cdot}$, 36%], 104 (30), 91 (100), 69 (62); HRMS: 202.1720, $C_{15}H_{22}$ requires $M^{+\cdot}$ 202.1722.
18. Typical procedure: lactone **9l–n** (0.5 mmol) was dissolved in dry THF (1.5 mL) and titanocene dichloride (1 mmol), the Nysted reagent (0.5 mmol, 20 wt % in THF) and ethyl pivalate (0.5 mmol) were added. The reaction mixture was irradiated in a Discover® CEM focussed microwave synthesis system (100 W, 75 °C, 22 min). This gave a black solution which was quenched and worked-up as before.[16] Flash column chromatography (neutral alumina, Brockmann V, Pet. ether–Et_2O) gave the enol ether **10l–n**.
19. The analytical data for enol ether **10n** are in agreement with the literature.[28] Data for enol ethers **10i–m** are as follows. Compound **10i** oil; R_f [Al_2O_3, Et_2O–Pet. ether (1:9)] 0.77; δ_H (400 MHz, $CDCl_3$) 2.48 (2H, t, J = 7.2 Hz, CH_2), 2.86 (2H, t, J = 7.2 Hz, CH_2), 3.93 (1H, d, J = 2.1 Hz, $=CH^AH^B$), 3.97 (1H, d, J = 2.1 Hz, $=CH^AH^B$), 4.36 (2H, s, OCH_2), 7.10–7.41 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.7 (CH_2), 36.9 (CH_2), 69.2 (CH_2), 82.1 (CH_2), 125.8 (CH), 125.8 (CH), 127.4 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 137.3 (C), 161.7 (C), 162.4 (C); IR (cm^{-1}) 3027 (Ar-H), 2924 (C–H), 1654 (C=C), 1495 (Ar); LRMS (CI^+): 239 [$(M+H)^+$, 37%], 113 (44), 107 (90); HRMS: 239.1434, $C_{17}H_{19}O$ requires $(M+H)^+$ 239.1346. Compound **10j** oil; R_f [Al_2O_3, Et_2O–Pet. ether (1:9)] 0.87; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.0 Hz, CH_3), 1.20–1.38 (8H, m, 4 × CH_2), 1.50–1.52 (2H, m, CH_2), 1.79 (2H, quint., J = 6.5 Hz, OCH_2CH_2), 3.82 (3H, s, OMe), 3.84 (2H, t, J = 6.4 Hz, OCH_2), 4.18 (1H, d, J = 2.5 Hz, $=CH^AH^B$), 4.62 (1H, d, J = 2.5 Hz, $=CH^AH^B$), 6.85 (1H, dt, J = 7.0, 2.4 Hz, 4-H or 6-H), 7.17–7.33 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.3 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 55.2 (CH_3), 67.8 (CH_2), 82.3 (CH_2), 111.1 (CH), 113.8 (CH), 118.0 (CH), 129.1 (CH), 138.2 (C), 159.4 (C), 159.8 (C); IR (cm^{-1}) 2928 (Ar-H), 1599 (C=C); LRMS (CI^+) 263 [$(M+H)^+$, 100%], 151 (53); HRMS: 263.2018, $C_{17}H_{27}O_2$ requires $(M+H)^+$ 263.2011. Compound **10k** oil; R_f [Al_2O_3, Et_2O–Pet. ether (1:9)] 0.83. δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 6.7 Hz, CH_3), 1.19–1.42 (8H, m, 4 × CH_2), 1.43–1.52 (2H, m, CH_2), 1.79 (2H, quint., J = 6.6 Hz, OCH_2CH_2), 3.84 (2H, t, J = 6.5 Hz, OCH_2), 4.22 (1H, d, J = 2.8 Hz, $=CH^AH^B$), 4.63 (1H, d, J = 2.8 Hz, $=CH^AH^B$), 7.24–7.29 (2H, m, ArH), 7.50 (1H, dt, J = 6.8, 1.8 Hz, 4-H or 6-H), 7.60 (1H, d, J = 2.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 68.0 (CH_2), 83.0 (CH_2), 123.5 (CH), 126.3 (CH), 129.3 (CH), 129.4 (CH), 134.1 (C), 138.6 (C), 157.7 (C); IR (cm^{-1}) 2925 (Ar-H) 1564 (C=C), 786 (C–Cl); LRMS (EI^+): 268 [$M^{+\cdot}$ (^{37}Cl), 40%], 266 [$M^{+\cdot}$ (^{35}Cl), 81], 188 (27), 157 (17) 155 (45), 136 (14) 134 (47), 91 (100); HRMS: 266.1465 and 268.1455, $C_{16}H_{23}O^{35}Cl$ requires $M^{+\cdot}$ 266.1437 and $C_{16}H_{23}O^{37}Cl$ requires $M^{+\cdot}$ 268.1413. Compound **10l** oil; R_f [Al_2O_3, Et_2O–Pet. ether (1:9)] 0.53; δ_H (400 MHz, $CDCl_3$) 2.78 (2H, t, J = 6.3 Hz, 4-CH_2), 3.64 (1H, d, J = 1.8 Hz, $=CH^AH^B$), 4.00 (2H, t, J = 6.3 Hz, OCH_2), 4.55 (1H, d, J = 1.8 Hz, $=CH^AH^B$), 7.25–7.32 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 40.0 (CH_2), 58.9 (C), 67.2 (CH_2), 84.7 (CH_2), 126.7 (CH), 128.2 (CH), 128.5 (CH), 143.6 (C), 167.4 (C); IR (cm^{-1}) 3058 (Ar-H), 1666 (Ar), 1491 (C=C); LRMS (FAB^+): 237 [$(M+H)^+$, 20%], 221 (20), 207 (20), 147 (20), 84 (100); HRMS: 237.1264, $C_{17}H_{17}O$ requires $(M+H)^+$ 237.1279. Compound **10m** amorphous solid; R_f [Al_2O_3, Et_2O–Pet. ether (1:19)] 0.67; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, s, 6′-Me), 0.86 (3H, s, 6′-Me), 0.88 (3H, s, 9a′-Me), 1.00 (1H, dd, 5a′-H, J = 12.5, 2.7 Hz), 1.05 (1H, dd, 7′-H_{ax}, J = 13.3, 2.5 Hz), 1.10–1.48 (5H, m, 4′-CH^AH^B, 5′-CH^AH^B, 7′-H_{eq}, 8′-CH^AH^B, 9′-CH^AH^B), 1.19 (3H, s, 3b′-Me), 1.52-1.73 (3H, m, 5′-CH^AH^B, 8′-CH^AH^B, 9′-CH^AH^B), 1.81 (1H, dq, 4′-CH^AH^B, J = 13.9, 3.8 Hz), 2.00 (1H, dt, 9b-H, J = 11.7, 3.3 Hz), 2.28–2.43 (2H, m, 1-H), 3.89 (1H, s, $=CH_2$), 4.22 (1H, s, $=CH_2$); δ_C (100 MHz, $CDCl_3$) 15.2 (CH_3), 18.3 (CH_2), 20.8 (CH_2), 21.0 (CH_3), 21.5 (CH_3), 27.5 (CH_2), 33.0 (CH), 33.4 (C), 36.2 (C), 39.1 (CH_2), 39.7 (CH_2), 42.3 (CH_2), 55.9 (CH_3), 59.8 (CH), 81.3 (CH_2), 84.4 (C), 161.9 (C); IR (cm^{-1}) 2927 (C–H), 1706 (C=C), 1671 (C=C); LRMS (EI^+) 248 [$(M)^+$ 21%], 196 (32), 177 (30), 84 (100); HRMS: 248.2138, $C_{17}H_{28}O$ requires, 248.2140; $[\alpha]_D^{25}$ +32.1 (*c* 0.8, $CHCl_3$); mp 72–74 °C.
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