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# Sequential *N*-acylamide methylenation–enamide ring-closing metathesis: a synthetic entry to 1,4-dihydroquinolines

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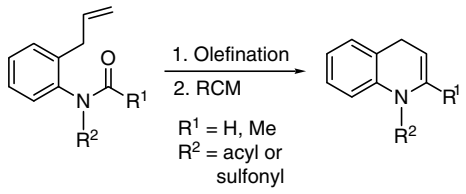
**Abstract**—A new synthetic entry to the 1,4-dihydroquinoline nucleus is reported. The procedure involves the dimethyltitanocene methylenation of *N*-(alkoxycarbonyl)amides derived from 2-allylanilines, followed by ring-closing metathesis of the resulting enamides.


Ruthenium-catalysed ring-closing metathesis (RCM) reactions[1] are well-established processes for the synthesis of nitrogen heterocycles, as illustrated by numerous reports dealing with the efficient construction of complex targets from suitable azadiene substrates.[2] Cyclisations involving ω-alkenyl enamides,[3] that is, azadienes in which the nitrogen atom is directly connected to one of the double bonds, are particularly interesting as the resulting cyclic enamides[4] constitute versatile moieties amenable to further functionalisation.[5] In this context, we envisaged the possibility that a variety of benzo fused bicyclic nitrogen compounds could be synthesised through RCM reactions of appropriate enamides. For the preparation of these substrates,[6] we planned to take advantage of olefination protocols, which, in combination with RCM, would make our heterocyclic targets conveniently available from olefinic amides. In this letter we report our preliminary results concerning the use of this amide olefination–enamide RCM reaction sequence for the construction of 1,4-dihydroquinoline system, starting from *N*-protected amides derived from 2-allylanilines (Scheme 1). This scheme would complement existing RCM-based syntheses of 1,2-dihydroquinolines from different precursors.[7]

Their ability to olefinate carboxylic acid derivatives makes titanium-based complexes distinctive reagents in organic synthesis.[8] Among them, the Tebbe,[9] Takai and co-workers,[10] and, to a lesser extent, Petasis reagent (dimethyltitanocene, $Cp_2TiMe_2$)[11] have proven to be very effective for the methylenation of esters.[12] Subsequent RCM of the resulting enol ethers is the key step of several brilliant approaches to cyclic enol ethers.[8,13] On the other hand, the methylenation of amides has clearly received less attention,[8] dimethyltitanocene appearing to be the reagent of choice,[14,15] in particular with *N*-protected lactams.[16]




**Scheme 1.**

Considering the above precedents, we set out to explore the behaviour of dimethyltitanocene with easily accessible model substrates, such as anilides **1** and **2**, which bear different electron-withdrawing substituents (sulfonyl or alkoxycarbonyl) at the nitrogen. Dimethyltitanocene was prepared by treatment of titanocene dichloride with methyl-lithium, following the reported procedure,[11] and was immediately treated with the amide substrate in toluene at reflux under conditions **A** or **B** (see Table 1).[17]

Our first assays using *N*-tosylacetanilide (**1a**) were discouraging since deacetylation rapidly took place in both conditions tried (**A** or **B**) to give aniline **5a** as the only product (entry 1). This undesired process could only

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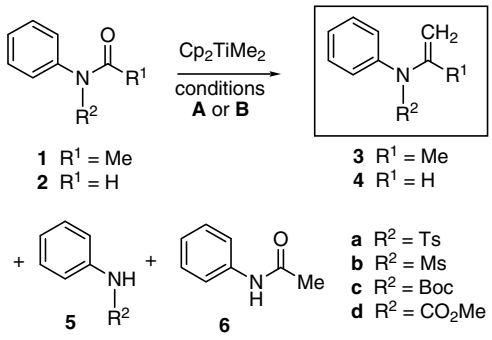
**Table 1.** Reaction of model anilides **1** and **2** with $Cp_2TiMe_2$




| Entry | Substrate | Conditions[a] | Products | Isolated yields (%) |
|---|---|---|---|---|
| 1 | **1a** | **A** or **B** | **5a** | [b] |
| 2 | **1b** | **A** | **5b** | [b] |
| 3 | **1b** | **B** | **3b** + **5b** (2.5:1)[c] | 10[d] |
| 4 | **1c** | **A** or **B** | **3c** | 85 |
| 5 | **1d** | **B** | **3d** + **6** (10:1)[c] | 75 |
| 6 | **2d** | **B** | **4d** | 40[d] |

[a] Conditions **A**: $Cp_2TiMe_2$ (2 mol), toluene, reflux, 12 h; **B**: $Cp_2TiMe_2$ (1.5 mol), 100:1 toluene–pyridine, reflux, 4 h.
[b] Total conversion determined by $^1H$ NMR.
[c] Ratio determined by $^1H$ NMR.
[d] Unstable enamide, which partially decomposes under chromatographic purification.

be minimised from *N*-mesyl derivative **1b** under milder (**B**) conditions to give a 2.5:1 mixture of the expected enamide **3b** and aniline **5b** (entry 3). Unfortunately, isolation of **3b** proved problematic as it was very sensitive to chromatography.

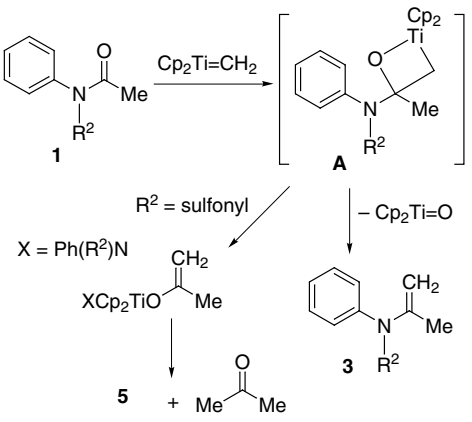
Given that the deacetylated products **5a** and **b** were already present in the crude reaction mixtures, their formation is hard to attribute to a fortuitous hydrolysis of enamides **3a** and **b**. A plausible explanation is that the oxatitanacyclobutane intermediate **A**, coming from the initial interaction of the titanium carbene with the carbonyl group of **1a** and **b**, undergoes at least partial elimination of the sulfonylamino moiety as depicted in Scheme 2, rather than the expected transfer of the methylene group.[18] This process would be particularly favoured in these series due to the presence of strong electron-withdrawing *N*-sulfonyl groups.

In full accordance with this proposal, no deacetylation was observed when the reaction was effected from acetanilides **1c** and **d**, which bear weaker electron-withdrawing *N*-alkoxycarbonyl groups. The best results were obtained from *N*-Boc derivative **1c**, providing enamide **3c** in high isolated yield (85%, entry 4). Similarly, *N*-(methoxycarbonyl)acetanilide **1d** gave enamide **3d** in good yield (75%, entry 5). However, in this case minor amounts of acetanilide (**6**), coming from the competitive interaction of the reagent with the methoxycarbonyl group, were detected in the reaction mixtures. Probably for steric reasons, the chemoselectivity was again complete in the reaction of formanilide **2d**, resulting in the unstable enamide **4d** as the only product (40% isolated yield, entry 6).

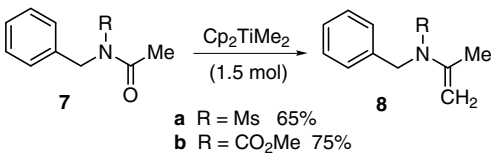
At this point, we wondered whether the dimethyltitanocene methylenation of *N*-sulfonylamides derived from aliphatic amines would take place, assuming that the elimination process depicted in Scheme 2 would be less favoured, given the presence of a poorer leaving group. Effectively, when submitted to the standard methylenation conditions, *N*-mesylacetamide **7a** cleanly afforded enamide **8a** (65% yield) without significant deacetylation (Scheme 3). On the other hand, the related enamide **8b** was obtained in 75% yield from *N*-(methoxycarbonyl)acetamide **7b**.

Having established the limitations of the methylenation of *N*-protected anilides, we turned our attention to the preparation of RCM substrates for the construction of the 1,4-dihydroquinoline system, that is, enamides which incorporate the *ortho*-allyl substituent needed for the ring-closure step. The required amide precursors **9** and **10** were easily prepared by conventional acylation protocols starting from 2-allylaniline,[19] as shown in Scheme 4.

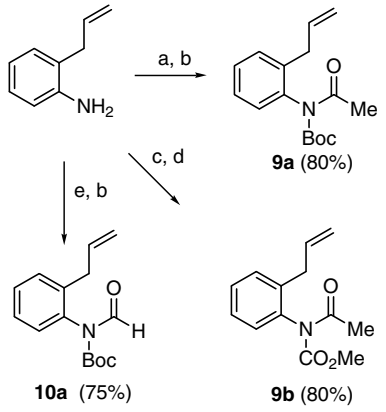
The dimethyltitanocene methylenation was first performed with acetanilides **9a** and **b** under the previous conditions[17] (**B**, see Table 1). Satisfactorily, both enamides **11a** and **b**[20] were isolated in consistent, reproducible 55% and 51% yield, respectively (Scheme 5). In the latter case, significant amounts (20%) of acetanilide (**17**) were also obtained, reflecting again (see Table 1, entry 5) an incomplete discrimination between the amide and carbamate carbonyl groups. As anticipated,[3] enamides **11a** and **b** underwent RCM upon treatment with the second generation Grubbs catalyst (**18**) at 80 °C in toluene.[21] The cyclisation proved to be unaffected by the steric hindrance of the enamide moiety, as both substrates gave the expected 1,4-dihydroquinolines **13a** and



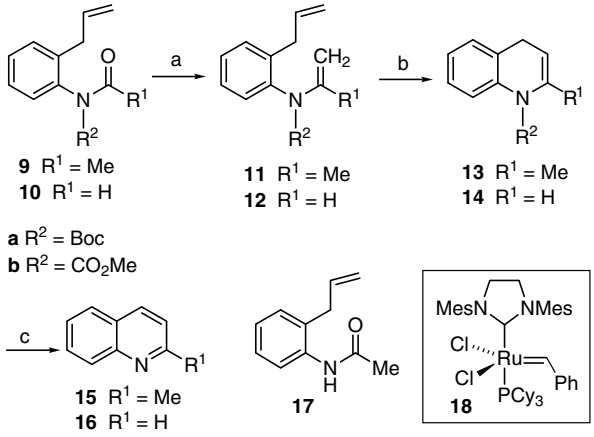

**Scheme 2.**




**Scheme 3.**




**Scheme 4.** Reagents and conditions: (a) $Ac_2O$, AcOH, reflux, 15 min; (b) $(Boc)_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 12 h; (c) $ClCO_2Me$, pyridine, THF, rt, 12 h; (d) NaH, MeCOCl, $CH_2Cl_2$, reflux, 20 h; (e) $Ac_2O$–$HCO_2H$, 55 °C, 2 h, then addition of the amine, THF, rt, 3 h.




**Scheme 5.** Reagents and conditions: (a) $Cp_2TiMe_2$ (1.5 mol), 100:1 toluene–pyridine, reflux 4 h, 55% (**11a**), 51% (**11b**); (b) 6 mol% **18**, toluene, 0.1 M, 80 °C, 4 h, 75% (**13a**), 75% (**13b**), 45% (**14a**, from **10a**); (c) 5% Pd–C, $O_2$, THF, reflux, 6 h, 80% (**15**), 85% (**16**).

**b**[22] in 75% yield. Similarly, when the methylenation-RCM sequence was effected from formanilide **10a** the unstable 1,4-dihydroquinoline **14a** was obtained through enamide **12a** (not isolated) in 45% overall yield. Finally, 1,4-dihydroquinolines **13** and **14** were easily oxidised to the respective fully aromatic heterocycles **15** and **16** in good yield.

It should be noted that, in our hands, dimethyltitanocene was unable to catalyse the RCM of enamides **11**, which seriously hampered the possibility of carrying out tandem reactions from amides **9**, similar to those reported by Nicolaou et al. in the context of the synthesis of cyclic enol ethers from olefinic esters.[13b,c] Treatment of either acetamides **9** or enamides **11** with excess dimethyltitanocene (2–4 mol) resulted in the formation of complex reaction mixtures, from which only the open-chain isomerised products **19** and **20** could be isolated in variable yields (20–30%, Fig. 1).

In conclusion, the methylenation of *N*-(alkoxycarbonyl)amides derived from 2-allylanilines with dimethyltitanocene in combination with a ruthenium-catalysed RCM step of the resulting enamides gives access to the 1,4-dihydroquinoline system.[23] Further extension of this reaction sequence to other heterocyclic systems is in progress.

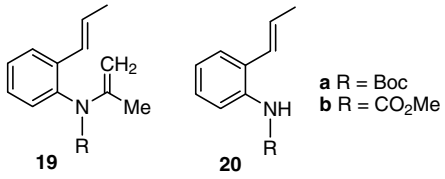



**Figure 1.**

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17. *General procedure for the dimethyltitanocene methylenation* (*conditions B*): a solution of freshly prepared[11] $Cp_2TiMe_2$ (1 mmol) in anhydrous toluene–pyridine (100:1, 6 mL) was added under Ar to a solution of the appropriate amide (0.67 mmol) in anhydrous toluene (1 mL) at rt, and the resulting mixture was stirred in the dark at reflux temperature for 4 h. The solvent was removed and the resulting residue was treated with 8:2 $Et_2O$–$CH_2Cl_2$. The precipitate was filtered and the filtrate concentrated under reduced pressure. The crude reaction mixture was analysed by $^1H$ NMR and then purified by flash chromatography (hexane–AcOEt) to give the pure enamide.
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20. Enamide **11b**: $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.07 (d, $J$ = 0.8 Hz, 3H), 3.29 (d, $J$ = 6.2 Hz, 2H), 3.65 (s, 3H), 4.52 (s, 1H), 4.68 (q, $J$ = 1.2 Hz, 1H), 5.06 (m, 1H), 5.13 (m, 1H), 5.88 (m, 1H), 7.12 (m, 1H), 7.20–7.30 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 21.8, 35.2, 52.9, 106.4, 116.4, 127.0, 127.7, 128.7, 130.0, 135.9, 137.7, 139.8, 144.1, 154.6; HRMS calcd for $C_{14}H_{17}NO_2$ + H: 231.1259. Found: 231.1338.
21. *General procedure for the RCM step*: a solution of the appropriate enamide **11** (1 mmol) and the Grubbs catalyst **18** (0.06 mmol) in anhydrous toluene was stirred at 80 °C under Ar for 4 h. The reaction mixture was concentrated. The resulting residue was purified by flash chromatography ($SiO_2$, 9:1 hexane–AcOEt) to give the pure 1,4-dihydroquinoline **13**.
22. 1,4-Dihydroquinoline **13b**: $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.17 (m, 3H), 3.15 (d, $J$ = 4.8 Hz, 2H), 3.80 (s, 3H), 5.52 (tq, $J$ = 1, 1, 1, 4.8, 4.8 Hz, 1H), 7.10 (m, 2H), 7.20 (m, 1H), 7.57 (d, $J$ = 7.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 20.1, 28.3, 52.9, 116.5, 124.3, 125.0, 125.5, 126.8, 133.0, 138.1, 139.2, 154.0.
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