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The reaction of dimethyltitanocene with *N*-substituted-β-lactams

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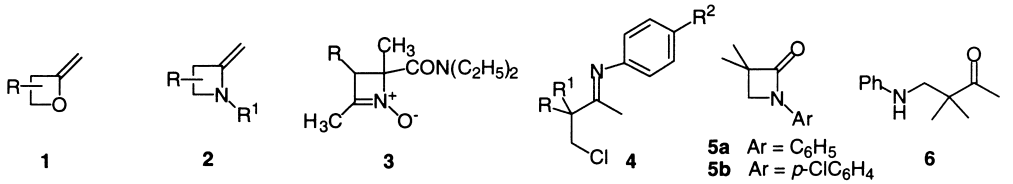
Abstract

2-Methyleneazetidines have been synthesized and isolated by the reaction of β-lactams with dimethyltitanocene, followed by chromatography on deactivated silica. Efficient conversion required that the lactam nitrogen be strongly deactivated. Methyl transfer predominated in reactions with phenyl and benzyl on the lactam nitrogen.

Our interest in strained heterocycles as versatile templates for the construction of more complex synthetic intermediates and molecular targets has recently centered on the exploitation of 2-methyleneoxetanes **1**. We developed a straightforward entry into this class of compounds by the methylenation of β-lactones with dimethyltitanocene.[1] Our anticipation of the flexibility of 2-methyleneoxetanes has already been confirmed by their conversion to homopropargylic alcohols,[2] fused ketals,[3] functionalized ketones[4] and 1,5-dioxaspiro[3.2]hexanes,[5] the latter themselves being fascinating and useful strained heterocyclic systems.[6] Further, a 2-methyleneoxetane analog of Orlistat, a β-lactone-containing pancreatic lipase inhibitor currently marketed as an anti-obesity agent, was found to be a potent pancreatic lipase inhibitor.[7] Because of the diverse reactivity and biological promise of 2-methyleneoxetanes, we became interested in exploring 2-methyleneazetidines **2**.



There are few examples of simple 2-methyleneazetidines in the literature.[8–11] The only reports describing the preparation of multiple 2-methyleneazetidines come from the groups of Reinhoudt[11]

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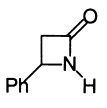
and De Kimpe.[9] The former reported the isolation of four examples when four-membered cyclic nitrones **3** were treated with acetyl chloride in the absence of water. De Kimpe and co-workers employed the base-promoted cyclization of *N*-aryl-β-chloro ketimines **4**. The requirement for α-disubstitution in this case limits the versatility of this approach. Because of our success in preparing 2-methyleneoxetanes by the reaction of β-lactones with dimethyltitanocene, we decided to pursue a similar strategy and to examine the methylenation of β-lactams. Herdeis and Heller reported the methylenation of δ-lactams with dimethyltitanocene.[12] In this communication a footnote stated that it was also possible to methylenate β-lactams, although no specific examples or characterization data were provided. Baldwin et al. found that the Wittig reaction of stabilized ylides with β-lactams proceeded only if strongly electron withdrawing groups were placed on the nitrogen,[13] thus restricting mesomeric resonance. Herdeis had also found that this was important for the methylenation of δ-lactams. Thus, we anticipated that the choice of functionality attached to the nitrogen would be crucial. We decided to examine the effect of a range of substituents to determine which were compatible with successful methylenation of the β-lactam carbonyl.

While we were preparing this manuscript, De Kimpe and co-workers reported the use of dimethyltitanocene for the methylenation of two *N*-aryl-β-lactams **5**.[14] Successful isolation of the resultant 2-methyleneazetidine was achieved by vacuum distillation for **5a**, but in 20% yield. It was reported that hydrolysis product **6** resulted when silica gel chromatography was employed for purification. Since our results with a 1-phenylazetidin-2-one were different from those of De Kimpe, and, since we were able to isolate a range of 2-methyleneazetidines under chromatographic conditions which we have previously described for 2-methyleneoxetanes,[15] we thought it worthwhile to communicate our results.

The precursor β-lactams were prepared by standard methods. Thus, 4-phenylazetidin-2-one (**7**),[16] benzyl 4-oxoazetidine-2-carboxylate (**8**)[17] and β-lactam **9**[18] were converted by known procedures[19] to Boc-protected lactams **10a**, **10c**, and **10e**,[20] respectively. Compounds **7** and **8** were also transformed by standard procedures[21] to Cbz-protected lactams **10b** and **10d** (see Table 1).[20] β-Lactam **7** was tosylated under conditions described[22] by Adlington et al. to give **10f**[23] and was treated with acetyl chloride[24] to provide **10h**.[23] Lactams **10g**[25] and **10i**[26] were prepared by literature procedures, and **7** was converted to **10j**[27] under conditions described by Murayama et al.[28]



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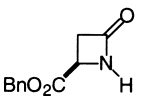

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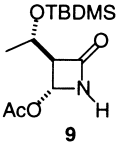

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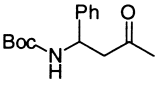
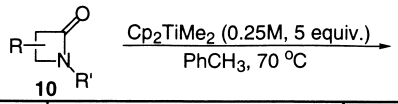


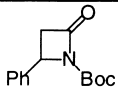
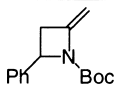
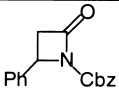
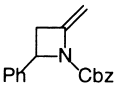
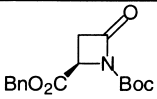
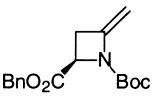
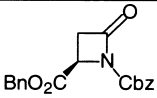
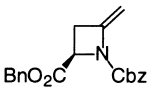
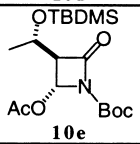
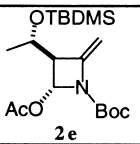
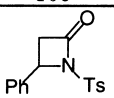
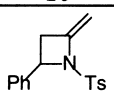
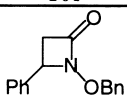
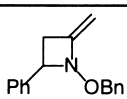
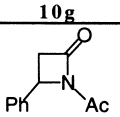
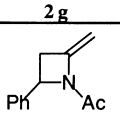
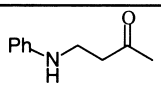
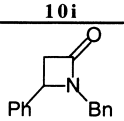
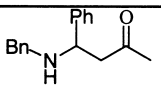
11c

The β-lactams **10** were dissolved in a solution of dimethyltitanocene in toluene (0.25 M, 5 equiv.) and heated under nitrogen in the dark until the starting material had disappeared, based on ^{1}H NMR.[29] Although reactions conducted with fewer equivalents of dimethyltitanocene gave similar yields, they tended to be slower. The best yields, not surprisingly,[12,13] were observed with the strongly electron withdrawing carbamates (**10a**–**10e**). There were, however, a number of unexpected results and interesting observations.

The lack of reactivity of dimethyltitanocene with the carbamate carbonyls is not surprising; however, dimethyltitanocene is known to methylenate esters.[30] With ester-containing lactams **10c**–**e**, we did not observe methylenation of the ester moieties as long as the reaction was quenched upon initial consumption of the β-lactams. This chemoselectivity was gratifying. With lactam **10h**, we were unable to isolate any pure product. Based on the crude ^{1}H NMRs and the impure

Table 1



Reactant	Product	Isolated Yield
 **10a**	 **2a**	76
 **10b**	 **2b**	75
 **10c**	 **2c**	69
 **10d**	 **2d**	45
 **10e**	 **2e**	81
 **10f**	 **2f**	10
 **10g**	 **2g**	see text
 **10h**	 **2h**	see text
 **10i**	 **11a**	55
 **10j**	 **11b**	see text

products isolated in multiple reactions, it appeared that methylenation was occurring almost equally at the lactam and acetyl carbonyls, but not at both. The methylenation of *O*-benzyl lactam **10g** was successful, based on crude ^{1}H NMR; however, repeated purification attempts did not result in any clearly identifiable product related to **2g**. The isolated yield of **2f** was low, and it was difficult to ascertain whether this reflected actual conversion. Of all of the reactions in which

methylenation was successful, this was the messiest. It did not appear that methyl transfer (vide infra) was occurring, and other than **2f**, no identifiable product was isolated. In spite of the low yield, **2f** is a particularly interesting product because a number of tosylated β-lactams are known inhibitors of elastases, and we are anxious to determine whether 2-methyleneazetidines can serve as isosteres for β-lactams.

The results with *N*-phenyllactam **10i** and *N*-benzyllactam **10j** were divergent from the other lactams we studied and from those reported for *N*-aryl-β-lactams by De Kimpe.[14] In our initial attempt to methylenate **10i**, ring-opened product **11a** was isolated in 55% yield. Assuming this resulted from inadvertent hydrolysis, the reaction was repeated; the result was the same. Examination of the crude ^{1}H NMRs of both reactions showed that **11a** appeared to be the only lactam-related material prior to purification. The reaction was repeated with extensive monitoring of the reaction by ^{1}H NMR. At no point did we observe any 2-methyleneazetidine; the only lactam-related materials throughout the course of the reaction were **10i** and **11a**. These results were mirrored by **10j**.[31] The outcomes of these reactions suggest that the nitrogens in **10i** and **10j** are Lewis basic enough to allow for their coordination with the titanium, leading to methyl transfer to the carbonyl moieties, rather than metathesis. Interestingly, in recent preparations of **2a** on a larger scale than our initial studies, we isolated **11c** (15%). Examination of the crude ^{1}H NMRs of these reactions confirmed the presence of **11c** prior to work-up. Thus, it appears that at least some of the material balance in these reactions may be accounted for by methyl transfer.

In summary, we have demonstrated that 2-methyleneazetidines can be prepared and isolated in good yields by the reaction of β-lactams with dimethyltitanocene, as long as the lactams are properly activated. It appears that methyl transfer represents an alternative pathway of reaction that predominates in cases where the Lewis basicity of the lactam nitrogen is not sufficiently dampened. We are currently investigating the potential of 2-methyleneazetidines as β-lactam isosteres and as novel molecular scaffolds.

Acknowledgements

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29. **General procedure for methylenation. *N*-(*tert*-Butoxycarbonyl)-4-phenyl-2-methyleneazetidine (2a).** A solution of dimethyltitanocene (0.25 M in toluene, 6.6 mL), *N*-(*tert*-butoxycarbonyl)-4-phenyl-2-azetidinone (**10a**) (0.10 g, 0.40 mmol), and pyridine (0.13 g, 1.6 mmol) was stirred in the dark at 70°C under nitrogen. The reaction was followed over a period of 1–3 hours by ^{1}H NMR. The cooled reaction mixture was added to petroleum ether (50 mL) and stirred for 1 h. The reaction mixture was filtered through celite and washed with petroleum ether until the filtrate was colorless. The filtrate was concentrated in vacuo and the residue purified by flash chromatography on silica gel (petroleum ether/EtOAc/NEt_3 94:5:1), affording the product as a pale yellow solid (74 mg, 76%): IR (KBr) 2978, 2929, 1713, 1632, 1456, 1153, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.11 (broad s, 1H), 5.03 (broad s, 0.5H), 4.73 (broad s, 0.5H), 4.22 (s, 1H), 3.19 (m, 1H), 2.65 (broad d, $J = 13.6$, 1H), 1.24 (broad s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 141.2, 129.0, 128.3, 126.5, 87.5, 62.3, 36.3, 30.2, 28.7; MS (EI) *m*/*z* 245 (M^+), 200, 189, 174, 144 (M^+-Boc) (100), 129, 104; Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.04; H, 7.94; N, 5.43.
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31. Compound **11b** not isolated; only product observed by ^{1}H NMR.