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New synthesis of 2-methyleneaziridines and 2-methyleneazetidines by dimethyl titanocene mediated methylenation of α- and β-lactams

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Abstract

2-Methyleneaziridines and 2-methyleneazetidines were synthesized via a titanium mediated olefination procedure starting from the corresponding α-lactams and β-lactams.

Keywords: azetidines; aziridines; olefination.

2-Methyleneazetidines and 2-methyleneaziridines belong to a group of strained cyclic enamines for which little information is available. The unique combination of functionalities, i.e. a reactive enamine and an exocyclic double bond, offers possibilities for further manipulation. To explore their reactivity and utility, ready access to 2-alkylideneazetidines and -aziridines is necessary. Only a few routes to functionalized 2-methyleneazetidines have been described, most of them being of little generality.[1–6]

The fact that until now only three fundamentally different synthetic approaches for the synthesis of 2-methyleneaziridines are available, combined with the increasing use of these reactive building blocks in organic synthesis, makes these compounds important synthetic targets.[7,8] An elementary retrosynthetic analysis would suggest connecting a β-lactam or α-lactam and an appropriate alkylidene equivalent (Fig. 1). Because the Wittig reaction of an ylid with a β-lactam is only possible in some isolated cases,[5] another method was required for the methylenation of the carbonyl compounds. Therefore, in this paper a novel application of Petasis' alkylidenation chemistry[9–11] for the conversion of *N*-aryl-2-azetidinones and 2-aziridinones to *N*-aryl-2-methyleneazetidines and 2-methyleneaziridines is disclosed.

A suitable reagent for the methylenation of heteroatom-substituted carbonyl compounds is dimethyl titanocene (Cp_2TiMe_2) **1**.[9–11] This compound was originally prepared by reaction of dicyclopentadienyltitanium dichloride with methyllithium in toluene.[9] For our purposes, **1** was synthesized by reaction of methylmagnesium chloride in THF with titanocene dichloride.[12] Because of the lower stability and

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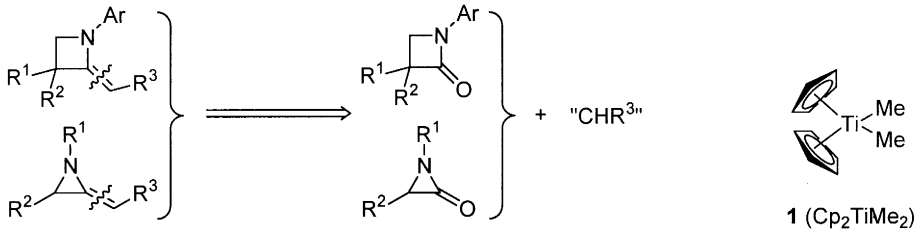
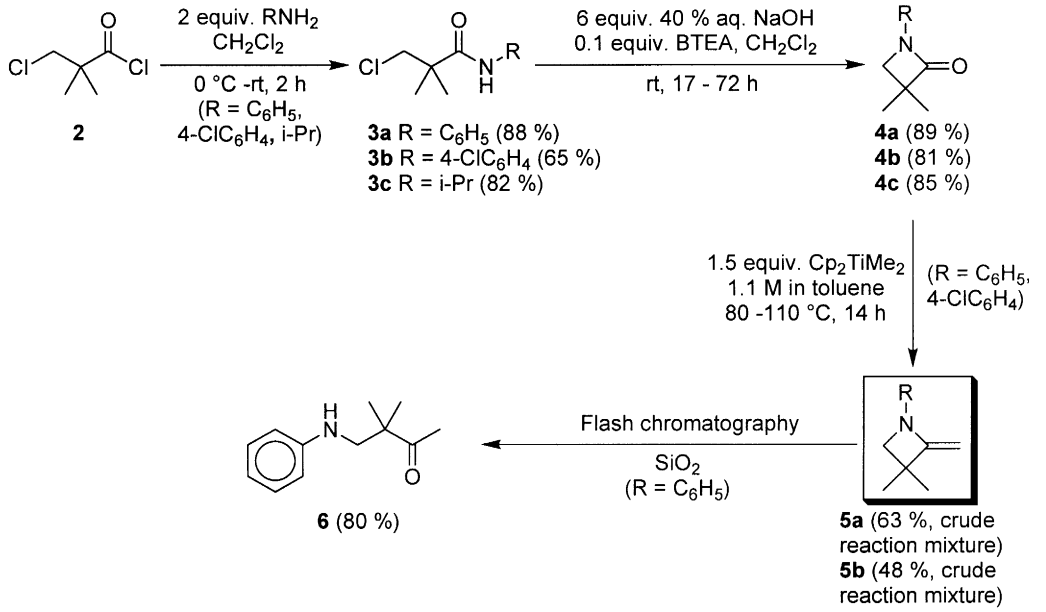


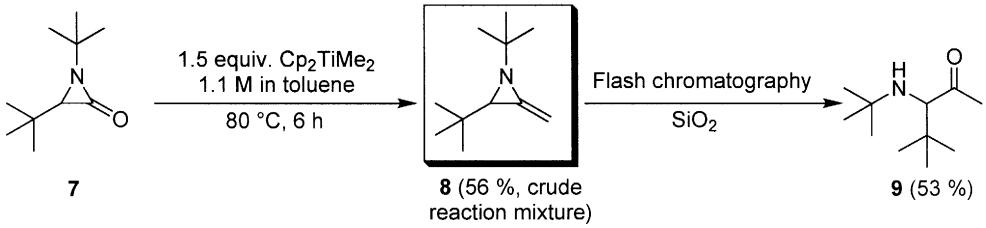
Fig. 1.

even pyrophoric properties of **1** in the solid phase, a 1.1 M solution in toluene:THF (ratio 95:5) was always used for the olefination reactions. The starting 1-aryl-2-azetidinones **4** were synthesized in a two-step procedure starting from 3-chloro-2,2-dimethylpropanoyl chloride **2**. This compound was reacted with 2 equivalents of an aromatic amine in dichloromethane, giving rise to β-chloro propanamides **3**, which could be cyclized to the required 1-aryl-2-azetidinones **4** by means of a phase transfer catalyzed reaction of benzyltriethylammonium chloride (BTEA) and sodium hydroxide.[13] In the case of 3-chloro-2,2-dimethyl-*N*-isopropylpropanamide **3c**, a much longer reaction time of 72 hours was necessary for complete cyclization to **4c**. In our first attempts to methylenate **4a**, 1.5 equivalents of a 0.6 M Cp_2TiMe_2 solution in toluene was heated at 80°C for several hours (6–24 h), thus affording mixtures of starting material **4a** (40–50%) and 2-methyleneazetidine **5a** (40–60%). If 2-azetidinone **4a** was heated under reflux for 14 hours with 1.5 equivalents of a 1.1 M Cp_2TiMe_2 solution, a mixture of 93% methyleneazetidine **5a** and 7% starting material **4a** was obtained (as observed by ^{1}H NMR). Attempted separation of both compounds by flash chromatography on silica gel (EtOAc:*n*-hexane: 1:4; R_f=0.15) or preparative gas chromatography (160°C) gave rise to complete hydrolysis of 3,3-dimethyl-2-methylene-1-phenylazetidine **5a** to the corresponding 3,3-dimethyl-4-(phenylamino)-2-butanone **6** (Scheme 1). By means of a Kugelrohr distillation (40–60°C/2.5 mmHg), the pure methyleneazetidine **5a** could be obtained in 20% yield.[14] This low yield is due to degradation during the distillation. The reaction of 1-(4-chlorophenyl)-3,3-dimethyl-2-azetidinone **4b** with 1.5 equivalents of Cp_2TiMe_2 in toluene for 14 hours at 80°C gave 100% conversion to the exocyclic enamine **5b** (Scheme 1).[15] In all cases the reaction mixtures were evaporated in vacuo, the residue suspended in pentane and the insoluble titanium salts removed by filtration over Celite. This procedure was repeated until no further precipitation occurred of titanium salts. Of course, such a workup procedure lowered the yields drastically. Finally, the reaction of 3,3-dimethyl-1-isopropyl-2-azetidinone **4c** with titanocene **1** under several circumstances gave either rise to starting material or to complex reaction mixtures, which were not further analyzed. This last experiment clearly demonstrates the need for an electron-withdrawing *N*-substituent in the methyleneazetidines to stabilize the electron-rich exocyclic enamine moiety.

Because of the success of the above described methylenation procedure, the same reaction was performed on a 2-aziridinone. As the methylenation reaction occurs at rather high temperatures and due to the known instability of α-lactams, 1,3-di*tert*-butyl-2-aziridinone **7**, was chosen as a model compound (decomposition starts at 140°C).[16] Compound **7** was heated with 1.5 equivalents Cp_2TiMe_2 **1** (1.1 M in toluene) for 6 hours under reflux. After non-aqueous workup, 1,2-di*tert*-butyl-3-methyleneaziridine **8** was isolated as a yellow oil in 56% yield (Scheme 2). An analytically pure sample of **8** could be obtained by preparative gas chromatography (140°C). Column chromatography on neutral alumina (EtOAc:*n*-hexane: 1:4; R_f=0.1) or vacuum distillation (24–26°C/1.3 mmHg) also afforded the pure methyleneaziridine **8**.[17] On the other hand, by column chromatography on silica gel, the labile enamine **8** was completely hydrolyzed to 3-(*tert*-butylamino)-4,4-dimethyl-2-pentanone **9** (Scheme 2).



Scheme 1.



Scheme 2.

In summary, an easy method was developed to convert strained α- and β-lactams into the corresponding 2-methyleneaziridines and 2-methyleneazetidines by means of an organotitanium reagent.

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14. The spectrometric data of compound **5a** are identical with those reported in Ref. 6.
15. As an example, the spectral data of 1-(4-chlorophenyl)-3,3-dimethyl-2-methyleneazetidine **5b** are given; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.32 (6H, s, Me_2C); 3.61 (2H, s, CH_2N); 3.81 and 4.07 (2×1H, 2×d, J=3.1 Hz, $C{=}CH_2$); 6.68 and 7.20 (2×2H, 2×d, J=8.90 Hz, $HC_{\textit{meta}}$ and $HC_{\textit{ortho}}$ resp.). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.52 (CMe_2); 39.69 (CMe_2); 60.39 (CH_2N); 74.61 ($CH_2{=}C$); 114.28 ($HC_{\textit{meta}}$); 128.91 ($HC_{\textit{ortho}}$); 129.00 and 129.13 (2×C_{quat}); 159.42 ($CH_2{=}C$). IR (NaCl, cm^{-1}): ν_{max}=3410, 3010, 1690, 1620, 1520, 1410, 1390, 1114, 930, 835. MS (70 eV) *m/z* (%): 207/209 (M^+, 80); 206/208 (13); 192 (7); 181 (6); 180 (10); 179 (13); 178 (9); 172 (6); 170 (7); 166 (11); 154 (17); 153 (14); 152 (27); 151 (34); 142 (14); 139/141 (100); 138 (23); 127 (9); 111/113 (23); 75 (18); 66 (15); 65 (6); 51 (11); 44 (12); 41 (13); 40 (70).
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17. As an example, the spectral data of 1,3-di*tert*-butyl-2-methyleneaziridine **8** are given; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 and 1.07 (2×9H, 2×s, 2×Me_3C); 1.90 (1H, t, J=0.65 Hz, CH); 4.43 (1H, t, J=1.1 Hz, (*H*)CH=); 4.46 (1H, d, J=0.65 Hz, (H)C*H*=). ^{13}C NMR (68 MHz, $CDCl_3$): δ 26.76 and 27.12 (2×CMe_3); 30.65 ($CHCMe_3$); 45.23 (CH); 54.41 ($NCMe_3$); 79.78 ($CH_2{=}C$); 137.32 ($CH_2{=}C$). MS (70 eV) *m/z* (%): 167 (M^+, 5); 152 (6); 124 (2); 112 (7); 111 (11); 110 (19); 108 (1); 98 (1); 96 (44); 95 (3); 94 (4); 93 (2); 83 (5); 82 (5); 81 (3); 80 (2); 79 (3); 71 (7); 70 (35); 69 (100); 68 (8); 67 (4); 58 (8); 57 (81); 56 (10); 55 (31); 54 (9); 53 (6); 43 (9); 42 (29); 41 (69). Bp 24–26°C/1.3 mmHg.