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Aza-annulation of β-enaminolactones: application to the synthesis of enantiopure difunctionalized bicyclic lactams

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ABSTRACT

Diastereoselective aza-annulation of seven-membered β-enaminolactones **2** gives access to bicyclic heterocyles **5**. Fragmentation of molecule **5a** with lithium methoxide affords *cis* or *trans* bicyclic lactams **8** with excellent stereoselectivities.

The aza-annulation of β-enaminocarbonyl compounds with acrylate derivatives, originally studied by Hickmott and Sheppard,[1] is a convenient, efficient and now well-known route for the synthesis of δ-lactams, and has been used successfully in the synthesis of various nitrogen heterocycles.[2]

Herein, we wish to present our first results concerning the aza-annulation of β-enaminolactones **2**. To our knowledge, the aza-annulation of enaminolactone derivatives has not yet been described.

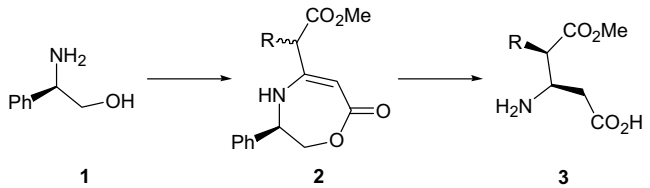
Recently, we reported the enantioselective synthesis of orthogonally protected β-aminodiacids **3** by using β-enaminolactones **2**.[3] These compounds were prepared in two steps by condensation of dimethyl acetonedicarboxylate with (*R*)-phenylglycinol **1** followed by a one-pot procedure -lactonization and regioselective alkylation in basic medium (Scheme 1) .

The aza-annulation of enaminolactones **2** (R = H, Me, Et, Bn) was performed by adding 1 equiv of acryloyl chloride to a solution of **2** in THF. After 10 h, the reactions were quenched with a saturated aqueous solution of sodium carbonate and extracted twice with dichloromethane. The results are presented in Scheme 2.

Cyclization of compounds **2a** and **2b** did not lead to the expected bicyclic products **4a** and **4b** but with total regio- and excellent stereoselectivity to bicyclic lactones **5a** and **5b** in good yields.[4] The (*R*) absolute configuration of the newly created stereocentre in product **5a** was established by X-ray analysis.[5] It is noteworthy that the stereoselectivity for the formation of **5a** decreased when the reaction was left for more then one day under the reaction conditions, that is, in acidic medium. After 5 days, the diastereomeric excess reached only 60%.

The postulated mechanism is presented in scheme 3. The unique formation of products **5** implies that there is an equilibration between enaminolactones **2** and their isomers **6**. It is noteworthy that these regioisomers **6** were not detected in the ^{1}H NMR spectrum of compounds **2**. The aza-annulation is believed to proceed via an initial 1,4-addition of the β-enaminoesters **7** to the α,β-unsaturated acid chloride followed by an intramolecular N-acylation.[6] The observed stereochemistry corresponds to an attack of acryloyl chloride in an *anti* orientation with respect to the phenyl group on the *Z* isomer, an internal hydrogen bonding may stabilize this *Z* configuration in compound **6** (Scheme 3).

Starting from compound **2b** (R = Me), product **5b** was obtained with a total diastereocontrol and in almost the same yield.[7,8] Nevertheless, the aza-annulation did not work with more bulky substituents such as ethyl and benzyl as in compounds **2c** and **2d,** respectively. In these cases, the starting materials were recovered unchanged.



1 2 3

Scheme 1.

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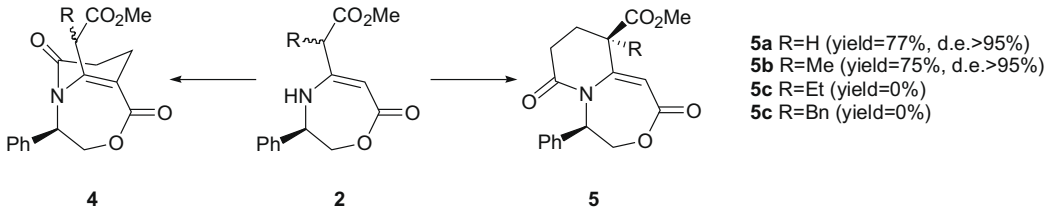
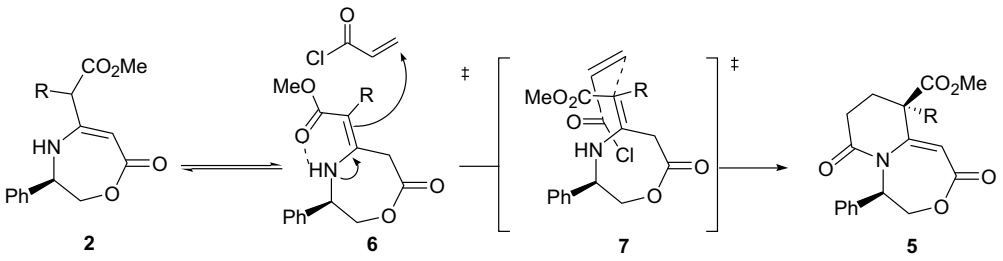


Scheme 2.



Scheme 3.

Next we examined the hydrogenation of enaminolactone **5a**. Hydrogenation using Pd/C or $Pd(OH)_2$ in methanol at 1 atm of hydrogen left compound **5a** unchanged. With the same catalyst and under a hydrogen pressure of 40 atm, we observed the formation of a complex mixture of products arising from the opening of the cyclic systems. With Raney Nickel in methanol and under 40 atm of hydrogen, we observed a fragmentation of the seven-membered ring and the formation of oxazolidine **8a** with total stereocontrol but with low conversion. Such fragmentation was also realized quantitatively using 1 equiv of MeOLi in different solvents (THF, methanol or a mixture of THF/MeOH: 90:10). In aprotic solvent, we observed only the epimerization of the starting enaminolactone **5a** to form isomer **5a**′. In pure methanol, the fragmentation was observed but in lower yields and the reaction was not reproducible. In contrast using 10% MeOH in THF, a mixture of *cis* and *trans* lactams **8a,a**′ were obtained (Scheme 4), the ratio depending on reaction time.

Study of the relative configuration of the newly formed stereocentre on the oxazolidine ring in products **8a,a**′ showed that only a cis configuration for the oxazolidine ring could be detected in the ^{1}H NMR spectrum of the crude product.[9] This is in agreement with our previous experiments on the intramolecular addition of alcoholates to β-enaminoesters.[10] The relative configuration on the lactam ring was established by NOE ^{1}H NMR experiments and, as was already noted in our laboratory for similar structures,[11] we observed that the chemical shift of the proton α to the ester moiety in the *cis* lactam diastereoisomers **8a** was found up field (2.74 ppm) from those of trans isomers **8a**′ (3.75 ppm).[11,12]

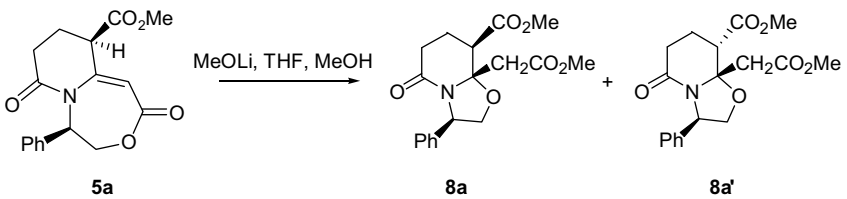
The stereochemistry of this original fragmentation was then examined. First, we have supposed that the first step is the addition of MeOLi to the lactone **5a** and formation of an intermediate alcoholate **9a** which then adds stereoselectively via a Michael addition on the resulting β-enaminoester giving *cis*-oxazolidine **8a**. Then, epimerization takes place, due to the abstraction of the proton α to the ester function giving the thermodynamically more stable epimer **8a**′ (Scheme 5).

Actually, under kinetic control (when the reaction was quenched with aqueous NH_4Cl 1 min after addition of 1 equiv of MeOLi to compound **5a**), *cis* bicyclic lactam **8a** was obtained with good diastereoselectivity de = (94%), total conversion and excellent yield (>90%).

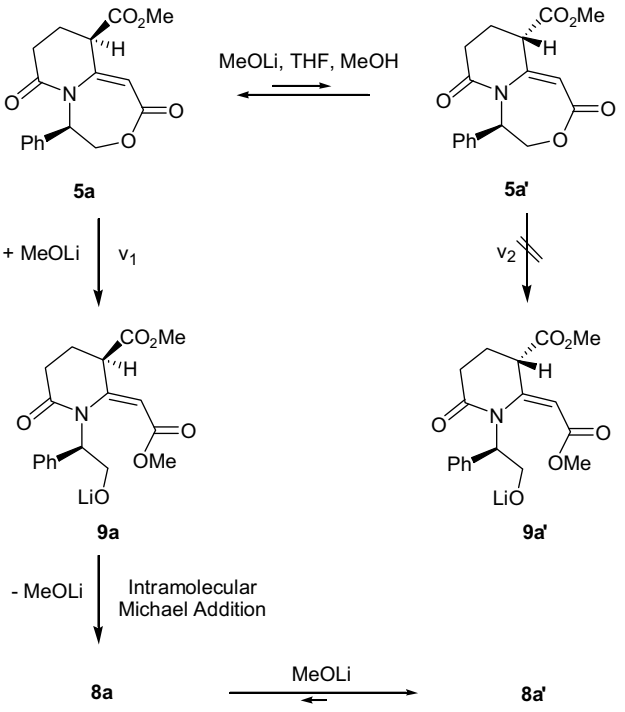
Under thermodynamically controlled conditions, that is, 1 equiv of MeOLi in THF/MeOH: 90:10 after 6 days at room temperature, *trans* lactam **8a**′ was obtained with good diastereoselectivity (**8a**′/**8a** = 90:10). It is noteworthy that neither alcohol **9a** nor alcohol **9a**′ was detected in the ^{1}H NMR of the crude mixtures even when the reactions were followed by ^{1}H NMR in deuterated THF.

We found exactly the same results in terms of diastereoselectivity when starting from epimer **5a**′ (Scheme 5). These results suggest that under these reaction conditions, there exists a rapid equilibration between the two diastereoisomers enaminolactones **5a** and **5a**′, which then react rapidly to give compound **8a** via enaminolactone **5a**. In contrast, oxazolidine **8a**′ which should arise from direct opening of enaminolactone **5a**′ is not observed under kinetic control indicating that $v_2 \ll v_1$.

In summary, we have found an easy and efficient route to chiral non-racemic *cis* bicyclic enaminolactone **5a,b** in three steps, starting from (*R*)-phenylglycinol. Complete diastereocontrol allows easy purification of compounds **5**. This protocol has allowed the synthesis of 10 g of compound **5a**, with 70% overall yield and one purification by chromatography on silica gel. We showed the first results concerning this new chiral scaffold **5a** in the enantioselective



Scheme 4.



Scheme 5.

synthesis of *cis* and *trans* bicyclic lactams **8a** and **8a**′ with good diastereoselectivities.[13] The stereochemistry of this new fragmentation was studied allowing the efficient synthesis of both stereoisomers in good yields and stereoselectivities. These original bicyclic lactams should allow an efficient enantioselective access to various *cis* and *trans* 2,3-disubstituted piperidines.

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4. *Spectral analysis for compound* **5a**: white solid, ^{1}H NMR (250 MHz, $CDCl_3$): 2.13–2.31 (m, 2H), 2.63–2.70 (m, 2H), 3.65 (t, 1H, J = 3.75 Hz), 3.75 (s, 3H), 4.45 (d, 1H, J = 13.75 Hz.), 4.73 (dd, 1H, J = 6.75 and 13.75 Hz), 5.19 (s, 1H), 6.18 (d, 1H, J = 6.5 Hz), 7.16–7.30 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 21.2, 28.6, 47.0, 53.0, 57.9, 66.5, 100.8, 125.7, 127.5, 128.5, 134.1, 143.8, 166.7, 168.4, 170.6. Mp: 164 °C; $[\alpha]_D^{20}$ −20 (*c* 0.92; $CHCl_3$). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found : C, 64.69; H, 5.60; N, 4.29.
5. Atomic coordinates, bond lengths and angles have been deposited at the Cambridge Crystallographical Data Center with the deposition number CCDC 635512.
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7. Absolute configuration on the newly created stereocentre was deduced from the configuration of compound **5a**.
8. The reaction was performed on a mixture of the two epimers **2b**.
9. Relative configurations of the *cis* lactams **8a** and *trans* lactams **8a**′ were established by NOE ^{1}H NMR experiments.
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12. *Spectral analysis for compound* **8a**: Colorless oil, ^{1}H NMR (250 MHz, $CDCl_3$): 2.06–2.13 (m, 2H), 2.38–2.55 (m, 1H), 2.64–2.70 (m, 1H), 2.74 (t, 1H, J = 5 Hz), 2.78 (d, 1H, J = 15.75 Hz), 2.91 (d, 1H, J = 15.75 Hz), 3.48 (s, 3H), 3.71 (s, 3H), 4.04 (dd, 1H, J = 7.25 and 9.25 Hz), 4.50 (d, 1H, J = 8.5 Hz); 5.37 (t, 1H, J = 7.75 Hz), 7.14–7.30 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 19.5, 29.2, 38.4, 49.5, 51.5, 52.1, 58.5, 69.6, 93.1, 125.4, 127.1, 128.3, 138.7, 168.6, 169.1, 170.8. $[\alpha]_D^{20}$ −68 (*c* 1.13; $CHCl_3$). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 61.23; H, 6.01; N, 3.90. *Spectral analysis for compound* **8a**′: Colorless oil, ^{1}H NMR (250 MHz, $CDCl_3$): 2.06–2.13 (m, 2H), 2.52–2.61 (m, 2H), 2.68 (d, 1H, J = 15 Hz), 2.87 (d, 1H, J = 14.75 Hz), 3.62 (s, 3H), 3.66 (s, 3H); 3.75 (t, 1H, J = 4.5 Hz), 3.97 (dd, 1H, J = 7.75 and 8.75 Hz), 4.41 (d, 1H, J = 8.5 Hz); 5.36 (d, 1H, J = 8 Hz), 7.15–7.31 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 19.7, 27.9, 41.4, 43.4, 52.0, 59.0, 70.1, 93.6, 125.5, 127.4, 128.7, 139.3, 168.8, 169.8, 171.1. $[\alpha]_D^{20}$ −35 (*c* 0.91; $CHCl_3$).
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