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Tetrahedron Letters 44 (2003) 757–760

TETRAHEDRON LETTERS

Diastereoselective synthesis of 3,6-disubstituted 3,6-dihydropyridin-2-ones

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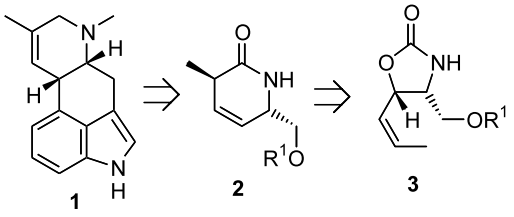
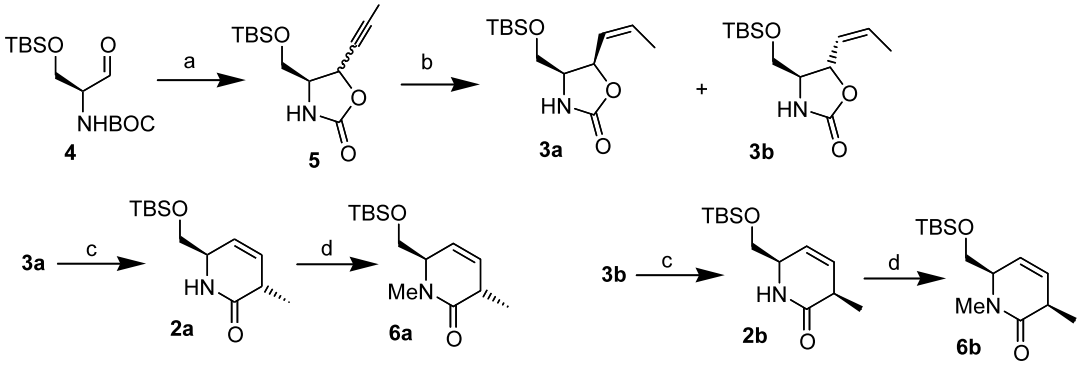
Received 14 October 2002; accepted 22 November 2002

Abstract—In a short sequence, 5-vinyloxazolidin-2-ones were converted into the 3,6-disubstituted 3,6-dihydropyridin-2-ones via Pd-catalysed carbonylation and enolate alkylation with high diastereoselectivity. Alkylation of 6-substituted *N*-methylpyridin-2-ones gives stereoselectively the 3,6-*anti* diastereoisomer with MeI, BuI and *i*-PrI. Alkylation of the corresponding *N*-BOC pyridinones gives the 3,6-*syn* diastereoisomer with high selectivity. © 2003 Elsevier Science Ltd. All rights reserved.

The piperidine ring is common to several classes of naturally occurring alkaloids. One of the most notable is the ergot alkaloids due to their pharmacological properties.[1] The total synthesis of *Agroclavine I* **1**[2–4] currently being undertaken in our group required a stereoselective synthesis of the 3,6-disubstituted pyridinone **2**.



We have recently reported the synthesis of 3,6-disubstituted pyridinones via diastereospecific palladium-catalysed carbonylation of 5-alkenyloxazolidinones.[5,6] In order to use this approach to the synthesis of **2** requires a *Z-syn* oxazolidinone such as **3**. In order to investigate this route, **3a** (R^1 = TBS) was prepared from serine. Addition of lithiated propyne to the protected serinal **4**[7] proceeded with in situ formation of a 3:2 mixture of epimeric oxazolidinones **5** which was reduced by Lindlar hydrogenation to give the *Z*-propenyloxazolidinones **3a**,**b** which were separated by column chromatography (Scheme 1).[8] As expected from our earlier work on related systems,[6] carbonylation of each of the diastereoisomeric oxazolidinones **3a** and **3b** gave a single pyridinone **2a** and **2b**, respectively. Since



Scheme 1. *Reagents and conditions*: (a) Propyne (excess), BuLi (2.5 equiv.), THF, −78°C, then **4**, −78°C to rt, 75%; (b) Lindlar catalyst, H_2, quinoline, EtOH, 98%; column chromatography **3a**/**3b** 3:2; (c) $PdCl_2(PPh_3)_2$ (10 mol%), EtOH, CO (65 atm), 60°C, 48 h, (**2a**, 27%; **2b**, 31%); (d) NaH (1 equiv.), MeI (2 equiv.), THF, 0°C to rt, (**6a**, 75%; **6b**, 78%).

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PII: S0040-4039(02)02677-1

Agroclavine I is *N*-methylated, pyridinones **2a**,**b** were also methylated (NaH, MeI) to give **6a**,**b** in good yield.

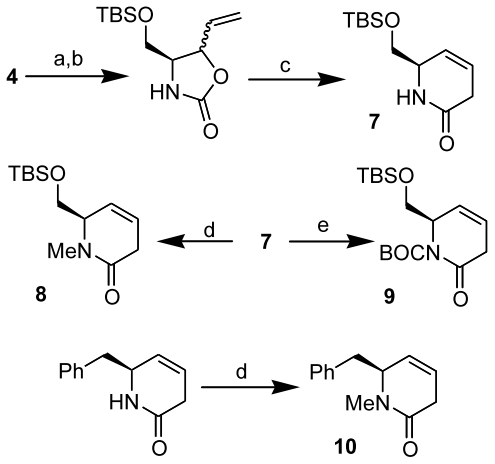
We have previously demonstrated the stereospecificity of the carbonylation[6] by comparison of the ^{1}H NMR spectra of a 3,6-disubstituted pyridinone product with that of the same compound prepared by a stereochemically unambiguous synthesis.[9] Thus, *Z-syn* oxazolidinones (such as **3a**) give 3,6-*anti* pyridinones (such as **6a**) and *Z-anti* oxazolidinones give 3,6-*syn* pyridinones. Unfortunately, in the case of the oxazolidinones **3a**,**b**, the carbonylations required a long time to reach completion and the yields of pyridinones were rather low. This, coupled with the low diastereoselectivity of alkynyl-lithium addition and the need for an elaborate diastereoisomer separation, has prompted us to look for an alternative stereoselective synthesis of pyridinone **2**.

One such approach is to introduce the 3-substituent by alkylation of the corresponding pyridinone enolate. The stereoselectivity of alkylation should then be controlled by the substituents on the 6-position and on nitrogen. While there have been several reports of the diastereoselective enolate alkylation of 6-substituted piperidin-2-ones,[10–15] we were surprised that the corresponding alkylation of pyridinones had not been reported.

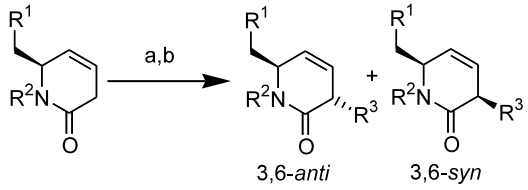
The 3-unsubstituted pyridinone **7** was prepared in three steps from the protected serinal **4** in good yield via our carbonylation methodology (Scheme 2). In order to investigate the influence of the group on nitrogen, the *N*-methyl **8** and *N*-Boc derivatives **9** were prepared.[16] Pyridinone **10**, which contains a non-coordinating substituent in the 6-position, was also prepared by *N*-methylation of the corresponding lactam[5] (Scheme 2).

The 6-substituted pyridin-2-ones **8**, **9**, and **10** were deprotonated (LDA, THF, −78°C) and alkylated with a range of alkyl halides (Scheme 3).[17]

The results of these alkylations are presented in Table 1. Alkylation of the *N*-methylpyridinone **8** with MeI gave the corresponding diastereoisomeric 3-methyl



Scheme 2. *Reagents and conditions*: (a) Vinylmagnesium bromide (2.5 equiv.), THF, −78°C to rt, 85%; (b) KO^{t}Bu, THF, 70%; (c) $PdCl_2(PPh_3)_2$ (10 mol%), EtOH, CO (65 atm), 60°C, 32 h, 85%; (d) NaH, THF, 0°C, then MeI, 0°C to rt, (**8**, 80%; **10**, 68%); (e) BOC_2O, DMAP (10 mol%), MeCN, 90%.



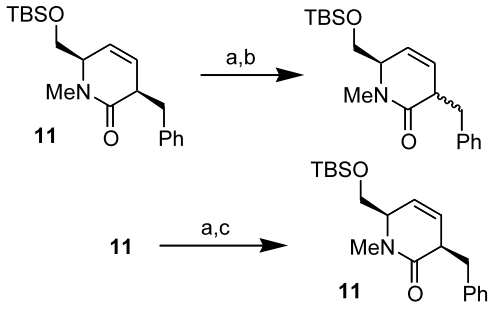
Scheme 3. *Reagents and conditions*: (a) LDA (1 equiv.), THF, −78°C; (b) R^3X (2 equiv.), −78 to 0°C.

pyridinones in an 82:18 ratio (Table 1, entry 1). The major isomer was identical to the 3,6-*anti* isomer **6a**, previously prepared via carbonylation of oxazolidinone **3a** (Scheme 1). The minor isomer was the 3,6-*syn* pyridinone **6b**. For the *N*-methylpyridinones **8** and **10** reacting with alkyl iodides, the *anti* selectivity increases with increasing size of the electrophile (entries 1–3, 9–10).[18] Exchange of the potentially coordinating CH_2OTBS substituent for benzyl has very little effect on the level of diastereoselectivity (compare entries 1 and 2 with 9 and 10). The nature of the group on

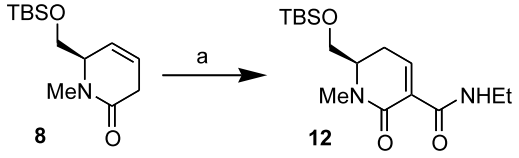
Table 1.

Entry	Lactam	R^1	R^2	R^3X	Yield[a] (%)	*anti*:*syn*[b]
1	**8**	OTBS	Me	MeI	80	82:18
2	**8**	OTBS	Me	BuI	71	86:14
3	**8**	OTBS	Me	^{i}PrI	72	100:0
4	**8**	OTBS	Me	BnBr	65	50:50
5	**8**	OTBS	Me	AllylBr	67	50:50
6	**9**	OTBS	BOC	MeI	89	0:100
7	**9**	OTBS	BOC	BuI	90	0:100
8	**9**	OTBS	BOC	BnBr	79	50:50
9	**10**	Ph	Me	MeI	75	78:22
10	**10**	Ph	Me	BuI	79	85:15
11	**10**	Ph	Me	BnBr	69	50:50

[a] Isolated yield.
[b] Measured by ^{1}H NMR.



Scheme 4. *Reagents and conditions*: (a) LDA, THF, −78°C, 30 min; (b) NH_4Cl (aq.), −78°C, 87% (*syn*:*anti* 1:1); (c) NH_4Cl (aq.), 0°C, 70% (*syn* only).



Scheme 5. *Reagents and conditions*: (a) LDA (1 equiv.), THF, −78°C; EtNCO (2 equiv.), −78 to 0°C, 86%.

nitrogen, however, has a profound influence on the sense of diastereoselection. Alkylation of *N*-BOC protected 6-substituted piperidin-2-ones is reported to be highly *anti* selective.[10–13] This has been attributed to pseudoallylic A(1,3) strain between the BOC group and the 6-substituent leading to a chair-like conformation in which the 6-substituent is axial and consequently favours alkylation to form the 3,6-*anti* product. In the present case, alkylation of the *N*-methyl pyridinones **8** and **10** was found to be *anti* selective. Remarkably, the *N*-BOC pyridinone **9** gives exclusively the *syn* isomer with MeI and BuI (entries 6 and 7) in complete contrast to the reported alkylations of the corresponding piperidinone systems. The reversal in stereoselectivity was confirmed by BOC deprotection[19] (TFA/CH_2Cl_2, 0°C, 20 min, 95%) of the major product from alkylation of **9** with MeI (Table 1, entry 6). This led to a compound identical to **2b**, the product of carbonylation of **3b**. Although we do not have an explanation for the unexpected *syn* selectivity of alkylation of **9**, it is presumably a reflection of the influence of the extra double bond on the transition state geometry. One would expect the enolate to be rather flatter than in the case of the corresponding piperidinone systems.

We were surprised to discover the loss in diastereoselectivity of alkylations with allyl and benzyl bromide (entries 4, 5, 8 and 11). Closer observation of these reactions indicated that the deep red colour of the enolate disappears much faster and at a lower temperature in the case of the enolate quench with these more reactive electrophiles than in the case of quench with alkyl iodides, which usually occurred only on warming of the reaction mixture to 0°C. It seems that the increased reactivity of these electrophiles leads to lower selectivity for alkylation.

In the related piperidinone system, isomerisation of a 3,6-*anti* diastereoisomer into the corresponding 3,6-*syn* compound has been accomplished by deprotonation followed by quench of the enolate with a proton source.[13] In order to investigate this sequence in the pyridinone system, the deep red enolate solution derived from the 3,6-*syn* benzyl bromide alkylation product **11** was quenched with ammonium chloride at both −78°C and at 0°C (Scheme 4). The quench at −78°C gave a 1/1 mixture of the *syn* and *anti* products in 87% yield. On the contrary, the quench of the enolate derived from **11** at 0°C gave the single *syn* pyridinone in a 70% yield, thus the substituent at the 6-position seems to exert a more pronounced effect on the stereoselectivity at higher temperature.

Our attempts to widen the range of electrophiles included reactions with benzaldehyde and ethyl isocyanate. The aldol reaction between the enolate derived from **8** and benzaldehyde produced an inseparable mixture of all four possible diastereomeric adducts in a 1:1:1.5:3 ratio. Reaction of the enolate with ethyl isocyanate gave the synthetically versatile enone **12** in excellent yield (Scheme 5). Presumably, migration of the double bond in this case is facilitated by reduction in the pK_a of the 3-hydrogen by the carboxamido substituent.

In conclusion: we have established a synthetic route towards 3,6-disubstituted 3,6-dihydropyridin-2-ones via a sequence of a palladium catalysed carbonylation of vinyl oxazolidinones, enolisation of the resulting 6-substituted pyridin-2-ones and stereoselective quench with a range of electrophiles. The alkylation of *N*-methylpyridinones is *anti* selective with MeI, BuI, and ^{i}PrI but is stereorandom with allyl and benzyl bromide. Alkylation of *N*-BOC pyridinones shows a remarkable reversal in selectivity to favour the *syn* product. Further investigations into the scope of the reaction will be presented in future publications.

Acknowledgements

We thank the EPSRC for funding.

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17. **Typical procedure**: To a stirred solution of diisopropylamine (101 mg, 1 mmol) in THF (5 ml) was added BuLi (0.32 ml, 2.5 M solution in hexanes, 0.8 mmol) at −78°C and the resulting solution was stirred for 20 min. A solution of pyridinone **8** (200 mg, 0.78 mmol) in THF (3 ml) was added dropwise. The dark red solution was stirred for 30 min and MeI (100 μl, 1.56 mmol) was added in one portion. Stirring was continued at −78°C for 1 h and the solution was allowed to slowly warm up to 0°C when it was quenched by addition of saturated aqueous NH_4Cl (2 ml). Ethyl acetate (30 ml) was added and the organic layer was washed with water (2×10 ml), dried ($MgSO_4$) and concentrated. Flash column chromatography (eluting with 4:1 petrol/ethyl acetate) afforded the *syn* **6b** and *anti* **6a** products as colourless oils. **6b**: (29.5 mg, 14%); $[\alpha]_D^{20}$ +104 (*c* 0.85, $CHCl_3$); ν_{max}/cm^{-1} (film) 2954, 1712; δ_H (500 MHz, $CDCl_3$) 5.73–5.64 (2H, m, vinylic H), 3.84 (1H, m, H-6), 3.69 (1H, dd, *J* 10.3, 4.6, one of CH_2OTBS), 3.58 (1H, dd, *J* 10.3, 3.9, one of CH_2OTBS), 2.98 (3H, s, NMe), 2.91–2.86 (1H, m, H-3), 1.28 (3H, d, *J* 7.4, *Me*C-3), 0.84 (9H, s, *t*-Bu), 0.00 (6H, s, Me_2Si); δ_C (125 MHz, $CDCl_3$) 172.0, 130.9, 122.7, 64.0, 62.5, 35.6, 33.4, 25.8, 18.3, 18.1, −5.4; *m*/*z* (CI+) 270 (MH^+, 45%), 254 (57), 212 (60), 124 (100). Found (MH^+) 270.2249, $C_{14}H_{28}NO_2Si$ requires 270.2253. **6a**: (144 mg, 66%); $[\alpha]_D^{20}$ +32.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 2954, 1712; δ_H (500 MHz, $CDCl_3$) 5.77 (1H, ddd, *J* 10.1, 4.3, 1.2; H-4), 5.63 (1H, ddd, *J* 10.1, 3.9, 0.9; H-5), 3.85–3.80 (1H, m, H-6), 3.62 (1H, dd, *J* 10.1, 4.9, one of CH_2OTBS), 3.59 (1H, dd, *J* 10.1, 4.6, one of CH_2OTBS), 2.98 (3H, s, NMe) 2.92–2.87 (1H, m, H-3), 1.25 (3H, d, *J* 7.4, Me-C3), 0.83 (9H, s, *t*-Bu), 0.00 (6H, s, Me_2Si); δ_C (125 MHz, $CDCl_3$) 172.0, 130.2, 122.4, 65.6, 62.4, 36.9, 33.7, 25.9, 20.7, 18.4, −5.4; *m*/*z* (EI+) 269 (M^+, 20%), 218 (42), 174 (57), 57 (100); Found (M^+) 269.1816, $C_{14}H_{27}NO_2Si$ requires 269.1818.
18. In both this and our previous work,[6] the appearance of the ^1H NMR resonances due to the vinyl protons of the 3,6-disubstituted pyridinones was found to be quite characteristic. In the 3,6-*syn* isomers, the two vinyl protons are very close in chemical shift ($\Delta\delta \approx 0.05$ ppm), whereas in the 3,6-*anti* isomers, the chemical shift difference is greater (ca. 0.12 ppm). This difference helped to assign the stereochemistry of the piperidinones for which an unambiguous assignment was not available by other means (i.e. Table 1, entries 2, 3, 7, 9 and 10).
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