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Facile synthesis of α,α′ disubstituted *N*-hydroxypyrrolidines and *N*-hydroxypiperidines via double 1,4-addition of hydroxylamine

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Abstract—A versatile synthesis of α and α′ disubstituted *N*-hydroxypiperidine and *N*-hydroxypyrrolidine by consecutive double 1,4-addition of hydroxylamine on the corresponding bis α,β-unsaturated diester is described. This reaction takes place an environmentally friendly (ethanol/water) system and at room temperature.
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N-Hydroxypiperidines and *N*-hydroxypyrrolidines are commonly used intermediates in organic synthesis.[1] There are several reports of the Michael addition of hydroxylamine to α,β-unsaturated carboxylate.[2,3] Diaz and co-workers have shown that hydroxylamine can simultaneously add to an α,β and α′,β′ bis unsaturated ketones to afford the corresponding *N*-hydroxypiperidine.[4a] Yamamura and Otto reported that 1,4-thiazinanes can be generated by double 1,4-addition to a 2,4-bis(methoxycarbonyl)-1,5-diaryl-3-thia-1,4-pentadiene.[4b] To the best of our knowledge, the 1,4-addition to a bis α,β-unsaturated diester to afford an *N*-hydroxypiperidine or an *N*-hydroxypyrrolidine has not been reported (Fig. 1).

Bis α,β-unsaturated diesters are readily accessible in a few steps. Octa-2,6-dienedioic acid diethyl ester **3**, or nona-2,6-dienedioic acid diethyl ester **3′**, can be synthesized from the succinaldehyde or glutaraldehyde.

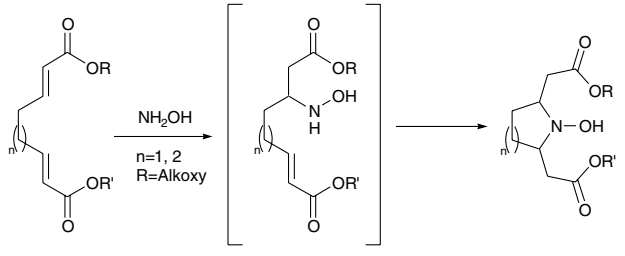
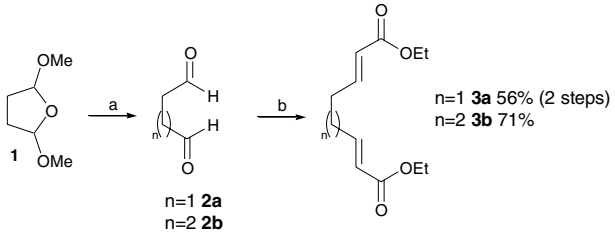


Figure 1.

While glutaraldehyde **2a** is commercially available, succinaldehyde **2b** can be prepared by heating 2-5-dimethoxyfuran **1** in 2 M hydrochloric acid.[5] These dialdehydes (**2a** and **2b**) are each treated with 2.2 equiv of (triphenyl-λ5-phosphanylidene)-acetic acid ethyl ester to afford the octa-2,6-dienedioic acid diethyl ester **3a** or nona-2,6-dienedioic acid diethyl ester **3b** in 56% (from the 2,5 dimethoxy-furane) and 71% yields, respectively (Scheme 1).

Previous reports show that additions of hydroxylamine to α,β-unsaturated esters are most efficient in protic solvents in the presence of a weak base such as triethylamine or sodium carbonate.[3] We found that the overnight treatment of the diethyl ester (**3a** or **3b**) with hydroxylamine at room temperature, in 90/10 ethanol water without any base affords the corresponding *N*-hydroxypyrrolidine (**4a *cis*** and **4a *trans***) or the corresponding *N*-hydroxypiperidine (**4b *cis*** and **4b *trans***) in good yield (60–80%).[5] This double 1,4-addition proceeds



Scheme 1. Reagents and conditions: (a) for $n = 1$ only: HCl 2 N; (b) $P\varphi_3CHCO_2Et$ 2.2 equiv CH_2Cl_2 rt.

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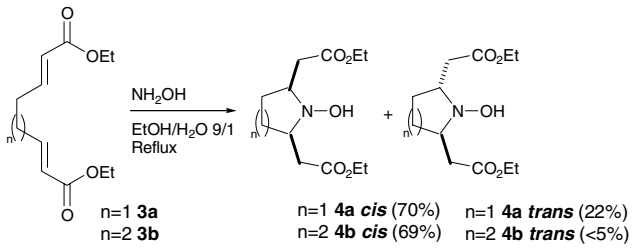


Scheme 2.

to a mixture of the *cis* and *trans* pyrrolidines with the cis isomer predominating (Scheme 2).

The selectivity is more pronounced for the piperidine system (**4a** ***cis***/**4a** ***trans*** = 3.5/1 for the *N*-hydroxypyrrolidine and **4b** ***cis***/**4b** ***trans*** > 95/5 for the *N*-hydroxypiperidine). In the *cis* **4b** both substituents are equatorial, while in *trans* **4b** one, is equatorial and the other is axial. Under the conditions used, the double Michael addition is reversible and leads to the thermodynamic mixture. The cis isomer is clearly favoured over the trans isomer (Fig. 2). The double 1,4-addition also works efficiently for spiro systems.

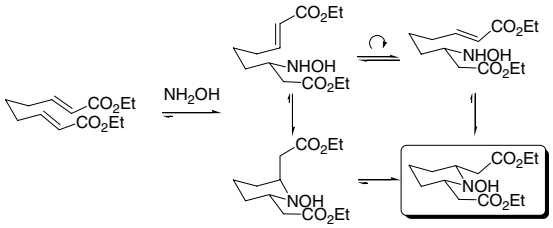
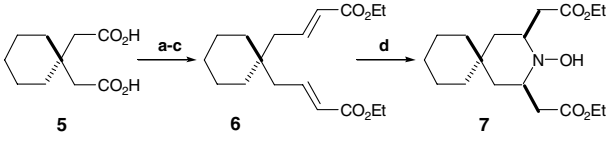


Figure 2.



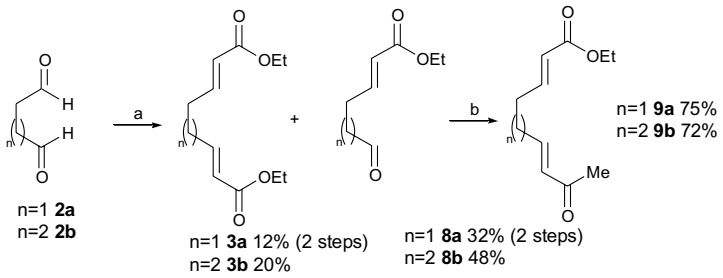
Scheme 3. Reagents and conditions: (a) $LiAlH_4$, 8 equiv, THF 0 °C to rt, 90%; (b) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2 −78 °C; (c) $P\varphi_3CMeCO_2Et$ 1 equiv, CH_2Cl_2 rt 52% (two steps); (d) $NH_2OH{\cdot}H_2O$ EtOH/H_2O 9/1 rt 73%.

The precursor can be prepared from the (1-carboxymethyl-cyclohexyl)-acetic acid **5**, which is reduced in high yields to the corresponding diol by treatment with lithium aluminium hydride in THF. This diol is oxidized to the dialdehyde using Swern conditions and then converted in the diester **6** by a double Wittig-Horner reaction (52% yield for two steps). When treated with hydroxylamine, the double addition proceeds to the 4-spiropiperidine **7** in 73% yield.[5] Again, the cis isomer is the major isomer for the reasons described previously (Scheme 3).

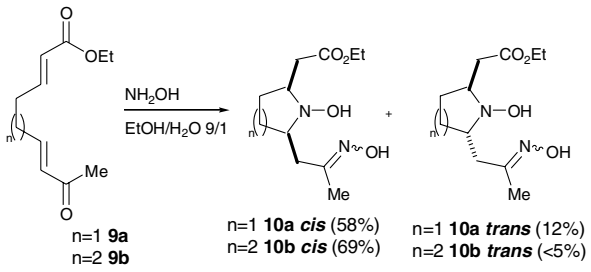
We felt it would be interesting to study the behaviour of a double 1,4-addition in the systems that contain, at least, one ketone. We were curious if the 1,2 addition would compete with the tandem 1,4 additions. We prepared the 1:2 mixture of diester (**3a** or **3b**) and formylmonoester (**8a** or **8b**) by addition of 0.5 equiv of (triphenyl-λ5-phosphanylidene)-acetic acid ethyl ester to the bisaldehyde (**2** or **2b**). The monoaldehyde can be isolated by chromatography. The α,β-unsaturated ketone (**9a** or **9b**) can be synthesized by an addition of 1-(triphenyl-λ5-phosphanylidene)-propan-2-one on the formyl-ester (**8a** or **8b**) (Scheme 4).

When **9a** or **9b** are stirred overnight with 3 equiv of hydroxylamine the expected *N*-hydroxypyrrolidine and *N*-hydroxypiperidine (**10a** ***cis***,***trans*** or **10b** ***cis***,***trans***) are obtained in reasonable yields (for the five as for the six member ring).[5] The ketone, however is also converted into the corresponding oxime. Diaz's group observed similar results when they synthesized *cis*-1-hydroxy-2,6-diphenyl-piperidinone oxime by condensation of hydroxylamine on dibenzalacetone[4a] (Scheme 5).

Two different routes can be considered for this transformation. Either the hydroxylamine reacts first with ketone to generate the oxime and then the double 1,4-addition occurs or the 1,4 addition occurs first followed by oxime formation (Fig. 3). To determine the order of reaction, the keto-ester was treated with 0.5 equiv of hydroxylamine. In addition to the starting material (**9a** or **9b**) three different compounds could be expected in the mixture. The *N*-hydroxyimino-pyrrolidine and *N*-hydroxyimino-piperidine (**10a** or **10b**), the *N*-hydroxyketo-pyrrolidine and *N*-hydroxyketo-piperidine (**11a** or **11b**) and the α,β-unsaturated oximes (**12a** or **12b**). Among these three products, **11a** or **b** turns out to be the major product in the mixture. The transformation



Scheme 4. Reagents and conditions: (a) $P(Ph)_3CHCO_2Et$ 0.5 equiv, CH_2Cl_2 rt. For $n = 1$: %($E/Z > 9/1$) and for $n = 2$: %($E/Z > 9/1$); (b) $P(Ph)_3CMeCO_2Et$ 1 equiv, CH_2Cl_2 rt. For $n = 1$: %($E/Z > 9/1$) and for $n = 2$: %($E/Z > 9/1$).



Scheme 5.

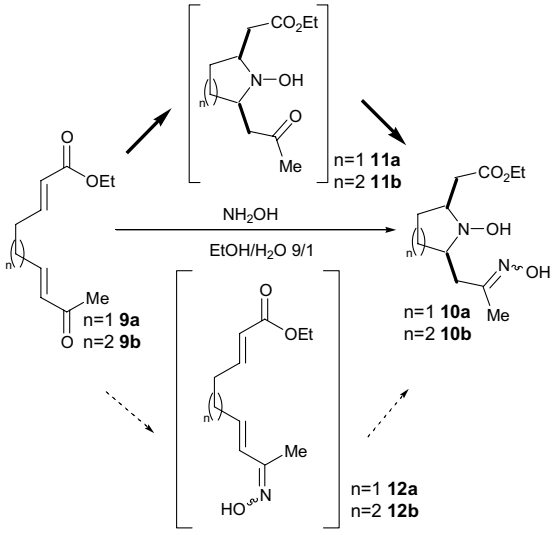


Figure 3.

of the ketone into oxime happens at a much slower rate than the double 1,4-addition. Consequently, by adjusting the amount of hydroxylamine it is possible to select for either the keto or the oximino *N*-hydroxypiperidine. The same is true for the oximino or keto *N*-hydroxypyrrolidine.

In conclusion, a versatile and efficient method to produce α,α′ disubstituted *N*-hydroxypiperidine and *N*-hydroxypyrrolidine is reported.

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5. Typical procedure for double 1,4-addition: To a solution of the bis α,β-unsaturated system in ethanol/water 9/1 (0.1 M) was added the hydroxylamine (3 equiv). The resulting mixture was stirred until TLC showed complete disappearance of starting material (typically overnight). The solvents were, then, evaporated under vacuum. Water and dichloromethane were poured in the system and the water layer was extract twice with the dichloromethane. The organic layers were then combined, washed with brine, dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude was purified by flash chromatography (typical eluant EtOAc/hexane 30/70).