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Synthesis of 3,4-disubstituted piperidines by ene cyclisation of 4-aza-1,7-dienes

Stephen M. Walker, Jodi T. Williams, Alexander G. Russell and John S. Snaith*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

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Abstract—Ene cyclisation of a variety of 4-aza-1,7-dienes affords 3,4-disubstituted piperidines. In particular, cyclisation of diesters **14** and **20** catalysed by $MeAlCl_2$ gives the corresponding *trans* 3,4-disubstituted piperidines with diastereomeric ratios of >200:1.

1. Introduction

Nitrogen heterocycles have always played a major role in the pharmaceutical and agrochemical industries due to their often potent physiological properties, which have resulted in numerous applications.[1] In particular, substituted piperidines occur as key components in an enormous array of biologically active natural and synthetic products, and as a consequence there is a drive towards the synthesis of diastereomerically and enantiomerically enriched piperidines. Whilst a variety of stereocontrolled approaches have been developed,[2] the range of functionality and substitution patterns encountered in piperidine targets continues to inspire new chemistry.[3]

The intramolecular ene reaction is a powerful ring-forming reaction, generating two contiguous stereocentres, often with a high degree of stereocontrol.[4] However, while the imino ene and carbonyl ene reactions have received considerable attention,[5] there have been few piperidine syntheses employing an ene reaction with an alkene as the enophile. Takacs and co-workers have published transition-metal-mediated piperidine syntheses involving the cross-coupling of a diene with either an allylic ether or another diene.[6] Although formally these processes can be regarded as [4+4]- or [4+6]-ene reactions, mechanistically they are far removed from the classical ene reaction.

One of the few examples of a type I ene reaction leading to a piperidine is from the work of Oppolzer, who explored the thermal ene reaction of a simple 4-aza-1,7-diene to produce a 3,4-disubstituted piperidine.[7] Intramolecular cyclisation was achieved at a high temperature (290 °C for 27 h) to give the 3,4-disubstituted diastereomeric piperidines in a combined 26% yield. The diastereomeric ratio was undetermined, but under the high-temperature conditions it is likely to have been poor.

We reasoned that activating the enophile with an electron-withdrawing group, such as an ester, should lower the thermal barrier to the ene reaction, potentially giving improved stereoselectivity. Moreover, the activating group could serve as a coordination site for a Lewis acid, thus opening up the possibility of Lewis acid catalysis of the reaction. Much elegant work on the Lewis acid-catalysed ene reaction leading to six-membered rings has been carried out by Tietze, and levels of stereocontrol can be impressive.[8]

2. Results and discussion

The cyclisation precursor **4** was readily prepared from 3-aminopropanol **1** (Scheme 1). *N*-Tosylation followed by *N*-alkylation with prenyl bromide gave **2**. Subsequent PCC oxidation cleanly afforded aldehyde **3**, which underwent a Wittig reaction with methyltriphenylphosphoranylidene acetate to give ester **4**, exclusively as the *E* diastereomer, in 65% yield after chromatography.

Surprisingly, addition of an ester group to the enophile did not significantly lower the barrier for thermal

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* Corresponding author. Tel.: +44 1214144363; fax: +44 1214144403; e-mail: j.s.snaith@bham.ac.uk

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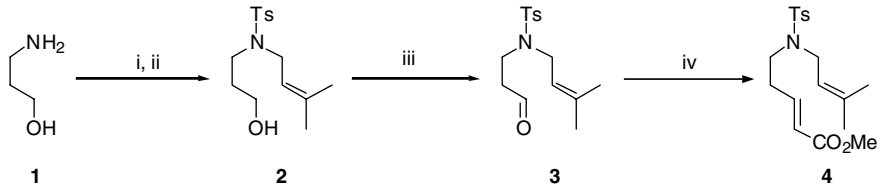
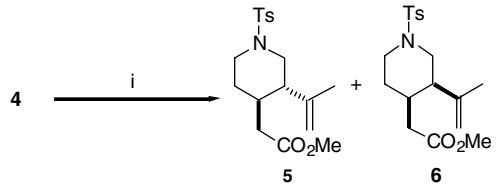


Scheme 1. Reagents and conditions: (i) TsCl, 2 equiv Et_3N, CH_2Cl_2, 0–25 °C, 1 h, 68%; (ii) Cs_2CO_3, MeCN, $BrCH_2CH{=}C(CH_3)_2$, 25 °C, 18 h, 93%; (iii) PCC, Celite, CH_2Cl_2, 25 °C, 2 h, 67%; (iv) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 25 °C, 18 h, 65%.



Scheme 2. Reagents and conditions: (i) Ph_2O, 259 °C, 7 h, 62%.

cyclisation compared with the system studied by Oppolzer. Thus, cyclisation of **4** could only be effected by heating in refluxing diphenyl ether (259 °C) for 7 h (Scheme 2). Removal of the solvent by distillation, followed by chromatography, afforded the piperidine products **5** and **6** in a combined yield of 62% as an inseparable mixture, with a *trans*:*cis* ratio determined as 3:2 by integration of the ^{1}H NMR spectrum.

Although substitution of the enophile with an electron-withdrawing group had only led to a small lowering of the thermal reaction barrier, we envisaged that coordination of a Lewis acid to the carbonyl group would further lower the activation barrier. The Lewis acids, ferric chloride, zinc bromide, methyl aluminium dichloride and scandium triflate, were screened for their ability to catalyse the cyclisation, at temperatures ranging from −78 to 180 °C.

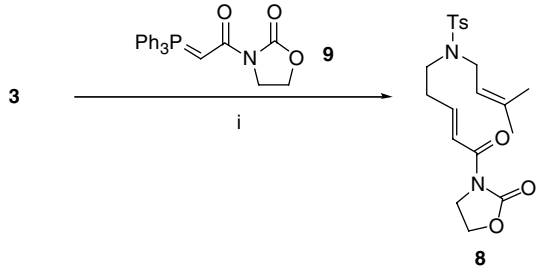
The results were disappointing, and in most cases unreacted starting material was recovered. In the reactions employing ferric chloride and scandium triflate at room temperature, smooth cleavage of the prenyl side chain was observed. It is likely that this is due to the coordination of the Lewis acid to the sulfonamide, facilitating the dissociation of a stabilised allylic cation which then loses a proton to afford **7** and 2-methylbutadiene (Fig. 1). The apparent preference for the Lewis acid to coordinate to the sulfonamide suggested that we needed to modify our enophile to make this the preferred site of coordination.

This prompted us to examine the cyclisation precursor **8**, in which the enophile is activated by an oxazolidinone group. We hoped that the two carbonyl groups would chelate a Lewis acid, overcoming the Lewis basicity of the sulfonamide.

Oxazolidinone **8** (*E*:*Z* 25:1) was readily prepared in 76% yield by a Wittig reaction between **3** and the known ylide **9** (Scheme 3).[9]

A number of Lewis acids were screened for their ability to catalyse the cyclisation (Table 1).

The inclusion of an oxazolidinone group sufficiently lowered the activation barrier so that the Lewis acid-catalysed cyclisation now occurred at ambient temperature. Fragmentation of the starting material was not observed, indicating that the Lewis acid was preferentially coordinating to the *N*-acyloxazolidinone rather than to the sulfonamide. Diastereomeric ratios were generally moderate, with titanium tetrachloride affording an 8.2:1 *trans*:*cis* inseparable mixture of piperidines **10**



Scheme 3. Reagents and conditions: (i) CH_2Cl_2, 25 °C, 72 h, 76%.

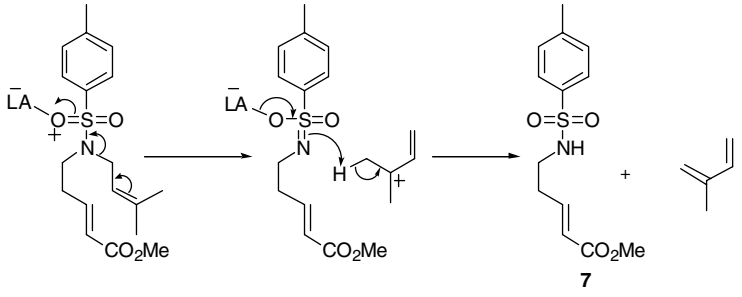
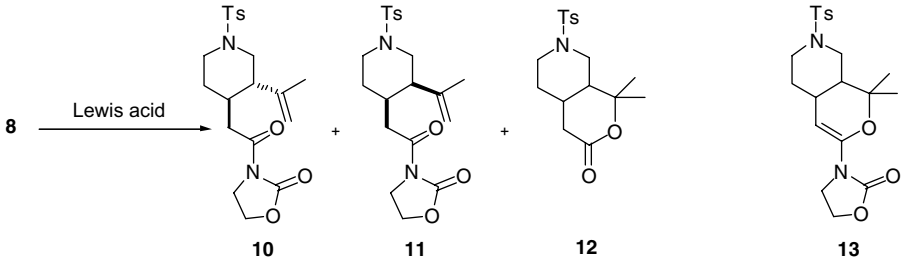


Figure 1.

Table 1. Results of Lewis acid screening for catalysis of cyclisation of **8**



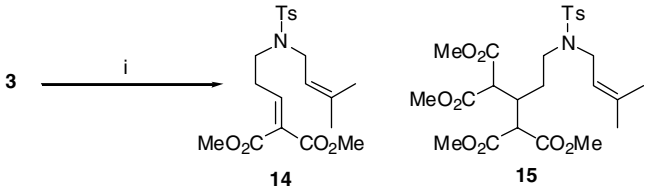
Lewis acid[a]	**10**:**11**:**12**	*trans*:*cis* ratio of ene product
Me_2AlCl	42:36:22	1.2:1
$MeAlCl_2$	59:27:14	2.2:1
$AlCl_3$	65:20:15	3.3:1
$FeCl_3$	32:11:57	2.9:1
$Sc(OTf)_3$	50:11:39	4.5:1
$ZnBr_2$	28:5:67	5.6:1
$TiCl_4$	49:6:45	8.2:1

[a] All reactions were performed with 1 equiv of Lewis acid at room temperature in dichloromethane. Ratios determined by integration of ^1H NMR spectra of crude cyclisation products.

and **11** in the best case. Crude reaction yields were high, but in all cases significant amounts of a side product, identified as lactone **12**, were present. It is reasonable to assume that this compound arises from hydrolysis of **13**, implying that **8** was undergoing a competing hetero Diels–Alder reaction.[10] In some cases, the yield of **12** was greater than the combined yields of the *trans* and *cis* piperidines. Lactone **12** was obtained as a single stereoisomer, most likely the *trans* isomer based upon the literature precedent for closely related systems[11] and the geometrical constraints inherent in such an intramolecular Diels–Alder reaction.

Although the lowering of the activation barrier by Lewis acid coordination to the oxazolidinone was encouraging, the competing Diels–Alder cyclisation pathway was disappointing, and so we turned our attention to the diester **14**. This cyclisation precursor has the advantage of two electron-withdrawing substituents on the enophile as well as the ability to chelate a Lewis acid. With aldehyde **3** in hand, the simplest route to our target appeared to be via a Knoevenagel condensation with dimethyl malonate (Scheme 4).

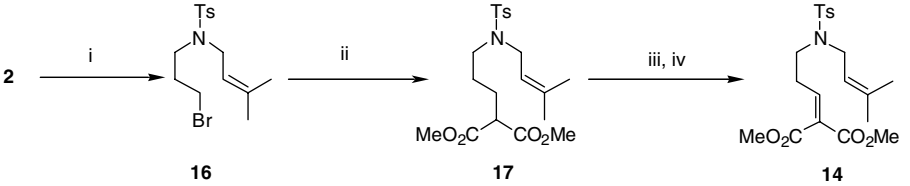
Surprisingly, under the standard conditions of piperidine and acetic acid, only trace amounts of the desired diester **14** were produced, inseparable from a complex mixture of compounds. Mass spectrometric evidence suggested that side-products had resulted from the addition of a second equivalent of malonate into the α,β-unsaturated diester to give **15**, as well as other products from base-mediated oligomerisation processes. The reportedly milder conditions employing ammonium acetate and acetic acid were similarly unsuccessful,[12] as was switching to malononitrile as the nucleophile.



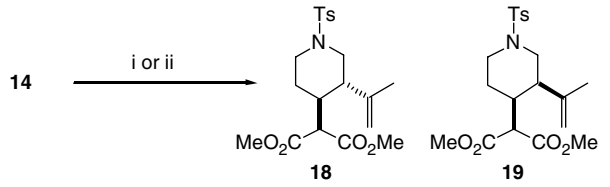
Scheme 4. Reagents and conditions: (i) dimethyl malonate, piperidine/acetic acid or ammonium acetate/acetic acid, CH_2Cl_2, 0–25 °C, 1 h.

The significant base sensitivity of **14** led us to adopt an approach in which the α,β-unsaturated system was introduced under essentially neutral conditions by selenoxide elimination (Scheme 5).

Alkylation of dimethylmalonate by bromide **16** proceeded smoothly to afford the saturated diester **17** in 78% yield. Phenylselenation followed by oxidation to the corresponding selenoxide led to spontaneous elimination at room temperature to afford **14** in 69% overall yield.



Scheme 5. Reagents and conditions; (i) PPh_3, CBr_4, CH_2Cl_2, 25 °C, 2 h, 94%; (ii) $(MeO_2C)_2CH_2$, NaHMDS, THF, 25 °C, 18 h, 78%; (iii) LDA, THF, −78 to 25 °C, 30 min then PhSeCl, THF, −78 to 25 °C, 18 h, 94%; (iv) H_2O_2, THF, 25 °C, 18 h, 73%.



Scheme 6. Reagents and conditions: (i) *o*-dichlorobenzene, 180 °C, 7 h, 74%; (ii) $MeAlCl_2$, CH_2Cl_2, −78 °C, 5 h, 72%.

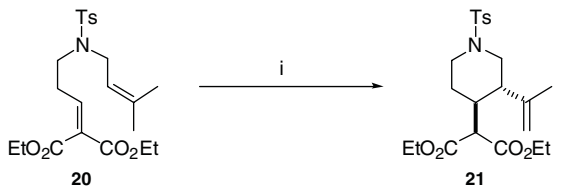
The diester was subjected to thermal cyclisation, and as anticipated, showed a lower activation barrier than the monoester, with cyclisation being complete within 7 h in refluxing *o*-dichlorobenzene (180 °C). Removal of the solvent by distillation, followed by flash chromatography, afforded an inseparable 4:1 mixture of piperidines **18** and **19** in 74% yield, with the thermodynamically more stable trans isomer in excess as expected (Scheme 6).

Encouraged by this result, we went on to examine catalysis of the cyclisation by methylaluminium dichloride. The alkyl aluminium halides have the advantage of being commercially available as anhydrous solutions and are able to scavenge small amounts of water, thereby minimising side reactions that could be promoted by the presence of traces of Brønsted acids.[13] Furthermore, the observation that $MeAlCl_2$ did not induce prenyl fragmentation in our attempts to cyclise monoester **4** suggested that it had a relatively low affinity for the sulfonamide, thereby minimising competitive binding of the catalyst to this site.

We were delighted to find that diester **14** cyclised at −78 °C in the presence of $MeAlCl_2$ to afford a 72% yield of the *trans* piperidine **18** after chromatography, with a diastereomeric ratio of >200:1, as determined by HPLC. Repeating the cyclisation with the diethyl analogue **20** afforded *trans* piperidine **21** in 67% yield, with equally high diastereoselectivity (Scheme 7).

Single crystals of **21** were grown from petrol and ethyl acetate, and the relative stereochemistry was confirmed by X-ray analysis (Fig. 2).

In conclusion, we have synthesised a number of precursors and investigated their conversion to 3,4-disubstituted piperidines by ene cyclisation. Monoester **4** was found to have a high barrier to thermal cyclisation, giving the corresponding *cis* and *trans* piperidines in a poor diastereomeric ratio; the cyclisation of **4** was not amenable to Lewis acid catalysis. Activation of the enophile



Scheme 7. Reagents and conditions: (i) $MeAlCl_2$, CH_2Cl_2, −78 °C, 5 h, 67%.

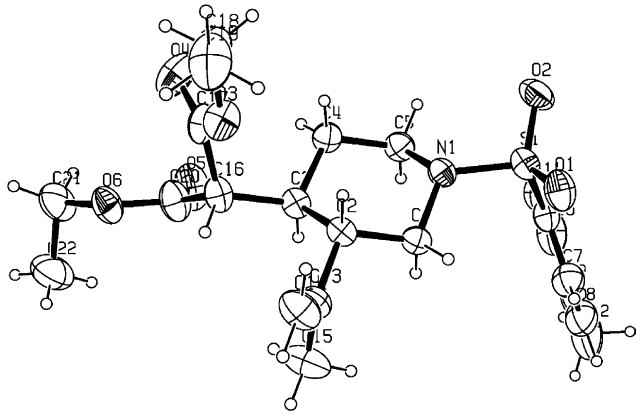


Figure 2. ORTEP[14] representation of **21**; ellipsoids drawn at 30% probability level.

with an oxazolidinone function, compound **8**, did allow the ene cyclisation to be catalysed by Lewis acids, yielding the corresponding piperidines in a *trans*:*cis* ratio of up to 8.2:1, but varying amounts of an intramolecular Diels–Alder cycloadduct were also formed under these conditions. Diesters **14** and **20** were found to undergo ene cyclisations catalysed by $MeAlCl_2$ at −78 °C to give the *trans* piperidines **18** and **21**, with diastereomeric ratios of >200:1. The methodology should find application in the synthesis of more complex targets.

2.1. Cyclisation procedure: Preparation of (3*R**,4*S**)-4-[bis(carboethoxy)methyl]-3-isopropenyl-1-(toluene-4-sulfonyl)piperidine (21)

Methyl aluminium dichloride (1 M soln. in hexanes, 0.12 cm^3, 0.12 mmol) was added to a solution of diester **20** (53 mg, 0.12 mmol) in CH_2Cl_2 (10 cm^3) at −78 °C. The resulting mixture was stirred at −78 °C for 5 h, after which it was quenched by the addition of water (10 cm^3). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 cm^3) and the combined organic phases were washed with brine (10 cm^3), dried over Na_2SO_4 and evaporated in vacuo to leave a colourless oil, which was purified by flash column chromatography (silica; eluent 3:1 petrol/ethyl acetate) to give piperidine **21** as a white crystalline solid (35 mg, 67%); ($R_f = 0.39$); mp = 84–86 °C (from petrol/ethyl acetate); (found: C, 60.41; H, 7.31; N, 3.09; S, 7.33. $C_{22}H_{31}NO_6S$ requires C, 60.39; H, 7.14; N, 3.20; S, 7.33); ν_{max}(neat)/cm^{-1} 2982 (CH), 2928 (CH), 1724 (C=O), 1643 (C=C), 1597 (C=C aromatic), 1342 (SO_2), 1157 (SO_2); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1, CH_2CH_3), 1.26 (3H, t, *J* 7.1, CH_2CH_3), 1.62–1.73 (4H, envelope, CH_3 and $CHHCH_2N$), 1.92–2.01 (2H, envelope, $CHHCH_2N$ and $CHCH_2CH_2N$), 2.09 (1H, t, *J* 11.2, $CHCHHN$), 2.22–2.28 (1H, m, CH_2CHHN), 2.37 (1H, dt, *J* 4.1 and 11.2, $CHCH_2N$), 2.43 (3H, s, $ArCH_3$), 3.52 (1H, d, *J* 2.9, $CH(CO_2Et)_2$), 3.71–3.76 (1H, m, $CHCHHN$), 3.79–3.85 (1H, m, CH_2CHHN), 4.08–4.19 (4H, m, $2 \times CH_2CH_3$), 4.78 (1H, br s, C=C*H*H), 4.93 (1H, t, *J* 1.5, C=CH*H*), 7.31 (2H, d, *J* 8.1, Ar C*H*), 7.62 (2H, d, *J* 8.1, Ar C*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 20.7 (CH_3), 21.5 (CH_3), 26.8 (CH_2, CH_2CH_2N), 38.3 (CH, $CHCH_2CH_2N$), 46.4 (CH, $CHCH_2N$), 46.5

(CH_2, CH_2CH_2N), 51.0 (CH_2, $CHCH_2N$), 52.0 (CH, $CH(CO_2Et)_2$), 61.2 (CH_2, CH_2CH_3), 61.3 (CH_2, CH_2CH_3), 114.6 (CH_2, $C{=}CH_2$), 127.6 (CH, Ar), 129.6 (CH, Ar), 133.1 (C^4), 143.3 (C^4, $C{=}CH_2$), 143.5 (C^4), 167.8 (C^4, CO_2Et), 168.9 (C^4, CO_2Et); *m/z* (EI) 437 (M^+, 4%), 392 (5), 346 (4), 282 (100), 278 (9), 241 (17), 210 (4), 184 (5), 155 (19), 122 (48), 107 (5), 96 (55), 91 (68), 65 (12), 42 (38).

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