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The first catalytic inverse-electron demand hetero-Diels-Alder reaction of nitroso alkenes using pyrrolidine as an organocatalyst

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Received 17th December 2003, Accepted 29th January 2004 First published as an Advance Article on the web 16th February 2004

The first catalytic inverse-electron demand hetero-Diels-Alder reaction of nitroso alkenes has been developed. Nitroso alkenes were generated in situ from α -halooximes and underwent [4 + 2]-cycloadditions with enamines as dienophiles formed from aldehydes and pyrrolidine (10 mol%) as an organocatalyst. The presence of a suitable heterogeneous buffer system was found to be essential and best results were obtained with sodium acetate trihydrate. The resulting 5.6-dihydro-4*H*-oxazines were obtained in moderate to good yields under mild reaction conditions. A catalytic cycle has been proposed and evidence for the cycloaddition mechanism has been obtained. Moderate asymmetric induction (42% ee) was observed when a chiral secondary amine was used.

Introduction

Over the last years, 5,6-dihydro-4H-oxazines have been shown to be versatile synthetic intermediates for the preparation of a large number of diverse products. It has been demonstrated in several reports that these oxazine derivatives of the generalised structure 1 can be readily converted into oxazinones, pyrrolidines, pyrroles, amino alcohols, amines, 1,3-dicarbonyl compounds and other products via simple oxidations, reductions or hydrolysis reactions (Scheme 1).¹



Scheme 1 Transformations of 5,6-dihydro-4*H*-oxazines 1.

As outlined in Scheme 2, the oxazines 1 are in turn easily accessible from α -halooximes 2 and olefinic substrates such as enol ethers, enamines, alkenes or allenes. Owing to the fundamental studies of Gilchrist et al. and the thorough investigations performed by Reißig and coworkers, these processes have been identified as hetero-Diels-Alder reactions with inverse-electron demand involving transient nitroso alkenes 3.2,3 These highly reactive intermediates can be generated through



Scheme 2 Synthesis of 5,6-dihydro-4H-oxazines 1 via hetero-Diels-Alder reactions involving transient nitroso alkenes.

10.1039/b316518c

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base-mediated dehydrohalogenations of the readily available α -halooximes and furnish the cycloadducts 1 in a highly regioselective fashion.

Although numerous applications of this reaction have been reported, severe restrictions have remained in place. Due to their high reactivity, only very few, sterically encumbered nitroso alkenes have been isolated and characterised.⁴ It is also known that processes involving these intermediates are prone to side reactions such as polymerisations. Similarly, long reaction times of up to 10 days are necessary to minimise the concentration of free nitroso alkenes and large excesses of the dienophiles are required in order to obtain acceptable yields. Furthermore, the requirement to preform reactive dienophiles such as enol ethers has limited the practicability of this otherwise very useful conversion.

In order to increase the reaction scope and enable its application to a large number of substrates, our investigations focused on the development of a catalytic hetero-Diels-Alder reaction of nitroso alkenes using inexpensive and readily available reagents and catalysts, with possible extensions to enantioselective variants. The results of these investigations are presented in this article.

Results and discussion

Lewis acid catalysts need to be avoided in processes involving nitroso alkenes as they are known to increase the high reactivity of these species even further and lead to the formation of undesired dimerisation products and polymers.⁵ Encouraged by recent advances in organocatalytic cycloaddition reactions, we decided to pursue such an approach.⁶ Mixtures of aldehydes and catalytic amounts of secondary amines such as pyrrolidine can reversibly generate electron-rich enamines. These compounds are suitable dienophiles for cycloadditions with inverse electron demand. The envisaged catalytic cycle is shown in Scheme 3.

Initial experiments with the preformed enamine 4, formed from isovaleraldehyde and pyrrolidine, and a-bromoacetophenone oxime (2a) revealed that both the anticipated aminoacetal 1a as well as the desired dihydro oxazine 1b were formed in this reaction (Scheme 4). Both products 1a and 1b could be isolated as mixtures of diastereomers. However, low yields and the formation of several unidentified by-products indicated that there were several challenges inherent to this reaction sequence which needed to be addressed.



Scheme 3 Catalytic cycle of the pyrrolidine-mediated hetero-Diels-Alder reaction of nitroso alkenes with enamines leading to 5,6-dihydro-4*H*-oxazines.



Scheme 4 Reaction of α -halooximes with preformed enamines.

It is well known that nitroso alkenes are highly susceptible to conjugate additions of heteroatom nucleophiles, especially amines.⁴ It was confirmed in the present case that an instantaneous addition of pyrrolidine to α -bromoacetophenone oxime (**2a**) took place at room temperature and the resulting tertiary amine **5** was isolated in high yield (Scheme 5).⁷ However, this side reaction could be completely suppressed when the oxime was added as the last reaction component to a solution containing the amine catalyst and an excess of the aldehyde, thereby shifting the initial equilibrium towards the enamine (see Scheme 3).



Scheme 5 Reaction of α -bromoacetophenone oxime with pyrrolidine.

Although pyrrolidine, or the corresponding enamines, were sufficiently basic to induce dehydrohalogenation of the α -halooxime, one equivalent of acid liberated in this process has to be neutralised in order to achieve catalytic turnover and the presence of a base is therefore necessary. In contrast, the hydrolytic cleavage of the intermediate aminoacetal to release the amine catalyst (see Scheme 3) calls for a slightly acidic medium.^{6a} In order to balance these apparently irreconcilable requirements we decided to employ heterogeneous buffer systems in order to keep the proton concentration in solution approximately constant throughout the reaction.⁸ Various buffers were examined for their ability to neutralise acid and enhance hydrolytic cleavage in the model reaction comprising

Table 1 Effect of solid bases/buffers on catalytic turnover

Ph + 0	2b Cl N (10 mol%) B Solid base (2 eq) 1 CDCl ₃ , r.t., 16 h	Ph Ph	N ^O w ^O H
		1a	1b
Entry	Base	Conversion (%)	Ratio 1a : 1b
1	No base	30	30:70
2	Na ₂ CO ₃	<i>a</i>	(100:0)
3	Na,CO, H,O	<i>a</i>	(100:0)
4	Na ₂ CO ₃ ·10H ₂ O	<i>a</i>	(100:0)
5	NaHCO ₃	50	20:80
6	KH ₂ PO ₄	30	30:70
7	Na ₂ HPO ₄ ·2H ₂ O	40	20:80
8	Na ₂ C ₂ O ₄	30	30:70
9	Na ₃ C ₆ H ₅ O ₇ ·2H ₂ O	30	30:70
10	NaOĂc	80	10:90
11	NaOAc•3H ₂ O	95	5:95
12	$NaOAc \cdot 3H_2O^b$	<i>c</i>	
^a Decom	position. ^b No pyrrolidin	e added. ^c No convers	ion.

 α -chloroacetophenone oxime (**2b**), isovaleraldehyde and catalytic amounts of pyrrolidine (10 mol%). The results of these studies are summarised in Table 1.

As expected, only moderate amounts of the hetero-Diels-Alder adducts were observed in the absence of base and conversion ceased after approximately 30% of the starting material had been consumed (Table 1, entry 1).9 Sodium carbonate (Na₂CO₃) and hydrates thereof (Na₂CO₃·nH₂O), which are the most commonly used bases for dehydrohalogenations of a-halooximes, were employed in initial experiments but were found to induce serious decomposition reactions and could not be used. Only traces of the aminoacetal 1a were detected in these cases (entries 2-4). In the presence of the less basic sodium hydrogen carbonate (NaHCO₃), conversion to the desired products was slightly enhanced (entry 5). In contrast, phosphate, oxalate and citrate salts turned out to be unsuitable buffers and virtually identical conversions compared to the base-free reaction were detected (entries 6-9). Sodium acetate (NaOAc), on the other hand, dramatically accelerated catalytic turnover to the desired hemiacetal 1b (entry 10) and an even more rapid reaction took place when sodium acetate trihydrate (NaOAc·3H₂O) was used (entry 11).¹⁰ It is likely that the acetate



buffer provides the correct combination of basicity/acidity as well as low nucleophilicity. A control experiment also confirmed that the role of NaOAc \cdot 3H₂O was indeed solely as a buffer as no product formation was observed in the absence of pyrrolidine (entry 12).

With a suitable buffer system in hand, further studies aimed at finding the optimum reaction conditions for the hetero-Diels–Alder reaction of the nitroso alkene generated from the α -chlorooxime **2b** were carried out (Table 2). While the reaction proceeded rapidly in dichloromethane and chloroform (entries 1,2), slower conversion and formation of the undesired ester **6** were observed in ether and toluene (entries 3,4). When more polar solvents such as THF, acetonitrile or nitromethane were used, **6** turned out to be the main product (entries 5–7). In these cases, the ester **6** is either formed *via* conjugate addition of acetate to the transient nitroso alkene or *via* a nucleophilic substitution pathway which is expected to be facilitated in dipolar aprotic solvents.¹¹

Although Gilchrist and Reißig and their coworkers presented compelling evidence for the electrocyclic nature of oxazine formation from α -halooximes (as a source of transient nitroso alkenes) and dienophiles, these findings cannot be transferred directly to reactions of enamines as these compounds are known to be strongly polarised and highly nucleophilic.^{2,3} To assess the ease of nucleophilic substitution reactions in the present system, the α -bromo- and α -chloro-O-methyloximes 7a and 7b were synthesised and employed under the established reaction conditions (Scheme 6). These α -halooximes are unable to generate nitroso alkenes via dehydrohalogenation, hence additions of enamines to these compounds have to proceed through substitution mechanisms. No products were detected after 5 days, confirming the involvement of intermediate nitroso alkenes and pointing towards a hetero-Diels-Alder cycloaddition pathway when the non-O-alkylated α -halooximes 2 are employed as substrates.¹²⁻¹⁴



Scheme 6 Reaction of *O*-methylated α -halooximes 7 with enamines.

Based on these results, the scope of the newly developed organocatalytic hetero-Diels–Alder reaction of nitroso alkenes was investigated using NaOAc·3H₂O as a heterogeneous buffer in dichloromethane (Table 3). Good yields of the cycloaddition products were obtained when α -chloroacetophenone oxime (**2b**) and α -unbranched aldehydes were used (entries 1–6). In this category, only acetaldehyde turned out to be an unsuitable

dienophile precursor due to rapid condensation reactions in the presence of pyrrolidine (entry 7).¹⁵ Both the α -chlorooxime **2b** and the analogous bromooxime 2a could be used and very similar yields were obtained (entry 1 vs. 8). Aldehydes bearing additional substituents in the *a*-position such as isobutyraldehyde and 2,2-diphenylacetaldehyde did not lead to the formation of the desired oxazine hetero-Diels-Alder adducts, probably due to increased steric demand and decreased reactivity of the corresponding enamines (entries 9,10). Similarly, electron-rich nitroso alkenes are known to be much less reactive than those bearing electron-withdrawing groups.¹ Therefore, it was not surprising when no conversion was observed with α chloro-4-methoxyacetophenone oxime (2c) under the standard reaction conditions (entries 11,12). However, the desired product could be obtained when stoichiometric amounts of pyrrolidine were used (entry 13). In contrast, the electron-poor α -bromo-4-nitroacetophenone oxime (2d) was found to be highly reactive and the oxazines 1i-1k were obtained in reduced reaction times (entries 14-16). In a similar manner, reactions with 3-bromopyruvate oxime (2e) furnished the hetero-Diels-Alder adducts within 24 h, but yields were lower than expected due to side reactions of the starting material (entries 17-20). In addition, NaOAc·3H₂O could not be used as a buffer in these cases because of competitive reactions of the starting material with acetate and a NaHCO3-based buffer had to be used instead.16

It is to be expected that the studies presented herein will greatly facilitate the development of a corresponding enantioselective access to oxazine derivatives. Initial experiments along this route were carried out using stoichiometric amounts of the chiral amine (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine and first results are promising as the oxazinone **8** could be obtained with 42% ee after oxidation of the hemiacetal **1h** with pyridinium chlorochromate(vI) (PCC) (Scheme 7). Preliminary studies on catalytic enantioselective reactions revealed that such processes are possible, but due to slower rates of the enamine formation and cycloaddition steps (see Scheme 3) yields were low and substantial amounts of by-products were formed. These drawbacks will be addressed in further studies.



Scheme 7 Formation of oxazine derivatives mediated by a chiral secondary amine.

Conclusion

In summary, the first catalytic hetero-Diels–Alder reaction of nitroso alkenes using simple and inexpensive catalysts and reagents such as pyrrolidine, aldehydes and NaOAc·3H₂O has been developed. Underlying mechanistic principles and key stages in the catalytic cycle as well as potential side reactions have been identified and a number of 5,6-dihydro-4*H*-oxazines have been prepared in moderate to good yields in one step from α -halooximes under mild reaction conditions. Preliminary results indicate that a catalytic enantioselective reaction is possible.

Table 3 Organocatalytic synthesis of oxazine derivatives from α-halooximes and aldehydes

	$R^{1} \xrightarrow{\text{Nach}} Hal + \begin{array}{c} O \\ R^{2} \\ 2a-e \end{array} \xrightarrow{R^{3}} R^{3} \\ CH_{2}Cl_{2}, r.t. \end{array} \xrightarrow{Nach} R^{1} \xrightarrow{Nach} R^{3} \\ R^{1} \xrightarrow{R^{2}} R^{3} \\ R^{2} \\ R^{1} \xrightarrow{R^{2}} R^{3} \\ R^{2} \\ R^{$								
Entry	Oxime	R ¹	Hal	R ²	R ³	<i>t/</i> h	Product	Yield (%)	
1	2b	Ph	Cl	^{<i>i</i>} Pr	Н	72	1b	81	
2	2b	Ph	Cl	Me	Н	72	1c	69	
3	2b	Ph	Cl	Et	Н	72	1d	89	
4	2b	Ph	Cl	"Pr	Н	72	1e	77	
5	2b	Ph	Cl	Ph	Н	72	1f	87	
6	2b	Ph	Cl	Bn	Н	72	1g	68	
7 ^a	2b	Ph	Cl	Н	Н	24	_	_ ^b	
8	2a	Ph	Br	ⁱ Pr	Н	72	1b	75	
9	2b	Ph	Cl	Me	Me	72	_	_ c	
10	2b	Ph	Cl	Ph	Ph	72	_	_ c	
11	2c	p-MeO-C ₆ H ₄	Cl	ⁱ Pr	Н	72	_	_ ^c	
12	2c	p-MeO-C ₆ H ₄	Cl	Bn	Н	72	_	_ ^c	
13 ^d	2c	p-MeO-C ₆ H ₄	Cl	ⁱ Pr	Н	2	1h	58	
14	2d	$p-NO_2-C_6H_4$	Br	ⁱ Pr	Н	24	1i	59	
15	2d	$p-NO_2-C_6H_4$	Br	Bn	Н	24	1j	68	
16	2d	$p-NO_2-C_6H_4$	Br	Me	Н	24	1 k	52	
17 ^e	2e	EtO ₂ C	Br	ⁱ Pr	Н	24	11	48	
18 ^e	2e	EtO ₂ C	Br	^e Pr	Н	24	1m	50	
19 ^{<i>e</i>}	2e	EtO ₂ C	Br	Et	Н	24	1n	44	
20 ^{<i>e</i>}	2e	EtO ₂ C	Br	Bn	Н	24	10	57	

Experimental

General details

NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz (1H) or 100 MHz (13C), respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals. The multiplicities of ¹H signals are designated by the following abbreviations: s = singlet; d = doublet; t =triplet; q = quartet; br = broad; m = multiplet, app = apparent. All coupling constants, J, are reported in Hertz. ¹³C NMR spectra were acquired on a broad band decoupled mode and the multiplicities were obtained using DEPT sequences. The following symbolisms are used for the multiplicities in ¹³C spectra: q = primary methyl; t = secondary methylene; d =tertiary methine; s = quaternary. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES⁺) ionisation techniques or on a Kratos MS890MS using electron ionisation (EI⁺) techniques. Flash column chromatography was carried out using Fluka Kieselgel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet irradiation or vanillin dip. Analytical grade solvents were used. All commercially available reagents were used as received. The a-halooximes 2a-e and the enamine 4 were prepared according to literature procedures.^{26,12,17} The ester **6** was identified through comparison with data reported in the literature.¹⁸ The methylene protons of **6** at $\delta_{\rm H}$ 4.98 and 5.31 (for *trans*- and *cis*-isomers, respectively) and the hemiacetal methine protons of the dihydro oxazines 1 were used to estimate conversion by ¹H NMR of crude reaction mixtures.

General procedure for the preparation of 5,6-dihydro-4*H*-oxazines. Pyrrolidine (4 μ l, 0.05 mmol) and the aldehyde (1.5 mmol) were added to a suspension of NaOAc·3H₂O (136 mg, 1.00 mmol) in CH₂Cl₂ and stirred for 5 min at ambient temperature. The α -halooxime (0.5 mmol) was added to this mixture and the reaction was monitored by TLC. Where

applicable, conversion was determined by NMR analysis of a filtered aliquot of the reaction mixture. Upon complete conversion of the α -halooxime, the mixture was adsorbed to silica gel (*ca.* 1.5 g) and the solvent was evaporated *in vacuo*. The product was purified by column chromatography. Diastereomeric ratios were estimated from the ¹H NMR signals of the hemiacetal methine protons of the products.¹⁹ Deviations from this procedure are noted with the individual experiments.

5-Isopropyl-3-phenyl-6-(pyrrolidin-1-yl)-5,6-dihydro-4H-[1,2]oxazine (1a). α -Bromoacetophenone oxime (2a) (214 mg, 1.00 mmol) was dissolved in a suspension of Na₂CO₃ (159 mg, 1.50 mmol) in CH_2Cl_2 (3 ml). The enamine 1-((*E*)-3-methylbut-1-enyl)-pyrrolidine (4) (328 µl, 2.00 mmol) was added dropwise at ambient temperature. After 2 h, the starting material had been completely consumed and the reaction products were separated by column chromatography. Apart from compound 1b (75 mg, 34%), two diastereomers of compound 1a were obtained as colourless oils (major diastereoisomer: 35 mg, 13%, minor diastereoisomer: 22 mg, 8%). Major diastereoisomer: R_f 0.60 (1 : 3 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃) 0.80 (3H, d, J 7.0, CH₃), 0.91 (3H, d, J 7.0, CH₃), 1.66-1.78 (4H, m, $2 \times CH_2$, 1.90–2.16 (2H, m, $2 \times CH$), 2.34 (1H, dd, J 17.8, 11.2, N=CCHH), 2.59 (1H, dd, J 17.8, 7.4, N=CCHH), 2.84-3.02 (4H, m, 2 × NCH₂), 4.48 (1H, d, J 10.0, OCH), 7.24–7.31 (3H, m, ArH), 7.62 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 16.1 (q), 20.6 (q), 23.8 (t), 25.2 (t), 26.9 (d), 38.2 (d), 47.0 (t), 92.5 (d), 125.5 (d), 128.6 (d), 129.4 (d), 136.2 (s), 155.1 (s); m/z (ES⁺) 273 (100%, MH⁺) [Found: (MH⁺) 273.1970. C₁₇H₂₅-N₂O requires MH, 273.1967]. Minor diastereoisomer: R_f 0.21 (1 : 3 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃) 0.98 (3H, d, J 6.8, CH_3), 1.02 (3H, d, J 6.8, CH_3), 1.75–1.91 (5H, m, 2 × CH_2 , CH), 2.03-2.10 (1H, m, (CH₃)₂CH), 2.62 (1H, dd, J 17.2, 6.1, N=CCHH), 2.80-2.89 (2H, m, NCH₂), 3.08 (1H, dd, J 17.2, 9.1, N=CCHH), 3.38-3.42 (2H, m, NCH₂), 4.98 (1H, d, J 6.7, OCH), 7.38-7.48 (3H, m, ArH), 8.35-8.41 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 19.4 (q), 20.3 (q), 24.9 (t), 31.2 (t), 31.5 (t), 41.4 (d), 47.9 (t), 93.3 (d), 127.3 (d), 128.6 (d), 130.2 (d),

138.8 (s), 155.6 (s); m/z (ES⁺) 273 (100%, MH⁺) [Found: (MH⁺) 273.1974. C₁₇H₂₅N₂O requires *M*H, 273.1967].

5-Isopropyl-3-phenyl-5,6-dihydro-4H-[1,2]oxazin-6-ol (1b). Compound 1b was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (88 mg, 81%). $R_{\rm f}$ 0.50 (1 : 3 pentane : ether); $\delta_{\rm H}$ (400 MHz, acetone- d_{60} ca. 60 : 40 mixture of diastereomers) 0.94-1.06 (6H, m, $2 \times CH_3$, 1.43–1.83 (2H, m, $2 \times CH$), 2.33 (0.6H, dd, J 17.6, 12.5, N=CCHH), 2.54 (0.4H, dd, J 18.0, 4.5, N=CCHH), 2.70 (0.6H, dd, J 17.6, 6.0, N=CCHH), 2.79 (0.4H, dd, J 18.0, 6.4, N=CCHH), 5.46 (0.6H, br d, J 4.0, O₂CH), 5.83 (0.4H, br d, J 4.0, O₂CH), 7.26–7.42 (3H, m, ArH), 7.70–7.81 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, acetone- d_6) 18.9 (q), 19.3 (q), 19.8 (q), 20.0 (q), 21.1 (t), 21.8 (t), 27.9 (d), 29.9 (d), 39.9 (d), 40.0 (d), 90.8 (d), 93.5 (d), 125.5 (d), 125.6 (d), 128.5 (2 × d), 129.3 (d), 129.4 (d), 136.8 (2 × s), 154.2 (2 × s); m/z (ES⁺) 242 (100%, MNa⁺) [Found: (MNa⁺) 242.1156. $C_{13}H_{17}NaNO_2$ requires *M*Na, 242.1157].

5-Methyl-3-phenyl-5,6-dihydro-4H-[1,2]oxazin-6-ol (1c). Compound 1c was prepared according to the general procedure and after 72 h the product was isolated as a dark yellow solid (66 mg, 69%). $R_{\rm f}$ 0.38 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, acetone-d₆, ca. 60: 40 mixture of diastereomers) 1.02 (1.2H, d, J 7.0, CH₃), 1.10 (1.8H, d, J 7.0, CH₃), 2.05–2.20 (1H, m, CH), 2.31 (0.6H, dd, J 17.6, 12.0, N=CCHH), 2.34 (0.4H, dd, J 18.0, 4.2, N=CCHH), 2.61 (0.6H, dd, J 17.6, 6.4, N=CCHH), 2.86 (0.4H, dd, J 18.0, 6.8, N=CCHH), 5.06 (0.4H, br d, J 3.8, O₂CH), 5.30 (0.6H, br d, J 2.0, O₂CH), 7.31-7.45 (3H, m, ArH), 7.66–7.79 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, acetone- d_6) 16.2 (q), 24.6 (t), 25.4 (t), 28.2 (d), 28.4 (d), 30.1 (q), 92.9 (d), 95.3 (d), 125.4 (2 × d), 128.5 (2 × d), 129.3 (d), 129.4 (d), 136.7 (s), 136.9 (s), 153.5 (s), 154.0 (s); m/z (ES⁺) 214 (100%, MNa⁺) [Found: (MNa⁺) 214.0844. C₁₁H₁₃NaNO₂ requires MNa, 214.0844].

5-Ethyl-3-phenyl-5,6-dihydro-4H-[1,2]oxazin-6-ol (1d). Compound 1d was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (91 mg, 89%). $R_{\rm f}$ 0.41 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, acetone- d_6 , ca. 60 : 40 mixture of diastereomers) 0.98 (1.2H, t, J 7.4, CH₃), 1.03 (1.8H, t, J 7.4, CH₃), 1.42-1.66 (2H, m, CH₂CH₃), 1.81-1.96 (1H, m, CH), 2.31 (0.6H, dd, J 17.6, 12.5, N=CCHH), 2.40 (0.4H, dd, J 18.0, 3.9, N=CCHH), 2.65 (0.6H, dd, J 17.6, 6.1, N=CCHH), 2.84 (0.4H, dd, J18.0, 6.8, N=CCHH), 5.08 (0.4H, br d, J 3.8, O₂CH), 5.38 (0.6H, br d, J 2.0, O₂CH), 7.38-7.42 (3H, m, ArH), 7.66–7.80 (2H, m, ArH); δ_c (100 MHz, acetone d_6 10.4 (q), 10.8(q), 22.9 (t), 23.2 (t), 24.0 (t), 24.8 (t), 34.9 (d), 35.3 (d), 91.8 (d), 94.1 (d), 125.4 (2 × d), 128.5 (2 × d), 129.2 (d), 129.3 (d), 136.8 (s), 136.9 (s), 153.8 (s), 154.0 (s). m/z (ES⁺) 228 (100%, MNa⁺) [Found: (MNa⁺) 228.0994. C₁₂H₁₅NaNO₂ requires MNa, 228.1000].

5-Propyl-3-phenyl-5,6-dihydro-4H-[1,2]oxazin-6-ol (1e). Compound le was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (84 mg, 77%). $R_{\rm f}$ 0.38 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, acetone- d_{67} ca. 60 : 40 mixture of diastereomers) 0.94-0.99 (3H, m, CH₃), 1.40–1.58 (4H, m, $2 \times CH_2$), 1.89–1.99 (1H, m, CH), 2.30 (0.6H, dd, J 17.6, 12.5, N=CCHH), 2.39 (0.4H, dd, J 18.0, 3.2, N=CCHH), 2.61 (0.6H, dd, J 17.6, 6.0), 2.84 (0.4H, dd, J 18.0, 6.6, N=CCHH), 5.14 (0.4H, br d, J 3.8, O₂CH), 5.38 (0.6H, br d, J 2.8, O₂CH), 7.35–7.46 (3H, m, ArH), 7.70–7.81 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, acetone- d_6) 13.8 (q), 13.9 (q), 19.4 (t), 19.8 (d), 23.1 (t), 23.5 (t), 33.0 (d), 33.4 (d), 33.5 (t), 34.2 (t), 92.0 (d), 94.3 (d), 125.4 (2 × d), 128.5 (2 × d), 129.2 (d), 129.3 (d), 136.8 (s), 136.9 (s), 153.9 (s), 154.1 (s); *m*/*z* (ES⁺) 242 (100%, MNa⁺) [Found: (MNa⁺) 242.1150. C₁₃H₁₇NaNO₂ requires MNa, 242.1157].

5-Phenyl-3-phenyl-5,6-dihydro-4H-[1,2]oxazin-6-ol (1f). Compound 1f was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (110 mg, 87%). $R_{\rm f}$ 0.35 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, acetone- d_6 , ca. 60 : 40 mixture of diastereomers) 2.82 (0.6H, dd, J 17.4,5.5, N=CCHH), 2.84 (0.4H, dd, J 18.2, 5.5, N=CCHH), 3.05 (0.6H, dd, J 17.4, 13.1, N=CCHH), 3.16 (0.4H, dd, J 18.2, 7.4, N=CCHH), 3.24-3.32 (1H, m, CH), 5.40 (0.4H, br d, J 4.6, O₂CH), 5.56 (0.6H, br d, J 2.3, O₂CH), 7.20-7.54 (8H, m, ArH), 7.77–7.83 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 23.7 (t), 24.9 (t), 39.5 (d), 39.6 (d), 92.8 (d), 94.5 (d), 125.9 (2 × d), 127.6 (d), 127.7 (d), 127.9 (d), 128.6 (2 × d), 128.8 (d), 128.9 (2 × d), 130.0 (d), 130.2 (d), 135.5 (s), 135.6 (s), 139.4 (s), 140.5 (s), 156.2 (s), 156.9 (s); *m*/*z* (ES⁺) 276 (100%, MNa⁺) [Found: (MNa⁺) 276.1007. C₁₆H₁₅NaNO₂ requires MNa, 276.1000].

5-Benzyl-3-phenyl-5,6-dihydro-4*H***-[1,2]oxazin-6-ol (1g).** Compound **1g** was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (91 mg, 68%). $R_{\rm f}$ 0.38 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, CDCl₃, *ca.* 60 : 40 mixture of diastereomers) 2.24–2.58 (3H, m, C*H*, PhC*H*₂), 2.71–2.90 (2H, m, N=CC*H*₂), 5.25 (0.4H, br d, *J* 2.8, O₂C*H*), 5.32 (0.6H, br d, *J* 2.8, O₂C*H*), 7.09–7.41 (8H, m, Ar*H*), 7.62–7.70 (2H, m, Ar*H*); $\delta_{\rm C}$ (100 MHz, CD₃NO₂, 60 °C) 22.6 (t), 23.1 (t), 35.1 (d), 35.2 (d), 36.9 (t), 37.6 (d), 91.9 (d), 93.8 (d), 125.5 (2 × d), 126.4 (2 × d), 128.2 (2 × d), 128.5 (2 × d), 129.2 (d), 129.3 (s), 155.5 (s); *m/z* (ES⁺) 290 (100%, MNa⁺) [Found: (MNa⁺) 290.1162. C₁₇H₁₇NaNO₂ requires *M*Na, 290.1157].

5-Isopropyl-3-(4-methoxyphenyl)-5,6-dihydro-4H-[1,2]oxazin-6-ol (1h). Compound 1h was prepared according to the general procedure in the absence of NaOAc·3H₂O, using a stoichiometric amount of pyrrolidine (42 µl, 0.5 mmol). The product was isolated as a colourless solid after 2 h (72 mg, 58%). Rf 0.43 $(4:1 \text{ CH}_2\text{Cl}_2: \text{ ether}); \delta_H$ (400 MHz, CDCl₃, ca. 75: 25 mixture of diastereomers) 0.93 (0.75H, d, J 6.0, CH₃), 0.98-1.01 (5.25H, m, CH_3), 1.54–1.80 (2H, m, 2 × CH), 2.35 (0.75H, dd, J 17.6, 12.4, N=CCHH), 2.42 (0.25H, dd, J 17.6, 3.6, N=CCHH), 2.60 (0.75H, dd, J17.6, 3.4, N=CCHH), 2.76 (0.25H, dd, J18.0, 6.8, N=CCHH), 3.82 (3H, s, OCH₃), 5.39 (0.25H, d, J 2.8, O₂CH), 5.55 (0.75H, d, J 2.4, O₂CH), 6.86–6.92 (2H, m, ArH), 7.63– 7.69 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 19.6 (2 × q), 20.1 (q), 20.3 (q), 20.8 (t), 21.9 (t), 28.0 (d), 29.6 (d), 39.5 (d), 39.8 (d), $55.3 (2 \times q), 90.8 (d), 93.2 (d), 113.7 (2 \times d), 126.8 (d), 126.9 (d),$ 128.1 (s), 128.2 (s), 155.3 (s), 156.6 (s), 160.6 (s), 160.7 (s); m/z (ES⁺) 272 (100%, MNa⁺) [Found: (MNa⁺) 272.1262. C₁₄H₁₉NNaO₃ requires MNa, 272.1263].

5-Isopropyl-3-(4-nitrophenyl)-5,6-dihydro-4*H***-[1,2]oxazin-6-ol** (**1i**). Compound **1i** was prepared according to the general procedure and after 24 h the product was isolated as a yellow oil (78 mg, 59%). $R_{\rm f}$ 0.32 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, CDCl₃, *ca.* 75 : 25 mixture of diastereomers) 0.95–1.03 (6H, m, 2 × CH₃), 1.58–1.85 (2H, m, 2 × CH), 2.42 (0.75H, dd, *J* 17.6, 12.1, N=CCHH), 2.48 (0.25H, dd, *J* 18.0, 3.0, N=CCHH), 2.62 (0.75H, dd, *J* 17.6, 5.9, N=CCHH), 2.83 (0.25H, dd, *J* 18.0, 7.0, N=CCHH), 5.43 (0.25H, br d, *J* 2.6, O₂CH), 5.60 (0.75H, br d, *J* 2.0, O₂CH), 7.82–7.90 (2H, m, ArH), 8.18–8.26 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 19.8 (q), 20.0 (q), 20.3 (q), 20.6 (q), 20.9 (t), 22.2 (t), 28.0 (d), 29.8 (d), 39.1 (d), 39.4 (d), 91.6 (d), 93.4 (d), 123.9 (d), 124.0 (d), 126.6 (2 × d), 141.8 (s), 141.9 (s), 148.5 (2 × s), 154.4 (s), 154.8 (s); *m*/z (EI⁺) 264 (36%, M⁺) [Found: (M⁺) 264.1108. C₁₃H₁₆N₂O₄ requires *M*, 264.1110].

5-Benzyl-3-(4-nitrophenyl)-5,6-dihydro-4*H***-[1,2]oxazin-6-ol** (1j). Compound 1j was prepared according to the general procedure and after 24 h the product was isolated as a yellow oil (106 mg, 68%). $R_{\rm f}$ 0.34 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz,

CDCl₃, ca. 60: 40 mixture of diastereomers) 2.28-2.58 (3H, m, CH, ArCH₂), 2.71-2.93 (2H, m, N=CCH₂), 5.29 (0.4H, br d, J 2.6, O₂CH), 5.36 (0.6H, br d, J 2.2, O₂CH), 7.18–7.38 (5H, m, ArH), 7.80-7.88 (2H, m, p-NO₂-ArH), 8.18-8.26 (2H, m, p-NO₂-ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 22.0 (t), 23.3 (t), 34.0 (d), 34.7 (d), 37.2 (t), 38.0 (t), 92.0 (d), 93.2 (d), 123.9 (d), 124.0 (d), 126.5 (d), 126.6 (d), 126.9 (2 × d), 128.9 (2 × d), 129.2 (d), 129.3 (d), 138.3 (s), 138.4 (s), 141.6 (s), 141.8 (s), 148.6 $(2 \times s)$, 154.1 (s), 154.6 (s); *m/z* (EI⁺) 312 (15%, M⁺) [Found: (M⁺) 312.1111. C₁₇H₁₆N₂O₄ requires M, 312.1110].

5-Methyl-3-(4-nitrophenyl)-5,6-dihydro-4H-[1,2]oxazin-6-ol

(1k). Compound 1k was prepared according to the general procedure and after 24 h the product was isolated as a yellow oil (61 mg, 52%). $R_{\rm f}$ 0.30 (3 : 1 pentane : THF); $\delta_{\rm H}$ (400 MHz, CDCl₃, ca. 60 : 40 mixture of diastereomers) 1.05 (1.2H, d, J 6.8, CH₃), 1.15 (1.8H, d, J 6.8, CH₃), 2.08–2.18 (1.8H, m, CH), 2.23-2.34 (1.2H, m, CH), 2.30 (0.4H, dd, J 18.0, 3.2, N=CCHH), 2.44 (0.6H, dd, J 17.6, 11.9, N=CCHH), 2.54 (0.6H, dd, J 17.6, 6.5, N=CCHH), 2.92 (0.4H, dd, J 18.0, 7.6, N=CCHH), 5.23 (0.4H, br d, J 3.0, O₂CH), 5.42 (0.6H, br d, J 2.5, O₂CH), 7.82–7.90 (2H, m, ArH), 8.18–8.24 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 16.6 (q), 16.8 (q), 24.8 (t), 24.9 (t), 27.3 (d), 27.7 (d), 93.6 (d), 95.2 (d), 123.9 (2 × d), 126.5 (2 × d), 141.7 (s), 142.0 (s), 148.5 (2 × s), 153.5 (s), 154.2 (s); m/z (EI⁺) 236 (43%, M⁺) [Found: (M⁺) 236.0794. C₁₁H₁₂N₂O₄ requires M, 236.0797].

6-Hydroxy-5-isopropyl-5,6-dihydro-4H-[1,2]oxazine-3-

carboxylic acid ethyl ester (11). Compound 11 was prepared according to the general procedure (with NaHCO₃ (84 mg, 1 mmol) and CF₃CO₂H (8 µl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (52 mg, 48%). $R_{\rm f}$ 0.25 (1 : 1 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃, ca. 70 : 30 mixture of diastereomers) 0.90 (0.9H, d, J 6.7, CHCH₃), 0.95 (0.9H, d, J 6.7, CHCH₃), 0.96 (2.1H, d, J 6.7, CHCH₃), 0.99 (2.1H, d, J 6.7, CHCH₃), 1.33 (3H, app t, J 7.2, CH₂CH₃), 1.35–1.72 (2H, m, 2 × CH), 2.11 (0.7H, dd, J 18.8, 12.8, N= CCHH), 2.45 (0.3H, dd, J19.1, 3.6, N=CCHH), 2.56 (0.3H, dd, J19.1, 6.8, N=CCHH), 2.63 (0.7H, dd, J18.8, 6.1, N=CCHH), 4.31 (2H, app q, J 7.2, CH₂CH₃), 5.41 (0.3H, br d, J 3.1, $O_{3}CH$), 5.56 (0.7H, br d, J 2.2, $O_{2}CH$); δ_{C} (100 MHz, CDCl₃) 14.3 $(2 \times q)$, 19.5 (t), 19.8 (q), 19.9 (q), 20.3 (q), 20.5 (q), 20.7 (t), 27.7 (d), 29.6 (d), 38.3 (d), 38.9 (d), 62.3 ($2 \times t$), 92.2 (d), 93.8 (d), 150.9 (s), 151.2 (s), 163.5 (2 × s); *m*/*z* (ES⁺) 238 (100%, MNa⁺) [Found: (MNa⁺) 238.1056. C₁₀H₁₇NaNO₄ requires MNa, 238.1055].

6-Hydroxy-5-propyl-5,6-dihydro-4H-[1,2]oxazine-3-

carboxylic acid ethyl ester (1m). Compound 1m was prepared according to the general procedure (with NaHCO₃ (84 mg, 1 mmol) and CF₃CO₂H (8 µl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (54 mg, 50%). $R_{\rm f}$ 0.25 (1 : 1 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃, *ca*. 60 : 40 mixture of diastereomers) 0.90 (1.2H, t, J 7.0, CH₂CH₃) 0.92 (1.8H, t, J7.0, CH₂CH₃), 1.29–1.50 (7H, m, CH₂CH₂, CH₂CH₂, CH₂CH₃), 1.81–1.90 (0.6H, m, CH), 1.96–2.06 (0.4H, m, CH), 2.12 (0.6H, dd, J 18.8, 12.8, N=CCHH), 2.32 (0.4H, dd, J 19.1, 2.5, N=CCHH), 2.53 (0.6H, dd, J 18.8, 6.0, N=CCHH), 2.60 (0.4H, dd, J 19.1, 7.1), 4.32 (2H, app q, J 7.2, OCH₂CH₃), 5.26 (0.4H, br d, J 2.8, O₂CH) 5.42 (0.6H, br d, J 2.1, O₂CH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 14.2 (q), 14.3 (q), 14.4 (2 × q), 19.5 (t), 19.9 (t), 21.5 (t), 21.9 (t), 31.5 (d), 31.8 (d), 32.8 (t), 33.5 (t), 62.3 (t), 62.4 (t), 93.2 (d), 94.7 (d), 150.5 (s), 151.1 (s), 163.4 (s), 163.5 (s); m/z (ES⁺) 238 (100%, MNa⁺) [Found: (MNa⁺) 238.1056. C₁₀H₁₇NaNO₄ requires *M*Na, 238.1055].

6-Hydroxy-5-ethyl-5,6-dihydro-4H-[1,2]oxazine-3-carboxylic acid ethyl ester (1n). Compound 1n was prepared according to the general procedure (with NaHCO₃ (84 mg, 1 mmol) and CF₃CO₂H (8 µl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (44 mg, 44%). R_f 0.16 (1 : 1 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃, *ca*. 60 : 40 mixture of diastereomers) 0.93 (1.2H, t, J 7.6, CH₂CH₃), 0.96 (1.8H, J 7.6, CH₂CH₃), 1.33 (3H, app t, J 7.2, OCH₂CH₃), 1.35-1.56 (2H, m, CH₂CH₃), 1.66–1.76 (0.6H, m, CH), 1.83–1.92 (0.4H, m CH), 2.13 (0.6H, dd, J 18.8, 12.7, N=CCHH), 2.32 (0.4H, dd, J 19.1, 2.8, N=CCHH), 2.53 (0.6H, dd, J 18.8, 6.0, N=CCHH), 2.59 (0.4H, dd, J 19.1, 7.1, N=CCHH), 4.29 (2H, app q, J 7.2, OCH₂CH₃), 5.29 (0.4H, br d, J 2.0, O₂CH), 5.44 $(0.6H, br d, J 1.4, O_2CH); \delta_C (100 MHz, CDCl_3) 11.0 (q), 11.4$ (q), $14.3 (2 \times q)$, 21.4 (t), 21.8 (t), 23.7 (t), 24.4 (t), 33.6 (d), 33.8 (t), 23.7 (t), 24.4 (t), 33.6 (d), 33.8 (t), 33.8 (t(d), $62.3 (2 \times t)$, 93.1 (d), 94.6 (d), 150.4 (s), 150.9 (s), 163.5 (s), 163.6 (s); m/z (ES⁺) 224 (100%, MNa⁺) [Found: (MNa⁺) 224.0900. C9H15NaNO4 requires MNa, 224.0899].

6-Hydroxy-5-benzyl-5,6-dihydro-4H-[1,2]oxazine-3-

carboxylic acid ethyl ester (10). Compound 10 was prepared according to the general procedure (with NaHCO₃ (84 mg, 1 mmol) and CF₃CO₂H (8 µl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (75 mg, 57%). $R_{\rm f}$ 0.13 (1 : 1 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃, ca. 60 : 40 mixture of diastereomers) 1.31 (1.8H, t, J 7.2, CH₂CH₃), 1.34 (1.2H, t, J 7.2, CH₂CH₃), 2.09–2.82 (5H, m, CH, N=CCH₂, ArCH₂), 4.28 (1.2H, q, J 7.2, CH₂CH₃), 4.31 (0.8H, q, J 7.2, CH₂CH₃), 5.23 (0.4H, br d, J 2.5, O₂CH), 5.32 (0.6H, br d, $J 2.0, O_2CH$, 7.15–7.34 (5H, m, ArH); δ_C (100 MHz, CDCl₃) 14.3 $(2 \times q)$, 21.3 (t), 22.0 (t), 33.6 (d), 34.3 (d), 37.0 (t), 37.7 (t), 62.3 (t), 62.4 (t), 92.6 (d), 93.7 (d), 126.8 (2 × d), 128.8 (d), 128.9 (d), 129.2 (d), 129.4 (d), 138.3 (s), 138.4 (s), 150.2 (s), 150.8 (s), 163.3 (s), 163.5 (s); *m/z* (ES⁺) 286 (100%, MNa⁺) [Found: (MNa⁺) 286.1052. C₁₄H₁₇NaNO₄ requires *M*Na, 286.1055].

1-Phenyl-2-(pyrrolidin-1-yl)ethanone oxime (5). Pyrrolidine (42 μ l, 0.5 mmol) was added to a solution of α -bromoacetophenone oxime (2a) (53 mg, 0.25 mmol) in CH₂Cl₂ (1 ml) and the solution was stirred at ambient temperature. TLC analysis immediately after addition of pyrrolidine revealed complete conversion of 2a. Compound 5 was isolated as a colourless oil after column chromatography (50 mg, 98%). $R_{\rm f}$ 0.10 (1 : 1 pentane : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃) 1.62–1.69 (4H, m, $2 \times CH_2$), 2.42–2.52 (4H, $2 \times NCH_2$), 3.43 (2H, s, N=CCH₂), 7.23-7.34 (3H, m, ArH), 7.46-7.51 (2H, m, ArH), 9.8 (1H, br s, OH); δ_c (100 MHz, CDCl₃) 23.7 (t), 54.3 (t), 59.9 (t), 128.3 (d), 128.5 (d), 129.2 (d), 133.1 (s), 155.2 (s); *m/z* (ES⁺) 205 (100%, MH⁺) [Found: (MH⁺) 205.1348. C₁₂H₁₇N₂O requires MH, 205.1341].

2-Bromo-1-phenylethanone O-methyl-oxime (7a). α-Bromoacetophenone (3.98 g, 20.0 mmol) and O-methyl hydroxylamine hydrochloride (2.50 g, 30.0 mmol) were dissolved in ethanol (50 ml) containing one drop of concentrated sulfuric acid. The mixture was stirred at ambient temperature for 2 h. The solvent was evaporated in vacuo to near dryness. Ether (50 ml) was added and the solution was washed with 1 M aqueous KHSO₄ $(2 \times 20 \text{ ml})$, saturated aqueous NaHCO₃ (20 ml) and water (20 ml). The organic phase was dried over Na₂SO₄, filtered and the solvent was evaporated in vacuo. Filtration of the crude product (dissolved in 3 : 1 pentane : CH₂Cl₂) through a short pad of silica gel and evaporation of the solvents in vacuo afforded the product as a colourless liquid (3.40 g, $\approx 75\%$).²⁰ $R_{\rm f}$ 0.40 (3 : 1 pentane : CH₂Cl₂); $\delta_{\rm H}$ (400 MHz, CDCl₃) 4.13 (3H, s, CH₃), 4.37 (2H, s, CH₂), 7.40–7.48 (3H, m, ArH), 7.72–7.78 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 18.3 (t), 63.1 (q), 126.4 (d), 128.9 (d), 129.9 (d), 133.7 (s), 152.9 (s); *m/z* (ES⁺) 228 (88%, MH⁺) [Found: (MH⁺) 228.0050. C₉H₁₁BrNO requires MH, 228.0024].

2-Chloro-1-phenylethanone O-methyl-oxime (7b). Compound **7b** was prepared from α -chloroacetophenone (1.54 g, 10.0

mmol) and *O*-methyl hydroxylamine hydrochloride (1.25 g, 15.0 mmol), following an analogous procedure as described for compound **7a**. The product was obtained as a colourless liquid (1.65 g, 90%). $R_{\rm f}$ 0.56 (1 : 1 pentane : CH₂Cl₂); $\delta_{\rm H}$ (400 MHz, CDCl₃) 4.08 (3H, s, CH₃), 4.53 (2H, s, CH₂), 7.38–7.42 (3H, m, ArH), 7.69–7.73 (2H, m, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 32.8 (t), 63.0 (q), 126.4 (d), 128.9 (d), 129.9 (d), 133.6 (s), 152.8 (s); m/z (ES⁺) 184 (100%, MH⁺) [Found: (MH⁺) 184.0533. C₉H₁₁-ClNO requires *M*H, 184.0529].

5-Isopropyl-3-(4-methoxyphenyl)-4,5-dihydro-[1,2]oxazin-6-

one (8). To an ice-cooled solution of 1h (27 mg, 0.11 mmol) in CH₂Cl₂ (1.5 ml) was added PCC (17 mg, 0.08 mmol). After stirring for 1.5 hours additional PCC (17 mg, 0.08 mmol) was added and the reaction mixture was left to warm to room temperature. After 16 hours the reaction product was separated by column chromatography (colourless oil, 16 mg, 58%). $R_{\rm f}$ 0.60 (9 : 1 CH₂Cl₂ : ether); $\delta_{\rm H}$ (400 MHz, CDCl₃) 1.01 (3H, d, J 6.4, CH₃), 1.07 (3H, d, J 6.8, CH₃), 2.29 (1H, app oct, J 6.6, CH(CH₃)₂), 2.51 (1H, app dt, J 10.0, 5.8, CHCO₂), 2.87 (1H, dd, J 16.8, 9.8, N=CCHH), 2.98 (1H, dd, J 17.2, 6.4, N=CCHH), 3.86 (3H, s, OCH₃), 6.96 (2H, d, J 9.2, ArH), 7.70 (2H, d, J 8.8, ArH); $\delta_{\rm C}$ (100 MHz, CDCl₃) 18.8 (q), 20.3 (q), 24.0 (t), 27.0 (d), 41.0 (d), 55.4 (q), 114.3 (d), 124.6 (s), 128.1 (d), 161.3 (s), 162.0 (s), 171.5 (s); m/z (ES⁺) 248 (100%, MH⁺) [Found: (MH⁺) 248.1285. C₁₄H₁₈NO₃ requires MH, 248.1287]. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AS columns (two columns in series) (hexane-*i*-PrOH (98 : 2); flow rate 1.0 ml min⁻¹; τ_{maior} = 123 min; $\tau_{\rm minor} = 116$ min).

Acknowledgments

This work was made possible by a grant from The Danish National Research Foundation and EU:HMPT-CT-2001-00317.

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