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Aust. J. Chem. **2007**, *60*, 898–904

www.publish.csiro.au/journals/ajc

Synthesis of 5-Aryloxazolidines via 1,3-Dipolar Cycloaddition Reaction of a Non-Stabilized Azomethine Ylide with Aromatic Aldehydes

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The 1,3-dipolar cycloaddition reaction of a non-stabilized azomethine ylide **4a**, formed in situ from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **5** and a catalytic amount of trifluoroacetic acid, with aromatic aldehydes **3** gives rise to *N*-benzyl-5-aryloxazolidines **1**. Under these conditions, 4-hydroxybenzaldehyde **3p** undergoes two-fold addition of azomethine ylide **4a** to afford bis adduct **11**.

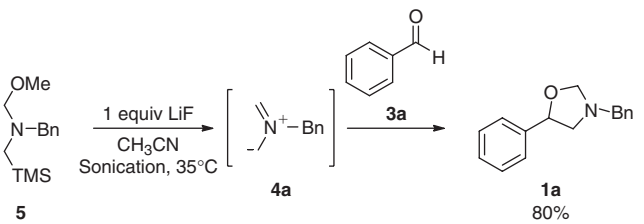
Manuscript received: 7 August 2007.
Final version: 21 September 2007.

Introduction

The 5-aryloxazolidine substructure is found within several synthetic compounds with interesting biological properties, including compounds that have been studied as β_3-adrenoceptor agonists,[1] anti-asthmatics,[2] herbicidal antidotes,[3] and stock-feed promoters.[4] There are two main approaches to the synthesis of the parent 5-aryloxazolidine structure **1** (Scheme 1). The most common approach involves condensation of formaldehyde with 1-aryl-2-aminoalcohols **2**,[2,3,5] which in turn are accessible using a variety of methods.[6] An alternative approach involves 1,3-dipolar cycloaddition reaction of an aromatic aldehyde **3** with an azomethine ylide **4**.[7,8] An advantage of the latter approach is that a wide variety of aromatic aldehydes are commercially available. Therefore, a range of the corresponding oxazolidines **1** could be generated by parallel synthesis in one synthetic step.

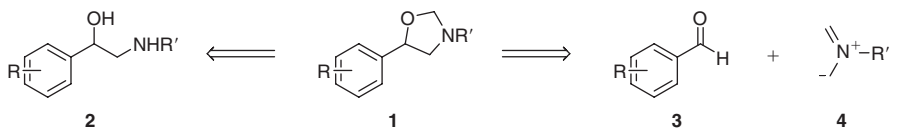
The 1,3-dipolar cycloaddition to give 5-aryloxazolidines **1** has received little attention except for early studies of stabilized azomethine ylides formed from the thermolysis of azidirines[9–11] and non-stabilized azomethine ylides from *N*-((trimethylsilyl)methyl)-substituted amines.[12–14] One of the most useful of the silylmethylamine reagents is *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **5**,[14–16] which has been frequently applied with alkenes to the formation of substituted pyrrolidines.[17] In the case of benzaldehyde as the dipolarophile, Padwa et al. found that treatment of reagent **5** with lithium fluoride in the presence of benzaldehyde under sonication at 35°C in acetonitrile afforded an 80% yield of the oxazolidine **1a** (Scheme 2).[18] Achiwa et al. showed that the same reactive intermediate **4a** could be formed on exposure of **5** to Bronsted or Lewis acid catalysts and found that trifluoroacetic acid (TFA) was the most effective catalyst for dipolar cycloaddition of **4a** with alkenes.[16] The reaction of aldehydes with the azomethine ylide **4a**, generated on treatment with catalytic trifluoroacetic acid, has not been explored.

Recently, an alternative method for generation of a non-stabilized azomethine ylide **4b** and subsequent addition to aryl aldehydes was explored by Nyerges et al. (Scheme 3).[19] This method involves condensation of sarcosine **6** with paraformaldehyde under Dean–Stark conditions and concomitant decarboxylation to give the azomethine ylide **4b**, which, in the presence of aryl aldehydes, provided the oxazolidines **7**. Although good yields of **7** were obtained, the forcing conditions (refluxing benzene for 1 to 15 h) and excess reagents (a 2-fold excess of



5 4a 1a 80%

Scheme 2. [18]



2 1 3 4

Scheme 1.

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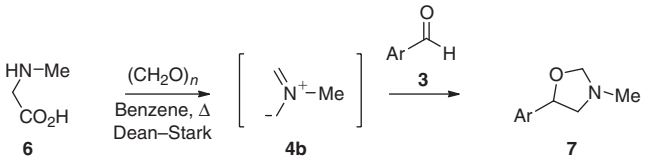
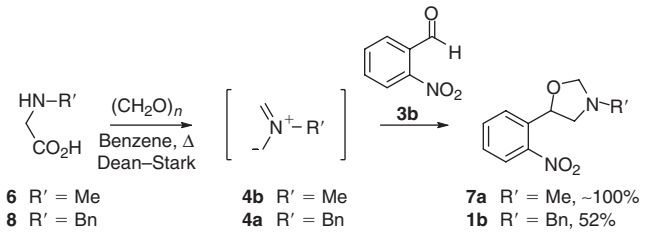


Scheme 3. [19]



Scheme 4.

amino acid and 5-fold excess of paraformaldehyde) required for high yields would not be suitable for substrates or products that were sensitive to heat or susceptible to side-reactions with the reagents.

For amine protecting groups, a benzyl group is generally preferred over a methyl group owing to the relative ease of removal of the benzyl group by Pd-catalyzed hydrogenolysis. Therefore, we repeated Nyerges' method with 2-nitrobenzaldehyde **3b** and found that although sarcosine **6** afforded a near-quantitative yield of oxazolidine **7a**, the use of *N*-benzylglycine **8** under these conditions afforded only a moderate yield of oxazolidine **1b** (Scheme 4). The moderate yields using this decarboxylative method with this model substrate led us to investigate the cycloaddition reaction of the azomethine ylide **4a**, formed from silylamine **5** and catalytic trifluoroacetic acid, with a wide range of aromatic and heteroaromatic aldehydes.

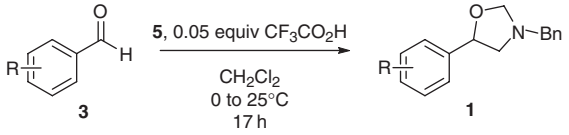
Results and Discussion

The benefits of generating a non-stabilized azomethine ylide **4a** from reagent **5** and a catalytic amount of trifluoroacetic acid in dry dichloromethane are that the reaction is initiated at low temperatures (0°C), usually proceeds to completion at ambient temperatures (0 to 25°C) and requires only a small excess of reagent **5**.[16] Also, the reaction workup is straightforward, involving concentration of the crude reaction mixture followed by crystallization or chromatographic purification. On submission of benzaldehyde **3a** to these reaction conditions, we obtained oxazolidine **1a** in 95% yield after chromatographic purification, a higher yield than that obtained using lithium fluoride with sonication at 35°C.[18]

We then applied this method to benzaldehydes substituted with electron-donating, electron-withdrawing, sterically demanding, basic, and acidic groups (Table 1). Much of the chemistry was performed in parallel using a Radley's Carousel Reaction Station and, after completion of the reactions, the mixtures were concentrated and the products were purified in high-throughput fashion on pre-packed Isolute normal-phase silica columns using an Argonaut Flashmaster II automated flash chromatography purification system. Notably, 2-nitrobenzaldehyde **3b** afforded a 75% yield of oxazolidine **1b** after chromatographic purification, a better result than we obtained using the decarboxylative method. High yields of oxazolidines **1** were obtained in the cases where the substituents were electron withdrawing (entries 2–7), electron donating (entries 8–11),

Table 1. Cycloaddition reaction of azomethine ylide 4a with aromatic aldehydes

All products showed satisfactory spectroscopic and analytical data[20]



Entry	Aldehyde	R	Product	Yield [%]
1	**3a**	H	**1a**	95
2	**3b**	2-NO_2	**1b**	75
3	**3c**	4-F	**1c**	89
4	**3d**	2,4-di-F	**1d**	80
5	**3e**	2-Br	**1e**	76
6	**3f**	4-Br	**1f**	86
7	**3g**	4-CN	**1g**	82
8	**3h**	4-NMe_2	**1h**	78
9	**3i**	4-OMe	**1i**	93
10	**3j**	3,4,5-tri-OMe	**1j**	~100
11	**3k**	4-NHAc	**1k**	78
12	**3l**	2,4,6-tri-Me	**1l**	80
13	**3m**	4-COOH	**1m**	59
14	**3n**	2-OH	**1n**	54
15	**3o**	3-OH	**1o**	–
16	**3p**	4-OH	**1p**	–

sterically demanding (entries 5 and 12), basic (entry 8), and acidic (entry 13).[21] The lower yield in the case of the carboxylic acid substituent (entry 13) reflected difficulty in isolation of the product **1m** rather than less efficient cycloaddition chemistry. The ^{1}H NMR spectrum of the crude product showed high conversion into the oxazolidine **1m**; however, attempted chromatographic purification resulted in poor recovery of the product, which we rationalized was because of its zwitterionic character. Purification of **1m** by crystallization gave a moderate recovery of analytically pure product. The chemoselectivity of the process was displayed by the 4-cyano example (entry 7), which gave the corresponding oxazolidine in high yield, as there was no evidence for competing addition to the nitrile to form an imidazoline-type structure.[22]

The success with the carboxylic acid-substituted benzaldehyde led us to explore whether the presence of a phenolic group in the benzaldehyde substrate would interfere with the cycloaddition process. Thus, 2-, 3-, and 4-hydroxybenzaldehydes were subjected to the reaction conditions (Table 1, entries 14–16). Salicylaldehyde **3n** underwent cycloaddition affording a moderate isolated yield of the expected oxazolidine **1n**. In this case, there were minor side-products in the crude product material, which resulted in a lower yield of the oxazolidine. In contrast, 3-hydroxybenzaldehyde (**3o**) gave a complex mixture with no trace of oxazolidine **1o** as evidenced by TLC and ^{1}H NMR analyses.

In the case of 4-hydroxybenzaldehyde **3p**, incomplete conversion was observed, so more azomethine ylide precursor **5** and trifluoroacetic acid were added. After workup, the major product isolated exhibited a mass spectral molecular ion of $M^{+\bullet}$ 388, indicating that two equivalents of azomethine ylide **4a** had been added to the starting material. Both the absence of a strong carbonyl stretch in the infrared spectrum of this product and a comparison of the NMR spectra of this product with the analogous oxazolidines **1a**–**n** provided strong evidence that the azomethine ylide **4a** had added to the carbonyl group of **3p** to give an oxazolidine. In addition, the NMR spectra showed that

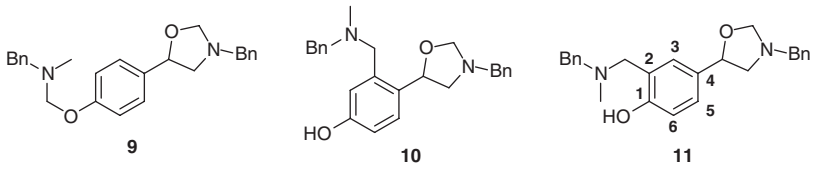
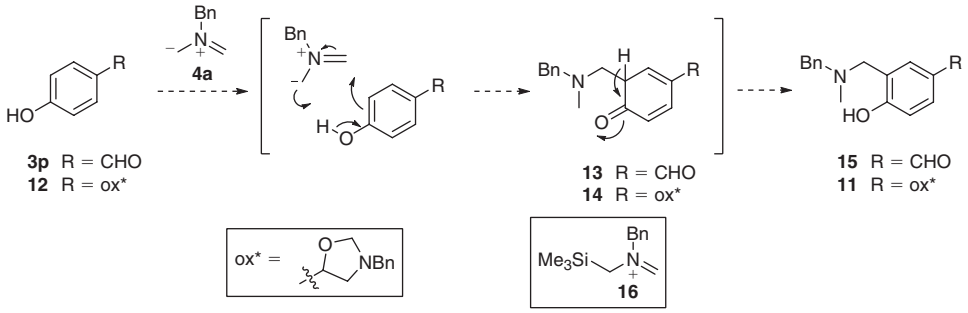


Fig. 1. Possible structures for the product produced from reaction of azomethine ylide **4a** with hydroxybenzaldehyde **3p**.



Scheme 5.

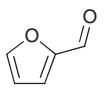
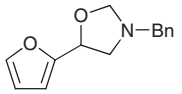
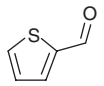
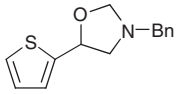
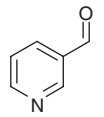
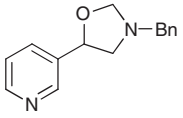
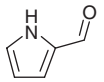
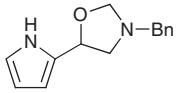
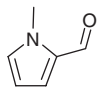
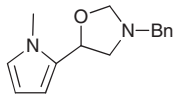
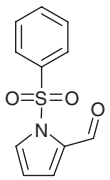
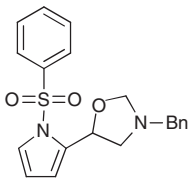
the second azomethine ylide **4a** had incorporated into the phenol structure as an *N*-benzyl-*N*-methyl-aminomethyl moiety. In principle, the three possibilities for incorporation of the second azomethine ylide into the phenol structure involved *O*-alkylation to give **9** or *C*-alkylation to give either **10** or **11** (Fig. 1). The *O*-alkylation structure **9** was easily discounted owing to evidence for the free phenol hydroxyl group, found in the infrared and ^{1}H NMR spectra. Furthermore, the disubstituted phenol ether structure **9** would be expected to exhibit 19 ^{13}C NMR signals; however, 21 ^{13}C NMR signals were observed in the spectrum of the product. A detailed examination of the NMR spectra (one- and two-dimensional) allowed us to unequivocally assign structure **11** to this product (for full details, see the Accessory Publication). In the ^{1}H NMR spectrum, the signals at δ 7.15 (dd, J 8.1 and 1.2), 7.02 (br s), and 6.84 (d, J 8.3) were assigned to H5, H3, and H6 respectively. The signal due to the lone aromatic proton (H3) showed strong nuclear Overhauser effect correlation spectroscopy (NOESY) correlations to the signals of the adjacent benzylic protons of the groups attached to C2 and C4. In the ^{13}C NMR spectrum, the upfield aromatic signals at δ 121.9 (quaternary) and 116.2 (methine) were assigned to carbons C2 and C6, respectively, which are strongly shielded through their *ortho* relationship to the phenol hydroxyl group. These NMR data are consistent with structure **11** and cannot be accounted for by alternative structure **10**.

The observation of a complex reaction product emanating from the reaction with 3-hydroxybenzaldehyde **3o** is thought to be a result of competing side-reactions involving Mannich-type substitution of **3o** with the incipient iminium moiety within the azomethine ylide.[23] These side reactions are less likely for 2- and 4-hydroxybenzaldehydes (**3n** and **3p**, respectively) as these species have fewer sites available, *ortho* and *para* to the phenol group, for electrophilic aromatic substitution. In addition, **3n** and **3p** are less reactive towards electrophilic aromatic substitution owing to conjugation of the phenol group with the electron-withdrawing aldehyde group. The reactions with 2-hydroxybenzaldehyde (salicylaldehyde, **3n**) are relatively clean, indicating little if any Mannich-type side reactions. The reactivity of 2-hydroxybenzaldehyde towards such electrophilic aromatic substitutions would be further reduced by the hydrogen-bonding stabilization of the *ortho*-phenolic residue by the aldehyde group.[24]

Compound **11** is a formal bis adduct of 4-hydroxybenzaldehyde **3p** and two equivalents of azomethine ylide **4a**. The product results from the expected 1,3-dipolar cycloaddition reaction of the aldehyde group with one azomethine ylide intermediate and a formal Mannich-type reaction of the phenol group with a second azomethine ylide intermediate. The mechanism for the Mannich-type reaction is not clear; however, one could envisage a stepwise or concerted process involving Mannich reaction and deprotonation of the phenol **3p** (or derived oxazolidine **12**) with azomethine ylide **4a** to give intermediate **13** (or **14**), which would readily undergo aromatization to the observed *ortho* alkylated product **15** (or **11**) (Scheme 5). Similar processes, involving an intermediate silyliminium species **16** (formed in situ from **5** and TFA) as the reactive species in the Mannich reaction, cannot be discounted at this stage. It is yet to be determined whether the Mannich-type azomethine ylide reaction occurs before or after the dipolar cycloaddition with the aldehyde of the starting material **3p**; however, the presence of the deactivating aldehyde group on **3p** may be expected to slow down the Mannich-type reaction through inductive effects. Mannich reactions of iminium ions with phenols are well known; however, the analogous reaction of an azomethine ylide with a phenol has not been reported.[25] The scope and mechanism of this transformation are under investigation and will be reported in due course.

The reaction scope was further explored by subjection of a range of heteroaromatic aldehydes to the cycloaddition conditions (Table 2). 2-Furan-, 2-thiophene-, and 3-pyridinecarboxaldehydes **17**–**19** were successfully converted into the corresponding oxazolidines **23**–**25** (entries 1–3). For 2-pyrrolecarboxaldehyde **20**, none of the expected oxazolidine **26** was detected in the reaction product (entry 4). Instead the product was a complex intractable mixture containing an appreciable amount of starting aldehyde. The presence of starting material indicated a much retarded reaction rate was at least partly the cause of the reaction failure, although competitive electrophilic aromatic substitution side-reactions could not be ruled out. We explored this effect through subjection of nitrogen-substituted pyrrole-2-carboxaldehyde analogues to the standard

Table 2. Reaction of heteroaromatic aldehydes with azomethine ylide 4a

Entry	Aldehyde	Product	Yield [%]
1	 **17**	 **23**	100
2	 **18**	 **24**	92
3	 **19**	 **25**	73
4	 **20**	 **26**	–
5	 **21**	 **27**	–
6	 **22**	 **28**	90

reaction conditions (entries 5 and 6). The *N*-methyl analogue **21** also resulted in a complex intractable mixture that contained some starting material but no oxazolidine (entry 5), whereas, for the *N*-benzenesulfonyl analogue **22**, an excellent yield of the cycloadduct **28** resulted (entry 6). We rationalize the lack of success for the pyrrole aldehydes **20** and **21** as being a result of the electron-rich nature of the heterocycle, which has two effects: reducing the reactivity of the aldehyde towards cycloaddition and increasing the reactivity of the heterocycle towards potential electrophilic aromatic substitution side-reactions. The reduction in reactivity of electron-rich aldehydes towards such cycloadditions would be due to a raised carbonyl lowest unoccupied molecular orbital (LUMO) energy and an overall increase in the azomethine ylide highest unoccupied molecular orbital (HOMO)-carbonyl LUMO energy gap.[14,26]

Conclusions

In summary, the 1,3-dipolar cycloaddition of a non-stabilized azomethine ylide **4a** with aromatic and heteroaromatic aldehydes proceeds under mild conditions to afford high isolated yields of the corresponding oxazolidines. In the case of phenolic aromatics or pyrrolic aldehydes, slower cycloaddition rates and competing side-reactions were observed. In the case of 4-hydroxybenzaldehyde **3p**, the major product isolated was a bis adduct formed via azomethine ylide cycloaddition and a formal azomethine ylide electrophilic aromatic substitution reaction. There is continued interest in the 1,3-dipolar cycloaddition chemistry of azomethine ylides and carbonyl compounds[27] and in revelations that this chemistry may be involved in biological processes.[28]

Experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AV400 spectrometer at 400 and 100 MHz, respectively, or a Bruker AV200 spectrometer at 200 and 50 MHz, respectively. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterated chloroform ($CDCl_3$) at 20°C. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CDCl_3$ (δ_H 7.26) was used as the internal reference, whereas for proton-decoupled ^{13}C NMR spectra, the central peak (δ_C 77.16) of the $CDCl_3$ triplet was used as the reference. ^{1}H NMR spectroscopic data are recorded as follows: chemical shift (δ_H) (relative integral, multiplicity, coupling constant(s) J (Hz)) whereby multiplicity is defined as: s for singlet; d for doublet; t for triplet; q for quartet or quintet; m for multiplet, or combinations thereof. Elemental analyses were performed by Campbell Microanalytical Laboratory, University of Otago, New Zealand. Melting points were recorded on an Electrothermal IA9300 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer SPECTRUM 2000 FTIR Spectrometer. Oils were analyzed neat as thin films on sodium chloride plates, whereas solids were dissolved in chloroform and deposited on sodium chloride plates with the solvent being allowed to evaporate before measurement of the spectra. Positive ion electron impact (EI) mass spectra were run on a ThermoQuest MAT95XL mass spectrometer using ionization energy of 70 eV. Accurate mass measurements were obtained on the same instrument with a resolution of 5000–10000 using perfluorokerosene (PFK) as the reference compound. Positive and negative ion atmospheric pressure chemical ionization (APCI) mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage of 50 V, and the source was maintained at 100°C. Nitrogen was used as the nebuliser and sheath gas, and the probe temperature was 400°C. The solvent system used was acetonitrile with a flow rate of 0.3 mL min^{-1}. Positive and negative ion electrospray mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage of 50 V and the source was maintained at 80°C. The solvent system used was acetonitrile with a flow rate of 0.04 mL min^{-1}. Flash chromatography was carried out on an Argonaut FlashMaster II purification system with FC 204 Fraction Collector, using Isolute normal-phase silica gel. Analytical TLC was conducted on Merck Kieselgel 60 F_{254} on aluminium sheets. All starting materials, reagents, and solvents were obtained from commercial sources and used as supplied unless otherwise noted. Dichloromethane was dried by passage through two sequential columns of activated neutral alumina. 2-Furaldehyde was distilled twice before use.

3-Methyl-5-(2′-nitrophenyl)oxazolidine ***7a***[19a]

A mixture of 2-nitrobenzaldehyde (0.76 g, 5.0 mmol), sarcosine (0.90 g, 10.0 mmol), and paraformaldehyde (0.75 g, 25.0 mmol) in toluene (50 mL) was heated at reflux for 1 h with azeotropic removal of water using a Dean–Stark trap. The mixture was concentrated, dissolved in acetone, and passed through a plug of silica, with acetone as eluent. Concentration of the acetone washings afforded the *title compound* (0.83 g, ~100%) as an oil. The ^{1}H NMR spectrum was consistent with reported data.[19a]

3-Benzyl-5-(2′-nitrophenyl)oxazolidine ***1b***

A mixture of 2-nitrobenzaldehyde (0.76 g, 5.0 mmol), *N*-benzylglycine hydrochloride (2.01 g, 10.0 mmol), sodium carbonate (2.65 g, 25.0 mmol), and paraformaldehyde (0.75 g, 25.0 mmol) in toluene (70 mL) was heated at reflux for 5 h with azeotropic removal of water using a Dean–Stark trap. The mixture was concentrated, then dissolved in acetone and passed through a plug of silica eluting with acetone. The acetone washings were concentrated, then purified by automated flash chromatography using a gradient (100% hexanes to 50:50 hexanes/dichloromethane) and afforded the *title compound* (0.74 g, 52%) as an oil. The ^{1}H NMR spectrum was identical to that obtained for **1b** produced by the alternative method reported below.

General Procedure for the Reaction of Aromatic and Heteroaromatic Aldehydes with Reagent ***5*** *and Catalytic Trifluoroacetic Acid*

3-Benzyl-5-phenyloxazolidine ***1a***[12,13]

The reaction of benzaldehyde **3a** is representative. To a solution of **3a** (420 mg, 3.96 mmol) in dichloromethane (8 mL) at 0°C under an atmosphere of nitrogen gas, was added *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **5** (1.55 mL, 6.06 mmol). To the resulting solution was added a solution of trifluoroacetic acid (1 M in dichloromethane, 0.2 mL, 0.2 mmol), dropwise with stirring. The resulting solution was allowed to warm to room temperature, and the reaction mixture was stirred until TLC indicated consumption of starting material (17 h). Solvent was removed under vacuum before purification by flash chromatography (silica; hexanes grading to 1:9 ethyl acetate/hexanes) to give the *title compound* (904 mg, 95%) as a white solid, mp 42–43°C. R_F 0.16 (1:9 EtOAc/hexanes). (Found: $[M-H]^+$ 238.1223. $C_{16}H_{16}NO$ requires $[M-H]^+$ 238.1226.) ν_{max}/cm^{-1} 3058, 3028, 2924, 2874, 2801, 1494, 1453, 998. δ_H (400 MHz) 7.51–7.19 (10H, m), 5.08 (1H, m), 4.63 (2H, s), 3.85 (2H, s), 3.45 (1H, dd, *J* 11.4 and 6.7), 2.85 (1H, dd, *J* 11.3 and 8.1). δ_C (100 MHz) 142.3, 138.8, 128.8, 128.6, 128.6, 127.5, 127.4, 125.7, 87.7, 76.7, 60.8, 58.5. *m/z* (EI) 238 (<1%, $[M-H]^+$), 133 (100%), 91 (80%).

3-Benzyl-5-(2′-nitrophenyl)oxazolidine ***1b***

2-Nitrobenzaldehyde **3b**: 602 mg, 3.99 mmol. Product **1b** (860 mg, 75%) isolated as a colourless oil. R_F 0.27 (25:75 EtOAc/hexanes). (Found: $M^{+\bullet}$ 284.1143. $C_{16}H_{16}N_2O_3$ requires $M^{+\bullet}$ 284.1155.) ν_{max} (neat)/cm^{-1} 3029, 2923, 2873, 2807, 1609, 1529, 1346, 995. δ_H (400 MHz) 8.06 (1H, dd, *J* 8.2 and 1.2), 7.93 (1H, br d, *J* 7.8), 7.66 (1H, ddd, *J* 8.8, 8.8 and 1.2), 7.42 (1H, m), 7.37–7.25 (5H, m), 5.58 (1H, m), 4.68 (1H, d, *J* 5.7), 4.61 (1H, d, *J* 5.7), 3.83 (2H, dd, *J* 17.7 and 13.1), 3.78 (1H, dd, *J* 12.0 and 7.1), 2.85 (1H, dd, *J* 12.1 and 6.7). δ_C (100 MHz) 147.1, 139.6, 138.6, 134.1, 128.9, 128.5, 128.0, 127.4, 127.3, 124.9, 87.7, 73.6, 60.4, 58.6. *m/z* (EI) 284 (<1%, $M^{+\bullet}$), 148 (22%), 133 (95%), 91 (100%).

3-Benzyl-5-(4′-fluorophenyl)oxazolidine ***1c***

4-Fluorobenzaldehyde **3c**: 496 mg, 4.00 mmol. Product **1c** (918 mg, 89%) isolated as white crystals, mp 29–30°C. R_F 0.16 (10:90 EtOAc/hexanes). (Found: $[M-H]^+$ 256.1127. $C_{16}H_{15}FNO$ requires $[M-H]^+$ 256.1132.) ν_{max} (neat)/cm^{-1} 3025, 2924, 2875, 2801, 1605, 1509, 1224, 834. δ_H (400 MHz) 7.42–7.25 (7H, m), 7.04 (2H, dd, *J* 8.7 and 8.7), 5.04 (1H, m), 4.60 (2H, s), 3.83 (2H, s), 3.41 (1H, dd, *J* 11.3 and 6.7), 2.80 (1H, dd, *J* 11.3 and 7.7). δ_C (100 MHz) 162.3 (d, J_{CF}• 245), 138.7, 138.0 (d, J_{CF}•3), 128.8, 128.6, 127.4 (d, J_{CF}• 5), 127.3, 115.4 (d, J_{CF}• 21), 87.6, 76.2, 60.7, 58.4. *m/z* (EI) 256 (1%, $[M-H]^+$), 133 (100%), 91 (76%).

3-Benzyl-5-(2′,4′-difluorophenyl)oxazolidine ***1d***

2,4-Difluorobenzaldehyde **3d**: 565 mg, 3.98 mmol. Product **1d** (878 mg, 80%) isolated as a colourless oil. R_F 0.18 (5:95 EtOAc:hexanes). (Found: $[M-H]^+$ 274.1033. $C_{16}H_{14}F_2NO$ requires $[M-H]^+$ 274.1038.) ν_{max} (neat)/cm^{-1} 3029, 2928, 2878, 2802, 1606, 1501, 1272. δ_H (400 MHz) 7.53 (1H, ddd, *J* 8.6, 8.6 and 6.8), 7.40–7.27 (5H, m), 6.90 (1H, td, *J* 8.5 and 2.4), 6.79 (1H, ddd, *J* 10.8, 8.8 and 2.4), 5.24 (1H, m), 4.58 (2H, m), 3.83 (2H, s), 3.52 (1H, dd, *J* 11.6 and 6.7), 2.83 (1H, dd, *J* 11.5 and 7.6). δ_C (100 MHz) 162.4 (dd, J_{CF} 242 and 12), 159.8 (dd, J_{CF} 242 and 12), 138.7, 128.8, 128.6, 127.8 (dd, J_{CF} 10 and 6), 127.5, 125.6 (dd, J_{CF}• 14 and 4), 111.3 (dd, J_{CF} 21 and 4), 103.8 (t, J_{CF} 25), 87.2, 71.0 (d, J_{CF} 2), 59.5, 58.4. *m/z* (EI) 274 (4%, $[M-H]^+$), 184 (2%), 133 (100%), 91 (96%).

3-Benzyl-5-(2′-bromophenyl)oxazolidine ***1e***

2-Bromobenzaldehyde **3e**: 739 mg, 3.99 mmol. Product **1e** (960 mg, 76%) as a white amorphous solid, mp 33–34°C. R_F 0.18 (5:95 EtOAc/hexanes). (Found: $[M(^{79}Br)-H]^+$ 316.0332. $C_{16}H_{15}BrNO$ requires $[M(^{79}Br)-H]^+$ 316.0332.) ν_{max} (neat)/cm^{-1} 2923, 2870, 2802, 1588, 1464, 1127, 1019. δ_H (400 MHz) 7.61 (1H, dd, *J* 7.9 and 1.6), 7.51 (1H, dd, *J* 7.9 and 1.0), 7.38–7.25 (6H, m), 7.13 (1H, td, *J* 7.9 and 1.7), 5.28 (1H, m), 4.63 (2H, m), 3.83 (2H, dd, *J* 15.4 and 13.0), 3.70 (1H, dd, *J* 11.7 and 7.0), 2.76 (1H, dd, *J* 11.9 and 7.1). δ_C (100 MHz) 142.2, 138.8, 132.7, 128.9, 128.7, 128.6, 127.8, 127.5, 126.5, 121.3, 87.6, 75.9, 59.6, 58.7. *m/z* (EI) 318 (<1%, $[M(^{81}Br)-H]^+$), 316 (<1%, $[M(^{79}Br)-H]^+$), 133 (100%), 91 (83%).

3-Benzyl-5-(4′-bromophenyl)oxazolidine ***1f***

4-Bromobenzaldehyde **3f**: 506 mg, 2.73 mmol. Product **1f** (752 mg, 86%) isolated as a white crystalline solid, mp 66–67°C. R_F 0.27 (15:85 EtOAc/exanes). (Found: C 60.5, H 5.1, N 4.4; $[M(^{79}Br)-H]^+$ 316.0321. $C_{16}H_{15}BrNO$ requires C 60.4, H 5.1, N 4.4%; $[M(^{79}Br)-H]^+$ 316.0332.) ν_{max} (neat)/cm^{-1} 2919, 2879, 1489, 1453, 1042. δ_H (400 MHz) 7.47 (2H, d, *J* 8.4), 7.38–7.25 (5H, m), 7.22 (2H, d, *J* 8.2), 5.01 (1H, m), 4.58 (2H, s), 3.81 (2H, s), 3.41 (1H, dd, *J* 11.3 and 6.7), 2.77 (1H, dd, *J* 11.4 and 7.7). δ_C (100 MHz) 141.5, 138.7, 131.7, 128.8, 128.6, 127.5, 127.4, 121.3, 87.8, 76.1, 60.6, 58.5. *m/z* (EI) 318 (<1%, $[M(^{81}Br)-H]^+$), 316 (<1%, $[M(^{79}Br)-H]^+$).

4-(3′-Benzyloxazolidin-5′-yl)benzonitrile ***1g***

4-Cyanobenzaldehyde **3g**: 523 mg, 3.99 mmol. Product **1g** (869 mg, 82%) isolated as white amorphous crystals, mp 65–66°C. R_F 0.21 (25:75 EtOAc/hexanes). (Found: $[M-H]^+$ 263.1177. $C_{17}H_{15}N_2O$ requires $[M-H]^+$ 263.1179.) ν_{max} (neat)/cm^{-1} 2924, 2879, 2806, 2228, 1609, 1493, 1451, 910. δ_H (400 MHz) 7.63 (2H, d, *J* 8.3), 7.45 (2H, d, *J* 8.3), 7.36–7.25 (5H, m), 5.08 (1H, m), 4.60 (2H, s), 3.80 (2H, s), 3.45 (1H, dd, *J* 11.4 and 6.9), 2.78 (1H, dd, *J* 11.4 and 7.4). δ_C (100 MHz) 148.1, 138.4, 132.5, 128.8, 128.6, 127.6, 126.2, 118.9, 111.3, 87.9, 75.9, 60.4, 58.3. *m/z* (EI) 263 (<1%, $[M-H]^+$), 133 (84%), 91 (100%).

[4-(3′-Benzyloxazolidin-5′-yl)phenyl]dimethylamine ***1h***

4-(Dimethylamino)benzaldehyde **3h**: 160 mg, 1.05 mmol. Product **1h** (230 mg, 78%) isolated as white flaky crystals, mp

73–74°C. R_F 0.29 (20:80 EtOAc/CH_2Cl_2). (Found: C 76.6, H 7.9, N 10.0, M^+ 282.1703. $C_{18}H_{22}N_2O$ requires C 76. 6, H 7.9, N 9.9%, M^+ 282.1727.) ν_{max} (neat)/cm^{-1} 3029, 2981, 2876, 2796, 1615, 1523, 1449, 1348, 818. δ_H (400 MHz) 7.43–7.23 (7H, m), 6.75 (2H, d, *J* 8.8), 5.01 (1H, m), 4.59 (2H, m), 3.85 (2H, s), 3.37 (1H, dd, *J* 11.1 and 6.8), 2.96 (6H, s), 2.86 (1H, dd, *J* 11.3 and 8.1). δ_C (100 MHz) 150.3, 139.0, 129.5, 128.8, 128.5, 127.3, 127.0, 112.7, 87.4, 76.9, 60.5, 58.5, 40.8. *m*/*z* (EI) 282 (35%, M^+), 133 (100%), 91 (40%).

3-Benzyl-5-(4′-methoxyphenyl)oxazolidine ***1i***

4-Methoxybenzaldehyde **3i**: 547 mg, 4.02 mmol. Product **1i** (1.01 g, 93%) isolated as a white amorphous solid, mp 46–47°C. R_F 0.25 (25:75 EtOAc/hexanes). (Found: C 75.6, H 7.1, N 5.3, M^+ 269.1403. $C_{17}H_{19}NO_2$ requires C 75.8, H 7.1, N 5.2%, M^+ 269.1410.) ν_{max} (neat)/cm^{-1} 2873, 2829, 1612, 1513, 1454, 1246, 1036, 830. δ_H (400 MHz) 7.42–7.25 (7H, m), 6.90 (2H, d, *J* 8.8), 5.03 (1H, m), 4.59 (2H, m), 3.84 (2H, s), 3.81 (3H, s), 3.39 (1H, dd, *J* 11.3 and 6.7), 2.83 (1H, dd, *J* 11.3 and 8.0). δ_C (100 MHz) 159.2, 138.9, 134.1, 128.8, 128.5, 127.4, 127.1, 114.0, 87.5, 76.6, 60.7, 58.5, 55.4. *m*/*z* (EI) 269 (<1%, M^+), 133 (100%), 91 (67%).

3-Benzyl-5-(3′,4′,5′-trimethoxyphenyl)oxazolidine ***1j***

3,4,5-Trimethoxybenzaldehyde **3j**: 197 mg, 1.00 mmol. Product **1j** (331 mg, ~100%) isolated as a colourless oil. R_F 0.15 (25:75 EtOAc/hexanes). (Found: M^+ 329.1614. $C_{19}H_{23}NO_4$ requires M^+ 329.1622.) ν_{max} (neat)/cm^{-1} 2937, 2875, 2833, 1591, 1232, 1127, 1006. δ_H (400 MHz) 7.38–7.18 (5H, m), 6.56 (2H, s), 4.98 (1H, m), 4.56 (2H, m), 3.82 (6H, s), 3.81 (3H, s), 3.79 (2H, s), 3.36 (1H, dd, *J* 11.3 and 6.6), 2.80 (1H, dd, *J* 11.3 and 7.5). δ_C (100 MHz) 153.2, 138.5, 137.8, 137.0, 128.5, 128.3, 127.1, 102.2, 87.3, 76.4, 60.6, 60.2, 58.1, 55.9. *m*/*z* (EI) 329 (2%, M^+), 298 (8%), 133 (100%), 91 (88%).

N-[4-(3′-Benzyloxazolidin-5′-yl)phenyl]acetamide ***1k***

4-Acetamidobenzaldehyde **3k**: 202 mg, 1.24 mmol. Product **1k** (287 mg, 78%) isolated as a white crystalline solid, mp 121–123°C. R_F 0.20 (60:40 EtOAc/CH_2Cl_2). (Found: C 72.3, H 6.8, N 9.4, $[M-2H]^{+\bullet}$ 294.1363. $C_{18}H_{20}N_2O_2$ requires C 73.0, H 6.8, N 9.5%, $[M-2H]^{+\bullet}$ 294.1363.) ν_{max} (neat)/cm^{-1} 3254, 3192, 3124, 3059, 2888, 1664, 1602, 1547, 1514, 1318, 834. δ_H (400 MHz) 7.47 (2H, d, *J* 8.4), 7.38–7.24 (7H, m), 7.17 (1H, br s), 5.02 (1H, m), 4.58 (2H, s), 3.81 (2H, s), 3.39 (1H, dd, *J* 11.3 and 6.8), 2.79 (1H, dd, *J* 11.3 and 7.8), 2.17 (3H, s). δ_C (100 MHz) 168.3, 138.8, 138.3, 137.2, 128.9, 128.6, 127.5, 126.5, 120.1, 87.7, 76.4, 60.7, 58.5, 24.8. *m*/*z* (APCI) 297 (39%, $[M+H]^+$), 267 (100%). *m*/*z* (EI) 294 (8%, $[M-2H]^{+\bullet}$), 133 (100%), 91 (63%).

3-Benzyl-5-(2′,4′,6′-trimethylphenyl)oxazolidine ***1l***

2,4,6-Trimethylbenzaldehyde **3l**: 592 mg, 3.99 mmol. Product **1l** (903 mg, 80%) isolated as a white amorphous solid, mp 36–37°C. R_F 0.16 (5:95 EtOAc/hexanes). (Found: $[M-2H]^{+\bullet}$ 279.1612. $C_{19}H_{23}NO$ requires $[M-2H]^{+\bullet}$ 279.1618.) ν_{max} (neat)/cm^{-1} 3023, 2922, 2870, 2796, 1612, 1453, 1355, 1074. δ_H (400 MHz) 7.48–7.29 (5H, m), 6.87 (2H, s), 5.51 (1H, dd, *J* 9.8 and 6.4), 4.70 (1H, d, *J* 4.6), 4.63 (1H, d, *J* 4.6), 3.92 (2H, s), 3.26 (1H, dd, *J* 11.0 and 6.3), 2.89 (1H, m), 2.43 (6H, s), 2.30 (3H, s). δ_C (100 MHz) 138.8, 136.7, 136.3, 132.3, 130.3, 128.8, 128.6, 127.4, 86.9, 75.4, 58.6, 56.8, 20.9, 20.8. *m*/*z* (APCI) 282 (46%, $[M+H]^+$), 252 (100%), 133 (30%). *m*/*z* (EI) 279 (<1%, $[M-2H]^{+\bullet}$), 133 (100%), 91 (77%).

4-(3-Benzyloxazolidin-5-yl)benzoic Acid ***1m***

Benzaldehyde-4-carboxylic acid **3m**: 152 mg, 1.01 mmol. A first crop was obtained by filtration of the crude reaction mixture. The filtrate was reduced and a second crop was obtained by recrystallization from dichloromethane. The crops were combined to give the *title compound* **1m** (105 mg, 59%) as a white solid, mp 139–140°C. (Found: C 71.9, H 6.0, N 5.0. $C_{17}H_{17}NO_3$ requires C 72.1, H 6.1, N 4.9%.) ν_{max} (neat)/cm^{-1} 3001, 2980, 2880, 2847, 2677, 2554, 1680, 1610, 1431, 1317, 1293, 1044, 994, 903, 853. δ_H (400 MHz) 8.09 (2H, d, *J* 8.1), 7.45 (2H, d, *J* 8.2), 7.39–7.24 (5H, m), 5.14 (1H, m), 4.64 (2H, s), 3.85 (2H, s), 3.50 (1H, m), 2.84 (1H, m). δ_C (100 MHz) 171.2, 148.4, 138.2, 130.6, 129.0, 128.7, 127.7, 125.6, 87.6, 76.3, 60.3, 58.4. *m*/*z* (ES+) 284 (5%, $[M+H]^+$), 91 (100%).

2-(3-Benzyloxazolidin-5-yl)phenol ***1n***

Salicylaldehyde **3n**: 110 μL, 1.03 mmol. Product **1n**: colourless waxy solid (142 mg, 54%). R_F 0.27 (2.5:97.5 EtOAc/CH_2Cl_2). Mp 64–65°C. (Found: C 75.1, H 6.7, N 5.5. $C_{16}H_{17}NO_2$ requires C 75.3, H 6.7, N 5.5%.) ν_{max} (neat)/cm^{-1} 3313, 3060, 3023, 2928, 2834, 2712, 1583, 1487, 1455, 1261. δ_H (400 MHz) 10.96 (1H, br s), 7.44–7.37 (4H, m), 7.37–7.30 (1H, m), 7.24 (1H, ddd, *J* 8.1, 7.4 and 1.7), 7.06 (1H, dd, *J* 7.5 and 1.7), 6.96 (1H, dd, *J* 8.1 and 1.1), 6.81 (1H, ddd, *J* 7.4, 7.4 and 1.2), 5.15 (1H, dd, *J* 7.9 and 2.4), 4.80 (1H, d, *J* 3.0), 4.06 (1H, d, *J* 3.0), 3.82 (1H, m), 3.28 (1H, dd, *J* 10.0 and 2.4), 2.99 (1H, dd, *J* 9.9 and 7.9). δ_C (100 MHz) 155.9, 136.2, 130.1, 129.9, 128.8, 128.6, 127.9, 125.6, 118.7, 117.5, 86.5, 79.5, 56.3, 55.4. *m*/*z* (ES+) 256 (20%, $[M+H]^+$), 224 (100%).

2-((Benzyl(methyl)amino)methyl)-4-(3-benzyloxazolidin-5-yl)phenol ***11***

4-Hydroxybenzaldehyde **3p**: 123 mg, 1.01 mmol; **5**: 0.78 mL, 3.03 mmol; TFA (1 M in dichloromethane): 0.1 mL, 0.1 mmol. Product **11**: colourless oil (209 mg, 53%). R_F 0.2 (15:85 EtOAc/CH_2Cl_2). (Found: M^+ 388.2136. $C_{25}H_{28}N_2O_2$ requires M^+ 388.2145.) ν_{max} (neat)/cm^{-1} 3061, 3028, 2844 (br s), 1601, 1494, 1453, 1355, 1258, 1149, 1116, 1074, 1017, 907, 856, 827, 745, 699. δ_H (200 MHz) 10.9 (1H, br s), 7.42–7.25 (m, 10H), 7.15 (1H, dd, *J* 8.1 and 1.2), 7.02 (1H, br s), 6.84 (1H, d, *J* 8.3), 4.97 (1H, m), 4.60–4.57 (2H, m), 3.84 (2H, s), 3.76 (2H, br s), 3.61 (2H, br s), 3.36 (1H, dd, *J* 11.2 and 6.5), 2.81 (1H, dd, *J* 11.2 and 8.1), 2.25 (3H, s). δ_C (50 MHz) 157.5, 138.7, 136.8, 132.3, 129.4 (2), 128.8 (2), 128.7 (2), 128.6 (2), 127.8, 127.4, 126.6, 126.3, 121.9, 116.2, 87.5, 76.9, 61.6, 61.0, 60.5, 58.5, 41.4. *m*/*z* (EI) 388 (10%, $[M]^{+\bullet}$), 134 (76%), 132 (100%), 120 (51%).

3-Benzyl-5-(furan-2-yl)oxazolidine ***23***

2-Furaldehyde **17** (distilled before use): 100 μL, 1.21 mmol. Product **23**: colourless oil (277 mg, 100%). R_F 0.27 (2.5:97.5 EtOAc/CH_2Cl_2). ν_{max} (neat)/cm^{-1} 2931, 2879, 1558, 1506, 1496, 1456, 1149, 1008, 737. δ_H (400 MHz) 7.44–7.25 (6H, m), 6.35 (1H, dd, *J* 3.2 and 1.8), 6.32 (1H, d, *J* 3.1), 5.03 (1H, m), 4.52 (2H, dd, *J* 9.9 and 5.8), 3.85 (2H, dd, *J* 18.5 and 13.1), 3.33 (1H, dd, *J* 11.9 and 7.1), 3.18 (1H, dd, *J* 11.8 and 7.5). δ_C (100 MHz) 153.9, 142.8, 138.9, 128.9, 128.6, 127.4, 110.4, 107.7, 87.0, 69.7, 58.5, 56.4. *m*/*z* (EI) 229 (2%, M^+), 133 (78%), 91 (100%).

3-Benzyl-5-(thiophen-2-yl)oxazolidine ***24***

2-Thiophenecarboxaldehyde **18**: 100 μL, 1.07 mmol. Product **24**: colourless oil (241 mg, 92%). R_F 0.27 (5:95 EtOAc/

CH_2Cl_2). (Found: M^+ 245.0866. $C_{14}H_{15}NOS$ requires M^+ 245.0869.) ν_{max} (neat)/cm^{-1} 3025, 2918, 2875, 2806, 1669, 1493, 1451, 909. δ_H (400 MHz) 7.41–7.24 (6H, m), 7.01–6.96 (2H, m), 5.29 (1H, m), 4.59 (1H, d, *J* 5.2), 4.51 (1H, d, *J* 5.2), 3.85 (2H, s), 3.42 (1H, dd, *J* 11.5 and 6.9), 3.02 (1H, dd, *J* 11.5 and 7.1). δ_C (100 MHz) 145.7, 138.7, 128.9, 128.6, 127.5, 126.9, 125.1, 124.4, 87.0, 72.9, 60.5, 58.4. *m*/*z* (EI) 245 (<1%, M^+), 133 (100%).

3-(3-Benzyloxazolidin-5-yl)pyridine ***25***

3-Pyridinecarboxaldehyde **19**: 100 μL, 1.06 mmol. Product **24**: colourless oil (186 mg, 73%). R_F 0.09 (5:94.5:0.5 EtOAc/CH_2Cl_2/Et_3N). (Found: $[M-H]^+$ 239.1181. $C_{15}H_{15}N_2O$ requires $[M-H]^+$ 239.1179.) ν_{max} (neat)/cm^{-1} 3029, 2918, 2876, 2802, 1577, 1453, 1427, 1354. δ_H (400 MHz) 8.55 (1H, d, *J* 2.0), 8.48 (1H, dd, *J* 4.8 and 1.6), 7.63 (1H, br d, *J* 8.0), 7.35–7.18 (6H, m), 5.01 (1H, m), 4.54 (2H, m), 3.76 (2H, s), 3.38 (1H, dd, *J* 11.3 and 6.8), 2.78 (1H, dd, *J* 11.3 and 7.5). δ_C (100 MHz) 148.9, 147.5, 138.4, 137.6, 133.2, 128.6, 128.4, 127.3, 123.3, 87.6, 74.4, 60.2, 58.1. *m*/*z* (EI) 239 (4%, $[M-H]^+$), 133 (100%).

*3-Benzyl-5-(1′-phenylsulfonyl-1*H*-pyrrol-2′-yl)-oxazolidine* ***28***

1-(Phenylsulfonyl)-1*H*-pyrrole-2-carboxaldehyde **22**: 239 mg, 1.02 mmol. Product **28**: colourless oil (338 mg, 90%). R_F 0.16 (25:75 EtOAc/hexanes). (Found: M^+ 368.1153. $C_{20}H_{20}N_2O_3S$ requires M^+ 368.1189.) ν_{max} (neat)/cm^{-1} 3063, 3028, 2928, 2875, 2815, 1448, 1368, 1178, 1152, 1090, 1050, 726, 685, 605, 590, 565. δ_H (400 MHz) 7.79 (2H, d, *J* 7.6), 7.57 (1H, dd, *J* 7.4 and 7.4), 7.47 (2H, m), 7.37–7.24 (6H, m), 6.39–6.35 (1H, m), 6.27 (1H, dd, *J* 3.3 and 3.3), 5.35 (1H, m), 4.46 (2H, m), 3.81 (2H, s), 3.44 (1H, dd, *J* 11.8 and 6.9), 2.96 (1H, dd, *J* 11.8 and 6.7). δ_C (100 MHz) 139.4, 138.7, 136.3, 133.9, 129.4, 128.8, 128.5, 127.4, 126.7, 123.4, 112.2, 112.0, 86.7, 70.1, 59.5, 58.5. *m*/*z* (EI) 368 (<1%, M^+), 133 (100%), 91 (59%).

Accessory Publication

An Accessory Publication containing ^1H and ^{13}C JMOD NMR spectra for compound **11**, as well as full assignment of these spectra, is available from the authors or available from the *Australian Journal of Chemistry* until December 2012.

Acknowledgements

We thank the CSIRO (Australia), the Australian Research Council, and the Victorian Endowment for Science, Knowledge and Innovation (VESKI) for financial support. Nadia Spiccia was the recipient of a CSIRO Summer Vacation Scholarship. We also thank Dr Roger Mulder and Dr Jo Cosgriff for assistance with collection of NMR data, and Dr Carl Braybrook for interpretation of MS data.

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