A Convenient Synthesis of 2-Aryl Derivatives of 4a,5,6,7,8,8a-Hexahydrospiro[4*H*-1,3-benzoxazine-4,1′-cyclohexane]†

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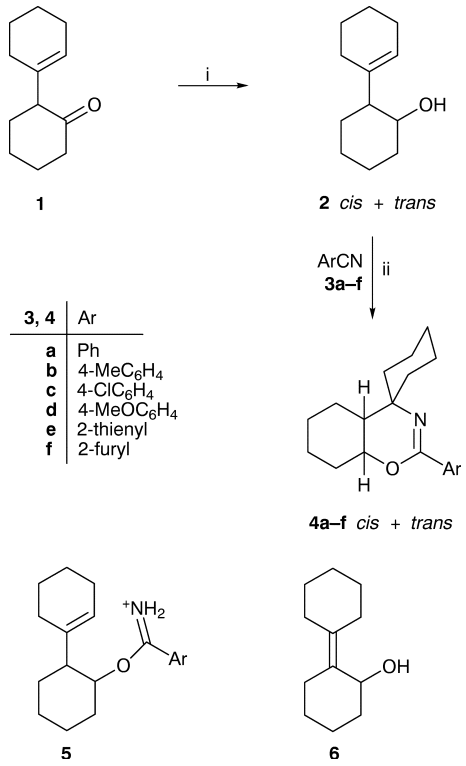
Various 2-aryl derivatives of 4a,5,6,7,8,8a-hexahydrospiro[4*H*-1,3-benzoxazine-4,1′-cyclohexane] have been efficiently prepared by the acid-catalysed reaction of 2-(1-cyclohexen-1-yl)cyclohexanol with aromatic carbonitriles.

5,6-Dihydro-4*H*-1,3-oxazines are a class of six-membered heterocyclic compounds that have found use in a wide variety of procedures. Thus, they are useful in the synthesis of surfactants[1] and liquid crystals[2] and have been used for cationic ring-opening polymerizations.[3,4] The oxazine ring system can be regarded as a masked carbonyl moiety[5] and chiral oxazines are valuable synthons for certain asymmetric syntheses.[6] In addition, derivatives of these ring systems have displayed various useful pharmacological activities. For example, they have been shown to be hydrocarbon antioxidants[7] and choline acetyl transferase inhibitors.[8]

However, the construction of architecturally sophisticated compounds with a spiro carbon centre embedded in their skeleton is particularly demanding and their elaboration still remains a synthetically challenging task.[9,10] We report here a convenient and efficient synthesis of the previously unattainable *cis*- and *trans*-2-aryl-hexahydrobenzoxazines possessing a spiro heterocyclic framework.

Several synthetic routes to partly or fully substituted 5,6-dihydro-4*H*-1,3-oxazines have been reported, including (a) the reaction of 2,4-diols,[11] 1,3-dioxanes[12] and unsaturated alcohols[13] with carbonitriles, (b) the photoinduced ring closure of aromatic dienamides[14] and (c) the heterocyclization of *N*-(γ-halogenoalkyl)amides with potassium fluoride on alumina.[15] However, the most efficient route relies upon the amidoalkylation of olefins.[16a] Some of these methods allow the formation of 4,4-disubstituted model compounds but are mainly confined to the synthesis of monocyclic 5,6-dihydro-4*H*-1,3-oxazines. Several synthetic strategies have been developed for the elaboration of cycloalkyl-fused bicyclic oxazines, namely by intramolecular [4 + 2] cycloaddition of *N*-acyliminium compounds with alkene dienophiles[16] but these methods are rather limited in scope and do not permit the incorporation of a spiro carbon centre.

Our strategy hinges upon the acid-catalysed reaction of *cis*- and *trans*-2-(1-cyclohexen-1-yl)cyclohexanol (**2**) with the aromatic carbonitriles **3a**–**f** and allows the synchronous formation of the hexahydrobenzoxazine framework[13] and the creation of the spiro carbon centre (Scheme 1). Initially the bicyclic γ,δ-unsaturated alcohol **2** was easily obtained as a mixture of *cis* and *trans* isomers (60:40)[17] by reduction of the parent 2-(1-cyclohexen-1-yl)cyclohexanone **1**, a product of the aldol dimerization of cyclohexanone.[18] After numerous attempts we found that completion of the annulation reaction was best achieved as a one-pot reaction by slow and dropwise sequential addition of the suitable carbonitriles **3a**–**f** followed by the alcohol **2** in ice-cooled sulfuric acid. The results of a representative series of products obtained by this method are presented in Table 1. The *cis*



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, THF, reflux 3 h; ii, H_2SO_4 (96%), 0 °C, then **3a**–**f**, then **2**, 0 °C, 10 h

and *trans* stereochemistry of the fused compounds **4a**–**f** obtained has been assigned from the chemical shift of the proton vicinal to the oxygen atom (*e.g.* cis-**4a**, $\delta = 4.51$ ppm; *trans*-**4a**, $\delta = 3.97$ ppm). Detailed analysis by NMR spectroscopy on related systems[19] has clearly established that the 8a-H chemical shifts of the *cis* isomers are invariably increased by 0.50–0.60 ppm compared with their *trans* counterparts. Moreover the spiro structure of **4a**–**f** was confirmed mainly by 75 MHz ^{13}C NMR spectroscopy, which clearly indicates the presence of three (**4a**,**e**,**f**) or four (**4b**–**d**) non-protonated carbon centres in the spiro annulated compounds **4**. In particular the non-protonated character of the carbon nucleus α to the nitrogen atom (*e.g.* δ 53.3 ppm for *trans*-**4a**) was unambiguously established by comparison of (DEPT) spectra with different pulse angles θ.

From a mechanistic point of view we can assume that the formation of the annulated products **4a**–**f** proceeds *via* the intermediacy of the protonated imidate **5** obtained after preliminary protonation of the carbonitrile **3** and nucleophilic attack of the unsaturated alcohol **2**. Subsequent addition on the protonated cycloalkenyl moiety ensures completion of the spiroannulation reaction. It is noteworthy that the use of a γ,δ-unsaturated alcohol is a prerequisite to the spiroannulation process since all attempts to perform

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Table 1 Selected data for 2-aryl-4a,5,6,7,8,8a-hexahydrospiro[4*H*-1,3-benzoxazine-4,1′-cyclohexanes] **4a–f**

Compound	Ar	Yield[a] (%)		Mp (*T*/ °C)	δ_H[b] (ppm)	δ_C (ppm)	Found (calc.) (%) C	H	N
4a	C_6H_5	65	*trans*	117–118	1.10–1.70 (13 H, m), 1.77–1.85 (4 H, m), 2.17–2.31 (2 H, m), 3.97 (1 H, dt, *J* 10.5, 4.5), 7.30–7.37 (3 H, m), 7.98–8.00 (2 H, m)	*C*, 53.3, 135.0, 150.4; *C*H, 47.9, 73.0, 127.1, 127.8, 129.7; CH_2, 21.3, 21.5, 24.4, 25.3, 26.3, 27.0, 33.0, 34.6, 36.6	80.4 (80.5)	8.9 (8.9)	5.0 (4.9)
			cis	79–80	1.04–1.85 (18 H, m), 2.19 (1 H, dt, *J* 10.4, 4.5), 4.51 (1 H, s), 7.31–7.41 (3 H, m), 7.93–7.99 (2 H, m)	*C*, 54.9, 134.6, 152.4; *C*H, 37.6, 69.3, 127.1, 127.8, 129.3; CH_2, 19.9, 21.2, 21.8, 21.9, 25.4, 26.1, 31.1, 35.7, 39.1			
4b	4-MeC_6H_4	63	*trans*	90–91			80.8 (80.8)	9.0 (9.15)	4.7 (4.7)
			cis	80–81					
4c	4-ClC_6H_4	66	*trans*	104–105			72.1 (71.8)	7.5 (7.6)	4.2 (4.4)
			cis	81–82					
4d	4-$MeOC_6H_4$	62	*trans*	93–94			76.5 (76.6)	8.7 (8.8)	4.5 (4.6)
			cis	79–80					
4e	2-Thienyl	50	*trans*	91–92	1.05–1.90 (13 H, m), 1.70–1.86 (4 H, m), 2.14–2.28 (2 H, m), 3.96 (1 H, dt, *J* 10.5, 4.4), 6.98 (1 H, dd, *J* 5.0, 3.6), 7.27 (1 H, dd, *J* 5.0, 1.25), 7.45 (1 H, dd, *J* 3.6, 1.25)	*C*, 53.5, 139.7, 147.3; *C*H, 48.0, 73.3, 126.8, 126.9, 127.7; CH_2, 21.2, 21.4, 24.3, 25.3, 26.2, 27.0, 32.9, 34.5, 36.5	70.8 (70.55)	8.0 (8.0)	4.85 (4.8)
			cis	102–103	1.01–1.88 (18 H, m), 2.13–2.17 (1 H, m), 4.50 (1 H, s), 6.99 (1 H, dd, *J* 5.0, 3.6), 7.29 (1 H, dd, *J* 5.0, 1.25), 7.50 (1 H, dd, *J* 3.6, 1.25)	*C*, 55.1, 138.9, 149.2; *C*H, 37.6, 69.7, 127.0, 127.1, 127.6; CH_2, 19.8, 21.2, 21.7, 21.9, 25.4, 26.0, 31.0, 35.5, 38.9			
4f	2-Furyl	42	*trans*	79–80			75.0 (74.8)	8.5 (8.6)	5.0 (5.1)
			cis	91–92					

[a]Yields determined for the mixture (*trans* + *cis*) before chromatographic separation. [b]*J* Values in Hz.

the same reaction with the isomeric allylic alcohol **6**[20] were unrewarding.

Experimental

General Procedure for the Preparation of 2-*Aryl*-4*a*,5,6,7,8,8*a*-*hexahydrospiro*[4H-1,3-*benzoxazine*-4,1′-*cyclohexanes*] **4a–f**.—To ice-cooled sulfuric acid (96%, 7 mL) was added the appropriate carbonitrile **3a–f** (6 mmol) by syringe over a period of 15 min. The mixture was then stirred under Ar for 5 min and the alcohol **3** (1 g, 5.5 mmol) was then slowly added to the sulfuric acid solution. The reaction mixture was stirred at 0 °C for an additional 10 h and the resulting solution was slowly and carefully transferred into a 100 mL beaker containing a vigorously stirred CH_2Cl_2–ice mixture (30 mL/30 g). After the addition was complete, concentrated aqueous KOH (30%), previously cooled in ice, was then carefully added until the solution was neutralized. The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). Removal of the solvent under vacuum afforded a residual viscous liquid which was purified by column chromatography on silica gel using AcOEt–hexane (5:95) as eluent. The *trans* isomers of compounds **4** were invariably eluted first in all cases.

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