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The Application of the Schmidt Reaction and Beckmann Rearrangement to the Synthesis of Bicyclic Lactams: Some Mechanistic Considerations

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The syntheses of some methoxy-substituted bicyclic lactams, of the types **3** and **4**, are reported employing two different conditions for the Schmidt reaction of appropriate ketones and employing two different conditions for the Beckmann rearrangement of the corresponding ketoximes. The alkyl to aryl migration ratios of the reactions were determined by high-performance liquid chromatography analysis of the reactions. The mechanisms of the reactions reported are discussed, some limitations of the reported mechanisms identified, and an alternative mechanism proposed in light of the outcomes of the various reactions. Application of the Schmidt reaction and Beckmann rearrangement was used for the synthesis of some chloro bicyclic lactams, of the types **3** and **4**.

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Introduction

Our group has had an interest in the synthesis and testing of clozapine derivatives[1,2] as a potential for the treatment of schizophrenia, a debilitating mental illness affecting ~1% of the world population.[3] Initial work involved the investigation of alkylaryl substitution on the distal nitrogen of clozapine (Fig. 1, **1**).[1,2] Progression of this investigation has involved investigating replacement of the important amino functional group with a solubilizing aminimide group, as aqueous solubility was beginning to limit the scope of the investigation.[4,5] Another approach to reducing the lipophilicity of the analogues has involved pruning the tricycle of clozapine to a bicycle (Fig. 1, **2**).[6]

Owing to stability issues associated with reactions of the bicyclic lactams **2** to give the amidine clozapine analogues (possibly due to the cyclic methylene group between two electron-withdrawing C=N bonds), we desired to explore analogues derived from less unsaturated lactams. As a result, we desired access to various less unsaturated bicyclic lactams, as key intermediates for the synthesis of new clozapine analogues (Fig. 2). Depending on which aromatic ring is pruned, access to two alternative lactams, **3** and **4**, is desired. The replacement of the nitrogen of clozapine (N5-H), with either methylene or oxygen, is to help address the proposed involvement of the N5-H of clozapine with its clinically limiting agranulocytosis.[7,8]

This paper explores synthetic approaches to bicyclic lactams derived from a variety of substituted tetralones and 4-chromanones, investigating factors influencing the ratio of the reaction products to provide optimal conditions for the synthesis of target bicyclic lactams.

The Schmidt reaction of cyclic ketones, and the Beckmann rearrangement of their corresponding ketoximes, has provided a method for the conversion of cyclic ketones to lactams. In the case of aryl alkyl ketones, a variety of migration product can be obtained depending on the reaction conditions utilized. This paper aims to examine the influence of the reaction conditions on the nature of the migration products obtained. In addition to the reaction conditions, some substituent effects are also investigated. The substituent investigated in detail is the methoxy group, a group that in resonance terms is electron-donating and in inductive terms electron-withdrawing (Hammet substituents constants; $\sigma_{p\text{-OMe}} = -0.27$; $\sigma_{m\text{-OMe}} = +0.12$). Application of the insight so gained is used to synthesize lactams derived from chloro-substituted tetralones and chromanones.

The reaction between hydrazoic acid and carbonyl compounds in the presence of a strong mineral acid is known as the Schmidt reaction.[9] Although many other functional groups (carboxylic acids, alcohols, alkenes) are known to react under the Schmidt reaction conditions, the present investigation is limited to the conversion of ketones to amides; in particular cyclic ketones to lactams. The Beckmann rearrangement refers to the rearrangement of oximes under acidic condition to yield *N*-substituted carboxamides.[10] Both ketoximes and aldoximes react but ketoximes are generally more reactive. Beckmann rearrangements have been achieved using acid-type catalysts such as concentrated sulfuric acid, polyphosphoric acid, phosphorus oxychloride, phosphorus pentachloride and thionyl chloride, and success has also been reported using silica gel[11] and microwave irradiation.[12,13]

Results

Results from the Schmidt reactions on the five bicyclic ketones **5**–**9** are tabulated in Table 1. Results from the Beckmann rearrangement on the corresponding *anti*-ketoximes **10**–**14** are also shown in Table 1. The alkyl:aryl migration ratio of individual reactions was determined and the most efficient route for the synthesis of the desired bicyclic lactams so determined.

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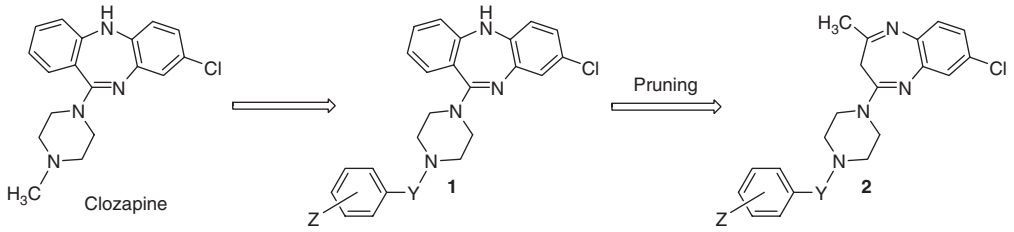


Fig. 1. Initial tricycle to bicycle pruning of clozapine analogues.

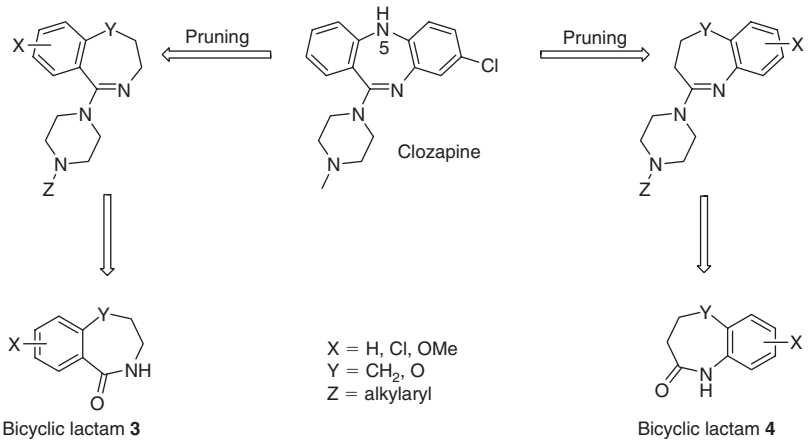
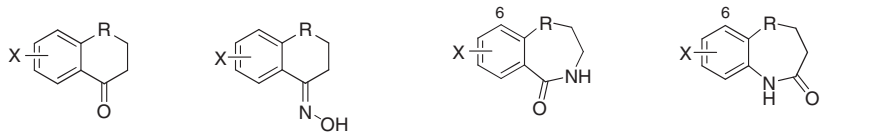


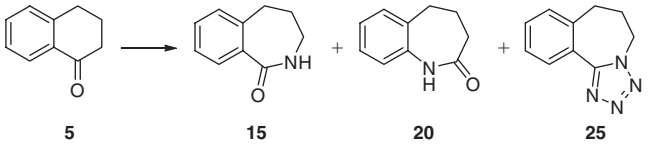
Fig. 2. Alternative tricycle to bicycle pruning of clozapine analogues.

Table 1. The alkyl:aryl migration ratios of the Schmidt reaction and Beckmann rearrangement



5 R = CH_2, X = H	**10** R = CH_2, X = H	**15** R = CH_2, X = H	**20** R = CH_2, X = H
6 R = O, X = H	**11** R = O, X = H	**16** R = O, X = H	**21** R = O, X = H
7 R = CH_2, X = 5-OMe	**12** R = CH_2, X = 5-OMe	**17** R = CH_2, X = 6-OMe	**22** R = CH_2, X = 6-OMe
8 R = CH_2, X = 6-OMe	**13** R = CH_2, X = 6-OMe	**18** R = CH_2, X = 7-OMe	**23** R = CH_2, X = 7-OMe
9 R = CH_2, X = 7-OMe	**14** R = CH_2, X = 7-OMe	**19** R = CH_2, X = 8-OMe	**24** R = CH_2, X = 8-OMe

Starting material	Reaction	Reagents	Products	Migration ratio (alkyl:aryl)	% Yield of major product
5	Schmidt	HCl/NaN_3	**15**, **20**	96:4	52
5	Schmidt	H_2SO_4/NaN_3	**15**, **20**	12:88	75
10	Beckmann	Polyphosphoric acid	**15**, **20**	0:100	60
10	Beckmann	$SOCl_2$	**15**, **20**	92:8	48
6	Schmidt	HCl/NaN_3	**16**, **21**	100:0	18
6	Schmidt	H_2SO_4/NaN_3	**16**, **21**	97:3	83
11	Beckmann	Polyphosphoric acid	**16**, **21**	96:4	56
11	Beckmann	$SOCl_2$	**16**, **21**	100:0	37
7	Schmidt	HCl/NaN_3	**17**, **22**	100:0	71
7	Schmidt	H_2SO_4/NaN_3	**17**, **22**	89:11	21
12	Beckmann	Polyphosphoric acid	**17**, **22**	0:100	47
12	Beckmann	$SOCl_2$	**17**, **22**	85:15	36
8	Schmidt	HCl/NaN_3	**18**, **23**	70:30	53
8	Schmidt	H_2SO_4/NaN_3	**18**, **23**	67:33	38
13	Beckmann	Polyphosphoric acid	**18**, **23**	73:27	71
13	Beckmann	$SOCl_2$	**18**, **23**	71:29	31
9	Schmidt	HCl/NaN_3	**19**, **24**	95:5	54
9	Schmidt	H_2SO_4/NaN_3	**19**, **24**	16:84	38
14	Beckmann	Polyphosphoric acid	**19**, **24**	0:100	47
14	Beckmann	$SOCl_2$	**19**, **24**	100:0	21



5 **15** **20** **25**

Scheme 1.

For the Schmidt reaction, concentrated hydrochloric acid and concentrated sulfuric acid were used, as the Schmidt reaction was found to behave differently in the two acids. For concentrated hydrochloric acid, the methods used by Mach et al.[14] and Meyers and Hutchings[15] were chosen, whereas for concentrated sulfuric acid, the method used by Sidhu et al.[16] was adopted. For the Beckmann rearrangement, the ketoximes were synthesized using hydroxylamine hydrochloride and sodium acetate in ethanol. The subsequent rearrangement was achieved by stirring the ketoximes in polyphosphoric acid at 95°C for 2 h, or in thionyl chloride at 50°C for 2 h.

Crude samples taken from each reaction were analyzed using high-performance liquid chromatography (HPLC). Standards were prepared from the bicyclic lactams previously isolated and purified. The peaks were identified by comparison of the retention time and the UV absorption profile with the standards, and quantitation was achieved by comparing the peak area with that of the relevant standard. The alkyl:aryl migration ratio for the Schmidt reaction and the Beckmann rearrangement are summarized above (Table 1).

The Schmidt reaction of 1-tetralone **5** using concentrated sulfuric acid gave the aryl-migration lactam **20** as the major product in 75% isolated yield, whereas using concentrated hydrochloric acid gave the alkyl-migration lactam **15** in 52% isolated yield. In the concentrated hydrochloric acid reaction, tetrazole **25** was also isolated in 8% yield, but it was not observed in the sulfuric acid reaction (Scheme 1).

The two lactams are distinguishable from each other by comparison of their melting points (**15**: 99–100°C; **20**: 139–140°C) with those from the literature (**15**: 101°C;[15] **20**: 139–140°C[17]). In addition, the splitting pattern of the H3 protons for lactam **15** shows an apparent quartet resonance at δ 3.12 suggesting that the NH group is at the 2-position, whereas **20** shows a triplet resonance at δ 2.36 for H3 protons, signifying that the NH is at the 1-position. The integrity of other ring-substituted bicyclic lactams made in the subsequent reactions was confirmed principally by comparing the H3 proton resonances. The alkyl:aryl migration ratio of 12:88 in concentrated sulfuric acid was consistent with that of Tomita et al.,[18] who reported 80% aryl migration under the same reaction conditions. The alkyl:aryl migration ratio of 96:4 observed for the concentrated hydrochloric acid reaction is a reversal of the selectivity of the reaction.

The Schmidt reaction of 4-chromanone **6**, 5-methoxy-1-tetralone **7**, 6-methoxy-1-tetralone **8**, and 7-methoxy-1-tetralone **9** using concentrated hydrochloric acid or concentrated sulfuric acid produced alkyl and aryl-migration lactams in the isolated yields shown in Table 1 with the alkyl:aryl migration ratio indicated (HPLC).

Reaction of 4-chromanone **6** using concentrated hydrochloric acid or concentrated sulfuric acid produced the alkyl-migration lactam **16** as the major product. This shows the importance of the resonance electronic effects of the ethereal oxygen on the *ortho* position relative to the ketone group. Although the reaction in concentrated hydrochloric acid was more selective than the concentrated sulfuric acid method, the low product yield detracts from the usefulness of this method. Similarly, 5-methoxy-1-tetralone **7** in concentrated hydrochloric acid or in concentrated sulfuric acid gave the alkyl-migration lactam **17** as the major product, with the concentrated hydrochloric acid reaction giving greater selectivity and yield. The use of concentrated sulfuric acid for the reaction of **7** has not been reported, but polyphosphoric acid[19] and trichloroacetic acid[20] have been reported to give **22** as the major product. The Schmidt reaction of 6-methoxy-1-tetralone **8** also demonstrates the contribution of the steric and electronic effects on the migration of the adjacent carbon, with a modest selectivity alkyl:aryl migration ratio compared with that of **6** and **7** under either reaction conditions. This suggests that the electronic effects are more influential than the steric effects and this is in good agreement with the literature reports.[21,22] 7-Methoxy-1-tetralone **9** mirrored that for the Schmidt reaction of 1-tetralone **5** with the reaction in concentrated hydrochloric acid, giving mostly alkyl migration and the concentrated sulfuric acid reaction giving predominately the aryl-migration product, observations consistent with the literature.[18,23,24]

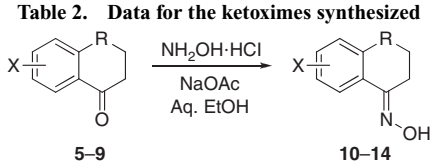
For the Beckmann rearrangement, conversion of the ketones to the ketoximes was achieved by refluxing the ketone with hydroxylamine hydrochloride and sodium acetate in ethanol for 2 h (Table 2).[25–29]

Literature procedures on the synthesis of ketoximes are not specific regarding the geometry (*syn* or *anti*) of the oxime group and full characterization is seldom performed as they are transitory. Hence, the ketoxime intermediates are reported as either non-specific or are assumed to be in the sterically favoured *anti*-arrangement. Papers reporting exclusive *syn*-ketoxime formation[30–33] are spectroscopically indistinguishable from the *anti*-ketoxime **10**,[34–36] adding a significant amount of uncertainty as far as the geometry is concerned. No paper identified the orientation of the oxime group for compounds **11**–**14**.

Of the five ketoximes synthesized below, X-ray crystal structures of **13** and **14** were determined (Fig. 3) (C. M. Forsyth, unpubl. data). As expected, the oxime group was in the sterically less-hindered *anti*-arrangement. Based on these crystal structures, it is assumed that other ketoximes are also in the *anti*-arrangement.

The Beckmann rearrangement of 1-tetralone oxime **10** in polyphosphoric acid gave the aryl-migration lactam **20**. This is in agreement with most of the literature but disputes the converse claim made by Mazzocchi et al.[37] that alkyl migration should predominate. In addition, the ytterbium triflate method as reported by Yadav et al.[38] was tried but the reaction did not proceed and failed to produce either of the bicyclic lactams in our

Table 2. Data for the ketoximes synthesized



5–9 **10–14**

Compound	R	X	Yield [%]	mp [°C]	Lit. mp [°C]
10	CH_2	H	79	100–101	101–103[25]
11	O	H	66	138–140	139–141[26]
12	CH_2	5-OMe	74	152–153	153–155[27]
13	CH_2	6-OMe	81	124–125	122–124[28]
14	CH_2	7-OMe	83	84–85	86–88[29]

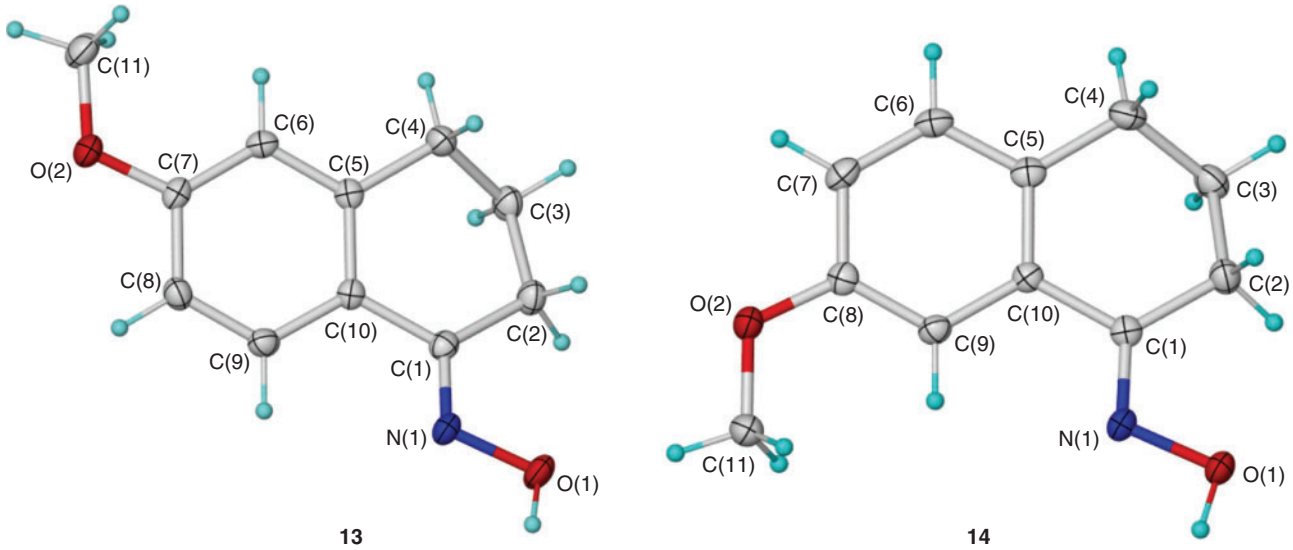


Fig. 3. X-ray crystal structures (*ORTEP* view) of oximes **13** and **14**.

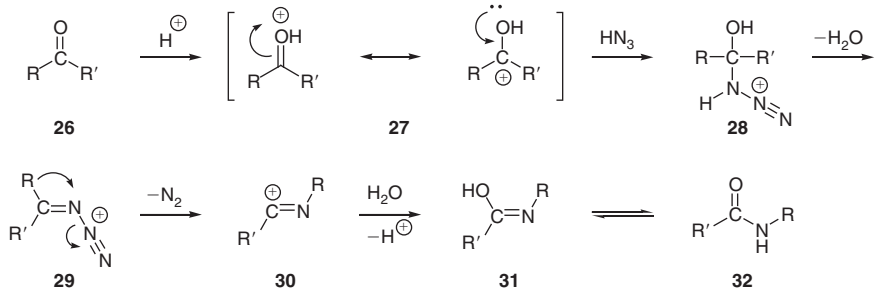


Fig. 4. Proposed mechanism of the Schmidt reaction.[47]

hands. However, treatment of **10** with thionyl chloride afforded the alkyl-migration lactam **15** as the major product. The reaction confirmed the results reported by Sudan et al.,[39] and could be used as an alternative Beckmann rearrangement method.

Reaction of 4-chromanone oxime **11** in polyphosphoric acid gave mainly the alkyl-migration lactam **16**, which is in agreement with the literature.[40] The reaction of **11** with thionyl chloride also gave **16** as the major product; no aryl migration was observed. 5-Methoxy-1-tetralone oxime **12** in polyphosphoric acid gave the aryl-migration lactam **22**; no alkyl-migration lactam **17** was observed. This confirmed results reported in the majority of the literature,[41,42] yet disputes the claim made by Martinez et al.[43] that the alkyl migration should predominate. In contrast, the Beckmann rearrangement of **12** in thionyl chloride gave mostly the alkyl-migration product **17**. 6-Methoxy-1-tetralone oxime **13** in both polyphosphoric acid and thionyl chloride gave alkyl-migration lactam **18** as the major product. Based on the yield, however, the use of polyphosphoric acid is preferred over thionyl chloride, as the former gives a cleaner reaction and higher yield. Unlike **13**, the Beckmann rearrangement of 7-methoxy-1-tetralone oxime **14** was more selective. In polyphosphoric acid, the rearrangement of **14** gave exclusively aryl-migration lactam **24**, and in thionyl chloride, **14** yielded exclusively alkyl-migration lactam **19**. The Beckmann rearrangement of **14** in the literature reports **24** as the only product[44–46] and the use of thionyl chloride to afford **19** is novel.

Generally, the use of the Schmidt reaction is favoured over the Beckmann rearrangement, as the former is a one-step procedure, except when the Schmidt reaction does not give the desired lactam or when the yield of the reaction is unacceptably low. The majority of the bicyclic lactams were synthesized in moderate to good yields but some of the aryl-migration lactams (**21**–**24**) suffered a bit from low yields but these were still acceptable for access to the required lactams. Synthesis of **21** proved to be a challenge, and in the future, this lactam might require a different approach.

Mechanistic Discussion: Schmidt Reaction

The mechanism of the Schmidt reaction is not fully elucidated; however, the mechanism shown above (Fig. 4) has been agreed on by many researchers as plausible.[47]

Under strongly acidic conditions, protonation of the ketone **26** occurs to give the resonance-stabilized cation **27**, and subsequent nucleophilic addition of the hydrazoic acid gives the hydroxyhydrazidinium intermediate **28**. On dehydration, **28** converts to the iminodiazonium ion **29** and a concerted elimination of the nitrogen and migration of the R-group (the group *anti* to the leaving group) afford the nitrilium intermediate **30**. Reaction with a water molecule, followed by tautomerization of **31**, gives the final amide **32**. Symmetrical ketones (R = R′) give only one amide product, but unsymmetrical ketones can give a mixture of the two amide products, where the ratio is determined by

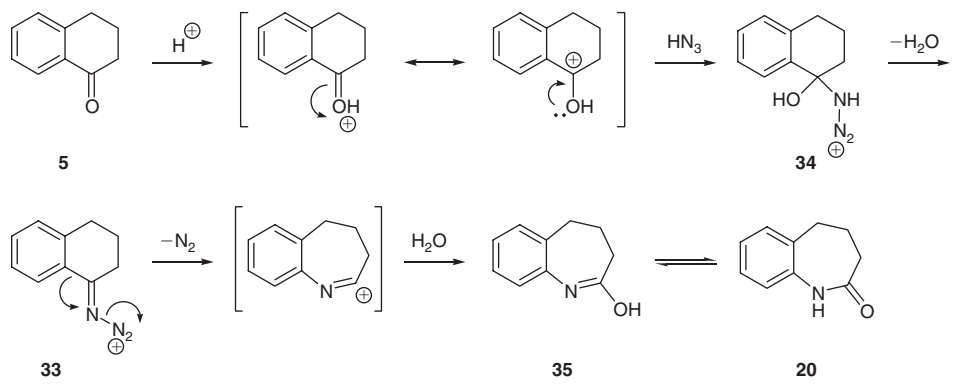


Fig. 5. Proposed Schmidt reaction mechanism of **5** in conc. sulfuric acid to give aryl-migration lactam **20**.

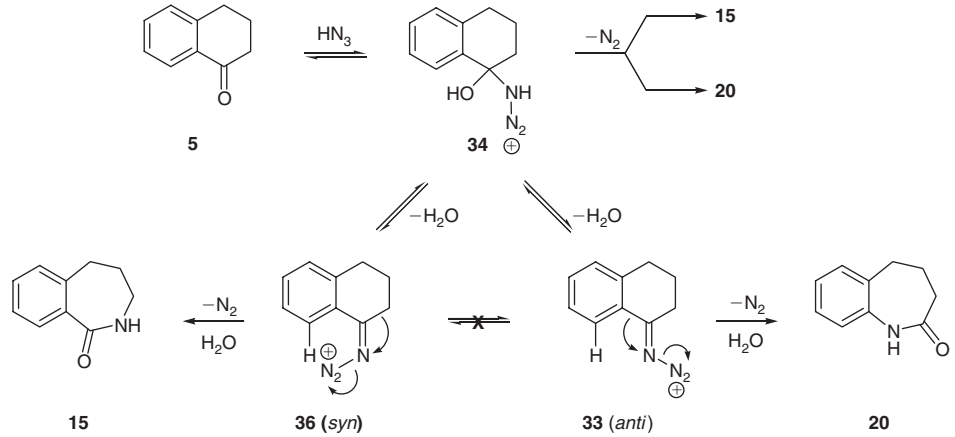


Fig. 6. Proposed Schmidt reaction mechanism of **5** under aqueous (conc. hydrochloric acid) and non-aqueous (conc. sulfuric acid) acids.[54]

the migratory aptitude of the relevant carbons. In the case of an alkyl aryl ketone, it is generally the aryl group that preferentially migrates, unless the alkyl group is also bulky.[48]

In concentrated sulfuric acid, it is predicted from the proposed mechanism of the Schmidt reaction that aryl migration will predominate over alkyl migration (Fig. 5). The use of concentrated sulfuric acid is reported to give the aryl-migration lactam (**20**) in 47–92% yield.[49–51] The use of trichloroacetic acid was also reported to proceed in 57–83% yield in favour of **20**.[17,52] Tomita et al.[18] have investigated the alkyl:aryl migration ratio of various unsymmetrical ketones using different types and strengths of acid and have found that the reaction of **5** in trichloroacetic acid, concentrated sulfuric acid and polyphosphoric acid gave 30:70, 20:80, and 10:90 for the alkyl:aryl migration ratios, respectively. The Schmidt reaction mechanism of 1-tetralone **5** in concentrated sulfuric acid is shown above (Fig. 5). The key step in the reaction mechanism is the formation of the *anti*-iminodiazonium intermediate (**33**) that is sterically favoured. Subsequent aryl migration, elimination of molecular nitrogen, hydration and tautomerization of **35** result in the formation of **20**.

In contrast, the Schmidt reaction of **5** in concentrated hydrochloric acid reported alkyl-migration lactam **15** as the major product, with yields ranging from 25 to 84%.[14,15,53] The low yield (25%) is probably due to the hydrolysis caused by the 1 M sodium hydroxide solution used during the neutralization step.[53] Use of a milder base, such as potassium carbonate, resulted in higher yields.[14,15] Grunewald and Dahanukar[54,55] have proposed explanations for the formation of **15** as the major product in concentrated hydrochloric acid and **20** in concentrated sulfuric acid (Fig. 6). The authors[54] have proposed that under the non-aqueous acid conditions (concentrated sulfuric acid), dehydration of the hydroxyhydrazidinium intermediate **34** is likely to occur, giving one of the two stereoisomers of the iminodiazonium intermediates **36** (*syn*) or **33** (*anti*). Owing to the steric hindrance with the *peri*-proton, the formation of the *syn*-iminodiazonium ion **36** is unfavoured and the reaction proceeds via the *anti*-iminodiazonium intermediate **33** to give **20**. The two iminodiazonium intermediates are not interchangeable as the calculation of the energy barrier for nitrogen inversion is well above that of room temperature.[56] However, dehydration of **34** is not likely to occur in aqueous acid (concentrated hydrochloric acid). The authors[54] claimed that a concerted rearrangement of **34** takes place to give **15** as the major product. This proposition is not supported by a detailed reaction mechanism, as most of the literature reports aryl migration as the preferred reaction, in difference with the proposition of Bach and Wolber.[56]

To account for some limitations in the explanation for the formation of **15** under the aqueous acid conditions, an alternative reaction mechanism is proposed (Fig. 7). Rather than a loss of a water molecule in the aqueous acid, the hydroxyhydrazidinium intermediate **34** can undergo a migration of either the alkyl or aryl carbons, giving the two possible cation intermediates **37** (Pathway A, alkyl migration) and **38** (Pathway B, aryl migration). In either case, subsequent loss of a proton results in formation of the stable amides **15** or **20**, respectively.

Comparison of the relative stabilities of the two cations, **37** and **38**, indicates that pathway A is energetically favoured over

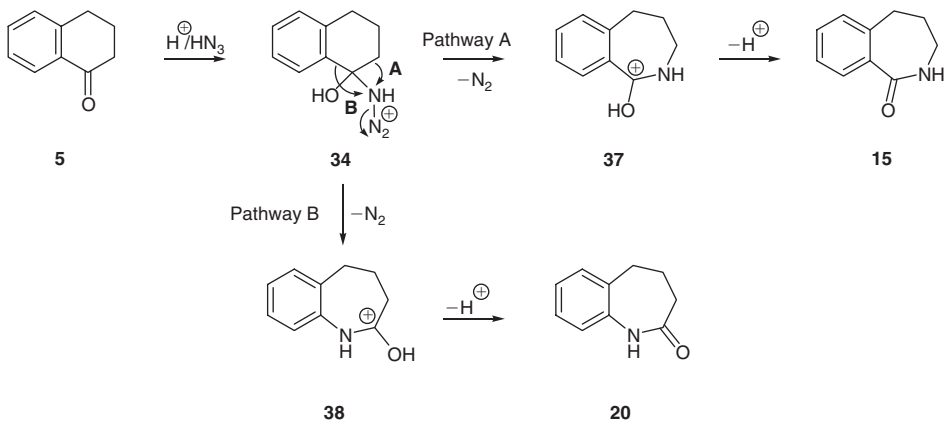


Fig. 7. Proposed Schmidt reaction mechanism of **5** under conc. hydrochloric acid; Pathway A (alkyl migration forms lactam **15**) and Pathway B (aryl migration forms lactam **20**).

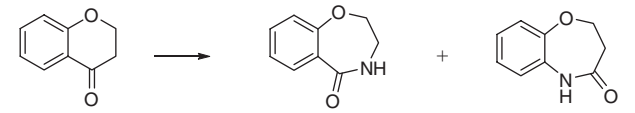


Fig. 8. Schmidt reaction of **6** and its potential products: alkyl (**16**) and aryl (**21**) migration lactams.

pathway B. The aliphatic cation intermediate **38** is resonance-stabilized by the lone pairs of electrons on two heteroatoms (N and O) and a remote inductive donation of electrons from the aromatic ring, whereas the benzylic cation intermediate **37** is stabilized by the lone pairs of electrons on two heteroatoms (N and O) and by the benzylic resonance stabilization from the aromatic ring. As the benzylic resonance-stabilizing effect is much stronger than a remote inductive effect, **37** is more stable than **38** and the reaction proceeds to favour the formation of **15**.

In contrast to the Schmidt reaction of 1-tetralone **5**, there are many literature reports of the alkyl-migration lactam **16** as the major reaction when 4-chromanone **6** is subjected to the Schmidt reaction conditions (Fig. 8). The use of concentrated sulfuric acid is reported to give **16** in 36–78% yield.[16,40,53,55,57] A combination of acetic acid and concentrated sulfuric acid was also used and reported to give **16** in ∼55% yield.[58,59] The use of concentrated hydrochloric acid has not been reported in the literature.

Based on steric effects alone the formation of the aryl-migration lactam **21** is predicted, as the sterically stable *anti*-iminodiazonium intermediate **39** is preferred (Fig. 9). The only reference to the formation of **21** is by Kamei et al.,[60] where it was isolated as a minor product in 2.6% yield. Evans and Lockhart[61] proposed that the preference of alkyl migration is due to the electronic effects of the '*ortho*' cyclic ether oxygen and presented a resonance structure of 4-chromanone (Fig. 10), which shows a partial double-bond character between the two carbon atoms (C4 and C4a) **40** making it difficult to migrate. Similar effects **41** were seen with 6-methoxy-1-tetralone **8** where the ether oxygen atom is *para* with respect to the ketone functionality.[62]

The resonance structures presented by Evans and Lockhart[61] below (Fig. 9) do explain the prevention of the aryl migration in 4-chromanone **6**; however, they do little in justifying why alkyl migration should occur, as the formation of the *anti*-iminodiazonium ion **39** is still favoured based on the steric effects of the aryl group. Therefore, a more detailed mechanism is proposed showing the full extent of the electronic effects of the ethereal oxygen on the migration of the alkyl carbon (Fig. 10).

Dehydration of the hydroxyhydrazidinium **42** would occur in concentrated sulfuric acid to produce the sterically favoured *anti*-iminodiazonium intermediate **39**. However, the lone pair of electrons from the oxygen can delocalize into the aromatic ring and can produce the resonance hybrid structure **43**. As shown, aryl migration would be prohibited owing to the partial double-bond character of the aryl carbon. At the same time, this partial double bond character reduces the energy barrier for the *anti–syn* interconversion and allows rotation of the C–N bond to produce the *syn*-iminodiazonium intermediate **44**; it can undergo alkyl migration to give the nitrilium cation **45**; subsequent hydration and tautomerization result in the formation of the alkyl-migration lactam **16**.

The Schmidt reactions of 5-methoxy-1-tetralone **7** gave a result consistent with the proposed Schmidt reaction mechanism in the aqueous acid. As the methoxy group on the 5-position does not take part in the resonance stabilization of the iminodiazonium intermediate, the formation of the aryl-migration lactam **22** is expected in concentrated sulfuric acid. Contrary to this expectation, the reaction of **7** in concentrated sulfuric acid gave **17** as the major product. The use of concentrated sulfuric acid for the reaction of **7** has not been reported in the literature, but the use of polyphosphoric acid[19] and trichloroacetic acid[20] have been reported, giving **22** as the major product. The formation of **22** in concentrated sulfuric acid supports the need for the revised mechanism.

Compared with other ketones, which showed greater than 95% propensity for the alkyl migration in concentrated hydrochloric acid, **8** gave an alkyl:aryl migration ratio of 70:30, with bicyclic lactams **18** and **23** being isolated in 53 and 15% yield, respectively. This suggests that the Schmidt reaction in concentrated hydrochloric acid does proceed via two different reaction mechanisms (Fig. 7), making it difficult to synthesize **23** as the major product.

Mechanistic Discussion: Beckmann Rearrangement

The Beckmann rearrangement of **46** (Fig. 11) is mechanistically similar to the Schmidt reaction (Fig. 4); the oxonium intermediate **47** is analogous to the iminodiazonium intermediate **29**, and the subsequent reaction with water and tautomerization of the iminol **31** to the amide **32** are identical to the Schmidt reaction

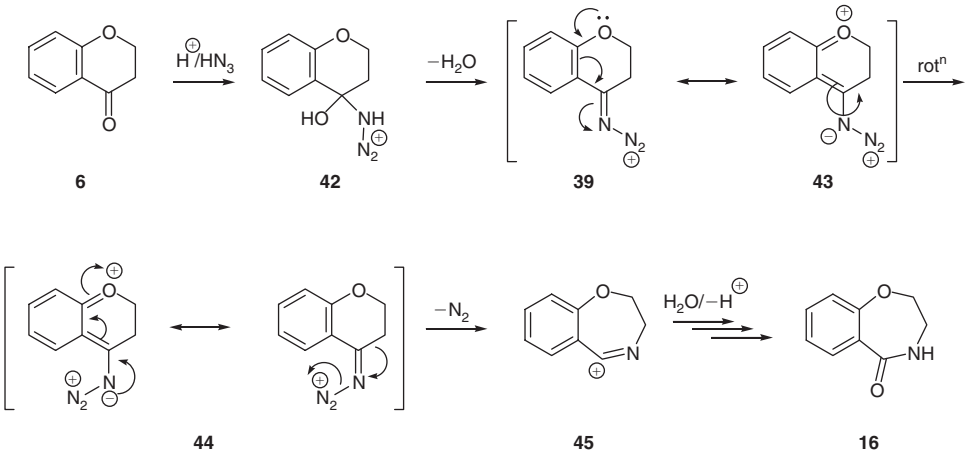


Fig. 9. Proposed Schmidt reaction mechanism of 4-chromanone **6** forming the alkyl-migration lactam **16**.

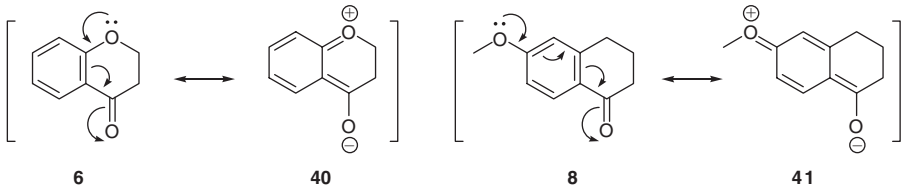


Fig. 10. Electronic effects of the ether oxygen in **6** and **8**.

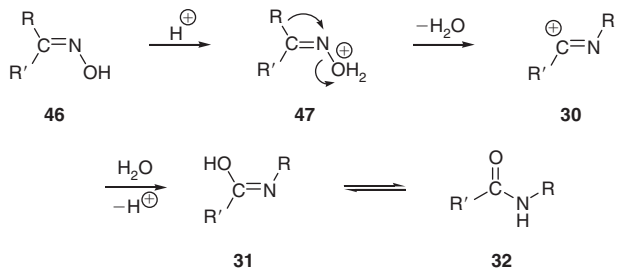


Fig. 11. Mechanism of the Beckmann rearrangement.[64]

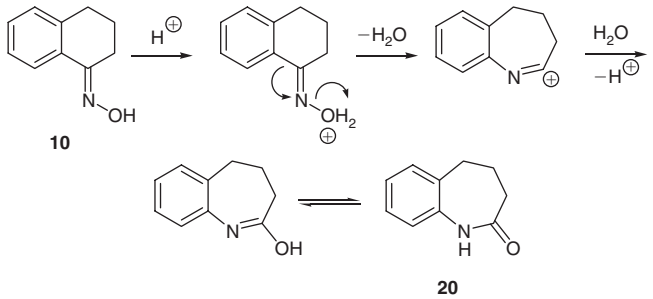


Fig. 12. Beckmann rearrangement mechanism of **10** leading to the aryl-migration lactam **20**.

mechanism. Unlike the Schmidt reaction, however, the geometry of the oxime group **46** is predetermined, and the migration of the group that is *anti* to the leaving group is generally favoured but it is not always unequivocal.[63]

Most literature on the Beckmann rearrangement of 1-tetralone oxime **10** reported aryl-migration lactam **20** as the major product. Stirring **10** in polyphosphoric acid for 5 to 10 min at 120–130°C is reported to give **20** in good yield.[65–68] Other methods using bismuth chloride,[69] indium chloride,[70] 2,4,6-trichloro[1,3,5]triazine,[71] gallium triflate,[72] aluminium chloride,[73] and sulfamic acid[74] all reported **20** in good yield (72–85%). The Beckmann rearrangement mechanism of **10** giving the aryl-migration lactam **20** is presented above (Fig. 12).

A search of the literature revealed only three papers reporting alkyl migration of **10**. Mazzocchi et al.[37] have reported the formation of the alkyl-migration lactam **15** in 80% yield using polyphosphoric acid. However, the reported melting point of 142.5–143.0°C is closer to **20** (139–140°C)[17] than to **15** (99–101°C).[75] The ^{1}H NMR spectral data provided showed greater concordance with that of **20** than that of **15**. Yadav et al.[38] have reported alkyl migration of **10** in 70% yield by using ytterbium triflate as the catalyst. However, their claim in the short communication is uncertain as no spectral data were provided for **15**. In addition, of the 11 unsymmetrical ketoximes studied, all but one proceeded to give aryl-migration product, which further questions their report. The third paper reporting the Beckmann rearrangement of **10** using thionyl chloride in 1,4-dioxan reported **15** in 60% yield.[39] The reported melting point of **15** (98–99°C) and spectral data are consistent with the alkyl-migration lactam. This method appears to provide synthetic access to **15**.

As with the Schmidt reaction of 4-chromanone **6**, the Beckmann rearrangement of 4-chromanone oxime **11** is driven by the electronic effects of the cyclic ether oxygen. Presented below is the proposed Beckmann rearrangement mechanism of **11** in polyphosphoric acid (Fig. 13). Analogous to the *anti*-iminodiazonium intermediate **39**, the *anti*-oxonium intermediate **48** is prohibited from aryl migration owing to the partial double-bond character of the aryl carbon. Instead, inversion of **48** to the *syn*-oxonium intermediate **49** occurs through resonance hybridization structures **50** and **51**, which can then undergo an alkyl migration to give the amide **16**.

Reports of the Beckmann rearrangement of **11** are uncommon. The polyphosphoric acid-catalyzed Beckmann

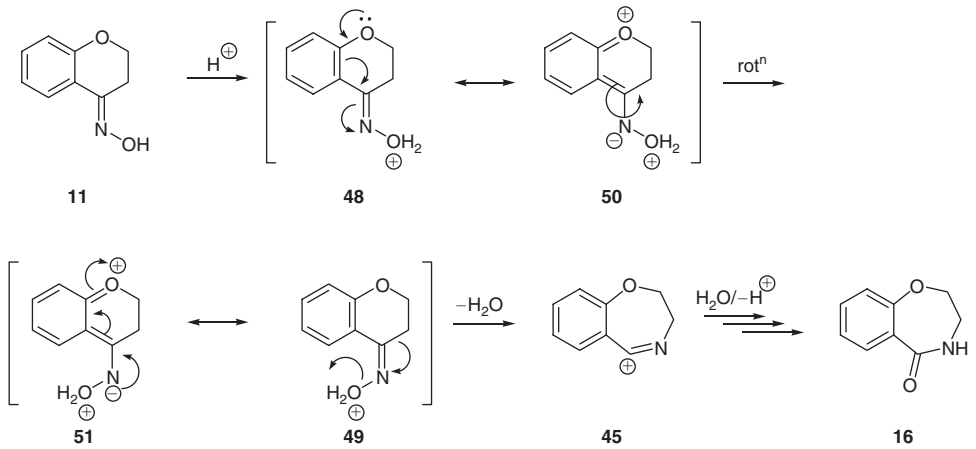


Fig. 13. Proposed mechanism of the Beckmann rearrangement of **11** to give the alkyl-migration lactam **16**.

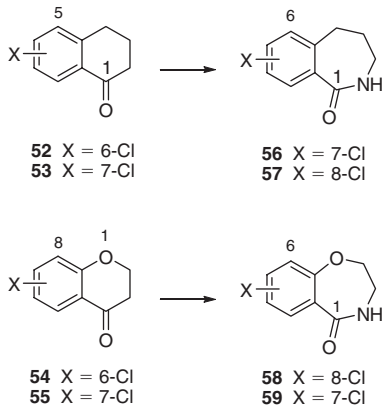


Fig. 14. Possible conversion of the chloro ketones (**52**–**55**) to the alkyl-migration lactams (**56**–**59**).

rearrangement of **11** afforded the alkyl-migration lactam **16** in 33% yield,[40] but an attempt to convert **11** to **21** using *p*-toluenesulfonyl chloride was not successful.[76] These results further support the proposed mechanism of the oxonium intermediate inversion (from *anti* to *syn*) arising from the electronic effects of the cyclic ether oxygen in the *ortho* position with respect to the ketone group.

The objective of a second series of bicyclic ring-substituted analogues (Fig. 2) was to investigate the effect of chlorine substitution on the eventual 7- and 8-positions of the bicyclic lactams. Chlorine was chosen as it is present in clozapine and also other antipsychotic drugs. In addition, analogues with isosteric replacement of the N5-H of clozapine with methylene and oxygen were also targeted. It was envisaged that applying the Schmidt reaction and Beckmann rearrangement on the corresponding chlorine-substituted ketones **52**–**55**, the chlorine-substituted bicyclic lactams (**56**–**59**) could be accessed (Fig. 14). Of the four chlorine-substituted ketones required, only the 6-chloro-4-chromanone **54** was commercially available and the other chlorine-substituted ketones were synthesized.

Conversion of 6-amino-1-tetralone **60** to 6-chloro-1-tetralone **52** has been achieved using the Sandmeyer reaction (Scheme 2).[77] 6-Amino-1-tetralone **60** can be accessed in many ways and the use of commercially available 6-hydroxy-1-tetralone **61** in the one-pot Smiles rearrangement has been recently reported (Scheme 2).[78,79] Addition of 2-bromo-2-methylpropanamide to a mixture of **60** and sodium hydroxide in *N*,*N*-dimethylacetamide resulted in the formation of the intermediate **62**. Further addition of excess sodium hydroxide resulted in the formation of the amide **63** through the Smiles rearrangement of **62**. Addition of water and heating to reflux gave 6-amino-1-tetralone **60** in 63% yield from **61**. The one-pot synthesis of 6-amino-1-tetralone **60** was attempted using the method reported by Mizuno et al.[79] The ^{1}H NMR spectrum of **60**, comparison of the melting point (129–131°C, lit.[80] 129–130°C) and electrospray ionization (ESI) mass spectrometry all confirmed formation of **60**. Conversion of the 6-amino-1-tetralone **60** to **52** was achieved under the Sandmeyer conditions (45% yield).

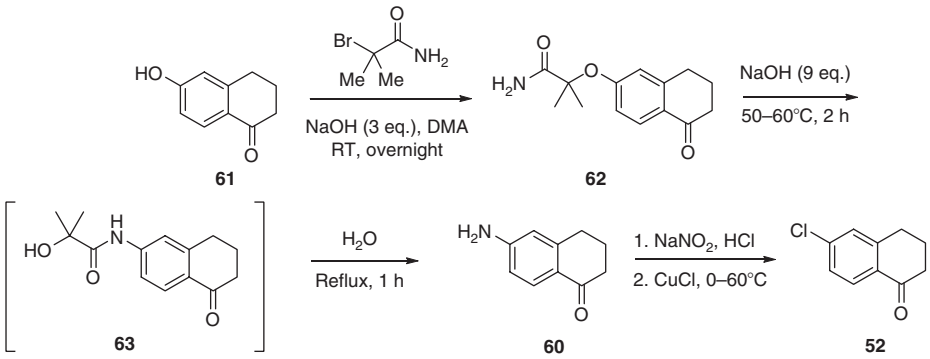
The two-step method for the synthesis of **53** has been reported by Harris et al.,[81] where Wolff–Kishner reduction of commercially available 3-(4-chlorobenzoyl)propionic acid **64** afforded **65**, and subsequent ring closure using polyphosphoric acid gave **53** (Scheme 3). In our hands, this method gave **65** and polyphosphoric acid ring closure afforded **53**.

Gresham et al.[82] have reported the conversion of 3-cholorophenol **66** to β-phenoxypropionic acid **67** using β-propiolactone under alkaline conditions, which was readily reproduced. Ring-closure of the intermediate **67** was achieved using polyphosphoric acid to afford **55** (Scheme 4).

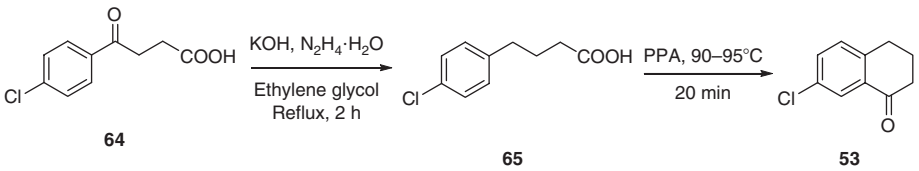
Having obtained the required chlorine-substituted 1-tetralones and 4-chromanones for the bicyclic ring-substituted analogues, conversion of these ketones to the lactams was attempted using the Schmidt reaction and Beckmann rearrangement (Fig. 14). The Schmidt reaction of **52** in concentrated hydrochloric acid gave the alkyl-migration lactam **56** (Fig. 14). The Schmidt reaction of **53** using concentrated hydrochloric acid gave the alkyl-migration lactam **57**. No aryl migration product was observed from the reaction of **53** in concentrated hydrochloric acid but the reaction gave a major by-product that was identified to be 2,2,7-trichloro-1-tetralone **68**, isolated in 53% yield (Scheme 5).

The ^{1}H NMR spectrum of **68**, elemental analysis and electron-impact (EI) mass spectrometry confirmed the presence of three chlorine atoms. An X-ray crystal structure was obtained for **68** that confirmed di-chlorination at the 2-position (Fig. 15).[83]

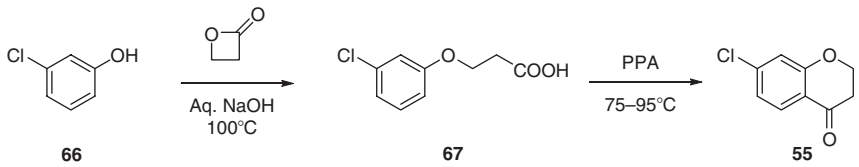
The Schmidt reaction of **54** in concentrated sulfuric acid gave the alkyl-migration lactam **58** as the major product. Comparison of the melting point with the literature value showed a significant difference and accordingly, the identity of **58** was further supported by elemental analysis. The aryl-migration lactam **69** was isolated in 5% yield by collection of the more mobile



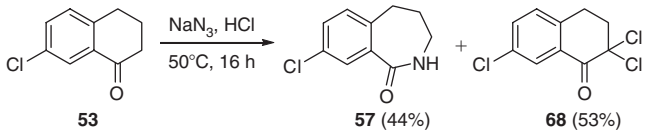
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

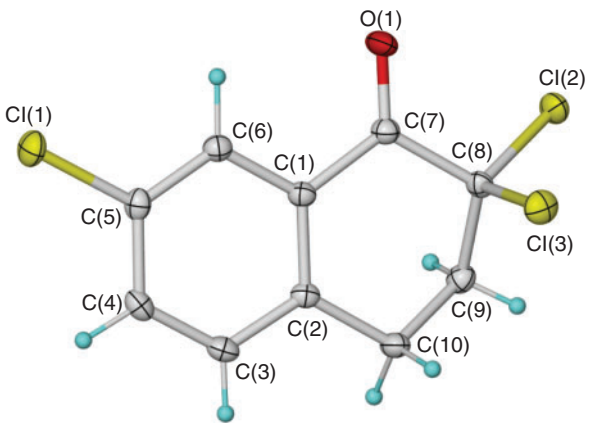
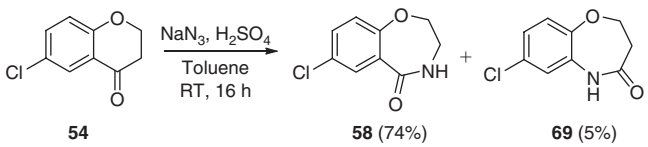


Fig. 15. X-ray crystal structure (*ORTEP* view) of 2,2,7-trichloro-1-tetralone **68**.

fractions (R_F 0.5) from flash chromatography of the above reaction. The aryl-migration product was fully characterized using spectral data and elemental analyses, as the compound is novel (Scheme 6).



Scheme 6.

The Schmidt reaction of **55** in concentrated sulfuric acid gave the alkyl-migration lactam **59** (Scheme 7); no aryl-migration lactam was isolated from the reaction. The alkyl-migration **59** was also fully characterized using spectral data and elemental analyses, as the compound was again novel. Owing to the limited quantities of the ketone **55**, an investigation of the directing effects of the Schmidt reaction and Beckmann rearrangement was not pursued.

The Beckmann rearrangement approach was investigated as an alternative route to the synthesis of **57** (Scheme 8). Newman and Hung[84] reported the synthesis of 7-chloro-1-tetralone oxime **71** using the hydroxylamine hydrochloride method. Using this oxime synthetic method, **71** was obtained. Comparison of the melting points (114–115°C, lit.[84] 124–125°C) showed some degree of uncertainty, even though the

oxime was recrystallized using the same solvent system and the characterization of **71** was supported by elemental analysis.

The subsequent Beckmann rearrangement of **71** was carried out immediately in neat thionyl chloride to afford **57** (Scheme 8). The use of polyphosphoric acid for the rearrangement of **71** was also investigated and gave the aryl-migration lactam **70** (Scheme 9). In agreement with the literature, **71** acted in a similar fashion to 1-tetralone oxime **10**.[18] Despite the two reaction steps, the overall yield for the synthesis of **57** using the Beckmann rearrangement (50%) is slightly greater than that of the Schmidt reaction (44%).

Conclusion

We have reported the Schmidt reaction of several unsubstituted and oxygenated bicyclic ketones (**5**–**9**) and Beckmann rearrangement of the corresponding ketoximes (**10**–**14**), each reaction type being carried out using two different experimental conditions. The alkyl to aryl migration ratios were determined by HPLC. The reported mechanisms of these reactions were examined and some limitations of these mechanisms discussed. The *syn* geometry of two ketoximes (**13** and **14**) was determined by X-ray crystallography as part of this investigation; stereochemical assignments had previously been ambiguously either *syn* or *anti*. We proposed modified mechanisms in light of the results from the various reactions reported. In general, it was found that the Schmidt reaction method, for the synthesis of the resulting bicyclic lactams, was more convenient than the Beckmann rearrangement approach. We applied the knowledge so gained to the synthesis of some chloro bicyclic lactams, of the types **3** and **4**. We aim to incorporate these chloro bicyclic lactams (**56**–**59**) into some bicyclic analogues of clozapine, with the aim of producing more stable and accessible bicyclic analogues than previously reported.[6]

Experimental

Refer to the Accessory Publication file for general experimental details, and the synthesis of the ketones and their precursors. The following ketoximes were prepared from commercially available 1-tetralones and 4-chromanones, and ketones synthesized in the previous section. The general method is exemplified for the synthesis of 1-tetralone oxime **10**.

1-Tetralone Oxime ***10***

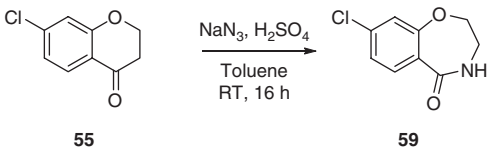
Hydroxylamine hydrochloride (9.50 g, 137 mmol) was added in one portion to a magnetically stirred solution of 1-tetralone **5** (10.0 g, 68.4 mmol) and sodium acetate (11.0 g, 134 mmol) in absolute ethanol (100 mL). Stirring was continued for 2 h while heating at reflux, after which the resulting solution was cooled, triturated with water (200 mL), filtered, and dried under vacuum. Recrystallization (dichloromethane/hexane) of this material afforded 1-tetralone oxime **10** (8.60 g, 79%) as white plate-like crystals, mp 100–101°C (lit.[85] 101–103°C). δ_H ($(CD_3)_2CO$) 10.08 (1H, s, NOH), 7.89 (1H, m, H8), 7.25–7.12 (3H, m, ArH), 2.78–2.72 (4H, m, H2, H4), 1.82 (2H, app p, *J* 6.5, H3). δ_C ($(CD_3)_2CO$) 153.1 (C_q), 139.2 (C_q), 131.4 (C_q), 128.5 (CH), 128.4 (CH), 126.0 (CH), 123.8 (CH), 29.5 (CH_2), 23.3 (CH_2), 21.4 (CH_2). *m/z* (ESI, 70 V) 162.0 (11%, $(M+H)^+$), 157 (16), 144 (27), 128 (25), 117 (67), 116 (100), 115 (70), 89 (71).

4-Chromanone Oxime ***11***

4-Chromanone **6** (741 mg, 5.00 mmol) and sodium acetate (820 mg, 10.0 mmol) in absolute ethanol (50 mL) were treated with hydroxylamine hydrochloride (417 mg, 6.00 mmol) and worked up as for the preparation of **10**. Recrystallization (dichloromethane/hexane) of this material afforded 4-chromanone oxime **11** (536 mg, 66%) as colourless prisms, mp 138–140°C (lit.[26] 139–141°C). δ_H ($(CD_3)_2CO$) 10.23 (1H, s, NOH), 7.85 (1H, dd, *J* 8, 2, H8), 7.23, 6.93–6.85 (1H, 2H, m, m, H5, H6, H7), 4.21 (2H, t, *J* 6, H2), 2.93 (2H, t, *J* 6, H3). δ_C ($(CD_3)_2CO$) 156.5 (C_q), 148.0 (C_q), 130.3 (CH), 123.8 (C_q), 121.0 (CH), 119.3 (CH), 117.5 (CH), 64.9 (CH_2), 23.2 (CH_2). *m/z* (ESI, 20 V) 164 (100%, $(M+H)^+$).

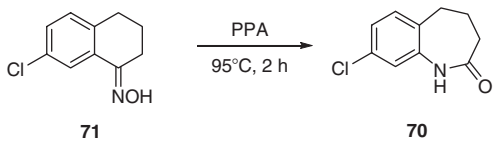
5-Methoxy-1-tetralone Oxime ***12***

5-Methoxy-1-tetralone **7** (881 mg, 5.00 mmol) and sodium acetate (820 mg, 10.0 mmol) in absolute ethanol (50 mL) were treated with hydroxylamine hydrochloride (417 mg, 6.00 mmol) and worked up as for the preparation of **10**. Recrystallization (ethyl acetate) of this material afforded 5-methoxy-1-tetralone oxime **12** (709 mg, 74%) as colourless prisms, mp 152–153°C (lit.[27] 153–155°C). δ_H ($(CD_3)_2CO$) 10.06 (1H, s, NOH), 7.54 (1H, d, *J* 8, H8), 7.11 (1H, app t, *J* 8, H7), 6.88 (1H, d, *J* 8, H6), 3.83 (3H, s, OCH_3), 2.75–2.67 (4H, m, H2, H4), 1.79 (2H, app p, *J* 6.5, H3). δ_C ($(CD_3)_2CO$) 156.8 (C_q), 153.3 (C_q), 132.4 (C_q), 127.9 (C_q), 126.1 (CH), 116.0 (CH), 109.8 (CH), 54.9 (CH_3), 22.7 (CH_2), 22.1 (CH_2), 20.8 (CH_2). *m/z* (ESI, 70 V) 192 (100%, $(M+H)^+$), 174 (16), 147 (25), 146 (41), 132 (30), 116 (44), 100 (77), 77 (37).



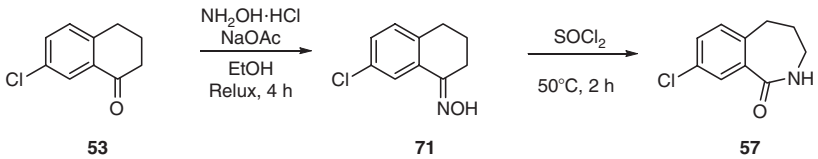
55 **59**

Scheme 7.



71 **70**

Scheme 9.



53 **71** **57**

Scheme 8.

*6-Methoxy-1-tetralone Oxime **13***

6-Methoxy-1-tetralone **8** (881 mg, 5.00 mmol) and sodium acetate (820 mg, 10.0 mmol) in absolute ethanol (50 mL) were treated with hydroxylamine hydrochloride (417 mg, 6.00 mmol) and worked up as for the preparation of **10**. Recrystallization (dichloromethane/hexane) of this material afforded 6-methoxy-1-tetralone oxime **13** (774 mg, 81%) as colourless rod-like crystals, mp 124–125°C (lit.[28] 122–124°C). δ_H ($(CD_3)_2CO$) 9.83 (1H, s, NOH), 7.84 (1H, d, *J* 8.5, H8), 6.74 (1H, dd, *J* 8.5, 2.5, H7), 6.70 (1H, d, *J* 2.5, H5), 3.78 (3H, s, OCH_3), 2.74–2.70 (4H, m, H2, H4), 1.80 (2H, app p, *J* 6.5, H3). δ_C ($(CD_3)_2CO$) 160.1 (C_q), 152.9 (C_q), 140.9 (C_q), 125.3 (CH), 124.1 (C_q), 112.8 (CH), 112.6 (CH), 54.6 (CH_3), 29.8 (CH_2), 23.2 (CH_2), 21.5 (CH_2). *m/z* (ESI, 70 V) 192 (78%, $(M+H)^+$), 175 (22), 147 (100), 132 (22), 117 (19), 91 (16).

*7-Methoxy-1-tetralone Oxime **14***

7-Methoxy-1-tetralone **9** (881 mg, 5.00 mmol) and sodium acetate (820 mg, 10.0 mmol) in absolute ethanol (50 mL) were treated with hydroxylamine hydrochloride (417 mg, 6.00 mmol) and worked up as for the preparation of **10**. Recrystallization (dichloromethane/hexane) of this material afforded 7-methoxy-1-tetralone oxime **14** (798 mg, 83%) as colourless prisms, mp 84–85°C (lit.[29] 86–88°C). δ_H ($(CD_3)_2CO$) 10.08 (1H, s, NOH), 7.46 (1H, d, *J* 3, H8), 7.06 (1H, d, *J* 8.5, H5), 6.82 (1H, dd, *J* 8.5, 3, H6), 3.75 (3H, s, OCH_3), 2.73 (2H, t, *J* 6.5, H2), 2.67 (2H, t, *J* 6, H4), 1.79 (2H, app p, *J* 6.5, H3). δ_C ($(CD_3)_2CO$) 158.1 (C_q), 153.2 (C_q), 132.2 (C_q), 131.6 (C_q), 129.5 (CH), 115.6 (CH), 107.5 (CH), 54.6 (CH_3), 28.7 (CH_2), 23.2 (CH_2), 21.6 (CH_2). *m/z* (ESI, 70 V) 192 (100%, $(M+H)^+$), 174 (60), 147 (65), 100 (48), 91 (36), 77 (32).

*7-Chloro-1-tetralone Oxime **71***

7-Chloro-1-tetralone **53** (903 mg, 5.00 mmol) and sodium acetate (820 mg, 10.0 mmol) in absolute ethanol (50 mL) were treated with hydroxylamine hydrochloride (417 mg, 6.00 mmol) and worked up as for the preparation of **10**. Recrystallization (ether/petroleum spirit) of this material afforded 7-chloro-1-tetralone oxime **71** (848 mg, 87%) as slightly yellow crystals (light-sensitive), mp 114–115°C (lit.[84] 124–125°C) (Found: C 61.4, H 5.2, N 7.2. $C_{10}H_{10}ClNO$ requires C 61.4, H 5.2, N 7.2%.) δ_H ($CDCl_3$) 8.37 (1H, br s, NOH), 7.88 (1H, d, *J* 2, H8), 7.22 (1H, dd, *J* 8, 2, H6), 7.08 (1H, d, *J* 8, H5), 2.81 (2H, t, *J* 6.5, H2), 2.73 (2H, t, *J* 6, H4), 1.86 (2H, app p, *J* 6.5, H3). δ_C ($CDCl_3$) 154.7 (C_q), 138.1 (C_q), 132.3 (C_q), 132.0 (C_q), 130.0 (CH), 129.2 (CH), 124.1 (CH), 29.3 (CH_2), 23.6 (CH_2), 21.1 (CH_2). *m/z* (ESI, 70 V) 198 (17%, $(M[^{37}Cl]+H)^+$), 196 (52, $(M[^{35}Cl]+H)^+$), 178 (36), 152 (38), 151 (51), 150 (100), 143 (52), 116 (25).

*Schmidt Reaction of 1-Tetralone **5** (Method 1)*

*2,3,4,5-Tetrahydro-1*H*-2-benzazepin-1-one **15** and 6,7-Dihydro-5*H*-tetrazolo[5,1-a][2]benzazepine **25***

Sodium azide (13.0 g, 200 mol) was added in portions to a magnetically stirred solution of 1-tetralone **5** (14.6 g, 100 mol) in concentrated hydrochloric acid (150 mL) maintained at ~0°C (ice-bath). The reaction mixture was warmed up to room temperature and stirring was continued overnight at 50°C. The mixture was then poured into ice-water, cautiously neutralized with potassium carbonate, extracted with dichloromethane (3 × 100 mL), and the combined extracts were concentrated under vacuum to afford a yellow oil. This material was subjected to flash chromatography (ethyl acetate), and recrystallization (ethyl acetate/hexane) of the major fraction (R_F 0.3) afforded 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one **15** (8.40 g, 52%) as slightly yellow prisms, mp 99–100°C (lit.[15] 101°C). δ_H ($CDCl_3$) 7.96 (1H, br s, NH), 7.67 (1H, dd, *J* 7.5, 1.5, H9), 7.35 (1H, app td, *J* 7.5, 1.5, H7), 7.29 (1H, app td, *J* 7.5, 1.5, H8), 7.14 (1H, dd, *J* 7.5, 1.5, H6), 3.12 (2H, app q, *J* 6.5, H3), 2.87 (2H, t, *J* 7, H5), 2.04 (2H, app p, *J* 6.5, H4). δ_C ($CDCl_3$) 174.1 (CO), 138.3 (C_q), 134.9 (C_q), 131.2 (CH), 128.5 (CH), 126.9 (CH), 39.5 (CH_2), 30.5 (CH_2), 30.2 (CH_2). *m/z* (ESI, 70 V) 162 (7%, $(M+H)^+$), 144 (7), 117 (45), 115 (16), 91 (100).

Concentration of the more mobile fraction (R_F 0.7) from the above reaction and recrystallization (ethyl acetate) afforded 6,7-dihydro-5*H*-tetrazolo[5,1-*a*][2]benzazepine **25** (1.49 g, 8%) as pale yellow prisms, mp 98–99°C (lit.[86] 100–101°C). δ_H ($CDCl_3$) 8.25 (1H, d, *J* 8, H11), 7.48–7.38 (2H, m, H9, H10), 7.31 (1H, d, *J* 8, H8), 4.61 (2H, t, *J* 6.5, H5), 2.99 (2H, br t, *J* 6, H7), 2.42 (2H, br app t, *J* 6.5, H6). δ_C ($CDCl_3$) 154.4 (C_q), 139.7 (C_q), 131.6 (CH), 130.2 (CH), 130.1 (CH), 127.5 (CH), 123.3 (C_q), 48.6 (CH_2), 32.7 (CH_2), 26.8 (CH_2). *m/z* (ESI, 20 V) 187 (100%, $(M+H)^+$).

*Schmidt Reaction of 1-Tetralone **5** (Method 2)*

*1,3,4,5-Tetrahydro-2*H*-1-benzazepin-2-one **20***

Sodium azide (650 mg, 10.0 mmol) was added in one portion to a magnetically stirred solution of 1-tetralone **5** (731 mg, 5.00 mmol) in toluene (30 mL) maintained at ~0°C (ice-bath). To this mixture was added concentrated sulfuric acid (2.5 mL) dropwise over 30 min. It was then warmed up to room temperature and stirring was continued overnight. The reaction was quenched with water (20 mL), extracted with toluene (3 × 20 mL), and concentrated under vacuum. This material was subjected to flash chromatography (60% ethyl acetate in hexane) and recrystallization (dichloromethane/hexane) afforded 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one **20** (604 mg, 75%) as colourless prisms, mp 139–140°C (lit.[17] 139–140°C). δ_H ($CDCl_3$) 8.71 (1H, br s, NH), 7.25–7.20 (2H, m, H8, H9), 7.12 (1H, app t, *J* 7.5, H7), 7.02 (1H, d, *J* 7.5, H6), 2.80 (2H, t, *J* 7, H5), 2.36 (2H, t, *J* 7, H3), 2.24 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 175.8 (CO), 138.2 (C_q), 134.3 (C_q), 129.9 (CH), 127.5 (CH), 125.6 (CH), 121.9 (CH), 32.9 (CH_2), 30.5 (CH_2), 28.7 (CH_2). *m/z* (ESI, 70 V) 162 (100%, $(M+H)^+$), 85 (23), 79 (75).

*Beckmann Rearrangement of 1-Tetralone Oxime **10** (Method 3)*

*1,3,4,5-Tetrahydro-2*H*-1-benzazepin-2-one **20***

1-Tetralone oxime **10** (161 mg, 1.00 mmol) in polyphosphoric acid (10 mL) was stirred for 2 h at 95°C and then poured into water (500 mL) and further stirred for 2 h at 75°C. The reaction mixture was then cooled, the resulting precipitate filtered, and dried under vacuum. Recrystallization (dichloromethane/hexane) of the crude material afforded 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one **20** (96 mg, 60%), identical to that prepared by Method 2.

*Beckmann Rearrangement of 1-Tetralone Oxime **10** (Method 4)*

*2,3,4,5-Tetrahydro-1*H*-2-benzazepin-1-one **15***

1-Tetralone oxime **10** (161 mg, 1.00 mmol) in thionyl chloride (5 mL) was stirred for 2 h at 50°C after which excess

thionyl chloride was removed under vacuum and the residue was partitioned between dichloromethane (20 mL) and saturated sodium bicarbonate solution (20 mL). The phases were separated, the aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined extracts were concentrated under vacuum to give a brown oil. This material was subjected to flash chromatography (ethyl acetate), and recrystallization (ethyl acetate/hexane) afforded 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one **15** (78 mg, 48%), identical to that prepared by Method 1.

*Schmidt Reaction of 4-Chromanone **6** (Method 1)*

*3,4-Dihydro-1,4-benzoxazepin-5(2*H*)-one **16***

4-Chromanone (148 mg, 1.00 mmol) in concentrated hydrochloric acid (7 mL) was treated with sodium azide (130 mg, 2.5 mmol) and worked up as for the preparation of **20** (Method 1). Recrystallization (ethyl acetate/hexane) of this material afforded 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **16** (30 mg, 18%) as colourless micro-needles, mp 115–116°C (lit.[40] 114–116°C). δ_H ($CDCl_3$) 7.99 (1H, dd, *J* 8, 1.5, H6), 7.43 (1H, ddd, *J* 8, 7, 1.5, H7), 7.13 (1H, m, H8), 7.02 (1H, dd, *J* 8, 1.5, H9), 6.76 (1H, br s, NH), 4.40 (2H, t, *J* 5, H2), 3.51 (2H, app q, *J* 5, H3). δ_C ($CDCl_3$) 170.6 (CO), 155.5 (C_q), 133.4 (CH), 131.8 (CH), 123.4 (C_q), 122.7 (CH), 121.2 (CH), 72.9 (CH_2), 41.5 (CH_2). *m/z* (ESI, 70 V) 186 (10%, $(M + Na)^+$), 164 (7, $(M + H)^+$), 121 (100), 93 (47), 91 (56), 77 (85), 65 (52).

*Schmidt Reaction of 4-Chromanone **6** (Method 2)*

*3,4-Dihydro-1,4-benzoxazepin-5(2*H*)-one **16** and 2,3-Dihydro-1,5-benzoxazepin-4(5*H*)-one **21***

A mixture of 4-chromanone **6** (5.00 g, 33.7 mmol) and sodium azide (5.60 g, 86.1 mmol) in toluene (150 mL) was treated with concentrated sulfuric acid (14 mL) and worked up as for the preparation of **20** (Method 2). Recrystallization (ethyl acetate/hexane) of the major fraction (R_F 0.3) afforded 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **16** (4.56 g, 83%) as colourless micro-needles, identical to that prepared using Method 1.

Concentration of the more mobile fraction (R_F 0.45) from the above reaction and recrystallization (ethyl acetate/hexane) afforded 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one **21** (110 mg, 2%) as pale yellow needles, mp 128–129°C (lit.[40] 126–127°C). δ_H ($CDCl_3$) 8.55 (1H, br s, NH), 7.05–6.98 (4H, m, ArH), 4.46 (2H, t, *J* 5.5, H2), 2.87 (2H, t, *J* 5.5, H3). δ_C ($CDCl_3$) 173.1 (CO), 148.7 (C_q), 129.0 (C_q), 125.4 (CH), 123.8 (CH), 122.2 (CH), 121.8 (CH), 68.8 (CH_2), 37.1 (CH_2). *m/z* (EI, 70 eV) 163 (85%, $M^{+\bullet}$), 120 (13), 109 (100), 80 (18), 55 (37).

*Beckmann Rearrangement of 4-Chromanone Oxime **11** (Method 3)*

*3,4-Dihydro-1,4-benzoxazepin-5(2*H*)-one **16***

4-Chromanone oxime **11** (163 mg, 1.00 mmol) was treated with polyphosphoric acid (10 mL) and worked up as for the preparation of **20** (Method 3). Recrystallization (ethyl acetate/hexane) of the crude material afforded 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **16** (91 mg, 56%), identical to that prepared using Method 1.

*Beckmann Rearrangement of 4-Chromanone Oxime **11** (Method 4)*

*3,4-Dihydro-1,4-benzoxazepin-5(2*H*)-one **16***

4-Chromanone oxime **11** (163 mg, 1.00 mmol) was treated with thionyl chloride (5 mL) and worked up as for the preparation of **15** (Method 4). Recrystallization (ethyl acetate/hexane) of this material afforded 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **16** (60 mg, 37%), identical to that prepared using Method 1.

*Schmidt Reaction of 5-Methoxy-1-tetralone **7** (Method 1)*

*2,3,4,5-Tetrahydro-6-methoxy-1*H*-2-benzazepin-1-one **17***

5-Methoxy-1-tetralone **7** (881 mg, 5.00 mmol) in concentrated hydrochloric acid (10 mL) was treated with sodium azide (650 mg, 10.0 mmol) and worked up as for the preparation of **15** (Method 1). Recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-6-methoxy-1*H*-2-benzazepin-1-one **17** (678 mg, 71%) as slightly yellow crystals, mp 104–106°C (Found: C 69.1, H 6.8, N 7.4. $C_{11}H_{13}NO_2$ requires C 69.1, H 6.9, N 7.3%.) δ_H ($CDCl_3$) 7.31–7.24 (2H, m, H8, H9), 6.98 (1H, dd, *J* 6.5, 2, H7), 6.51 (1H, br s, NH), 3.84 (3H, s, OCH_3), 3.10 (2H, app q, *J* 6.5, H3), 2.95 (2H, t, *J* 7, H5), 1.95 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 173.6 (CO), 156.2 (C_q), 136.7 (C_q), 127.5 (CH), 126.7 (C_q), 120.7 (CH), 113.2 (CH), 55.9 (CH_3), 39.8 (CH_2), 29.8 (CH_2), 21.0 (CH_2). *m/z* (ESI, 70 V) 214 (19%, $(M + Na)^+$), 192 (58, $(M + H)^+$), 121 (40), 91 (100).

*Schmidt Reaction of 5-Methoxy-1-tetralone **7** (Method 2)*

*2,3,4,5-Tetrahydro-6-methoxy-1*H*-2-benzazepin-1-one **17***

A mixture of 5-methoxy-1-tetralone **7** (881 mg, 5.00 mmol) and sodium azide (813 mg, 12.5 mmol) in toluene (30 mL) was treated with concentrated sulfuric acid (2.5 mL) and worked up as for the preparation of **20** (Method 2). Recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-6-methoxy-1*H*-2-benzazepin-1-one **17** (200 mg, 21%), identical to that prepared using Method 1.

*Beckmann Rearrangement of 5-Methoxy-1-tetralone Oxime **12** (Method 3)*

*1,3,4,5-Tetrahydro-6-methoxy-2*H*-1-benzazepin-2-one **22***

5-Methoxy-1-tetralone oxime **12** (176 mg, 1.00 mmol) was treated with polyphosphoric acid (10 mL) and worked up as for the preparation of **20** (Method 3). Recrystallization (dichloromethane/hexane) of this material afforded 1,3,4,5-tetrahydro-6-methoxy-2*H*-1-benzazepin-2-one **22** (90 mg, 47%) as colourless plates, mp 164–165°C (lit.[19] 162–163°C). δ_H ($CDCl_3$) 7.74 (1H, br s, NH), 7.16 (1H, app t, *J* 8, H8), 6.72 (1H, d, *J* 8, H9), 6.61 (1H, d, *J* 8, H7), 3.83 (3H, s, OCH_3), 2.88 (2H, t, *J* 7, H5), 2.35 (2H, t, *J* 7, H3), 2.18 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 175.3 (CO), 157.7 (C_q), 139.2 (C_q), 127.3 (CH), 122.8 (C_q), 114.3 (CH), 107.8 (CH), 55.8 (CH_3), 33.2 (CH_2), 27.8 (CH_2), 21.9 (CH_2). *m/z* (ESI, 70 V) 192 (48%, $(M + H)^+$), 143 (29), 79 (100).

*Beckmann Rearrangement of 5-Methoxy-1-tetralone Oxime **12** (Method 4)*

*2,3,4,5-Tetrahydro-6-methoxy-1*H*-2-benzazepin-1-one **17***

12 (176 mg, 1.00 mmol) was treated with thionyl chloride (5 mL) and worked up as for the preparation of **15** (Method 4). Recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-6-methoxy-1*H*-2-benzazepin-1-one **17** (63 mg, 36%), identical to that prepared using Method 1.

*Schmidt Reaction of 6-Methoxy-1-tetralone **8** (Method 1)*

*2,3,4,5-Tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18** and 1,3,4,5-Tetrahydro-7-methoxy-2*H*-1-benzazepin-2-one **23***

6-Methoxy-1-tetralone **8** (176 mg, 1.00 mmol) in concentrated hydrochloric acid (3 mL) was treated with sodium azide (130 mg, 2.00 mmol) and worked up as for the preparation of **15** (Method 1). Flash chromatography (5% acetone in chloroform) and recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18** (100 mg, 53%) as slightly yellow crystals, mp 156–158°C (lit.[87] 159–160°C). δ_H ($CDCl_3$) 7.68 (1H, d, *J* 8.5, H9), 6.89 (1H, br s, NH), 6.84 (1H, dd, *J* 8.5, 2.5, H8), 6.71 (1H, d, *J* 2.5, H6), 3.84 (3H, s, OCH_3), 3.14 (2H, app q, *J* 6.5, H3), 2.84 (2H, t, *J* 7, H5), 2.01 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 174.1 (CO), 161.9 (C_q), 140.7 (C_q), 130.9 (CH), 127.5 (C_q), 114.3 (CH), 111.9 (CH), 55.3 (CH_3), 39.8 (CH_2), 30.8 (CH_2), 30.5 (CH_2). *m/z* (ESI, 20 V) 405 (22%, $(2M + Na)^+$), 232 (29, $(M + K)^+$), 214 (27, $(M + Na)^+$), 192 (100, $(M + H)^+$).

Concentration of the more mobile fraction (R_F 0.4) from the above reaction and recrystallization (dichloromethane/hexane) afforded 1,3,4,5-tetrahydro-7-methoxy-2*H*-1-benzazepin-2-one **23** (29 mg, 15%) as slightly brown plate-like crystals, mp 145–146°C (lit.[87] 143–144°C). δ_H ($CDCl_3$) 8.19 (1H, br s, NH), 6.94 (1H, d, *J* 7, H9), 6.76–6.73 (2H, m, H6, H8), 3.80 (3H, s, OCH_3), 2.77 (2H, t, *J* 7, H5), 2.33 (2H, t, *J* 7, H3), 2.21 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 175.4 (CO), 157.4 (C_q), 135.9 (C_q), 131.0 (C_q), 123.1 (CH), 115.2 (CH), 112.3 (CH), 55.5 (CH_3), 32.6 (CH_2), 30.6 (CH_2), 28.3 (CH_2). *m/z* (ESI, 20 V) 405 (10%, $(2M + Na)^+$), 214 (22, $(M + Na)^+$), 192 (100, $(M + H)^+$).

*Schmidt Reaction of 6-Methoxy-1-tetralone **8** (Method 2)*

*2,3,4,5-Tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18** and 1,3,4,5-Tetrahydro-7-methoxy-2*H*-1-benzazepin-2-one **23***

8 (881 mg, 5.00 mmol) and sodium azide (813 mg, 12.5 mmol) in toluene (30 mL) were treated with concentrated sulfuric acid (2.5 mL) and worked up as for the preparation of **20** (Method 2). Flash chromatography (5% acetone in chloroform) and recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18** (360 mg, 38%), identical to that prepared using Method 1.

Concentration of the more mobile fraction (R_F 0.4) from the above reaction and recrystallization (dichloromethane/hexane) afforded 1,3,4,5-tetrahydro-7-methoxy-2*H*-1-benzazepin-2-one **23** (200 mg, 21%), identical to that prepared using Method 1.

*Beckmann Rearrangement of 6-Methoxy-1-tetralone Oxime **13** (Method 3)*

*2,3,4,5-Tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18***

13 (176 mg, 1.00 mmol) was treated with polyphosphoric acid (10 mL) and worked up as for the preparation of **20** (Method 3). Recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18** (125 mg, 71%), identical to that prepared using Method 1.

*Beckmann Rearrangement of 6-Methoxy-1-tetralone Oxime **13** (Method 4)*

*2,3,4,5-Tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18***

13 (176 mg, 1.00 mmol) was treated with thionyl chloride (5 mL) and worked up as for the preparation of **15** (Method 4). Recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one **18** (55 mg, 31%), identical to that prepared using Method 1.

*Schmidt Reaction of 7-Methoxy-1-tetralone **9** (Method 1)*

*2,3,4,5-Tetrahydro-8-methoxy-1*H*-2-benzazepin-1-one **19***

7-Methoxy-1-tetralone **9** (881 mg, 5.00 mmol) in concentrated hydrochloric acid (10 mL) was treated with sodium azide (650 mg, 10.0 mmol) and worked up as for the preparation of **15** (Method 1). Recrystallization (diethyl ether) of this material afforded 2,3,4,5-tetrahydro-8-methoxy-1*H*-2-benzazepin-1-one **19** (520 mg, 54%) as pale orange prisms, mp 102–104°C (lit.[18] 100–101°C). δ_H ($CDCl_3$) 7.25 (1H, d, *J* 2.5, H9), 7.10 (1H, d, *J* 8.5, H6), 6.95 (1H, dd, *J* 8.5, 2.5, H7), 6.62 (1H, br s, NH), 3.83 (3H, s, OCH_3), 3.13 (2H, app q, *J* 6, H3), 2.80 (2H, t, *J* 7, H5), 1.99 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 173.7 (CO), 158.7 (C_q), 130.7 (C_q), 130.0 (CH), 124.3 (C_q), 118.0 (CH), 113.0 (CH), 55.5 (CH_3), 39.8 (CH_2), 30.6 (CH_2), 29.4 (CH_2). *m/z* (ESI, 20 V) 405 (40%, $(2M + Na)^+$), 214 (28, $(M + Na)^+$), 192 (100, $(M + H)^+$), 83 (12).

*Schmidt Reaction of 7-Methoxy-1-tetralone **9** (Method 2)*

*1,3,4,5-Tetrahydro-8-methoxy-2*H*-1-benzazepin-2-one **24***

A mixture of 7-methoxy-1-tetralone **9** (881 mg, 5.00 mmol) and sodium azide (813 mg, 12.5 mmol) in toluene (30 mL) was treated with concentrated sulfuric acid (2.5 mL) and worked up as for the preparation of **20** (Method 2). Recrystallization (dichloromethane/hexane) of this material afforded 1,3,4,5-tetrahydro-8-methoxy-2*H*-1-benzazepin-2-one **24** (250 mg, 38%) as buff-coloured platelets, mp 132–133°C (lit.[44] 131–132°C). δ_H ($CDCl_3$) 8.16 (1H, br s, NH), 7.10 (1H, d, *J* 8.5, H6), 6.68 (1H, dd, *J* 8.5, 2.5, H7), 6.56 (1H, d, *J* 2.5, H9), 3.79 (3H, s, OCH_3), 2.73 (2H, t, *J* 7, H3), 2.36 (2H, t, *J* 7.5, H5), 2.19 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 175.5 (CO), 159.1 (C_q), 138.8 (C_q), 130.5 (CH), 126.4 (C_q), 111.0 (CH), 107.8 (CH), 55.5 (CH_3), 32.9 (CH_2), 29.5 (CH_2), 28.7 (CH_2). *m/z* (ESI, 20 V) 405 (17%, $(2M + Na)^+$), 383 (6, $(2M + H)^+$), 214 (36, $(M + Na)^+$), 192 (100, $(M + H)^+$), 83 (33).

*Beckmann Rearrangement of 7-Methoxy-1-tetralone Oxime **14** (Method 3)*

*1,3,4,5-Tetrahydro-8-methoxy-2*H*-1-benzazepin-2-one **24***

14 (176 mg, 1.00 mmol) was treated with polyphosphoric acid (10 mL) and worked up as for the preparation of **20** (Method 3). Recrystallization (dichloromethane/hexane) of this material afforded 1,3,4,5-tetrahydro-8-methoxy-2*H*-1-benzazepin-2-one **24** (83 mg, 47%), identical to that prepared using Method 2.

*Beckmann Rearrangement of 7-Methoxy-1-tetralone Oxime **14** (Method 4)*

*2,3,4,5-Tetrahydro-8-methoxy-1H-2-benzazepin-1-one **19***

14 (176 mg, 1.00 mmol) was treated with thionyl chloride (5 mL) and worked up as for the preparation of **15** (Method 4). Recrystallization (dichloromethane/hexane) of this material afforded 2,3,4,5-tetrahydro-8-methoxy-1*H*-2-benzazepin-1-one **19** (37 mg, 21%), identical to that prepared using Method 1.

*Schmidt Reaction of 6-Chloro-1-tetralone **52** (Method 1)*

*7-Chloro-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one **56***

6-Chloro-1-tetralone **52** (243 mg, 1.35 mmol) in concentrated hydrochloric acid (5 mL) was treated with sodium azide (195 mg, 3.00 mmol) and worked up as for the preparation of **15** (Method 1). Recrystallization (ethyl acetate/hexane) of this material afforded 7-chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one **56** (153 mg, 58%) as white plate-like crystals, mp 181–182°C (lit.[18] 183–184°C). δ_H ($CDCl_3$) 7.65 (1H, d, *J* 8.5, H9), 7.33 (1H, dd, *J* 8.5, 2, H8), 7.21 (1H, d, *J* 2, H6), 7.12 (1H, br s, NH), 3.14 (2H, app q, *J* 6.5, H3), 2.85 (2H, t, *J* 7, H5), 2.03 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 173.2 (CO), 140.3 (C_q), 137.1 (C_q), 133.5 (C_q), 130.4 (CH), 128.8 (CH), 127.2 (CH), 39.5 (CH_2), 30.3 (CH_2), 30.2 (CH_2). *m/z* (EI, 70 eV) 197 (27%, $M[^{37}Cl]^{+\bullet}$), 195 (100%, $M[^{35}Cl]^{+\bullet}$), 166 (75), 138 (43), 102 (28), 77 (24).

*Schmidt Reaction of 6-Chloro-4-chromanone **54** (Method 2)*

*8-Chloro-3,4-dihydro-1,4-benzoxazepin-5(2H)-one **58** and 7-Chloro-2,3-dihydro-1,5-benzoxazepin-4(5H)-one **69***

A mixture of 6-chloro-4-chromanone **54** (4.00 g, 22.0 mmol) and sodium azide (3.57 mg, 55.0 mmol) in toluene (100 mL) was treated with concentrated sulfuric acid (12 mL) and worked up as for the preparation of **20** (Method 2). Recrystallization (dichloromethane/hexane) of this material afforded 8-chloro-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **58** (3.16 g, 74%) as white needle-like crystals, mp 122–124°C (lit.[16] 109°C) (Found: C 54.8, H 4.1, N 7.1. $C_9H_8ClNO_2$ requires C 54.7, H 4.1, N 7.1%.) δ_H ($CDCl_3$) 8.17 (1H, br s, NH), 7.95 (1H, d, *J* 2.5, H6), 7.36 (1H, dd, *J* 8.5, 2.5, H8), 6.96 (1H, d, *J* 8.5, H9), 4.39 (2H, t, *J* 5, H2), 3.52 (2H, app q, *J* 5, H3). δ_C ($CDCl_3$) 169.5 (CO), 154.2 (C_q), 133.3 (CH), 131.4 (CH), 128.0 (C_q), 124.6 (C_q), 122.9 (CH), 73.1 (CH_2), 41.5 (CH_2). *m/z* (ESI, 70 V) 222 (21%, $(M[^{37}Cl] + Na)^+$), 220 (62%, $(M[^{35}Cl] + Na)^+$), 200 (33, $(M[^{37}Cl] + H)^+$), 198 (100, $(M[^{35}Cl] + H)^+$), 180 (15), 157 (23), 155 (83), 153 (34), 127 (30), 91 (45), 70 (77).

Concentration of the more mobile fraction (R_F 0.5) from the reaction of **54** and recrystallization (dichloromethane/hexane) afforded 8-chloro-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one **69** (217 mg, 5%) as pale yellow micro-needles, mp 129–130°C (Found: C 54.7, H 4.1, N 7.1. $C_9H_8ClNO_2$ requires C 54.7, H 4.1, N 7.1%.) δ_H ($CDCl_3$) 8.76 (1H, br s, NH), 7.03–6.95 (3H, m, ArH), 4.45 (2H, t, *J* 5.5, H2), 2.88 (2H, t, *J* 5.5, H3). δ_C ($CDCl_3$) 173.1 (CO), 147.4 (C_q), 130.0 (C_q), 128.6 (C_q), 125.3 (CH), 123.3 (CH), 121.5 (CH), 68.9 (CH_2), 37.1 (CH_2). *m/z* (ESI, 70 V) 198 (22%, $(M[^{35}Cl] + H)^+$), 142 (31), 85 (21), 79 (100).

*Schmidt Reaction of 7-Chloro-1-tetralone **53** (Method 1)*

*8-Chloro-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one **57** and 2,2,7-Trichloro-1-tetralone **68***

7-Chloro-1-tetralone **53** (1.00 g, 5.54 mmol) in concentrated hydrochloric acid (50 mL) was treated with sodium azide (1.30 g, 20.0 mmol) and worked up as for the preparation of **15** (Method 1). Recrystallization (acetone) of this material afforded 8-chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one **57** (472 mg, 44%) as white micro-needles, mp 159–161°C (lit.[18] 160–161°C). δ_H ($CDCl_3$) 7.82 (1H, br s, NH), 7.69 (1H, d, *J* 2, H9), 7.36 (1H, dd, *J* 8, 2, H7), 7.14 (1H, d, *J* 8, H6), 3.13 (2H, app q, *J* 6.5, H3), 2.84 (2H, t, *J* 7, H5), 2.02 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 173.0 (CO), 136.8 (C_q), 136.7 (C_q), 132.9 (C_q), 131.1 (CH), 130.2 (CH), 128.7 (CH), 39.4 (CH_2), 30.3 (CH_2), 29.8 (CH_2). *m/z* (ESI, 70 V) 198 (18, $(M[^{37}Cl] + H)^+$), 196 (55, $(M[^{35}Cl] + H)^+$), 178 (33), 153 (60), 151 (86), 125 (100), 116 (21).

Concentration of the more mobile fraction (R_F 0.8) from the above reaction and recrystallization (chloroform/hexane) afforded 2,2,7-trichloro-1-tetralone **68** (200 mg, 53%) as slightly brown crystals, mp 162–163°C (Found: C 48.1, H 2.9, Cl 42.6. $C_{10}H_7Cl_3O$ requires C 48.1, H 2.8, Cl 42.6%.) δ_H ($CDCl_3$) 8.12 (1H, d, *J* 2.5, H8), 7.52 (1H, dd, *J* 8, 2.5, H6), 7.23 (1H, d, *J* 8, H5), 3.18 (2H, t, *J* 6, H4), 2.95 (2H, t, *J* 6, H3). δ_C ($CDCl_3$) 183.0 (C_q), 140.4 (C_q), 134.6 (CH), 133.9 (C_q), 130.3 (CH), 129.8 (C_q), 129.4 (CH), 85.7 (C_q), 43.0 (CH_2), 27.0 (CH_2). *m/z* (EI, 70 eV) 254 (1%, $M[^{37}Cl]_3^{+\bullet}$), 252 (7, $M[^{35}Cl][^{37}Cl]_2^{+\bullet}$), 250 (24, $M[^{35}Cl]_2[^{37}Cl]^{+\bullet}$), 248 (26, $M[^{35}Cl]_3^{+\bullet}$), 213 (20), 152 (100), 124 (36), 89 (19).

*Schmidt Reaction of 7-Chloro-1-tetralone **53** (Method 2)*

*8-Chloro-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one **59***

A mixture of 7-chloro-1-tetralone **53** (500 mg, 2.77 mmol) and sodium azide (450 mg, 6.92 mmol) in toluene (20 mL) was treated with concentrated sulfuric acid (1.6 mL) and worked up as for the preparation of **20** (Method 2). Recrystallization (ethyl acetate/hexane) of the major fraction (R_F 0.5) afforded 8-chloro-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one **59** (438 mg, 81%) as colourless micro-needles, mp 142–144°C (lit.[17] 140–142°C). δ_H ($CDCl_3$) 8.44 (1H, br s, NH), 7.15 (1H, d, *J* 8, H6), 7.10 (1H, dd, *J* 8, 1.5, H7), 7.03 (1H, d, *J* 1.5, H9), 2.78 (2H, t, *J* 7, H3), 2.37 (2H, t, *J* 7, H5), 2.23 (2H, app p, *J* 7, H4). δ_C ($CDCl_3$) 175.4 (C_q), 139.1 (C_q), 132.8 (C_q), 132.7 (C_q), 130.9 (CH), 125.7 (CH), 122.0 (CH), 32.8 (CH_2), 29.9 (CH_2), 28.3 (CH_2). *m/z* (ESI, 70 V) 198 (32%, $(M[^{37}Cl] + H)^+$), 196 (100, $(M[^{35}Cl] + H)^+$), 186 (22).

*Beckmann Rearrangement of 7-Chloro-1-tetralone Oxime **71** (Method 3)*

*8-Chloro-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one **59***

7-Chloro-1-tetralone oxime **71** (195 mg, 1.00 mmol) was treated with polyphosphoric acid (10 mL) and worked up as for the preparation of **20** (Method 3). Recrystallization (dichloromethane/hexane) of this material afforded 8-chloro-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one **59** (123 mg, 63%), identical to that prepared above (Method 2).

*Beckmann Rearrangement of 7-Chloro-1-tetralone Oxime **71** (Method 4)*

*8-Chloro-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one **57***

7-Chloro-1-tetralone oxime **71** (990 mg, 5.06 mmol) was treated with thionyl chloride (5 mL) and worked up as

for the preparation of **15** (Method 4). Recrystallization (dichloromethane/hexane) of this material afforded 8-chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one **57** (565 mg, 57%), identical to that prepared above (Method 1).

*Beckmann Rearrangement of 7-Chloro-4-chromanone Oxime **55** (Method 2)*

*7-Chloro-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **59***

A mixture of 7-chloro-4-chromanone oxime **55** (300 mg, 1.64 mmol) and sodium azide (270 mg, 4.15 mmol) in toluene (20 mL) was treated with concentrated sulfuric acid (1 mL) and worked up as for the preparation of **20** (Method 2). Recrystallization (dichloromethane/hexane) of this material afforded 7-chloro-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one **59** (201 mg, 62%) as white needles, mp 161–162°C (Found: C 54.6, H 4.2, N 7.1. $C_9H_8ClNO_2$ requires C 54.7, H 4.1, N 7.1%.) δ_H ($CDCl_3$) 7.96 (1H, d, *J* 8.5, H6), 7.48 (1H, br s, NH), 7.09 (1H, dd, *J* 8.5, 2, H7), 7.03 (1H, d, *J* 2, H9), 4.41 (2H, t, *J* 4.5, H2), 3.52 (2H, app q, *J* 4.5, H3). δ_C ($CDCl_3$) 169.4 (CO), 156.2 (C_q), 139.0 (C_q), 133.5 (CH), 123.0 (CH), 121.3 (C_q), 121.2 (CH), 73.0 (CH_2), 41.7 (CH_2). *m/z* (ESI, 70 eV) 199 (25%, $M[^{37}Cl]^{+\bullet}$), 197 (81, $M[^{35}Cl]^{+\bullet}$), 168 (56), 139 (100), 110 (19), 75 (18), 63 (22).

Accessory Publication

General experimental details and the synthesis of the ketones and their precursors are available on the Journal's website.

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