# Preparation of the Maleic Anhydride Nucleus from Dichloro γ-Lactams: Focus on the Role of the N-Substituent in the Functional Rearrangement and in the Hydrolytic Steps

Franco Ghelfi,*[a] Mariella Pattarozzi,[a] Fabrizio Roncaglia,[a] Andrew F. Parsons,[b] Fulvia Felluga,[c] Ugo M. Pagnoni,[a] Ennio Valentin,[c] Adele Mucci,[a] Franco Bellesia[a]

[a] Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, 41100 Modena, Italy
Fax +39(59)373543; E-mail: ghelfi.franco@unimore.it

[b] Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK

[c] Dipartimento di Scienze Chimiche, Università di Trieste, via Licio Giorgieri 1, 34127 Trieste, Italy

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**Abstract:** The preparation of the 3,4-dialkyl-substituted maleic anhydride nucleus, through the functional rearrangement of dichloro γ-lactams, allowed the comparison of various N-substituents in the functional rearrangement step. The 2-pyridyl group proved to be the most appropriate N-substituent for the hydrolysis of the 5-methoxy-1,5-dihydro-2*H*-pyrrol-2-one intermediate into the 5-hydroxy adduct, and for the hydrolysis of the maleimide nucleus into the maleic anhydride. The oxidation of the 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one into the corresponding maleimide was achieved with manganese(IV) oxide.

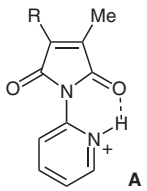
**Key words:** rearrangement, radical reactions, substituent effects, halo compounds, γ-lactams

Many natural products containing the maleic anhydride ring show special biological activity including enzymatic inhibition.[1] Maleic anhydrides, in addition, are useful synthons widely used in the construction of new organic skeletons.[2] Several routes to this important cyclic skeleton have been reported,[1–3] but the development of new synthetic paths for their preparation is still a useful and challenging task, which adds new arrows to the chemist's quiver.

Recently, we exploited the functional rearrangement of 3-alkyl-3-chloro-4-(dichloromethyl)-1-(2-pyridyl)pyrrolidin-2-ones, completed by a one-pot hydrolytic step, to construct disubstituted maleic anhydrides.[4] This route, however, suffers from a particularly inefficient use of 2-aminopyridine for the preparation, by alkylation with 1,3-dichloropropene, of the starting 2-(3-chloroprop-2-enylamino)pyridine component (toluene, 100 °C, 20 h; 20–30% yield). This monohalogenated amine was then acylated with a 2,2-dichloroacyl chloride and the resulting amide was converted, by atom-transfer radical cyclization (ATRC), into the 3-alkyl-3-chloro-4-(dichloromethyl)-1-(2-pyridyl)pyrrolidin-2-one intermediate.

The use of 1,3-dichloropropene limits the widespread applicability of the strategy because: (i) it is the only commercially available γ-chloroallyl chloride, (ii) the preparation of higher homologues are not straightforward,[5] and (iii) the only way to get the starting amine is by amino-dehalogenation.

Interesting is the role played by the 2-pyridyl moiety, which besides facilitating the solubility of **A** in water/$H^+$, may take part in the hydrolytic mechanism to form the maleic anhydride, owing to the likely interaction, through a hydrogen bridge, between the carbonyl group and the protonated pyridyl nitrogen of the maleimide **A** (Figure 1). Since the preparation of the analogous amines 3-(3-chloroprop-2-enylamino)pyridine and 4-(3-chloroprop-2-enylamino)pyridine by alkylation of the corresponding aminopyridine with 1,3-dichloropropene failed, we were unable to clarify the role played by the 2-pyridyl moiety in the hydrolysis of **A**. Bowman, who first performed the same hydrolysis step in his route to pyrochinconic anhydride, did not disclosed the mechanism of this reaction.[6]




**A**

**Figure 1**

With the scope to develop a more versatile procedure for the preparation of disubstituted maleic anhydrides and solve the aforementioned problems, we judged that the use of secondary γ-nonhalogenated allylamines, as radicophilic building blocks, might be more advantageous from a synthetic point of view, since a substantial number of commercial starting materials are available and, in addition, their preparation can be easily accomplished with trustworthy strategies, such as: (i) nucleophilic substitution of primary allylamines using compounds carrying good nucleofuges, (ii) nucleophilic substitution reactions between a primary allylamine and an allylic system containing a good leaving group, and (iii) reductive amination of carbonyl compounds.

This structural simplification has, however, an important consequence on the synthetic path, since an oxidative step

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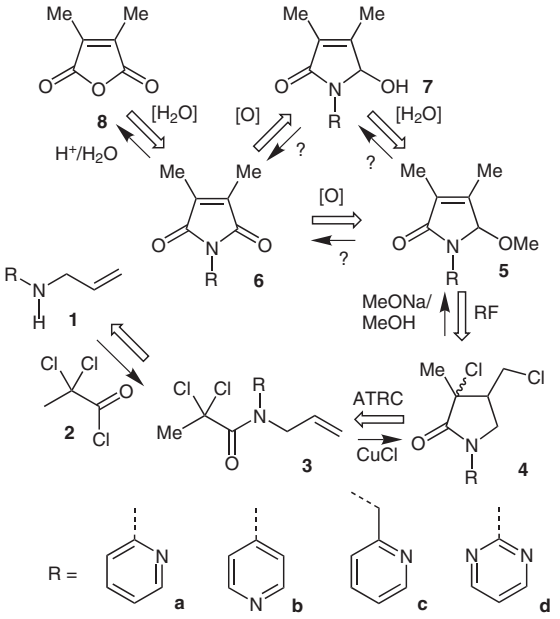
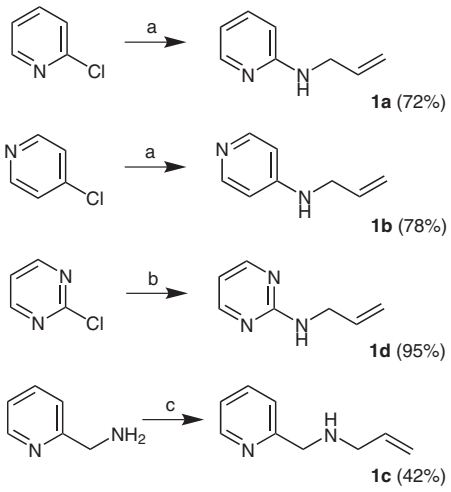
is now needed for adjusting the oxidation level of the C5 site of the 5-methoxy-1,5-dihydro-2*H*-pyrrol-2-one **5**, afforded by the functional rearrangement product of the dihalogenated pyrrolidin-2-one **4** (Scheme 1).

Herein we report that pyrocinchonic anhydride, chosen as archetype of the class and, by itself, a very useful building block in organic synthesis,[7] can be smoothly obtained with the new strategy. In addition, the crucial role played by the 2-pyridyl moiety bound to the starting amide, in the two intermediate hydrolysis steps (Scheme 1) is discussed. The possibility to test a number of N-substituents in the functional rearrangement step allowed the detection of an interesting effect, albeit not exploitable in practical terms.



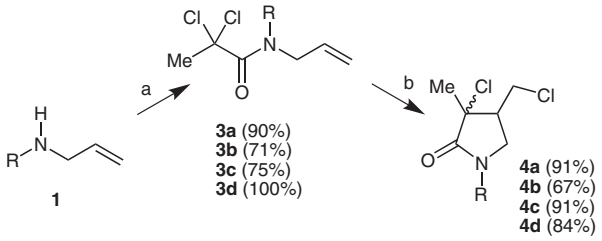

**Scheme 1** Atom-transfer radical cyclization (ATRC) and functional rearrangement (FR) in the synthesis of 5-methoxy-1,5-dihydro-2*H*-pyrrol-2-ones and their hydrolysis.




**Scheme 2** *Reagents and conditions*: (a) allylamine, argon, 140 °C, 72 h; (b) allylamine, argon, r.t., 2 h; (c) 3-chloropropene, $K_2CO_3$, THF, reflux, 18 h.

To understand the influence of the 2-pyridyl group in the hydrolysis of **A**, we planned the preparation of a series of maleimides, where the N-substituents differ in the number of nitrogen atoms and in their location. The preparation of precursors **4a**–**d**, as a first step toward the synthesis of the pyrocinchonic imides **6a**–**d**, was accomplished as outlined in Scheme 1. The starting allylamines **1a**, **1b**, and **1d** were efficiently prepared via nucleophilic aromatic substitution reactions between allylamine and either 2-chloropyridine, 4-chloropyridine, or 2-chloropyrimidine, respectively (Scheme 2).[8] Differently from that reported in the literature, we carried out the reactions in the absence of solvent, making the procedure more attractive from a practical and economic perspective. For the preparation of 2-[(prop-2-enylamino)methyl]pyridine (**1c**), instead, we resorted to a nucleophilic substitution reaction between 2-(aminomethyl)pyridine and allyl chloride; in this way **1c** was secured in an acceptable 42% yield.

The amides **3** were effectively attained by reaction between allylamines **1a**–**d** and 2,2-dichloropropanoyl chloride (**2**) (Scheme 3). Afterwards they were rearranged into the corresponding dihalopyrrolidin-2-ones **4**, applying transition-metal-catalyzed atom-transfer radical cyclization (TMC-ATRC) (Scheme 3),[9] an example of isohypsic[10] transformation.



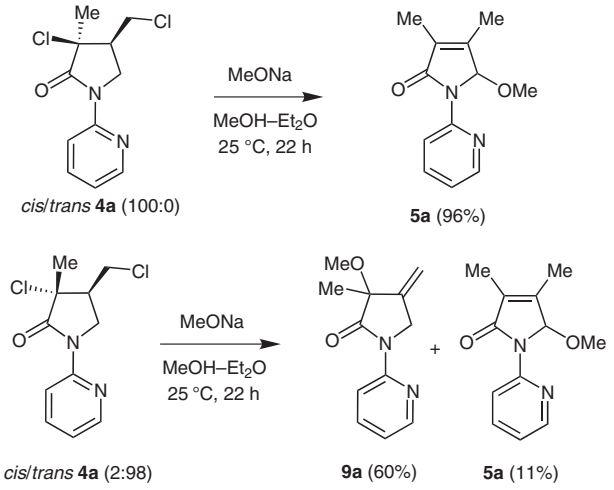

**Scheme 3** *Reagents and conditions*: (a) $MeCCl_2COCl$ (**2**), pyridine, $CH_2Cl_2$, r.t., 5 h; (b) CuCl–TMEDA, MeCN, argon, r.t., 24 h.

The functional rearrangement of 4-methylpyrrolidin-2-ones chlorinated at the C3 and C6 positions is a fairly general reaction that takes place when the halogenated γ-lactam is treated with a solution of alkaline methoxide in methanol. In practice, the C–Cl groups at the C3 and C6 positions are replaced by a double bond between carbons C3 and C4, and one or two methoxy groups at C5 (the functional rearrangement is also an isohypsic transformation).[11] We discovered that for an effective functional rearrangement, the configuration of the starting α,γ-halogenated pyrrolidin-2-one is critical and should be arranged so that an initial *endo* elimination between the C3 and C4 positions is possible.[4] This is so only for the more stable *cis*-3-alkyl-3-chloro-4-(chloromethyl)pyrrolidin-2-ones, which have a *trans* geometry between the C4–H and the C3–Cl bonds. In contrast, the *trans*-pyrrolidinone isomer undergoes an unproductive *exo* elimination.[4]

As experienced in previous studies,[4] the C3 stereogenic center of the 3-alkyl-3-chloro-4-(chloromethyl)pyrrolidin-2-ones **4** appears configurationally unstable under the reaction conditions of TMC-ATRC. Therefore, the stereo-

chemistry of the halogenated γ-lactams **4** is under thermodynamic control and the isomer that predominates carries the larger substituents at C3 and C4 on the opposite sides of the ring. Since C3 epimerization is a gradual process, higher temperatures and longer reaction times generally improve the selectivity toward the more stable isomer [in this case, the *cis*-3-alkyl-3-chloro-4-(chloromethyl)pyrrolidin-2-one]. Regardless of the above considerations, the cyclization of amides **3** was carried out at room temperature so as to increase, as far as possible, the amount of the *trans*-pyrrolidin-2-one **4**, thereby giving a significant amount of product derived from *exo* elimination, which simplifies product characterization.

At the beginning, we investigated the effect of the system ROH/RONa on the reaction pathway, using **4a** as model compound (*cis*/*trans* 62:38). The four systems, which we compared at room temperature under standard reaction conditions,[11] were, in order of increasing basicity: (i) MeOH/MeONa, (ii) EtOH/EtONa, (iii) *i*-PrOH/*i*-PrONa, and (iv) *t*-BuOH/*t*-BuONa. Under the most basic conditions (EtOH/EtONa, *i*-PrOH/*i*-PrONa and *t*-BuOH/*t*-BuONa) the *exo*-elimination product **9a** did not form or it degraded, whereas the yields of the 5-alkoxy-1,5-dihydro-2*H*-pyrrol-2-ones (the functional rearrangement products) gradually diminished [5-methoxy-1,5-dihydro-2*H*-pyrrol-2-one **5a** (63%), 5-ethoxy-1,5-dihydro-2*H*-pyrrol-2-one (49%), 5-isopropoxy-1,5-dihydro-2*H*-pyrrol-2-one (30%), 5-*tert*-butoxy-1,5-dihydro-2*H*-pyrrol-2-one (0%)].

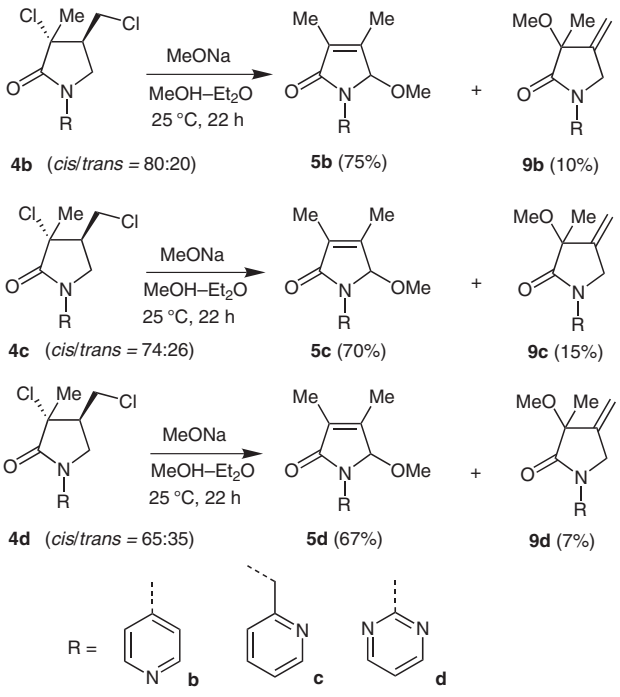



**Scheme 4**

As MeOH/MeONa gives the highest yield of the functional rearrangement product, we subjected the *cis*- and *trans*-isomers of **4a** to this reagent. As expected, *cis*-**4a** gave selectively the 5-methoxy-3,4-dimethyl-1-(2-pyridyl)-1,5-dihydro-2*H*-pyrrol-2-one (**5a**), whereas the corresponding *trans*-isomer of **4a** gave the adduct **9a**, as the main product, through an *exo* dehydrohalogenation, followed by the nucleophilic replacement of the Cl atom at C3 by the methoxide ion (Scheme 4). Astonishingly, *trans*-**4a** also afforded some **5a**, the yield of which cannot be explained by the residual amount of *cis*-**4a** isomer present in the starting sample of *trans*-**4a** (Scheme 4).

When the functional rearrangement of **4a**, as a 61:39 mixture of *cis*/*trans* isomers, was carried out at 0 °C, we succeeded in obtaining the selective and complete conversion of the *cis*-isomer of **4a** into **5a** (yield 62%), while the *trans*-isomer **4a** was quantitatively recovered. This experimental protocol offers two important practical advantages: first, *trans*-**4a** can be separated from **5a** more easily than from the *cis*-**4a** isomer, and second, once recovered, *trans*-**4a** can be epimerized with copper(I) chloride–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine into the *cis*-structure, thus improving the global effectiveness of the functional rearrangement step.

The functional rearrangement was then investigated using dichloro γ-lactams **4b**, **4c**, and **4d** and gave the expected products (Scheme 5). Considering the straightforward preparation of **4d**, we examined, in greater detail, its functional rearrangement in MeOH/MeONa (Table 1). The results collected in Table 1 resemble those obtained with **4a**. Specifically, it is evident that the reaction of *trans*-**4d** with sodium methoxide produced a small amount of the otherwise forbidden product **5d** (Table 1, entry 3). In addition, as for **4a**, it was also possible with **4d** to stop the transformation of the minor *trans*-isomer, by lowering the reaction temperature (Table 1, entry 4).




**Scheme 5**

The likely origin of the functional rearrangement product obtained from the *trans*-**4** diastereomers can be ascribed to a partial epimerization to the *cis*-isomer. However, we were unable to replace the chloro group at the C3 position of *trans*-**4d** in methanol at 25 °C with $Br^-$ (from NaBr or KBr) or $I^-$ (from NaI or KI). Moreover, no epimerization

was observed when chloride ion was introduced as tetraethylammonium chloride. On these experimental grounds we judged it more plausible that the methoxide ion was responsible for inversion of the configuration at the C3 position (then followed by rapid elimination of MeOH). This view is supported by literature examples of substitutions of tertiary alkyl halides α to amide groups by N- or O- nucleophiles (the formation of **9** can be included in the series).[12–14]

**Table 1** Functional Rearrangement of **4d** (*cis*/*trans* 65:35)[a,b]

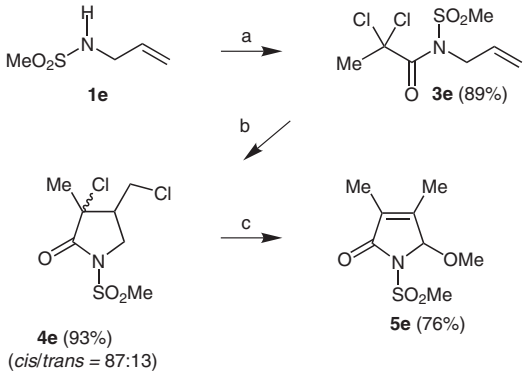
| Entry | Temp (°C) | Time (h) | Conversion[c] (%) | Yield[d] (%) | |
|---|---|---|---|---|---|
| | | | | **5d** | **9d** |
| 1 | 25 | 22 | 100 | 67 | 7 |
| 2 | 10 | 24 | 100 | 69 | 12 |
| 3[e] | 10 | 24 | 100 | 6 | 57 |
| 4 | –10 | 24 | 74 | 65 | 0 |

[a] **4d** (4 mmol), MeOH (12 mL), MeONa (12 mmol).
[b] All the reactions were performed under argon.
[c] GC values.
[d] Determined on isolated material.
[e] Reaction performed on *trans*-**4d** alone.

Since the proclivity to nucleophilic substitution of the halide ion in the α-halo-(CO) compounds is gradually augmented when increasingly electron-withdrawing groups are bound to the carbonyl group,[15] we considered it interesting to study the functional rearrangement of pyrrolidin-2-one **4e** carrying a strongly electronegative substituent at N1, such as the methylsulfonyl group (Scheme 6).

The dichlorinated γ-lactams **4e** were synthesized by atom-transfer radical cyclization of amide **3e**, using as redox catalyst the complex copper(I) chloride/*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA) (Scheme 6). As expected, the amount of *trans*-**4e** (*cis*-**4e**/*trans*-**4e** 87:13) was lower than that observed in the preceding cases. This is due to facile radical epimerization encouraged by the electronic effect of the methylsulfonyl group.[16] Unfortunately, the functional rearrangement of **4e** gave inconclusive and unsatisfactory results. A first reaction, run at 25 °C, was disappointing, affording **5e** in only 23% yield. A much higher yield of **5e** (76%) was achieved at –10 °C. Notwithstanding the improvement, it is apparent that the selectivity in the transformation of **4e** is worse than that attained with **4a–d**, and as a consequence the study of the functional rearrangement of **4e** was abandoned.

Given that 1,5-dihydro-2*H*-pyrrol-2-ones can be hydroxylated with oxygen in the presence of a base,[17,18] for the oxidation of the C5–OMe moiety of **5a**, we investigated the functional rearrangement of **4a** under oxygen and the oxidation of **5a** with potassium hydroxide/acetone/oxygen, but unsuccessfully.[19] The Baeyer–Villiger oxidation of **5a** with peracids[20] or sulfuric acid/hydrogen peroxide[21] was equally fruitless.




**Scheme 6** *Reagents and conditions*: (a) $MeCCl_2COCl$ (**2**), NaH, $Et_2O$, r.t., 1 h; (b) CuCl–PMDETA, toluene, argon, r.t., 18 h; (c) Na, MeOH, toluene, –10 °C, 22 h.

After these failures, we speculated that the corresponding 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones **7** could be easily converted into the maleimides **6** (Scheme 1). Thus, we attempted the hydrolysis of the 5-methoxy-1,5-dihydropyrrol-2-ones **5** and the results are collected in Table 2. The lactams **5a** and **5c** were effectively hydrolyzed at 140 and 100 °C, respectively (Table 2, entries 5 and 7), using a solution of sulfuric acid in water. The best reaction conditions for **5d** gave, instead, relatively low yields (Table 2, entry 8); hence 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one **5d** was set aside. In contrast, substrate **5b** appeared completely unreactive at 140 °C (Table 2, entry 6). An attempt to form **7a**, from the functional rearrangement of **4a** using a biphasic system of toluene and 50% aqueous sodium hydroxide under phase-transfer catalysis (tetrabutylammonium bromide) failed.

The successful hydrolysis of **5** into **7** is evidently linked to the involvement of an intramolecular hydrogen bridge between the protonated basic nitrogen and the ethereal oxygen, which makes viable the replacement of the methoxy group under relatively mild reaction conditions. This opportunity is not possible for **5b**. The greater hydrolytic susceptibility of **5c**, compared to **5a**, is likely a consequence of the reduced electron-withdrawing effect of the 2-pyridyl appendage, caused by the methylene tether. As a result the methoxy oxygen of **5c** is more basic, and consequently more liable to acid catalysis, than the corresponding oxygen of **5a**.

Before dealing with the conversion of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones **7** into the corresponding maleimides **6**, we deemed it more helpful to study in advance the hydrolysis of **6**, prepared by another route.[22] Since it was ascertained that **6a** can be effortlessly hydrolyzed with aqueous 2 M sulfuric acid (1 equiv) at 110 °C,[4,6] we tested, under the same reaction conditions, the substrates **6b** (to understand the influence on hydrolysis, of the pyridylic nitrogen location) and **6c** (Scheme 7). The outcome was unexpected, while the hydrolysis of **6b** was successful, maleimide **6c** was recovered quantitatively (Scheme 7).

In contrast to the efficient hydrolysis of 5-methoxy-1,5-dihydro-2*H*-pyrrol-2-ones **5**, where an intramolecular

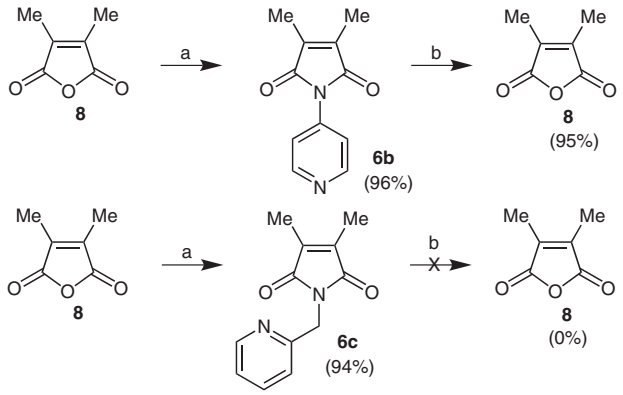
**Table 2** Hydrolysis of **5**[a]

| Entry | Substrate | Volume $H_2SO_4/H_2O$ (mL)[b] | Temp (°C) | Time (h) | Conversion[c] (%) | Yield[c] (%) of **7** |
|---|---|---|---|---|---|---|
| 1 | **5a**[d] | 0.5/0 | 80 | 4 | 0 | 0 |
| 2 | **5a**[d] | 0.5/0 | 100 | 5 | 0 | 0 |
| 3 | **5a** | 0.3/0.2 | 120 | 7 | 100 | 96 |
| 4 | **5a** | 0.3/0.2 | 140 | 3 | 100 | 96 |
| 5 | **5a** | 0.25/0.25 | 140 | 3 | 100 | 83[e] |
| 6 | **5b** | 0.25/0.25 | 140 | 3 | 0 | 0 |
| 7 | **5c** | 0.25/0.25 | 100 | 3 | 96 | 76[e] |
| 8 | **5d** | 0.25/0.25 | 120 | 3 | 91 | 52[e] |

[a] **5** (0.5 mmol).
[b] 2 M $H_2SO_4$.
[c] GC values.
[d] **5** (0.25 mmol).
[e] Yield of isolated product.

acid catalysis was required, the hydrolysis of **6** is promoted by the increased electronegativity of the N-substituent, after protonation of the pyridyl group, and by the possibility that this increment can be directly transferred to the maleimidic nitrogen. This makes the C=O function more electrophilic and then more susceptible to attack by water molecules (this was the case for substrates **6a** and **6b**, whereas **6c** is unreactive, since a methylene tether is between the pyridinium moiety and the maleimide nitrogen). On the basis of these results it was evident that the choice of the intermediate to be oxidized to the maleimide was restricted to **7a**.

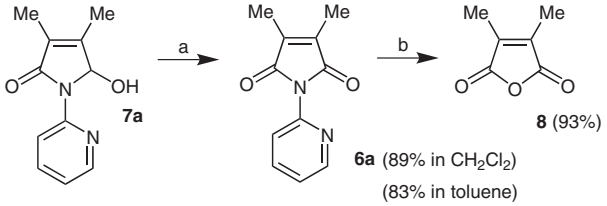
After a number of unsuccessful attempts, we realized that the oxidation of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one **7a** into the corresponding maleimide **6a** can be only achieved using manganese(IV) oxide.[23,24] This reagent is particularly attractive from an industrial point of view owing to a number of helpful properties: low toxicity, low cost, easy handling, commercial availability, recyclability.[25] Pleasingly, **7a** was smoothly transformed by manganese(IV) oxide into maleimide **6a** (Scheme 8), when toluene (83% yield) or dichloromethane (89% yield) was used as the solvent. In the end the hydrolysis of **6a** with 2 M sulfuric acid gave the expected pyrochinconic anhydride **8** in high yield (93% yield).




**Scheme 7** *Reagents and conditions*: (a) 2-aminopyridine or 2-(aminomethyl)pyridine, xylene, reflux, 2 h; (b) 2 M $H_2SO_4$, 110 °C, 3 h.

The route described herein from dichloro γ-lactams to the disubstituted maleic anhydride nucleus is more practical than that from trichloro γ-lactams, since both the preparations of the starting materials and of all the intermediates were completed with simple, economic, and high yielding procedures. The outcome of the functional rearrangement of **4a** may be further increased on carrying out the atom-transfer radical cyclization of **3** under thermodynamic control, so to get an even more favorable *cis*-**4a**/*trans*-**4a** ratio.

This new method, in particular, was helpful in the recognition of a positive effect, albeit in practice unexploitable, of the N-substituent on the generation of **5** from the γ-lactams *trans*-**4**, which are the isomers endowed of an unfavorable configuration for the functional rearrangement in MeONa/MeOH.[4] The pivotal role played by the N-substituent along the synthetic path, for the conversion of the 5-methoxy-1,5-dihydro-2*H*-pyrrol-2-ones into the corresponding 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones and for the effective hydrolysis of maleimides **6** into anhydride **8** was also understood. Incidentally, the 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones are interesting compounds potentially usable as agrochemicals for crops protection, e.g. **7a** was patented by Ciba-Geigy AG.[26]




**Scheme 8** *Reagents and conditions*: (a) $MnO_2$, solvent, r.t., 20 h; (b) 2 M $H_2SO_4$, 110 °C, 3 h.

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka, or RdH, and used without further purification, except MeCN and $CH_2Cl_2$, which were dried over three batches of 3 Å sieves (5% w/v, 12 h). The flash chromatography used Silica Gel 60 Merck (0.040–0.063 mm); PE = petroleum ether (bp 40–60 °C). 2-{[(Prop-2-enyl)amino]methyl}pyridine (**1c**) was prepared by N-alkylation of 2-(aminomethyl)pyridine with 3-chloropropene, following the procedure of Shipman.[27] The maleimides **6b** and **6c** were obtained from commercial pyrocinchonic anhydride and 4-aminopyridine or 2-(aminomethyl)pyridine, respectively, exploiting the procedure described by Padwa.[22] *N*-(Prop-2-enyl)methanesulfonamide (**3e**)[28] and 2,2-dichloropropanoyl chloride (**2**)[4] were prepared according to given protocols.

$^1$H NMR, IR, and MS spectra were recorded on Bruker DPX 200 and Bruker Avance 400, Perkin Elmer 1600 Series FTIR, and HP 5890 GC - HP 5989A MS instruments, respectively.

The structural assignment of compounds **4a**–**e**, **5a**–**e**, and **9a**–**e** was determined by heteronuclear H,C inverse-detection NMR correlation techniques and for **4a**–**e** also by homonuclear nuclear Overhauser enhancement. The direct and long-range H,C correlations allowed us to establish unambiguously the regiochemistry of the products, whereas NOESY experiments enabled the relative stereochemistry at the C3 and C4 carbons in **4a**–**e** to be determined. The presence of an equilibrium (in soln) between 2 rotamers of compound **3c** was evidenced by NMR (hindered rotation around the amide bond). An exchange spectroscopy experiment (EXSY) permitted the reported assignments.

### 2-(Prop-2-enylamino)pyridine (1a); Typical Procedure

To a Schlenk tube, fitted with a pierceable septum (blocked by a screw cap) and a stirrer bar, was added under argon 2-chloropyridine (9.5 mL, 100 mmol) and allylamine (15.0 mL, 200 mmol). The soln was stirred vigorously and heated at 140 °C for 72 h. It was then cooled to r.t., neutralized with 10% aq NaOH, and extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were evaporated and the crude product thus obtained was purified by fractional distillation to give **1a** (9.65 g, 72%) as a pale yellow liquid; bp 104–106 °C/5.33 mbar.

IR (film): 3264 cm$^{-1}$ (N–H).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 3.89 (m, 2 H, $CH_2$N), 5.02 (br s, 1 H, NH), 5.10 (m, 1 H, =$CH_2$), 5.22 (m, 1 H, =$CH_2$), 5.91 (m, 1 H, C*H*=$CH_2$), 6.34 (d, *J* = 8.4 Hz, 1 H, H3$_{py}$), 6.52 (dd, *J* = 7.2, 5.1 Hz, 1 H, H5$_{py}$), 7.35 (dd, *J* = 8.4, 7.2 Hz, 1 H, H4$_{py}$), 8.05 (br d, *J* = 5.1 Hz, 1 H, H6$_{py}$).

MS (EI, 70 eV): *m*/*z* (%) = 135 (6) [M + 1]$^+$, 134 (39) [M]$^+$, 133 (32) [M – 1]$^+$, 119 (100), 107 (38), 79 (25), 78 (36).

Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.87. Found: C, 71.5; H, 7.5; N, 21.0.

### 4-(Prop-2-enylamino)pyridine (1b)

Following the typical procedure for **1a** using 4-chloropyridine·hydrochloride (15.0 g, 100 mmol) and allylamine (22.5 mL, 300 mmol) gave **1b** (10.45 g, 78%) as a colorless liquid, which then became a white solid; bp 140–142 °C/6.7 mbar; mp 66–68 °C.

IR (KBr): 3238 cm$^{-1}$ (N–H).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 3.79 (m, 2 H, $CH_2$), 4.67 (br s, 1 H, NH), 5.18 (m, 1 H, =$CH_2$), 5.25 (m, 1 H, =$CH_2$), 5.88 (m, 1 H, C*H*=$CH_2$), 6.42 (m, 2 H, H3$_{py}$, H5$_{py}$), 8.16 (m, 2 H, H2$_{py}$, H6$_{py}$).

MS (EI, 70 eV): *m*/*z* (%) = 135 (12) [M + 1]$^+$, 134 (100) [M]$^+$, 133 (83) [M – 1]$^+$, 107 (98), 78 (45), 51 (43).

Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.87. Found: C, 71.6; H, 7.5; N, 20.9.

### 2-(Prop-2-enylamino)pyrimidine (1d)

Following the typical procedure for **1a** using 2-chloropyrimidine (11.5 g, 100 mmol) and allylamine (15.0 mL, 200 mmol). The mixture was cooled in a water bath at r.t., to control the exothermic reaction and stirred vigorously at r.t. for 2 h. Workup as for **1a**, but using $Et_2O$ (3 × 20 mL), gave **1d** (12.83 g, 95%) as a pale yellow liquid; bp 89–90 °C/1.2 mbar.

IR (film): 3270 cm$^{-1}$ (N–H).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.05 (tt, *J* = 1.6, 5.6 Hz, 2 H, $CH_2$), 5.11 (dq, *J* = 10.3, 1.6 Hz, 1 H, =$CH_2$), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1 H, =$CH_2$), 5.88 (br s, 1 H, NH), 5.94 (ddt, *J* = 17.2, 10.3, 5.3 Hz, 1 H, C*H*=$CH_2$), 6.49 (t, *J* = 4.8 Hz, 1 H, H5$_{py}$), 8.24 (d, *J* = 4.8 Hz, 2 H, H4$_{py}$, H6$_{py}$).

MS (EI, 70 eV): *m*/*z* (%) = 136 (8%) [M + 1]$^+$, 135 (52) [M]$^+$, 134 (44) [M – 1]$^+$, 120 (100), 108 (27), 79 (21).

Anal. Calcd for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.3; H, 6.8; N, 31.1.

### *N*-Allyl-2,2-dichloro-*N*-(2-pyridyl)propanamide (3a)

To a 100-mL, 2-necked round-bottomed flask fitted with a dropping funnel and a reflux condenser, closed on the top with a $CaCl_2$ tube, was added $CH_2Cl_2$ (60 mL), **1a** (16.55 g, 124 mmol), and pyridine (13 mL, 155 mmol). The mixture was stirred and cooled in an ice bath and a soln of 2,2-dichloropropanoyl chloride (**2**, 21.94 g, 136 mmol) in $CH_2Cl_2$ (30 mL) was then carefully added over 10 min. The bath was removed and the mixture was stirred at r.t. for 20 h. The mixture was made basic with 5% aq NaOH (110 mL) and extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic phases were concentrated and the crude product was subjected to flash chromatography (silica gel, PE–$Et_2O$, gradient from 10:0 to 5:5) to afford **3a** (28.73 g, 90%) as a brownish oil.

IR (film): 1665 cm$^{-1}$ (C=O).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, $CH_3$), 4.72 (td, *J* = 6.0, 1.2, Hz, 2 H, $CH_2$), 5.05 (dq, *J* = 10.2, 1.2 Hz, 1 H, =$CH_2$), 5.08 (dq, *J* = 17.2, 1.2 Hz, 1 H, =$CH_2$), 5.82 (ddt, *J* = 17.2, 10.2, 6.0 Hz, 1 H, C*H*=$CH_2$), 7.18 (dd, *J* = 5.2, 7.0 Hz, 1 H, H5$_{py}$), 7.37 (d, *J* = 7.8 Hz, 1 H, H3$_{py}$), 7.70 (td, *J* = 7.8, 1.3 Hz, 1 H, H4$_{py}$), 8.49 (dd, *J* = 5.2, 1.3 Hz, 1 H, H6$_{py}$).

MS (EI, 70 eV): *m*/*z* (%) = 259 (3) [M + 1]$^+$, 258 (10) [M]$^+$, 257 (2) [M – 1]$^+$, 223 (15), 161 (92), 133 (100), 78 (20), 41 (38).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.99; H, 4.67; N, 10.81. Found: C, 51.0; H, 4.7; N, 10.8.

### *N*-Allyl-2,2-dichloro-*N*-(4-pyridyl)propanamide (3b)

To a Schlenk tube, fitted with a pierceable septum (blocked by a screw cap) and a stirrer bar, was added under argon **1b** (3.35 g, 25 mmol), pyridine (2.25 mL, 30 mmol), and $CH_2Cl_2$ (20 mL). The soln was stirred and cooled in an ice bath and a soln of 2,2-dichloropropanoyl chloride (**2**, 4.84 g, 30 mmol) in $CH_2Cl_2$ (20 mL) was carefully added with a syringe. After 30 min the bath was removed and the mixture was stirred at r.t. for 20 h at r.t.. The mixture was then diluted with brine (20 mL), made basic with 5% aq NaOH (25 mL), and extracted with $Et_2O$–$CH_2Cl_2$ (1:1, 3 × 20 mL). The combined organic phases were concentrated and the crude product was subjected to flash chromatography (silica gel, PE–$Et_2O$, 5:5) to give **3b** (4.64 g, 71%) as a white solid; mp 93–95 °C.

IR (KBr): 1665 cm$^{-1}$ (C=O).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, $CH_3$), 4.57 (td, *J* = 5.9, 1.3, Hz, 2 H, $CH_2$), 5.10 (dq, *J* = 17.1, 1.3 Hz, 1 H, =$CH_2$), 5.18 (dq, *J* = 10.1, 1.3 Hz, 1 H, =$CH_2$), 5.87 (ddt, *J* = 17.1, 10.1, 5.9 Hz, 1 H, C*H*=$CH_2$), 7.26 (m, 2 H, H3$_{py}$, H5$_{py}$), 8.57 (m, 2 H, H2$_{py}$, H6$_{py}$).

MS (EI, 70 eV): *m*/*z* (%) = 259 (5) [M + 1]$^+$, 258 (33) [M]$^+$, 223 (37), 187 (20), 161 (100), 133 (42), 78 (8), 41 (97).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.99; H, 4.67; N, 10.81. Found: C, 50.9; H, 4.7; N, 10.7.

**_N_-Allyl-2,2-dichloro-_N_-[(2-pyridyl)methyl]propanamide (3c); Typical Procedure**

To a 100-mL 2-necked round-bottomed flask fitted with a dropping funnel and a reflux condenser, closed on the top with a $CaCl_2$ tube, was added $CH_2Cl_2$ (50 mL), **1c** (14.72 g, 100 mmol), and pyridine (10 mL, 133 mmol). The mixture was stirred and cooled in an ice bath and a soln of 2,2-dichloropropanoyl chloride (**2**, 16.14 g, 100 mmol) in $CH_2Cl_2$ (20 mL) was then carefully added over 10 min. The bath was removed and the mixture was stirred at r.t. for 20 h. The mixture was made basic with 5% aq NaOH (80 mL) and extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic phases were concentrated and the crude product was subjected to flash chromatography (silica gel, PE–$Et_2O$, gradient from 10:0 to 7:3) to afford **3c** (20.47 g, 75%) as a pale yellow oil.

IR (film): 1656 cm$^{-1}$ (C=O).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, $CH_3$ major), 2.36 (s, 3 H, $CH_3$ minor), 4.00 (d, *J* = 5.2 Hz, 2 H, $CH_2C$= minor), 4.53 (d, *J* = 5.7 Hz, 2 H, $CH_2C$= major), 4.69 (s, 2 H, $CH_2$py major), 5.12 (d, *J* = 17.4 Hz, 1 H, =$CH_2$ minor), 5.18 (d, *J* = 10.3 Hz, 1 H, =$CH_2$ minor), 5.21 (s, 2 H, $CH_2$py minor), 5.27 (d, *J* = 17.0 Hz, 1 H, =$CH_2$ major), 5.29 (d, *J* = 9.5 Hz, 1 H, =$CH_2$ major), 5.77 (ddt, *J* = 16.4, 10.1, 6.1 Hz, 1 H, C*H*=$CH_2$ minor), 5.92 (ddt, *J* = 16.7, 10.6, 6.0 Hz, 1 H, C*H*=$CH_2$ major), 7.17 (m, 2 H, $H3_{py}$, $H5_{py}$ major), 7.21 (dd, *J* = 7.8, 5.3 Hz, 1 H, $H5_{py}$ minor), 7.29 (d, *J* = 8.0 Hz, 1 H, $H3_{py}$ minor), 7.65 (t, *J* = 7.7 Hz, 1 H, $H4_{py}$ major), 7.69 (t, *J* = 7.7 Hz, 1 H, $H4_{py}$ minor), 8.54 (d, *J* = 4.6 Hz, 1 H, $H6_{py}$ major), 8.58 (d, *J* = 4.7 Hz, 1 H, $H6_{py}$ minor).

MS (EI, 70 eV): *m*/*z* (%) = 273 (1) [M + 1]$^+$, 272 (1), [M]$^+$, 201 (15), 175 (11), 147 (15), 93 (100).

Anal. Calcd for $C_{12}H_{14}Cl_2N_2O$: C, 52.76; H, 5.17; N, 10.26. Found: C, 52.8; H, 5.1; N, 10.2.

**_N_-Allyl-2,2-dichloro-_N_-(pyrimidin-2-yl)propanamide (3d)**

Following the typical procedure for **3c** using **1d** (13.51 g, 100 mmol) gave, after flash chromatography of the crude product (silica gel, $CH_2Cl_2$–MeOH, gradient from 10:0 to 9.5:0.5), **3d** (26.32 g, 100%) as a pale orange solid; mp 34–36 °C.

IR (KBr): 1673 cm$^{-1}$ (C=O).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, $CH_3$), 4.76 (dt, *J* = 5.7, 1.4 Hz, 2 H, $CH_2$), 5.09 (dq, *J* = 10.3, 1.4 Hz, 1 H, =$CH_2$), 5.19 (dq, *J* = 17.1, 1.4 Hz, 1 H, =$CH_2$), 5.91 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 1 H, C*H*=$CH_2$), 7.17 (t, *J* = 4.8 Hz, 1 H, $H5_{py}$), 8.71 (d, *J* = 4.8 Hz, 2 H, $H4_{py}$, $H6_{py}$).

MS (EI, 70 eV): *m*/*z* (%) = 260 (1) [M + 1]$^+$, 259 (8) [M]$^+$, 162 (100), 134 (80), 108 (8), 79 (20), 41(65).

Anal. Calcd for $C_{10}H_{11}Cl_2N_3O$: C, 46.17; H, 4.26; N, 16.15. Found: C, 46.1; H, 4.2; N, 16.1.

**_N_-Allyl-_N_-(2,2-dichloropropanoyl)methanesulfonamide (3e)**

To a 100-mL, 3-necked round-bottomed flask fitted with a mechanical stirrer and a reflux condenser, closed on the top with a $CaCl_2$ tube, was added **1e** (20.27 g, 150 mmol) and $Et_2O$ (200 mL). Then NaH (60% dispersion in mineral oil, 6.0 g, 157 mmol) was carefully added to the flask. When $H_2$ evolution ceased, a soln of 2,2-dichloropropanoyl chloride (**2**, 19.36 g, 120 mmol) in $Et_2O$ (100 mL) was slowly added through the dropping funnel. After the acyl halide addition, the mixture was stirred for 1 h and then diluted with toluene–water (8 mL–2 mL) and acidified with 10% aq HCl. Then, sufficient $H_2O$ was added to dissolve the formed salt and the mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic phases were concentrated and the crude product was subjected to flash chromatography (silica gel, PE–$Et_2O$, gradient from 10:0 to 8:2) to afford **3e** (27.78 g, 89%) as a yellow oil.

IR (film): 1696 cm$^{-1}$ (C=O).

$^1$H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, $CCl_2CH_3$), 3.31 (s, 3 H, $SCH_3$), 4.86 (dt, *J* = 5.8, 1.4 Hz, 2 H, $CH_2$), 5.33 (dq, *J* = 10.3, 1.2 Hz, 1 H, =$CH_2$), 5.19 (dq, *J* = 17.1, 1.2 Hz, 1 H, =$CH_2$), 5.97 (ddt, *J* = 17.1, 10.3, 5.8 Hz, 1 H, C*H*=$CH_2$).

MS (EI, 70 eV): *m*/*z* (%) = 259 (1) [M]$^+$, 180 (14), 162 (16), 97 (17), 41 (100).

Anal. Calcd for $C_7H_{11}Cl_2NO_3S$: C, 32.32; H, 4.26; N, 5.38. Found: C, 32.3; H, 4.3; N, 5.4.

**3-Chloro-4-(chloromethyl)-3-methyl-1-(2-pyridyl)pyrrolidin-2-one (4a); Typical Procedure**

CuCl (1.09 g, 11.1 mmol) and **3a** (28.73 g, 111 mmol) were weighed in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirrer bar. Anhyd MeCN (90 mL) and TMEDA (3.3 mL, 22.2 mmol) were then added under argon. The mixture was stirred at r.t. for 20 h and then diluted with $H_2O$ (30 mL) and $CH_2Cl_2$ (50 mL) and extracted with toluene (3 × 50 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography (silica gel, PE–$Et_2O$, 7:3) to give pyrrolidinones *cis*-**4a** (16.02 g, 56%) and *trans*-**4a** (10.24 g, 35%) both as white crystalline solids.

***cis*-3-Chloro-4-(chloromethyl)-3-methyl-1-(2-pyridyl)pyrrolidin-2-one (*cis*-4a)**

Mp 72–75 °C.

IR (KBr): 1727 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3 H, $CH_3$), 2.67 (m, 1 H, H4), 3.66 (dd, *J* = 11.4, 9.8 Hz, 1 H, H5), 3.78 (dd, *J* = 11.2, 8.7 Hz, 1 H, $CH_2Cl$), 3.90 (dd, *J* = 11.2, 5.6 Hz, 1 H, $CH_2Cl$), 4.50 (dd, *J* = 11.4, 7.2 Hz, 1 H, H5), 7.08 (dd, *J* = 7.1, 5.3 Hz, 1 H, $H5_{py}$), 7.71 (td, *J* = 7.9, 1.8 Hz, 1 H, $H4_{py}$), 8.36 (m, 2 H, $H3_{py}$, $H6_{py}$).

$^{13}$C NMR (400 MHz, $CDCl_3$): δ = 25.0 ($CH_3$), 42.0 ($CH_2Cl$), 46.6 (C4), 47.7 (C5), 70.5 (C3), 114.9 ($C3_{py}$), 120.4 ($C5_{py}$), 137.9 ($C4_{py}$), 147.7 ($C6_{py}$), 151.0 ($C2_{py}$), 170.4 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 258 (23) [M]$^+$, 223 (28), 209 (17), 187 (67), 173 (100), 159 (27), 145 (32), 121 (42), 78 (38).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.99; H, 4.67; N, 10.81. Found: C, 51.1; H, 4.7; N, 10.8.

***trans*-3-Chloro-4-(chloromethyl)-3-methyl-1-(2-pyridyl)pyrrolidin-2-one (*trans*-4a)**

Mp 90–93 °C.

IR (KBr): 1712 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.74 (s, 3 H, $CH_3$), 3.06 (m, 1 H, H4), 3.56 (dd, *J* = 11.2, 9.1 Hz, 1 H, $CH_2Cl$), 3.82 (dd, *J* = 11.2, 4.5 Hz, 1 H, $CH_2Cl$), 4.00 (dd, *J* = 11.7, 5.3 Hz, 1 H, H5), 4.38 (dd, *J* = 11.7, 7.1 Hz, 1 H, H5), 7.10 (br t, *J* = 5.9 Hz, 1 H, $H5_{py}$), 7.73 (td, *J* = 7.9, 1.3 Hz, 1 H, $H4_{py}$), 8.38 (m, 2 H, $H3_{py}$, $H6_{py}$).

$^{13}$C NMR (400 MHz, $CDCl_3$): δ = 21.5 ($CH_3$), 42.3 ($CH_2Cl$), 47.2 (C4), 47.5 (C5), 69.3 (C3), 115.0 ($C3_{py}$), 120.4 ($C5_{py}$), 137.9 ($C4_{py}$), 147.7 ($C6_{py}$), 151.0 ($C2_{py}$), 170.6 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 258 (23) [M]$^+$, 223 (28), 209 (17), 187 (67), 173 (100), 159 (27), 145 (32), 121 (42), 78 (38).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.99; H, 4.67; N, 10.81. Found: C, 51.0; H, 4.6; N, 10.7.

**3-Chloro-4-(chloromethyl)-3-methyl-1-(4-pyridyl)pyrrolidin-2-one (4b)**

Following the typical procedure **4a**, **3b** (2.60 g, 10 mmol) gave, after flash chromatography of the crude product (silica gel, PE–MeOH, 95:5), **4b** (1.73 g, 67%) as a white crystalline solid; *cis*/*trans* 80:20 ($^1$H NMR).

IR (KBr): 1726 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ (*cis*) = 1.87 (s, 3 H, $CH_3$), 2.74 (m, 1 H, H4), 3.63 (t, *J* = 9.8 Hz, 1 H, H5), 3.81 (dd, *J* = 11.3, 9.4 Hz, 1 H, $CH_2Cl$), 3.91 (dd, *J* = 11.3, 5.1 Hz, 1 H, $CH_2Cl$), 4.04 (dd, *J* = 9.8, 7.1 Hz, 1 H, H5), 7.63 (d, *J* = 5.7 Hz, 2 H, $H3_{py}$, $H5_{py}$), 8.60 (br s, 2 H, $H2_{py}$, $H6_{py}$); δ (*trans*) = 1.75 (s, 3 H, $CH_3$), 3.11 (m, 1 H, H4), 3.54 (dd, *J* = 11.3, 9.2 Hz, 1 H, $CH_2Cl$), 3.74 (dd, *J* = 10.2, 4.4 Hz, 1 H, H5), 3.83 (dd, *J* = 11.3, 5.2 Hz, 1 H, $CH_2Cl$), 4.18 (dd, *J* = 10.2, 6.9 Hz, 1 H, H5), 7.63 (d, *J* = 5.7 Hz, 2 H, $H3_{py}$, $H5_{py}$), 8.60 (br s, 2 H, $H2_{py}$, $H6_{py}$).

$^{13}$C NMR (400 MHz, $CDCl_3$): δ (*cis*) = 24.7 ($CH_3$), 41.7 ($CH_2Cl$), 46.8 (C4), 48.3 (C5), 69.3 (C3), 113.2 ($C3_{py}$,5), 145.2 ($C4_{py}$), 150.9 ($C2_{py}$,6), 170.7 (C=O); δ (*trans*) = 21.4 ($CH_3$), 42.2 ($CH_2Cl$), 47.2 (C4), 47.8 (C5), 68.0 (C3), 113.2 ($C3_{py}$,5), 145.2 ($C4_{py}$), 150.9 ($C2_{py}$, $C6_{py}$), 170.6 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 258 (100) [M]$^+$, 224 (53), 188 (53), 173 (33), 159 (40), 142 (83), 121 (70), 107 (88), 89 (78), 78 (78).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.99; H, 4.67; N, 10.81. Found: C, 51.0; H, 4.6; N, 10.8.

**3-Chloro-4-(chloromethyl)-3-methyl-1-[(2-pyridyl)methyl]pyrrolidin-2-one (4c)**

Following the typical procedure for **4a**, **3c** (2.73 g, 10 mmol) gave, after flash chromatography of the crude product (silica gel, PE–$Et_2O$, gradient from 10:0 to 5:5), **4c** (2.49 g, 91%) as a pale yellow oil; *cis*/*trans* 74:26 ($^1$H NMR).

IR (film): 1721 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ (*cis*) = 1.81 (s, 3 H, $CH_3$), 2.60 (m, 1 H, H4), 3.18 (dd, *J* = 10.2, 9.1 Hz, 1 H, H5), 3.54 (dd, *J* = 10.2, 7.1 Hz, 1 H, H5), 3.66 (dd, *J* = 11.2, 9.1 Hz, 1 H, $CH_2Cl$), 3.81 (dd, *J* = 11.2, 5.5 Hz, 1 H, $CH_2Cl$), 4.52 (d, *J* = 15.0 Hz, 1 H, $NCH_2$), 4.72 (d, *J* = 15.0 Hz, 1 H, $NCH_2$), 7.20 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1 H, $H5_{py}$), 7.22 (br d, *J* = 7.8 Hz, 1 H, $H3_{py}$), 7.65 (td, *J* = 7.8, 1.8 Hz, 1 H, $H4_{py}$), 8.53 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1 H, $H6_{py}$); δ (*trans*) = 1.66 (s, 3 H, $CH_3$), 2.94 (m, 1 H, H4), 3.29 (dd, *J* = 10.4, 4.8 Hz, 1 H, H5), 3.46 (dd, *J* = 11.0, 9.7 Hz, 1 H, $CH_2Cl$), 3.69 (dd, *J* = 10.4, 7.0 Hz, 1 H, H5), 3.72 (dd, *J* = 11.0, 4.5 Hz, 1 H, $CH_2Cl$), 4.59 (d, *J* = 15.3 Hz, 1 H, $NCH_2$), 4.64 (d, *J* = 15.3 Hz, 1 H, $NCH_2$), 7.19 (m, 1 H, $H5_{py}$), 7.24 (br d, *J* = 7.8 Hz, 1 H, $H3_{py}$), 7.65 (td, *J* = 7.8, 1.8 Hz, 1 H, $H4_{py}$), 8.52 (m, 1 H, $H6_{py}$).

$^{13}$C NMR (400 MHz, $CDCl_3$): δ (*cis*) = 25.0 ($CH_3$), 42.0 ($CH_2Cl$), 47.7 (C4), 48.4 (C5), 48.8 ($NCH_2$), 68.8 (C3), 122.1 ($C3_{py}$), 122.7 ($C5_{py}$), 137.0 ($C4_{py}$), 149.5 ($C6_{py}$), 155.5 ($C2_{py}$), 171.2 (C=O); δ (*trans*) = 21.4 ($CH_3$), 42.3 ($CH_2Cl$), 47.9 (C5), 48.5 (C4), 48.7 ($NCH_2$), 67.8 (C3), 122.2 ($C3_{py}$), 122.7 ($C5_{py}$), 137.0 ($C4_{py}$), 149.4 ($C6_{py}$), 155.4 ($C2_{py}$), 171.3 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 273 (1) [M]$^+$, 236 (22), 201 (64), 187 (100), 119 (9), 93 (99).

Anal. Calcd for $C_{12}H_{14}Cl_2N_2O$: C, 52.76; H, 5.17; N, 10.26. Found: C, 52.7; H, 5.1; N, 10.3.

**3-Chloro-4-(chloromethyl)-3-methyl-1-(pyrimidin-2-yl)pyrrolidin-2-one (4d)**

Following the typical procedure for **4a**, **3d** (2.60 g, 10 mmol) gave, after flash chromatography of the crude product (silica gel, $CH_2Cl_2$–MeOH, gradient from 100:0 to 97:3), **4d** (2.19 g, 84%) as a pale pink powder; *cis*/*trans* 65:35 ($^1$H NMR).

IR (KBr): 1735 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ (*cis*) = 1.88 (s, 3 H, $CH_3$), 2.68 (m, 1 H, H4), 3.72 (dd, *J* = 11.1, 9.9 Hz, 1 H, H5), 3.79 (dd, *J* = 11.3, 8.9 Hz, 1 H, $CH_2Cl$), 3.90 (dd, *J* = 11.3, 5.4 Hz, 1 H, $CH_2Cl$), 4.38 (dd, *J* = 11.1, 7.1 Hz, 1 H, H5), 7.09 (t, *J* = 4.8 Hz, 1 H, $H5_{py}$), 8.69 (d, *J* = 4.8 Hz, 2 H, $H4_{py}$, $H6_{py}$); δ (*trans*) = 1.76 (s, 3 H, $CH_3$), 3.04 (m, 1 H, H4), 3.53 (dd, *J* = 11.2, 9.4 Hz, 1 H, $CH_2Cl$), 3.81 (dd, *J* = 11.2, 4.4 Hz, 1 H, $CH_2Cl$), 4.01 (dd, *J* = 11.6, 4.6 Hz, 1 H, H5), 4.37 (dd, *J* = 11.6, 6.7 Hz, 1 H, H5), 7.10 (t, *J* = 4.8 Hz, 1 H, $H5_{py}$), 8.70 (d, *J* = 4.8 Hz, 2 H, $H4_{py}$, $H6_{py}$).

$^{13}$C NMR (400 MHz, $CDCl_3$): δ (*cis*) = 24.7 ($CH_3$), 41.8 ($CH_2Cl$), 46.5 (C4), 48.4 (C5), 70.0 (C3), 117.3 ($C5_{py}$), 157.2 ($C2_{py}$) 158.2 ($C4_{py}$, $C6_{py}$), 169.3 (C=O); δ (*trans*) = 21.4 ($CH_3$), 42.2 ($CH_2Cl$), 47.0 (C4), 48.0 (C5), 68.8 (C3), 117.3 ($C5_{py}$), 157.2 ($C2_{py}$) 158.2 ($C4_{py}$, $C6_{py}$), 169.5 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 260 (5) [M + 1]$^+$, 259 (39) [M]$^+$, 224 (87), 210 (30), 188 (54), 174 (100), 160 (19), 122 (67).

Anal. Calcd for $C_{10}H_{11}Cl_2N_3O$: C, 46.17; H, 4.26; N, 16.15. Found: C, 46.1; H, 4.2; N, 16.1.

**3-Chloro-4-(chloromethyl)-1-mesyl-3-methylpyrrolidin-2-one (4e)**

CuCl (0.10 g, 1 mmol) was weighed in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirrer bar. Toluene (8 mL) and PMDETA (0.208 mL, 1 mmol) were then added under argon. The mixture was stirred at r.t. for ~0.5 h, after which **3e** (5.20 g, 20 mmol), solubilized in toluene (12 mL), was introduced. The stirring was continued for a further 18 h. The mixture was then diluted with $H_2O$ (30 mL) and $CH_2Cl_2$ (50 mL) and extracted with toluene (3 × 50 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography (silica gel, $CH_2Cl_2$–$Et_2O$, 9:1) to give **4e** (4.84 g, 93%) as a pale yellow powder; inseparable *cis*/*trans*-diastereomers 87:13 ($^1$H NMR).

IR (KBr): 1742 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ (*cis*) = 1.77 (s, 3 H, $CH_3$), 2.69 (m, 1 H, H4), 3.22 (s, 3 H, $SCH_3$), 3.43 (dd, *J* = 10.1, 9.7 Hz, 1 H, H5), 3.66 (dd, *J* = 11.4, 8.5 Hz, 1 H, $CH_2Cl$), 3.80 (dd, *J* = 11.4, 5.8 Hz, 1 H, $CH_2Cl$), 4.07 (dd, *J* = 10.1, 7.1 Hz, 1 H, H5); δ (*trans*) = 1.70 (s, 3 H, $CH_3$), 2.98 (m, 1 H, H4), 3.23 (s, 3 H, $SCH_3$), 3.57 (dd, *J* = 11.7, 7.2 Hz, 1 H, $CH_2Cl$), 3.74 (dd, *J* = 11.7, 4.2 Hz, 1 H, $CH_2Cl$), 3.75 (dd, *J* = 10.6, 3.5 Hz, 1 H, H5), 4.10 (dd, *J* = 10.6, 7.8 Hz, 1 H, H5).

$^{13}$C NMR (400 MHz, $CDCl_3$): δ (*cis*) = 23.7 ($CH_3$), 39.8 ($SCH_3$), 40.8 ($CH_2Cl$), 46.6 (C4), 47.0 (C5), 68.9 (C3), 169.9 (C=O); δ (*trans*) = 20.5 ($CH_3$), 40.2 ($SCH_3$), 42.3 ($CH_2Cl$), 46.5 (C5), 46.7 (C4), 67.5 (C3), 170.0 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 260 (2) [M + 1]$^+$, 259 (16) [M]$^+$, 180 (5), 38 (37),102 (34), 89 (100), 56 (52).

Anal. Calcd for $C_7H_{11}Cl_2NO_3S$: C, 32.32; H, 4.26; N, 5.38. Found: C, 32.4; H, 4.2; N, 5.4.

**5-Methoxy-3,4-dimethyl-1-(2-pyridyl)-1,5-dihydro-2*H*-pyrrol-2-one (5a); Typical Procedure**

To a Schlenk tube, fitted with a pierceable septum blocked by a screw cap, was added $Et_2O$–MeOH (1:1, 15 mL) and *cis*-**4a** (2.59 g, 10 mmol). The soln was thermostated at 25 °C. In a second Schlenk tube, Na (0.69 g, 30 mmol) was carefully dissolved in MeOH (15 mL) and, when the effervescence ceased, the alkaline soln was thermostated at 25 °C, after which it was poured into the first Schlenk tube and the mixture was stirred for 22 h. Then it was diluted with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were collected and concentrated. The crude product was subjected to flash chromatography (silica gel, PE–

$Et_2O$, gradient 10:0 to 5:5) to afford **5a** (2.1 g, 96%) as a pale orange oil.

IR (film): 1712 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 3 H, C3-$CH_3$), 1.99 (s, 3 H, C4-$CH_3$), 3.09 (s, 3 H, $OCH_3$), 6.22 (s, 1 H, H5), 7.00 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1 H, $H5_{py}$), 7.68 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1 H, $H4_{py}$), 8.12 (dt, *J* = 8.4, 1.0 Hz, 1 H, $H3_{py}$), 8.38 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1 H, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.2 (C3-*C*$H_3$), 11.5 (C4-*C*$H_3$), 50.7 ($OCH_3$), 87.4 (C5), 114.8 ($C3_{py}$), 119.3 ($C5_{py}$), 130.7 (C3), 137.7 ($C4_{py}$), 147.7 (C4), 147.9 ($C6_{py}$), 150.3 ($C2_{py}$), 170.1 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 218 (5) $[M]^+$, 203 (60), 188 (100), 175 (10), 159 (42), 78 (35).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.0; H, 6.4; N, 12.9.

**3-Methoxy-3-methyl-4-methylene-1-(2-pyridyl)pyrrolidin-2-one (9a)**

Following the typical procedure for *cis*-**4a**, *trans*-**4a** (1.05 g, 4 mmol) gave **9a** (0.523 g, 60%) as a pale orange oil. **5a** (0.096 g, 11%) was also recovered.

IR (film): 1720 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 3 H, $CH_3$), 3.21 (s, 3 H, $OCH_3$), 4.57 (dt, *J* = 15.5, 2.4 Hz, 1 H, H5), 4.66 (dt, *J* = 15.5, 2.1 Hz, 1 H, H5), 5.36 (t, *J* = 2.4 Hz, 1 H, =$CH_2$), 5.41 (t, *J* = 2.1 Hz, 1 H, =$CH_2$), 7.05 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1 H, $H5_{py}$), 7.69 (ddd, *J* = 8.5, 7.3, 1.9 Hz, 1 H, $H4_{py}$), 8.34 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1 H, $H6_{py}$), 8.51 (dt, *J* = 8.2, 0.9 Hz, 1 H, $H3_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 24.8 ($CH_3$), 49.1 (C5), 52.4 ($OCH_3$), 81.4 (C3), 110.8 (=$CH_2$), 115.1 ($C3_{py}$), 120.0 ($C5_{py}$), 137.7 ($C4_{py}$), 140.4 (C4), 147.5 ($C6_{py}$), 150.9 ($C2_{py}$), 173.1 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 219 (2) $[M + 1]^+$, 218 (7) $[M]^+$, 203 (100), 188 (27), 175 (45), 159 (10), 133 (18), 43 (70).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.1; H, 6.5; N, 12.8.

**5-Methoxy-3,4-dimethyl-1-(4-pyridyl)-1,5-dihydro-2*H*-pyrrol-2-one (5b) and 3-Methoxy-3-methyl-4-methylene-1-(4-pyridyl)pyrrolidin-2-one (9b)**

Following the typical procedure for *cis*-**4a**, **4b** (*cis*/*trans* 80:20, 1.30 g, 5 mmol), reaction time 20 h, gave, after flash chromatography of the crude product (silica gel, $Et_2O$–MeOH, 9:1), **5b** (0.82 g, 75%) as white crystals and **9b** (0.11 g, 10%) as light yellow fine crystals.

**5-Methoxy-3,4-dimethyl-1-(4-pyridyl)-1,5-dihydro-2*H*-pyrrol-2-one (5b)**

Mp 92–96 °C.

IR (KBr): 1718 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3 H, C3-$CH_3$), 1.97 (s, 3 H, C4-$CH_3$), 2.90 (s, 3 H, $OCH_3$), 5.68 (s, 1 H, H5), 7.87 (br s, 2 H, $H3_{py}$, $H5_{py}$), 8.70 (v br s, 2 H, $H2_{py}$, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.4 (C3-*C*$H_3$), 11.4 (C4-*C*$H_3$), 48.2 ($OCH_3$), 87.9 (C5), 113.3 ($C3_{py}$, $C5_{py}$), 132.4 (C3), 144.2 ($C4_{py}$), 146.9 (C4), 150.4 ($C2_{py}$, $C6_{py}$), 170.4 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 219 (10) $[M + 1]^+$, 218 (60) $[M]^+$, 203 (27), 187 (100), 159 (20), 105 (15), 78 (23).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.0; H, 6.4; N, 12.8.

**3-Methoxy-3-methyl-4-methylene-1-(4-pyridyl)pyrrolidin-2-one (9b)**

Mp 125–128 °C.

IR (KBr): 1708 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, $CH_3$), 3.21 (s, 3 H, $OCH_3$), 4.32–4.42 (m, 2 H, $CH_2$), 5.44 (t, *J* = 2.0 Hz, 1 H, =$CH_2$), 5.46 (t, *J* = 2.0 Hz, 1 H, =$CH_2$), 7.75 (br s, 2 H, $H3_{py}$, $H5_{py}$), 8.70 (v br s, 2 H, $H2_{py}$, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 24.4 ($CH_3$), 49.3 (C5), 52.5 ($OCH_3$), 80.8 (C3), 111.8 ( =$CH_2$), 113.3 ($C3_{py}$, $C5_{py}$), 139.4 (C4), 144.2 ($C4_{py}$), 150.4 ($C2_{py}$, $C6_{py}$), 173.7 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 219 (1) $[M + 1]^+$, 218 (4) $[M]^+$, 203 (57), 188 (100), 175 (11), 159 (44), 78 (50).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.0; H, 6.5; N, 12.9.

**5-Methoxy-3,4-dimethyl-1-[(2-pyridyl)methyl)]pyrrolidin-2-one (5c) and 3-Methoxy-3-methyl-4-methylene-1-[(2-pyridyl)methyl]pyrrolidin-2-one (9c)**

Following the typical procedure for *cis*-**4a**, **4c** (*cis*/*trans*, 74:26, 2.74 g, 10 mmol) gave, after flash chromatography of the crude product (silica gel, $Et_2O$–MeOH, gradient from 100:0 to 99:1), **5c** (1.62 g, 70%) as a yellow oil and **9c** (0.35 g, 15%) as a yellow oil.

**5-Methoxy-3,4-dimethyl-1-[(2-pyridyl)methyl)]pyrrolidin-2-one (5c)**

IR (film): 1706 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3 H, C3-$CH_3$), 1.86 (s, 3 H, C4-$CH_3$), 2.95 (s, 3 H, $OCH_3$), 4.30 (d, *J* = 15.6 Hz, 1 H, $NCH_2$), 4.95 (d, *J* = 15.6 Hz, 1 H, $NCH_2$), 5.16 (s, 1 H, H5), 7.12 (ddd, *J* = 7.6, 4.8, 0.9 Hz, 1 H, $H5_{py}$), 7.22 (dt, *J* = 7.8, 0.9 Hz, 1 H, $H3_{py}$), 7.59 (td, *J* = 7.8, 1.8 Hz, 1 H, $H4_{py}$), 8.50 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.4 (C3-*C*$H_3$), 11.3 (C4-*C*$H_3$), 44.9 ($NCH_2$), 49.5 ($OCH_3$), 88.5 (C5), 122.2 ($C5_{py}$), 122.2 ($C3_{py}$), 131.5 (C3), 136.6 ($C4_{py}$), 146.2 (C4), 149.3 ($C6_{py}$), 157.1 ($C2_{py}$), 171.2 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 231 (1) $[M - 1]^+$, 218 (17), 217 (100), 201 (14), 93 (25), 92 (45), 65 (10).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.2; H, 7.0; N, 12.0.

**3-Methoxy-3-methyl-4-methylene-1-[(2-pyridyl)methyl]pyrrolidin-2-one (9c)**

IR (film): 1702 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, $CH_3$), 3.12 (s, 3 H, $OCH_3$), 3.91 (t, *J* = 2.2 Hz, 2 H, H5), 4.60 (d, *J* = 15.1 Hz, 1 H, $NCH_2$-py), 4.64 (d, *J* = 15.1 Hz, 1 H, $NCH_2$-py), 5.22 (t, *J* = 2.2 Hz, 1 H, =$CH_2$), 5.29 (t, *J* = 2.2 Hz, 1 H, =$CH_2$), 7.14 (ddd, *J* = 7.6, 4.9, 1.0 Hz, 1 H, $H5_{py}$), 7.18 (dt, *J* = 7.6, 1.0 Hz, 1 H, $H3_{py}$), 7.61 (td, *J* = 7.6, 1.8 Hz, 1 H, $H4_{py}$), 8.47 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1 H, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 24.5 ($CH_3$), 48.2 ($NCH_2$), 49.4 (C5), 52.2 ($OCH_3$), 79.7 (C3), 110.6 (=$CH_2$), 122.0 ($C3_{py}$), 122.5 ($C5_{py}$), 136.9 ($C4_{py}$), 141.5 (C4), 149.3 ($C6_{py}$), 155.7 ($C2_{py}$), 173.1 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 232 (1) $[M]^+$, 217 (7), 200 (26), 93 (100).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.3; H, 7.0; N, 12.1.

**5-Methoxy-3,4-dimethyl-1-(pyrimidin-2-yl)pyrrolidin-2-one (5d) and 3-Methoxy-3-methyl-4-methylene-1-(pyrimidin-2-yl)pyrrolidin-2-one (9d)**

Following the typical procedure for *cis*-**4a**, but working under argon (in this way the workup was easier), **4d** (*cis*/*trans* 65:35, 1.04 g, 4 mmol) gave, after flash chromatography of the crude product (silica

gel, $Et_2O$–MeOH, gradient from 100:0 to 99:1), **5d** (0.587 g, 67%) as a white solid and **9d** (0.061 g, 7%) as yellow oil.

**5-Methoxy-3,4-dimethyl-1-(pyrimidin-2-yl)pyrrolidin-2-one (5d)**

Mp 77–79 °C.

IR (KBr): 1714 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3 H, C3-$CH_3$), 1.98 (s, 3 H, C4-$CH_3$), 3.08 (s, 3 H, $OCH_3$), 5.68 (br s, 1 H, H5), 7.02 (t, *J* = 4.8 Hz, 1 H, $H5_{py}$), 8.68 (d, *J* = 4.8 Hz, 2 H, $H4_{py}$, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.3 (C3-*C*$H_3$), 11.5 (C4-*C*$H_3$), 50.2 ($OCH_3$), 87.9 (C5), 116.5 ($C5_{py}$), 131.4 (C3), 147.6 (C4), 156.2 ($C2_{py}$), 158.2 ($C4_{py}$, $C6_{py}$), 168.8 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 219 (1) $[M]^+$, 204 (26), 189 (100), 188 (51), 160 (40), 79 (23).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.2; H, 6.0; N, 19.2.

**3-Methoxy-3-methyl-4-methylene-1-(pyrimidin-2-yl)pyrrolidin-2-one (9d)**

IR (film): 1722 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 3 H, $CH_3$), 3.26 (s, 3 H, $OCH_3$), 4.53 (dt, *J* = 15.3, 2.4 Hz, 1 H, H5), 4.66 (dt, *J* = 15.3, 2.0 Hz, 1 H, H5), 5.39 (t, *J* = 2.4 Hz, 1 H, =$CH_2$), 5.41 (t, *J* = 2.0 Hz, 1 H, =$CH_2$), 7.09 (t, *J* = 4.8 Hz, 1 H, $H5_{py}$), 8.70 (d, *J* = 4.8 Hz, 2 H, $H4_{py}$, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 25.0 ($CH_3$), 49.8 (C5), 52.5 ($OCH_3$), 81.4 (C3), 110.8 ( =$CH_2$), 117.0 ($C5_{py}$), 140.2 (C4), 157.1 ($C2_{py}$), 158.1 ($C4_{py}$, $C6_{py}$), 172.5 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 219 (2) $[M]^+$, 204 (38), 189 (4), 176 (16), 134 (7), 98 (14), 97 (32), 43 (100).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.2; H, 6.0; N, 19.1.

**1-Mesyl-5-methoxy-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (5e)**

Following the typical procedure for *cis*-**4a**, but replacing the $Et_2O$ with toluene and thermostating the mixture at –10 °C, **4e** (*cis*/*trans* 87:13, 1.04 g, 4 mmol) gave, after flash chromatography of the crude product (silica gel, PE–$Et_2O$, gradient from 1:1 to 2:8), **5e** (0.66 g, 76%) as a colorless thick oil.

IR (KBr): 1733 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, C3-$CH_3$), 1.97 (s, 3 H, C4-$CH_3$), 3.29 (s, 3 H, $SCH_3$), 3.38 (s, 3 H, $OCH_3$), 5.68 (br s, 1 H, H5).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.1 (C3-*C*$H_3$), 12.0 (C4-*C*$H_3$), 41.9 ($SCH_3$), 54.0 ($OCH_3$), 89.9 (C5), 129.7 (C3), 151.4 (C4), 169.3 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 219 (2) $[M]^+$, 189 (35), 188 (72), 110 (100).

Anal. Calcd for $C_8H_{13}NO_4S$ C, 43.82; H, 5.98; N, 6.39. Found: C, 43.9; H, 6.0; N, 6.4.

**5-Hydroxy-3,4-dimethyl-1-(2-pyridyl)-1,5-dihydro-2*H*-pyrrol-2-one (7a); Typical Procedure**

To a Schlenk tube was added **5a** (2.18 g, 10 mmol), 2 M $H_2SO_4$ (5 mL), and $H_2O$ (5 mL). The mixture, under vigorous stirring, was heated to 140 °C for 3 h, after which time it was neutralized with 1 M NaOH and extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were concentrated under vacuum. Flash chromatography of the crude product (silica gel, $CH_2Cl_2$–MeOH, gradient from 100:0 to 95:5) gave **7a** (1.73 g, 83%); crystallization of the crude product ($Et_2O$–PE) provided comparable results; white crystals; mp 92–94 °C.

IR (KBr): 3423 (OH), 1698 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, C3-$CH_3$), 2.02 (s, 3 H, C4-$CH_3$), 5.67 (br s, 1 H, OH), 5.94 (s, 1 H, H5), 6.95 (dd, *J* = 7.3, 5.0 Hz, 1 H, $H5_{py}$), 7.66 (td, *J* = 7.9, 1.9 Hz, 1 H, $H4_{py}$), 8.21 (dd, *J* = 5.0, 1.9 Hz, 1 H, $H6_{py}$), 8.32 (d, *J* = 8.5 Hz, 1 H, $H3_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.3 (C3-*C*$H_3$), 11.5 (C4-*C*$H_3$), 83.6 (C5), 113.1 ($C3_{py}$), 118.7 ($C5_{py}$), 130.1 (C3), 138.6 ($C4_{py}$), 147.1 (C4), 149.3 ($C6_{py}$), 151.6 ($C2_{py}$), 169.7 (C=O).

MS (EI): *m*/*z* (%) = 204 (25) $[M]^+$, 203 (40), 189 (100), 175 (20), 161 (22), 121 (30), 78 (40).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.7; H, 6.0; N, 13.8.

**5-Hydroxy-3,4-dimethyl-1-[(2-pyridyl)methyl]-1,5-dihydro-2*H*-pyrrol-2-one (7c)**

Following the typical procedure for **7a**, but thermostating the mixture at 100 °C, **5c** (1.16 g, 5 mol) gave, after flash chromatography of the crude product (silica gel, PE–$Et_2O$, gradient from 2:8 to 0:100, followed by $Et_2O$–MeOH, from 100:0 to 97.5:2.5), **7c** (0.83 g, 76%) as a pale yellow oil.

IR (film): 3423 (OH), 1685 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, C3-$CH_3$), 1.98 (s, 3 H, C4-$CH_3$), 4.55 (d, *J* = 15.9 Hz, 1 H, $NCH_2$), 4.95 (d, *J* = 15.9 Hz, 1 H, $NCH_2$), 5.22 (s, 1 H, H5), 7.08 (br s, 1 H, OH), 7.20 (dd, *J* = 7.6, 4.8 Hz, 1 H, $H5_{py}$), 7.37 (dd, *J* = 7.9, 0.9 Hz, 1 H, $H3_{py}$), 7.66 (td, *J* = 7.8, 1.9 Hz, 1 H, $H4_{py}$), 8.43 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1 H, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.4 (C3-*C*$H_3$), 11.4 (C4-*C*$H_3$), 46.4 ($NCH_2$), 85.1 (C5), 122.6 ($C5_{py}$), 122.7 ($C3_{py}$), 128.1 (C3), 137.7 ($C4_{py}$), 148.4 ($C6_{py}$), 150.2 (C4), 157.0 ($C2_{py}$), 171.4 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 218 (7) $[M]^+$, 217 (20), 203 (45), 107 (15), 93 (100), 92 (48).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.1; H, 6.4; N, 12.8.

**5-Hydroxy-3,4-dimethyl-1-(pyrimidin-2-yl)-1,5-dihydro-2*H*-pyrrol-2-one (7d)**

Following the typical procedure for **7a**, but thermostating the mixture at 120 °C, **5d** (1.10 g, 5 mmol) gave, after flash chromatography of the crude product (silica gel, $CH_2Cl_2$–MeOH, gradient from 100:0 to 95:5), **7d** (0.54 g, 52%) as a pale brownish solid; mp 150–152 °C.

IR (KBr): 3218 (OH), 1719 $cm^{-1}$ (C=O).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3 H, C3-$CH_3$), 2.06 (s, 3 H, C4-$CH_3$), 5.18 (br s, 1 H, OH), 5.93 (s, 1 H, H5), 7.26 (t, *J* = 4.8 Hz, 1 H, $H5_{py}$), 8.65 (d, *J* = 4.8 Hz, 2 H, $H4_{py}$, $H6_{py}$).

$^{13}C$ NMR (400 MHz, $CDCl_3$): δ = 8.4 (C3-*C*$H_3$), 11.6 (C4-*C*$H_3$), 83.6 (C5), 116.0 ($C5_{py}$), 130.7 (C3), 149.3 (C4), 156.9 ($C2_{py}$), 158.3 ($C4_{py}$, $C6_{py}$), 168.4 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 205 (33) $[M]^+$, 204 (28), 190 (100), 176 (13), 162 (30), 122 (42), 79 (22).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.6; H, 5.4; N, 20.4.

***N*-(2-Pyridyl)-3,4-dimethylmaleimide (6a)**

To a 250-mL round-bottom flask, **7a** (2.04 g, 10 mmol), $MnO_2$ (20 g), and $CH_2Cl_2$ (100 mL) were added in sequence. The mixture was vigorously stirred at r.t. (GC monitoring). After 20 h the mixture was filtered and the filtrate evaporated under reduced pressure. In

this way maleimide **6a** (1.80 g, 89%) was obtained as white crystals; mp 116–118 °C.[6]

**Pyrocinchonic Anhydride (8)**

To a Schlenk tube was added **6a** (2.02 g, 10 mmol), 2 M $H_2SO_4$ (5 mL), and $H_2O$ (5 mL). The mixture, under vigorous stirring, was heated to 110 °C for 3 h. After cooling, it was extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were dried ($Na_2SO_4$). Evaporation of the solvent gave **8** (1.17 g, 93%) as a white powder; mp 92–94 °C.[6]

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