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A new method for the synthesis of plurisubstituted pyrroles

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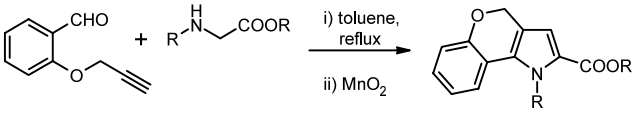
Abstract—A versatile method for the synthesis of pyrroles is described using an intramolecular [3+2] cycloaddition reaction. This method allows the expedient preparation of 'plurisubstituted' compounds in which functionality is incorporated by choice, using appropriate readily available starting materials. Polycyclic pyrrole derivatives as well as 2-aryl monocyclic analogues are described. Several families of compounds are synthesized by sequential transformations. The method is designed to allow the creation of libraries with increased diversity of functionality by combinatorial or parallel synthesis.

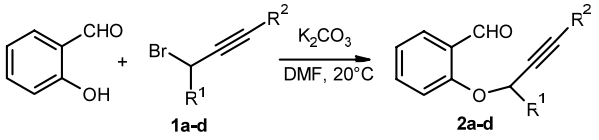
Pyrroles are important substructures of pharmaceutically important compounds and also of numerous natural products.[1] The synthesis of pyrroles containing various substituents with specifically required regiochemistry is a subject of continued research.[2] In this paper we describe a general synthesis for the preparation of pyrroles by use of the versatile [3+2] cycloaddition reaction.[3] Our method is complementary to existing procedures and overall yields are satisfactory. Moreover the synthetic approach is particularly convenient in that it was designed to accommodate parallel synthetic or combinatorial preparations of diversified libraries of pyrroles amenable to pharmaceutical research and for new lead generation or lead optimization. The approach we employed makes use of low cost, easily available starting materials and mild experimental conditions, allowing for a large variety of substituents. In our approach, *O*-propargylic salicylaldehydes[4] are treated with *N*-alkylglycinate derivatives in a neutral solvent such as toluene at reflux, then the reaction mixture is treated with manganese dioxide at room temperature to provide directly the required pyrroles (Scheme 1).

The initial, expected product which is a pyrroline is not isolated by this procedure, although it is possible to arrest the reaction at that stage. A variety of substituted amino esters were used, either commercial or readily available, alongside a number of different propargylic derivatives of salicylic aldehyde containing varying degrees of substitution and functionality. Salicylaldehyde is readily alkylated using a propargylic halide in DMF in the presence of potassium carbonate. Indeed, a number of *O*-propargylic salicylaldehydes were prepared in yields generally almost quantitative (Table 1). The required compounds were extracted from the reaction medium in excellent purity and required no further purification. The choice of the propargylic reagents was such that the resulting substituted salicylaldehydes had diverse degrees of functionality in order to explore the relative reactivity in the subsequent cycloaddition reaction.



Scheme 1. Overall one-pot regioselective synthesis of pyrroles.

Table 1. Preparation of *O*-propargylic salicylaldehydes



Entry	Halide	Product	Yield (%)
1	**1a** 3-bromopropyne	**2a**	94
2	**1b** 3-bromo-1-phenylpropyne	**2b**	94
3	**1c** 4-bromobut-2-yne	**2c**	79
4	**1d** 3-bromobutyne	**2d**	95

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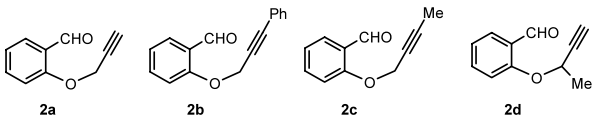
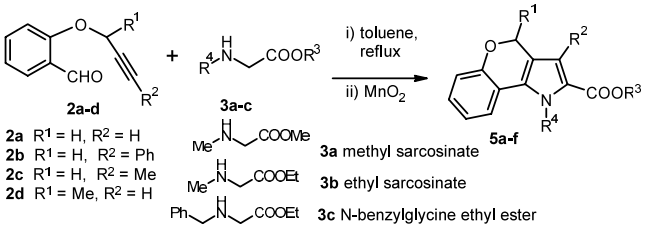
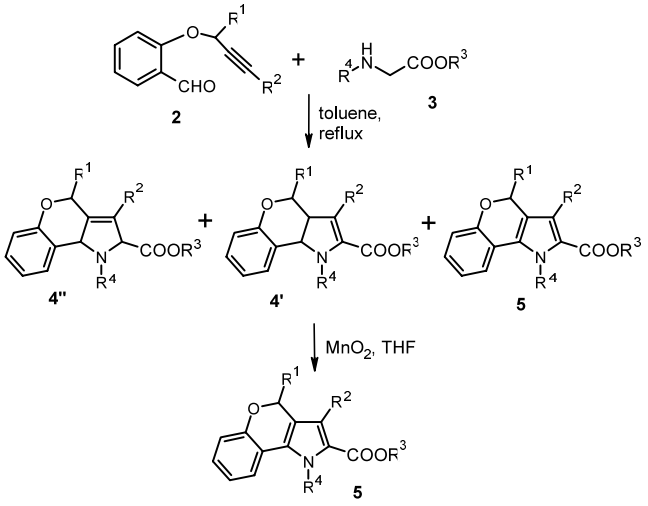


Figure 1. *O*-Propargylic salicylaldehydes **2a–d**.

Table 2. Synthesis of pyrroles from *O*-propargylic salicylaldehydes



Entry	Aldehyde/ aminoester	Time (h)	Product	Yield (%)
1	**2a**/**3a**	1.5	**5a**	65
2	**2a**/**3b**	1.5	**5b**	69
3	**2b**/**3a**	2.5	**5c**	71
4	**2b**/**3c**	4.5	**5d**	96
5	**2c**/**3a**	5	**5e**	50
6	**2c**/**3c**	8	**5f**	68
7	**2d**/**3a**	2	**5g**	54
8	**2d**/**3c**	4.5	**5h**	60



Scheme 2. Cycloaddition reactions of *O*-propargylic salicylaldehydes and *N*-substituted glycinate esters, followed by oxidation.

Starting secondary halide 3-bromobutyne **1d** (entry 4) and primary halide 4-bromobut-2-yne **1c** (entry 3) were prepared from the corresponding propargylic alcohol by treatment with phosphorus tribromide (PBr_3), in 67% and 89% yields, respectively (Fig. 1).

Compounds **2a–d** were then treated with 2 equivalents of *N*-alkylglycinate derivatives **3a–d** in anhydrous toluene at reflux for varying times (Table 2). The reactions were followed by thin layer chromatography (TLC) as well as gas liquid chromatography (GLC). The intermediate Δ^3-pyrrolines **4a–g** were indeed formed and were monitored by GLC during the course of the reaction (Scheme 2). In some cases the Δ^2-isomer and the corresponding pyrrole were also observed. In order to characterize all products formed, in some of the examples, the three components were isolated by flash column chromatography on silica gel and fully characterized. However, this isolation step was not necessary and, in fact, the crude reaction mixture was subsequently simply cooled to room temperature and treated directly with manganese dioxide (MnO_2).[5] The overall yields of tricyclic pyrroles were good, ranging from 50 to 96% (Table 2). Such yields compare very favourably with other methods.[1]

Table 2 illustrates the reactants, the times of reaction and the overall yields of pyrroles, starting from *O*-propargylic salicylaldehydes (see Fig. 2 for structures).

As a further investigation of the extent of the cycloaddition reaction on *O*-propargylic salicylaldehydes with amino acid derivatives, the reaction was investigated using amino acids instead of amino esters. Thus, sarcosine **6a** and *N*-methyl-L-alanine **6b** were employed. We were hoping to observe in situ aromatizing decarboxylation, which would lead directly to pyrroles, analogues to the examples above. However the products obtained were the Δ^3-pyrroline derivatives **4i–m**, which had not aromatized during the course of the reaction (Table 3, below). Attempts to oxidize pyrrolines **4i–m** as described above were fruitless, probably due to the lack of activating carboxylic substituents. Decarboxylation probably occurs during the reaction to provide the azomethine ylide by a mechanism different to that with the ester analogues.[4] Nethertheless the oxidation of the pyrrolines **4i–m** was performed using Pd/C in refluxing ethyl acetate[3] giving pyrroles **7i–m** in moderate to good yields (Table 3, Fig. 3).

The chemistry of our pyrrole synthesis was further extended by an interesting sequence of modifications, to furnish monocyclic pyrroles **9** (Scheme 3). Thus, tri-

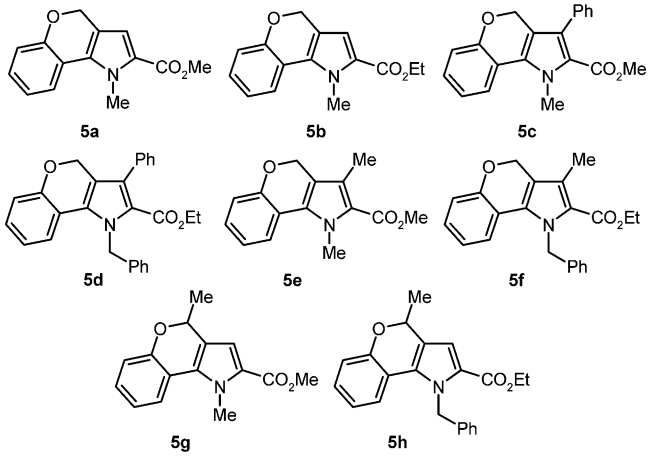
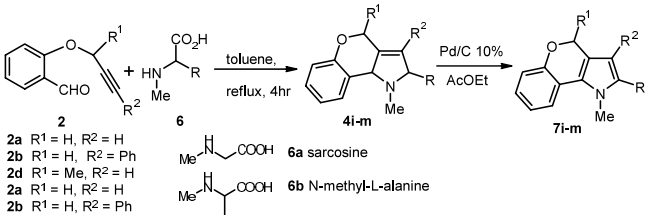


Figure 2. Pyrroles synthesized by cycloaddition.

Table 3. Cycloaddition in presence of sarcosine and *N*-methyl-L-alanine and aromatization giving the corresponding pyrroles



Entry	Aldehyde/amino acid	Pyrrolines/yield (%)	Pyrroles/yield (%)
1	**2a**/**6a**	**4i**/87	**7i**/57
2	**2b**/**6a**	**4j**/72	**7j**/54
3	**2d**/**6a**	**4k**/69	**7k**/56
4	**2a**/**6b**	**4l**/64	**7l**/72
5	**2b**/**6b**	**4m**/68	**7m**/57

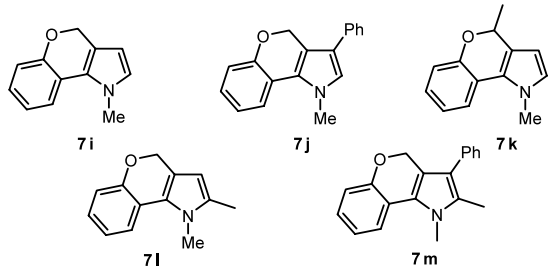
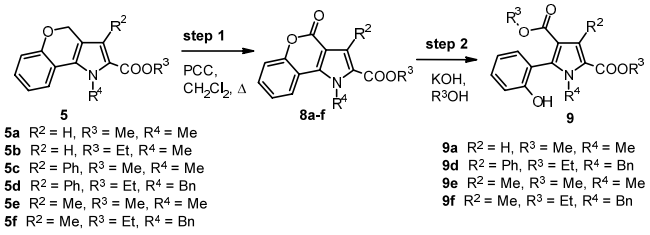


Figure 3. Pyrroles synthesized by cycloaddition of amino acids followed by oxidation with Pd/C.



Scheme 3. Modification and 'functionalising simplification' of tricyclic pyrroles.

cyclic pyrroles **5a**–**f** were first transformed to their corresponding coumarin analogues by oxidation using pyridinium chlorochromate (PCC) (Table 4).[6] These

Table 4. PCC oxidation to coumarin compounds (step 1)

Entry	Pyrrole	Time (h)	Product	Yield (%)
1	**5a**	22	**8a**	65
2	**5b**	20	**8b**	69
3	**5c**	17	**8c**	71
4	**5d**	20	**8d**	96
5	**5e**	24	**8e**	50
6	**5f**	16.5	**8f**	68

new lactonic compounds are now susceptible to attack and ring-opening by nucleophiles leading to 'functionalising simplification'. We have currently only exploited this possibility using potassium hydroxide[7] in alcoholic solvents, but further work is underway to employ other heteroatomic or carbon-based nucleophiles.

Following nucleophilic attack and ring-opening by alkoxide anion, the monocyclic pyrroles below were obtained (Table 5 and Figs. 4 and 5).

Typical experimental procedure for cycloaddition and typical spectral data: To a solution of 6.25 mmol of *O*-propargylic salicylaldehyde **2** in toluene or xylene were added 12.5 mmol of amino ester **3**. The resulting solution was heated to reflux, preferably using a Dean-

Table 5. Nucleophilic ring-opening of coumarin compounds (step 2)

Entry	Coumarin	Time (h)	Product	Yield (%)
1	**8a**	2	**9a**	62
2	**8d**	2	**9d**	54
3	**8e**	2	**9e**	62
4	**8f**	2	**9f**	68

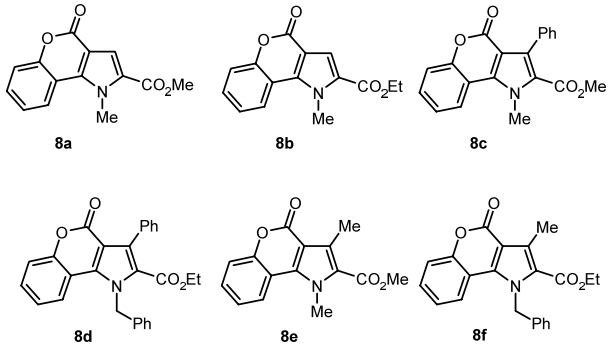


Figure 4. Coumarin compounds obtained by oxidation with PCC.

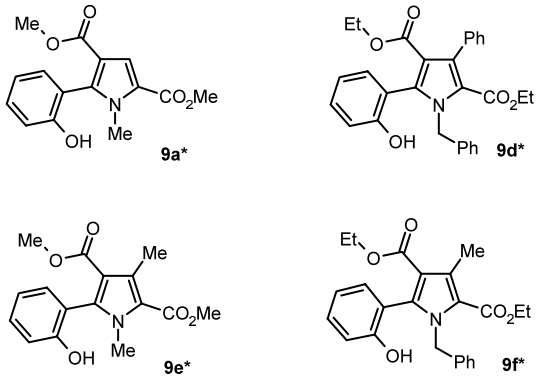


Figure 5. Monocyclic pyrroles. * The letters in the numbering are maintained so as to coincide with substituent patterns in all series.

Stark apparatus, and the reaction was monitored by thin layer chromatography (TLC) or gas chromatography (GC) until total consumption of the aldehyde.

After cooling to room temperature, an excess (156 mmol) of activated manganese dioxide was added and the mixture was stirred for 20 h. The mixture is then filtered on celite to remove the oxidant and the resulting solution was evaporated to dryness. The crude mixture was then purified by column chromatography on silica gel to provide pyrrole **5**. Example **5d**: NMR ^{1}H ($CDCl_3$): 7.50–7.10 (m, 12H); 6.70 (dd, 1H, *J* 1.2 and 8.1 Hz); 6.82 (td, 1H, *J* 1.2 and 7.6 Hz); 5.90 (s, 2H); 5.04 (s, 2H); 3.96 (q, 2H, *J* 7.1 Hz); 0.86 (t, 3H, *J* 7.1 Hz).

In conclusion, this paper describes the use of a versatile [3+2] cycloaddition reaction for the synthesis of a variety of pyrroles. Regiochemically-controlled formation of tricyclic pyrroles proceeded in high yields. These compounds were then sequentially transformed into coumarins, then to monocyclic 2-arylpyrroles by nucleophilic ring-opening. The reaction was explored using various substitutions in order to study the consequences of increased steric or activating effects, and provides diversity of molecular structures. The method is complementary to other syntheses of pyrroles with overall yields that compare favourably. Moreover, this approach allows the creation of diversity by simple choice of readily-available starting materials.

Acknowledgements

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