An organocatalytic route to 2-heteroarylmethylene decorated N-arylpyrroles

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Abstract

A concise and regioselective preparation of 2-heteroarylmethylene decorated N-arylpyrroles is described through a metal-free Mannich/Wittig/hydroamination sequence followed by isomerization of the N-arylpyrrolidine adducts. Furthermore, the C–H regioselective oxidation of these substrates is demonstrated, extending the molecular diversity and versatility of these scaffolds.

Introduction

Due to their presence in some natural products [1] and pharmaceuticals [2-4], the preparation of N-arylpyrroles is an active field of investigation [5]. Depending on their substituents, N-arylpyrroles could also be electron donor/acceptor molecules with a dual fluorescence ability suggesting attractive optoelectronic applications [6,7]. If the N-arylation of pyrroles is possible by Ullmann-type condensation [8-10], the regioselective functionalization of pyrroles is less trivial when asymmetric substrates are targeted. An indirect solution, based on the construction of substituted pyrrolidines that oxidize into elaborated pyrroles, can be employed fruitfully [11,12]. We recently described a one-pot organo-catalyzed synthesis of N-heteroarylmethylene pyrrolidines 4 [13] from readily available aldehydes 1 and imine 2 by a sequence of Mannich coupling [14-24], Wittig olefination with phosphonium 3, and proton-mediated hydroamination (Scheme 1). In the course of our investigations, we observed that pyrrolidine 4 could be converted into the corresponding pyrrole 5 by a simple isomerization, avoiding the use of oxidants. We describe herein the details of these observations and the scope of this methodology for the concise preparation of substituted 2-heteroaromatic decorated N-arylpyrroles.
Results and Discussion

We first observed the unexpected formation of pyrrole 5a in 50% yield after treatment of pyrrolidine 4a with KCN in DMF (Scheme 2, conditions a). Although obtained in modest yield, we found the original and unique structure of the substituted pyrrole 5a interesting, especially with the 2-pyridylmethylene decoration. In an attempt to rationalize the formation of 5a, we hypothesized that KCN acted as a nucleophilic and weak base since the level of oxidation of 4a and 5a was the same. To improve the efficiency of the transformation, a stronger nucleophilic base such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was tested [25]. Pleasingly, when pyrrolidine 4a was exposed to DBU in CH₂Cl₂, 5a was obtained in excellent yield (98%, 1 h, conditions b; Scheme 2). The reaction can also be promoted by a catalytic amount of DBU (0.2 equiv) delivering 5a (96%) after prolonged reaction time (22 h, conditions c, Scheme 2). Interestingly and despite its strong nucleophilic character, DABCO (1,4-diazabicyclo[2.2.2]octane) was unable to promote the isomerization (conditions d, Scheme 2) and the starting material was recovered.

As presented in Scheme 3, the methodology was next attempted in a one-pot process. Hence, the transformation of aldehyde 1a and imine 2a into pyrrolidine 4a was followed by the introduction of DBU leading to pyrrole 5a in 26% yield. However, proceeding stepwise and isolating the pyrrolidine 4a by a simple filtration on silica gel before isomerization is more rewarding: following this route, the global yield for the whole process reaches 59% yield. Applying this procedure, various 2-heteroarylmethyleneppyrolidines 4b–h prepared from aldehydes 1b–h and imine 2a were exposed to DBU (1.1 equiv). Pleasingly, pyrrolidines 4b–h were transformed into the corresponding pyroles 5b–i with homogeneous efficiency. Hence, the chemistry proved to be compatible with substrates containing meta-, para-pyridyl and quinolinyl substituents, allowing the preparation of 5b (81%), 5c (78%) and 5d (98%). Pyrrolidine 4e containing an electronically deficient pyridyl residue was also converted into 5e (80%) while pyrrolidine 4f bearing a pyrazine core underwent aromatization with high efficiency to give 5f (97%). The C₂-symmetric scaffold 4g was efficiently converted into 5g (86%) and similar treatment of pyrimidine 4h provided pyrrole 5h in high yield (91%).

The Mannich coupling was next attempted with different imines 2b–e in order to modulate the nature of the aryl moiety (Scheme 4). The electronic nature of the aniline being crucial...
Scheme 3: Preparation of N-arylpyrroles 5a–h (unless otherwise specified, yields in brackets refer to the isomerization step while yields in square brackets refer to the two-step procedure from the corresponding aldehyde).

Scheme 4: Variation of imines.
for the stability of the imine and the hydroamination step, electronically rich anilines were selected to form imines 2b,c. Hence, when imines 2b,c were exposed to aldehyde 1a in the presence of catalyst 6 (available in racemic form), the Mannich adducts 7i,j were obtained and directly reacted with phosphonium salt 3. In line with our procedure, the resulting acyclic anilines 8i,j were then exposed to TFA to promote the cyclization into pyrrolidines 4i,j which upon treatment with DBU were converted into pyrroles 5i,j in 41% and 52% overall yields. While p-alkoxy substituted (R = OAllyl, OBn) anilines are compatible, the methodology proved troublesome with o-alkoxy substituted anilines, the main limitation being the formation of the corresponding imines. Similarly, imine 2d prepared from para-bromoaniline was found to be unstable and only degradation was observed during the Mannich reaction. When imine 2e, derived from the para-iodoaniline, was engaged in the process, the hydroamination step turned out to be problematic, which prevented the isolation of the corresponding pyrrolidine.

Even if not completely elucidated, a mechanism of the isomerization can be suggested in which the acrylate moiety is crucial. Indeed, without this unsaturation, it was not possible to observe the isomerization of the exo-enamine into the endo compound under basic treatment [26]. These observations suggest that DBU or KCN behave as base to promote the deconjugation of the acrylate moiety of 4a [27]. The resulting product 4a’ would lead under basic treatment to pyrrole 4a” from which aromatization to 5a would be expected to follow (Scheme 5).

Having established a practical methodology for the preparation of substituted N-arylpyrroles, we next undertook synthetic transformations to extend the molecular diversity of the substrates. While attempts to perform an oxidation of the bis(heteroaryl)methylene position promoted by CAN has been reported [29], this is the first example of bis(heteroaryl)methylene oxidation employing this reagent [30]. In order to increase the local electron deficiency of the scaffold, 9a was oxidized with 2-iodoxybenzoic acid (IBX) into ketone 10a (98%), which presents an ideal push–pull configuration tunable with the pH by protonation of the pyridine ring. This is likely to lead to applications of 10a such as for new water-soluble molecular probes.

**Conclusion**

A new catalytic and regioselective preparation of substituted N-arylpyrroles decorated with various 2-heteroaromatic scaffolds is reported. Based on the isomerization of pyrrolidines prepared by a simple and efficient sequence of Mannich/Wittig olefination/hydroamination reactions, no oxidant or metallic catalysts were employed [31]. This study also led us to investigate the feasibility of this process with different anilines and enlarge the molecular diversity of the scaffold. So far, the methodology is limited to electron-rich anilines due to the formation and reactivity of the corresponding imines and the stability of the Mannich adduct for the hydroamination step. However, this electronic configuration is ideal for the preparation of electron donor/acceptor N-arylpyrroles as demonstrated in this study. In addition, we documented an efficient C–H oxidation of the bis(heteroaryl)methylene position promoted by CAN.

**Experimental**

**General:** 1H and 13C NMR spectra were recorded in deuterated chloroform on Bruker Avance DPX 400 or 300 spectrometers and were referenced to residual chloroform (7.26 ppm, 1H; 77.00 ppm, 13C). Chemical shifts are expressed in parts per million (ppm). Data for 1H are reported as follows: chemical
Scheme 6: Bis(heteroaryl)methylene oxidation of 5a–f.

#### Ethyl 3-(3-methoxy-3-oxopropyl)-1-(4-methoxyphenyl)-5-(pyridin-2-ylmethyl)-1H-pyrrole-2-carboxylate (5a):

Representative procedure: In a flask containing a stirred solution of 4a (432 mg, 1.02 mmol, 1.0 equiv) in CH₂Cl₂ (10.2 mL) at room temperature was introduced DBU (168 µL, 1.12 mmol). The mixture was allowed to react at this temperature for 1 h. Then, the volatiles were removed under reduced pressure and the crude was purified by flash column chromatography (CH₂Cl₂/MeOH 99:1) on silica gel to yield 5a (432 mg, 99%) as an orange oil. 

1H NMR (300 MHz, CDCl₃) 1.08 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 2.65 (br t, J = 7.9 Hz, 2H), 3.11 (br t, J = 7.9 Hz, 2H), 3.67 (s, 3H), 3.81 (s, 3H), 3.83 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 5.92 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.8 Hz, 2H), 7.06 (m, 1H), 7.52 (td, J = 1.5, 7.8 Hz, 1H), 8.45 (d, J = 4.3 Hz, 1H) ppm; 

13C NMR (75 MHz, CDCl₃) 173.7, 160.8, 158.9, 158.4, 149.1, 137.6, 136.3, 132.4, 132.1, 128.8 (2*CH), 122.8, 121.3, 120.7, 113.5 (2*CH), 110.4, 59.3, 55.2, 51.3, 35.8, 34.9, 23.5, 13.9 ppm. IR: 2920, 1690, 1512, 1438, 1245, 1169, 1080, 910, 727
**Ethyl 5-(hydroxy(pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (9a):** Representative procedure: In a flask containing a well stirred solution of CAN (269 mg, 0.490 mmol, 3.0 equiv) in 
H₂O (3.1 mL) at 0 °C was introduced dropwise a solution of 5a (69 mg, 0.164 mmol in 2.4 mL of CH₂CN) over 10 min. Then, the mixture was allowed to react at this temperature for 3 h and was quenched by the addition of an aqueous solution of Na₂S₂O₃ (1 M). The resulting mixture was extracted with AcOEt (3×), and the combined organic layers were washed with brine, dried over MgSO₄, and filtered. The volatiles were removed under reduced pressure to give 58 mg of the crude product, which was purified by flash column chromatography (CH₂Cl₂/MeOH 99:1) on silica gel to yield 9a (49 mg, 71%) as an orange oil.

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1H NMR (300 MHz, CDCl₃), 7.80 (dt, J = 7.7 Hz, 1H), 7.41–7.46 (ddd, J = 1.6, 7.8 Hz, 1H), 7.05 (d, J = 7.0 Hz, 2H), 3.67 (s, 3H), 3.82 (s, 3H), 4.11 (q, J = 7.1 Hz, 2H), 3.06 (m, 2H), 3.64 (CH₂Cl₂/MeOH 99:1).

**Supporting Information**

**Supporting Information File 1**

Physical and spectroscopic data of 5b–j, 9b–e and 1H and 13C spectra of all new compounds.

[http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-9-168-S1.pdf]

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