Tetrahedron Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-mediated Chan-Evans-Lam *N*-arylation of 5-methylene-4-aryl-1,5-dihydro-2*H*-pyrrol-2-one derivatives

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ARTICLE INFO

Article history:
Received 28 November 2017
Revised 8 January 2018
Accepted 16 January 2018
Available online xxxx

Keywords:
Chan-Evans-Lam coupling reaction
Pyrrole-2-one
Quorum sensing

ABSTRACT

A simple and efficient procedure for the synthesis of *N*-aryl 5-methylene-4-aryl-1,5-dihydro-2H-pyrrol-2-one derivatives has been developed through copper-mediated C—N bond formation. The synthetic protocol allows for versatile and robust C—N arylation with a range of readily available boronic acids under mild conditions.

Introduction

Bacteria utilize intercellular chemical signaling mechanisms to coordinate group behaviour, including the regulation of virulence factor production and biofilm formation, in a process known as quorum sensing (QS).[1,2] Therefore, significant interest has been devoted to the development of compounds that interfere with bacterial signaling as a potential antibacterial strategy. A number of halogenated furanones, also known as fimbrolides, exhibit antimicrobial activities against several bacteria through the disruption of QS-mediated phenotypes.[3] However, the use of fimbrolides has been limited by their cytotoxicity to mammalian cells and high efflux rate.[4] To circumvent these issues, our group has previously synthesised 1,5-dihydropyrrol-2-ones (DHPs) bearing γ-methylene substituents as isosteric analogues of furanones.[5] These DHPs demonstrated good antimicrobial properties against several bacterial strains with low cytotoxicity toward mammalian cells.[5] Additionally, the DHPs were not bactericidal and therefore have low propensity to induce resistance.[5] Other γ-methylene-γ-lactams, targeting the ecdysone receptor with potential as insecticides, have also been reported in the literature.[6] However, *N*-aryl analogues of DHPs, based on the 5-methylene-4-aryl-1,5-dihydro-2*H*-pyrrol-2-one scaffold **1** (Fig. 1), have been relatively unexplored.

In line with our continuing interest in developing DHPs as antimicrobial agents, we sought to further functionalise these DHPs at the basic nitrogen atom, as this modification has not been previously studied. To install the *N*-aryl motif, we employed the Chan-Evans-Lam reaction, which is a C—N forming bond method that proceeds *via* the oxidative coupling of an arylboronic acid and an amine group catalysed by cupric acetate under mild conditions.[7] The Chan-Evans-Lam reaction has been widely used for the synthesis of biologically active compounds, including *N*-aryl substituted heterocyclic systems such as *N*-aryl isatin,[8] *N*-aryl pyridin-2(1*H*)-one[9], *N*-aryl purine,[10] and *N*-aryl pyridone, as part of the process leading to the marketed anti-epileptic drug, perampanel (Fycompa).[11] We report herein a synthetic protocol for the versatile and robust C—N arylation of DHPs with a range of readily available boronic acids under mild conditions.

Results and discussion

Our initial attempts to prepare *N*-aryl DHPs utilized a synthetic sequence employing the lactone-lactam conversion method previously developed within our group (Scheme 1).[5,12] Briefly, the synthesis starts with the acid-catalysed condensation of phenylacetones **2** with glyoxylic acid **3**, producing 5-hydroxyfuranones **4**. The 5-hydroxyfuranones **4** were treated with thionyl chloride to form the 5-chlorofuranones **5**. In the key lactone-lactam conversion step, furanones **5** were treated with amines to provide the intermediate 5-hydroxy-lactams **6**, which can be subsequently

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https://doi.org/10.1016/j.tetlet.2018.01.039
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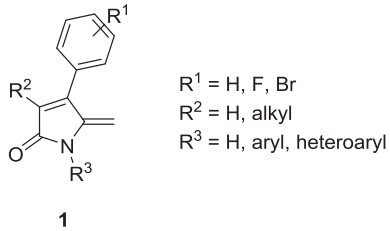

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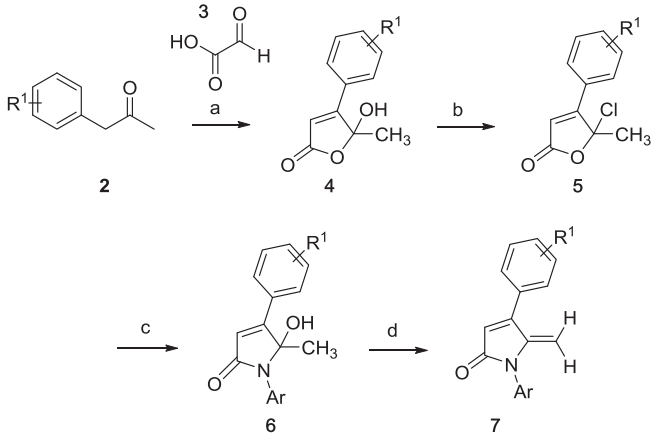
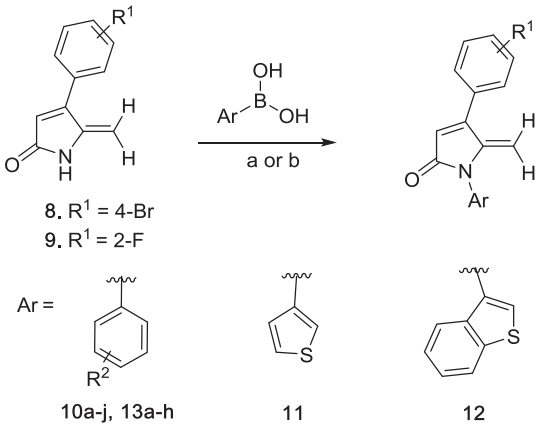
Fig. 1. General structure of *N*-aryl 5-methylene-4-aryl-1,5-dihydro-2*H*-pyrrol-2-one **1**.



Scheme 1. Lactone-lactam conversion procedure.[5] Reagents and conditions: (a) H_3PO_4, 75 °C, 5 h, then rt, 10 h; (b) $SOCl_2$, reflux, 2 h; (c) Ar-NH_2, CH_2Cl_2, rt, 24 h; (d) P_2O_5, CH_2Cl_2, rt, 30 min.

dehydrated with P_2O_5 (or $BF_3{\cdot}Et_2O$) to produce the γ-methylene DHPs **7**. However, while reactions with ammonia and alkylamines have previously proceeded smoothly at room temperature giving high yields of products,[5,12] the reactions with aniline derivatives were slow and low-yielding. This was attributed to the low basicity and nucleophilicity of aniline derivatives compared to ammonia or alkylamines. Therefore, an alternative method was needed to install *N*-aryl substituents on the DHP scaffold.

As the Chan-Evans-Lam coupling reaction had been previously used to synthesise *N*-aryl substituted heterocyclic systems, we investigated the application of this method to access the desired *N*-aryl DHP scaffold. The starting DHPs **8–9** were prepared from the reaction of glyoxylic acid **3** with 4-bromophenylacetone and 2-fluorophenlacetone, respectively, following the procedure described in Scheme 1 with the use of ammonia instead of substituted amines.[5] The Chan-Evans-Lam reaction conditions were then optimised using DHP **8** and phenylboronic acid as model substrates, with copper(II) acetate as catalyst (Table 1). Our results showed that the highest yield of product **10a** was obtained when triethylamine and pyridine were used as bases in 2 and 4 equivalents, respectively, with CH_2Cl_2 as solvent, a temperature of 40 °C and a reaction time of 24 h (Table 1, Entry 4). The use of triethylamine only (Table 1, Entry 1), pyridine only (Table 1, Entry 2) or a 2:2 mixture of triethylamine and pyridine (Table 1, Entry 3) led to drastically lower yields. Moreover, changing the solvent to EtOH (Table 1, Entry 5) or THF (Table 1, Entry 6) led to decreased yields. These results indicate that both the nature of the solvent and the molar equivalent ratios of the bases were highly important for the success of this reaction using DHP derivatives.



Scheme 2. Synthesis of *N*-aryl DHPs using the Chan-Evans-Lam coupling reaction. Reagents and conditions: (a) compound **8**, $Cu(OAc)_2$ (1.5 eq.), CH_2Cl_2, TEA (2 eq.), pyridine (4 eq.), molecular sieves 3 Å, 40 °C, 24 h, yielding compounds **10a-j, 11** and **12**; (b) for compound **9,** the reaction was carried out at room temperature, yielding compounds **13a-h**.

Table 2
N-aryl DHP derivatives synthesised *via* Scheme 2.

Entry	R^1	R^2	Product	Yield[a] (%)
1	4-Br	H	**10a**	50
2	4-Br	3-F	**10b**	40
3	4-Br	4-F	**10c**	45
4	4-Br	4-Cl	**10d**	26
5	4-Br	3-Br	**10e**	20
6	4-Br	4-Br	**10f**	51
7	4-Br	4-CH_3	**10g**	24
8	4-Br	4-OMe	**10h**	35
9	4-Br	4-CF_3	**10i**	37
10	4-Br	4-SO_2Me	**10j**	20
11	4-Br	–	**11**	15
12	4-Br	–	**12**	9
13	2-F	H	**13a**	70
14	2-F	3-F	**13b**	60
15	2-F	3-Cl	**13c**	53
16	2-F	4-Cl	**13d**	56
17	2-F	3-Br	**13e**	78
18	2-F	4-Br	**13f**	91
19	2-F	3-CH_3	**13g**	44
20	2-F	4-CH_3	**13h**	39

[a] Isolated yields.

Table 1
Optimization of the Chan-Evans-Lam reaction.

Entry	Base	Solvent	Time (h)	Temp (°C)	Yield of 10a[a] (%)
1	TEA (2 eq.)	DCM	72	RT	7
2	Py (2 eq.)	DCM	24	RT	10
3	TEA/Py (2:2 eq.)	DCM	72	40	11
4	TEA/Py (2:4 eq.)	DCM	24	40	50
5	TEA/Py (2:4 eq.)	EtOH	48	40	N/A
6	TEA/Py (2:4 eq.)	THF	24	40	9

[a] Isolated yields. Reagents and conditions: DHP **8**, phenylboronic acid (2 eq. for entries 1–3, and 4 eq. for entries 4–6), molecular sieves 3 Å, copper(II) acetate (1.5 eq.).

Please cite this article in press as: Almohaywi B., et al. Tetrahedron Lett. (2018), https://doi.org/10.1016/j.tetlet.2018.01.039

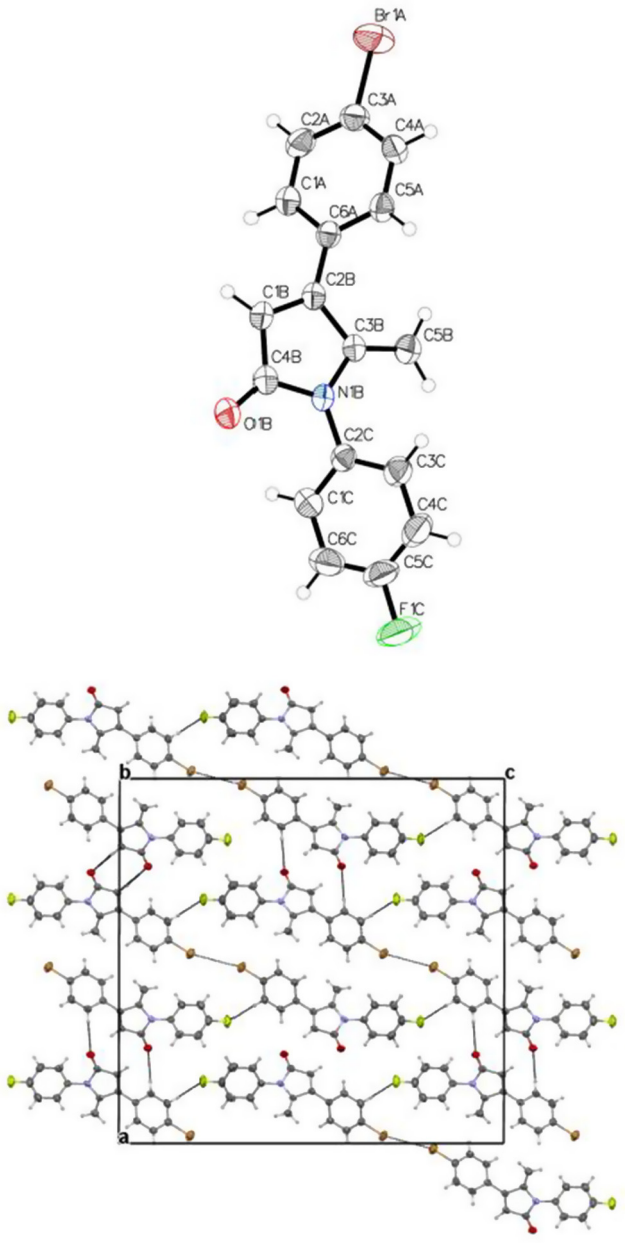


Fig. 2. ORTEP representation of compound **10c**.

The optimized conditions[13] were applied to the synthesis of a library of *N*-aryl DHPs using DHPs **8** and **9** and a variety of commercially available boronic acids as the substrates (Scheme 2). To examine the scope and limitations of this reaction, a range of electronically diverse arylboronic acids were used. To improve the yield, 3–4 equivalents of the boronic acids were added to allow isolation of the products after 24 h. The lower solubility of DHP **7** required heating at 40 °C (Scheme 2, Method a) to obtain sufficient yields of the *N*-aryl DHPs **10a-j** (Table 2, Entries 1–10). Under similar conditions, the reaction between DHP **8** and 3-thienyl boronic acid and thianaphthene-3-boronic acid produced *N*-heteroaryl DHPs **11** and **12**, respectively (Table 2, Entries 11–12). Interestingly, the reactions between DHP **9** and the phenylboronic acids proceeded smoothly even at room temperature (Scheme 2, Method b), producing *N*-aryl DHPs **13a-h** (Table 2, Entries 13–20) in moderate to high yields. Most of the products were obtained in moderate to good yields after purification by column chromatography.

Overall, the results showed that the reaction conditions were tolerated amongst a wide range of various electron-deficient, electron-rich and electron-neutral boronic acids. Generally, halogen-containing boronic acids produced higher yields than non-halogen containing boronic acids. Moreover, compounds derived from starting DHP **9** were produced in higher yields than those derived from **8**, which could be due to the solubility issue mentioned above.

The synthesised *N*-aryl DHPs were fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and by high-resolution mass spectrometry. In the ^{1}H NMR spectrum of 4-(4-bromophenyl)-1-(4-fluorophenyl)-5-methylene-1,5-dihydro-2*H*-pyrrol-2-one **10c**, the characteristic C3 proton was observed as a singlet at 6.36 ppm. The two protons (C=$\underline{CH_2}$) in the exocyclic double bond were observed as doublets at 5.00 ppm. In the ^{13}C NMR spectrum, the characteristic C3 carbon was observed at 121.3 ppm, and the identity of this carbon signal was further confirmed by 2D HSQC NMR spectroscopy. Finally, high-resolution mass spectrometry gave the anticipated mass of the molecular ion (*m*/*z* 344.0081).

Compound **10c** was crystallized from methanol to yield colourless crystals suitable for single crystal X-ray diffraction. The ORTEP view of the molecule is shown in Fig. 2. As expected, the molecule is not planar. The two pendant phenyl rings are rotated by ~50° to the central five-membered ring, thereby avoiding unfavourable H···H interactions.[14] In the crystal structure, molecules associate via C—H···O, C—H···F and Br···Br hydrogen bonding and halogen bonding interactions.

Conclusion

In summary, we have developed a robust and simple procedure for the synthesis of *N*-aryl DHP derivatives by employing the Chan-Evans-Lam coupling reaction between DHP starting precursors and commercially available boronic acid derivatives in the presence of copper(II) acetate as catalyst and a combination of triethylamine and pyridine as base. Generally, we found that this synthetic strategy tolerated the majority of substituted phenyl and heterocyclic boronic acids. The diversity and the wide scope of the reaction is promising and has provided us with diverse analogues necessary for our investigation of active quorum sensing inhibitors.

Acknowledgments

We thank the NMR and BMSF facility, University of New South Wales. The authors would like to acknowledge the Saudi Ministry of Education and King Khalid University for Endowment Fund and financial support given to B. Almohaywi.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.039.

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13. Representative procedure for compound 10c: To a mixture of 4-(4-bromophenyl)-5-methylene-1,5-dihydro-2H-pyrrol-2-one (0.80 mmol, 0.20 g), triethylamine (1.6 mmol, 0.22 mL), pyridine (3.2 mmol, 0.32 mL) and 4-fluorophenylboronic acid (3.2 mmol, 0.45 g) and 3 Å molecular sieves in CH_2Cl_2 (5 mL) was added $Cu(OAc)_2$ (1.2 mmol, 0.22 g) and the reaction mixture stirred at 40 °C for 24 h. The reaction mixture was filtered through a silica pad and celite to remove the catalyst and eluted with ethyl acetate (100 mL), and the combined organic layers washed with 2 M HCl (2 × 5 mL) and brine, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography with gradient elution from 70% CH_2Cl_2/hexane to 5% ethyl acetate in CH_2Cl_2. The product was then recrystallized from methanol to give the product as colorless needles (45%). m.p. 165.0–166.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, *J* = 4 Hz, 2H, C=CH_2), 6.36 (s, 1H, CH), 7.22–7.40 (m, 6H, ArCH), 7.65 (d, *J* = 8 Hz, 2H, ArCH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 98.6 (C=$\underline{CH_2}$), 116.4 (ArCH), 121.3 (CH), 124.1 ($\underline{C}$=CH_2), 129.8 (ArCH), 130.3 (ArCH), 130.7 (C), 132.1 (ArCH), 146.2 (C), 149.3 (C), 160.7 (C), 163.2 (C), 168.4 (C=O); IR (ATR): ν_{max} 730, 825, 1069, 1232, 1393, 1509, 1707 cm^{-1}. UV-VIS (MeOH): λ_{max} 280 nm (ε 13767 cm^{-1} M^{-1}). HRMS ($C_{17}H_{11}{}^{79}BrFNO$) calcd *m/z* 344.0081 $[M+H]^+$, obsd *m/z* 344.0076 $[M+H]^+$.

14. X-ray crystallography: A suitable single crystal of 10c (CCDC 1579466) obtained from methanol was selected under a polarizing microscope (Leica M165Z) mounted on a MicroMount (MiTeGen, USA) consisting of a thin polymer tip with a wicking aperture.[15] Crystal data: $C_{17}H_{11}BrFNO$, MW = 344.1834, Monoclinic, Cell dimensions: a = 26.198 (3) Å, b = 3.9841 (4) Å, c = 27.569 (3) and beta = 90.140 (3) Å. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1579466. A copy of the data can be obtained free of charge from CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK or e-mail: deposit@ccdc.cam.ac.uk.

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