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Unexpected synthesis of 3-imino-2-(pyrrol-2-yl) isatogen derivatives affords facile access to a 2-pyrrolyl isatogen

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Abstract
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Unexpected synthesis of 3-imino-2-(pyrrol-2-yl) isatogen derivatives affords facile access to a 2-pyrrolyl isatogen

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KEYWORDS: 3-imino isatogen; 2-pyrrolyl isatogen; p-phenylenediamine; N,N-dimethyl-p-phenylenediamine; antiplasmodial

Running Head: 2-Pyrrolyl Isatogen Synthesis
ABSTRACT

2-Aryl isatogens and their 3-imino derivatives have been extensively studied but to date there have been no reported variants carrying pyrrolyl substituents at the 2-position. This study describes the unexpected synthesis of two novel 3-imino-2-(pyrrol-2-yl) isatogen derivatives upon attempted amide couplings with (E)- or (Z)-3-(3,5-dimethyl-1H-pyrrol-2-yl)-2-(2-nitrophenyl)acrylic acids and p-phenylenediamines in the presence of uronium-based coupling reagents. Imine hydrolysis of one derivative under mild acid conditions afforded a 2-pyrrolyl isatogen in high yield. The compound showed potent in vitro antimalarial activity against *Plasmodium falciparum*. 
Introduction

2-Substituted-3-\textit{H}-indol-3-one-N-oxides (isatogens) are a well-known class of compounds that possess, for example, antiplasmodial, antifungal and antibacterial activities, with active derivatives carrying a variety of alkyl and (hetero)aryl groups at C2 and substituents on the 6-membered ring (e.g. 1 and 2, Figure 1). The broad antimicrobial properties of the class have been attributed to redox processes within cells and the N-oxide reduction potential. Some isatogens are useful as spin traps for detecting short lived radicals in electron paramagnetic spectroscopy and as quenchers in radical polymerisation chemistry. Strategies for the synthesis of isatogens include metal-catalysed cyclisation of 2-nitrophenylacetylides and oxidation of 2-nitrophenylalkenes to diketones, followed by nitro reduction and cyclisation.

The closely related 3-imino isatogens are another well-studied class that, among other applications, can be useful as synthetic intermediates. For example, 3-phenylimino-2-phenyl isatogen 3 undergoes 1,3-dipolar cycloadditions with electron deficient alkenes to provide isoxazolidine derivatives. Synthesis of 3-arylimino isatogens can be achieved via reaction of 2-substituted indole-N-oxides with nitrosoarenes. While there is a rich literature surrounding isatogens and their 3-imino derivatives, there are no reported examples from either class containing pyrrolyl substituents at C2. This paper reports the unexpected synthesis of two novel 3-arylimino -2-(pyrrol-2-yl) isatogens and a facile hydrolytic cleavage that provided a 2-pyrrolyl isatogen.

Results and Discussion

In 2013 we reported the synthesis and preliminary evaluation of (\textit{E})- and (\textit{Z})-3,5-dimethyl-1\textit{H}-pyrrol-2-yl-2-arylacrylate esters and amides 4 (Scheme 1) as a new class of angiogenesis inhibitors related to sunitinib (Sutent\textsuperscript{®}). At the outset of this previous study, we envisaged that esters/amides 4
should be accessible from the corresponding acids (E)-5 and (Z)-5, respectively, using standard ester/amide coupling chemistry. However, attempts to couple these acids (both isomers) with a variety of alcohols and amines resulted in pyrrole N-acylation/cyclisation to the 5,7-dimethyl-2-aryl-3H-pyrrrolizin-3-one 6 (Scheme 1(a)). An alternative route to the target esters and amides was eventually identified using a novel adaptation of the Knoevenagel reaction, where pre-formed 2-(2-nitrophenyl) esters/amides are reacted with an N-methylcarbamoyl pyrrole-2-carbaldehyde.\[^{[10]}\] We also recently reported a divergent one-pot synthesis of substituted 5,7-dimethyl-2-aryl-3H-pyrrrolizin-3-ones and showed that these too, constitute a new class of angiogenesis inhibitors.\[^{[11]}\]

Acids (E)-5 and (Z)-5 were obtained for the current work in identical yields (84%) from the reported allyl esters (Z)-7 and (E)-7\[^{[10]}\] via Pd-catalysed deallylation in the presence of morpholine (Scheme 1(a)). Crystals of (Z)-5 suitable for X-ray analysis were obtained from Et\(_2\)O/pet spirit and its structure was determined. The X-ray data confirmed the structure of (Z)-5 while also revealing the presence of an intramolecular hydrogen bond between the pyrrole NH and carbonyl oxygen atoms (NH---O distance 1.9 Å), which served to stabilise the molecule into a pseudo-7-membered ring conformation (Scheme 1(b)). Evidence that the H-bond was retained in solution was found in the compound’s \(^1\)H NMR spectrum (CDCl\(_3\)), where the pyrrole NH signal for (Z)-5 appeared far downfield at 11.87 ppm (c.f. 6.78 ppm for (E)-5). The equivalent H-bond was observed previously in the allyl ester (Z)-7.\[^{[10]}\]

While studying amidation reactions of 5 it was noted that attempted amide coupling of (E)-5 and N,N-dimethyl-p-phenylenediamine (DMPD) 8 in CH\(_2\)Cl\(_2\) using 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU) in the absence of tertiary amine base resulted in very different reactivity. Rather than forming the amide or the dark red
pyrrolizin-3-one 6, a deep purple solid was obtained as the major product. Proving difficult to
c caracterise by spectroscopic methods, a crystal of the compound was grown from Et$_2$O/pet spirit and
its X-ray structure determined. The compound was revealed to be the novel 3-imino 2-(2-pyrrolyl)
isatogen 10, containing an intramolecular H-bond between the pyrrole NH and N-oxide oxygen atoms
(NH---O distance 1.9 Å) that stabilised the molecule into a pseudo-6-membered ring conformation
(Scheme 2(a)). The H-bond was also evident in CDCl$_3$ solution, as indicated by the far downfield
chemical shift of the pyrrole NH signal (11.86 ppm) in the $^1$H NMR spectrum of 10. With the structure
of 10 confirmed, the yield of the reaction was calculated at 40%. Similar yields were obtained with the
cis-acid (Z)-5 and when the coupling reagent was switched to 2-(1H-benzotriazol-1-yl)-1,1,3,3-
tetramethyluronium hexafluorophosphate (HBTU).

Reaction of (Z)-5 with $p$-phenylenediamine (PPD) 9 under the same conditions using HATU
gave the analogous 3-imino-2-(pyrrol-2-yl) isatogen 11 in 56% yield. Compound 11 was found to be
unstable, however, degrading over the course of days in air at ambient temperature to mixtures that
contained, among other compounds, the 2-(pyrrol-2-yl) isatogen 12 and PPD, suggesting hydrolytic
lability of the imine bond. Treatment of freshly prepared 11 with 1 M HCl$_{aq}$/THF (1:1) at room
temperature for 30 min was subsequently found to deliver 12 in quantitative yield. A crystal of 12 was
obtained from Et$_2$O/pet spirit and its structure confirmed by X-ray analysis (Scheme 2(b)). As with 10,
the X-ray structure of 12 revealed an intramolecular H-bond between the pyrrole NH and N-oxide
oxygen atoms (NH---O distance 2.2 Å), consistent with the downfield chemical shift (11.64 ppm)
observed for the pyrrole NH signal in its $^1$H NMR spectrum (CDCl$_3$).

Isatogen 12 was tested using the microdilution radioisotope technique for antiplasmodial
activity against the K1 (multidrug resistant) strain of Plasmodium falciparum at the National Centre for
Genetic Engineering and Biotechnology (BIOTEC) Thailand, where it returned an IC$_{50}$ = 381 nM.$^{[12]}$

Cytotoxicity of 12 in Vero cells was measured using the Alamar blue viability assay$^{[13]}$ at CC$_{50}$ = 58.4 µM (selectivity index = 153). The activity/selectivity of 12 was consistent with previous values for closely related 2-aryl isatogens (e.g. compound 2, IC$_{50}$ = 227 nM FcB1 strain, CC$_{50}$ = 31 µM MCF7 cells, selectivity index = 136).$^{[2]}$

In summary, 2-((2-nitrophenyl) acrylates (E)-5 and (Z)-5, prepared in high yield from the reported allyl esters (E)-7 and (Z)-7, were found to undergo unprecedented reactions with p-phenylenediamines and HATU/HBTU in CH$_2$Cl$_2$ to form novel 3-imino-2-(pyrrol-2-yl) isatogen derivatives 10 and 11 in moderate yields. Whilst not speculated on here, the mechanism of this intriguing transformation warrants further investigation. Compound 11 could be rapidly and quantitatively hydrolysed under mild, acidic conditions to the parent ketone 12 – the first reported 2-pyrrolyl isatogen. Compound 12 showed potent in vitro antiplasmodial activity and low eukaryotic cell toxicity, in line with literature data for structurally similar 2-aryl isatogens.

**Experimental – Sample Procedure**

(E)-2-((3,5-dimethyl-1H-pyrrol-2-yl)-3-((4(dimethylamino)phenyl)imino)-3H-indole-1-oxide (10)

HATU (372 mg, 0.98 mmol) was added to a stirring solution of (E)-5 (201 mg, 0.70 mmol) in CH$_2$Cl$_2$ (10 mL) and the mixture stirred at room temperature for 5 minutes, before adding N,N-dimethyl-p-phenylenediamine 8 (95.3 mg, 0.70 mmol) in one portion. The reaction was stirred at room temperature and monitored by TLC analysis (3:7 EtOAc:pet spirit). After 3 h the mixture was extracted with EtOAc (3 x 25 mL) and the combined organic phase washed with brine (2 x 25 mL), dried over anhydrous MgSO$_4$ and concentrated. The crude residue was purified by silica gel column chromatography using a gradient from 100% pet spirit to 8:2 pet spirit:EtOAc to give 3-imino isatogen 10 (100 mg, 40%) as a
deep purple solid. Use of the same procedure with (Z)-7 or with HBTU resulted in similar yields of 10.

M.P. 146-148 °C. \(^1^H\) NMR (CDCl\(_3\), 500 MHz): \(\delta\) 2.33 (s, 3H), 2.51 (s, 3H), 3.04 (s, 6H), 5.96 (d, 1H, \(J = 2.1\) Hz), 6.80 (d, 2H, \(J = 8.5\) Hz), 7.05 (d, 2H, \(J = 9.0\) Hz), 7.07 (t, 1H, \(J = 7.5\) Hz), 7.12 (d, 1H, \(J = 7.5\) Hz), 7.44 (t, 1H, \(J = 7.5\) Hz), 7.63 (d, 1H, \(J = 7.5\) Hz), 11.86 (br s, 1H, NH). \(^1^C\) NMR (CDCl\(_3\), 126 MHz): \(\delta\) 13.6, 16.7, 40.9, 106.6, 112.8, 113.1, 113.9, 117.3, 119.0, 121.7, 123.8, 127.9, 128.8, 132.0, 132.6, 139.5, 148.1, 149.3, 154.8. HRMS-ESI: \(m/z\) calcd for C\(_{22}\)H\(_{23}\)N\(_4\)O [M+H]\(^+\) 359.1866; observed 359.1868. FTIR: neat (cm\(^{-1}\)) 2920, 2340, 1730, 1595, 1521, 1448, 1350, 1277, 1205, 1185, 1117.

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Supporting Information

Full experimental details, \(^1^H\) and \(^1^C\) NMR spectra and X-ray crystallography data. This material can be found via the “Supplementary Content” section of this article’s webpage.

References


Figures and Schemes

**Figure 1.** Structures of representative isatogens and 3-phenylimino-2-phenyl isatogen.

**Scheme 1.** (a) Synthesis of acids (E)-5 and (Z)-5. Reagents and conditions: a. Pd(PPh₃)₄ (10 mol%), morpholine, THF, rt, 2 h; (E)-5 84% from (E)-7, (Z)-5 84% from (Z)-7. (b) X-ray crystal structure of (Z)-5. Anisotropic displacement ellipsoids represent 30% probability levels. Hydrogen atoms are drawn as circles with small radii. (CCDC accession number: (Z)-5 490884).
Scheme 2. (a) Synthesis of 3-imino-2-(pyrrol-2-yl) isatogens 10 and 11 from (E)-5 or (Z)-5. (b) Acid hydrolysis of 11 afforded the 2-(pyrrol-2-yl) isatogen 12 in quantitative yield. X-ray structures of 10 and 12 are shown at right. Anisotropic displacement ellipsoids represent 30% probability levels. Hydrogen atoms are drawn as circles with small radii. (CCDC accession numbers: 10 1490885, 12 1490886).