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

Nicholas Kirk
University of Wollongong, nsk597@uowmail.edu.au

Geraud Sansom
University of Wollongong, gs254@uowmail.edu.au

Pichit Sudta
Phetchaburi Rajabhat University, Srinakharinwirot University

Sunit Suksamrarn
Srinakharinwirot University

Anthony C. Willis
Australian National University

See next page for additional authors

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Abstract

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Authors

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

Nicholas S. Kirk,[†] Geraud N. Sansom,[†] Pichit Sudta,[§,¥] Sunit Suksamrarn,[¥] Anthony C. Willis,[‡] John B. Bremner,[†] Michael J. Kelso[†]*

[†]*Illawarra Health and Medical Research Institute, School of Chemistry, University of Wollongong, NSW 2522, Australia,* [§]*Division of Chemistry, Phetchaburi Rajabhat University, Phetchaburi 76000, Thailand,* [¥]*Department of Chemistry, Srinakharinwirot University, Bangkok 10110, Thailand,* [‡]*Single Crystal X-ray Diffraction Unit, Research School of Chemistry, Australian National University, Canberra, ACT 2601, Australia*

*To whom correspondence should be addressed. Phone: +61 2 4221 5085. Fax: +61 2 4221 4287. E-mail: mkelso@uow.edu.au

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-1*H*-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 antiplasmodial activity against *Plasmodium falciparum*.

Introduction

2-Substituted-3-*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).[1-4] The broad antimicrobial properties of the class have been attributed to redox processes within cells and the *N*-oxide reduction potential.[1,2] Some isatogens are useful as spin traps for detecting short lived radicals in electron paramagnetic spectroscopy and as quenchers in radical polymerisation chemistry.[5,6] Strategies for the synthesis of isatogens include metal-catalysed cyclisation of 2-nitrophenylacetylides[2,4,5] and oxidation of 2-nitrophenylalkenes to diketones, followed by nitro reduction and cyclisation.[2,6]

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.[7] Synthesis of 3-arylimino isatogens can be achieved via reaction of 2-substituted indole-*N*-oxides with nitrosoarenes.[8,9] 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 (*E*)- and (*Z*)-3,5-dimethyl-1*H*-pyrrol-2-yl-2-arylacrylate esters and amides **4** (Scheme 1) as a new class of angiogenesis inhibitors related to sunitinib (Sutent®).[10] 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-3*H*-pyrrolizin-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-3*H*-pyrrolizin-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_2O/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_2Cl_2 using 1-[bis(dimethylamino)methylene]-1*H*-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 characterise by spectroscopic methods, a crystal of the compound was grown from Et_2O/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-(1*H*-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_2O/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_2Cl_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-1*H*-pyrrol-2-yl)-3-((4(dimethylamino)phenyl)imino)-3*H*-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_2Cl_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): δ 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). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 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 $C_{22}H_{23}N_4O$ $[M+H]^+$ 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 ^{13}C NMR spectra and X-ray crystallography data. This material can be found via the "Supplementary Content" section of this article's webpage.

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Figures and Schemes

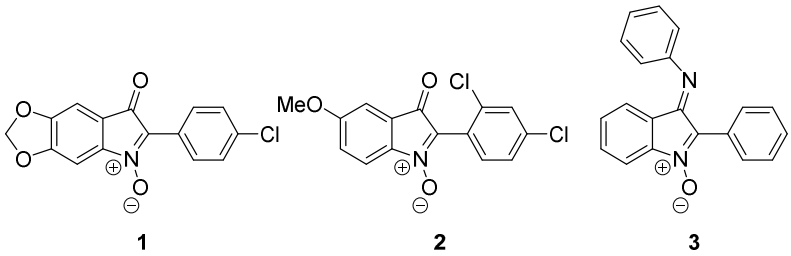
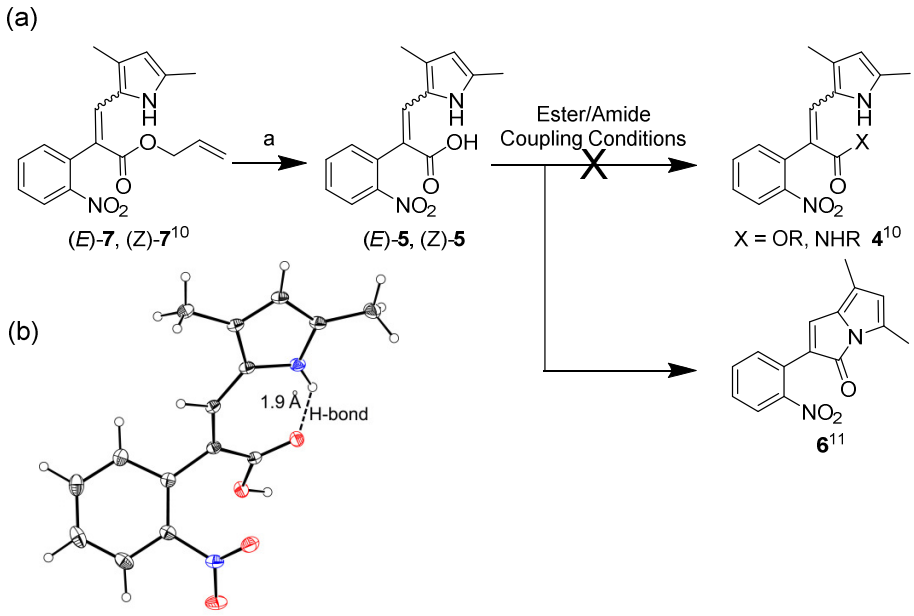
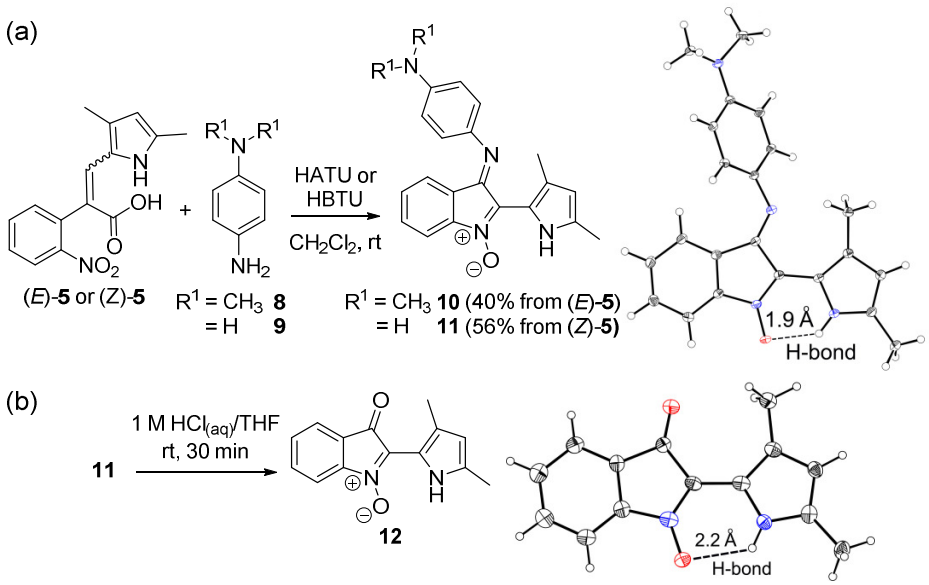


Figure 1. Structures of representative isatogens and 3-phenylimino-2-phenyl isatogen.



Scheme 1. (a) Synthesis of acids (*E*)-**5** and (*Z*)-**5**. Reagents and conditions: a. $Pd(PPh_3)_4$ (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).