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

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*.

Disciplines

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

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

17
18 **Running Head: 2-Pyrrolyl Isatogen Synthesis**

25 **ABSTRACT**

26 2-Aryl isatogens and their 3-imino derivatives have been extensively studied but to date there
27 have been no reported variants carrying pyrrolyl substituents at the 2-position. This study describes the
28 unexpected synthesis of two novel 3-imino-2-(pyrrol-2-yl) isatogen derivatives upon attempted amide
29 couplings with (*E*)- or (*Z*)-3-(3,5-dimethyl-1*H*-pyrrol-2-yl)-2-(2-nitrophenyl)acrylic acids and *p*-
30 phenylenediamines in the presence of uronium-based coupling reagents. Imine hydrolysis of one
31 derivative under mild acid conditions afforded a 2-pyrrolyl isatogen in high yield. The compound
32 showed potent in vitro antiplasmodial activity against *Plasmodium falciparum*.

33 Introduction

34 2-Substituted-3-*H*-indol-3-one-*N*-oxides (isatogens) are a well-known class of compounds that
35 possess, for example, antiplasmodial, antifungal and antibacterial activities, with active derivatives
36 carrying a variety of alkyl and (hetero)aryl groups at C2 and substituents on the 6-membered ring (e.g.
37 **1** and **2**, Figure 1).^[1-4] The broad antimicrobial properties of the class have been attributed to redox
38 processes within cells and the *N*-oxide reduction potential.^[1,2] Some isatogens are useful as spin traps
39 for detecting short lived radicals in electron paramagnetic spectroscopy and as quenchers in radical
40 polymerisation chemistry.^[5,6] Strategies for the synthesis of isatogens include metal-catalysed
41 cyclisation of 2-nitrophenylacetylides^[2,4,5] and oxidation of 2-nitrophenylalkenes to diketones, followed
42 by nitro reduction and cyclisation.^[2,6]

43
44 The closely related 3-imino isatogens are another well-studied class that, among other
45 applications, can be useful as synthetic intermediates. For example, 3-phenylimino-2-phenyl isatogen
46 **3** undergoes 1,3-dipolar cycloadditions with electron deficient alkenes to provide isoxazolidine
47 derivatives.^[7] Synthesis of 3-arylimino isatogens can be achieved via reaction of 2-substituted indole-
48 *N*-oxides with nitrosoarenes.^[8,9] While there is a rich literature surrounding isatogens and their 3-imino
49 derivatives, there are no reported examples from either class containing pyrrolyl substituents at C2.
50 This paper reports the unexpected synthesis of two novel 3-arylimino -2-(pyrrol-2-yl) isatogens and a
51 facile hydrolytic cleavage that provided a 2-pyrrolyl isatogen.

53 Results and Discussion

54 In 2013 we reported the synthesis and preliminary evaluation of (*E*)- and (*Z*)-3,5-dimethyl-1*H*-
55 pyrrol-2-yl-2-arylacrylate esters and amides **4** (Scheme 1) as a new class of angiogenesis inhibitors
56 related to sunitinib (Sutent[®]).^[10] At the outset of this previous study, we envisaged that esters/amides **4**

57 should be accessible from the corresponding acids (*E*)-**5** and (*Z*)-**5**, respectively, using standard
58 ester/amide coupling chemistry. However, attempts to couple these acids (both isomers) with a variety
59 of alcohols and amines resulted in pyrrole *N*-acylation/cyclisation to the 5,7-dimethyl-2-aryl-3*H*-
60 pyrrolizin-3-one **6** (Scheme 1(a)). An alternative route to the target esters and amides was eventually
61 identified using a novel adaptation of the Knoevenagel reaction, where pre-formed 2-(2-nitrophenyl)
62 esters/amides are reacted with an *N*-methylcarbamoyl pyrrole-2-carbaldehyde.^[10] We also recently
63 reported a divergent one-pot synthesis of substituted 5,7-dimethyl-2-aryl-3*H*-pyrrolizin-3-ones and
64 showed that these too, constitute a new class of angiogenesis inhibitors.^[11]

65

66 Acids (*E*)-**5** and (*Z*)-**5** were obtained for the current work in identical yields (84%) from the
67 reported allyl esters (*Z*)-**7** and (*E*)-**7**^[10] via Pd-catalysed deallylation in the presence of morpholine
68 (Scheme 1(a)). Crystals of (*Z*)-**5** suitable for X-ray analysis were obtained from Et₂O/pet spirit and its
69 structure was determined. The X-ray data confirmed the structure of (*Z*)-**5** while also revealing the
70 presence of an intramolecular hydrogen bond between the pyrrole NH and carbonyl oxygen atoms
71 (NH...O distance 1.9 Å), which served to stabilise the molecule into a pseudo-7-membered ring
72 conformation (Scheme 1(b)). Evidence that the H-bond was retained in solution was found in the
73 compound's ¹H NMR spectrum (CDCl₃), where the pyrrole NH signal for (*Z*)-**5** appeared far downfield
74 at 11.87 ppm (c.f. 6.78 ppm for (*E*)-**5**). The equivalent H-bond was observed previously in the allyl
75 ester (*Z*)-**7**.^[10]

76

77 While studying amidation reactions of **5** it was noted that attempted amide coupling of (*E*)-**5**
78 and *N,N*-dimethyl-*p*-phenylenediamine (DMPD) **8** in CH₂Cl₂ using 1-[bis(dimethylamino)methylene]-
79 1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) in the absence of tertiary
80 amine base resulted in very different reactivity. Rather than forming the amide or the dark red

81 pyrrolizin-3-one **6**, a deep purple solid was obtained as the major product. Proving difficult to
82 characterise by spectroscopic methods, a crystal of the compound was grown from Et₂O/pet spirit and
83 its X-ray structure determined. The compound was revealed to be the novel 3-imino 2-(2-pyrrolyl)
84 isatogen **10**, containing an intramolecular H-bond between the pyrrole NH and *N*-oxide oxygen atoms
85 (NH---O distance 1.9 Å) that stabilised the molecule into a pseudo-6-membered ring conformation
86 (Scheme 2(a)). The H-bond was also evident in CDCl₃ solution, as indicated by the far downfield
87 chemical shift of the pyrrole NH signal (11.86 ppm) in the ¹H NMR spectrum of **10**. With the structure
88 of **10** confirmed, the yield of the reaction was calculated at 40%. Similar yields were obtained with the
89 *cis*-acid (*Z*)-**5** and when the coupling reagent was switched to 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-
90 tetramethyluronium hexafluorophosphate (HBTU).

91

92 Reaction of (*Z*)-**5** with *p*-phenylenediamine (PPD) **9** under the same conditions using HATU
93 gave the analogous 3-imino-2-(pyrrol-2-yl) isatogen **11** in 56% yield. Compound **11** was found to be
94 unstable, however, degrading over the course of days in air at ambient temperature to mixtures that
95 contained, among other compounds, the 2-(pyrrol-2-yl) isatogen **12** and PPD, suggesting hydrolytic
96 lability of the imine bond. Treatment of freshly prepared **11** with 1 M HCl_(aq):THF (1:1) at room
97 temperature for 30 min was subsequently found to deliver **12** in quantitative yield. A crystal of **12** was
98 obtained from Et₂O/pet spirit and its structure confirmed by X-ray analysis (Scheme 2(b)). As with **10**,
99 the X-ray structure of **12** revealed an intramolecular H-bond between the pyrrole NH and *N*-oxide
100 oxygen atoms (NH---O distance 2.2 Å), consistent with the downfield chemical shift (11.64 ppm)
101 observed for the pyrrole NH signal in its ¹H NMR spectrum (CDCl₃).

102

103 Isatogen **12** was tested using the microdilution radioisotope technique for antiplasmodial
104 activity against the K1 (multidrug resistant) strain of *Plasmodium falciparum* at the National Centre for

105 Genetic Engineering and Biotechnology (BIOTEC) Thailand, where it returned an $IC_{50} = 381$ nM.^[12]
106 Cytotoxicity of **12** in Vero cells was measured using the Alamar blue viability assay^[13] at $CC_{50} = 58.4$
107 μ M (selectivity index = 153). The activity/selectivity of **12** was consistent with previous values for
108 closely related 2-aryl isatogens (e.g. compound **2**, $IC_{50} = 227$ nM FcB1 strain, $CC_{50} = 31$ μ M MCF7
109 cells, selectivity index = 136).^[2]

110

111 In summary, 2-(2-nitrophenyl) acrylates (*E*)-**5** and (*Z*)-**5**, prepared in high yield from the
112 reported allyl esters (*E*)-**7** and (*Z*)-**7**, were found to undergo unprecedented reactions with *p*-
113 phenylenediamines and HATU/HBTU in CH_2Cl_2 to form novel 3-imino-2-(pyrrol-2-yl) isatogen
114 derivatives **10** and **11** in moderate yields. Whilst not speculated on here, the mechanism of this
115 intriguing transformation warrants further investigation. Compound **11** could be rapidly and
116 quantitatively hydrolysed under mild, acidic conditions to the parent ketone **12** – the first reported 2-
117 pyrrolyl isatogen. Compound **12** showed potent *in vitro* antiplasmodial activity and low eukaryotic cell
118 toxicity, in line with literature data for structurally similar 2-aryl isatogens.

119

120 **Experimental – Sample Procedure**

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

122 HATU (372 mg, 0.98 mmol) was added to a stirring solution of (*E*)-**5** (201 mg, 0.70 mmol) in CH_2Cl_2
123 (10 mL) and the mixture stirred at room temperature for 5 minutes, before adding *N,N*-dimethyl-*p*-
124 phenylenediamine **8** (95.3 mg, 0.70 mmol) in one portion. The reaction was stirred at room temperature
125 and monitored by TLC analysis (3:7 EtOAc:pet spirit). After 3 h the mixture was extracted with EtOAc
126 (3 x 25 mL) and the combined organic phase washed with brine (2 x 25 mL), dried over anhydrous
127 $MgSO_4$ and concentrated. The crude residue was purified by silica gel column chromatography using a
128 gradient from 100% pet spirit to 8:2 pet spirit:EtOAc to give 3-imino isatogen **10** (100 mg, 40%) as a

129 deep purple solid. Use of the same procedure with (*Z*)-**7** or with HBTU resulted in similar yields of **10**.
130 M.P. 146-148 °C. ¹H NMR (CDCl₃, 500 MHz): δ 2.33 (s, 3H), 2.51 (s, 3H), 3.04 (s, 6H), 5.96 (d, 1H, *J*
131 = 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* =
132 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). ¹³C NMR (CDCl₃, 126
133 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,
134 132.6, 139.5, 148.1, 149.3, 154.8. HRMS-ESI: *m/z* calcd for C₂₂H₂₃N₄O [M+H]⁺ 359.1866; observed
135 359.1868. FTIR: neat (cm⁻¹) 2920, 2340, 1730, 1595, 1521, 1448, 1350, 1277, 1205, 1185, 1117.

136

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139 Postgraduate Awards. P. Sudta and S. Suksamrarn acknowledge financial support from the Thailand
140 Research Fund through the Royal Golden Jubilee PhD Program. M. Kelso acknowledges partial
141 financial support from the University of Wollongong. We thank the National Centre for Genetic
142 Engineering and Biotechnology (BIOTEC) Thailand for antiplasmodial testing of **12**.

143

144 **Supporting Information**

145 Full experimental details, ¹H and ¹³C NMR spectra and X-ray crystallography data. This material can
146 be found via the “Supplementary Content” section of this article’s webpage.

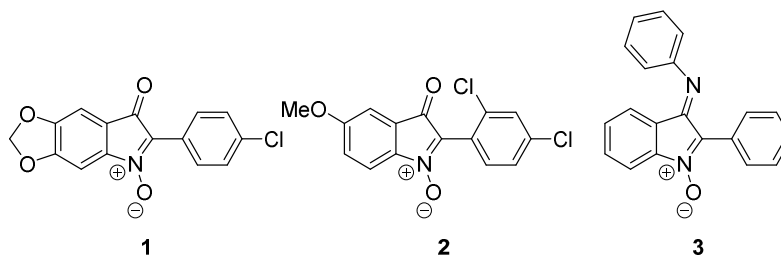
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148 **References**

- 149 [1] Reybier, K.; Nguyen, T. H. Y.; Ibrahim, H.; Perio, P.; Montrose, A.; Fabre, P.-L.; Nepveu, F.
150 *Bioelectrochemistry* **2012**, *88*, 57–64.
- 151 [1] Nepveu F.; Kim, S.; Boyer, J.; Chatriant, O.; Ibrahim, H.; Reybier, K.; Monje, M.-C.; Chevalley,
152 S.; Perio, P.; Lajoie, B. H.; Bouajila, J.; Deharo, E.; Sauvain, M.; Tahar, R.; Basco, L.; Pantaleo,

- 153 A.; Turini, F.; Arese, P.; Valentin, A.; Thompson, E.; Vivas, L.; Petit, S.; Nallet, J.-P. *J. Med.*
154 *Chem.* **2010**, *53*, 699–714.
- 155 [3] Ibrahim, H.; Furiga, A.; Najahi, E.; Hénocq, C. P.; Nallet, J.-P.; Roques, C.; Aubouy, A.;
156 Sauvain, M.; Constant, P.; Daffé, M.; Nepveu, F. *J. Antibiot.* **2012**, *65*, 499–504.
- 157 [4] Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675–5677.
- 158 [5] Rosen, G. M.; Tsai, P.; Barth, E. D.; Dorey, G.; Casara, P.; Spedding, M.; Halpern, H. J. *J. Org.*
159 *Chem.* **2000**, *65*, 4460–4463.
- 160 [6] Boyer, J.; Bernardes-Genisson, V.; Farines, V.; Souchard, J.-P.; Nepveu, F. *Free Radical Res.*
161 **2004**, *38*, 459–471.
- 162 [7] Astolfi, P.; Bruni, P.; Greci, L.; Stipa, P.; Righi, L.; Rizzoli, C. *Eur. J. Org. Chem.* **2003**, *2003*,
163 2626–2634.
- 164 [8] Bruni, P.; Colonna, M. *Tetrahedron* **1973**, *29*, 2425–2435.
- 165 [9] Colonna, M.; Monti, A. *Gazz. Chim. Ital.* **1961**, *91*, 914–918.
- 166 [10] Sudta, P.; Kirk, N.; Bezos, A.; Gurlica, A.; Mitchell, R.; Weber, T.; Willis, A. C.; Prabpai, S.;
167 Kongsaree, P.; Parish, C. R.; Suksamrarn, S.; Kelso, M. J. *Aust. J. Chem.* **2013**, *66*, 864–873.
- 168 [11] Kirk, N. S.; Bezos, A.; Willis, A. C.; Sudta, P.; Suksamrarn, S.; Parish, C. R.; Ranson, M.;
169 Kelso, M. J. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1813–1816.
- 170 [12] Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.*
171 **1979**, *16*, 710–718.
- 172 [13] O'Brien, J.; Wilson, I.; Orton, T.; Pognan, F. *Eur. J. Biochem.* **2000**, *267*, 5421–5426.

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

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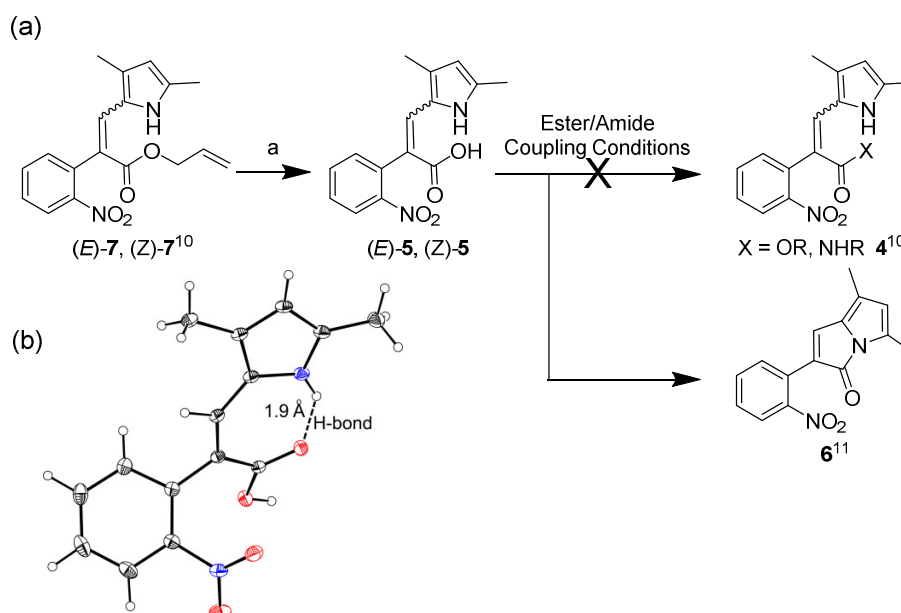
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191 **Scheme 1.** (a) Synthesis of acids (E)-5 and (Z)-5. Reagents and conditions: a. Pd(PPh₃)₄ (10 mol%),

192 morpholine, THF, rt, 2 h; (E)-5 84% from (E)-7, (Z)-5 84% from (Z)-7. (b) X-ray crystal structure of

193 (Z)-5. Anisotropic displacement ellipsoids represent 30% probability levels. Hydrogen atoms are drawn

194 as circles with small radii. (CCDC accession number: (Z)-5 490884).

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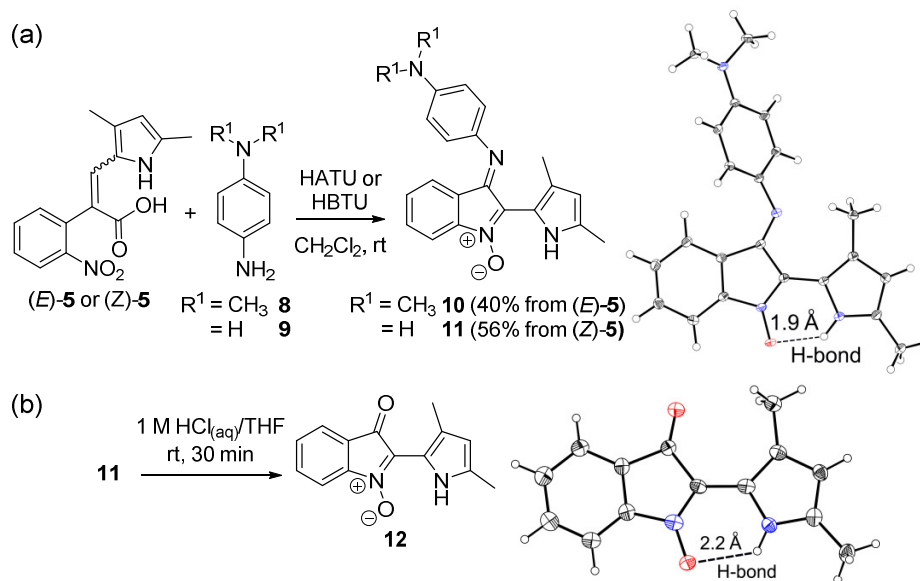
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208 **Scheme 2.** (a) Synthesis of 3-imino-2-(pyrrol-2-yl) isatogens **10** and **11** from (*E*)-**5** or (*Z*)-**5**. (b) Acid

209 hydrolysis of **11** afforded the 2-(pyrrol-2-yl) isatogen **12** in quantitative yield. X-ray structures of **10**

210 and **12** are shown at right. Anisotropic displacement ellipsoids represent 30% probability levels.

211 Hydrogen atoms are drawn as circles with small radii. (CCDC accession numbers: **10** 1490885, **12**

212 1490886).

213

214