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Development of a Scaleable Synthesis of a Partial Nicotinic Acid Receptor Agonist

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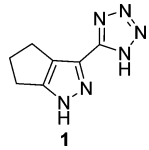
Abstract:

A practical and efficient synthesis of 1,4,5,6-tetrahydro-3-(1*H*-tetrazol-5-yl)cyclopenta[*c*]pyrazole, 1, is described. A new one-pot process has been developed, starting from the commercially available 1*H*-tetrazole-5-carboxylic acid-ethyl ester sodium salt which is reacted in a *pseudo*-Claisen condensation reaction with cyclopentanone, followed by the addition of hydrazine.

Introduction

1,4,5,6-Tetrahydro-3-(1*H*-tetrazol-5-yl)cyclopenta[*c*]pyrazole, **1**, is found to be a partial nicotinic acid (niacin) receptor (NAR) agonist that has been shown to suppress adipocyte lipolysis[1] both *in vitro* and *in vivo*. Due to these properties **1** was chosen as a development candidate for the potential treatment for atherosclerosis.[2] A scaleable synthetic route to this drug candidate was therefore required to generate clinical supplies of this material for support of toxicology and clinical studies. Our aim was to initially exploit the medicinal chemistry strategy for a rapid, first bulk delivery, whilst developing a new shorter synthesis which could be employed for any subsequent, larger deliveries as the compound progressed through the development phases.



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The First-Generation Synthesis

The original medicinal chemistry synthesis of **1** was achieved in seven steps with an overall yield of 39% as outlined below, (Scheme 1).[3] The starting point for this sequence was the *pseudo*-Claisen condensation reaction of cyclopentanone **2** with diethyl oxalate **3** in the presence of KO^{t}Bu in DMF. The resulting intermediate was then acidified prior to treatment with hydrazine hydrochloride to afford the known ester **4**[4] in 71% yield. Ester **4** was then converted, under pressure, to amide **5** using methanolic ammonia in a sealed vessel at 95 °C. Benzyl protection of **5** with benzyl bromide in aqueous THF using sodium hydroxide was uneventful and afforded *N*-benzyl protected primary amide **6** in a 98% yield. Dehydration of the primary amide **6** with thionyl chloride in DMF gave the corresponding nitrile, which underwent a zinc bromide-catalyzed [3 + 2] cycloaddition at 120 °C when treated with sodium azide, to afford tetrazole **7** in a 70% yield. Finally, benzyl deprotection of tetrazole **7** was effected under standard transfer hydrogenation conditions with formic acid employed as the hydrogen source. It should be noted that that superstoichiometric amounts of palladium black (1.55 equiv) were required to achieve complete debenzylation and cleanly afford **1** in a 73% isolated yield.

Modified Medicinal Chemistry Synthesis

Several reactions in the medicinal chemistry route were highlighted as potential problems, and as such, we investigated modifications to make this route more amenable to scale up (Scheme 2). The development work focused on three key challenges in the original route: the use of a high-pressure aminolysis for the formation of amide **5**, the use of sodium azide at elevated temperature and the use of a protecting group necessitating what appeared to be a difficult deprotection step.

The *pseudo*-Claisen condensation step was slightly modified to allow more convenient scale-up. Thus, the reaction was run in ethanol in the presence of potassium ethoxide and then followed by condensation with aqueous hydrazine in the presence of hydrochloric acid (1.2 equiv) rather than with hydrazine hydrochloride. The new modifications allowed the condensation reaction to be run at a higher concentration and provided **4**[4] in 88% isolated yield. The reaction temperature was found to be important in both steps. For solubility reasons, the initial condensation had to be performed at 30 °C, whilst the hydrazine condensation step was best performed at temperatures below −5 °C to avoid the generation of significant colour in the product.

Next, our attention turned to addressing the amide formation step. When the reaction was performed under the original

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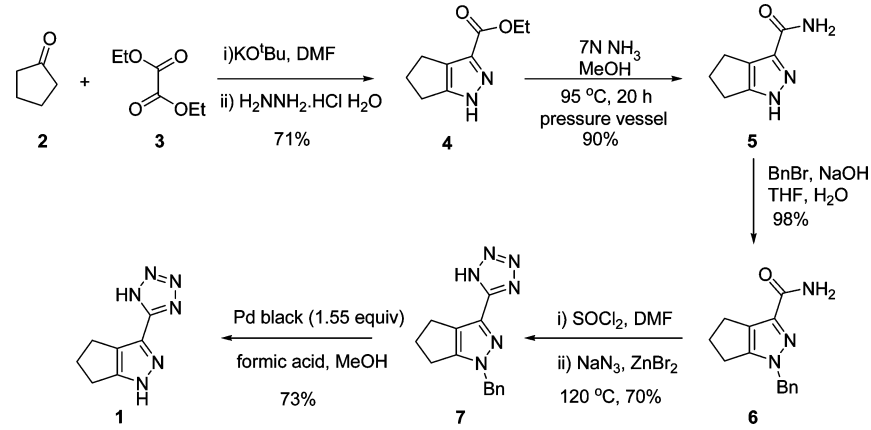
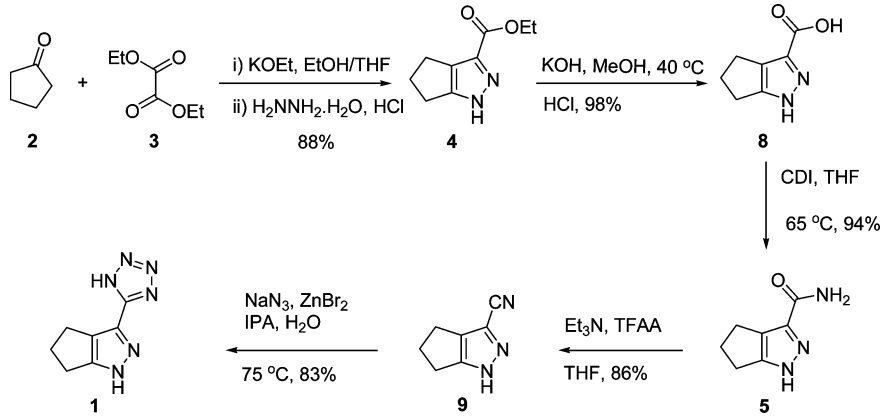
Scheme 1



Scheme 2



conditions (reaction of ester **4** with methanolic ammonia in a sealed vessel at 95 °C), vessel pressures in excess of 200 psi were generated. This pressure was beyond our vessel capabilities. Initially milder reaction conditions were screened, namely treatment of ester **4** with aqueous ammonia (35% w/w) in THF at room temperature. These conditions were found to be unacceptable and led to a substantially lower yield of amide **5** (63−75% yield based on recovered starting material). In addition the biphasic reaction was sluggish with incomplete conversion observed even after prolonged aging (240 h at 20 °C). Alternatively switching the solvent to 2-propanol and adding catalytic DMAP did increase the rate of the reaction; however, this increase was still insufficient, and incomplete conversion was observed after 96 h.

With the aminolysis performing poorly when milder conditions were employed, an alternative approach to **5** was pursued. The ester **4** was first hydrolyzed to the previously described acid[4] **8**. Saponification of **4** was achieved by treatment with potassium hydroxide in methanol at 40 °C, and following a pH adjustment with hydrochloric acid the desired acid **8** could be isolated in 98% yield as a white crystalline solid (Scheme 2). It was anticipated that **8** could be activated towards amide bond formation using standard methodology. However, a number of the standard techniques to convert **8** to amide **5** (i.e., formation of the corresponding acid chloride, mixed anhydride or using a carbodiimide-based coupling reagent) failed to provide any product, this was thought to be due to a combination of low solubility and apparent competitive reactivity of the pyrazole moiety with the electrophiles. Ultimately a wider screen of common coupling reagents identified 1,1-carbonyldiimidazole (CDI) as a potential activating agent for this transformation.

When acid **8** was treated with (CDI) in THF, clean formation of the imidazolide intermediate was achieved. Subsequently warming the resulting slurry to 60 °C in the presence of aqueous ammonia transformed the imidazolide to amide **5** which could be isolated as a crystalline solid in 94% yield. Warming the reaction mixture during CDI addition gave a steady and controllable rate of carbon dioxide extrusion, thus eliminating any potential risk of overpressurization. This scaleable alternative route to **5** adequately replaced the high-pressure aminolysis conditions.

Changing to milder amide dehydration conditions also proved critical in eliminating the need for benzyl protection of the pyrazole from the original route. Thus, dehydration of **5** with trifluoroacetic anhydride (TFAA) and triethylamine in THF yielded nitrile **9** as a crystalline solid in 86% yield. With the protecting group no longer required, attention was turned towards finding milder conditions for the tetrazole formation. It was found that tetrazole **1** could be formed at an acceptable rate and, more importantly, at a significantly lower temperature when the conditions reported by Sharpless[5,6] (NaN_3/$ZnBr_2$/IPA/H_2O), were employed. As a safety precaution the reaction was run at 75 °C with slow addition of an aqueous sodium azide solution. Under these conditions, the reaction was complete within 10 h and provided **1** in 83% yield. Operational hazard

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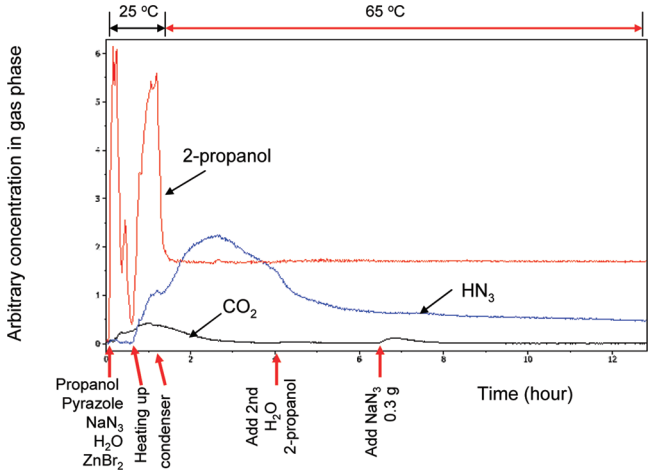

Figure 1. **Profiles of hydrazoic acid (HN_3), propanol in the headspace of the reaction at 65 °C in IPA and water.**

evaluation of this chemistry showed no untoward exotherms; however, analysis by ReactIR showed the presence of significant amounts of hydrazoic acid (HN_3) in the vapour phase (Figures 1 and 2). Hydrazoic acid is volatile, highly toxic, and potentially explosive.[5] No process modifications could be identified to significantly reduced this risk, and therefore this azide reaction was deemed too hazardous for scale-up.

The Second-Generation Synthesis

With the [3 + 2] cycloaddition reaction prohibiting the use on scale of the modified medicinal chemistry route, we were forced to adapt our second-generation synthesis for the provision of all bulk material for development. The second-generation approach relied on the ability to use tetrazole ester **10** as the coupling partner in the *pseudo*-Claisen reaction. The incorporation of a preformed tetrazole moiety in a starting material was obviously an attractive strategy for us as it obviated the use of azide as well as furnishing a more streamlined approach to **1**. In addition the use of the commercially available tetrazole ester[7] **10** in *pseudo*-Claisen reactions with ketones has previously been described.[8] This suggested that a new and much shorter synthesis of **1** might be possible by condensing cyclopentanone first with **10** followed by a reaction of the resulting intermediate **11** with hydrazine to generate **1** directly (Scheme 3).

Hence, a screen of appropriate solvents and bases was performed to identify optimal conditions for the condensation of **2** with **10**. The limited solubility of the sodium salt **10a** in most solvents necessitated the use of polar aprotic solvents, whilst the high solubility of diketone **11** (and/or its corresponding enol) in these solvents made any isolation difficult. We therefore focused on developing a one-pot process, wherein hydrazine was added directly to an acidified reaction mixture of the intermediate **11** to form **1** directly. As the free acid, **10b** is known to be shock sensitive and thermally unstable at

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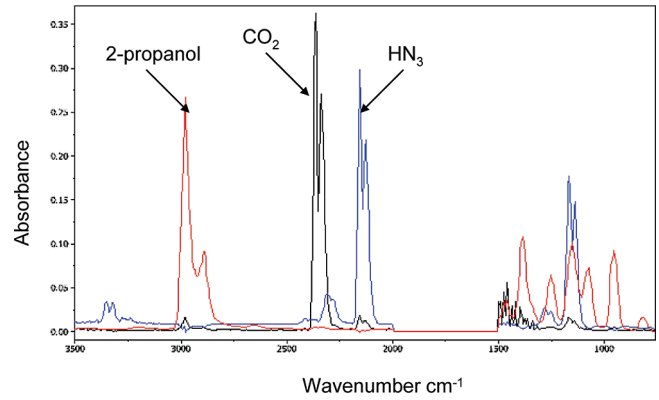
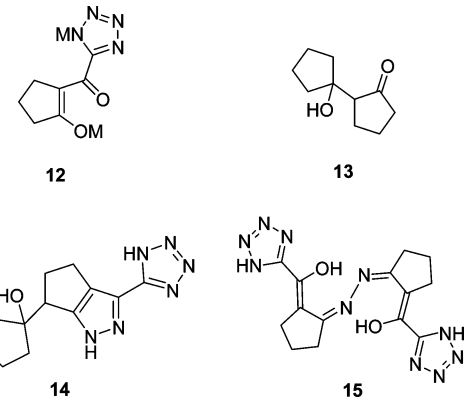


Figure 2. **Corresponding component spectra of hydrazoic acid (HN_3), propanol, and carbon dioxide for the reaction.**

elevated temperatures;[9] we therefore considered sodium salt **10a** as the reagent of choice.

The solvent screen identified that addition of a solution of KO^{t}Bu (2 equiv) in DMF to a solution of sodium salt **10a** and cyclopentanone **2** (1.3 equiv) in DMF between $-5 < T < 5$ °C gave optimum assay yields of salt **12** (50−60%). After acidification of the crude reaction mixture with concentrated hydrochloric acid (2.5 equiv) the stream was treated with 37% aqueous hydrazine (1 equiv) at 20 °C afford **1** in 48% assay yield. The formation of the hydroxy tetrazole **14** was typically observed as a byproduct in 4−5% yield.[10] Thus, these conditions became the basis of our process for the first bulk synthesis of **1**.



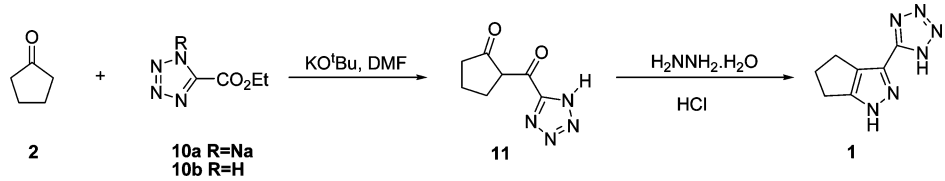
In an effort to optimize the reaction further we examined an inverse addition protocol in which **2** was added as a limiting reagent to a solution of **10a** in order to minimize the formation of **13**. Furthermore, it was found that the formation of **13** was reversible under the reaction conditions.[11] There were also concerns about the stability of **10a** in the reaction medium; however, experimentation showed that, whilst the presence of water was found to cause degradation of **10a**, anhydrous solutions were found to be stable and performed well in the

(9) Sodium salt **10a** and its corresponding free acid **10b** (prepared from the sodium salt **10a** by acidification and extraction into ethyl acetate) were characterized by DSC and drop-weight testing. Free acid **10b** proved thermally unstable at elevated temperature (140 °C) and was shock sensitive.

(10) The hydroxy tetrazole **14** is derived from the *pseudo*-Claisen condensation reaction of the sodium salt **10a** with the aldol product **13**.

(11) Subjecting **13** to typical condensation reaction conditions with **10a** generates mainly **1**, with <5% of **14** observed.

Scheme 3



condensation reaction.[12] Thus, under the optimal conditions, cyclopentanonone **2** was slowly added to a dry mixture of **10a** (1.2 equiv) and KO^{t}Bu (1.5 equiv) in DMF at −5 °C. Using these optimal conditions typically gave yields of the intermediate **11** in 88−96% yield, based on **2**. For the pyrazole formation step, it was found that quenching **12** with hydrochloric acid (2.25 equiv) was necessary prior to charging an excess of the 35.5 wt % hydrazine in water (2.20 equiv). If the hydrazine was undercharged (1.66 equiv), an orange reaction mixture with a low assay yield of **1** (67%) was observed. Under these conditions formation of hydrazone **15** was prevalent.[13] If a second charge of hydrazine (0.54 equiv) was added to this mixture, all of hydrazone **15** could be turned over to **1**. Under these optimized conditions **1** could be obtained in 92−93% overall assay yield, based on **2**. Impurity **14** is typically detected at <1% at the end of the reaction whilst **13** is not observed.

Finally a new convenient method to isolate the desired product from the crude reaction mixture was developed. After concentration of the mixture to a minimal volume *via* a vacuum distillation, a solvent switch to water and adjustment to pH 1 provided a slurry of **1** which could be simply isolated by filtration in a 90% yield. Analysis of this product determined it to be >99% pure.

Conclusions

We have developed and demonstrated on scale a new one-pot process for synthesis of the partial nicotinic acid receptor agonist **1**. The original discovery route required seven steps to yield **1** with an overall yield of 39%. This more streamlined approach provides a more practical and scaleable alternative synthesis, whilst increasing the overall isolated yield for the formation of **1** to 90%. The latter process also represents a viable manufacturing route to **1**, and successful demonstrations on 70-kg scale have been undertaken without incident.

Experimental Section

All reactions were carried out under a positive pressure of nitrogen. ^{1}H NMR spectra were obtained at 400 MHz, in the solvent indicated on a Bruker DPX 400 spectrometer. All purity values were obtained by HPLC analysis at 210 and 235 nm. The analysis for hydrazoic acid in the reaction headspace was carried out using an FTIR analyzer (ReactIR4000) equipped with an online gas cell (30 cc), connected to a 250 mL jacketed resin kettle.

1,4,5,6-Tetrahydro-3-(1*H*-tetrazol-5-yl)cyclopenta[*c*]pyrazole (1). Cyclopentanone (**2**, 3.36 kg; 40 mol) was added over 1 h to a solution of the 1*H*-tetrazole-5-carboxylic acid ethyl ester sodium salt (**10a**, 7.87 kg; 48 mol) and potassium *tert*-butoxide (6.74 kg; 60 mol) in DMF (75 L) between −2.5 and −5 °C. The batch was aged at 0 °C for an hour. Hydrochloric acid (9.88 L, 11 M) was added over 85 min, maintaining the temperature below 6 °C. A 35.5 wt % solution of hydrazine in water (8 L; 88.8 mol) was added over 35 min, maintaining the temperature below 10 °C. The reaction mixture was then aged for 18 h. HPLC analysis showed the assay yield of **1** was 92%. The mixture was distilled under reduced pressure, removing 65 L of solvent. Water (25 L) was added, and further solvent (31 L) was distilled off under reduced pressure. Water (125 L) was added, and the mixture was aged overnight to crystallize. Concentrated hydrochloric acid (11 M; 5.74 kg) was added to pH 1. The mixture was then aged for 2 h at 20−25 °C. The product was collected by filtration and washed with water (3 × 25 L), and dried *in vacuo* at 45 °C for 72 h, to give 1,4,5,6-tetrahydro-3-(1*H*-tetrazol-5-yl)cyclopenta[*c*]pyrazole (**1**, 6.33 kg) as a pale-yellow solid in 90% yield (>99% pure containing <0.2% aldol impurity **14**). ^{1}H NMR (d_6-DMSO): δ 2.73 (4H, m); 2.52 (2H, m). ^{13}C NMR (d_6-DMSO): δ 153.0, 150.5, 130.3, 126.3, 30.9, 23.7, 23.4. IR (KBr) 2932 (s, br), 2862 (s), 2676 (s, br), 1617 (s), 1419 (m), 1304 (s), 1161 (m), 1128 (m), 1077 (m), 1011 (s), 988 (m), 893 (m), 819 (m, br), 758 (m) cm^{-1}. Anal. Calcd for $C_7H_8N_6$: C, 47.72; H, 4.58: N, 47.70. Found: C, 47.69; H, 4.59; N, 47.70.

1,4,5,6-Tetrahydro-cyclopenta[*c*]pyrazole-3-carboxylic Acid Ethyl Ester (4). Potassium ethoxide (24.2 g; 288 mmol) was dissolved in ethanol (100 mL). This solution was added over 10 min to a mixture of cyclopentanone (**2**, 25 mL; 283 mmol) and diethyl oxalate (**3**, 39.2 mL; 288 mmol) in ethanol (125 mL). The mixture was heated to 29 °C, and held at this temperature for 1.5 h. The mixture was then cooled to 3 °C. Concentrated hydrochloric acid (28 mL; 12.2 M; 342 mmol) was added over 5 min, maintaining the temperature less than 10 °C. The reaction mixture was cooled to 0 °C, and a 55% solution of hydrazine hydrate (18.1 g; 311 mmol) was added over 20 min, maintaining the temperature below 2 °C. The reaction mixture was aged at this temperature for 1.5 h. The mixture was warmed to 10 °C, and then distilled under reduced pressure to remove 225 mL of solvent with simultaneous addition of water (225 mL). To the resulting pale-yellow slurry was charged a 5% solution of sodium bicarbonate (150 mL), and the resulting mixture was aged at 25 °C for 40 min. The slurry was then cooled to 10 °C and the product collected by filtration, washed with cold water (40 mL), and dried *in vacuo* at 65 °C to give 1,4,5,6-tetrahydro-cyclopenta[*c*]pyrazole-3-carboxylic acid ethyl ester (**4**, 45.0 g) as a off white solid (>99%

(12) It is important that the starting materials and the solvent are dry for the condensation reaction. The variance in assay yield for the formation of **1** appears to be directly attributable to water content with the highest yields deriving from the lowest KF reactions.

(13) Structure of the hydrazone **15** was determined by single-crystal X-ray diffraction analysis.

pure) in 88% yield,. ^{1}H NMR ($CDCl_3$): δ 10.00 (1H, broad s); 4.36 (2H, q, J=7.2 Hz); 2.80 (4H, m); 2.48 (2H, m); 1.37 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 160.8, 129.3, 60.8, 30.2, 24.4, 23.7, 14.3. IR (KBr) 2940 (s), 2863 (s), 1718 (s), 1524 (s), 1445 (s), 1388 (s), 1244 (s), 1113 (s), 1055 (s), 1023 (s), 873 (s), 846 (s), 785 (s) cm^{-1}. HRMS (+EI): found 181.0977 (Calcd 181.0982). The NMR data was consistent with known data of **4** in the literature.[4]

1,4,5,6-Tetrahydro-cyclopenta[*c*]pyrazole-3-carboxylic Acid (8). 1,4,5,6-Tetrahydro-cyclopenta[*c*]pyrazole-3-carboxylic acid ethyl ester (**4**, 10 g; 55.5 mmol) was slurried in methanol (50 mL), and then 4 M potassium hydroxide solution (31 mL; 122.1 mmol) was added. The mixture was heated to 43 °C and aged at this temperature for 1.5 h. The mixture was cooled to 10 °C, and 4 M hydrochloric acid (32 mL) was added over 5 min. The product precipitated out of solution. The slurry was chilled to 5 °C for 15 min. The product was collected by filtration, washed with cold water (10 mL) and dried *in vacuo* at 65 °C to give 1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylic acid (**8**, 8.31 g) as a white solid (>99.7% pure) in 98% yield. ^{1}H NMR (d_6-DMSO): δ 12.90 (1H, broad s); 2.64 (4H, m); 2.38 (2H, m). ^{13}C NMR (d_6-DMSO): δ 161.9, 128.7, 30.3, 24.2, 23.7. IR (KBr) 3252 (s, br), 2939 (s, br), 1704 (s), 1555 (s), 1469 (s), 1328 (s), 1304 (s), 1252 (s), 1205 (m), 1126 (s), 1060 (s), 785 (s), 711 (s) cm^{-1}. HRMS (+EI): found 153.0664 (calcd 153.0663). The NMR data was consistent with known data of **8** in the literature.[4]

1,4,5,6-Tetrahydro-cyclopenta[*c*]pyrazole-3-carboxamide (5). A mixture of 1,4,5,6-Tetrahydro-cyclopenta[*c*]pyrazole-3-carboxylic acid (**8**, 13 g; 85.5 mmol) and 1,1-carbonyldiimidazole (15.25 g; 94.1 mmol) in THF (195 mL) was heated to 60 °C over the course of an hour. The reaction initially became a thick slurry, and the emission of carbon dioxide was observed. At the end of this period a clear brown solution had formed. The reaction was cooled down to 25 °C, and a 35% solution of ammonium hydroxide (12.5 mL) was added in one portion. The slurry was aged at 25 °C for 30 min and then cooled to 7 °C. The product was collected by filtration, washed with chilled (0 °C) THF (20 mL) and dried *in vacuo* to give 1,4,5,6-tetrahydro-cyclopenta[*c*]pyrazole-3-carboxamide (**5**, 12.18 g) as a white solid (>99.7% pure) in 94% yield. ^{1}H NMR (d_6-DMSO): δ 12.38 (1H, broad s); 6.78 (2H, broad s); 2.68 (4H, m); 2.47 (2H, m). ^{13}C NMR (d_6-DMSO): δ 163.2, 126.4, 30.81, 24.0, 23.7. IR (KBr) 3362 (m), 3179 (s), 2929 (s), 2858 (s), 1671 (m), 1636 (s), 1597 (s), 1572 (s), 1492 (m), 1444 (m), 1295 (s), 1256 (s), 1132 (m), 1076 (s), 1042 (m), 839 (m), 771 (m), 645 (s) cm^{-1}. HRMS (+EI): found 152.0824 (calcd 152.0826).

1,4,5,6-Tetrahydro-3-cyano-cyclopenta[*c*]pyrazole (9). A suspension of 1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxamide (**5**, 8 g; 52.9 mmol) in THF (40 mL) was cooled to −10 °C. To the mixture was added triethylamine (11 mL), followed by the slow addition of trifluoroacetic anhydride (15.7 mL) over 40 min whilst maintaining the temperature between −10 and −5 °C. The reaction was aged for 3 h and then quenched by the slow addition of saturated sodium bicarbonate solution (200 mL) to the mixture, maintaining the temperature below 0 °C. The THF was removed by distillation under reduced pressure, to give a suspension. The product was collected by filtration, washed with water (50 mL), and dried *in vacuo* to 50 °C to give 1,4,5,6-tetrahydro-3-cyano-cyclopenta[*c*]pyrazole (**9**, 6.4 g) as a white crystalline solid (>99.7% pure) in 90% yield. ^{1}H NMR (d_6-DMSO): δ 13.50 (1H, broad s); 2.68 (4H, m); 2.50 (2H, m). ^{13}C NMR (d_6-DMSO): δ 152.0, 131.0, 117.9, 115.5, 30.9, 23.6, 22.5. IR (KBr) 3264 (s), 2982 (m), 2961 (m), 2936 (m), 2242 (s), 1556 (s), 1515 (s), 1466 (m), 1446 (m), 1306 (m), 1297 (s), 1258 (s), 1210 (m), 1122 (s), 1053 (s), 824 (s), 611 (s) cm^{-1}. HRMS (+EI): found 175.0984 (calcd 175.0979).

1,4,5,6-Tetrahydro-3-(1*H*-tetrazol-5-yl)cyclopenta[*c*]pyrazole (1). 1,4,5,6-Tetrahydro-3-cyano-cyclopenta[*c*]pyrazole (**9**, 2.6 g; 19.5 mmol), sodium azide (2.0 g; 30.8 mmol) and zinc bromide (4.5 g, 20.0 mmol) were dissolved in a mixture of propan-2-ol (90 mL) and water (35 mL). The solution was stirred and heated at 75 °C for 7.5 h. A second charge of sodium azide (0.3 g, 4.6 mmol) was added, and the mixture was heated for a further 5 h and then cooled to 25 °C. The mixture was acidified with 2 M hydrochloric acid (50 mL) to give a clear, pale-yellow solution. The propan-2-ol was distilled under reduced pressure and the resulting slurry diluted with water (100 mL). The product was collected by filtration, washed with water (50 mL), and dried *in vacuo* at 50 °C to give 1,4,5,6-tetrahydro-3-(1H-tetrazol-5-yl)cyclopenta[*c*]pyrazole (**1**, 2.9 g) as a white crystalline solid (>99.1% pure) in 85% yield.

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