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A General, One-Step Synthesis of Substituted Indazoles using a Flow Reactor

Rob C. Wheeler,* Emma Baxter, Ian B. Campbell, and Simon J. F. Macdonald

GlaxoSmithKline, Gunnels Wood Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

Supporting Information

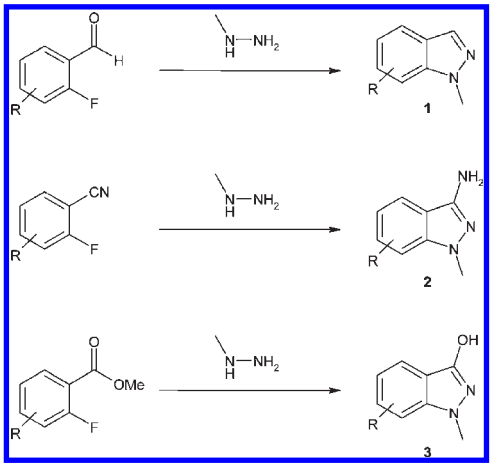
ABSTRACT: Flow chemistry is a rapidly emerging technology within the pharmaceutical industry, both within medicinal and development chemistry groups. The advantages of flow chemistry, increased safety, improved reproducibility, enhanced scalability, are readily apparent, and we aimed to exploit this technology in order to provide small amounts of pharmaceutically interesting fragments via a safe and scalable route, which would enable the rapid synthesis of multigram quantities on demand. Here we report a general and versatile route which utilises flow chemistry to deliver a range of known and novel indazoles, including 3-amino and 3-hydroxy analogues.

INTRODUCTION

As part of an ongoing medicinal chemistry program, we were interested in synthesising a range of 5- and 6-substituted *N*-methylindazoles (**1**), which can be synthesised via the condensation of methylhydrazine with the corresponding 2-fluorobenzaldehyde (scheme 1). This approach was particularly attractive to us due to the relatively large set of commercial 2-fluorobenzaldehydes available, but we were surprised to find the reaction is not widely precedented, and we were only able to locate isolated examples in the literature.[1] Condensations with hydrazine are slightly more common, and although recent publications by Lukin[2] and Slade[3] demonstrate the versatility of the reaction, the yields are variable (0−82% and 38−66%, respectively) and the reaction times long (3−36 h). We also reasoned that this approach could be applied to give 3-aminoindazoles (**2**) and 3-hydroxyindazoles (**3**) from 2-fluorobenzonitriles and benzoates respectively (scheme 1). Once again, we were surprised to learn that, although the S_NAr condensation between hydrazines and 2-fluorobenzonitriles is fairly well reported,[4] there are very few reported procedures for the synthesis of 3-hydroxyindazoles from 2-fluorobenzoates.[5] Additionally, we hoped to identify a generic route which would utilise unsubstituted hydrazine, thus enabling us to diversify around the 1-position at a later date. However, the hazards with using hydrazines under forcing conditions are well-known,[6] and this issue, together with the long reaction times cited in the literature, pointed towards a potentially scale-limited route.

We therefore considered utilising flow chemistry techniques as a means of providing a safe, scalable alternative in order to deliver the small quantities of monomers required, and also to facilitate scale-up on-demand. Flow chemistry reactions are now widely documented in the literature,[7,8] and the technology is becoming increasingly prominent in the pharmaceutical industry.[9] Our group has previously demonstrated the use of flow reactors to safely control reaction exotherms,[10] and also the use of flow microwaves to achieve selective bromination of a substituted benzene.[11] Indeed, one of the perceived advantages of flow chemistry is the ability to safely perform reactions at elevated temperatures and pressures, and as such it is often compared to microwave synthesis.[12] We aimed to exploit this approach to enable us to safely synthesise a range of indazoles using a Vapourtec R4,[13] a commercial flow reactor system which has the capacity to heat reactions to 250 °C.

Scheme 1. Routes to indazoles, including the 3-amino and 3-hydroxy analogues



RESULTS AND DISCUSSION

We elected to use 5-nitro-2-fluorobenzaldehyde as a model compound in order to assess any solvent, temperature, and reaction time effects on the reaction profile (Scheme 2). Using only mild conditions, in order to ensure that we did not drive the reaction to completion so that we could ascertain the effect of changing the conditions on the reaction profile (75 °C, 15 min), we studied a short-range of solvents which had been selected to give us good predicted solubilities of both reagents and products. We performed

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Scheme 2. Two common reaction pathways for the hydrazone intermediate (4), giving either the indazole (1) or the azine (5)

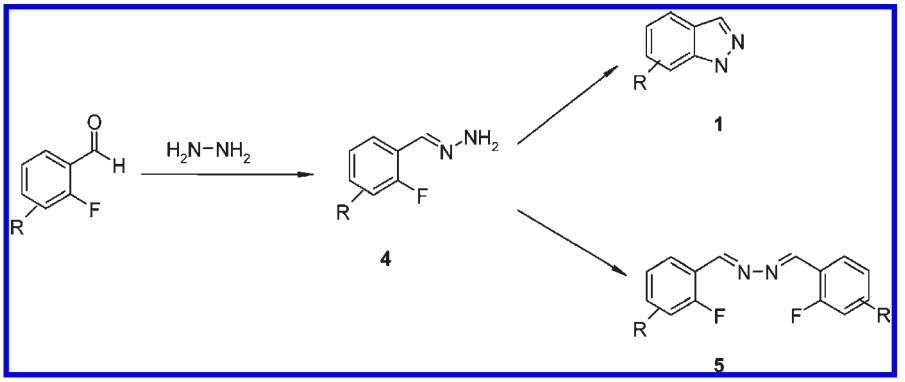
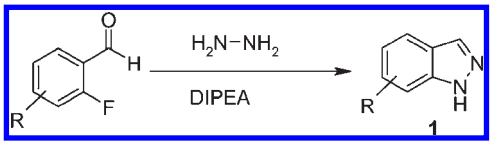


Figure 1. Vapourtec R4 flow reactor setup.

these optimisation studies on a Vapourtec R4+ (Figure 1), injecting 1 mL each of the aldehyde and hydrazine solutions in the appropriate solvent (0.5M). The collected reactions were analysed by LC/MS (Table 1), and the results indicated a mixture of the required indazole (**1**), the hydrazone intermediate (**4**), and a dimer formed between the condensation of the hydrazone with a second molecule of the aldehyde (the azine, **5**) in all cases. However, we observed good conversion to the required indazole/hydrazone in NMP and DMA, whereas dioxane, ethanol, and methanol began to favour unacceptably high conversion to the azine. Hence, we selected DMA as our solvent of choice, due to its ease of removal compared to NMP, and we found that we could drive the reaction to near completion by increasing the temperature to 150 °C (entry 6). Reducing the reaction time under these conditions had no effect on the reaction profile (entries 6−8).

Using an arbitrary reaction time of 30 min, we then applied these conditions to the more electron-rich 4-methoxy-2-fluorobenzaldehyde, and the azine was the major component detected by LC/MS (entry 9). This result was presumably due to the inductive effect of the *p*-methoxy group increasing the nucleophilicity of the hydrazone NH_2 whilst simultaneously deactivating the ring towards nucleophilic attack. We therefore reasoned that reducing the temperature to 25 °C might enable quantitative formation of the hydrazone, which could then be heated in a second reactor to induce cyclisation; however, when this was attempted, we still observed almost complete conversion to the azine (entry 10). Increasing the temperature to 250 °C resulted

Table 1. Conversion to the indazole 1 by LCMS analysis



entry	aldehyde	time (min)	solvent	temp. (°C)	indazole (%)	hydrazone (%)	azine (%)
1	5-NO2	15	Dioxan	75	10	16	49
2	5-NO2	15	DMA	75	63	29	9
3	5-NO2	15	NMP	75	63	28	9
4	5-NO2	15	MeOH	75	39	25	36
5	5-NO2	15	EtOH	75	29	23	45
6	5-NO2	15	DMA	150	82	5	10
7	5-NO2	10	DMA	150	82	5	10
8	5-NO2	5	DMA	150	83	5	12
9	4-OMe	30	DMA	150	3	9	72
10	4-OMe	30	DMA	25	0	9	80
11	4-OMe	30	DMA	250	12	6	53
12	4-OMe	30	DMA	250[a]	12	5	3
13	H	30	DMA	150	trace	17	53
14	4-Br	30	DMA	150	3	76	15
15	4-Me	30	DMA	150	0	24	74
16	H	30	DMA	250	trace	11	30
17	4-Br	30	DMA	250	46	0	5
18	4-Me	30	DMA	250	trace	9	69

[a] 10 equiv hydrazine used.

in a small increase in conversion to the indazole together with a marked decrease in the amount of azine produced (entry 11), although a number of side reactions involving the hydrazone and decomposing DMA were also observed. Using a large excess of hydrazine, in accordance with the mechanism outlined by Lukin,[2] did not offer any advantage (entry 12). Other, less electron-rich benzaldehydes also afforded the indazole in either poor conversion (150 °C, entries 13−15) or in low purity (250 °C, entries 16−18), with a major product being the *N*-acetylhydrazone. Use of alternative solvents (NMP, DMSO, EtOH, dioxane) and bases (DBN, DABCO, Barton's base) to alleviate this issue offered no

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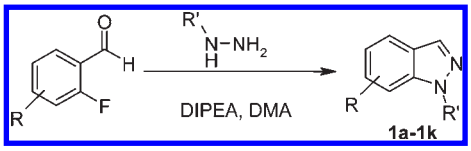
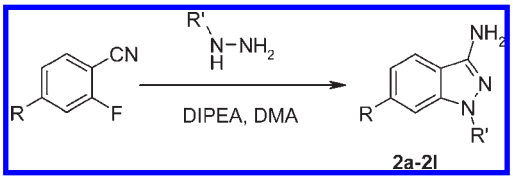
Table 2. Conditions and isolated yields for compounds 1a−1k



entry	aldehyde	R′	temp (°C)	isolated yield (%)
1a	5-NO2	H	250	69
1b	4-OMe	H	250[a]	18
1c	4-Br	H	250	28
1d	5-NO2	Me	150	71
1e	H	Me	250	41
1f	4-OMe	Me	250	65
1 g	4-Br	Me	250	49
1 h	4-Me	Me	250	44
1i	aacetophenone	Me	250	57
1j	3-Aza	Me	250	73
1k	5-NO2	Bn	250	18

[a] 10 equiv hydrazine used.

Table 3. Conditions and isolated yields for compounds 2a−2l

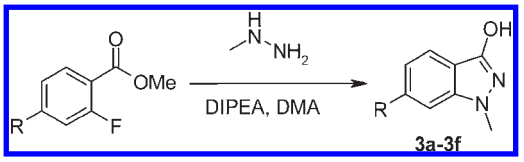


entry	nitrile	R′	isolated yield (%)
2a	4-NO2	H	54
2b	H	H	38
2c	5-OMe	H	29
2d	4-Br	H	49
2e	4-Me	H	64
2f	3-Aza-nitrile	H	0[a]
2g	4-NO2	Me	63
2h	H	Me	43
2i	5-OMe	Me	0[b]
2j	4-Br	Me	62
2k	4-Me	Me	25
2l	3-Aza-nitrile	Me	57

[a] Reactor blocked. [b] 6% conversion by LC/MS.

improvement in conversion, with large amounts of dimerisation still observed with neutral and electron-rich benzaldehydes. Regrettably, this would appear to be a fundamental problem with this approach, and may account for the minimal precedent and low yields in the literature. Nevertheless, we did successfully isolate three 1-*H* indazoles in this manner (Table 2, entries **1a**−**1c**), although we recognise that the yields may be further improved by more research in this area.

Table 4. Conditions and isolated yields for compounds 3a−3f



entry	benzoate	isolated yield (%)
3a	4-NO2	76
3b	H	55
3c	4-OMe	12
3d	4-Br	70
3e	4-Me	25
3f	3-Aza-ester	57

We therefore decided to pursue the synthesis of a range of 1-methylindazoles using this approach, as we were curious as to whether it would be possible to selectively synthesise these compounds by condensing the appropriate 2-fluorobenzaldehyde with a *limiting* amount of methylhydrazine. We also reasoned that the risk of dimer formation would be suppressed by virtue of the reduced nucleophilicity of the methylated hydrazone. Indeed, we observed that a 30-min reaction at 250 °C with methylhydrazine afforded the desired *N*-methylindazoles in moderate yield, although the reaction with benzylhydrazine proceeded less satisfactorily (Table 2, entries **1d**−**1k**). Using these semioptimised conditions, we successfully scaled-up entry **1d** to give 14.4 g of the 5-nitroindazole in 69% yield. It should be noted that we observed some off-gassing in the lines containing the methylhydrazine solution during this large-scale reaction, although we found that the pump was able to cope with the small amount of gas produced and we detected almost no change in the reaction profile over the course of the reaction.

We next applied these conditions (30 min, 250 °C) to the synthesis of 3-aminoindazoles via the condensation of methylhydrazine with the appropriate 2-fluorobenzonitrile. LC/MS analysis indicated a poor reaction profile in most cases, with a major impurity being the 2-(dimethylamino)benzonitrile, derived from the decomposition of DMA. We therefore elected to repeat the experiments at a lower temperature, arbitrarily selected as 150 °C, and observed acceptable, although moderate, conversion in most cases (the exception being the electron-rich 4-methoxy compound) and with only low amounts of the impurity detected. These preliminary results indicate that a range of 3-aminoindazoles can be prepared in this manner, although we recognise that the moderate conversions reported here may be improved upon with further optimisation (Table 3, entries **2g**−**2l**). Furthermore, condensation of these benzonitriles with unsubstituted hydrazine (10 equiv) under these conditions gave modest conversion to the 1*H*-aminoindazole (Table 3, entries **2a**−**2e**). Upon scale-up (compound **2b**, 50 mmol), we observed no change in the reaction profile by LC/MS and successfully isolated the required compound in 41% yield.

Finally, we utilised these semioptimised conditions (150 °C, 30 min, DMA) to synthesise a short range of substituted 3-hydroxyindazoles in acceptable yield (compounds **3a**−**3f**, Table 4), with the exception of the electron-rich 4-methoxybenzoate (entry **3c**). These results further validate the methodology, which successfully enabled us to rapidly synthesise a diverse set of interesting

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analogues without investing any further time in reaction optimisation.

CONCLUSION

Here we have presented a versatile route to enable the rapid and safe syntheses of a range of N-methylated indazoles and analogues, both known and novel. Although we recognise that, in most cases, the yields are somewhat moderate, these semi-optimised "fit for purpose" conditions facilitated rapid synthesis and scale-up as required without the need for any further optimisation. Furthermore, this approach represents a safe, practical, and scalable method of performing high-temperature reactions involving hydrazine, which would otherwise be potentially hazardous in batch mode.

EXPERIMENTAL SECTION

All reagents and solvents were of analytical grade and were used without further purification. NMR spectra were recorded on a Bruker Avance Ultrashield 400 using tetramethylsilane (TMS) as an internal standard. LC/MS analyses were carried out on an Agilent Series 1100 HPLC coupled to a Waters Micromass ZQ mass spectrometer. Chromatography was performed using IST Isolute Flash Si cartridges.

Flow Reactor Setup. A Vapourtec R4+ was used in all flow reactions, and a 10-mL stainless steel reactor was used to perform the optimisation and small-scale reactions. The entire system was first flushed with DMA and the temperature allowed to stabilise before manually injecting the reagents (2 mL of each) via the Rheodyne valves. DMA was used as the system solvent. The large-scale reactions were carried out using 4 × 10 mL PFA reactors linked together in series. The collected reactions were then either analysed by LC/MS or worked up as below.

General Procedure A. *Synthesis of Indazoles.* Solution A = benzaldehyde (1.0 mmol) + DMA (2 mL); solution B = methylhydrazine (1.2 mmol) + DIPEA (1.05 mmol) + DMA (2 mL). Solutions injected 1:1 (v/v) and driven through the system (10-mL stainless steel reactor, set to either 150 or 250 °C, using a 250-psi backpressure regulator at the reactor output) at a total flow rate of 0.334 mL/min using DMA as the system solvent. The collected reactions were concentrated under reduced pressure, and the residue was purified by flash column chromatography (20 g silica, 0−100% EtOAc in cyclohexane) to give the desired indazole.

5-Nitro-1H-indazole (1a): yield: 69% as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (1H, d, J = 1.8), 8.33 (2H, m), 7.60 (1H, d, J = 9.0). No NH observed.

6-(Methyloxy)-1H-indazole (1b): yield 18% as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.9 (1H, bs), 7.98 (1H, s), 7.62 (1H, d, J = 8.8), 6.88 (1H, bs), 6.85 (1H, dd, J = 8.8, 2.3), 3.88 (3H, s).

6-Bromo-1H-indazole (1c): yield 28% as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (1H, s), 7.70 (1H, s), 7.64 (1H, d, J = 8.5), 7.29 (1H, dd, J = 8.5, 1.3).

1-Methyl-5-nitro-1H-indazole (1d): yield 71% as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (1H, d, J = 2.0), 8.30 (1H, dd, J = 9.3, 2.0), 8.21 (1H, s), 7.47 (1H, d, J = 9.3), 4.16 (3H, s).

1-Methyl-1H-indazole (1e): yield 41% as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (1H, s), 7.74 (1H, d, J = 8.0), 7.41 (2H, m), 7.16 (1H, m), 4.10 (3H, s).

1-Methyl-6-(methyloxy)-1H-indazole (1f): yield 65% as a pale-pink solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (1H, s), 7.58 (1H, d, J = 8.8), 6.81 (1H, dd, J = 8.8, 2.0), 6.72 (1H, bs), 4.03 (3H, s), 3.91 (3H, s).

6-Bromo-1-methyl-1H-indazole (1g): yield 49% as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (1H, bs), 7.60 (2H, m), 7.26 (1H, m), 4.05 (3H, s).

1,6-Dimethyl-1H-indazole (1h): yield 44% as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (1H, s), 7.61 (1H, d, J = 8.0), 7.18 (1H bs), 6.99 (1H, d, J = 8.3), 4.05 (3H, s), 2.52 (3H, s).

1,3-Dimethyl-1H-indazole (1i): yield 57% as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (1H, d, J = 8.3), 7.37 (2H, m), 7.14 (1H, m) 4.01 (3H, s), 2.58 (3H, s).

1-Methyl-1H-pyrazolo[3,4-b]pyridine (1j): yield 73% as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (1H, dd, J = 4.5, 1.5), 8.06 (1H, dd, J = 8.1, 1.5), 8.00 (1H, s), 7.11 (1H, dd, J = 8.1, 4.5), 4.17 (3H, s).

5-Nitro-1-(phenylmethyl)-1H-indazole (1k): yield 18% as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (1H, d, J = 2.0), 8.30 (1H, s), 8.27 (1H, dd, J = 9.2, 2.1), 7.44 (1H, d, J = 9.3), 7.23−7.41 (5H, m), 5.69 (2H, s).

Synthesis of 3-Aminoindazoles. General procedure A was followed, with the temperature of the flow reactor set to 150 °C.

6-Nitro-1H-indazol-3-amine (2a): yield 54% as an orange solid. ^{1}H NMR (400 MHz, DMSO): δ = 12.11 (1H, bs), 8.12 (1H, d, J = 1.8), 7.91 (1H, d, J = 8.8), 7.72 (1H, dd, J = 8.8, 2.0), 5.70 (2H, bs).

1H-Indazol-3-amine (2b): yield 38% as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (1H, d, J = 8.3), 7.35 (2H, m), 7.09 (1H, t, J = 7.3), 3.78 (3H, bs).

5-(Methyloxy)-1H-indazol-3-amine (2c): yield 29% as a pale-pink solid. ^{1}H NMR (400 MHz, MeOD): δ = 7.20 (1H, d, J = 9.0), 7.12 (1H, d, J = 2.3), 6.99 (1H, dd, J = 9.0, 2.3), 3.82 3H, s).

6-Bromo-1H-indazol-3-amine (2d): yield 49% as a pale-pink solid. ^{1}H NMR (400 MHz, MeOD): δ = 7.59 (1H, d, J = 8.5), 7.47 (1H, d, J = 1.3), 7.09 (1H, dd, J = 8.5, 1.5).

6-Methyl-1H-indazol-3-amine (2e): yield 64% as a white, crystalline solid. ^{1}H NMR (400 MHz, DMSO): δ = 11.16 (1H, s), 7.53 (1H, d, J = 8.3), 6.98 (1H, s), 6.72 (1H, dd, J = 8.3), 5.21 (2H, s), 2.36 (3H, s).

1-Methyl-6-nitro-1H-indazol-3-amine (2g): yield 63% as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (1H, d, J = 1.5), 7.87 (1H, dd, J = 8.9, 1.9), 7.64 (1H, d, J = 8.8), 4.15 (2H, bs), 3.96 (3H, s).

1-Methyl-1H-indazol-3-amine (2h): yield 43% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (1H, d, J = 8.0), 7.35 (1H, m), 7.22 (1H, d, J = 8.5), 7.02 (1H, t, J = 7.4), 4.04 (2H, bs), 3.86 (3H, s).

6-Bromo-1-methyl-1H-indazol-3-amine (2j): yield 62% as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (2H, m), 7.11 (1H, m), 4.03 (2H, bs), 3.81 (3H, s).

1,6-Dimethyl-1H-indazol-3-amine (2k): yield 25% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (1H, d, J = 8.3), 6.99 (1H, s), 6.85 (1H, d, J = 8.3), 4.04 (2H, bs), 3.81 (3H, s), 2.48 (3H, s).

1-Methyl-1H-pyrazolo[3,4-b]pyridin-3-amine (2l): yield 57% as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (1H, dd, J = 4.8, 1.5), 7.88 (1H, dd, J = 7.8, 1.5), 6.93 (1H, dd, J = 7.9, 4.7), 3.97 (2H, bs), 3.92 (3H, s).

Synthesis of 3-Hydroxyindazoles. General Procedure A was followed, with the temperature of the flow reactor set to 150 °C.

1-Methyl-6-nitro-1,2-dihydro-3H-indazol-3-one (3a): yield 76% as a yellow solid. ^{1}H NMR (400 MHz, DMSO): δ = 11.03 (1H, bs), 8.50 (1H, d, J = 1.5), 7.84 (1H, m), 7.77 (1H, m), 3.93 (3H, s).

1-Methyl-1,2-dihydro-3H-indazol-3-one (3b): yield 55% as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (1H, d, J = 8.1), 7.60 (1H, bs), 7.44 (1H, t, J = 7.7), 7.23 (1H, d, J = 8.4), 7.09, (1H, t, J = 7.5), 3.85 (3H, s).

1-Methyl-6-(methyloxy)-1,2-dihydro-3H-indazol-3-one (3c): yield 12% as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ = 10.52 (1H, bs), 7.45 (1H, d, J = 8.4), 6.87 (1H, d, J = 1.8), 6.59 (1H, dd, J = 8.6, 2.0), 3.81 (3H, s), 3.65 (3H, s).

6-Bromo-1-methyl-1,2-dihydro-3H-indazol-3-one (3d): yield 70% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (1H, d, J = 8.5), 7.43 (1H, s), 7.19 (1H, dd, J = 8.5, 1.3), 3.83 (3H, s). No OH observed.

1,6-Dimethyl-1,2-dihydro-3H-indazol-3-one (3e): yield 25% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (1H, bs), 7.65 (1H, d, J = 8.1), 7.00 (1H, s), 6.92 (1H, d, J = 8.4), 3.79 (3H, s), 2.50 (3H, s).

1-Methyl-1,2-dihydro-3H-pyrazolo[3,4-b]pyridin-3-one (3f): yield 57% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (1H, dd, J = 4.6, 1.6), 8.12 (1H, dd, J = 8.0, 1.5), 7.07 (71H, dd, J = 7.9, 1.6). No OH observed.

General Procedure B. *Synthesis of 2-Fluorobenzoates.* To a suspension of benzoic acid (10 mmol) in DCM (30 mL) was added oxalyl chloride (10.5 mmol) and DMF (2−3 drops). The reaction was then stirred until a solution had formed and no further gas evolution was observed before treating with methanol (5 mL). After stirring at RT for 30 min, the volatiles were stripped under reduced pressure, and the residue was partitioned between water/DCM. The organics were washed with $NaHCO_3$ solution, passed though a hydrophobic frit, and dried to give the methylbenzoate.

2-Fluoro-4-(methyloxy)benzoic acid: yield 93% as a white solid ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (1H, t, J = 8.7), 6.73 (1H, dd, J = 8.8, 2.5), 6.64 (1H, dd, J = 12.7, 2.4), 3.91 (3H, s), 3.86 (3H, s).

Methyl-4-bromo-2-fluorobenzoate: yield 97% as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (1H, m), 7.37 (2H, m), 3.94 (3H, s).

Methyl-2-fluoro-4-methylbenzoate: yield 92% as an off-white solid ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (1H, t, J = 7.9), 7.01 (1H, d, J = 8.0), 6.95 (1H, d, J = 11.8), 3.92 (3H, s), 2.40 (3H, s).

■ ASSOCIATED CONTENT

Supporting Information. Detailed NMR characterisation data for representative *N*-methylindazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
rob.c.wheeler@gsk.com

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