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A flexible synthesis of C-6 and N-1 analogues of a 4-amino-1,3-dihydroimidazo[4,5-*c*]pyridin-2-one core

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ABSTRACT

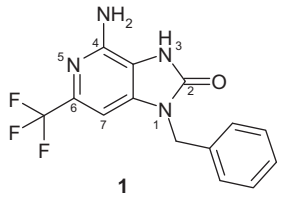
A flexible route which enables access to derivatives of 4-amino-1,3-dihydroimidazo[4,5-*c*]pyridin-2-ones is described. Issues of selectivity, reaction safety, and low yields in original routes are overcome with the key improvements to the route, including a Negishi cross-coupling and use of a carbamate as a protecting group and intrinsic carbonyl source. The new route enables variation of C-6 and N-1 substituents.

As part of a programme to indentify small molecule agonists of the TLR7 receptor for antiviral applications, we recently reported the discovery of a potent and selective lead, PF-4171455 (**1**, Fig. 1)[1–3] and subsequent optimisation of this lead.[4] As part of this optimisation, analogues of **1** that replaced the C-6 trifluoromethyl and N-1 benzyl groups with heterocyclic functionality were considered attractive targets. At the time, there were no known routes in the literature to allow flexible variation at both of these positions. Therefore, a new route was devised which utilised a cross-coupling strategy. Issues of selectivity and low yields in our initial routes were overcome to allow these targets to be synthesised in an efficient and flexible manner.

Our initial strategy is exemplified by the disconnection of oxazole target **2** (Scheme 1). The target was disconnected to the bromo-pyridine intermediate **6** and commercial 2-tributylstannyloxazole (**7**). In the forward direction, Stille coupling of these components should yield intermediate **5**. The nitro group could then be reduced and the resulting product could be cyclised with a suitable carbonyl equivalent, such as *N,N′*-carbonyldiimidazole (CDI) or triphosgene. Selective debenzylation would lead to **2**.

The synthesis of the desired pyridine coupling partner **6** is shown in Scheme 2. 2,6-Dibromopyridine was *N*-oxidised using urea hydrogen peroxide (UHP) and trifluoroacetic anhydride (TFAA) to give **9**. Nitration under forcing conditions yielded **10**. Selective reduction of the nitro and *N*-oxide moieties followed by a second nitration and rearrangement yielded **13**. Diazotisation in the presence of HCl gave **14** which was reacted with an excess of benzylamine to yield **6**. Each step in this initial sequence required great care due to the exothermic profile of many of the reaction steps and the potential high energy nature of *N*-oxide and nitro compounds.[5]

Pyridine derivative **6** was then used in the first successful synthesis of the target **2**, shown in Scheme 3. The Stille coupling was carried out under microwave irradiation. Catalytic hydrogenation over Raney Ni reduced the nitro group to yield the triaminopyridine **4**. CDI cyclisation gave an inseparable mixture of regioisomers (in an approximate 1:1 ratio). Debenzylation of the mixture with concentrated H_2SO_4 yielded the desired product **2**, which was separated from its regioisomer by preparative HPLC.[6] There were several problems with this initial route which required



1

Figure 1. PF-4171455 (**1**) lead molecule with atom numbering of the core.

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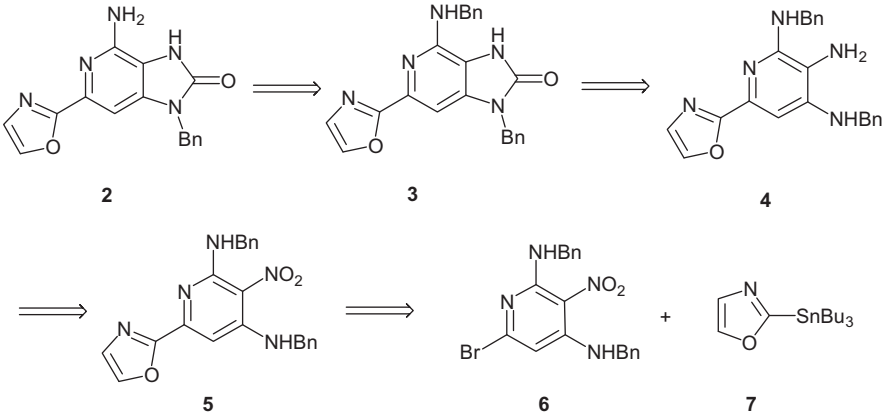
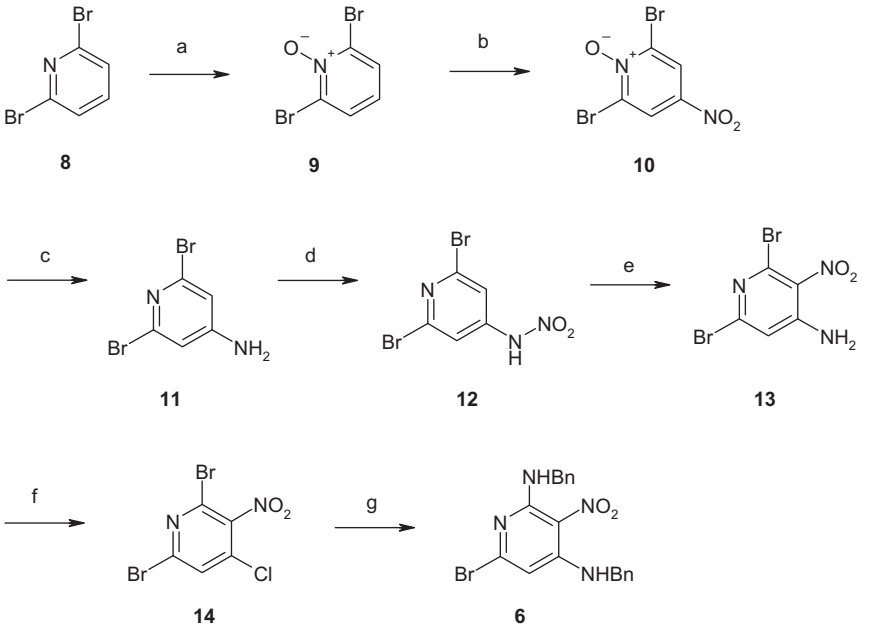


Scheme 1. Disconnection of a C-6 oxazole target.

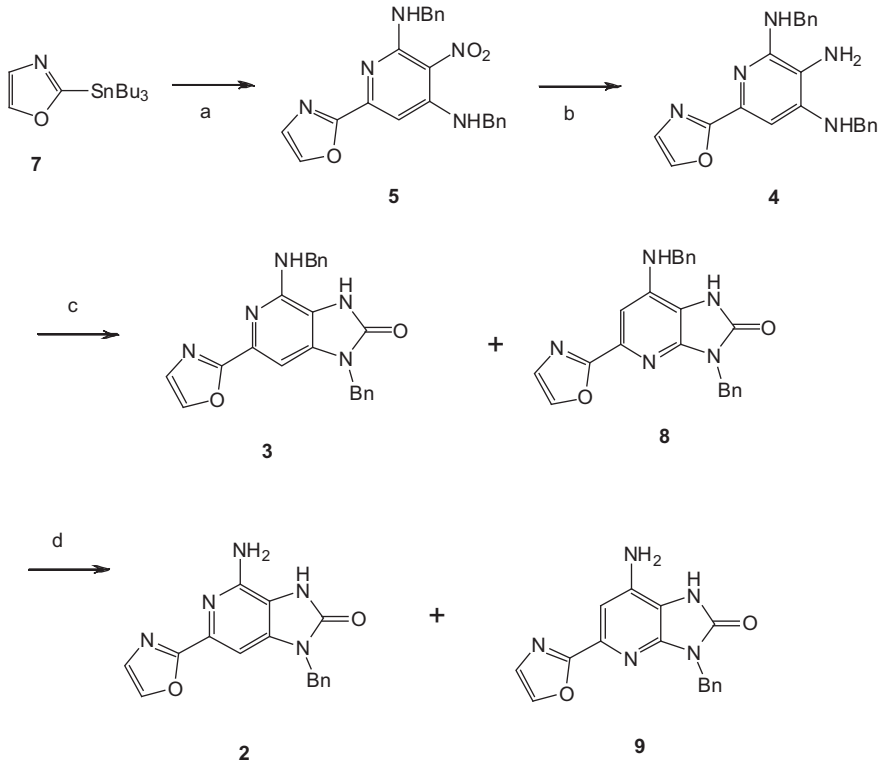


Scheme 2. Reagents and conditions: (a) UHP, TFAA, CH_2Cl_2, rt, 57%; (b) fuming HNO_3, concd H_2SO_4, 85 °C, 93%; (c) Fe/AcOH, 30–40 °C, 90%; (d) concd HNO_3, concd H_2SO_4, 5 °C, quant.; (e) concd H_2SO_4, 50–55 °C, 83%; (f) $NaNO_2$, concd HCl; (g) $BnNH_2$, THF, 50 °C, 61% (over two steps).

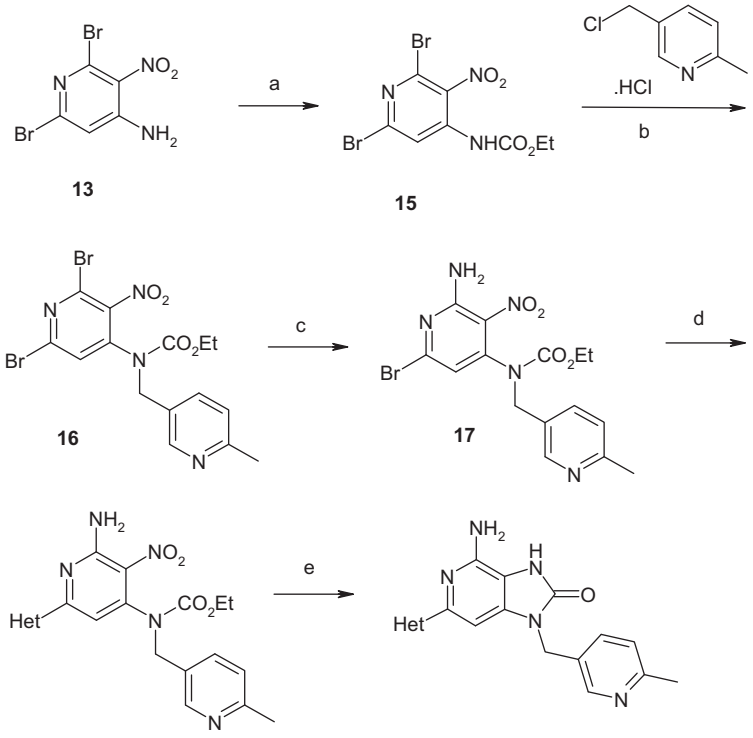
improvement in order to synthesise more analogues. The main issues were the lack of regioselectivity in the cyclisation and low yielding debenzylation using highly corrosive concentrated H_2SO_4. The low yield was partly due to losses following a difficult HPLC separation, but there was also significant decomposition to baseline impurities under these harsh conditions. Additional issues with the route included the use of toxic organotin reagents and by-products and moderate yield of the Stille coupling. Even more significant was the lack of flexibility to introduce alternative N-1 substituents. A new route was therefore devised to overcome these challenges.

The optimised route is shown in Scheme 4. Here, a carbamate was introduced as the amine protecting group. Importantly, this group can act as an intrinsic carbonyl source which can subsequently undergo acidic cyclisation to yield the desired dihydroimidazo[4,5-*c*]pyridin-2-one cores.[3,7,8] Carbamates also serve to acidify the N–H group to which they are attached, making possible mild base-promoted substitution at this point. Therefore, **13** was reacted with ethyl chloroformate to give the carbamate **15**. This was then alkylated to provide appropriate N-1 functionality, in this case 5-chloromethyl-2-methyl-pyridine was used as the alkylating agent. Selective S_NAr substitution with ammonia displaced the bromide adjacent to the nitro group. Using a bi-phasic mixture of concentrated ammonia solution and 2-methyltetrahydrofuran (Me–THF) gave a near quantitative yield of the mono-displaced product **17**.

Heterocyclic zincates were considered suitable alternatives to stannanes as they should be more reactive and the by-products more benign.[9] These were therefore prepared by C-2 deprotonation of the heterocycles with *n*-BuLi followed by transmetallation with $ZnCl_2$.[10] The zincates were prepared fresh and used immediately in the Negishi coupling with **17**. The couplings proceeded in moderate to good yields. The products from this step were worked-up using an aqueous wash with dilute ammonia to remove zinc salts. The nitro reduction and cyclisation were carried out in one step using acetic acid as the solvent. The nitro group was reduced by hydrogenation over Raney Ni or Pd/C, or alternatively using Zn powder. The final products were further purified by trituration or crystallisation as required. A set of C-6 analogues made using the optimised route is shown in Table 1. Various



Scheme 3. Original route. Reagents and conditions: (a) **6**, $Pd(PPh_3)_2Cl_2$, toluene, MW 130 °C, 2 h, 33%; (b) H_2, Raney Ni, THF/MeOH, rt, quant.; (c) CDI, THF, rt, 50%; (d) concd H_2SO_4, 2% (yield of **2**).

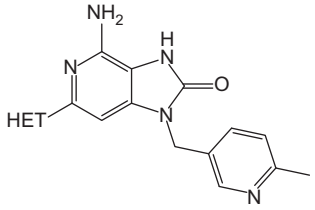


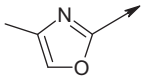
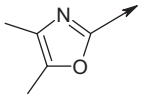
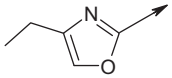
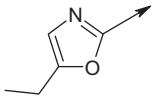
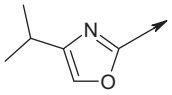
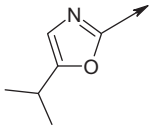
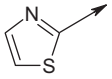
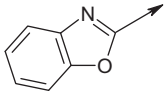
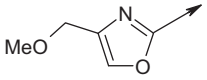
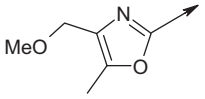
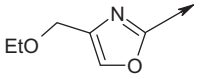
Scheme 4. Optimised route. Reagents and conditions: (a) EtOCOCl, NEt_3, Me–THF, 68%; (b) NaI, K_2CO_3, acetone, 62%; (c) 0.88 NH_3, Me–THF, quant.; (d) RZnCl, $Pd(PPh_3)_2Cl_2$, THF, MW 60 °C, 33–85%; (e) various reduction/cyclisation procedures — see Table 1.

substituted oxazole, benzoxazole, and thiazole targets were synthesised.

As previously discussed, the new route also allowed for flexibility in varying the N-1 substituent. A selection of N-1 targets is

Table 1
C-6 analogues



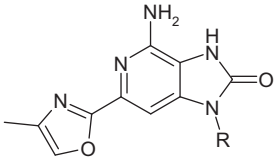
Entry	C-6 Substituent (Het)	Negishi yield[a] (%)	Reduction/cyclisation yield (%)
1		85	51[b]
2		72	25[b]
3		71	54[c]
4		48	29[b]
5		66	53[c]
6		45	42[b]
7		78	34[b]
8		41	69[d]
9		74	32[b]
10		63	4[b]
11		33	10[b]

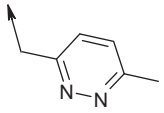
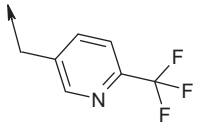
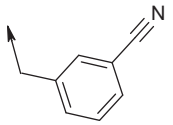
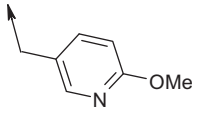
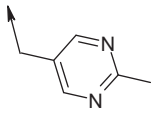
[a] $Pd(PPh_3)_2Cl_2$, THF, MW 60 °C, 15 min.
[b] H_2 (80 psi), Raney Ni, AcOH.
[c] Zn/AcOH, rt.
[d] H_2 (100 psi), 10% Pd/C, AcOH, rt.

shown in Table 2. In the case of entry 1, a concern was over-reduction of the pyridazine ring when reducing the nitro group. Hydrogenation was therefore carried out in a flow apparatus so that the reaction could be carefully monitored and stopped immediately after the desired product had formed.

In summary, several improvements were made to the initial route to enable flexible variation of C-6 and N-1 substituents of a dihydroimidazo[4,5-*c*]pyridin-2-one core. Key amongst the improvements was the Negishi cross-coupling and use of a carbamate protecting group to overcome selectivity and deprotection issues, and give an acidic handle for alkylation.

Table 2
N-1 analogues



Entry	N-1 Substituent (R)	Negishi yield (%)	Reduction/cyclisation yield (%)
1		75[a]	36[e]
2		44[b]	57[f]
3		65[c]	52[f]
4		80[b]	17[g]
5		88[d]	17[g]

[a] $Pd(PPh_3)_2Cl_2$, THF, 65 °C, 1 h.
[b] $Pd(PPh_3)_2Cl_2$, THF, MW 90 °C, 5 min.
[c] $Pd(PPh_3)_2Cl_2$, THF, MW 60 °C, 15 min.
[d] $Pd(PPh_3)_2Cl_2$, THF, MW 75 °C, 10 min.
[e] (i) H-Cube®, H_2 (1 bar), 10% Pd/C CatCart®30, AcOH (0.05 M, 1 ml/min), rt; (ii) 50 °C.
[f] Zn/AcOH, rt.
[g] (i) Raney Ni (10%), EtOH/THF (1:1); (ii) AcOH, rt.

Acknowledgements

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Supplementary data

Supplementary data (representative experimental details) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.119.

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