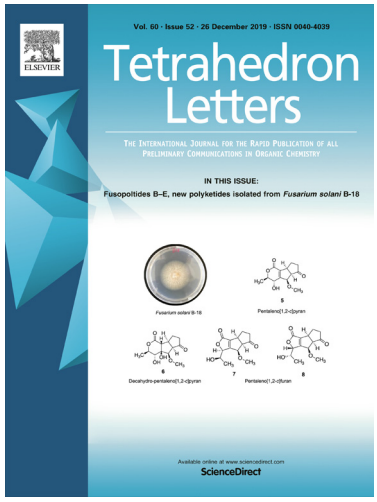
Journal Pre-proofs



Significant rate enhancement via potassium pivalate in a Miyaura borylation approach to verinurad

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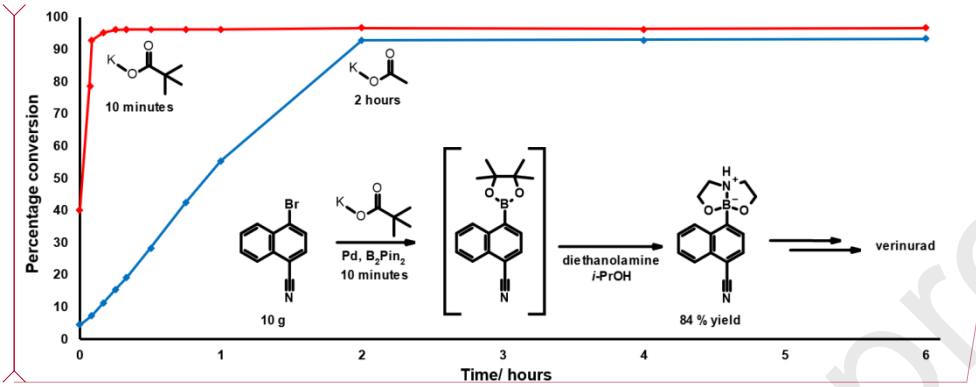
Graphical Abstract:



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Title:

Significant rate enhancement via potassium pivalate in a Miyaura borylation approach to verinurad

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Key Words:

Miyaura borylation, Suzuki, kinetics, route design.

Abstract:

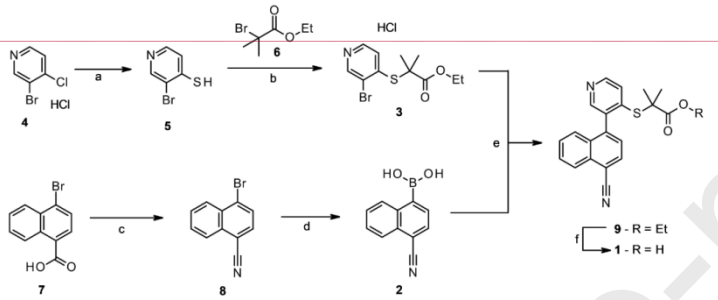
We describe herein the significant rate-enhancing effect of employing potassium pivalate as a base in a Miyaura borylation. The manufacturing route to verinurad currently employs a Suzuki-Miyaura cross-coupling, requiring cryogenic conditions to generate the boronic acid coupling partner. This process has manufacturability challenges including those associated with low temperature operations and thus an alternative Miyaura borylation approach is described. ~~Combining h~~High throughput screening ~~and rational design~~was employed to investigate the effects of various carboxylate bases and their corresponding counterions on reactivity. ~~were investigated.~~ Our results highlight potassium pivalate as producing exceptional rate acceleration~~Our results highlighted potassium pivalate as producing exceptional rate accelerating properties~~. To the best of our knowledge this base has not previously been reported for use in Miyaura borylations. Diethanolamine transesterification is also reported as a facile and robust boronate isolation protocol. Successful application of this diethanolamine boronate ester in downstream cross-coupling chemistry has demonstrated the potential for this new route in commercial manufacture of verinurad.

Introduction:

Studies have shown that hyperuricaemia and gout are intricately linked with hypertension and chronic kidney disease.[1] A number of studies also suggest hyperuricaemia and gout are independent risk factors for the development of cardiovascular disease.[1] Verinurad **1** is a highly potent URAT1 inhibitor with a greater than 100-fold potency increase compared to other uric acid transporters.[2] Studies investigating a combination therapy of **1** and xanthine oxidase inhibitors suggest that **1** is highly selective and reduces serum uric acid levels in the body.[2, 3] These promising clinical results have prompted a re-evaluation of the current route with the aim of developing a long-term manufacturing route to **1**.

Palladium catalysed coupling reactions are now a central tool for the synthesis of biologically active compounds in the pharmaceutical industry.[4] Verinurad **1** is currently manufactured using a convergent synthetic route with a Suzuki-Miyaura cross-coupling of building blocks **2** and **3** in the penultimate stage (Scheme 1).[5, 6] This current route involves the formation of **2** by lithium/bromine exchange followed by a tri-*iso*-propyl borate quench. Lithium/bromine exchange requires cryogenic conditions to inhibit uncontrolled nucleophilic attack on the sensitive nitrile group. These conditions are unfavourable from a manufacturability perspective due to limited reactor availability, the high costs associated with long operation times and the high energy cost of cooling reactors.[7, 8] Unfavourable physical properties displayed by **2** led to slow filtration with concomitant impurity formation. Concerns were raised in-

house due to the propensity of **2** to readily form oligomers such as boroxines, which could lead to artificially high purity assay readings and therefore the potential to jeopardise accurate charging in the following stage. [9] The resulting development work aimed to alleviate the described issues through the investigation of alternative, plant-feasible routes, the removal of cryogenics and the isolation of intermediates as stable single species, facilitating the delivery of **1** for further clinical studies.



Scheme 1: Current verinurad manufacturing route. Reagents and conditions: a *i)* KSAc; water; 35 °C; *ii)* NaOH (aq); 20 °C; **b** K_2CO_3; *i*PrAc; acetone; 40 °C; **c** *i)* $SOCl_2$; toluene; DMF; 60 °C; *ii)* $SO(NH_2)_2$; sulfolane; 120 °C; **d** *i)* $B(OiPr)_3$; THF, *n*-hexLi; -80 °C, *ii)* HCl (aq); **e** $Pd_2(dba)_3$; $[(t\text{-}Bu)_3PH]BF_4$; Na_2CO_3; NaOH; *n*-BuOH; water; 75 °C; **f** NaOH (aq); MeOH; 27 °C.

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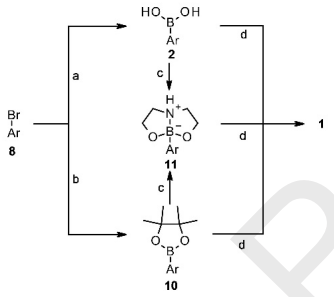
Results and Analysis:

To explore alternatives to the Suzuki-Miyaura cross-coupling approach, organomagnesium and organozinc derivatives of both **3** and **8** were generated for use in Kumada [10] and Negishi [11] transformations. Poor organometallic intermediate stability, low starting material conversions and difficulties in the purification of **9** led to alternative approaches being sought. Direct iridium catalysed oxidative borylation *via* C-H activation of cyanonaphthalene was explored initially *in silico*. Combinations of calculated pK_a values [12], NMR shifts [13], bond dissociation energies [14] and transition state modelling as described by Green and co-workers~~et. al~~. [15] were explored. These computational results consistently failed to identify strong selectivity towards the desired regioisomer. This was verified experimentally in the laboratory with multiple by-products observed, resulting in this approach being abandoned. Initial scouting of a Miyaura borylation [16] approach (Scheme 2) ~~was more fruitful and~~ led to optimisation studies *via* high throughput screening, ~~rational design~~ and reaction ~~profiling~~monitoring.



Scheme 2: Miyaura borylation and Suzuki-Miyaura cross coupling route. Reagents and cConditions: a *i)* $B(O/Pr)_3$; THF, *n*-hexLi; -80 °C, *ii)* HCl (aq); **b** B_2Pin_2; Pd-cat; base; solvent; **c** diethanolamine, *i*PrOH; **d** *i)* $Pd_2(dba)_3$; $[(t\text{-}Bu)_3PH]BF_4$; Na_2CO_3; NaOH; *n*-BuOH; water; 75 °C; *ii)* NaOH (aq); MeOH; 27 °C.

The Miyaura borylation was initially investigated using a 96 well screening plate (screen 1) in which combinations of 8 catalysts, 6 acetate bases and 2 solvents were explored. Conditions were selected based on literature precedent and in-house knowledge. [16-19] Results from screen 1 indicated combinations of $Pd(PPh_3)_2Cl_2$, KOAc, CsOAc and NMe_4OAc, afforded the highest conversion and were further investigated to assess their scalability. Although complete consumption of **8** was achieved when scaling $Pd(PPh_3)_2Cl_2$ and KOAc in 2-MeTHF to 43 mmol (10 g), isolation of **10** by crystallisation proved difficult due to its high solubility, with consistently poor isolated yields and purity obtained. A facile boronate ester isolation process can be achieved through transesterification to a diethanolamine (DEA) boronate ester as illustrated in Scheme 2. Due to the characteristic low solubility of such boronate esters in non-polar organic solvents, isolation by crystallisation has been reported in high yields. [9, 20, 21]

To aid in the development of a transesterification isolation process, solubility studies were performed on **10** and **11**. This data was considered alongside the results from screen 1 to design a second borylation screen (Table 1) in which Miyaura borylation reactivity in six transesterification-appropriate solvents was assessed.

	2 hHours			24 hours		
	KOAc	CsOAc	NMe_4OAc	KOAc	CsOAc	NMe_4OAc
2-MeTHF	95.0	72.5	85.3	96.2	93.0	90.3
THF	28.5	65.3	36.2	94.6	94.6	77.2
chlorobenzene	8.2	31.7	88.0	87.2	48.0	89.6
toluene	8.6	51.8	89.2	86.0	91.7	88.5
anisole	10.8	53.3	94.1	92.4	93.9	91.0
cyclohexanone	5.0	86.2	58.6	78.1	90.0	71.5

Table 1: Borylation screen 2: Aryl bromide 2 (4.3 mmol); B_2Pin_2 (1.1 eq); base (3.0 eq); $Pd(PPh_3)_2Cl_2$ (1.0 mol %), 60 - 80 ℃. Percentage area product by HPLC. Conversion: low (red) → high (green).

Complete conversion of **8** was achieved after 2 hours when employing KOAc in 2-MeTHF with the lowest levels of the expected homo-dimer and protodehalogenation by-product formation. A visual increase in base solubility (KOAc < CsOAc < Me_4NOAc) was observed across the six solvents suggesting counterion size had an impact on solubility. No clear trend could be drawn between counterion size and the rate of conversion. CsOAc and Me_4NOAc were observed to be highly hygroscopic upon weighing, resulting in the development of a process using these bases becoming more difficult.

Considering conversion to **8**, hygroscopicity, cost of goods, ease of work-up and solvent miscibility with free DEA, conditions utilising KOAc in 2-MeTHF were selected for scale up. Upon scaling to 216 mmol (50 g), ~~reaction stalling was observed~~the reaction was observed to stall at 70 % conversion~~.~~ which was initially attributed to poor agitation. Repeating the reaction with improved agitation failed to prevent the reaction stalling. Increasing the KOAc charge from 3 to 5 equivalents was shown to force the reaction to complete conversion, however this “quick fix” was considered risky in terms of robustness upon further scale-up. Reaction stalling could be attributed to a number of factors in the solid-liquid heterogeneous system linked to reactor design, base particle size distribution or impeller type. [22] It was hypothesised that the precipitation of KBr could also have partially coated the KOAc particles, inhibiting dissolution and hence availability of the base. [22] It was envisaged that increasing base solubility, and hence base availability, could be a means of overcoming this issue and therefore this led to us revisiting the base selection.

As previously demonstrated in screens 1 and 2, cation modification of the acetate base had a positive impact on solubility but was linked to increased hygroscopicity and indirectly to by-product formation. Further investigation into cation modification was therefore not pursued. Consideration of the reaction mechanism suggested two critical properties of acetate bases could be key to their use in Miyaura borylations. In contrast to stronger bases such as carbonates which can promote homo coupling, acetates are weak Brønsted bases. [17] Acetates can also be considered

hard Lewis bases. Following oxidative addition, this latter property allows for ligand exchange with the arylpalladiumhalide complex, forming an arylpalladiumacetate species. [16] This complex has high reactivity towards bispinacolatodiboron based on two factors: high oxophilicity of the boron centres and a weak palladium-oxygen bond. [19] Any modification to the base with the aim of increasing solubility would therefore also have to ensure the following criteria were met: low hygroscopicity, low Brønsted basicity and "hard" Lewis base character.

potassium bases	pK_a (H_2O)	LogP	1 hour	24 hours
acetate	4.76	-0.170	55.4	96.2
propionate	4.87	0.604	51.2	94.2
pivalate	5.03	1.240	95.2	95.4

Table 2. Borylation screen 3: pK_a [23, 24] and Maestro [12] LogP (corresponding acid - octanol/water) calculated values. Aryl bromide **2** (4.3 mmol); B_2Pin_2 (1.1 eq); base (3.0 eq); $Pd(PPh_3)_2Cl_2$ (1.0 mol %), 80 °C. Percentage area product by HPLC. Conversion: low (red) → high (green).

As indicated in Table 2 alongside meeting the discussed criteria above, potassium propionate and pivalate (KOPiv) were selected for investigation due to their increased lipophilicity and likely increased solubility in 2-MeTHF. C-H activation cross-coupling reactions employing pivalates have also previously been reported. [25-27] Base solubility was visually observed to increase with lipophilicity (acetate < propionate <<< pivalate). Small scale reactions (4.30 mmol 1 g) showed significant rate enhancement with the visually more soluble KOPiv by comparison to acetate or propionate (Table 2). Complete conversion to **10** was observed with KOPiv in less than 1 hour. To investigate robustness on a larger scale (43 mmol 10 g), a comparison between KOAc (5.0 eq) and KOPiv (1.1, 1.5 and 3.0 eq) was performed and conversion to **10** monitored. (Fig. 1~~Figure 1~~).

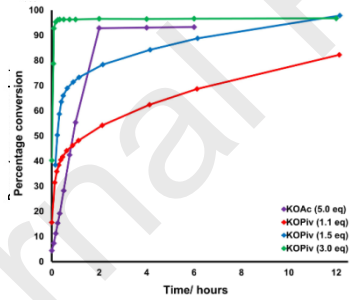


Figure 1: KOPiv vs KOAc Miyaura borylation: Percentage conversion to product ~~area %~~ by HPLC.

Replacement of KOAc (5.0 eq) with KOPiv (3.0 eq) resulted in a 12-fold increase in borylation rate. It is postulated this increase could result from a combination of solubility and steric factors. Increased base solubility and hence availability could increase the rate of arylpalladiumhalide ligand exchange. Improved base availability could also increase the degree of bispinacolatodiboron activation, in turn increasing the~~at~~ rate of transmetalation. The presence of the bulky *tert*-butyl group of the arylpalladiumpivalate complex could also lead to steric congestion around the catalytic centre, resulting in elongation and weakening of the palladium-oxygen bond, again promoting transmetalation.

[16-19] Further investigation ~~would~~ will be required to explain the observed differences in reaction ~~the observed reaction~~ progression (Fig. 1~~Figure 1~~) between acetate and pivalate in order to generate a full understanding of the reaction mechanism.

Aqueous work-up, followed by transesterification with DEA led to the isolation of **11** in 84 % yield and in excellent purity. The viability of replacing **2** with **11** in the Suzuki-Miyaura cross-coupling transformation was then assessed. The reaction was observed to reach completion within 4 hours with the same impurity profile compared to the corresponding reaction with **2**. This is expected due to the reaction proceeding by rapid hydrolysis of **11** to **2** *in situ*. [6] Subsequent telescoped ester hydrolysis led to the isolation of **1** in 63% yield and in excellent purity.

Conclusion:

A Miyaura borylation approach was identified as a viable alternative route to a boronate precursor of **1**. Multiple rounds of screening were employed to explore the impact of solvents, catalyst and base on reactivity. These results, together with thoughts as to the desired properties of the base led to the choice of potassium pivalate as a novel, significantly rate accelerating base for the reaction. Implementation of a DEA transesterification protocol allowed the facile isolation of **11** in high yield and purity. This new boronate ester was successfully employed in the subsequent Suzuki-Miyaura cross-coupling transformation, affording **1** after hydrolysis in high yield and purity. This alternative route removed boroxine linked analytical complications, unfavourable physical properties displayed by **2** and the need for cryogenic reaction conditions.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights:

- Potassium pivalate was identified as producing exceptional rate accelerating properties.
- Diethanolamine transesterification is reported as a facile boronate isolation protocol.
- The diethanolamine boronate was shown to perform excellently in the following Suzuki reaction.