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Microwave-assisted synthesis of mGluR1 ligands: carbon, nitrogen and oxygen linked derivatives of pyrido[3,4-*d*]pyrimidin-4-ylamines

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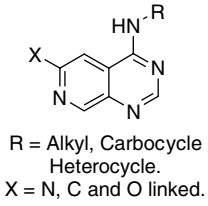
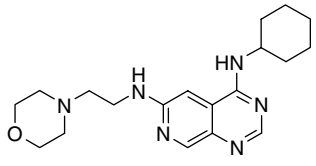
Abstract—The syntheses of 6-fluoropyrido[3,4-*d*]pyrimidin-4-ylamine derivatives is reported herein. Methods for generating C, N and O linked analogues under microwave irradiation are described.

Receptor antagonists of the mGluR1 subtype have been reported to be analgesic.[1–3] As part of our investigations into mGluR1 antagonists, we studied 6-substituted pyrido[3,4-*d*]pyrimidin-4-ylamines of the general structure **A**. Earlier efforts in this direction had allowed us to discover **1** as an interesting lead.[4,5] We thus sought a convenient synthetic strategy to enable the preparation of carbon, nitrogen and oxygen linked compounds. Herein, we report the microwave-assisted[6] synthesis of the aforementioned compounds.

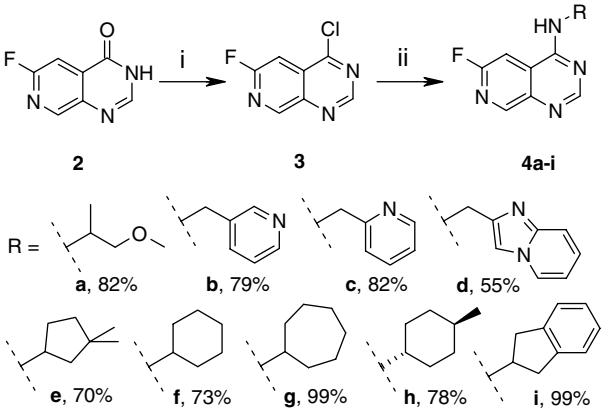


A



1

At the heart of the strategy was 6-fluoro-3*H*-pyrido[3,4-*d*]pyrimidin-4-one, **2**, which provides a means of accessing common advanced intermediates, **4a**–**i** (Scheme 1). Pyrimidinone **2** was prepared in five steps from 2-fluoro-4-nitropyridine as reported by Rewcastle et al.[7] Chlorination with thionyl chloride yielded reactive aryl chloride **3**.[8] Nucleophilic aromatic substitution with amines proceeded rapidly at room temperature in CH_2Cl_2 to generate the fluoroheterocyclic advanced intermediates, **4a**–**i**.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, CH_2Cl_2, DMF, reflux, 18 h; (ii) RNH_2, $^iPr_2NEt$, CH_2Cl_2, rt, 18 h.

The route also provided an opportunity to alkylate the heterocycle directly with nitroalkanes. Alkylation proceeded at room temperature with DBU in DMSO to generate the alkylated intermediates **5a**–**b** (Scheme 2). However, instead of alkylating at C2 as reported for similar compounds,[5] alkylation proceeded at C8 and this observation was supported by X-ray crystallographic data (Fig. 1).[9] No reaction was observed with 2-nitropropane or ethyl nitroacetate. The result was in

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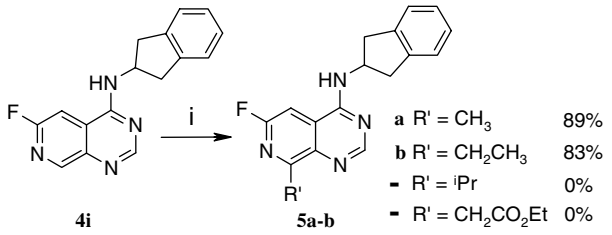


Scheme 2. Reagents and conditions: (i) $R'CH_2NO_2$, DBU, DMSO, rt, 18 h.

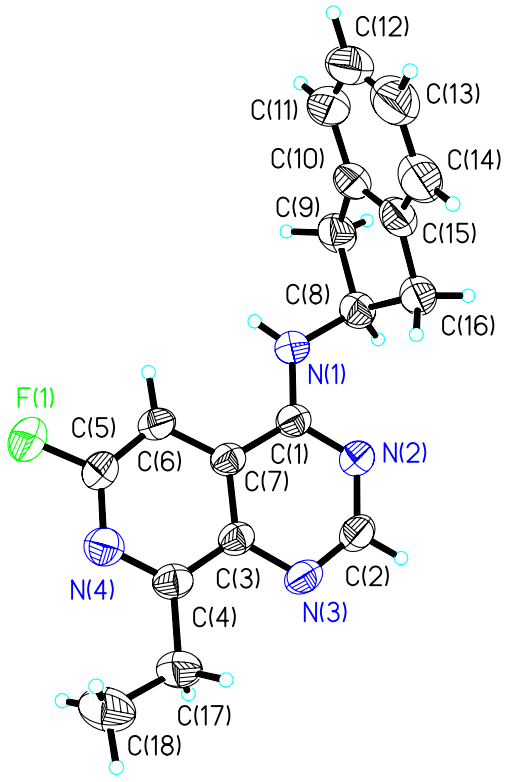
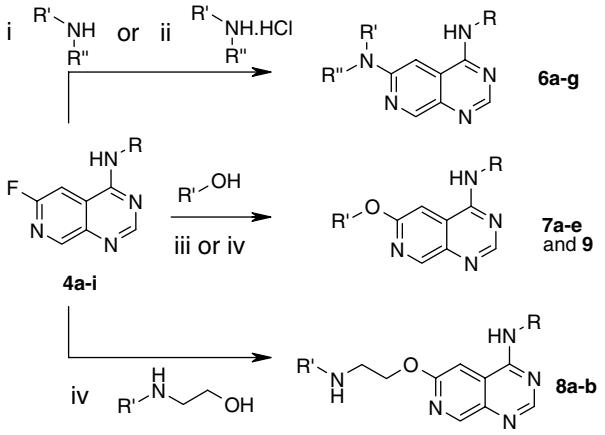


Figure 1. ORTEP diagram of **5b**.

agreement with observations made by Yanai et al. on the reaction of substituted pyridazines with nitromethane and nitroethane, in which nucleophilic C-alkylation occurs.[10,11]

Fluoride displacements on fluoro-intermediates, **4a**–**i** were carried out with amines and alcohols. Reactions performed with conventional heating required a large excess of amine or alcohol (up to 10 equiv) and prolonged heating at 100 °C for 1–3 days in *N*,*N*-dimethylacetamide. Careful tuning of reagents and conditions under microwave[12] irradiation resulted in more rapid and reliable production of analogues.

Reactions were conducted at temperatures between 180 and 200 °C, and as a result, the reaction durations were reduced to between 10 and 30 min. Scheme 3 summarises the conditions used for N and O derivatives. In order to achieve the high temperatures that the technique enables, high boiling solvents with the ability to



Scheme 3. All reactions carried out in NMP under microwave irradiation.[12] Reagents and conditions: (i) method A:[14] $^{i}Pr_2NEt$, 180 °C, 500–1000 s; (ii) method B:[15] KO^{t}Bu, $^{i}Pr_2NEt$, 200 °C, 1000–2000 s; (iii) method C:[16] KO^{t}Bu, 180 °C, 400–1000 s; (iv) method D:[17] NaH, rt, then 180 °C, 800 s.

absorb and distribute microwave energy were sought. We wished to avoid *N*,*N*-dimethylformamide with bases at high temperature and dimethylsulfoxide led to complex mixtures.[13] These considerations culminated in the use of *N*-methylpyrrolidinone as it satisfied our requirements for a solvent.

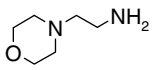
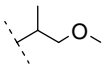
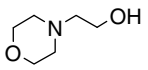
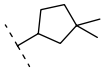
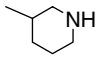
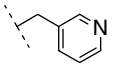
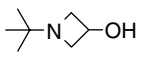
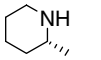
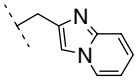
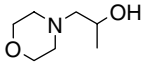
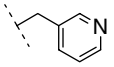
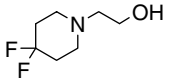
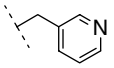
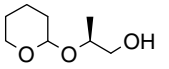
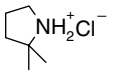
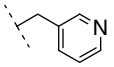
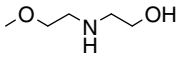
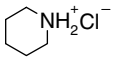
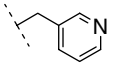
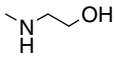
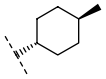
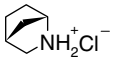
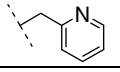
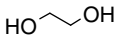
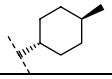
Heating amines with **4a**–**i** in the presence of Hünig's Base yielded compounds **6a**–**e** (method A). Potassium *tert*-butoxide added to ammonium salts (method B) led to a faster reaction than cases where excess Hünig's Base was used, giving compounds **6f**–**g**. As illustrated in Table 1, the conditions were used to generate reliable derivatives from a range of amines (entries 1–8), and deterioration of yields was only observed with sterically hindered examples.

O-Linked compounds such as **7** were formed in a similar fashion using stronger bases (Table 1, entries 9–16). Potassium *tert*-butoxide (method C) was a suitable base for the in situ formation of alkoxide nucleophiles and benefits from being easy to handle. Alternatively, the sodium alkoxides can be preformed from alcohols and sodium hydride at room temperature prior to adding electrophiles, **4a**–**i**, and heating (method D). Sodium alkoxides reacted more cleanly than potassium salts with fewer impurities, and reliably generated alkyl ethers, **7a**–**e**.

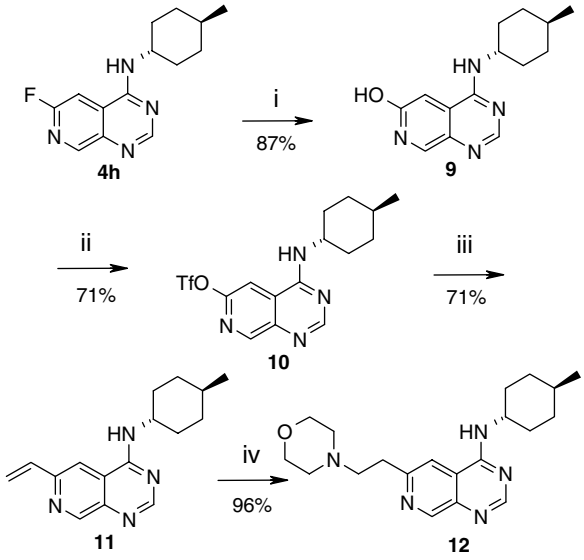
Acetal protecting groups were tolerated (entry 13) and allowed scope for further elaboration. As with amines, sterically hindered secondary alcohols (entry 11) were slower to react. The method also enabled alcohols to react selectively over secondary amines resulting in O-linked compounds featuring NH side chains such as **8a**–**b** (entries 14 and 15).

When ethylene glycol (entry 16) was subjected to the same conditions, hydroxylated intermediate **9** (Scheme 4) was formed in good yield via the degradation of the hydroxyethoxy compound. Compounds such as **9** were

Table 1. Nucleophilic aromatic substitution of fluoride with alcohols and amines[a]

Entry	Amine	Method[b]	R	Product yield[c] (%)	Entry	Alcohol	Method[b]	R	Product yield[c] (%)
1		A		**6a**, 41	9		D		**7a**, 74
2		A		**6b**, 95	10		C		**7b**, 69
3		A		**6c**, 18	11		D		**7c**, 34
4		A		**6d**, 93	12		D		**7d**, 84
5		A		**6e**, 8	13		D		**7e**, 70
6		B		—, 0	14		D		**8a**, 61
7		B		**6f**, 78	15		D		**8b**, 62
8		B		**6g**, 89	16		C		**9**, 87[d]

[a] All reactions were performed in NMP under microwave irradiation.
[b] See Refs. 14–17.
[c] Isolated yield.
[d] Product is hydroxyaromatic compound, **9**.



Scheme 4. Reagents and conditions: (i) method C:[16] $(CH_2OH)_2$ (4.0 equiv), NMP, KO^{t}Bu, microwave irradiation, 180 °C, 400–1000 s; (ii) Tf_2O (2.5 equiv), pyridine, 0 °C to rt, 45 min; (iii) vinylboronic anhydride pyridine complex (1.2 equiv), $Pd(PPh_3)_4$, K_2CO_3, DME, 150 °C, 1800 s, microwave irradiation; (iv) morpholine (4.0 equiv), ^{i}PrMgCl (3.3 equiv), THF, 0 °C to rt.

often formed as trace side products during reactions with amines and alcohols due to small amounts of water present in the solvent. However, in this case the product was not formed as a result of water since the hydroxyethoxy intermediate could be isolated from the reaction mixture. Upon further heating the intermediate degrades to yield **9**. When **4h** was heated with potassium hydroxide in the absence of ethylene glycol, lower yields were observed. The outcome of the reaction with ethylene glycol was utilised to prepare the aryl hydroxide, which was converted to the triflate in moderate yield to form **10**, a precursor enabling C–C cross couplings to be carried out.

A Suzuki–Miyaura cross coupling opened a gateway to C-linked compounds, incorporating the vinylboronic anhydride (pyridine complex) developed by O'Shea and Kerins.[18] When heated with **10** in the presence of potassium carbonate and palladium tetrakis(triphenylphosphine) in 1,2-dimethoxyethane, the coupling gave **11** in good yield (71%).[19] The influence of microwave irradiation again allowed for a shorter reaction time, but also a marked improvement in yield over a conventionally refluxed procedure, where the product was obtained in 43% yield only, along with several side products.

Although alkene **11** could be heated with amines to add in a Michael fashion to form **12**, purifications were often difficult and yields low. Rhodium catalysts have been reported by Beller on the anti-Markovnikov addition of amines to vinylpyridines,[20] and more recently, Hartwig has enhanced the scope towards styrenes.[21]

Compound **11** was reacted with morpholine (4.0 equiv) and $[Rh(COD)_2]BF_4$:PPh_3 (1:2, 5 mol %) in refluxing THF. After 3 h no reaction was observed. Remarkably, pre-forming the magnesium amide with isopropylmagnesium chloride at 0 °C in THF, then adding the vinyl substrate and warming to room temperature, the addition proceeded to give **12** in excellent yield. To the best of our knowledge, the use of ^{i}PrMgCl to facilitate the anti-Markovnikov addition of amines to vinylarenes has not been reported. Further findings associated with this reaction will be published.

In summary, we have demonstrated how microwave irradiation can shorten reaction times by providing a practical means of heating reactions above their normal reflux temperatures, and how ^{i}PrMgCl can be used to generate magnesium amides that react more favourably than the corresponding amines. In addition, we have reported some remarkable observations around the regioselectivity of the aromatic substitution of nitroethane and nitromethane.

Acknowledgements

Thanks to Thomas Ryckmans and Dafydd Owen for helpful discussions.

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14. General method for substitution of fluoride with amines, method A: 6-fluoropyrido[3,4-*d*]pyrimidin-4-ylamine, **4a**–**i**, (0.2 mmol), amine (2.5 equiv, 0.5 mmol) and diisopropylethylamine (2.5 equiv, 0.5 mmol) were heated in *N*-methylpyrrolidinone (2 mL) at 180 °C for 500–1000 s using microwave irradiation. Water (5 mL) was added and the precipitate was collected by filtration. Compounds which did not precipitate upon the addition of water were extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Silica gel chromatography yielded the pure compounds.
15. General method for substitution of fluoride with amine hydrochloride salts, method B: 6-fluoropyrido[3,4-*d*]pyrimidin-4-ylamine, **4a**–**i**, (0.2 mmol), amine (2.5 equiv, 0.5 mmol), potassium *tert*-butoxide (2.5 equiv, 0.5 mmol) and diisopropylethylamine (2.5 equiv, 0.5 mmol) were heated in *N*-methylpyrrolidinone (2 mL) at 200 °C for 1000–2000 s using microwave irradiation. Workup as in method A.
16. General method for substitution of fluoride with alcohols, method C: 6-fluoropyrido[3,4-*d*]pyrimidin-4-ylamine, **4a**–**i**, (0.2 mmol), alcohol (4.0 equiv, 0.8 mmol) and potassium *tert*-butoxide (4.0 equiv, 0.8 mmol) were heated in *N*-methylpyrrolidinone (2 mL) at 180 °C for 400–1000 s using microwave irradiation. Workup as in method A.
17. General method for substitution of fluoride with alcohols, method D: An Emrys™ Process Vial was charged with NaH (3 equiv, 0.6 mmol) under a flow of N_2. The relevant alcohol (3 equiv, 0.6 mmol) in *N*-methyl pyrrolidinone (2 mL) was added and the mixture was stirred at room temperature for 5 min. 6-Fluoro-pyrido[3,4-*d*]pyrimidin-4-ylamine, **4a**–**i**, (0.2 mmol) was added and the mixture was heated to 180 °C for 800 s using microwave irradiation. Workup as in method A.
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19. Procedure for cross couplings with vinyl boronic anhydride pyridine complex: Aryl triflate, **10** (300 mg, 0.77 mmol), vinyl boronic anhydride pyridine (222 mg, 0.92 mmol), tetrakis(triphenylphosphino)palladium (89 mg, 0.077 mmol) and potassium carbonate (128 mg, 0.92 mmol) were heated to 150 °C in 1,2-dimethoxyethane (3 mL) for 30 min using microwave irradiation. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified on a silica gel column, eluting with ethyl acetate:pentane (1:3 to 1:1) to afford 123 mg of an off-white solid (71%); ^{1}H NMR (400 MHz; $CDCl_3$) $\delta = 0.98$ (d, $J = 6.63$ Hz, 3H), 1.13–1.27 (m, 2H), 1.33–1.51 (m, 3H), 1.81 (m, 2H), 2.19 (m, 2H), 4.20–4.28 (m, 1H), 5.53 (d, $J = 10.53$ Hz, 1H), 6.39 (d, $J = 17.16$ Hz, 1H), 6.89 (dd, $J = 17.16$, 10.92 Hz, 1H), 7.50 (s, 1H), 8.66 (s, 1H), 9.21 (s, 1H).
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