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The Dimroth rearrangement as a probable cause for structural misassignments in imidazo[1,2-*a*]pyrimidines: A ^{15}N-labelling study and an easy method for the determination of regiochemistry

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ABSTRACT

Structural misassignments are often seen for complex natural products, but this can also be an issue with seemingly simpler structures. In this paper, we describe how, using a ^{15}N-labelled analogue, we established that the Dimroth rearrangement can occur in imidazo[1,2-*a*]pyrimidines and result in an incorrect regiochemical assignment of such compounds. These studies supported a rearrangement mechanism involving addition of hydroxide ion followed by ring opening. It was also observed that C(2) and C(3) substituted regioisomers could be readily distinguished using ^{1}H NMR spectroscopy.

1. Introduction

The imidazo[1,2-*a*]pyrimidine scaffold is an emerging heterobicyclic scaffold of significant interest in the contemporary medicinal chemistry literature. In recent years there have been an increasing number of reports of activity of this class of compound against various different targets (mGlu2, mGlu5, D_1, Lp-PLA_2, TNF, PI3K, SUV39H2, IAP-BIR and DPP-4) [1–9] and in multiple therapeutic areas (AIDS, antiparasitic, antiproliferative, autotaxine associated disease, Peyronie's disease, spinal muscular atrophy) [10–15], as well as their use as blue fluorescent light emitters [16]. A more comprehensive list on the potential therapeutic areas can be found in a recent review on synthetic approaches for this scaffold [17]. Furthermore, imidazo[1,2-*a*]pyrimidines are found in a number of commercially available compound libraries, probably due to their privileged physicochemical properties and their resemblance to natural substrates such as purines.

A feature of aza heterocycles such as imidazo[1,2-*a*]pyrimidines is that they can undergo the Dimroth rearrangement when subjected to appropriate reaction conditions. This transformation is described as a translocation of two heteroatoms in a heterocyclic system with or without changes in the ring structure, and it is an often undesired side reaction that occurs, usually in basic media, and as a result can lead to structure misassignments for the products. Even though the first mention of a Dimroth-type ring opening in the literature dates back to 1888 [18], it is not uncommon for incomplete data to be provided for new analogues and regiochemical assignments made by comparison (often erroneously) with existing literature data, as the use of more complicated and time-consuming X-ray studies to unequivocally assign the regiochemistry is frequently not carried out.

Many factors influence the propensity of aza-heterocycles to undergo the Dimroth rearrangement. In general, decreasing the π electron density of the fused 6-ring increases the rate of rearrangement. Thus, aza-substitution in the imidazo[1,2-*a*]pyridine system to give the corresponding imidazo[1,2-*a*]pyrimidine leads to more facile nucleophilic attack at position 5 (Fig. 1), and the same is observed with electron withdrawing groups. As a result 2-

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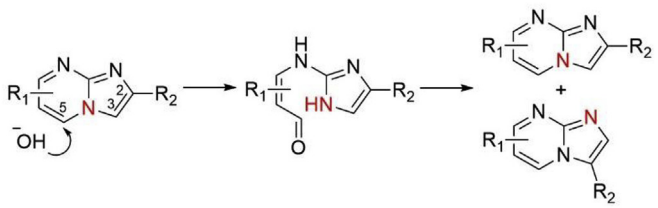


Fig. 1. Postulated mechanism of the Dimroth rearrangement under basic conditions in the imidazo[1,2-*a*]pyrimidine ring.

phenylimidazo[1,2-*a*]pyridine does not undergo the rearrangement under alkaline conditions, however, the same ring system will undergo a rearrangement in the presence of electron withdrawing substituents such as a nitro group at C6 or C8 [19]. The rate of rearrangement is dependent on pH, with the product distribution usually dependent on the substituents [20,21]. Of the rearrangements that have been described for the imidazo[1,2-*a*]pyrimidine core [20,22–25], the most common occurrence was with the use of hydrolytic [23,25] or haloformic conditions [22,24], as outlined above. The Dimroth rearrangement can also take place in acidic conditions or with photo-activation in other aza-heterocycles and especially triazolo species, although such transformations have not been observed with the imidazo[1,2-*a*]pyrimidine system.

Mechanistic aspects of the rearrangement have been described, including some important kinetic and computational calculations, which have been provided by Guerret et al. [20] identifying the minimal characteristics of aza-heterocycles to undergo the Dimroth rearrangement. In this study the authors recognise the possibilities of water addition by other mechanisms such as 1,4-addition or tautomerism, but conclude their data best supports a mechanism involving nucleophilic attack at C5/ring opening (as depicted in Fig. 1).

Interestingly, in surveying the literature data on this class of heterocycle, we noted that there was surprisingly little supporting evidence for the assigned structures, particularly in the patent literature where often more limited data are provided. In most cases the authors assigned either of the two regioisomers based on previous observations. Moreover, there were frequently discrepancies in the spectroscopic data even where the same regioisomer was claimed. Given the emergence of the scaffold in multiple commercially available compound libraries, and the increasing frequency with which these compounds are mentioned in the literature, it is crucial to be able to distinguish between the two possible regioisomeric products, as well as to characterize the conditions that induce the rearrangement.

2. Results and discussion

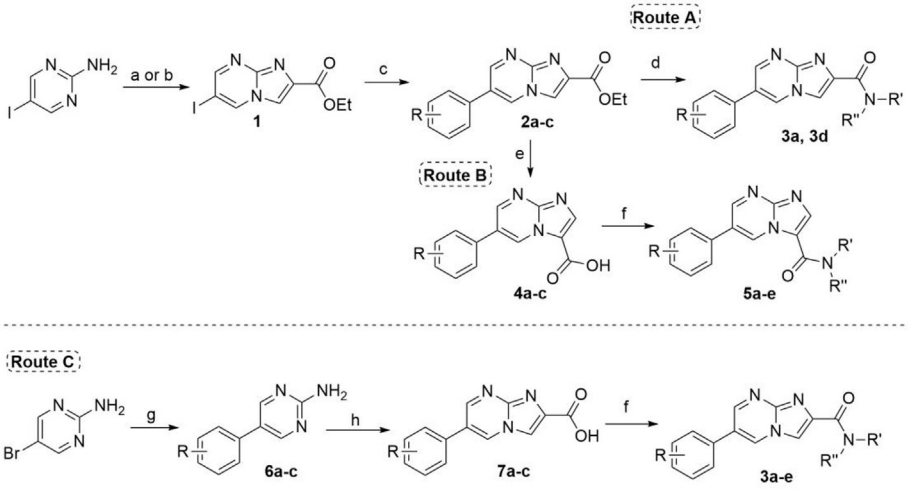
We became interested in these ring systems whilst investigating access to a range of imidazo[1,2-*a*]pyrimidine analogues substituted at C2 and C6. We initially followed a route wherein the bicyclic core was formed by reaction of 2-amino-5-iodopyrimidine with ethyl bromopyruvate. A Suzuki reaction was then followed by a direct conversion of esters **2** to the corresponding amides **3** (Scheme 1, Route A). A small series of amide analogues was prepared using this method (compounds **3a**, **3d**, **3e** Table 1). However, when an alternative route was employed involving initial hydrolysis of esters **2** followed by amide coupling of the resultant carboxylic acids **4** (Scheme 1, Route B, compounds **5a-e**, Table 1) we noted that there was a discrepancy in the analytical data of the products formed. For example, the products **3a** and **5a** were of the same mass, but their NMR spectra and TLC retention factors differed significantly. We suspected this may have been caused by a Dimroth rearrangement of ester intermediate **2a**. However, we needed to unambiguously determine the regiochemistry within products **3a** and **5a**.

The reaction of 2-aminopyrimidines with α-halocarbonyl species to afford the C2 regioisomer as the kinetic product is very well precedented, and mixtures of isomers can usually be obtained in different ratios by subsequent rearrangement under aqueous basic conditions [20,25,26]. Given that intermediates **1** and **2** and products **3** were all obtained as a single regioisomer, and that each transformation in Route A was conducted under anhydrous conditions, we initially tentatively assigned the structures as the C2-substituted regioisomers. Regioisomer **3** could also be accessed via a different route avoiding a basic saponification step wherein the imidazo[1,2-*a*]pyrimidine-2-carboxylic acids **7a-c** were synthesized directly from reaction of 2-aminopyrimidines **6a-c** with bromopyruvic acid. Amide coupling of carboxylic acids **7a-c** gave products **3a-e** each as a single regioisomer (Scheme 1, Route C, Table 1).

In Route B we reasoned that the isomerization must have occurred either at the hydrolysis or the amide formation steps, most plausibly at the ester hydrolysis step as this proceeded under aqueous basic conditions. We therefore tentatively assigned **4a** and **5a** as the C3 substituted regioisomers. However, on comparing the ^{1}H NMR data for **3a**, **4a** and **5a** with very similar compounds in the literature assigned as C2 regioisomers we noticed a discrepancy (Supplementary Information, Table 2, Entries 1 and 3) [27]. These compounds had been prepared using basic hydrolysis conditions from the corresponding ethyl ester, but no supporting evidence for the regiochemical assignment was provided. However, their data was not in agreement with several other literature sources reporting spectroscopic data for the C2 regioisomer where a significant deshielding effect in the shift of H-5 is observed with electron withdrawing substituents at C3 [22–24]. As these data were contradictory and there are no unambiguous assignments for both regioisomers made possible through correlation with techniques such as X-ray crystallography, we decided to prepare a small array of unlabelled and ^{15}N-labelled analogues both to use as mechanistic probes and to attempt to assign unambiguously the regiochemistry of each C2 and C3 isomer (Scheme 2).

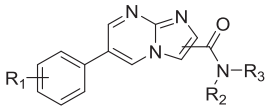
Thus, samples of ^{14}N-C2-substituted ethyl ester and the corresponding carboxylic acid were prepared following a two-step protocol from 2-amino-5-iodopyrimidine. A Suzuki cross-coupling with phenylboronic acid afforded 2-aminopyrimidine intermediate **6** and subsequent cyclisation with either ethyl bromopyruvate or bromopyruvic acid gave the desired 2-substituted imidazo[1,2-*a*]pyrimidines **8a** and **8b** respectively. The ^{15}N-labelled counterparts **8c** and **8d** were accessed via a three-step procedure from 5-bromo-2-chloropyrimidine involving Suzuki cross-coupling, substitution at C2 using $^{15}NH_4Cl$ under mildly basic conditions and cyclisation with either ethyl bromopyruvate or bromopyruvic acid. To ensure that no rearrangement had occurred under these latter reaction conditions, samples of **6**, **8a** and **8b** were also prepared by this route: analytical data were shown to be identical (Scheme 2). Formation of 3-carboxylic acid **11a** as a single regioisomer was achieved by subjecting ethyl ester **8a** to the basic saponification conditions described above (Scheme 3).

The regiochemistry within **11a** was confirmed by full assignment and NOESY correlations (Supporting Information). As expected, there are NOE correlations between the two protons of the pyrimidine ring and the phenyl *ortho* protons (**11a**), while in the case of **8b** there is a further correlation between H-5 and H-3 (Fig. 2). This was further corroborated by ^{15}N NMR, as described below. It is also apparent that there is deshielding of H-5 in 3-regioisomers and this was observed in all the analogues synthesized (Supplementary Table 1). Interestingly this effect was more

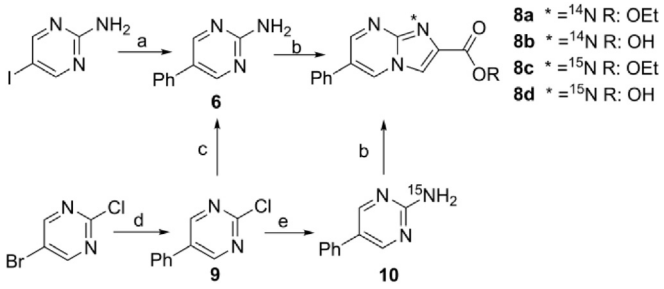


Scheme 1. Synthetic routes towards carboxylic acid derivatives of imidazo[1,2-*a*]pyrimidines. a. 1) ethyl bromopyruvate, THF, rt, 2 h, 2) EtOH, 95 °C, 1 h b. ethyl bromopyruvate, EtOH, 95 °C, 6 h, 52% over two steps c. arylboronic acid, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, CsF, DME, 90 °C, 20 h, 22–75% d. $CaCl_2$, amine, MeOH, 70 °C, 1 h, 10–34% e. NaOH, EtOH, THF, H_2O, 60 °C, 3 h, f. amine, HBTU, TEA, MeCN, rt, 2 h, 17–64% for 3a-e, 37–45% over two steps for 5a-e, g. arylboronic acid, $Pd(dppf)Cl_2$, K_2CO_3, dioxane/H_2O, rt, 15 min, 73–93% h. bromopyruvic acid, DMF, rt, 4d, 67–74%.

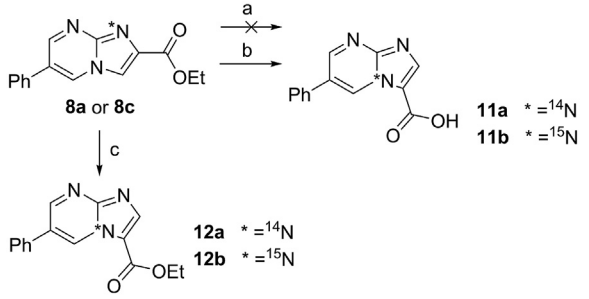
Table 1
Amides **3a-e** and **5a-e** produced via Routes A and B in Scheme 1.



Cpd	R_1	R_2	R_3	Route	Yield
3a	3-OMe	N-morpholino		A	33%
				C	64%
3b	3-Cl,4-Cl	Me	Et	C	40%
3c	3-CF_3	Me	Et	C	17%
3d	3-OMe	Me	Et	A	10%
				C	49%
3e	3-OMe	N-pyrrolydinyl		A	63%
5a	3-OMe	N-morpholino		B	37% (from 2a)
5b	3-Cl,4-Cl	Me	Et	B	39% (from 2a)
5c	3-CF_3	Me	Et	B	39% (from 2a)
5d	3-OMe	Me	Et	B	41% (from 2a)
5e	3-OMe	N-pyrrolydinyl		B	45% (from 2a)



Scheme 2. Synthetic routes for both the ^{15}N-labelled and ^{14}N-imidazo[1,2-*a*]pyrimidines. a. $PhB(OH)_2$, $Pd(OAc)_2$, K_3PO_4, EG, 80 °C, 2 h, 90% b. ethyl bromopyruvate or bromopyruvic acid, DMF, rt, 4d, 18–41% c. NH_4Cl, 1 M NaOH, 150 °C, MW, 30 min, 61% d. $PhB(OH)_2$, $Pd(OAc)_2$, Na_2CO_3, H_2O/EtOH, 45 °C, 0.5 h, 80% e. $^{15}NH_4Cl$, 1 M NaOH, 150 °C, MW, 30 min, 81%.



Scheme 3. Products obtained from the ester derivatives **8a** or **8c** under different conditions. a. 5% NaOH, MeOH, H_2O, 70 °C, 18 h, 0% b. NaOH, EtOH, THF, H_2O, 60 °C, 6 h, 51–55% c. EtONa, EtOH, 95 °C, 20 h, 26–29%.

pronounced when $CDCl_3$ was used as a solvent (rather than MeOH-d_4, MeCN-d_3 or DMSO-d_6) where the corresponding increase in chemical shift was greater than 1 ppm, possibly due to the presence of acid in $CDCl_3$. No major differences were observed in the shifts of the other two protons of interest, H-7 and H-2 or H-3. Assignment of the pyrimidine protons could be readily achieved from their coupling constant (2–3 Hz) and it was also observed that the ^{13}C chemical shifts were also diagnostic (C-7: 150–152 ppm, C-5: 130–134 ppm, C-3: 115–120 ppm and C-2: 139–144 ppm). This strongly supports that the NMR shift of H-5 can be used to provide an initial indication of which regioisomer is produced, with further supporting evidence being derived from more detailed NMR analysis, such as HSQC correlations. A final confirmation with NOESY or HMBC would be required for unambiguous characterisation, but at least in this manner one would have a quick indication of which isomer to expect.

Although others have performed kinetic and computational analyses to yield insights into the rearrangement mechanism, to our knowledge, no isotopic labelling studies of imidazo[1,2-*a*]pyrimidines have been performed to support the proposed mechanism of the rearrangement. In order to establish whether the transformation observed was a result of the Dimroth rearrangement, we investigated the reaction of ^{15}N-labelled aminopyrimidines **8c** under basic conditions.

The ester **8c** was first subjected to the previously reported

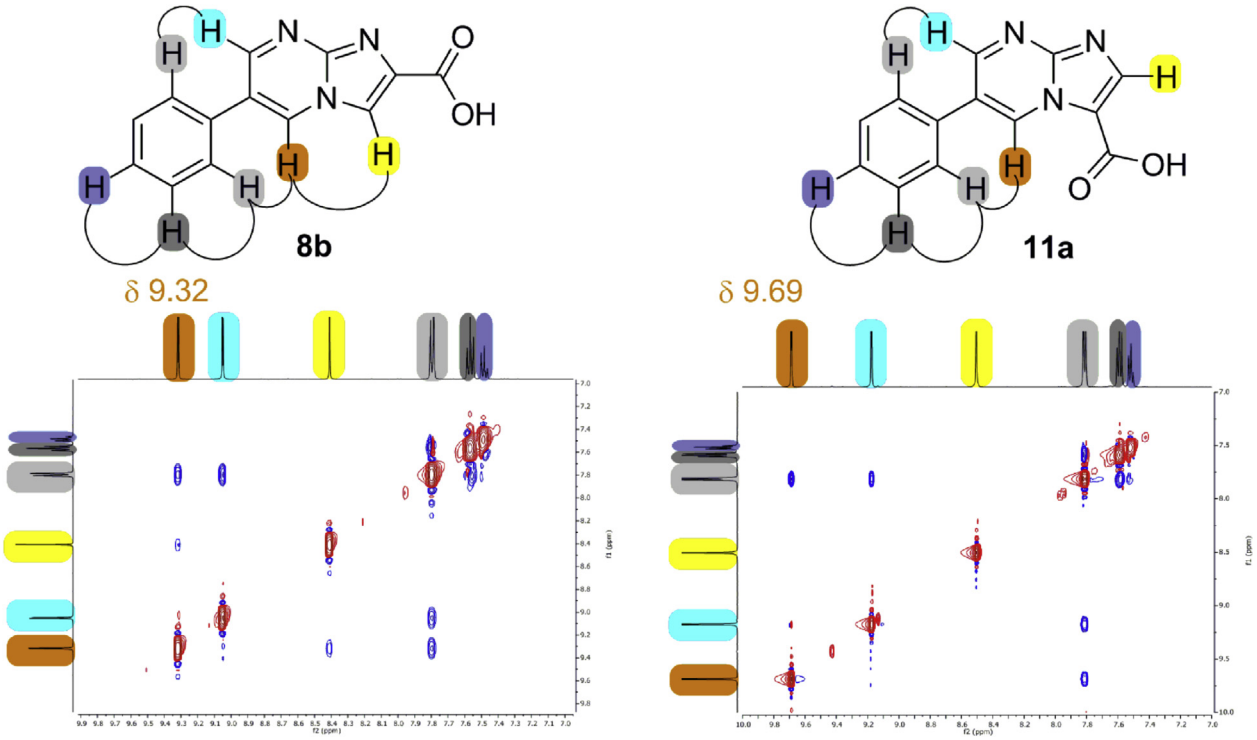


Fig. 2. 2D NOESY spectra showing nOe correlations in compounds **8b** and **11a**.

Dimroth conditions ([a] 5% NaOH aqueous methanolic solution, Scheme 3). Interestingly, we observed only limited conversion to the other isomer, some hydrolysis in the case of the ester, but mainly decomposition. The use of THF as a co-solvent has been described as facilitating the rearrangement and minimizing decomposition in other substrates [28]. Treatment of esters **8a** and **8c** under these conditions gave the corresponding carboxylic acids **11a** and **11b** in good yields (Scheme 3, [b]). The rearrangement was also observed upon treatment of **8a** with EtONa in EtOH allowing access to the respective 3-substituted esters (**12a-b**). We further wanted to investigate if a rearrangement takes place in this ring system in the presence of acid or by photoactivation. No conversion was observed in the presence of formic acid after 24 h or after irradiation at 365 nm (100 W) for 30 min for either 2- and 3-regioisomeric esters **8a** or **11a**.

Extensive NMR characterization verified the regiochemistry of all the ^{15}N-labelled compounds and showed that indeed the ^{15}N atom initially occupying position 1 in analogue **8c** was in position 4 in analogues **11b** and **12b** after the rearrangement had taken place. A decrease in chemical shift was observed for ^{15}N from 239.9 and 241.1 ppm for **8c** and **8d** respectively, to 188.5 and 187.7 ppm for **11b** and **12b** respectively, when the ^{15}N was positioned at the ring junction within the bicyclic system in the two latter analogues, and consistent with the change from sp^2 to sp^3 environments. Further confirmation came from the ^{1}H-^{15}N HMBC correlations for **8c** and **12b** (Fig. 3). For **8c** all $^{n}J_{NH}$ coupling constants of the labelled nitrogen were very small (<1 Hz), being unresolved in the ^{1}H and the ^{1}H-coupled ^{15}N spectra. As such, the ^{15}N HMBC correlation intensities for **8c** were very sensitive to the J_{NH} value chosen for the HMBC acquisition (5 or 2 Hz). This also meant correlations to unlabelled nitrogen centres were of comparable intensity to those of the labelled nitrogen in the 5 Hz optimised HMBC in particular (NMR Supplementary Material). For **12b**, the J_{NH} couplings of H2 and H5 were clearly resolved in the ^{1}H spectrum (3.0 and 1.3 Hz respectively) and gave rise to the dominant correlations in the 5 Hz-optimised HMBC. Finally, the multiplicities of protons and carbons neighboring ^{15}N also changed accordingly (NMR Supplementary Material).

Having investigated the spectroscopic properties of these compounds, we next used this information to assess whether there were any other apparent misassignments of such compound structures in the literature. We conducted a literature search in Reaxys (December 2017, Fig. 4): 9302 substances were found containing the imidazo[1,2-*a*]pyrimidine core in 1426 research papers and 936 patents. It was thus confirmed that this is indeed a ubiquitous scaffold. The quantity and quality of the data used to assign structure for these examples was analysed in detail, as it was this that was of particular interest. We then narrowed our search down to 2,6- and 3,6-disubstituted analogues, because these were the scaffolds of direct relevance to the studies we had conducted. 1354 2,6-Disubstituted imidazo[1,2-*a*]pyrimidines derivatives were reported in 138 research papers and 116 patents. Out of the 1354 compounds only 284 were reported with ^{1}H NMR data (in 44 out of 138 research papers and 29 out of 116 patents). Similar observations were noted for 3,6-disubstituted imidazo[1,2-*a*]pyrimidines (355 reported compounds in 55 research papers and 47 patents), where again only 73 out of 355 compounds had ^{1}H NMR data reported (25 research papers and 19 patents). Of particular note was that the vast majority of these documents did not unambiguously verify the structure using further crystallographic or 2D-NMR data. Most tellingly, we were able to find a matched pair of ^{1}H NMR and X-ray data in only in one patent and a single research paper. Rassapali et al. [29] confirmed their structure with X-ray in the total synthesis of oroidin and related alkaloids. However, in this case the authors were interested only in one of the two regioisomers and spectroscopic data for the regioisomer was not provided. Also, in the patent application WO2006071752 [30] the authors confirmed the structure of their 2-substituted carboxylic acid / ester derivatives using X-ray crystallography, but again ^{1}H NMR data is provided only for the 2-regioisomer.

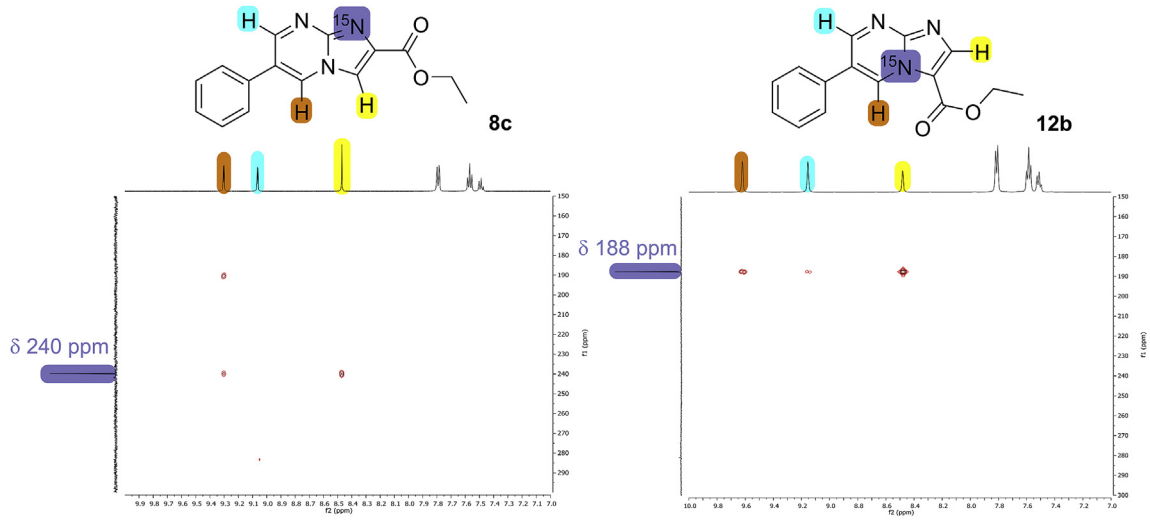


Fig. 3. ^{1}H-^{15}N HMBC correlations in compounds **8c** and **12b** (spectra optimised to $J_{NH} = 2$ Hz for **8c** and 5 Hz for **12b**).

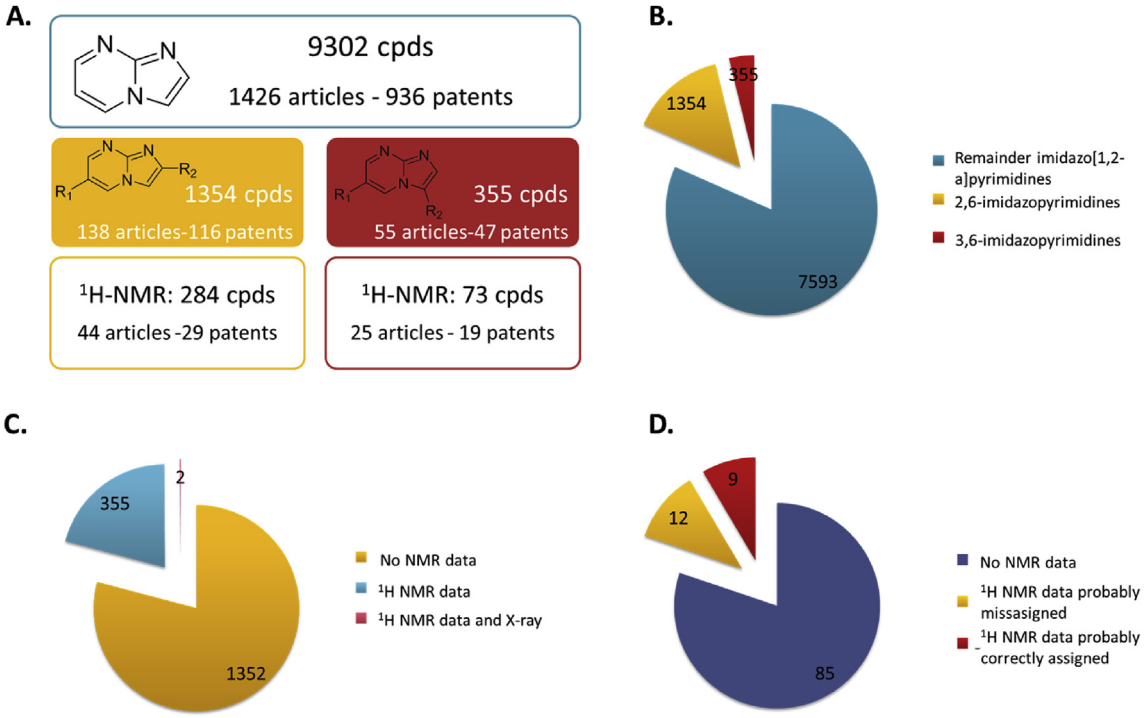


Fig. 4. Schematic representation of the literature findings. A. Imidazo[1,2-*a*]pyrimidines and sub-classes occurrence in the literature and respective spectral data B. Pie chart showing the regioisomeric subclasses of interest. C: Pie chart illustrating the availability of structural characterization data in 2,6- and 3,6-disubstituted imidazo[1,2-*a*]pyrimidines D. Pie chart illustrating the availability of ^{1}H NMR data in carboxylic acid derivatives of 2,6- and 3,6-imidazo[1,2-*a*]pyrimidines and incidences of correct or incorrect regiochemical assignments.

As the only available crystal structures were on carboxylic acid derivatives, and our synthetic efforts were targeting such scaffolds, we focused our search on this type of compound. It was very concerning that out of 106 reported compounds in Reaxys only 21 had associated NMR data. The ^{1}H NMR data available is reported in Supplementary Table 2 (Supplementary Information). There we looked for the characteristic H-5 shifts to assess the regiochemistry of the compounds. Even in this small sample, we observed that 12 (>50%) compounds have potentially misassigned structures across 7 documents. This finding confirms that this is a very important issue that needs to be brought to the attention of the scientific community.

3. Conclusion

In order to explore further an unexpected Dimroth rearrangement observed whilst synthesizing some imidazo[1,2-*a*]pyrimidine derivatives, we synthesized unlabelled and ^{15}N-labelled analogues in order to unambiguously assign the regiochemistry of the 2- and 3-substituted isomers and elucidate the reaction mechanism. These

studies supported a rearrangement mechanism involving addition of hydroxide ion followed by ring opening. Confirmation of structure with X-ray is the usual way to determine regioisomerism for most derivatives, but for mono-substituted imidazo[1,2-*a*]pyrimidines on the imidazole ring, the structure can be determined with a NOESY or an HMBC experiment. In fact, the chemical shifts of the pyrimidine ring protons in conjunction with an HSQC can also serve as a first indication, since the H-5 proton appears to be significantly deshielded in 3-substituted derivatives, due to the presence of the carbonyl substituent. However, final confirmation with either two 2D-NMR experiments or X-ray crystallography would allow more confidence in the regiochemical assignment. This has potentially far reaching consequences both in terms of similar effects with related ring systems, but also provides a cautionary tale against relying directly on published data for structural assignments.

4. Experimental

4.1. General

All reactions involving moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform. Melting points were recorded on a EZ-Melt Automated Melting Point Apparatus (EZ Melt) and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance III spectrometers (at 400, 500 or 600 MHz) using the deuterated solvent stated and at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. The J_{NH} value for the ^{1}H-^{15}N HMBC acquisition was 5 Hz unless otherwise stated. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass. For the UV irradiation experiments a UVP High-Intensity UV Inspection Lamp Model B-100AP was used.

4.2. Ethyl 6-iodoimidazo[1,2-a]pyrimidine-2-carboxylate (**1**)

Ethyl bromopyruvate (1.51 mL, 10.86 mmol) was added dropwise to a solution of 2-amino-4-iodopyrimidine (0.80 g, 3.62 mmol) in dry THF (40 mL). The mixture was stirred at rt for 2 h after which it was filtered. This solid was then dissolved in ethanol (20 mL) and refluxed for 1 h. The reaction mixture was cooled down, concentrated *in vacuo* and partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1 to 1:6) afforded **1** as a white solid (0.59 g, 52%): mp 209–211 °C; ν_{max} (cm^{-1}) 1721 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) 8.77 (d, $J = 2.0$ Hz, 1H), 8.69 (d, $J = 2.0$ Hz, 1H), 8.10 (s,1H), 4.45 (q, $J = 7.0$ Hz, 2H), 1.42 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.6, 157.0, 146.1, 138.3, 114.8, 75.6, 61.7, 14.5; HRMS (ESI^+) $C_9H_9O_2N_3^{127}I^+$ $[M+H]^+$ requires 317.9734; found 317.9725.

4.3. General Method A. Synthesis of ethyl 6-arylimidazo[1,2-a] pyrimidine-2-carboxylate

Ethyl 6-iodoimidazo[1,2-*a*]pyrimidine-2-carboxylate **1** (1 eq), caesium fluoride (2.5 eq), arylphenylboronic acid (2 eq), tri(o-tolyl) phosphine (0.1 eq) and palladium acetate (0.05 eq) were dissolved in 1,2-dimethoxyethane (0.1 M) and the mixture was evacuated and degassed. The reaction mixture was stirred at 90 °C for 20 h, after which it was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1 to 1:5). Representative spectra for cpd **2a** are given below.

4.3.1. Ethyl 6-(3-methoxyphenyl)imidazo[1,2-a]pyrimidine-2-carboxylate (***2a***)

Yield: 75%. mp 207–208 °C; ν_{max} (cm^{-1}) 1722 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) 8.90 (d, $J = 2.5$ Hz, 1H), 8.57 (d, $J = 2.5$ Hz, 1H), 8.18 (s, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 7.08 (s, 1H), 7.01 (dd, $J = 8.0$, 1.8 Hz, 1H), 4.47 (q, $J = 7.0$ Hz, 2H), 3.88 (s, 3H), 1.45 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.0, 160.6, 152.8, 147.6, 138.6, 134.9, 130.8, 130.5, 124.6, 119.5, 115.5, 114.4, 113.2, 61.6, 55.6, 14.5; HRMS (ESI^+) $C_{16}H_{16}O_3N_3^+$ $[M+H]^+$ requires 298.1186; found 298.1183.

4.4. General Method B. Synthesis of amides via route A

To a suspension of **2a** (1 eq) in anhydrous MeOH (0.1 M), $CaCl_2$ (1 eq) and the appropriate amine (1 eq) were added and refluxed for 1 h. The solvent was then removed *in vacuo* and **3a-e** were isolated after flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1 to 1:1).

4.4.1. (6-(3-Methoxyphenyl)imidazo[1,2-a]pyrimidin-2-yl)(morpholino)methanone (***3a***)

Yield: 33%. mp 273–275 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, $J = 2.5$ Hz, 1H, H-7), 8.58 (d, $J = 2.5$ Hz, 1H, H-5), 8.18 (s, 1H, H-3), 7.50–7.40 (m, 1H, H-5′), 7.15 (ddd, $J = 7.7$, 1.8, 0.9 Hz, 1H, H-6′), 7.09 (t, $J = 2.1$ Hz, 1H, H-2′), 7.01 (ddd, $J = 8.3$, 2.6, 0.9 Hz, 1H, H-4′), 4.52 (t, $J = 4.8$ Hz, 2H, H-2″), 3.89 (s, 3H, OCH_3), 3.86–3.77 (m, 6H, H-2″ and H-3″); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 162.3 (C=O), 160.6 (C-3′), 152.0 (C-7), 146.4 (C-9), 142.6 (C-2), 134.9 (C-1′), 130.8 (C-5′), 130.4 (C-5), 124.4 (C-6), 119.5 (C-6′), 115.8 (C-3), 114.3 (C-4′), 113.2 (C-2′), 67.6 (C-3″), 67.1 (C-3″), 55.6 (OCH_3), 47.5 (C-2″), 43.4 (C-2″); HRMS (ESI^+) $C_{18}H_{19}N_4O_3^+$ ($[M+H]^+$) requires 339.14572; found 339.14506.

4.4.2. N-Ethyl-6-(3-methoxyphenyl)-N-methylimidazo[1,2-a] pyrimidine-2-carboxamide (***3d***)

Yield: 10%. mp 178–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (t, $J = 2.9$ Hz, 1H, H-7), 8.58 (d, $J = 2.5$ Hz, 1H, H-5), 8.13 (s, 1H, H-3), 7.44 (app t, $J = 8.0$ Hz, H-5′), 7.15 (ddd, $J = 7.6$, 1.8, 0.9 Hz, 1H, H-6′), 7.08 (t, $J = 2.1$ Hz, 1H, H-2′), 7.00 (ddd, $J = 8.3$, 2.6, 0.9 Hz, 1H, H-4′), 4.15 (q, $J = 7.1$ Hz, 1.1H, $C\underline{H}_2CH_3$ rotamer 1), 3.88 (s, 3H, $OC\underline{H}_3$), 3.62 (q, $J = 7.2$ Hz, 0.9H, $C\underline{H}_2CH_3$ rotamer 2), 3.59 (s, 1.3H, $NC\underline{H}_3$ rotamer 1), 3.13 (s, 1.7H, $NC\underline{H}_3$ rotamer 2), 1.31 (t, $J = 7.1$ Hz, 1.7H, $CH_2C\underline{H}_3$, rotamer 1), 1.26 (t, $J = 7.2$ Hz, 1.3H, $CH_2C\underline{H}_3$, rotamer 2); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 163.6–163.2 (C=O), 160.5 (C-3′), 151.6–151.5 (C-7), 146.5–146.4 (C-9), 143.5–143.3 (C-2), 135.1 (C-1′), 130.8 (C-5′), 130.4 (C-5), 124.2 (C-6), 119.5 (C-6′), 115.1 (C-3), 114.2 (C-4′), 113.1 (C-2′), 55.6 ($O\underline{C}H_3$), 45.7–43.8 ($\underline{C}H_2CH_3$), 36.5–34.1 ($N\underline{C}H_3$), 14.3–12.2 ($CH_2\underline{C}H_3$); HRMS (ESI^+) $C_{17}H_{19}N_4O_2^+$ ($[M+H]^+$) requires 311.15080; found 311.14994.

4.5. General Method C. Synthesis of amides via route C

A solution of **7a-c** (1 eq), HBTU (2.0 eq) and triethylamine (1.5 eq) in acetonitrile (0.1 M) was stirred at rt for 15 min. Then the amine (1.5 eq) was added and the resulting mixture was stirred at rt for further 2 h. The solvent was evaporated *in vacuo*, and the residue was dissolved in EtOAc and extracted with water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1 to 1:3) gave **3a-e** (Yields:17–64%)

4.5.1. (6-(3-Methoxyphenyl)imidazo[1,2-a]pyrimidin-2-yl)(morpholino)methanone (**3a**)

Yield: 64%. Same as the product obtained from Route A.

4.5.2. N-Ethyl-6-(3,4-dichlorophenyl)-N-methylimidazo[1,2-a] pyrimidine-2-carboxamide (**3b**)

Yield: 40%. mp 201–202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (t, J = 2.9 Hz, 1H, H-7), 8.60 (d, J = 2.5 Hz, 1H, H-5), 8.16 (s, 1H, H-3), 7.69 (d, J = 2.1 Hz, 1H, H-2′), 7.61 (d, J = 8.3 Hz, 1H, H-5′), 7.43 (dd, J = 8.3, 2.2 Hz, 1H, H-6′), 4.14 (q, J = 7.0 Hz, 1.1H, CH_2CH$_3$), 3.63 (q, J = 7.2 Hz, 0.9H, CH_2CH$_3$), 3.59 (s, 1.4H, NCH_3), 3.14 (s, 1.6H, NCH_3), 1.32 (t, J = 7.0 Hz, 1.6H, CH$_2$CH_3), 1.26 (t, J = 7.1 Hz, 1.4H, CH$_2$CH_3); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 163.3–163.0 (C=O), 150.6 (C-7), 146.3 (C-9), 144.0–143.8 (C-2), 134.1 (C-1′), 133.8 (C-2′), 131.7 (C-5′), 130.6–130.5 (C-5′), 129.0 (C-2′), 126.4 (C-6′), 122.2–122.1 (C-6), 115.3–115.2 (C-3), 45.7–43.8 (CH$_2$CH$_3$), 36.5–34.1 (NCH$_3$), 14.3–12.2 (CH$_2$CH$_3$); HRMS (ESI$^+$) $C_{16}H_{15}Cl_2N_4O^+$ ([M+H]$^+$) requires 349.06229; found 349.06152.

4.5.3. N-Ethyl-6-(3-trifluorophenyl)-N-methylimidazo[1,2-a] pyrimidine-2-carboxamide (**3c**)

Yield: 17%. mp 200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (dd, J = 3.7, 2.5 Hz, 1H, H-7), 8.66 (d, J = 2.6 Hz, 1H, H-5), 8.18 (s, 1H, H-3), 7.83 (s, 1H, H-4′), 7.78 (d, J = 7.7 Hz, 1H, H-6′), 7.76–7.72 (m, 1H, H-2′), 7.68 (app t, J = 7.7 Hz, 1H, H-5′), 4.14 (q, J = 7.1 Hz, 1.1H, CH_2CH$_3$ rotamer 1), 3.62 (q, J = 7.2 Hz, 0.9H, CH_2CH$_3$ rotamer 2), 3.59 (s, 1.3H, NCH_3 rotamer 1), 3.14 (s, 1.7H, NCH_3 rotamer 2), 1.32 (t, J = 7.1 Hz, 1.7H, CH$_2$CH_3, rotamer 1), 1.26 (t, J = 7.1 Hz, 1.3H, CH$_2$CH_3, rotamer 2); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 163.4–163.0 (C=O), 150.9–150.8 (C-7), 146.4–146.3 (C-9), 144.0–143.7 (C-2), 134.7 (C-1′), 132.2 (q, J = 32.6 Hz, C-3′), 130.8 (s, C-5), 130.5 (C-6′), 130.3 (C-5′), 125.8 (q, J = 4.0 Hz, C-2′), 124.0 (q, J = 3.9 Hz, C-4′), 123.9 (q, J = 272.6 Hz, CF$_3$), 123.0 (d, J = 3.1 Hz, C-6), 115.3–115.2 (C-3), 45.7–43.8 (CH$_2$CH$_3$), 36.5–34.1 (NCH$_3$), 14.3–12.2 (CH$_2$CH$_3$); HRMS (ESI$^+$) $C_{17}H_{16}F_3N_4O^+$ ([M+H]$^+$) requires 349.12762; found 349.12645.

4.4.4. N-Ethyl-6-(3-methoxyphenyl)-N-methylimidazo[1,2-a] pyrimidine-2-carboxamide (**3d**)

Yield: 49%. Same as the product obtained from Route A.

4.5.5. (6-(3-Methoxyphenyl)imidazo[1,2-a]pyrimidin-2-yl)(pyrrolidin-1-yl)methanone (**3e**)

Yield: 63%. mp 214–216 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, J = 2.5 Hz, 1H, H-7), 8.58 (d, J = 2.5 Hz, 1H, H-5), 8.20 (s, 1H, H-3), 7.43 (app t, J = 8.0 Hz, 1H, H-5′), 7.15 (ddd, J = 7.6, 1.8, 0.9 Hz, 1H, H-6′), 7.08 (t, J = 2.1 Hz, 1H, H-2′), 7.00 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H, H-4′), 4.25 (t, J = 6.8 Hz, 2H, H-2″), 3.88 (s, 3H, OCH_3), 3.71 (t, J = 6.9 Hz, 2H, H-2″), 2.00 (pd, J = 6.6, 1.1 Hz, 2H H-3″), 1.93 (pd, J = 6.7, 1.2 Hz, 2H H-3″); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 161.8 (C=O), 160.5 (C-3′), 151.5 (C-7), 146.7 (C-9), 143.6 (C-2), 135.1 (C-1′), 130.8 (C-5′), 130.4 (C-5), 124.2 (C-6), 119.5 (C-6′), 114.9 (C-3), 114.2 (C-4′), 113.1 (C-2′), 55.6 (OCH$_3$), 49.2 (C-2″), 47.3 (C-2″), 26.8 (C-3″), 23.9 (C-3″); HRMS (ESI$^+$) $C_{18}H_{19}N_4O_2^+$ ([M+H]$^+$) requires 323.15080; found 323.14988.

4.6. General Method D. Synthesis of amides via route B

To a refluxing solution of **2a-c** (1 eq) in THF/EtOH (1:1, 0.15 M), 1 M NaOH in H_2O (3 eq, 1:1) was added and the reaction refluxed for 3 h. It was then cooled to rt, pH was adjusted to 8 ($NaHCO_3$) and extracted with EtOAc. Then, the aqueous phase was further acidified to pH 3 (1 N HCl), and the white precipitate formed was collected, washed with Et_2O to obtain crude **4a-c.** The latter were converted to the respective amides following the procedure described in General Method C.

4.6.1. (6-(3-Methoxyphenyl)imidazo[1,2-a]pyrimidin-3-yl)(morpholino)methanone (**5a**)

Yield from **2a**: 37%. mp 204–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, J = 2.6 Hz, 1H, H-5), 8.93 (d, J = 2.5 Hz, 1H, H-7), 8.05 (s, 1H, H-2), 7.46–7.39 (m, 1H, H-5′), 7.19 (ddd, J = 7.7, 1.8, 0.9 Hz, 1H, H-6′), 7.13 (dd, J = 2.5, 1.8 Hz, 1H, H-2′), 6.99 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H, H-4′), 3.93–3.89 (m, 4H, H-2″), 3.88 (s, 3H, OCH_3), 3.80 (dd, J = 5.7, 4.0 Hz, 4H, H-3″); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 160.5 (C-3′), 160.3 (C=O), 152.3 (C-7), 149.8 (C-9), 139.0 (C-2), 135.2 (C-1′), 133.1 (C-5), 130.7 (C-5′), 124.5 (C-6), 119.7 (C-6′), 116.0 (C-3), 114.2 (C-4′), 113.2 (C-2′), 67.0 (C-3″), 55.6 (OCH$_3$), 44.4 (C-2″); HRMS (ESI$^+$) $C_{18}H_{19}N_4O_3^+$ ([M+H]$^+$) requires 339.14572; found 339.14502.

4.6.2. N-Ethyl-6-(3,4-dichlorophenyl)-N-methylimidazo[1,2-a] pyrimidine-3-carboxamide (**5b**)

Yield from **2b**: 39%. mp 105–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H, H-5), 8.87 (d, J = 2.6 Hz, 1H, H-5), 8.16 (s, 1H, H-2), 7.72 (d, J = 2.2 Hz, 1H, H-2′), 7.59 (d, J = 8.3 Hz, 1H, H-5′), 7.47 (dd, J = 8.3, 2.2 Hz, 1H, H-6′), 3.71 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 3.29 (s, 3H, NCH_3), 1.34 (s, 3H, CH$_2$CH_3); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 160.9 (C=O), 151.2 (C-7), 149.5 (C-9), 139.4 (C-2), 134.0 (C-3′), 133.9 (C-4′), 133.7 (C-5), 133.4 (C-1′), 131.5 (C-5′), 129.1 (C-2′), 126.5 (C-6′), 122.1 (C-6), 117.0 (C-3), 44.3 (CH$_2$CH$_3$), 35.8 (NCH$_3$), 13.1 (CH$_2$CH$_3$); HRMS (ESI$^+$) $C_{16}H_{15}Cl_2N_4O^+$ ([M+H]$^+$) requires 349.06229; found 349.06178.

4.6.3. N-Ethyl-6-(3-trifluorophenyl)-N-methylimidazo[1,2-a] pyrimidine-3-carboxamide (**5c**)

Yield from **2c**: 39%. mp 132–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H, H-5), 8.98 (d, J = 2.6 Hz, 1H, H-7), 8.17 (s, 1H, H-2), 7.86 (d, J = 1.8 Hz, 1H, H-4′), 7.81 (dt, J = 7.8, 1.4 Hz, 1H, H-6′), 7.72 (dd, J = 7.5, 1.6 Hz, 1H, H-2′), 7.65 (app t, J = 7.8 Hz, 1H, H-5′), 3.71 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 3.29 (s, 3H, NCH_3), 1.35 (t, J = 7.4 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 161.0 (C=O), 151.5 (C-7), 149.5 (C-9), 139.3 (C-2), 135.0 (C-1′), 133.9 (s, C-5), 132.1 (q, J = 32.5 Hz, C-3′), 130.8 (C-6′), 130.1 (C-5′), 125.6 (q, J = 3.8 Hz, C-2′), 124.2 (q, J = 3.8 Hz, C-4′), 124.1 (q, J = 272.6 Hz, CF$_3$), 123.0 (C-6), 117.0 (C-3), 44.4 (CH$_2$CH$_3$), 35.5 (NCH$_3$), 13.1 (CH$_2$CH$_3$); HRMS (ESI$^+$) $C_{17}H_{16}F_3N_4O^+$ ([M+H]$^+$) requires 349.12762; found 349.12651.

4.6.4. N-Ethyl-6-(3-methoxyphenyl)-N-methylimidazo[1,2-a] pyrimidine-3-carboxamide (**5d**)

Yield from **2a**: 41%. mp 96–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H, H-5), 8.90 (d, J = 2.6 Hz, 1H, H-7), 8.15 (s, 1H, H-2), 7.40 (app t, J = 8.0 Hz, H-5′), 7.18 (ddd, J = 7.6, 1.9, 0.9 Hz, 1H, H-6′), 7.12 (t, J = 2.1 Hz, 1H, H-2′), 6.96 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H, H-4′), 3.86 (s, 3H, OCH_3), 3.68 (p, J = 7.3, 6.5 Hz, 2H, CH_2CH$_3$), 3.26 (s, 3H, NCH_3), 1.32 (t, J = 7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 161.0 (C=O), 160.4 (C-3′), 152.0 (C-7), 149.6 (C-9), 139.0 (C-2), 135.3 (C-1′), 133.5 (C-5), 130.6 (C-5′), 124.2 (C-6), 119.7 (C-6′), 116.8 (C-3), 114.1 (C-4′), 113.1 (C-2′), 55.6 (OCH$_3$), 44.1 (CH$_2$CH$_3$), 35.3 (NCH$_3$), 13.1 (CH$_2$CH$_3$); HRMS (ESI$^+$) $C_{17}H_{19}N_4O_2^+$ ([M+H]$^+$) requires 311.15080; found 311.15001.

*4.6.5. (6-(3-Methoxyphenyl)imidazo[1,2-a]pyrimidin-3-yl)(pyrrolidin-1-yl)methanone (**5e**)*

Yield from **2a**: 45%. mp 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (d, J = 2.6 Hz, 1H, H-5), 8.94 (d, J = 2.6 Hz, 1H, H-7), 8.24 (s, 1H, H-2), 7.41 (app t, J = 8.0 Hz, 1H, H-5′), 7.21 (ddd, J = 7.6, 1.8, 0.9 Hz, 1H, H-6′), 7.14 (t, J = 2.1 Hz, 1H, H-2′), 6.98 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H, H-4′), 3.88 (s, 3H, OCH_3), 3.87–3.83 (m, 2H, H-2″), 3.78–3.70 (m, 2H, H-2″), 2.16–1.96 (m, 4H, H-3″); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 160.5 (C-3′), 159.8 (C=O), 152.2 (C-7), 149.5 (C-9), 139.6 (C-2), 135.4 (C-1′), 133.9 (C-5), 130.6 (C-5′), 124.3 (C-6), 119.8 (C-6′), 117.7 (C-3), 114.2 (C-4′), 113.1 (C-2′), 55.6 (OCH_3), 48.7 (C-2″), 47.1 (C-2″), 26.8 (C-3″), 24.1 (C-3″); HRMS (ESI$^+$) $C_{18}H_{19}N_4O_2^+$ ([M+H]$^+$) requires 323.15080; found 323.15025.

*4.7. 2-Amino-5-phenylpyrimidine (**6**)*

4.7.1. Method 1

Based on a literature method [34] 2-amino-5-iodopyrimidine (2.00 g, 9.05 mmol), phenylboronic acid (1.66 mg, 13.57 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol) and $K_3PO_4{\cdot}7H_2O$ (3.84 mg, 18.1 mmol) in ethylene glycol (36 mL) were heated at 80 °C for 120 min. The reaction was then allowed to cool to rt, and it was added to brine, extracted with Et_2O (3 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Then NaOH (3.6 g) was added and stirred for 2 h. The mixture was added to brine and extracted with Et_2O (3 × 100 mL) to give **6** as a light yellow solid (1.40 g, 90%). mp 161–163 °C (lit. 158–159 °C [35]), ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.53 (s, 2H), 7.56–7.49 (m, 2H), 7.47–7.39 (m, 2H), 7.37–7.30 (m, 1H).

4.7.2. Method 2

A solution of 1 M aq NaOH (5.0 mL), 2-chloro-5-phenylpyrimidine **6** (100 mg, 0.53 mmol) and NH_4Cl (253 mg, 4.72 mmol) were added to a 10–20 mL vial, sealed with a crimp cap and placed in a CEM Discover Lab Mate reactor microwave cavity. After irradiation at 150 °C for 30 min, the reaction mixture was cooled to rt and the precipitate was filtered, and washed with water to provide a white crystalline solid (55 mg, 61%). mp 162–163 °C (lit. 158–159 °C [35]), ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.53 (s, 2H), 7.56–7.28 (m, 5H).

*4.8. 2-Chloro-5-phenylpyrimidine (**9**)*

Based on a literature method [31] 5-bromo-2-chloropyrimidine (1.00 mg, 5.17 mmol), phenylboronic acid (1.26 g, 10.34 mmol), $Pd(OAc)_2$ (58 mg, 0.26 mmol) and Na_2CO_3 (1.10 g, 10.34 mmol) in H_2O/EtOH (4:1, 50 mL) were heated at 45 °C for 30 min. The reaction was then allowed to cool at rt, and it was added to brine, extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2) gave **8** as a white solid (1.57 g, 80%). mp 132 °C (lit. 132 °C [32]; 131–133 °C [33]), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 2H), 7.62–7.44 (m, 5H).

4.9. General Method E. Synthesis of 2-substituted 6-arylimidazo[1,2-a]pyrimidines

To a solution of **6**, **6a-c** or **10** (1 eq) in DMF (0.1 M) the appropriate bromo pyruvate reagent (2 eq) was added and the reaction mixture was stirred under Ar at r.t. for 4 days. For the ethyl ester derivatives, the reaction mixture was then poured into saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with water, and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The esters were purified with flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1 to 1:1), followed by recrystallization from EtOH. For the acid derivatives, the reaction mixture was poured into saturated $NaHCO_3$, adjusted to pH 8 and extracted with CH_2Cl_2. Then, the aqueous phase was adjusted to pH 3 with conc. HCl and extracted with iPrOH/$CHCl_3$ (1:3 v/v), dried over Na_2SO_4 and concentrated *in vacuo*. The final products were obtained after recrystallization with EtOH. Representative spectra for cpds **8a-d** follow.

*4.9.1. Ethyl 6-phenylimidazo[1,2-a]pyrimidine-2-carboxylate (**8a**)*

Yield: 47%. mp 234–235 °C, ν_{max} 1724 (CO) cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (d, J = 2.7 Hz, 1H), 9.06 (d, J = 2.6 Hz, 1H), 8.46 (s, 1H), 7.81–7.77 (m, 2H), 7.60–7.54 (m, 2H), 7.51–7.46 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 162.4, 152.7, 146.9, 136.4, 133.4, 132.6, 129.4, 128.6, 126.8, 122.6, 116.8, 60.5, 14.2. HRMS (ESI$^+$) $C_{15}H_{14}N_3O_2^+$ ([M+H]$^+$) requires 268.10805; found 268.10777.

*4.9.2. 6-Phenylimidazo[1,2-a]pyrimidine-2-carboxylic acid (**8b**)*

Yield 20%. mp 232–233 °C, ν_{max} 3147 (OH), 1687 (CO) cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.01 (bs, 1H), 9.31 (d, J = 2.6 Hz, 1H), 9.04 (d, J = 2.6 Hz, 1H), 8.40 (s, 1H), 7.82–7.77 (m, 2H), 7.60–7.54 (m, 2H), 7.51–7.46 (m, 1H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.8, 152.4, 146.8, 137.4, 133.5, 132.6, 129.3, 128.6, 126.8, 122.5, 116.5. HRMS (ESI$^+$) $C_{13}H_{10}N_3O_2^+$ ([M+H]$^+$) requires 240.07675; found 240.07682.

*4.9.3. ^{15}N-Ethyl 6-phenylimidazo[1,2-a]pyrimidine-2-carboxylate (**8c**)*

Yield: 41%. mp 234–235 °C, ν_{max} 1712 (CO) cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (d, J = 2.7 Hz, 1H), 9.06 (d, J = 2.6 Hz, 1H), 8.46 (s, 1H), 7.81–7.76 (m, 2H), 7.59–7.53 (m, 2H), 7.50–7.46 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 162.9 (d, J = 7.7 Hz), 153.2 (d, J = 3.8 Hz), 147.3 (d, J = 6.6 Hz), 136.9, 133.9, 133.1, 129.8, 129.1, 127.3, 123.1, 117.2, 61.0, 14.7, ^{15}N NMR (60 MHz, DMSO-d_6) δ 239.9. HRMS (ESI$^+$) $C_{15}H_{14}N_2^{15}NO_2^+$ ([M+H]$^+$) requires 269.10509; found 269.10504.

*4.9.4. ^{15}N-6-Phenylimidazo[1,2-a]pyrimidine-2-carboxylic acid (**8d**)*

Yield: 18%. mp 229–231 °C, ν_{max} (film) 3147 (OH), 1687 (CO) cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.02 (bs, 1H), 9.31 (d, J = 2.7 Hz, 1H), 9.04 (d, J = 2.6 Hz, 1H), 8.40 (s, 1H), 7.81–7.76 (m, 2H), 7.59–7.53 (m, 2H), 7.51–7.46 (m, 1H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.8 (d, J = 7.7 Hz), 152.4 (d, J = 4.3 Hz), 146.8 (d, J = 6.1 Hz), 137.3, 133.5, 132.6, 129.3, 128.6, 126.8, 122.5, 116.5, ^{15}N NMR (60 MHz, DMSO-d_6) δ 241.1. HRMS (ESI$^+$) $C_{13}H_{10}N_2^{15}NO_2^+$ ([M+H]$^+$) requires 241.07379; found 241.07370.

*4.10. 2-^{15}N-Amino-5-phenylpyrimidine (**10**)*

A solution of 1 M aq NaOH (5.0 mL), 2-chloro-5-phenylpyrimidine **6** (100 mg, 0.53 mmol) and $^{15}NH_4Cl$ (257 mg, 4.72 mmol) were added to a 10–20 mL vial, sealed with a crimp cap and placed in a CEM Discover Lab Mate reactor microwave cavity. After irradiation at 150 °C for 30 min, the reaction mixture was cooled to rt and the precipitate was filtered, and washed with water to provide a white crystalline solid (74 mg, 81%). mp 161–163 °C, ν_{max} 3146 (NH_2) cm^{-1}, ^{1}H NMR (400 MHz, MeOH-d_4, 9:1 mixture δ 8.43 (s, 2H), 7.50–7.45 (m, 2H), 7.42–7.37 (m, 2H), 7.30–7.23 (m, 1H); 8.53 (s, 2H), 7.57–7.52 (m, 2H), 7.45–7.42 (m, 2H), 7.37–7.32 (m, 1H). HRMS (ESI$^+$) $C_{10}H_{10}N_2^{15}N^+$ ([M+H]$^+$) requires 173.08396; found 173.08406.

4.11. 6-Phenylimidazo[1,2-a]pyrimidine-3-carboxylic acid (**11a**)

Following a similar procedure to the first step of General Method D, to a refluxing solution of **8a** (100 mg) in THF/EtOH (1/1 mL), 1 M NaOH in H_2O (1.12 mL in 1.5 mL) was added and the reaction refluxed for 3 h. It was then cooled to rt, pH was adjusted to 8 ($NaHCO_3$) and extracted with EtOAc. Then, the aqueous phase was further acidified to pH 3 (1 N HCl), and the white precipitate formed was collected, washed with Et_2O to obtain **11a** (49 mg, 55%). mp 225–227 °C, ν_{max} (film) 3286 (OH), 1692 (CO) cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6) δ 13.56 (bs, 1H), 9.68 (d, J = 2.5 Hz, 1H), 9.17 (d, J = 2.6 Hz, 1H), 8.50 (s, 1H), 7.86–7.77 (m, 2H), 7.62–7.55 (m, 2H), 7.56–7.48 (m, 1H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 161.1, 152.6, 149.1, 141.1, 133.3, 132.4, 129.5, 128.8, 127.2, 123.9, 115.1. HRMS (ESI^+) $C_{13}H_{10}N_3O_2^+$ ($[M+H]^+$) requires 240.07675; found 240.07669.

4.12. ^{15}N-6-Phenylimidazo[1,2-a]pyrimidine-3-carboxylic acid (**11b**)

Following a similar procedure to that for the preparation of **11a**, from **8c**. Yield: 51%. mp 230–232 °C, ν_{max} (film) 3286 (OH), 1686 (CO) cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6) δ 13.44 (bs, 1H), 9.67 (m, 1H), 9.13 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 2.9 Hz, 1H), 7.85–7.77 (m, 2H), 7.63–7.55 (m, 2H), 7.54–7.47 (m, 1H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 161.2 (d, J = 3.2 Hz), 152.0 (d, J = 4.2 Hz), 149.7 (d, J = 8.0 Hz), 142.2 (d, J = 5.1 Hz), 133.5, 132.2 (d, J = 12.6 Hz), 129.4, 128.7, 127.1, 123.5, 115.0 (d, J = 16.3 Hz), ^{15}N NMR (60 MHz, DMSO-d_6) δ 188.5. HRMS (ESI^+) $C_{13}H_{10}N_2^{15}NO_2^+$ ($[M+H]^+$) requires 241.07379; found 241.07368.

4.13. Ethyl 6-phenylimidazo[1,2-a]pyrimidine-3-carboxylate (**12a**)

A degassed suspension of **8a** (52 mg, 0.195 mmol) and EtONa (132 mg, 1.95 mmol) in EtOH (2.0 mL) was heated at reflux for 18 h. It was then cooled to rt, added to $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (10 mL × 4), washed with water (10 mL), and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1 → 1:1), gave **12a** as a white crystalline solid (15 mg, 29%). mp 127–129 °C, ν_{max} (film) 1694 (CO) cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6) δ 9.59 (d, J = 2.6 Hz, 1H), 9.14 (d, J = 2.6 Hz, 1H), 8.46 (s, 1H), 7.83–7.76 (m, 2H), 7.60–7.54 (m, 2H), 7.52–7.46 (m, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 159.6, 152.3, 149.8, 142.3, 133.3, 132.2, 129.4, 128.7, 127.1, 123.7, 114.3, 60.6, 14.3. HRMS (ESI^+) $C_{15}H_{14}N_3O_2^+$ ($[M+H]^+$) requires 268.10805; found 268.10834.

4.14. ^{15}N-Ethyl 6-phenylimidazo[1,2-a]pyrimidine-3-carboxylate (**12b**)

Following a similar procedure to that for the preparation of **12a**, a degassed suspension of **8c** (62 mg, 0.231 mmol) and EtONa (158 mg, 2.31 mmol) in EtOH (2.0 mL) was heated at reflux for 18 h. It was then cooled to rt, added to $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (10 mL × 4), washed with water (10 mL), and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1 → 1:1), gave **12b** as a white crystalline solid (16 mg, 26%). mp 129–131 °C, ν_{max} (film) 1693 (CO) cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6) δ 9.61 (dd, J = 2.6, 1.4 Hz, 1H), 9.15 (dd, J = 2.6, 0.9 Hz, 1H), 8.47 (d, J = 2.8 Hz, 1H), 7.84–7.77 (m, 2H), 7.62–7.55 (m, 2H), 7.53–7.47 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 160.1 (d, J = 2.9 Hz), 152.8 (d, J = 4.5 Hz), 150.3 (d, J = 8.5 Hz), 142.8 (d, J = 5.1 Hz), 133.8, 132.7 (d, J = 12.7 Hz), 129.9, 129.2, 127.6, 124.2, 114.7 (d, J = 17.3 Hz), 61.1, 14.7, ^{15}N NMR (60 MHz, DMSO-d_6) δ 187.7. HRMS (ESI^+) $C_{15}H_{14}N_2^{15}NO_2^+$ ($[M+H]^+$) requires 269.10509; found 269.10472.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.06.033.

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