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Oxone®-mediated Dakin-like reaction to synthesize hydroxyarenes: an approach using pyrazolo[1,5-a]pyrimidines†

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A simple and efficient methodology was developed for converting formyl(hetero)arenes into the corresponding hydroxylated derivatives in high yields (95–99%) using Oxone® as the oxidant. This Dakin-like reaction proceeded via C–C bond cleavage with the insertion of an oxygen atom into the formyl group, forming the corresponding formyl esters (up to 99%), which then underwent basic hydrolysis to yield the desired alcohols. Although the substrate scope mainly included 3-hydroxypyrazolo[1,5-a]pyrimidines, other substrates featuring typical fluorophores (e.g., triphenylamine, anthracene, pyrene, fluorene, and coumarin) were also tested. Moreover, we demonstrated the functionalization of the representative 3-hydroxypyrazolo[1,5-a]pyrimidine derivatives obtained using our developed methodology involving alkylation, acylation, and sulfonylation reactions.

Introduction

The functionalization reactions of N-heteroaromatic compounds face significant challenges in their organic synthesis as heteroatoms confer unique electronic properties that govern and possibly limit their performance. The reactivity of substrates under acidic, oxidizing, or hydrolytic conditions limits their utility owing to the potential formation of chelates, salts, N-oxides, or ring-opening products.^{1–4} Moreover, the presence of diverse π -excessive or π -deficient rings hinders the incorporation of the desired functional group. For example, a hydroxyl group (OH) is frequently introduced in π -deficient rings using nucleophilic aromatic substitution (NAS) reactions, although this reaction does not usually occur on π -excessive rings;^{4–6} thus, obtaining hydroxylated (N-hetero) arenes is a great challenge (Fig. 1a).^{7–9} Nevertheless, the presence of OH groups in diverse rings is crucial as this functional group allows access to different and relevant chemicals in biological (e.g., carbamates)^{10,11} and photophysical (hybrid dyes)^{12,13} fields. The photophysical field requires the use of fluorophoric reagents, which are highly conjugated or π -excessive rings^{12–14} in which the OH insertion is complex, but its presence facilitates relevant charge transfer (CT) or excited state intramolecular proton transfer (ESIPT) phenomena (Fig. 1b).^{15–17} It is important to note that the synthesis of functional fluorophores is a recurrent

objective of our research group,^{18,19} mainly for chemodetection applications,²⁰ with relevant results achieved using the pyrazolo[1,5-a]pyrimidine (Pp) scaffold;²¹ a dipolar 5:6 fused ring system containing three nitrogen atoms essential to synthesize various biologically active compounds (Fig. 1c, left).^{4,22–26}

Alternatively, the Baeyer–Villiger (BV) reaction,²⁷ using (hetero)arylaldehydes with π -excessive rings as substrates, is a Dakin-like reaction that offers an alternative protocol to access hydroxylated fluorophores. Specifically, a Dakin reaction involves converting hydroxy- or alkoxy-benzaldehydes into the respective phenols.²⁸ This transformation is based on the

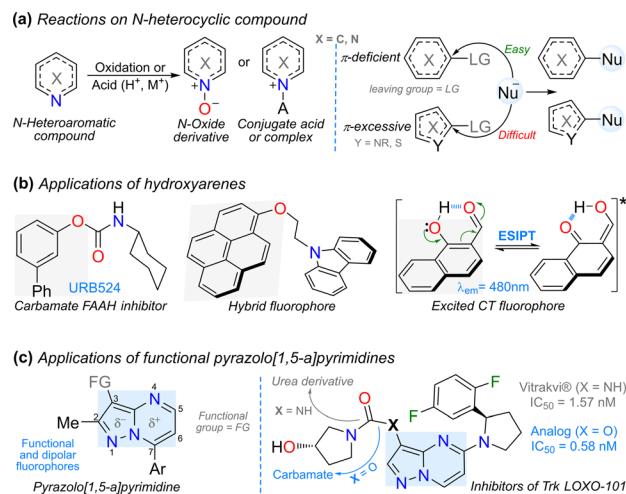
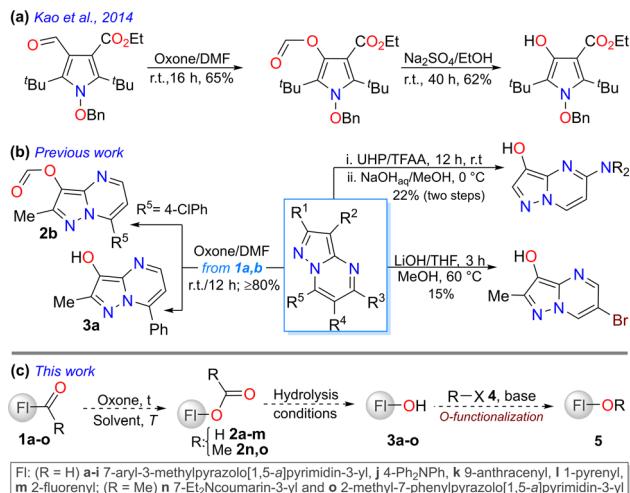


Fig. 1 (a) Reactions on (N-hetero) arenes including NAS. (b) Hydroxylated arenes and (c) pyrazolo[1,5-a]pyrimidines with relevant applications.

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Scheme 1 Synthesis of hydroxylated N-heterocyclic compounds (a) by Kao *et al.* and (b) in previous work. (c) Research proposal.

Table 1 Optimization of reaction conditions for the Dakin reaction of **1a**^a

Entry	Oxone®	Solvent	t (h)	T (°C)	2a/3a,
					yield (%)
1	1 equiv.	Dry DMF	12	r.t.	10/85 ^b
2			4		80/15 ^b
3			2		99/—
4			1		57/—
5			0.5 ^c		40/25 ^{b,d}
6			2	50	73/15 ^{b,d}
7		DMF	2	r.t.	58/—
8	0.5 equiv.	Dry DMF	5	r.t.	43/—
9	1 equiv.	MeOH	2	r.t.	—/75 ^d
10	1 equiv.	DCM, DMSO, or MeCN	5	100	—/—

^a Reaction conditions: 50 mg of **1a** (0.21 mmol) and Oxone® (32 mg, 1 equiv.) in 1 mL of solvent at r.t. ^b Determined by ¹H NMR using 1,3,5-(MeO)₃C₆H₃ as a standard. ^c Under MW in a 10 mL sealed tube. ^d Decomposition products were observed.

oxidative cleavage of carbon–carbon bonds adjacent to a carbonyl group, with the insertion of an oxygen atom to convert aldehydes or ketones into esters. Peracids (*e.g.*, *m*-CPBA), basic hydrogen peroxide (H₂O₂), or acidic urea–hydrogen peroxide (UHP) conditions are generally unsuitable for all substrates as they often lead to overoxidation.^{27–29} Oxone® (a triphasic monopersulfate-based salt: KHSO₅· $\frac{1}{2}$ KHSO₄· $\frac{1}{2}$ K₂SO₄) is a cost-effective, easier-to-handle, efficient, and sustainable oxidizing agent owing to its high solubility in water and decomposition into environmentally friendly waste (K₂SO₄) during reactions.^{27–30} Although this reagent has been used in the oxidation of aldehydes to carboxylic acids (*via* the BV

reaction) or formyl esters (*via* the Dakin reaction), the latter transformation has been mainly studied for obtaining phenol derivatives from π -excessive benzaldehydes. Remarkably, only two articles were reported in this respect, where Oxone® was preliminarily used on N-heteroaldehydes; in the first one, a 3-formylpyrrole derivative was oxidized to the respective ester to access the desired alcohol (Scheme 1a),³¹ and in the second one, 3-formylpyrazolo[1,5-*a*]pyrimidines **1a–b** offered a formyl ester (**2b**) and an alcohol (**3a**) (Scheme 1b, left).³² The second report was a correction³² to an article we published in 2018, in which the reaction was only explored as a preliminary test.¹⁹

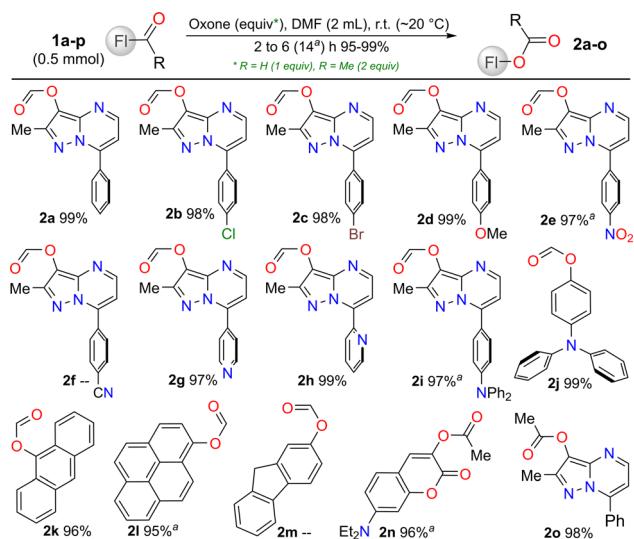
In addition to the Oxone®-mediated Dakin reaction of **1a–b**, only one patent was found using the same heterocyclic core, in which the oxidation was performed on a 3-acetylpyrazolopyrimidine using hydrogen peroxide–urea (UHP), but in poor yield; then, the acetyl ester intermediate underwent basic hydrolysis to form the desired alcohol (Scheme 1b, top right).³³ A similar compound was reported in another patent but *via* a different route, in which a substitution reaction of bromine with a hydroxyl group was carried out in poor yield using lithium hydroxide (Scheme 1b, bottom right).³⁴ The first patent reported a biologically valuable alcohol (Fig. 1c, right), as evidenced by the high inhibitory activity of its carbamate derivative (IC₅₀ = 0.58 nM) towards Trk (LOXO-101), which proved to be more active than the commercial drug urea derivative Vitrakvi (IC₅₀ = 1.57 nM).³³ Therefore, the Oxone®-mediated Dakin reaction of **1a–b** is a promising reaction, despite its result being very preliminary and unexpected.³² Indeed, in 2018, we reported the preparation and synthetic utility of 3-formylpyrazolo[1,5-*a*]pyrimidines, in which this reaction was studied to obtain the respective carboxylic acid¹⁹ under conditions reported by Travis *et al.*³⁵ Nevertheless, last year, we attempted to replicate the reaction and irregularities were observed because the ester **2b** and alcohol **3a** were isolated as oxidation products instead of the desired carboxylic acids (Scheme 1b, left).

Considering this unexpected and fascinating results of the Oxone®-mediated reaction of **1a–b**³² (substrates bearing an emergent fluorophore^{4,21}), we aimed to optimize the reaction conditions that lead to a new series of 3-hydroxypyrazolo[1,5-*a*]pyrimidines **3a–i**. We used these alcohols in alkylation, acylation, and sulfonylation reactions (to obtain **5a–h**) to explore their synthetic versatility. We also extended the reaction scope to some typical fluorophore-based substrates (*i.e.*, triphenylamine, anthracene, pyrene, fluorene, and coumarin) to yield alcohols **3j–n** (Scheme 1c), which are usually difficult to access (due to multistep synthesis and the high cost of commercial compounds)^{36–39} but could facilitate innovative research.^{15,16,36–39}

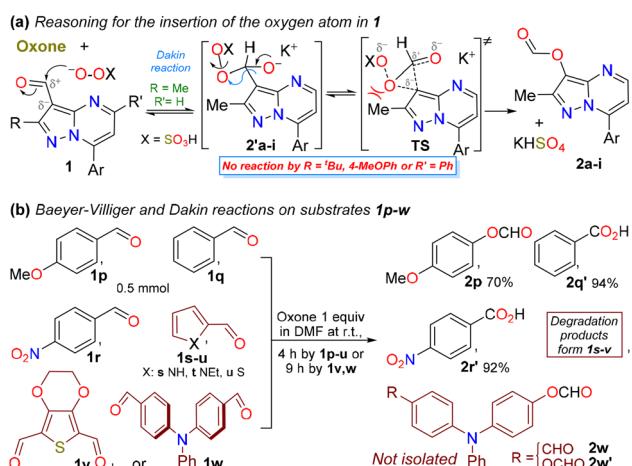
Results and discussion

Our study to obtain alcohols **3a–i**, starting from heteroaldehydes **1a–i**, began with the optimization of reaction conditions (solvent, equiv., temperature, and time) using the model substrate **1a** under the preliminary conditions of Oxone®/1 equiv. in dry DMF at room temperature (~20 °C) for 12 h followed by HCl aq workup,³² and initially only the reaction time was varied. Although the results were reproducible, the





Scheme 2 Substrate scope for the synthesis of esters 2a–o.



Scheme 3 (a) Oxone®-mediated operation on 3-formylpyrazolo[1,5-a]pyrimidines 1 and (b) other products obtained from the Oxone®-mediated oxidation reaction.

intermediate ester **2a** was also isolated under these conditions. Remarkably, the time control facilitated the formation of ester **2a** as a single product, and application of microwave irradiation was unfavorable for this reaction (Table 1, entries 1–5). Subsequently, we observed that increasing the temperature and the degree of moisture affected the reaction yield; thus, the reaction was carried out in a closed vessel at ~ 20 °C in anhydrous DMF under a nitrogen atmosphere to afford quantitative results. In addition, reducing the equivalents of Oxone® decreased the reaction yield (Table 1, entries 6–8 vs. 3), making entry 3 the optimal reaction condition. When we attempted to purify **2a** using flash chromatography, the amount of alcohol **3a** increased,³² obscuring the isolation of **2a**; however, the crude ester (a solid residue) was successfully purified by adding cold pentane to remove residual DMF. We also explored changing the solvent to ease the purification process (which was already

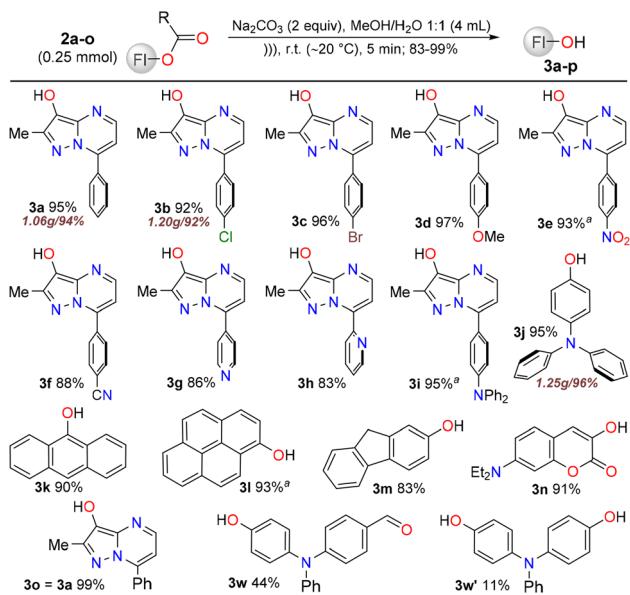
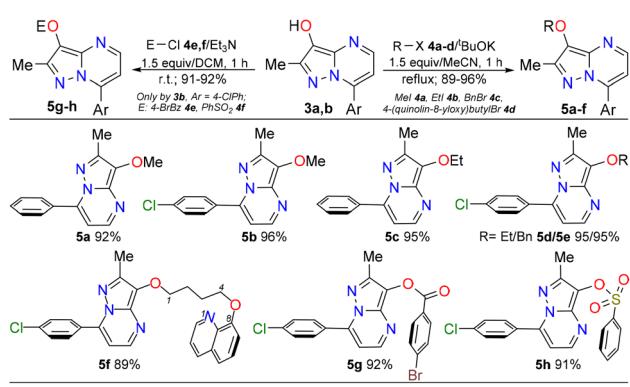
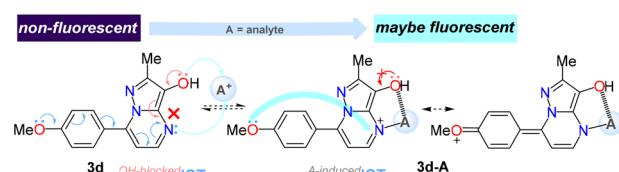
easy using DMF); however, the reaction only proceeded in MeOH, yielding decomposed products (entry 9 vs. 10). Finally, to demonstrate the importance of Oxone® in this transformation, other oxidizing agents (1 equiv. of KOH/H₂O₂, *m*-CPBA, and UHP) were used; however, no changes were observed with any of them after 5 hours of reaction at ~ 20 °C in dry DMF.

Subsequently, we studied the reaction scope using substrates **1b–i**, which were substituted with a ring of diverse electronic natures at position 7, and notably, only those bearing electron-withdrawing groups (EWGs) affected the reaction time. The reaction was also efficient starting from typical fluorescent aldehydes **1j–m**, and even from ketones **1n,o**, which required 2 equivalents of Oxone® (Scheme 2). Rings bearing EWGs were expected to affect the migratory capacity of the pyrazolo[1,5-a]pyrimidine core during the reaction, generating the desired carboxylic acids;¹⁹ however, this outcome was not observed, and the respective esters were formed in high yields, indicating that the strong donor effect at position 3 of the heterocyclic core^{3,40} dominated in this oxidation reaction. However, some esters (*i.e.*, **2f** and **2m**) were not isolated, as they were formed together with traces of alcohol, and these esters were hydrolyzed to the corresponding alcohol during the separation of the mixture using flash chromatography (Scheme 2).¹⁹

We also investigated the scope of the reaction by varying the substituents on the heterocyclic core at positions 2 (Me vs. ¹Bu or 4-MeOPh) and 5 (H vs. Ph); however, the reaction did not advance owing to strong steric effects at the reactive center (the HSO_5^- anion was large) or perhaps owing to the high stability conferred by the substituents (aryl vs. Me/H),⁴ which limited the ability to reach the transition state (TS) required during the migration (Scheme 3a). By using other aldehydes available in our laboratory, bearing phenyl **1q**, π -excessive (4-MeOPh **1p** and pyrrole **1s,t** or thiophene **1u**) or π -deficient (4-O₂NPh **1r**) rings or two formyl groups **1v,w** (Scheme 3b), the Dakin reaction was observed only from **1p,w**, while the Baeyer–Villiger oxidation occurred from arylaldehydes **1q,r**. Notably, the decomposed products were observed from the reactions of heteroaldehydes **1s–v**, possibly owing to their high reactivity towards oxidizing agents (pyrrole and thiophene are π -excessive rings, and **1t,v** bear EDGs), and less stable monocyclic structures;^{1,5,7} *e.g.*, the Oxone®-mediated reaction reported by Kao *et al.*³¹ from a 3-formylpyrrole derivative yielded the desired ester (Scheme 1a above), likely because the substrate was stabilized by EGWs, such as CO_2Et and BnO , on the nitrogen atom. Ultimately, the dicarbaldehydes **1v,w** were used as substrates to test the selectivity of this transformation; however, only the triphenylamine (TPA) derivative **1w** was converted into the corresponding monoester **2w** and diester **2w'**, since the substrate **1v** offered the decomposed products (Scheme 3b). Although intermediate esters **2w** and **2w'** were not isolated, they must be hydrolyzed later for discussion of their respective properties.

With the formyl **2a–m,w** or acetyl **2n,o** esters in hand, we then tested their hydrolysis reaction, which was efficiently performed owing to their high reactivity and the presence of a good leaving group (heteroaryloxy). The reaction was carried out in a methanol/water mixture (1 : 3) under basic conditions (2



Scheme 4 Substrate scope for the synthesis of alcohols $3a\text{-}o$.Scheme 5 Synthetic applications of 3-hydroxypyrazolo[1,5-a]pyrimidine $3a,b$.Fig. 2 Possible fluorescence process implied in ICT probe $3d$.

equiv. of Na_2CO_3) and ultrasound (US) irradiation (5 min at $\sim 20^\circ\text{C}$); this hydrolysis reaction occurred efficiently using an ultrasound probe (0.2 MHz, 750 W), as the cavitation effect significantly enhanced the reagent solubility.⁴¹ Gratifyingly, the products were obtained in excellent yields (up to 99%), and $3a$ and $3e$ did not require any further purification beyond extraction (Scheme 4); however, alcohols $3f\text{-}h$ presented challenges during extraction owing to their high solubility in water,

resulting in lower yields (83–86%). Finally, the hydroxyaldehyde $3w$ and the diol $3w'$ were obtained when the hydrolysis residue was purified using flash chromatography on silica gel (eluent: (i) DCM and (ii) DCM/MeOH 4:1 v/v). The first fraction eluted contained $3w$ (44%), while the second fraction contained traces of $3w'$ (11%); despite the substrate being consumed during oxidation, the moderate isolated yields of these alcohols were owing to their retention on the silica gel during purification. Therefore, the selectivity of the Dakin reaction was established towards the alcohol $3w$, possibly due to the use of 1 equivalent of Oxone®. Notably, the TPA derivatives $3w$, $3w'$, and $3j$ are highly valuable compounds in materials chemistry³⁶ (with $3j$ costing approximately \$116 per gram⁴²), anthracen-9-ol ($3k$) rapidly isomerizes to anthracen-9(10H)-one (90%); fluoren-2-ol ($3m$) has a high commercial cost (\$125 per gram (ref. 43)), and the coumarin-3-ol ($3n$) is a novel dye. Three of these alcohols were obtained on a gram scale (from 5.0 mmol) in 95% (1.07 g/ $3a$), 93% (1.22 g/ $3b$), and 96% (1.25 g/ $3j$) yields.

Finally, we investigated the synthetic application of the obtained alcohols using $3a$ and $3b$ in O-functionalizations such as alkylation, acylation, and sulfonylation reactions. The synthesis of ethers $5a\text{-}f$ via the reaction of $3a,b$ with 1.5 equiv. of $^t\text{BuOK}$ /haloalkane (*i.e.*, MeI $4a$, EtI $4b$, BnBr $4c$, or 8-quinolinyl-O(CH_2)₄Br $4d$) at reflux in MeCN for 1 hour efficiently resulted in high yields (Scheme 5, right); likewise, the acylation and sulfonylation reactions of $3b$ were successfully realized using $\text{Et}_3\text{N}/4\text{-BrBzCl}$ $4e$ or $\text{Et}_3\text{N}/\text{PhSO}_3\text{H}$ $4f$ but at $\sim 20^\circ\text{C}$ in DCM (Scheme 5, left). These results suggested that the chemistry of 3-hydroxypyrazolo[1,5-a]pyrimidines is similar to those of other hydroxylated (hetero)arenes,^{35–38} considering the high nucleophilicity of their OH group.²³

Notably, unlike the aldehydes $1a\text{-}i$ ¹⁹ and their non-functionalized precursors $6a\text{-}i$ ⁴⁴ (see structures in ESI†), none of the hydroxylated pyrazolo[1,5-a]pyrimidines $3a\text{-}i$ were found to be fluorescent compounds; this might be possibly owing to the intramolecular charge transfer (ICT) process of the fluorophore family being blocked by the presence of the electron-donating hydroxyl group. Consequently, we aim to explore future applications of this type of alcohols, particularly in chemodetection, through a turn-on fluorescence upon interaction of the hydroxyl group with an analyte of interest that would restore the ICT phenomenon (*e.g.*, using the compound $3d$, Fig. 2).

Conclusions

In summary, the Oxone®-mediated Dakin-type oxidation of 3-formylpyrazolo[1,5-a]pyrimidines to 3-hydroxy derivatives was successfully carried out in high yields under mild conditions and using cost-effective reagents. Notably, this synthetic methodology was conveniently extended to other (hetero)arenes bearing typical fluorophores, enabling the preparation of commercially valuable derivatives that are highly expensive but highly promising for photophysical studies. Furthermore, the reaction proved to be selective for the formation of a mono-hydroxylated derivative from a dialdehyde upon controlling the Oxone® equivalents. In addition, the synthetic applications



of two 3-hydroxypyrazolo[1,5-*a*]pyrimidines were evaluated using simple methods (alkylation, acylation, and sulfonylation) and readily available reagents. Therefore, the alcohol derivatives obtained herein serve as spearheads for directing novel and varied applications of pyrazolopyrimidines owing to the “almost unprecedented” acquired functionality and the high synthetic and photophysical versatility of this compound family.

Experimental section

Comment. Structures of some novel precursors (*i.e.*, **1e,f**), other relevant precursors (*i.e.*, **1n,o** and alkylating agent **4d**), esters **2a-o**, alcohols **3a-w**, and O-functionalization products **5a-h** were determined using NMR measurements and HRMS analysis (see Fig. S1–S72 in ESI[†]). Detailed experimental procedures and characterization data for all the synthesised compounds, including their general information, are provided in the ESI.[†] General experimental procedures for the synthesis of compounds **2a-o**, **3a-o**, and **5a-h** are described below.

General procedures

General procedure for the Dakin-like reaction from (hetero)aryl aldehydes **1a-w.** A mixture of aldehyde or ketone **1a-w** (0.5 mmol) and Oxone® (76 mg/0.5 mmol for aldehydes or 152 mg/1 mmol for ketones **1n,o**) was added into a ball of 5.0 mL and subjected to vacuum for 2 min. Next, the mixture was placed under an N₂ atmosphere, and anhydrous DMF (2 mL) was added, and the mixture was stirred at ~20 °C for 2 h. Subsequently, distilled water (5 mL) was added, and the resulting mixture was extracted with DCM (3 × 7 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and the resulting solution was concentrated under reduced pressure. Finally, 4 mL of cold pentane was added to the residue to remove traces of grease and residual DMF (recrystallisation), affording various pure products. Notably, the reaction of methyl ketones **1n,o** required 2 equiv. of Oxone® for complete conversion. In addition, esters **2f**, **2m**, **2w**, and **2w'** (*i.e.*, using substrates with 7-(4-NCPh)Pp **1f** or fluorene **1m**, or the dialdehyde **1w**) were not isolated as they were formed together with traces of the corresponding alcohols; when we tried to purify these esters, they were hydrolyzed to alcohols during the separation of the mixture using flash chromatography,¹⁹ making their isolation impossible.

General procedure for the hydrolysis of esters **2 to alcohols **3**.** A mixture of the respective ester **2a-o,w,w'** (0.25 mmol) and Na₂CO₃ (53 mg, 0.5 mmol) in MeOH/H₂O 1:1 (4 mL) was subjected to ultrasound irradiation at room temperature for 5 min in a 25 mL TNPSFH glass container. Distilled water (6 mL) was added to the resulting mixture, and it was extracted with DCM (3 × 10 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Finally, the residue was purified using flash chromatography (eluent: (i) DCM, (ii) DCM/MeOH 30:1 v/v) to afford the desired (hetero)aryl alcohols **3a-o** in high yields (83–99%); however, the

mixture of hydroxaldehyde **3w** and diol **3w'** was separated using (i) DCM (**3w**, 44%) and (ii) DCM/MeOH (**3w'**, 11%) 4:1 v/v.

General procedure for the synthesis of 3-alkoxy derivatives **5a-f**.

A mixture of 7-aryl-3-hydroxypyrazolo[1,5-*a*]pyrimidine **3a,b** (0.5 mmol) and 'BuOK (1.5 equiv., 98%, 86 mg) in MeCN (2 mL) was stirred under reflux for 5 min to generate the de alkoxide anion. The alkyl agent **4a-d** (1.5 equiv.) was added to the mixture dropwise for 1 min. The reaction mixture was then stirred under reflux for 1 hour. After completion, distilled water (5 mL) was added, and the resulting mixture was extracted with DCM (3 × 10 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified using flash chromatography (eluent: DCM/MeOH 50:1 v/v) to afford the desired products **5a-f** in high yields (89–96%).

General procedure for synthesising the aroyl **5g and sulphonyl **5h** esters.** A mixture of nucleophilic reagent 3-hydroxy-7-(4-chlorophenyl)2-methylpyrazolo[1,5-*a*]pyrimidine (**3b**, 130 mg, 0.5 mmol) and triethylamine (Et₃N, 99.5%, 105 μL/0.75 mmol) in DCM (2 mL) was stirred for 5 min at room temperature (~20 °C). Then, either 4-bromobenzoyl chloride (**4e** 98%, 157 mg, 0.75 mmol) or phenylsulfonyl chloride (**4f** 99%, 97 μL, 0.75 mmol) was added to the mixture, and it was stirred for 30 min. Afterwards, distilled water (5 mL) was added, and the resulting mixture was extracted using DCM (3 × 10 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and the solution was concentrated under reduced pressure; the residue was purified using flash chromatography (eluent: DCM/MeOH 50:1 v/v) to afford the desired 4-bromobenzoyl **5g** (yellow solid, 203 mg, 92%) and phenylsulphonyl **5h** (white solid, 182 mg, 91%) esters.

Data availability

The data supporting the findings of this study are available within the article and its ESI.[†] Supporting data for this article are provided in the ESI,[†] which include the experimental procedures and characterization data, HRMS analysis with spectral copies, and ¹H NMR, ¹³C NMR, and DEPT-135 spectral copies.

Author contributions

The individuals listed as authors have contributed to the development of this manuscript, and no other person was involved. The author contributions are as follows: C. C. and M. C. carried out the experiments (synthesis and characterization of products) and conducted literature review, while J. P. developed and composed the original draft, supervised it, and provided sources. All authors have read and agreed to the published version of this manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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