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Phosphate mediated biomimetic synthesis of tetrahydroisoquinoline alkaloids†

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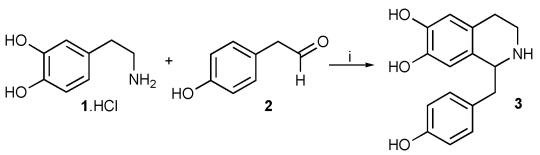
A one-pot synthesis of tetrahydroisoquinoline alkaloids in a phosphate buffer has been achieved, and a reaction mechanism proposed. The utilisation of mild reaction conditions readily afforded a range of isoquinolines, including norcoclaurine.

The benzylisoquinoline alkaloids (BIAs) form one of the most varied groups of natural products found in plants and mammals.[1] BIAs, one of the major classes of tetrahydroisoquinolines, have been identified as pharmacologically active, showing antitumor,[2] anti-microbial,[2,3] anti-inflammatory,[4] anti-HIV,[5] and analgesic activities.[6] While naturally occurring tetrahydroisoquinoline alkaloids can be obtained by plant extraction methods, the yield is alkaloid dependent and most compounds are found in very small quantities or as part of a complex mixture. More recently metabolic engineering strategies have started to be investigated for the generation of larger quantities of alkaloids.[7] In plants norcoclaurine synthases (NCSs), catalyse the first committed step in the BIA biosynthetic pathway, between dopamine **1** and 4-hydroxyphenylacetaldehyde (4-HPAA) **2**.[8] However, studies to date have demonstrated that native NCSs exert a poor tolerance for non-natural substrate analogues,[9] and therefore at present for greater structural diversity chemical synthesis is required. A key synthetic approach to tetrahydroisoquinolines is the Pictet–Spengler reaction which originally described the reaction between β-phenethylamine and formaldehyde dimethyl acetal with hydrochloric acid.[10] In general, less harsh conditions are required with indoles than phenethylamines, where high temperatures and strong acids or superacids are normally needed, which are incompatible with poorly stable aldehydes or amines.[11] More recently, the coupling of dopamine and L-DOPA with glyceraldehyde and glucose under physiologically relevant (pH 7.4 phosphate buffer) and rigorous anaerobic conditions have been described, although the reasons for the enhancement of the Pictet–Spengler reaction were not rationalised.[12] However, to prepare BIAs alternative chemical strategies are used such as the multi-step Bischler–Napieralski cyclisation and dehydration procedure, together with protecting group manipulations.[13]



Scheme 1 Formation of **3**. *Reaction conditions*: (i) 1 : 1 co-solvent/buffer (0.1 M), 37–50 °C (Table 1).

For this reason new concise but versatile synthetic methodologies are highly sought after, indeed recently procedures using a calcium-based Lewis acid catalyst and *o*-benzenedisulfonamide as a reusable acid catalyst have been reported.[14] Here, we report a high yielding biomimetic reaction for the synthesis of BIAs and analogues from variously decorated phenethylamines and aldehydes.

With the aim of developing facile Pictet–Spengler reaction conditions the coupling of dopamine **1** and 4-HPAA **2** to give norcoclaurine **3** was investigated (Scheme 1). The main synthetic challenge in this reaction is the poor stability of both substrates: dopamine readily undergoes oxidative degradation, while 4-HPAA polymerises under both basic and acidic conditions. 4-HPAA **2** was synthesised using the previously reported Parikh–Doering oxidation of 2-(4-hydroxyphenyl)ethanol.[15] Initially the synthesis of **3** was investigated using **1**·HCl (4 mM) and **2** (4.8 mM) in a 1 : 1 mixture of acetonitrile (to aid full substrate solubility) and potassium phosphate buffer (KP_i, 0.1 mM) at physiological pH and temperature. This yielded norcoclaurine **3** in limited quantities (5% after 1 h). This was interesting since some publications where NCSs are used have referred to a minor background chemical reaction, although others use KP_i as buffer and similar reaction conditions with no reported non-enzymatic reaction.[8d,9,16] Further studies established that in acetonitrile/KP_i at pH < 4 and pH > 8 no **3** was formed, and under alkaline conditions 4-HPAA **2** underwent rapid degradation. At intermediate pHs the reaction proceeded smoothly, and yields reached 40% at pH 6 after 1 h. The conversion rate was further increased to 77% by elevating the reaction temperature to 50 °C: higher temperatures lead to the degradation of both **1** and **2**. These results were intriguing since the condensation usually requires strong acid catalysis, but our data suggested that the buffer might be a key component in the reaction, acting as an effective but mild catalyst. To verify this hypothesis the synthesis of norcoclaurine was carried out in various buffers including HEPES, Tris, MOPS and different phosphates. The results unequivocally showed that phosphates promoted the reaction (Scheme 1 and Table 1).

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† Electronic supplementary information (ESI) available: Characterisation data for **3**, **4**, **6** and **8**. See DOI: 10.1039/c0cc05282e

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Table 1 Influence of buffer on the formation of **3** (Scheme 1)

Buffer	Conversion (%)	Buffer	Conversion (%)
Tris	<1	KH_2PO_4	77
HEPES	<1	NaH_2PO_4	75
$B(OH)_3$	<1	UMP	75
Na_3VO_4	<1	Glc-1-P	74
$KHCO_3$	2	$Na_4P_2O_7$	45
$KHSO_4$	4	Water	<1

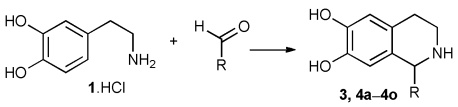
Reaction conditions: **1**·HCl (4 mM), **2** (4.8 mM), 1 : 1 CH_3CN/buffer (0.1 M), pH 6, 50 °C, 1 h. Conversions determined by HPLC.

Potassium or sodium salts of phosphate, uridine-5′-monophosphate (UMP) as well as glucose-1-phosphate (Glc-1-P) all acted as efficient catalysts. Other buffers, whether carbonate, sulfate or amines, had a negligible effect. Borate and vanadate have been reported to act as phosphate mimics, but no **3** was generated.[17,18] Taken together, these results suggested that the phosphate moiety was essential for the observed biomimetic synthesis of norcoclaurine. It was demonstrated that the reaction also displayed a large tolerance for co-solvents (see ESI†), where the highest conversions were achieved using acetonitrile, methanol and DMSO.

The general applicability of the reaction was then explored for the production of variously decorated isoquinolines. Dopamine·HCl was reacted with a set of aldehydes (Table 2). Aliphatic as well as aromatic and heteroaromatic aldehydes readily reacted to generate the tetrahydroisoquinolines (**4a–b**, **4c–k** and **4l–n**, respectively) in 31% to 88% isolated yields. For example, phenylacetaldehyde gave 14-deoxy-norcoclaurine **4k** in 73% yield. These results demonstrated that the reaction is highly versatile and provides an attractive tool for the rapid synthesis of naturally occurring (*e.g.* norcoclaurine) and non-natural isoquinoline alkaloids.

The reaction did not require any protection of phenolic functionalities, which could easily be used in subsequent derivatisation to rapidly generate still greater structural diversity. The reaction also proved attractive for the synthesis of a deuterated analogue **4k-$^2H_2$**, simply prepared by pre-treatment of the aldehyde in D_2O. This together with the synthesis of the quinolinyl and ferrocenyl derivatives (**4n** and **4o**, respectively) highlighted the utility of the reaction in rapidly preparing labelled (including radiolabelled), fluorescent, or electrochemical probes.

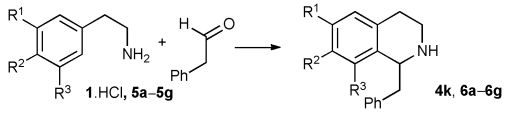
Table 2 Reaction of dopamine with selected aldehydes to give **4a–4o**



R	Product	Yield (%)	R	Product	Yield (%)
4-$HOC_6H_4CH_2$	**3**	63	4-BrC_6H_4	**4i**	47
Me	**4a**	75	4-FC_6H_4	**4j**	41
Cyclopropyl	**4b**	60	$PhCH_2$	**4k**	73
Ph	**4c**	75	$PhCD_2$ (90%)	**4k-$^2H_2$**	83
4-$O_2NC_6H_4$	**4d**	51	2-Thienyl	**4l**	79
4-$MeOC_6H_4$	**4e**	31	3-Pyridinyl	**4m**	77
4-HOC_6H_4	**4f**	35	3-Quinolinyl	**4n**	88
3-HOC_6H_4	**4g**	80	Ferrocenyl	**4o**	44
2-HOC_6H_4	**4h**	86			

Reaction conditions: **1**·HCl (1 equiv.), aldehyde (1.2 equiv.), 1 : 1 CH_3CN/KP_i (0.1 M) pH 6, 50 °C, 12 h for larger scale reactions (see ESI†).

Table 3 Reaction of phenylacetaldehyde with phenethylamines **5a–5g**



Amine	Product	Yield (%)
1, R^1 = OH, R^2 = OH, R^3 = H	**4k**	73
5a, R^1 = OH, R^2 = OH, R^3 = OH	**6a**	9
5b, R^1 = H, R^2 = OH, R^3 = H	**6b**	0
5c, R^1 = OH, R^2 = H, R^3 = H	**6c**	74
5d, R^1 = OMe, R^2 = OMe, R^3 = H	**6d**	0
5e, R^1 = H, R^2 = H, R^3 = H	**6e**	0
5f, R^1 = NO_2, R^2 = H, R^3 = H	**6f**	0
5g, R^1 = NH_2, R^2 = H, R^3 = H	**6g**	52

Reaction conditions: **1**·HCl or **5a–5g** (1 equiv.), aldehyde (1.2 equiv.), 1 : 1 CH_3CN/KP_i (0.1 M) pH 6, 50 °C, 12 h.

We anticipate that reactions giving products in lower yields could be optimised using alternative co-solvents, since the smaller quantities of product generated probably reflected poor substrate solubility in the solvent mixture used.

In sharp contrast to the aldehydes, and consistent with previous studies on the Pictet–Spengler condensation,[19] a limited array of phenethylamines acted as substrates for the reaction (Table 3). Although dopamine **1**, 5-hydroxydopamine **5a**, and 3-hydroxyphenethylamine **5c** all yielded the corresponding isoquinoline products with phenylacetaldehyde to give **4k**, **6a** and **6c**, in the absence of the 3-hydroxyl functionality in regioisomer **5b**, and analogues **5d–5f** the reaction did not proceed. Interestingly, when a 3-methoxy group was present in **5d** this also precluded the formation of product. However, the presence of a 3-amino group in **5g** readily gave the isoquinoline **6g** in 52% yield. Taken together, these results suggested that an available hydroxyl or amine electron donating group *meta* to the ethylamine substituent is required for cyclisation. In addition, these reactions were highly regioselective with cyclisation at the least hindered *para* position, relative to the amine and phenolic groups, and consistent with a cyclisation mechanism involving direct formation of the 6-membered isoquinoline, rather than a 5-membered spirocyclic intermediate.[9,11a]

In order to explore the synthesis of stereochemically enriched isoquinoline alkaloids, analogous reactions were performed using single isomer amines **7a** and **7b** or aldehydes (Table 4). All reactions again proceeded well giving **8a–8d** in 43% to 94% yield, further demonstrating the versatility of the reaction. Stereoselectivities were observed for the reaction between amine **7a** and phenylacetaldehyde, and **1**·HCl and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde to give **8a** and **8c** (deprotection of the diol from its isopropylidene ketal occurred during the reaction), respectively. The highest diastereomeric ratio (dr) (1 : 2.6) was observed in tetraol **8c**, where the major product formed (1*R*,1′*S*) was consistent with the Felkin-Ahn model of asymmetric induction, as previously.[12d] Substrates with more remote stereocentres not surprisingly gave lower stereoselectivities, although with norepinephrine (**7a**) a dr of 1 : 1.6 was observed in **8a**. This may have been due to phosphate complexation at C4-OH, reducing access to one face of the imine. Three of the four diastereoisomers

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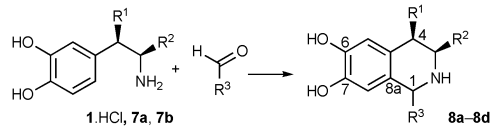
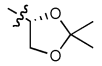
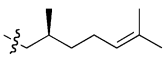
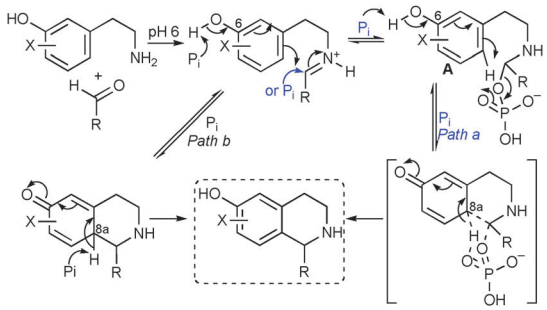
Table 4 Stereoselective synthesis of tetrahydroisoquinolines



Amine	Aldehyde	Product dr	Yield
7a R^1 = OH, R^2 = H	R^3 = $PhCH_2$	**8a** 1 : 1.6	27% (1*S*,4*R*)[a] 43% (1*R*,4*R*)[a]
7b R^1 = H, R^2 = CO_2H	R^3 = $PhCH_2$	**8b** 1 : 1.2	30% (1*R*,3*S*) 35% (1*S*,3*S*)
1·HCl R^1 = R^2 = H	R^3 = 	**8c** 1 : 2.6 (deprotected tetraol)	26% (1*S*,1′*S*) 68% (1*R*,1′*S*)
1·HCl R^1 = R^2 = H	R^3 = 	**8d** 1 : 1	43% (not resolved)

Reaction conditions: Amine (1 equiv.), aldehyde (1.2 equiv.), 1 : 1 CH_3CN/KP_i (0.1 M) pH 6, 50 °C, 12 h.[a] Tentatively assigned (see ESI†).



Scheme 2 Proposed phosphate mediated mechanism for the Pictet–Spengler reaction. P_i is inorganic phosphate.

synthesised could be resolved by preparative HPLC, and provided rapid access to the single isomer products.

Overall, the results observed suggest that phosphate plays an essential role in this Pictet–Spengler cyclisation (Scheme 2). The first step will involve formation of the iminium intermediate at pH 6. A phosphate anion or dianion can then undergo nucleophilic attack onto the iminium intermediate, to produce a highly reactive aminophosphate **A**, in equilibrium with the iminium species.

Phosphate can then act as a base, deprotonating C6-OH (or C6-$^+NH_3$ in **5g**) and activating the ring for addition to the imine at the *para*-position, or the aminophosphate **A**, resulting in cyclisation. This would explain the non-reactivity of **5b** and **5d–5f** in the reaction. Rearomatisation could finally proceed by a phosphate mediated intra- (path a) or intermolecular (path b) abstraction of the 8a-H proton. In previous work by Sutherland and co-workers the role of phosphate in prebiotic chemistry and nucleophilic addition to cyanamide has been proposed, as well as acting as a general base catalyst and buffer.[20] The uniqueness of phosphate in catalysing the reaction here is believed to result from its basicity (abstraction of C6-OH and 8a-H protons) and potential intermediacy of aminophosphate **A** and ability to form a six-membered intermediate (path a) facilitating rearomatisation.

To summarise, reaction conditions have been identified for the phosphate mediated Pictet–Spengler cyclisation of phenethylamines with aldehydes, generating structurally diverse tetrahydroisoquinolines. Phosphates are excellent catalysts for the reaction which shows high tolerance for the aldehyde component. This one-step methodology involves mild reaction conditions, and is a versatile alternative to previously reported chemical routes to tetrahydroisoquinoline alkaloids. In addition, the concomitant use of single isomer substrates allowed the preparation of alkaloid diastereoisomers. Finally, a mechanism highlighting the essential role of phosphate has been proposed. This reaction is one example of the essential role phosphate can play as a catalyst and may have had an evolutionary role in isoquinoline alkaloid biosynthetic pathways.

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