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Calcium catalysed Strecker-type reactions towards α-aminonitriles†

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We report an operationally simple calcium catalysed Strecker type reaction for the synthesis of α-aminonitriles from readily available *N,O*-acetals. The reaction is tolerant to a wide range of useful functional groups, including heterocycles, and provides the product in good to excellent yields. Additionally, the reaction does not require the need for anhydrous or air-free conditions, making it a suitable candidate for high throughput experimentation.

α-Amino nitriles are privileged scaffolds in synthetic chemistry,[1,2] having found use as a useful building block in the synthesis of a wide range of important scaffolds including α-amino acids and 1,2-diamines. They are also found in bioactive natural products and pharmaceuticals,[3,4] with increased usage across medicinal chemistry programmes to treat a range of conditions including diabetes and cancer (Fig. 1).[5]

The traditional approach to synthesise these motifs is *via* the classical Strecker reaction, in which the treatment of an aldehyde with an amine donor (typically ammonia) in the presence of HCN produces the desired product. Although successful, the use of gaseous HCN and other issues with functional group tolerance and overall applicability has led to a concerted effort from the community to realise an alternative to the Strecker reaction (Scheme 1).[1] This has led to several elegant methods employing cyanide surrogates, transition metal[6–9] and main group element[10,11] catalysed transformations, organocatalysis[12,13] and photoredox catalysis.[14] Further examples including direct displacement with cyanide surrogates have been shown to improve substrate scope, with indium[15] and zinc[16,17] both performing well. Our interest in these α-amino nitriles developed from an ongoing medicinal chemistry programme developing type III kinase inhibitors, in which we required ready access to α-functionalised amines. Owing to the group's

interest in calcium catalysed direct functionalisation reactions,[18–20] we wondered if we could employ a similar tactic to afford this privileged scaffold (Scheme 1(D)).

As such, we began our study by reacting **1a** with TMSCN in the presence of Ca(NTf$_2$)$_2$/nBu$_4$NPF$_6$ in DCM at room temperature for 12 hours, afforded **2a** in 22% yield (entry 1). A survey of solvents quickly showed that 1,2-DCE was optimum (entries 2–5). Further optimisation concentrating on catalyst loading, temperature and reagent equivalents (entries 6–10) resulted in **2a** being produced in 86% isolated yield (entry 10) (Table 1).

With these conditions now in hand, our attention turned to establishing the limits of the reaction in terms of functional group tolerance (Fig. 2). As shown in Fig. 2, the reaction is tolerant to a range of groups with differential electronics and sterics. Regarding the groups derived from the amide starting material, electron donating groups worked well (**2b–c**), however a moderate reduction in yield was observed when electron withdrawing groups were present on the aromatic ring (**2d–g**). However, this drop is reversed if an electron withdrawing group was present in the *ortho*-position of the aryl ring (**2h–i**). Heteroatoms were also tolerated well, with furan (**2j**), thiophene (**2k**) and pyrazine (**2l**) motifs providing the desired product in good yields.

Moving onto substrates derived from altering the aldehyde portion of the starting material, the reaction was, in general, much less variable. Each substrate performed admirably, with electron withdrawing (**2m–n**) and donating groups reacting similarly (**2o**). Interestingly, one repeated failure was the *para*-NO$_2$ group (**2p**), which resulted in a complex mixture of products after
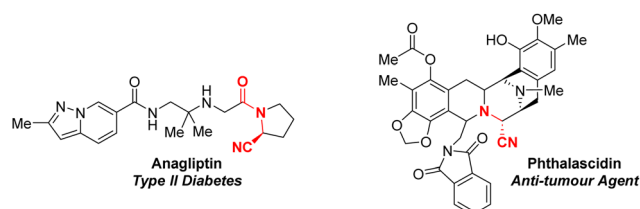
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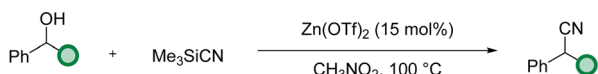[b] *School of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast, UK. E-mail: mark.mclaughlin@qub.ac.uk*

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Fig. 1 Selected examples of α-aminonitriles.

Scheme 1 Alternative approaches to α-aminonitriles and derivatives.

(A) Lalitha, 2012

(B) Oshima, 2022

(C) Kim, 2024

(D) This work

Table 1 Optimisation studies

Entry	Cat. loading (mol%)	Solvent	TMSCN (equiv.)	Temp (°C)	Yield[a] (%)
1	2	DCM	3	25	22
2	2	DCM	3	40	29
3	2	1,2-DCE	3	40	30
4	2	EtOAc	3	40	<5
5	2	HFIP	3	40	<5
6	2	1,2-DCE	3	80	66
7	2	1,2-DCE	6	80	89
8	1	1,2-DCE	6	80	66
9	0	1,2-DCE	6	80	nr
10	2	1,2-DCE	6	80	86[b]

[a] NMR yield 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield after flash column chromatography.

each attempt. Substitution around the aromatic ring did not alter the efficiency, with *ortho*-(**2r**), *meta*-(**2q**) and doubly substituted working well (**2s**). Thiophene was also tolerated (**2t**), as was [i]Pr (**2u**), which provided the leucine-type derivative in good yields.

We next wanted to explore if protecting groups other than benzoyl were applicable in the reaction (Fig. 3). To this end, we synthesised a range of Fmoc protected substrates and subjected them to the reaction conditions. Pleasingly, all but the aliphatic substrate worked well (**4a–4d**), thus providing access to a range of Fmoc-protected amino acids if required.

We also attempted the same reaction with the Boc protected amine, however the major product under the optimised conditions was the deprotected amine, which was isolated in 29% yield. We reasoned that the deprotection was a result of the well-established thermal degradation of Boc carbamates in the presence of protic solvents.[21,22] We therefore attempted to
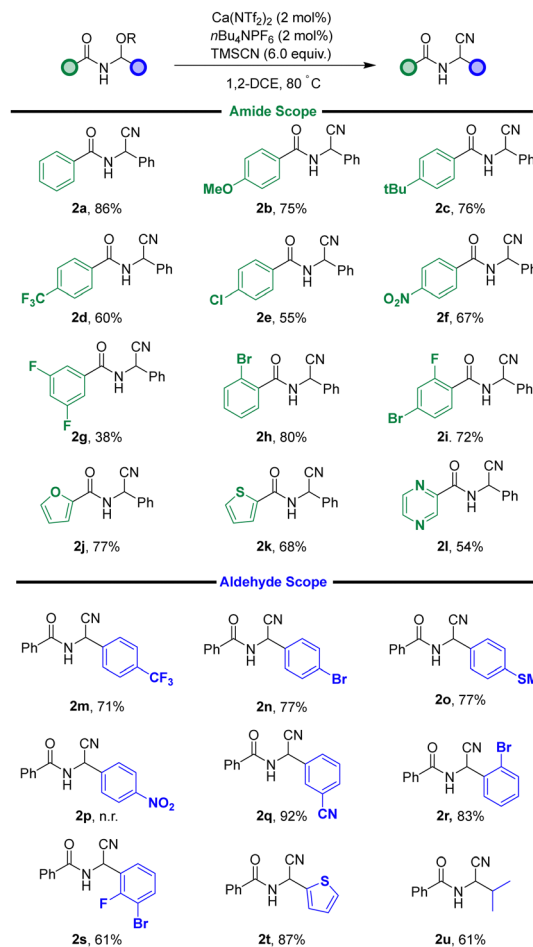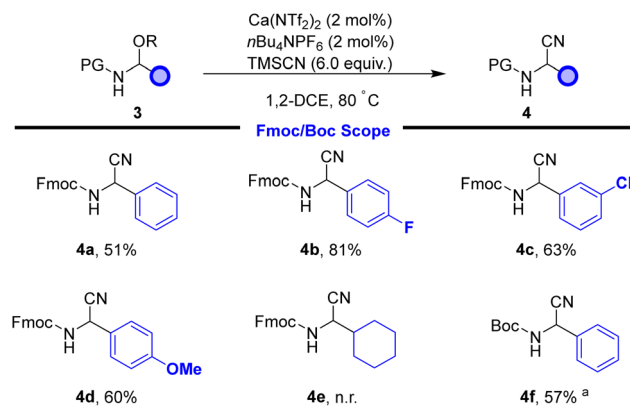
Fig. 2 Substrate scope.

Fig. 3 Protecting group substrate scope.

retard the deprotection by simply lowering the temperature to 60 °C, which proved successful, affording the desired product (**4f**) in 57% yield.

Finally, we wanted to show the utility of the products towards further derivatisation. A such, we subjected **4b** to catalytic hydrolysis employing the highly active, yet easily
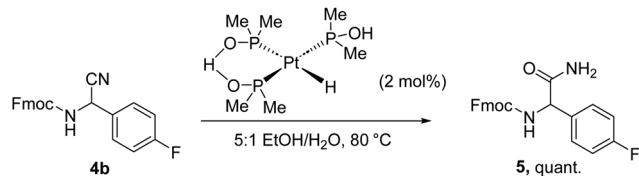
Scheme 2 Ghaffar–Parkins hydrolysis.
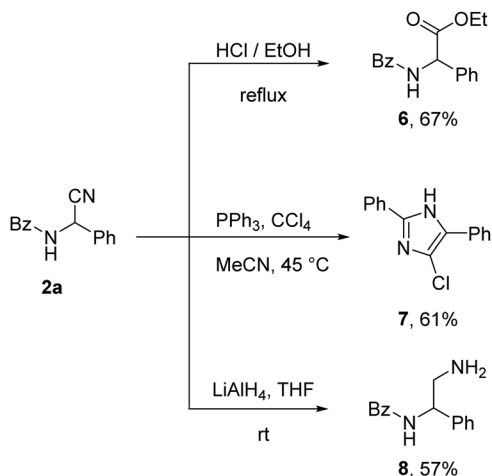
Scheme 3 Further derivatisations.

accessible, Ghaffar-Parkins catalyst,[23,24] which afforded Fmoc-protected primary amide **5** in quantitative yield (Scheme 2).

Moving on to other derivatisations, we took Bz protected amino nitrile **2a** and produced the corresponding ester **6** and primary amine **8** in good yields. Furthermore, imidazole **7** can be produced using PPh_3/CCl_4 in MeCN in synthetically useful yields (Scheme 3).[25]

In conclusion, we have developed a high yielding synthesis of α-aminonitriles employing a calcium catalysed Strecker type reaction. The transformation is tolerant to a wide range of functional groups including heterocycles as well as having the ability to use useful amine protecting groups.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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