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Isonitrile Alkylations: A Rapid Route to Imidazo[1,5-a]pyridines

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Metalated arylmethylisonitriles readily add to 2-chloropyridines to afford imidazo[1,5-a]pyridines. Analogous additions to imidoyl chlorides and a chloroquinoline provide imidazoles and an imidazo[1,5-*a*]quinolone which, like imidazo[1,5-a]pyridines, are valuable heterocycles for pharmaceutical synthesis.

The imidazo[1,5-a]pyridine core is a valuable scaffold for preparing electronic devices, N-heterocyclic carbenes, and pharmaceutical leads.[1] Representative of this bioactivity is the kinase inhibitor **1** that is currently in phase I trials as a tumour inhibitor[2] and the imidazo[1,5-a]quinolone **2** that was identified as a neurokinin antagonist with potential for alleviating side effects from chemotherapy and surgery.[3] The role of imidazo[1,5-a]pyridine as a pharmacophore, and the paucity of methods for synthesizing the heterocycle core,[4] stimulated a new strategy that exploits the under-developed chemistry of metalated isonitriles.[5]

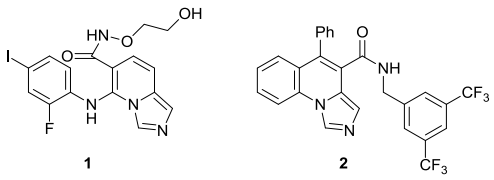
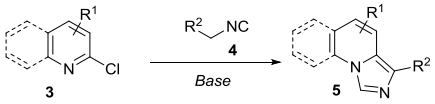


Fig. 1. Core imidazo[1,5-a]pyridines as pharmaceutical leads.

Isonitriles are challenging to deprotonate because of the low kinetic and thermodynamic acidity of the protons adjacent to the isonitrile group.[6] Once deprotonated, metalated isonitriles are prone to self-condensation by nucleophilic attack onto the carbenoid-like isonitrile carbon.[7] Consequently, most metalated isonitriles are generated from precursors bearing an adjacent electron withdrawing group to facilitate deprotonation, increasing the stability of the organometallic, with alkylation limited to alkyl halide and carbonyl electrophiles.[5] Described below is an imidazo[1,5-a]pyridine synthesis[8] that uses metalated arylmethylisonitriles in condensations with 2-chloropyridine-type precursors **3** to generate valuable heterocycles **5** while addressing the deficiencies in metalated isonitrile alkylations (Eq. 1).[5]



Eq. 1 Metalated isonitrile route to imidazo[1,5-a]pyridines

Exploratory arylations were probed with 2-chloropyridine (**6a**) and lithiated benzylisonitrile because benzylisonitrile (**4a**) is commercially available and readily deprotonated by treatment with BuLi (Scheme 1).[7b] Optimization experiments revealed that deprotonation was best accomplished at -78 °C for 5 minutes; longer reaction times led to a diminished yield through formation of high molecular weight materials assumed to arise from self-condensation. After generating lithiated benzylisonitrile, 2-chloropyridine was added and, after 30 min, the reaction was allowed to warm to rt. Reaction monitoring revealed that the alkylation did not proceed until 0 °C, though the reaction was slow and best coaxed toward completion by warming to rt. The optimized procedure gave imidazo[1,5-a]pyridine **8a**[9] in 29% yield (Scheme 1), though exactly the same procedure with 2-chloro-6-methylpyridine (**6b**) gave **8b** in 72% yield. The significant yield increase was suspected to arise from proton transfers involving the 6-methyl group,[10] a suspicion subsequently confirmed by deuterium labeling.[11] Recognition of the potential benefit of a weak acid led to screening of bases with conjugate acids capable of facilitating proton transfer. KHMDS emerged as the most effective base affording the imidazo[1,5-a]pyridine **8a** in 53% yield from benzylisonitrile (**4a**).

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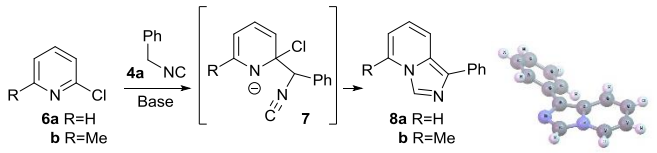
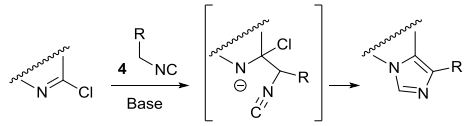


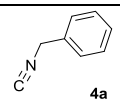
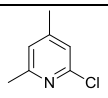
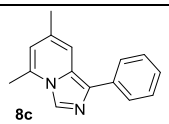
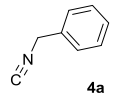
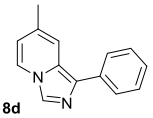
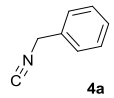
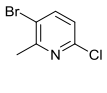
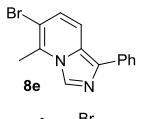
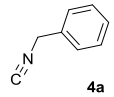
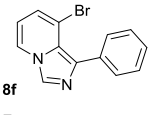
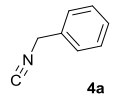
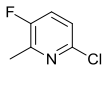
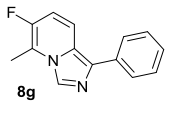
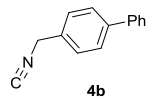
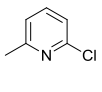
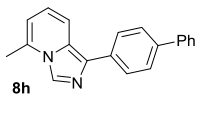
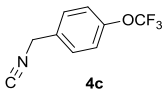
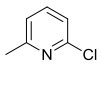
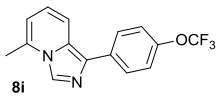
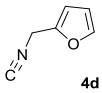
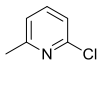
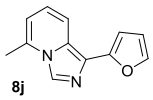
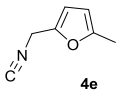
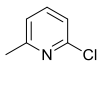
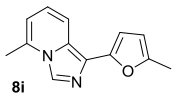
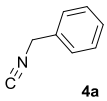
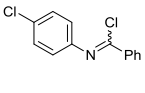
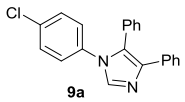
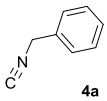
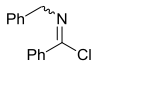
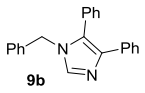
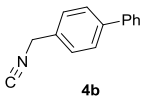
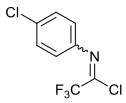
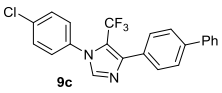
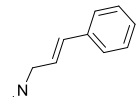
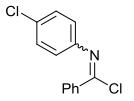
Scheme 1 Metalated isonitrile route to imidazo[1,5-a]pyridines

Having gained insight into the imidazo[1,5-a]pyridine synthesis, the substrate scope was examined (Table 1). Methyl substitution on the pyridine ring is readily tolerated (entries 1-2) as are bromine substituents (entries 3-4). However, the fluorine substituent was competitively displaced through nucleophilic aromatic substitution (entry 5).[12] Phenyl and methoxy substituents on the aromatic ring of benzylisonitrile are tolerated (**4b** and **4c**, entries 6-7) as are the furylmethylisonitriles **4d** and **4e**.[13]

In a related alkylation, the metalated arylmethylisonitriles derived from **4a**, **4b**, and **4f** were found to efficiently add to imidoyl chlorides[14] to form imidazoles **9** (entries 10-13).[15] The reaction extends the union of imidoyl chlorides with TosMIC[16] to less stabilized metalated isonitriles. Lithiated benzylisonitrile reacts with a chloroquinoline to afford the quinoline **10a** (entry 14) while the isonitrile **4b** was found to react with 2-chloro-4,6-dimethylpyrimidine to afford **11a** (entry 15).

Table 1. Metalated Isonitrile Condensations to Heterocycles[a]



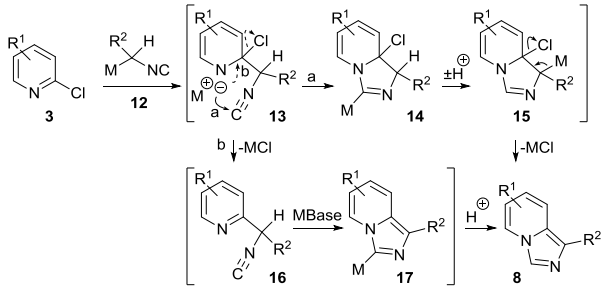
Entry	Isonitrile	Electrophile	Heterocycle	Yield (%)
1	 **4a**		 **8c**	77[b]
2	 **4a**		 **8d**	55
3	 **4a**		 **8e**	77[c]
4	 **4a**		 **8f**	59
5	 **4a**		 **8g**	38[d]
6	 **4b**		 **8h**	90
7	 **4c**		 **8i**	84
8	 **4d**		 **8j**	63
9	 **4e**		 **8i**	56
10	 **4a**		 **9a**	50[b]
11	 **4a**		 **9b**	61[b]
12	 **4b**		 **9c**	60
13	 **4f**		**9d**	57
14	**4a**		**10a**	82[b]
15	**4b**		**11a**	76

[a] KHMDS was employed as the base unless otherwise stated. [b] BuLi was employed in place of KHMDS. [c] Use of BuLi as the base afforded **8e** in 51% yield. [d] Accompanied by 30% of the isonitrile **8g'** resulting from nucleophilic aromatic substitution of fluorine.

Two mechanisms can be envisioned for the imidazo[1,5-a]pyridine synthesis (Scheme 2): an addition-cyclization-elimination sequence (**13** → **14** → **15** → **8**) or an addition-elimination-cyclization (**13** → **16** → **17** → **8**). Although no trace of intermediate pyridine **16** was detected during the reaction,[17] the addition of lithiated (1-isocyanoethyl)benzene (**12**, R^2=Ph, H=Me) afforded detectable amounts of the corresponding pyridine **16** (R^1=H, R^2=Ph, H=Me) implying the cyclization proceeds through **16** and **17**.[18]

The efficacious role of KHMDS in these cyclizations is likely related to the ability of hexamethyldisilazane, generated after deprotonation of the isonitrile, to facilitate the proton transfers.[6] Typically 1.3 equivalents of KHMDS are employed; one equivalent is consumed in deprotonating the arylmethylisonitrile and a second is required for the cyclization **16** → **17**. Protonation of **17** by

hexamethyldisilazane regenerates KHMDS thereby avoiding the requirement for two equivalents of base. Condensations with BuLi require pyridines with an acidic substituent for synthetically acceptable yields or imidoyl chlorides which cyclize without excess base.[19]



Scheme 2 Potential cyclization mechanisms for imidazo[1,5-a]pyridine formation.

Addition of metalated arylmethyl isonitriles to 2-chloropyridines efficiently generates a range of substituted imidazo[1,5-a]pyridines. Analogous additions to a chloroquinoline, a pyrimidine, and imidoyl chlorides generates an imidazo[1,5-a]quinoline, an imidazo[1,5-a]pyrimidine, and imidazoles, respectively. Mechanistic analyses indicate that KHMDS is the optimal base because the hexamethyldisilazane facilitates proton transfers. The heterocycle syntheses are rapid, convenient, and represent an advance in alkylations of metalated isonitriles.

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[9] The identity of **8a** was confirmed by x-ray crystallography (CCDC# 1430826) because of a discrepancy in some of the NMR signals with those of a material previously isolated: M.-S. Yu, W.-C. Lee, Chih-Hao Chen, F.-Y. Tsai, T.-G. Ong *Org. Lett*. **2014**, *16*, 4826-4829.
[10] In the absence of a suitable proton source the labile intermediate is prone to polymerization (cf. Scheme 2).
[11] The cyclization of dideuterated benzylisonitrile with 2-chloro-6-methylpyridine leads to considerable deuterium incorporation within the methyl group consistent with KHMDS facilitating the proton transfer. Details provided in the supporting information.
[12] Use of lithiated isonitrile afforded **8g** in 12% and the substituted isonitrile **8g'** in 51% yield.
[13] Prepared from the corresponding amine: B. S. Fowler, P. J. Mikochik, S. J. Miller *J. Am. Chem. Soc.* **2010**, *132*, 2870-2871.
[14] Prepared from the corresponding amides by treatment with thionyl chloride: J.-P. Lin, F.-H. Zhang, Y.-Q. Long *Org. Lett*., **2014**, *16*, 2822-2825.
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[16] D. van Leusen, A. M. van Leusen *Org. React*. **2001**, *57*, 417-679.
[17] The cyclization of **16** (R^1=R^2=H) to **8** occurs in the presence of *t*-BuOK (30% yield): U. Schöllkopf, E. Eilers, K. Hantke, *Liebigs Ann. Chem*. **1976**, 969-977.
[18] Unfortunately the isonitrile was unstable to purification.
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added base although deprotonation with catalytic base cannot be ruled out.