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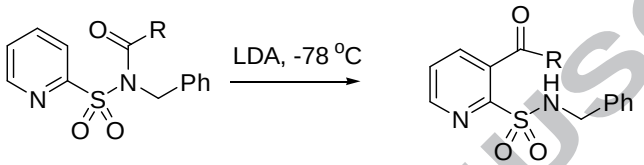

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Novel nitrogen to carbon rearrangement forming nicotinic acid sulfonamides

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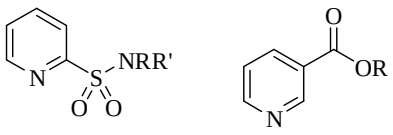
ABSTRACT

The synthesis of nicotinic acid derivatives via the base-mediated nitrogen to carbon rearrangement of N-substituted pyridine 2-sulfonamides is reported. This noteworthy isomerisation of the pyridine sulfonamide protecting group has implications for the use of this protecting group in synthesis.

The pyridine sulfonamide **1** and nicotinic acid **2** functionalities are two important structural subunits whose properties have been exploited in a number of biologically important molecules. Derivatives of nicotinic acids are a very common structural motif in natural product and medicinal chemistry, with nicotinic acid itself being classified as one of the 80 essential nutrients required for human health. Commercially important nicotinic acids include the vasodilatory drug, Nicorandil and the respiratory stimulant, Nikethamide. As such, the development of novel approaches to nicotinic acids continues to engage the interest of synthetic chemists and numerous approaches to this important system have been reported.[1] Pyridine sulfonamides have been shown to act as chelators of metal ions[2] and heteroaromatic sulfonamides have been found to be effective inhibitors of carbonic anhydrase.[3] A reliable route to derivatives of nicotinic acid sulfonamides would therefore seem to offer the opportunity to explore further the properties of these biologically important subunits.



1 **2**

Figure 1: The pyridine sulfonamide and nicotinic acid cores

The chemistry arising from the interaction of protecting groups with substrates and reagents can frequently lead to unexpected difficulties in synthetic manipulations. Sometimes, however, the resultant chemistry can give rise to useful transformations in their own right.[4]

The work presented in this communication establishes that the pyridine sulfonamide protecting group can participate in a base-mediated nitrogen to carbon rearrangement to yield potentially useful nicotinic acid sulfonamide derivatives.

As part of a study being undertaken in our laboratory into the alkylation of amino acid derivatives that could potentially exploit the property of axial chirality,[5] we required access to orthogonally protected amino acid derivatives. The pyridine-2-sulfonamide entity has found increasing use as a protecting group in synthetic chemistry.[6] It is resistant to a number of chemical conditions; moreover, the products from sulfonamide protection tend to be crystalline solids. We hypothesised that the use of the pyridine sulfonamide group in conjunction with a carbamate protecting group would give rise to the conditions whereby axial chirality along the carbon nitrogen bond could be established.

To this end, treatment of 2-mercaptopyridine **3** with sodium hypochlorite and hydrochloric acid gave 2-pyridinesulfonylchloride **4**.[7] It was found advantageous not to isolate this compound as it was unstable to air, and instead immediate treatment of the crude solution of **4** with the *tert*-butyl ester of valine gave the corresponding sulfonamide . Protection of the sulfonamide as its *tert*-butyl carbamate delivered **5** as a crystalline solid in excellent overall yield. With orthogonally protected valine in hand, we next investigated its treatment with base to form the ester enolate, and subsequent trapping of the enolate with methyl iodide to give **6**. However, upon treatment of **5** with LDA at -78 ^{o}C, we were surprised to note that within two minutes a new lower-running spot was observed by TLC. Complete conversion to this new compound was achieved within 5 minutes, with no methyl iodide having been added.

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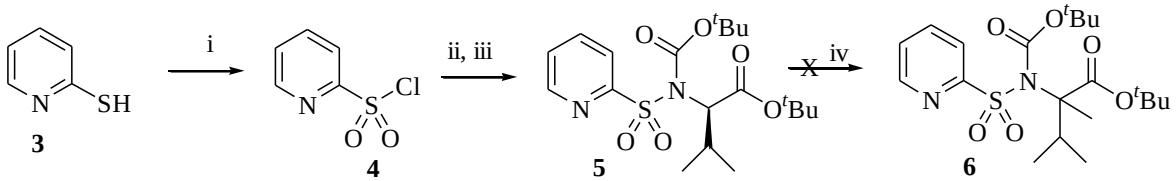


Scheme 1. Reagents and conditions: (i) HCl, NaOCl, CH_2Cl_2, 0 °C - rt. (ii) *t*-butylvaline ester, Et_3N, CH_2Cl_2, rt. (iii) Boc_2O, Et_3N, CH_2Cl_2, rt. (iv) LDA, -78 °C, CH_3I, THF

The compound isolated was subjected to spectral analysis to determine its structure. The FTIR spectrum contained diagnostic peaks at ν_{max} 3200 cm^{-1} (medium intensity, N-H stretch of sulfonamide), 1727 cm^{-1} (strong, C=O stretch of aromatic ester), 1307 and 1138 cm^{-1} (strong, asymmetric and symmetric S=O stretches, respectively, of conjugated sulfonamide). ^1H NMR showed the loss of H-3 in the pyridine ring and an HMBC experiment gave a correlation between an ester carbon and H-4 of the pyridine ring. High resolution ESI^+ mass spectrometry (on the prominent MH^+ ion) established that the product had the same molecular formula ($C_{19}H_{30}N_2O_6S$) as **5**. The nicotinic acid derivative **7** was consistent with all the spectroscopic data obtained.

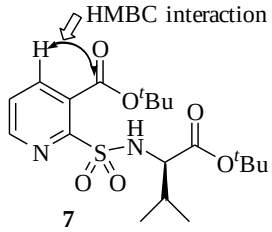


Figure 2: Spectral indication of structure

The transformation represented by **5** to **7** can be thought of as a base-mediated nitrogen to carbon rearrangement. Several examples of this type of reaction have been reported in the literature, most notably in the amino-Chan reaction[8] where, upon treatment with a strong base, an acyl group is transposed from the nitrogen to the carbon of **8** to give the β-ketoester anion **9**. In the current case, the initial anion on pyridine has been formed exclusively at the 3-position. This, coupled with the fact that the protons on pyridine cannot normally be removed with LDA, would seem to suggest that either the sulfone or the carbamate was involved in the deprotonation step, via formation of a chelate species involving either a 5 or 7-membered ring, **10** and **11**, respectively (Figure 3).[9]

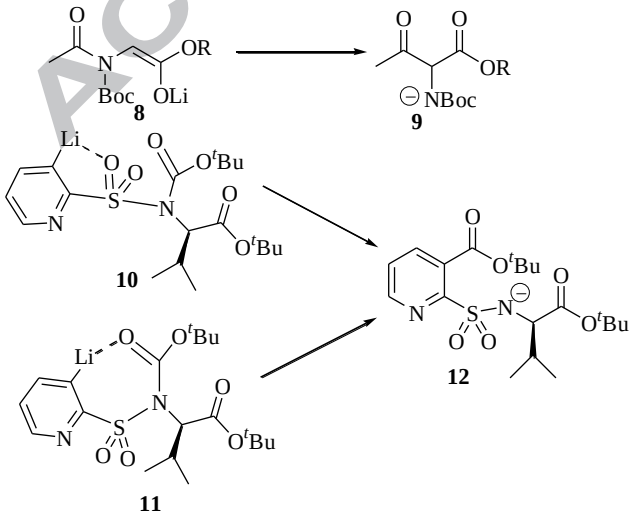
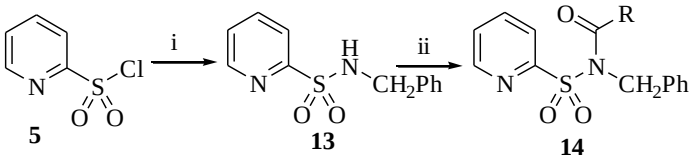


Figure 3: The amino-Chan rearrangement - comparison with the present case

Irrespective of the precise mechanism, subsequent rearrangement of either species would then generate the nicotinic acid derivative **12**. It can be suggested that the driving force for the amino-Chan rearrangement is the lower pK_a of the resultant carbamate anion compared to that of the ester enolate. Presumably the analogous difference in the pK_a of the conjugate acids of the initial anion and the rearranged product anion is also a driving force in the present case.

Intrigued to determine the scope of this reaction, a number of N-substituted pyridine sulfonamides were synthesised. Pyridine sulfonyl chloride **4** was prepared as described above, and then addition of benzylamine gave sulfonamide **13** as a crystalline solid.[10] Treatment of **13** with sodium hydride and the appropriate acyl chloride, or in the case of entry 6, with the anhydride, gave a range of N-substituted pyridine sulfonamide products **14** in moderate to good overall yield. In certain cases where the acid chloride bears an acidic proton the reaction mixture had to be treated with a second equivalent of base and acid chloride to bring the reaction to completion.



Scheme 2. Reagents and conditions: (i) $PhCH_2NH_2$, Et_3N, CH_2Cl_2, 98% (ii) NaH, THF, RCOCl, 0 °C - rt or RCO_2COR, DMAP, py.

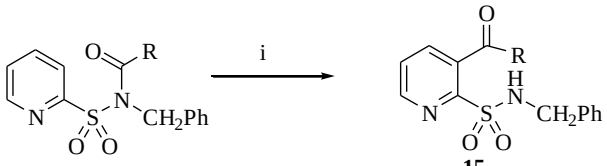
Table 1 – Formation of N-acyl derivatives

Entry	R	Yield[a]
1	C_6H_5	80%
2	OCH_3	75%
3	$OC(CH_3)_3$	95%
4	$C(CH_3)_3$	75%
5	$CHClCH_3$	78%
6	CH_3	95%
7	C_5H_{11}	82%
8	$CH(C_6H_5)CH_2CH_3$	77%
9	$CH_2CH_2CHCH_2$	75%
10[b]	N-CH_2CHCH_2	92%

[a] Isolated yield after purification by flash column chromatography

[b] Formed by treatment of **13** with NaH, and CH_2CHCH_2Br

The N-substituted pyridine sulfonamides were then subjected to the rearrangement conditions of treatment with 1.5 equivalents of LDA at -78 °C, to give, in most cases, the corresponding nicotinic acid compounds **15** (Scheme 3). Reaction times were generally short, with complete consumption of the starting material being observed within 5 minutes by TLC. Two cases did not deliver the desired product, however. The acetyl derivative, Table 1 entry 6, gave an intractable mixture of products, possibly due to competing deprotonation on the acetyl group. The N-allyl substituted compound, Table 1 entry 10, returned the sulfonamide **13**, presumably due to competing nucleophilic displacement of the allyl group to give the nitrogen anion. However, a number of nicotinic acid derivatives were successfully synthesized, with both esters and ketones formed cleanly and in good yield (Figure 4).



14 **15**

Scheme 3. Reagents and conditions: (i) LDA, -78 °C, THF

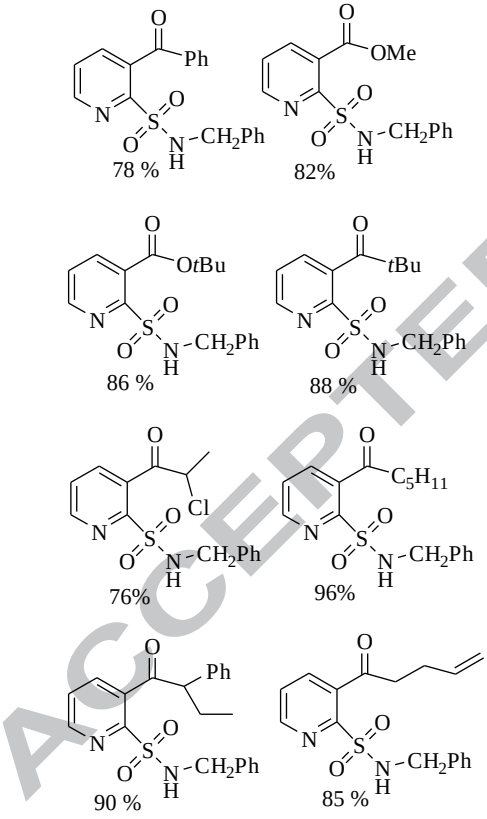


Figure 4. Structures of the synthesized nicotinic acid sulfonamides

In conclusion, a new method is presented for the synthesis of potentially biologically interesting nicotinic acid sulfonamide derivatives, with the possibility of quickly forming a library of related compounds. The latent reactivity of the 2-pyridinesulfonamide protecting group is also highlighted, with the observation that the pyridine can participate in base-mediated rearrangement chemistry.

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Supplementary Material

General experimental procedures and NMR data for all new compounds are provided.