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COMMUNICATION

Arylation and Alkenylation of Activated Alkyl Halides using Sulfonamides

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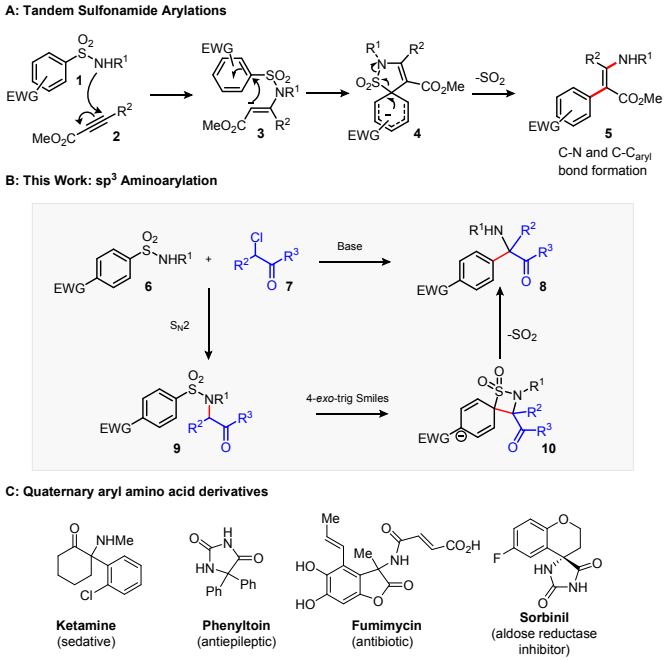
A variety of quaternary aryl amino acid derivatives can be synthesised using tandem S_N2 / Smiles rearrangement chemistry involving aryl sulfonamides and α-chloro carbonyl compounds. The reaction harnesses a sulfur dioxide extrusion pathway to construct a C-N and C-C_{aryl} bond under simple conditions with no requirement for organometallics or transition metal catalysts. The reaction is also successful for alkenyl sulfonamides, producing sterically congested quaternary alkene amino acid derivatives.

Tandem reactions of sulfonamides create powerful arylation pathways to nitrogenous aromatic structures of the type commonly found in pharmaceuticals. The concept is set out in Scheme 1, and involves reacting sulfonamide **1**, frequently commercially available or easily prepared, with a suitable electrophile to create a C-N bond. The intermediate anionic structure **3** can then undergo a Smiles aryl transfer reaction,[1] creating a C-Caryl bond with extrusion of SO_2.[2] Overall, the process accesses valuable arenes under simple reaction conditions, with no recourse to the precious metal catalysis that is frequently required for arylation and C-N bond forming chemistry. The intramolecular S_NAr step does generally require an electron-poor or heteroaromatic moiety for successful reaction, but this constriction is mitigated by these functional groups being commonly represented in biologically active molecules.

We have previously explored sp and sp^2 electrophiles in this tandem Smiles process, and were interested in expanding this idea to sp^3 centres to create new routes to amino-arylated products.[3] Alkyl halides are readily available and versatile electrophiles that could react *via* S_N chemistry, setting up a rearrangement as shown in Scheme 1B, creating a particularly valuable quaternary arylated amine motif **8**. The proposed Smiles reaction formally requires a strained four-membered Meisenheimer intermediate **10**, distinct from our earlier work with π-electrophiles that create pentacylic re-arrangements for aryl transfer. There is good precedent in the literature, however, for this step with a number of nosylated amino acid derivatives being observed to rearrange on treatment with base.[4] Successful reaction would produce quaternary α-aryl amino acid derivatives, common motifs in drugs, agrochemicals and peptidomimetics (Scheme 1C).[5]



Scheme 1: Proposed tandem Smiles aminoarylation

We began by screening reaction conditions for the tandem S_N2 / Smiles arylation of ethyl α-chlorophenylacetate **7a** with *N*-methylnosylamide **6a**. We were pleased to observe that simple K_2CO_3 treatment in hot DMF led to successful conversions, with optimal conditions being a 2:1 ratio of alkyl halide to sulfonamide, 3 equiv of base and heating to 70 °C, forming **8a** in high yield (Scheme 2). Some simple mapping of functional group scope established that the reaction favoured *N*-substitution on the sulfonamide; primary sulfonamides gave **8b** in very low yield and *N*,*N*-disubstituted sulfonamides were unreactive. A ketone in place of the ester group led to

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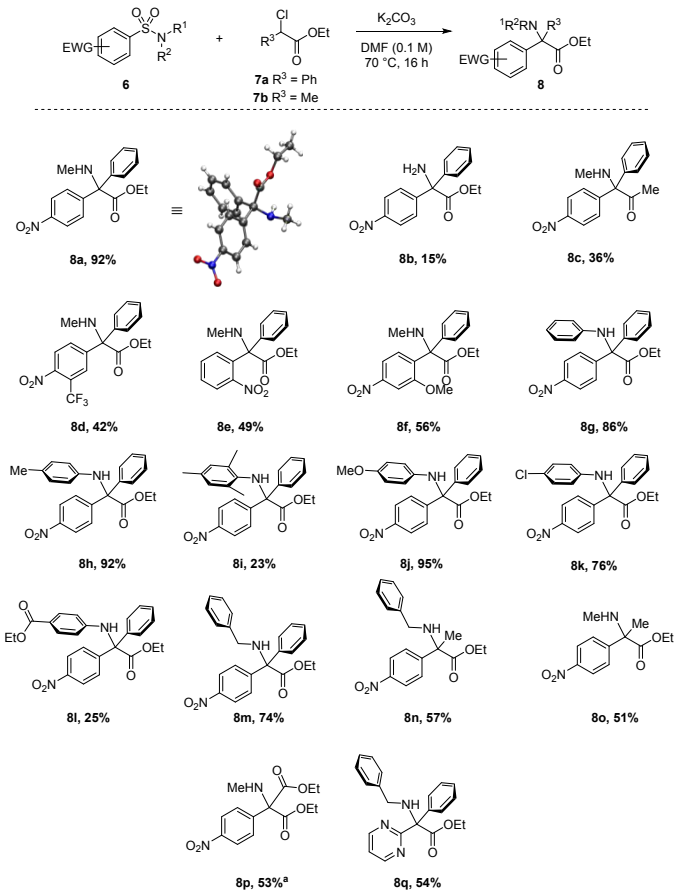
substantially diminished yields (**8c**), so we retained the ester group for scope studies. A range of aryl-substituted *N*-methylnosylamides were productive (**8a** – **8f**), along with several weakly nucleophilic *N*-arylnosylamides (products **8g** – **8l**). Electron donating arene substituents were noticeably more effective than electron withdrawing ones (*e.g.* **8h** and **8j** *v* **8l**), but steric hindrance on the sulfonamide (*e.g. N*-mesityl **8i**) lowered yields considerably. Changing the phenyl group in the alkyl halide substrate was feasible, with methyl groups being tolerated (**8n** and **8o**) and the malonate substrate successfully affording the versatile diester product **8p**. Finally, the heterocyclic pyrimidine sulfonamide was productive to yield the novel amino acid derivative **8q** in 54% yield.



Scheme 2: Scope of tandem S_N2/Smiles rearrangement. [a] Reaction carried out at room temp.

Reaction of the unsubstituted ethyl chloroacetate **7c** with *N*-aryl substituted sulfonamides unexpectedly gave rise to imine products (Scheme 3). It appears that the initial secondary aryl Smiles product is undergoing oxidation under the basic conditions with adventitious air in the reaction.[6] The transformation was general for *N*-arylnosylamides, affording the Schiff base aryl glyoxalate derivatives **11a** – **f**. The aryl glycine derivative **12a** could be accessed through a Ni-catalyzed borohydride reduction of the imine **11a**.

Having established an effective aminoarylation protocol, we wondered if we could achieve an amino*alkenylation* using similar sulfonamide S_N2 / Smiles rearrangement chemistry (Scheme 4). Alkenyl transfer through desulfonylative processes is precedented in the radical regime,[7] but anionic reactions are rare.[8] A successful metal-free synthesis of quaternary alkenyl amino acid derivatives would complement existing routes, which typically involve addition of sp organometallics to the appropriate imine and subsequent hydrogenation to the alkene.[9] In the event, we were pleased to observe the known alkenyl sulfonamide **13a**[10] undergoing successful tandem S_N / alkenyl transfer reaction under the standard conditions, to give **14a**, albeit in a low 35% yield. The *N*-methyl sulfonamide **13b** was more efficient, producing the alkene **14b** in 59% yield.

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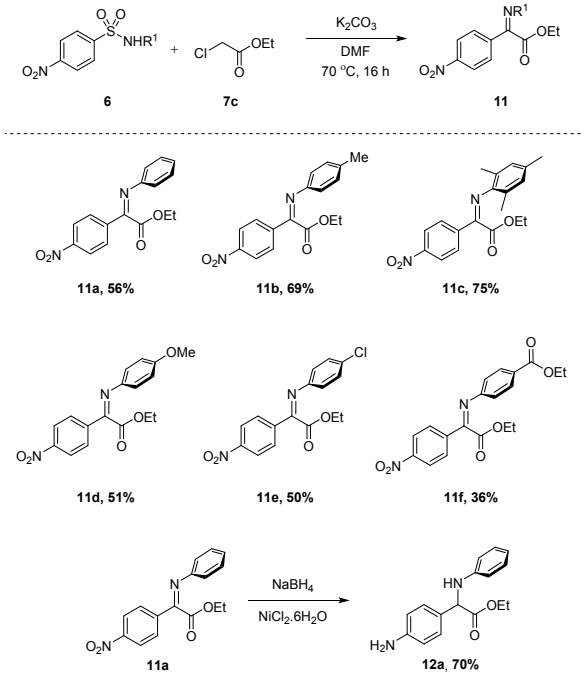
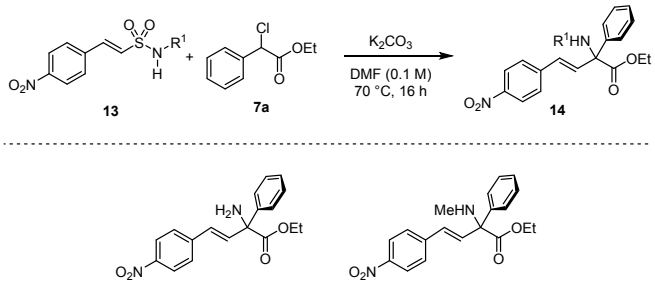


Scheme 3: Substituted imine scope using ethyl chloroacetate



Scheme 4: Vinylogous Smiles rearrangement for alkenylation

In conclusion, we have developed a new tandem process for the rapid construction of quaternary amino acid derivatives. The protocol takes commercially available sulfonamides and alkyl halides, and effects C-N and C-C_{aryl} bond formation under simple, metal-free conditions. The reaction could be extended to imine synthesis, using ethyl chloroacetate, and a novel vinylogous Smiles process to access alkenylated quaternary amino acids.

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Conflicts of interest

There are no conflicts to declare.

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