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Arylation using sulfonamides: Phenylacetamide synthesis through tandem acylation-Smiles rearrangement

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Amide-bond formation / Smiles rearrangement

ABSTRACT: A range of electron-poor and heterocyclic sulfonamides react with phenylacetyl chlorides to produce benzhydryl derivatives in a single step. The reaction proceeds *via* tandem amide bond formation – Dohmori-Smiles rearrangement under simple conditions of aqueous base. In the case of *o*-nosylamides further reaction takes place at the nitro group to yield indazoles.

Aryl and heteroaryl structures are fundamental to natural products and man-made molecules, and are frequently synthesized using stoichiometric organometallics and precious transition metal catalysts. These methods, while effective and hugely influential, are costly and environmentally unsustainable, making metal-free arylation methods¹ a key objective for future strategies in synthetic chemistry. We are interested in harnessing simple aryl sulfonamides as metal-free aryating agents in this regard, through the process set out in Scheme 1. The nitrogen atom acts as a nucleophilic trap for an electrophilic coupling partner, a benzyne in this example, generating an incipient carbanion (**3**) that triggers a 1,5-desulfonylative Smiles rearrangement.^{2,3,4} Overall, the process repositions a cheap and readily available building block as both an aryating and aminating agent, critical transformations in the pharmaceutical industry, whilst proceeding without recourse to metal reagents.

We have previously shown that sulfonamides can react with *sp*-electrophiles for the synthesis of biaryl and enamine products,⁵ and were interested in extending the chemistry to *sp*² components. Trapping a ketene, **7**, for example, with a sulfonamide **1**, would generate an enolate **8** that could rearrange via Smiles reaction to afford phenylacetamide derivatives **9**. This process would use sulfonamides to install aryl groups at *sp*³ centres, producing phenylacetamides, a fundamental pharmacophore in medicinal chemistry. The Smiles rearrangement of acyl-sulfonamide enolates akin to **8** has precedent in seminal studies from Dohmori and co-workers in the 1950s, representing the earliest examples of carbon nucleophiles participating in Smiles processes.⁶

Our previous work indicates that electron poor sulfonamides are required for anionic desulfonylative Smiles processes, in line with literature precedent of an S_NAr-type

mechanism that proceeds through a Meisenheimer intermediate (*e.g.* **4** in Scheme 1).⁷

Scheme 1. Proposed ketene Smiles rearrangement

Previous work: *sp* electrophiles for biaryl synthesis

Proposal: *sp*² electrophiles for phenylacetamide synthesis

Accordingly, we began our studies using *p*-nosylamide **1a**, and screened reaction with excess phenylacetyl (**10a**) and propionyl chloride (**10b**) under ketene-forming conditions in terms of solvent and temperature (Table 1). Unfortunately, no Smiles reaction could be observed, with the simple acylated product being identified as the main product in each case (entries 1-7). A further trial with the diketene acetone adduct at 120 °C, to generate acylketene *in situ*, likewise yielded the acylated sulfonamide only. It appeared that the 1,5-desulfonylative Smiles reaction, in contrast to some 1,4 processes on related enolate systems,⁸ requires more basic conditions to proceed. This proved to be the case, as a survey of simple inorganic bases identified aq NaOH as enabling the two step procedure (entry 8). Using aqueous THF as solvent, *p*-nosylsulfonamide reacted with phenylacetyl chloride at 80 °C to give the Smiles product **9a** in a very good yield.

Table 1. Reaction optimization

entry	R ¹	base	solvent	T (°C)	product
1	Ph	<i>i</i> Pr ₂ NEt (2.0)	DCM	r.t.	11
2	Ph	proton sponge (1.1)	DCM	40	11
3	Ph	proton sponge (1.1)	DCM	r.t.	11
4	Ph	<i>i</i> Pr ₂ NEt (2.0)	THF	70	11
5	CH ₃	<i>i</i> Pr ₂ NEt (2.0)	THF	100	11
6	CH ₃	<i>i</i> Pr ₂ NEt (2.0)	toluene	100	11
7	CH ₃	proton sponge (1.1)	THF	100	11
8 ^b	Ph	NaOH (aq)	THF	80	9a (87%) ^c

^a Reaction conditions: **1** (1 equiv) in solvent at 0 °C, then the base was added, followed by **10** (1 equiv), stirred at T °C for 16 h ^b 5 equiv of **10**, 1 h ^c Isolated yield.

With reaction conditions in hand we examined substrate scope in terms of aryl halide and sulfonamide component (Scheme 2). The reaction was successful for a variety of phenacetyl chlorides, affording the benzhydrol primary amides **9a** – **9o** in generally good yield. The reaction could be demonstrated on a 1 mmol scale for the synthesis of **9a**, proceeding in an excellent 89% yield. Some restrictions were noted in terms of substitution at the enolic position of the acyl component, with di-substitution at this position shutting down the Smiles process. Turning to the sulfonamide partner, the reaction tolerated N-substitution (e.g. **9h** and **9i**) without problem, but not N,N-disubstitution. Electron poor *p*-nosylamides were generally productive, and we were pleased to see that heterocyclic sulfonamides such as pyrimidyl (**9m**), pyrimidyl (**9n**) and benzothiazoyl (**9o**) underwent successful reaction. Arylation of sp³ centres with these valuable heteroarenes moieties under simple metal-free conditions is a particular strength of the approach, as it represents a challenging transformation for contemporary transition-metal catalyzed methods.

Screening *o*-nosylamide **1e** in the reaction led to the unexpected formation of 3-phenyl-1*H*-indazole **12a** in 54%

yield (Scheme 3A). The reaction appears general for phenylacetyl chlorides, with the electron rich and electron poor substrates giving the indazoles **12a** – **12f** in moderate yields.

Scheme 2. Acyl chloride substrate scope^{a,b}

^a Reaction conditions: **1** (1 equiv) in THF at 0 °C. Dropwise addition of aq NaOH followed by **10** (5 equiv), then heat to 120 °C in sealed vial for 1 hr.

Assembly of this important heterocycle from sulfonamides, in a single step, has not previously been reported and clearly involves a significant degree of bond reorganization. There is, however, some limited precedent in work from Dohmori and Sundberg who observed indazole synthesis from Smiles products via cinnoline N-oxides.^{6,9,10} A feasible pathway is shown in Scheme 3B, whereby the sulfonamide undergoes acylative Smiles rearrangement to afford **9p**, which can then undergo intramolecular N-N bond formation to form the cinnoline N-Oxide **13**. From here, basic hydrolysis of the cinnoline amide group and dehydration would form the diazonium

intermediate **14**, and intramolecular amination of enolates analogous to **14** is a well-described method for synthesizing indazoles.¹¹ A final decarboxylation gives the product **12**.

Scheme 3. 1H-Indazole synthesis^{a,b}

^a General conditions as Scheme 2. ^b Isolated yields.

To conclude, we have described a new application of sulfonamides that captures their amphiphilic character as electrophilic arylating and nucleophilic aminating agents. The transformation is based on classical observations from Dohmori and co-workers on the facility of desulfonylative Smiles processes to mimic enolate arylation chemistry. In contrast to conventional enolate arylations, however, the process requires no metal catalysts and proceeds under very simple conditions. In the case of *o*-nosylamides, a 3-aryl-1H-indazole synthesis has been developed that involves substantial changes in bond connectivity to create an important heteroarene moiety from cheap and readily available starting materials.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds are available in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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