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Synthesis of Aryl Ketoamides via Aryne Insertion into Imides

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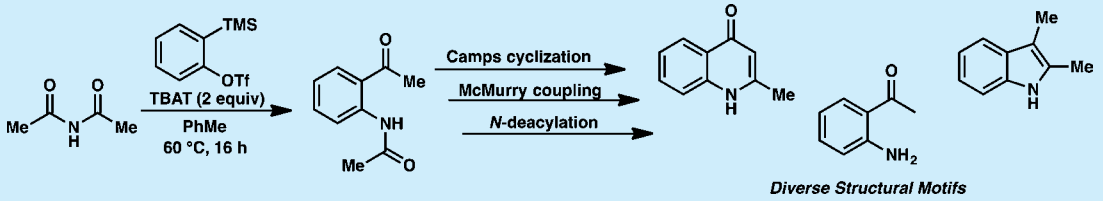
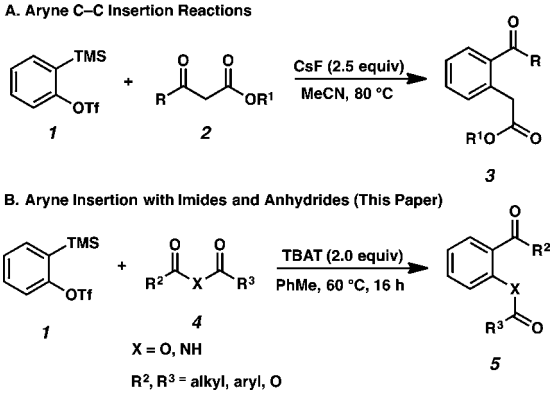
Supporting Information



ABSTRACT: An insertion of arenes into both imides and anhydrides via reactive aryne intermediates is presented. The reaction is performed under exceptionally mild conditions, and the corresponding ketoamide products are amenable to derivatization to deliver a variety of synthetically useful motifs such as quinolones, indoles, and ketoanilines.

The insertion of aromatic systems into carbon−carbon and carbon−heteroatom σ bonds is a desirable transformation in organic synthesis.[1] In 2005, our group reported an insertion of arenes into β-ketoesters to form acyl-alkylated products (Scheme 1A) using arynes generated in situ from *ortho*-silylphenyl triflates

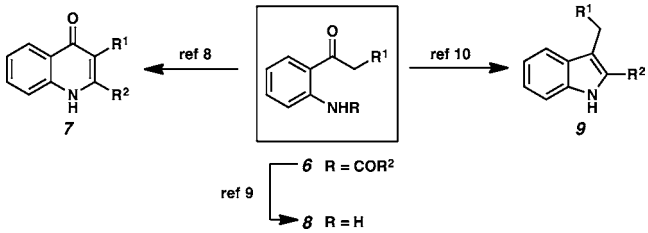
Scheme 1. Aryne Insertion Methods



under mild reaction conditions.[2] Following this report, other aryne insertions were disclosed using a variety of substrates, including malononitriles,[3] α-cyanocarbonyls,[4] acylated fluorenes,[5] and β-ketosulfones.[6]

More recently, Saito and co-workers developed a procedure for inserting pyridynes into cyclic ureas to construct various bicyclic heterocycles.[7] Herein, we expand the scope of this aryne reaction manifold to include acyclic imides and anhydrides to produce ketoamido- and ketoacyloxyarenes (Scheme 1B). The ketoamide products accessed by this method have been used to generate a variety of valuable structural motifs such as quinolones (**7**),[8] *ortho*-acylanilines (**8**),[9] and indoles[10] (**9**, Scheme 2). Work from the Greaney group demonstrated that the insertion of

Scheme 2. Derivatization of Aryl Ketoamides



amides into arynes afforded similar acyl-aminated products.[11] However, the scope of their method was limited to N-arylated amide substrates, prohibiting subsequent derivatization.

We initiated our synthetic studies by optimizing conditions for the insertion reaction using acetylacetamide **10** and silylaryl triflate **1** (Table 1). Implementing CsF as the fluoride source to trigger aryne generation, we observed a mixture of the desired

Table 1. Reaction Optimization

entry	fluoride source	temperature (°C)	solvent	yield (%)	11/12
1	CsF	80	MeCN	49	1.25:1
2	KF/18-crown-6	23	THF	37	10:1
3	TBAT	23	THF	21	10:1
4	TBAT	60	PhMe	62	>20:1

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ketoamide **11** and undesired imide byproduct **12**. Presumably, **12** is formed via nucleophilic addition of **10** to the aryne formed from **1** followed by proton quenching of the resultant aryl anion intermediate (see Figure 1). Although all three fluoride reagents

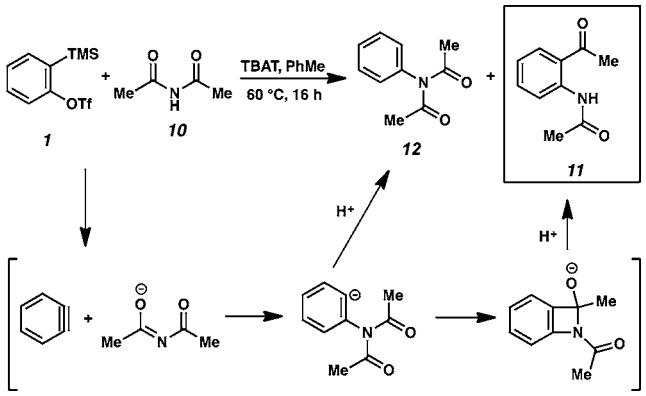
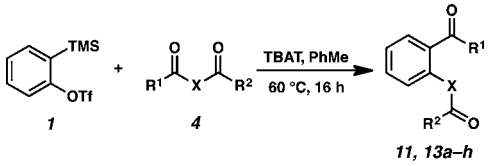


Figure 1. Plausible mechanism for formation of ketoamide **11** and imide byproduct **12**.

afforded the desired product, KF and tetrabutylammonium difluorotriphenylsilicate (TBAT) substantially improved selectivity for the desired amide. Additional screening of solvent and temperature demonstrated that using TBAT in PhMe at 60 °C maximized product yields and minimized byproduct formation (entry 4).

With optimized conditions in hand, we explored the substrate scope with respect to the imide substrate (Table 2). Imides

Table 2. Imide Substrate Scope[a]



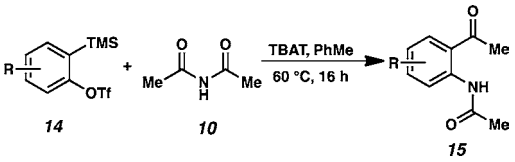
entry	product	R^1	R^2	X	yield (%)[b]
1	**11**	Me	Me	NH	89
2	**13a**	Et	Et	NH	88
3	**13b**	Ph	Ph	NH	68
4	**13c**	*i*-Pr	*i*-Pr	NH	78
5	**13d**	*i*-Bu	*i*-Bu	NH	79
6	**13e**	OMe	Bn	NH	24
7	**13f**	Me	Me	NMe	0
8	**13g**	Me	Me	O	54
9	**13h**	Ph	Ph	O	0

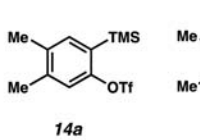
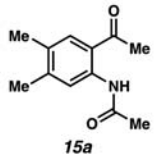
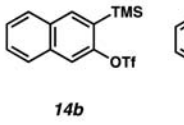
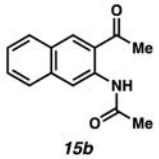
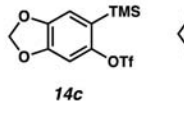
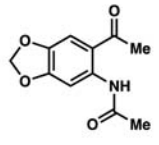
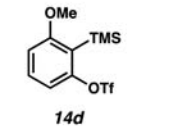
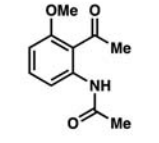
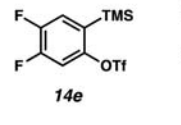
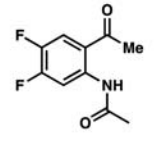
[a]Reaction conditions: TBAT (2.0 equiv), **4** (0.08 M in PhMe), and **1** (1.5 equiv), 60 °C, 16 h. [b]All reported yields are for isolated products.

possessing either aliphatic or aromatic substituents afforded the corresponding ketoamides in moderate to good yields (entries 1−5). An acylated urethane also undergoes insertion, albeit with reduced yield (entry 6). However, N-substituted imides afforded no product (entry 7). Acetic anhydride was found to be a suitable substrate, delivering the corresponding ketoacyloxyarene (entry 8) in 54% yield. Unfortunately, benzoic anhydride failed to provide any insertion product (entry 9).

Next, we investigated the tolerance of the reaction to various aryne precursors (Table 3). Substituted carbocyclic substrates (**14a−d**) offered moderate yields of the corresponding aryl

Table 3. Aryne Substrate Scope[a]



entry	aryne precursor	major product	yield (%)[b]
1	 **14a**	 **15a**	31
2	 **14b**	 **15b**	44
3	 **14c**	 **15c**	65
4	 **14d**	 **15d**	47
5	 **14e**	 **15e**	0

[a]Reaction conditions: TBAT (2.0 equiv), **10** (0.08 M in PhMe), and **14** (1.5 equiv), 60 °C, 16 h. [b]All reported yields are for isolated products.

ketoamide products (**15a−d**). Furthermore, we observed that insertion into an unsymmetrical aryne such as **15d** occurred with good regioselectivity. Unfortunately, a substrate bearing electron-withdrawing fluoride substituents (**14e**) failed to undergo insertion.

To demonstrate the synthetic utility of this method, we elaborated several of these acylamide insertion products to substituted quinolones via a base-initiated Camps cyclization in a two-step, one-pot sequence (Figure 2).[8] Gratifyingly, quinolones **16a−c** were directly produced in moderate yield. Moreover, formation of **16b** and **16c** occurred with high regioselectivity for the aryne insertion, producing a single isolable structural isomer in each case.

In summary, we developed a method for inserting arynes into acyclic imides and anhydrides to generate aryl ketoamides and ketoacyloxyarenes, respectively. These products are capable of further derivatization to provide an array of useful scaffolds such as quinolones, indoles, and ketoanilines. Our laboratory is

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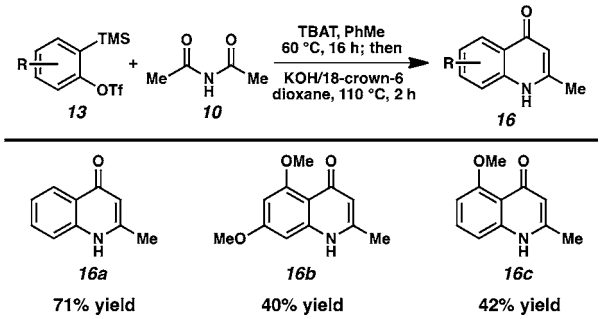

Figure 2. Camps cyclization of ketoamide insertion products to provide quinolones.

pursuing further development of this technology as it relates to other derivatizations and application in multistep synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00994.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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