Multicomponent Reactions

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Benzannulated Bicycles by Three-Component Aryne Reactions**

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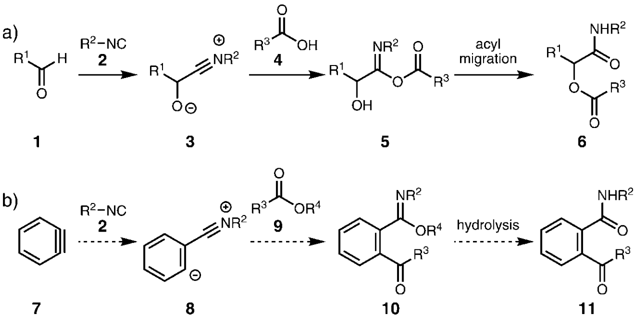
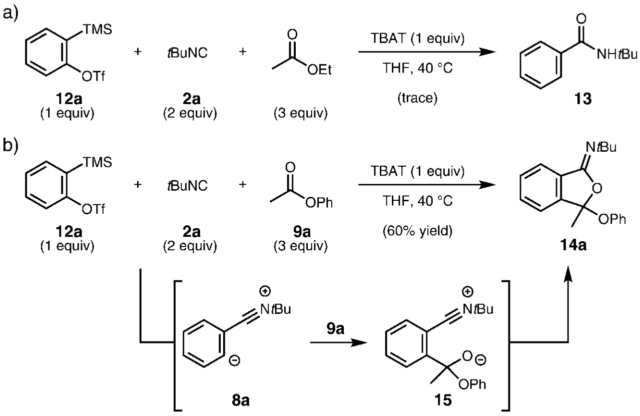
Benzyne has been an integral tool for the discovery of new multicomponent reactions for over 70 years.[1] In particular, the ability to function as a relay species between a nucleophile and an electrophile makes this reactive intermediate well suited to the rapid preparation of 1,2-disubstituted arene scaffolds.[2] In designing an approach toward new multicomponent aryne reactions, we began by considering reactivity patterns of classic transformations. In the Passerini synthesis of α-acyloxyamides (e.g., **6**),[3] an aldehyde component (**1**) acts as both an electrophile and a latent nucleophile (i.e., **1**→**6**)[4] during the course of the reaction (Scheme 1a).



Scheme 1. a) Passerini reaction. b) Aryne analogue of the Passerini reaction.

We postulated that this rudimentary mechanism could be adapted to the synthesis of *o*-ketobenzamides (**11**) by replacing the aldehyde component with an aryne (Scheme 1b). In analogy to the formation of zwitterion **3**, nucleophilic addition of the isocyanide to benzyne (**7**) has been shown to form aryl nitrilium **8**.[5] In the presence of a carboxylic acid, however, this intermediate would be expected to undergo protonation at the aryl anion. In order to avoid this outcome, we envisioned that the third component be replaced with an ester (**9**), which would instead undergo nucleophilic attack. Subsequent expulsion of the alkoxide ($^-$OR^4) to generate the benzylic ketone and recombination with the nitrilium cation would ultimately generate *o*-ketobenzimidate **10**. Further access to the corresponding *o*-ketobenzamide (**11**) could then be gained through hydrolysis.

Our initial attempt to accomplish this three-component transformation employed ethyl acetate with 2-(trimethylsilyl)phenyl triflate (**12a**) and *tert*-butyl isocyanide (**2a**) in the presence of tetra-*N*-butylammonium difluorotriphenylsilicate (TBAT) (Scheme 2a). Unfortunately, this ester failed to provide the desired *o*-ketobenzimidate, instead producing trace quantities of *N-tert*-butylbenzamide (**13**) through hydration of zwitterion **8** ($R^1 = t$Bu).[5] Reasoning that a more electrophilic ester would display greater reactivity toward the aryl anion, we decided to employ phenyl acetate (**9a**). However, under the same conditions, we were surprised to find that instead of the expected benzimidate, phenoxy iminoisobenzofuran **14a** was isolated in 60% yield. Presumably, this heterocycle is formed through intramolecular attack of the tetrahedral alkoxide on the nitrilium cation (**15**) and results in formation of a formal dipolar cycloaddition product (Scheme 2b),[6] akin to reactivity previously observed by Yoshida and Kunai et al. using aldehydes[7] and aldimines.[8,9] To our knowledge, this method represents the first preparation of a stable phenoxy-substituted iminoisobenzofuran.[10,11]



Scheme 2. a) Attempted three-component coupling using ethyl acetate. b) Phenoxy iminoisobenzofuran synthesis by three-component coupling of benzyne, *tert*-butyl isocyanide, and phenyl acetate.

Intrigued by this new three-component coupling reaction and the unusual heterocyclic scaffold observed in the product, we examined the scope of the reaction. By altering the stoichiometry of the reagents involved, optimized conditions

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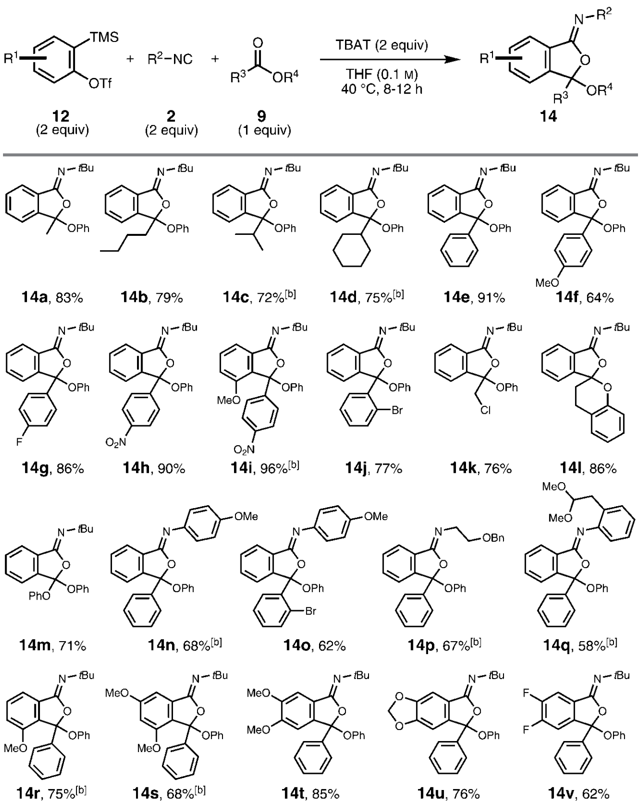
were found wherein a THF solution containing a limiting amount of the ester (**9**) and two equivalents each of the silyl aryl triflate (**12**), isocyanide (**2**), and TBAT is heated to 40 °C for 8–12 h. By employing these reaction conditions, we found the scope to be reasonably broad with respect to all three components.

We initially examined a number of substituted phenyl esters prepared directly from the corresponding carboxylic acids (Table 1). Esters bearing linear (**14b**), branched (**14c**), and cyclic aliphatic substituents (**14d**) performed well under the established reaction conditions, as did benzoic esters (**14e–j**). Not surprisingly, we found that electron-withdrawing substituents (**14g–j**) promoted greater reactivity than electron-donating substituents (**14f**). Despite concerns that an α-haloester would react unfavorably with *tert*-butyl isocyanide, phenyl chloroacetate produced the expected three-component adduct in comparable yield (**14k**). Notably, even dihydrocoumarin and phenyl carbonate gave rise to interesting spirocyclic (**14l**) and masked orthoester products (**14m**), respectively.

Table 1: Synthesis of phenoxy iminoisobenzofurans.[a]



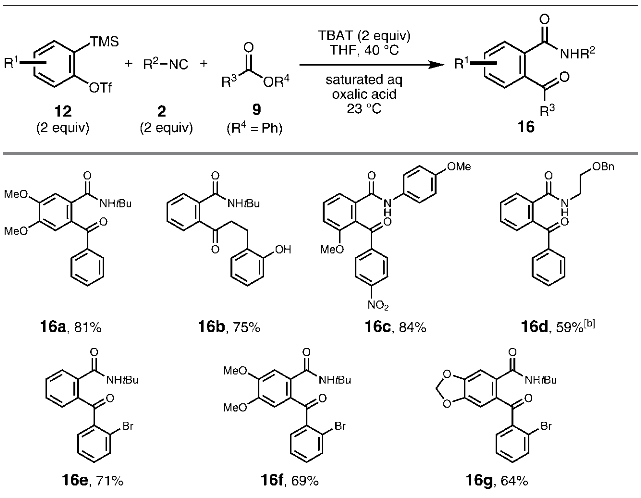
[a] Yield of isolated product. [b] Reaction performed at 60 °C.

Next, we evaluated the isocyanide component, replacing *tert*-butyl isocyanide with 4-methoxyphenyl isocyanide, leading to N-arylated products **14n** and **14o**. Additionally, 2-benzyloxyethyl isocyanide furnished imidate **14p**. Moreover, we tested the unusual *o*-(β-dimethoxyethyl)phenyl isocyanide, reported by Kobayashi et al.,[12] which produced the desired iminoisobenzofuran (**14q**) in 58 % yield.

Finally, we performed the three-component coupling with a series of heteroatom-functionalized aryne precursors to generate aryl-substituted adducts **14r–v**. Importantly, when unsymmetrical arynes were employed, the reaction proceeded regioselectively to provide phenoxy iminoisobenzofurans **14r** and **14s** as single isomers.[13,14]

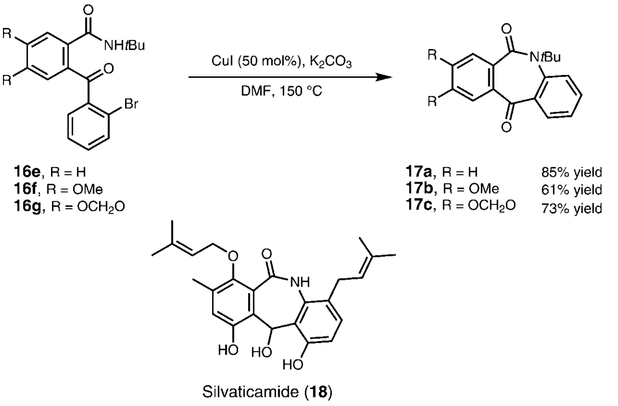
Although we had yet to prepare an *o*-ketobenzamide using our multicomponent approach, we recognized that the phenoxy iminoisobenzofurans had only to undergo hydrolysis in order to produce this originally targeted structure. We therefore examined conditions under which the three-component coupling adducts could be hydrolyzed to generate *o*-ketobenzamides (i.e., **16**) in a single sequence (Table 2). A thorough evaluation of various protic acids led to the identification of oxalic acid as the optimal catalyst for phenoxy iminoisobenzofuran hydrolysis (i.e., **14**→**16**). Upon completion of the three-component coupling, the addition of a saturated aqueous solution of oxalic acid to the cooled reaction mixture resulted in hydrolytic production of *o*-ketobenzamides **16a–g**. In this way, we are able to generate di- (**16b**, **d**, and **e**), tri- (**16c**), and tetrasubstituted (**16a**, **f**, and **g**) *o*-ketobenzamides in good yield from readily available *o*-silyl aryl triflates (**12**), isocyanides (**2**), and phenyl esters (**9**) as starting materials.

Table 2: One-pot synthesis of *o*-ketobenzamides.[a]



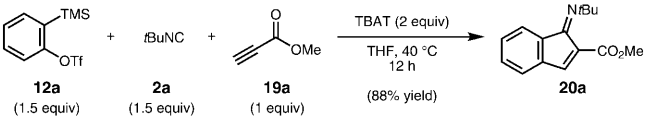
[a] Yield of isolated product. [b] Three-component coupling reaction performed at 60 °C.

In order to demonstrate the synthetic utility of the *o*-ketobenzamides, we carried out an intramolecular cyclization of bromobenzamides **16e–g** to generate caprolactams (Scheme 3). By heating the substrates in the presence of copper(I) iodide and potassium carbonate in DMF, dibenzoketocaprolactams **17a–c** are formed in 61–85 % yield. The structural similarity that these polycycles share with bioactive natural products such as the antifungal agent, silvaticamide (**18**),[15] suggests the enabling role this method could play in total synthesis.



Scheme 3. Dibenzoketocaprolactam synthesis.

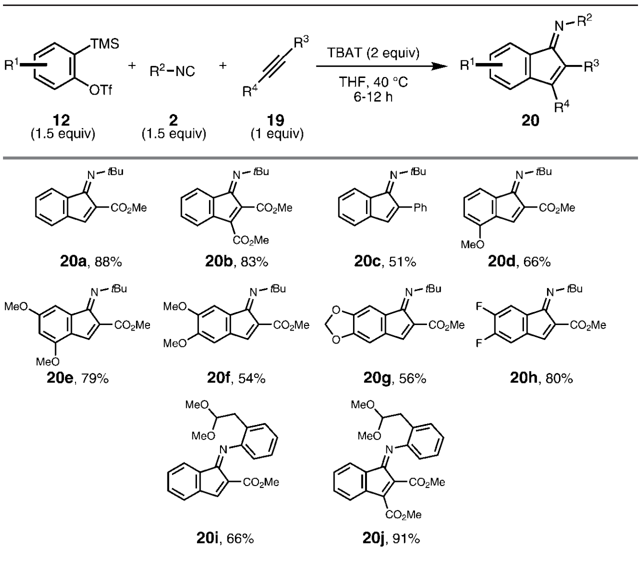
Recognizing that the ester constituent of our three-component coupling reaction was essentially a dipolarophile in a [3+2] cycloaddition, we investigated additional substrates capable of reacting in a similar ambiphilic manner. We reasoned that a conjugate acceptor (e.g., **19a**) could potentially fill this role, and thus examined a series of α,β-unsaturated carbonyl compounds with the aim of generating carbocyclic adducts (e.g., **20a**). Ultimately, methyl propiolate (**19a**) was found to react with 2-(trimethylsilyl)phenyl triflate (**12a**) and *tert*-butyl isocyanide (**2a**) to produce iminoindenone **20a** in 88% yield (Scheme 4).[16]



Scheme 4. Iminoindenone synthesis by three-component coupling of benzyne, *tert*-butyl isocyanide, and methyl propiolate.

With this initial result in hand, we evaluated the scope of this new three-component coupling reaction and again found it to be tolerant of changes to all three pieces. Dimethyl acetylenedicarboxylate was found to be an equally competent substrate, providing access to a 2,3-disubstituted iminoindenone (**20b**). Interestingly, replacing the conjugate acceptor with phenyl acetylene furnished a 2-phenyliminoindenone (**20c**) in 51% yield.[17] As in the previous multicomponent coupling, this reaction proved amenable to the incorporation of a number of substituted aryne motifs. Both symmetrical and unsymmetrical heteroatom-functionalized arynes formed the expected three-component adducts in good yields (**20d–h**) as single isomers (i.e., **20d** and **20e**). Additionally, Kobayashi's isocyanide[12] could be employed to efficiently generate **20i** and **20j** (Table 3).

Table 3: Synthesis of iminoindenones.[a]



[a] Yield of isolated product.

In summary, during the course of our efforts to develop an aryne-intercepted version of the Passerini reaction, we discovered a novel three-component coupling of arynes, isocyanides, and phenyl esters that furnishes unusual phenoxy iminoisobenzofuran motifs (i.e., **14**). This reaction is tolerant of considerable substitution on each of the three reaction partners, giving rise to a wide array of heterocyclic adducts. In combination with a subsequent hydrolysis step, this methodology enables the rapid, one-pot synthesis of *o*-ketobenzamides (i.e., **16**), useful synthetic building blocks that can be advanced to functionalized dibenzoketocaprolactams (e.g., **17a–c**). Furthermore, we have translated the observed reactivity of this three-component coupling to the formation of carbocyclic iminoindenones (i.e., **20**) by employing electron-deficient alkynes in place of the ester component. Current efforts are directed toward the discovery of additional relay species and the application of these methodologies within the realm of natural product total synthesis.

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Keywords: arynes · heterocycles · isocyanides · multicomponent reactions · polycycles

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[16] Attempts were made to carry out similar transformations using methyl acrylate, methyl methacrylate, 2-cyclopentenone, and 2-cyclohexenone in place of methyl propiolate (**19a**). However, each failed to generate the corresponding iminoindanone under the reaction conditions.

[17] Efforts to employ additional alkynes lacking conjugate acceptors (e.g., cyclohexylacetylene, ethoxyacetylene, and diphenylacetylene) failed to generate the corresponding three-component adducts.

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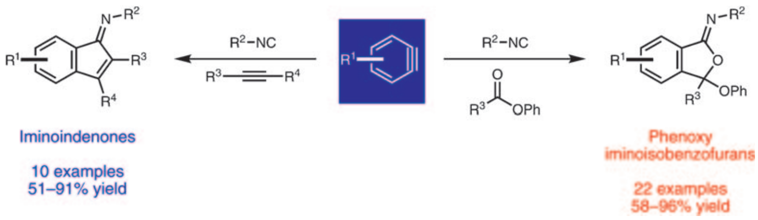

Triple crown: A pair of three-component coupling reactions between arynes, isocyanides, and either activated alkynes or phenyl esters generates unusual iminoindenones or phenoxy iminoisobenzofurans (see scheme), the latter of which may be advanced to *o*-ketobenzamides by performing direct hydrolysis. The synthetic utility of these compounds is demonstrated in a rapid preparation of substituted dibenzoketocaprolactams.