

The Direct Acyl-Alkylation of Arynes

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While arynes have historically received much attention from physical organic chemists, their use as reagents in synthetic organic chemistry has been somewhat limited.¹ This is partially attributable to the harsh conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species. In 1983, Kobayashi described a mild method for the in situ preparation of benzyne (i.e., **3**) at moderate temperatures that exploits the fluoride-induced elimination of *ortho*-silyl aryltriflates (e.g., **1**).² In conjunction with our recent efforts to synthesize stereogenic quaternary carbon centers,³ we envisioned that arynes generated by this method could serve as a platform for the production of quaternary benzylic stereocenters. Specifically, we anticipated that the mild conversion of **1** to benzyne (**3**) in the presence of β -ketoester **2** would produce **6** (Scheme 1). To our surprise, in addition to obtaining the expected β -ketoester **6**, we observed the interesting *ortho*-substituted product **7** in comparable yield. The acyl-alkylation product **7** is the net result of benzyne insertion into the α,β C–C single bond of the β -ketoester, presumably by a formal [2 + 2] cycloaddition/fragmentation cascade (i.e., **1** \rightarrow **3** \rightarrow **4** \rightarrow **5** \rightarrow **7**). While aryne insertions into heteroatom–hydrogen⁴ and heteroatom–carbon⁵ bonds have been reported under mild conditions, we were intrigued by our result because it represents the first mild and direct aryne insertion into a carbon–carbon bond.⁶ Herein, we describe our explorations into the scope of this acyl-alkylation of arynes as an efficient method for the generation of interesting *ortho*-disubstituted arenes and benzannulated carbocycles.

As we began our investigation into the formation of the acyl-alkylation product, we hypothesized that β -ketoesters lacking α -substitution may form the putative benzocyclobutene intermediate (i.e., **5b**) more readily, thus suppressing the α -arylation product. In support of this hypothesis, higher yields of the *ortho*-disubstituted product were obtained from the treatment of non α -substituted β -ketoesters (i.e., **8a–h**) with **1** in the presence of CsF (Table 1). The reaction tolerates substitution at the γ -position (entries 2–6), including aliphatic and aromatic groups. Heteroatoms may also be incorporated into the β -ketoester side chain, albeit in slightly lower yields (entry 5). Additionally, the ester moiety can be varied while maintaining the efficiency of the reaction. For example, β -ketoesters of more complex alcohols such as menthol and cholesterol provide

Scheme 1

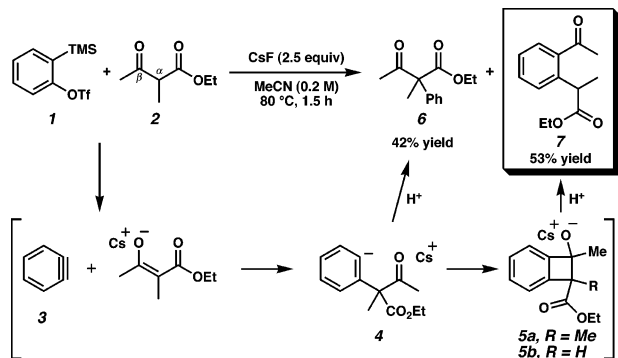


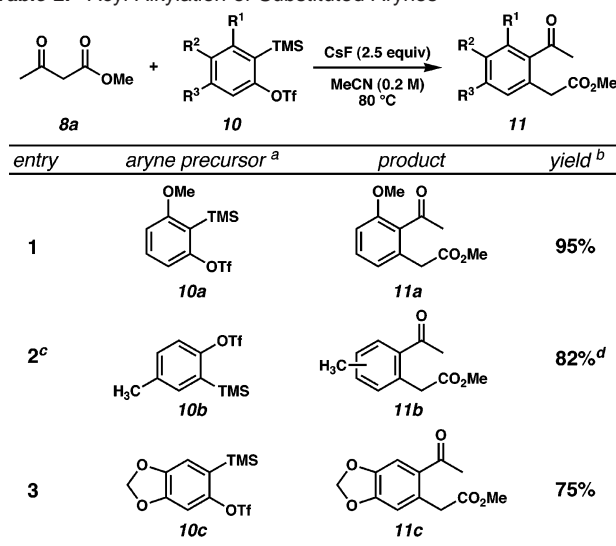
Table 1. Acyl-Alkylation of Benzyne

| entry | substrate ^a | product | yield ^b |
|----------------|------------------------|---------|--------------------|
| 1 | | | 90% |
| 2 | | | 78% |
| 3 | | | 84% |
| 4 ^c | | | 85% |
| 5 | | | 53% |
| 6 | | | 99% |
| 7 | | | 72% |
| 8 | | | 75% |

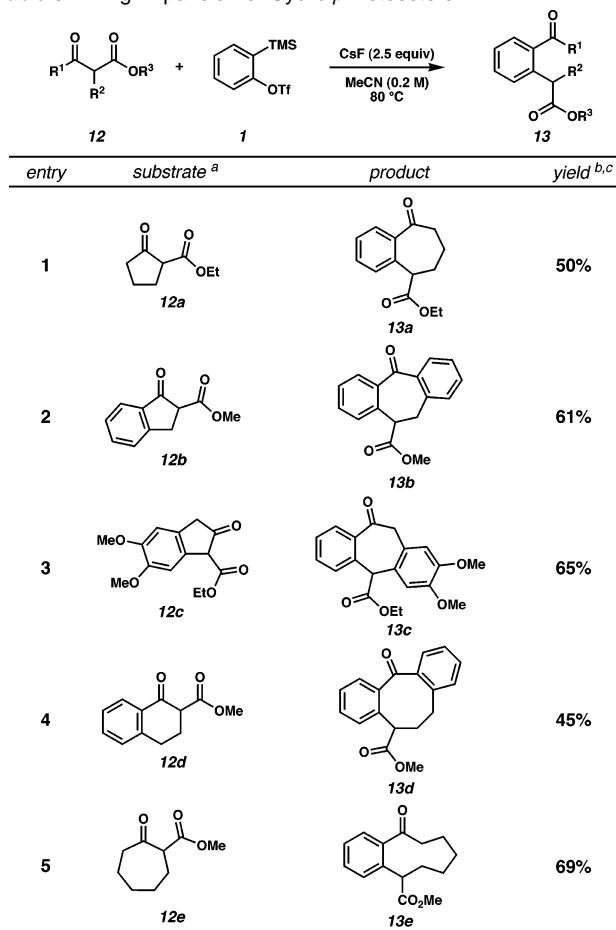
^a 1.25 equiv of **1** relative to β -ketoester **8**. ^b Isolated yield. ^c 2 equiv of **1** relative to **8d**.

the desired acyl-alkylation products in good yield (entries 7 and 8). In general, the mild reaction conditions allow for a considerable degree of substitution on the β -ketoester subunit.

We next examined the coupling of substituted aryne precursors **10a–c** with methyl acetoacetate (Table 2). To our delight, this simple β -ketoester reacted with arynes possessing monosubstitution at the *ortho*- and *meta*-positions (entries 1 and 2) as well as disubstitution (entry 3) to produce high yields of the corresponding acyl-alkylation products (**11a–c**). Additionally, entries 1 and 3 demonstrate that heteroatom substituents are well-tolerated. Of particular note is the complete regioselectivity and excellent isolated yield observed in the coupling of methoxy substituted aryne precursor **10a** with **8a**. This high selectivity points toward stepwise

Table 2. Acyl-Alkylation of Substituted Arynes

^a 2 equiv of **10** relative to **8a**. ^b Isolated yield. ^c 1.25 equiv of **10b** relative to **8a**. ^d Mixture of meta- and para-regioisomers (1.2:1).

Table 3. Ring Expansion of Cyclic β -Ketoesters

^a 1.25 equiv of **1** relative to β -ketoester **12**. ^b Isolated yield. ^c In most cases the α -arylated β -ketoester was isolated as the major side product. See Supporting Information.

production of the key benzocyclobutene intermediate, analogous to the mechanism depicted in Scheme 1.

At this stage, we revisited β -ketoesters with α -substitution. We anticipated difficulty for such reactions based on our original observation that competitive formation of α -arylated products

occurred, presumably due to steric congestion en route to the key benzocyclobutene. Nevertheless, we believed that these reactions could provide efficient access to an interesting class of structures that would otherwise be difficult to obtain. Specifically, we envisioned that cyclic β -ketoesters would undergo ring expansion to furnish medium-sized carbocycles, which continue to be difficult structures to synthesize despite their prevalence in natural products and drug substances.⁷ We applied our optimized conditions to a series of cyclic β -ketoesters of varying ring size (Table 3, **12a–e**). Gratifyingly, we were able to synthesize seven-membered benzanulated structures in synthetically useful yields by employing five-membered ring β -ketoesters (entries 1–3). While the insertion into a six-membered ring was less efficient (entry 4), the expansion of a seven-membered ring furnished a nine-membered carbocycle in 69% yield (entry 5).

In summary, we have developed a mild, direct, and efficient process for the acyl-alkylation of arynes to produce interesting ortho-substituted arenes via an unusual reaction cascade. Overall, the transformation results in the formation of two new C–C bonds by the net insertion of an arene unit into the α,β single bond of a β -ketoester. This facile methodology provides convergent, single-step, high-yielding access to a variety of substituted arenes and benzanulated structures that would otherwise be difficult to obtain. Notably, cyclic β -ketoesters can be expanded to generate medium-sized carbocycles. The utility of this intriguing reaction in complex natural product synthesis is currently under investigation.

Acknowledgment. This work is dedicated to our friend and colleague Professor John D. Roberts, the father of benzyne.⁸ We are grateful to the NDSEG (predoctoral fellowship to U.K.T.), the A. P. Sloan Foundation, the Research Corporation, Pfizer, Novartis, Merck, Amgen, Lilly, Roche, Abbott, AstraZeneca, GlaxoSmith-Kline, and Caltech for financial support.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA050859M