Efficient Synthesis of 3H-Indoles Enabled by the Lead-Mediated α-Arylation of β-Ketoesters or γ-Lactams Using Aryl Azides

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Supporting Information

ABSTRACT: The development of a lead-mediated α-arylation reaction between aryl azides and β-ketoesters or γ-lactams that facilitates the formation of 3H-indoles is disclosed. Twenty-five examples are included which demonstrate the generality of this reaction to access aryl azides bearing tetrasubstituted α-alkyl substituents. When paired with a Staudinger reduction, this reaction streamlines the synthesis of functionalized 3H-indoles.

The development of new efficient processes to construct N-heterocycles continues to motivate synthetic groups because of the ubiquitous nature of these structural motifs in bioactive and electronic molecules. Our group believes that these important compounds could be efficiently synthesized through transition-metal-catalyzed C–H bond amination, which would create the ArN–C bond from aryl azides. While we have successfully developed a series of C–H bond amination processes, the number of steps often required to access the aryl azide substrates diminished the overall efficiency of our N-heterocycle synthesis. In our intramolecular sp²-C–H bond amination studies, seven linear steps were required to introduce the fully substituted α-alkyl substituent present in the aryl azide (e.g., 1) (Scheme 1). This study underscored the need to streamline our substrate construction, and we anticipated that a modular synthesis could be achieved if the aryl azide moiety was installed through an H bond amination process, which would create the ArN–C bond from a carbonyl compound. We were surprised, however, to find that no examples of this reaction existed with aryl azides.

Herein, we report the first α-arylation of β-ketoesters and γ-lactams with aryl azides and leverage this reaction to efficiently synthesize 3H-indoles.

While there are many catalyzed and noncatalyzed α-arylation reactions of carbonyl compounds, our survey of popular methods and environmentally benign arylation reagents found them to be incompatible with the α-azide moiety. The failure of these methods prompted us to examine the α-arylation of β-ketoesters using an arylead as the electrophilic reagent. Although the use of these complexes is well-established, there are no examples of using an aryl azide substituent (much less an α-azide) in the α-arylation processes. The requisite 2-azidoaryllead acetate was readily prepared from either the 2-azidoarylbromonic acid pinacolate ester or analogous stannane using the conditions reported by Pinhey and co-workers without any decomposition of the azido group. With 4a in hand, a variety of conditions were screened to find the optimal conditions for the α-arylation of β-ketoester 9a...

Table 1. Determination of the Optimal Conditions for α-Arylation

| entry | base (equiv) | 4a (equiv) | 9a (equiv) | yield (%) |
|-------|-------------|-----------|-----------|-----------|
| 1     | none        | 1         | 5         | 90        |
| 2     | none        | 1         | 3         | 89        |
| 3     | none        | 1         | 1.05      | 59        |
| 4     | dabc (3)    | 1         | 1.05      | 44        |
| 5     | phenanthline (3) | 1        | 1.05      | 62        |
| 6     | pyridine (3) | 1         | 1.05      | 78        |
| 7     | pyridine (3) | 1         | 1.05      | 87        |
| 8     | pyridine (3) | 1.05      | 1         | 83        |
| 9     | pyridine (3) | 3         | 1         | 88        |
| 10    | pyridine (3) | 1         | 1.05      | 45        |

*As determined using 1H NMR spectroscopy using CH3Br2 as an internal standard. Reaction performed at 50 °C. Two-step yield from 8a.

Scheme 1. Current Challenges To Synthesizing 2-Substituted Aryl Azides

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For the initial screen, an excess of 9a was used (entries 1−3). We found that the equivalents of 9a could be reduced to three without attenuating the yield of 6a. A significant reduction in conversion was observed, however, when a slight excess of the β-ketoester was used (entry 3). To improve the conversion, several amine bases were screened (entries 4−6).11d While the addition of dabco, phenanthroline, or pyridine did improve the yield, it plateaued at 78%. Using pyridine, a further improvement was realized by increasing the temperature of the reaction to 50 °C (entry 7). Next, we examined if the stoichiometry of our α-arylation could be reversed in order to enable the use of the 2-azidoaryllead acetate as a reagent for the α-arylation of more valuable β-ketoesters (entries 8 and 9). To our delight, we found that yield diminished only slightly, and if 3 equiv of 4a was used, the yield recovered to 88%. Finally, we attempted the α-arylation in one-flask directly from 2-azidophenylboronic pinacolate ester 8a without isolation the 2-azidoaryllead acetate to afford 6a in 45% (entry 10).

Using these optimal conditions, a series of β-ketoesters were examined to determine the scope and limitations of our α-arylation reaction (Table 2). We found that the ring size of the β-ketoester could be modified without affecting the yield of our α-arylation reaction to provide functionalized aryl azides 6b−d (entries 1−3). Acyclic β-ketoesters, such as 4e, could even be smoothly converted to product without much attenuation of the yield (entry 4). Next, the effect of the composition of the β-ketoester on the yield of the arylation was examined (entries 5−7): indanone 9f, 4-tetrahydropyranone 9g, and 4-amino-cyclohexanone 9h produced aryl azides 6f−h in good yields. To our surprise, while the α-arylation of amides has generated considerable excitement,16,17 γ-lactams have never been used in these processes despite the synthetic utility of these molecules. We found that they could be efficiently arylated to produce 6i.

Table 2. Effect of Changing the Identity of the β-Ketoester

| entry | β-ketoester 9 | aryl azide 6 | % yield | yield of 6 after silica gel chromatography; only product obtained. |
|-------|--------------|-------------|---------|---------------------------------------------------------------|
| 1     | b            | ElO₂C₂       | 89      | 89                                                            |
| 2     | c            | MeO₂C₂       | 97      | 97                                                            |
| 3     | d            | MeO₂C₂       | 97      | 97                                                            |
| 4     | e            | ElO₂C₂       | 79      | 79                                                            |
| 5     | f            | ElO₂C₂       | 75      | 75                                                            |
| 6     | g            | ElO₂C₂       | 53      | 53                                                            |
| 7     | h            | N₃-Pb(OAc)₃  | 86      | 86                                                            |
| 8     | i            | d.r. 91:9    | 79      | 79                                                            |
| 9     | j            | d.r. 91:9    | 63      | 63                                                            |
| 10    | k            | d.r. 91:9    | 63      | 63                                                            |
| 11    | l            | d.r. 50:50   | 54      | 54                                                            |
| 12    | m            | n.r.         | 54      | 54                                                            |

*Reaction performed using 1 equiv of 4a, 1.05 equiv of 9, 3 equiv of pyridine in CHCl₃ at 50 °C. Isolated yield of 6 after silica gel chromatography; only product obtained.

Table 3. Determination of the Optimal Conditions for α-Arylation

| entry | 4 | R¹ | R² | 9 | 6 | % yield |
|-------|---|----|----|---|---|---------|
| 1     | b | F  | H  | a | o | 67      |
| 2     | c | Cl | H  | a | p | 67      |
| 3     | d | Me| H  | a | q | 77      |
| 4     | e | H | OMe| a | r | 94      |
| 5     | f | H | Me | a | s | 94      |
| 6     | g | H | F  | a | t | 58      |
| 7     | h | N₃-Pb(OAc)₃| a | u | 67 |
| 8     | i | F  | H  | i | v | 75      |
| 9     | c | Cl | H  | i | w | 56      |
| 10    | d | Me| H  | i | x | 52      |
| 11    | f | H | Me | i | y | 89      |
| 12    | g | H | F  | i | z | 42      |

*Reaction performed using 1 equiv of 4, 1.05 equiv of 9, 3 equiv of pyridine in CHCl₃ at 50 °C. Isolated yield of 6 after silica gel chromatography; only product obtained. 3 equiv of 4 used.
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Table 4. Conversion of Aryl Azides to 3H-Indoles

| entry | # | aryl azide 6 | 3H-indole 7 | %, yield |
|-------|---|-------------|-------------|---------|
| 1     | a | 6a          | 7a          | 96      |
| 2     | b | 6b          | 7b          | >95<sup>a</sup> |
| 3     | c | 6c          | 7c          | 84      |
| 4     | g | 6g          | 7g          | 90      |
| 5     | h | 6h          | 7h          | 95      |
| 6     | i | 6i          | 7i          | 91      |
| 7     | k | 6k          | 7k          |         |

<sup>a</sup>Isolated yield of 7 after silica gel chromatography. <sup>b</sup>As determined using <sup>1</sup>H NMR spectroscopy; 3H-indole 7b rapidly decomposed upon exposure to air.

in good yield (entry 8). Next, the stereoselectivity of our α-arylation reaction was investigated. Exposure of 4-tert-butyl-substituted β-ketoester 9a to our reaction conditions furnished 6j with 10:1 diastereoselectivity (entry 9). To our delight, the selectivity was not affected by the size of the 4-substituent: the diastereoselectivity remained 10:1 when the 4-tert-butyl group was replaced with a smaller 4-phenyl group (entry 10). Finally, we examined the effect of changing the nature of the carbonate group (entries 11–13). We found that an ester was necessary for the α-arylation reaction. While the methyl ester could replaced with either an allyl or menthol (albeit with no diastereoselectivity observed), β-ketoamides proved to be unreactive in our process.

The effect of adding substituents to the 2-azidoaryllead acetate on the α-arylation of β-ketoester 9a to γ-lactam 9i was examined next (Table 3). For β-ketoester 9a, we found that the arylation reaction tolerated halide, alkyl, or ether substituents (entries 1–6). The yield, however, did depend on the electronic nature of 4 with the highest yields observed for the electron-rich or electron-neutral arylleads bearing methoxy- or methyl groups (entries 4 and 5). Further, the azide group could be placed at the 4-position without much diminishment of the yield of the arylation reaction (entry 7). To determine the generality of our reaction, we next examined the α-arylation of γ-lactam 9i, a substrate never reported as nucleophile in this process (entries 8–12).<sup>17</sup> To our delight, we found that a range of different 2-azidoaryllead acetates reacted with γ-lactam 9i. Its reactivity, however, was diminished in comparison to β-ketoester 9a. To obtain comparable yields, it was often necessary to increase the amount of the 2-azidoaryllead to 3 equiv (entries 10–12).

The synthetic utility of our α-arylation reaction was demonstrated next by exposing aryl azides 6 to a Staudinger reduction (Table 4).<sup>18</sup> We found that exposure of aryl azides 6 to triphenylphosphine produced 3H-indoles 7 in nearly quantitative yield. Although the ring size of the β-ketoester could be modified in between the 5- and 7-carbons without affecting the Staudinger reaction, 3H-indole 7b readily decomposed when exposed to air (entries 1–3). The reduction tolerated heteroatoms in the β-ketoester to enable access to important N-heterocyclic structural motifs,<sup>19</sup> such as γ-carboline 7h (entries 4 and 5). The Staudinger reaction could even be extended to γ-lactams to efficiently access 3H-pyrolloindole 7i in nearly quantitative yield (entry 6), whose structure is ubiquitous in bioactive alkaloids.<sup>20</sup> Finally, submission of aryl azide 6k to the reduction conditions furnished 3H-indole 7k in good yield without loss of any diastereoselectivity (entry 7). Together these results illustrate that when paired with a Staudinger reduction our α-arylation reaction to diastereoselectively access a range of 3H-indoles.

In conclusion, we developed an α-arylation reaction of β-ketoesters using 2-azidoaryllead acetates to afford a range complex, functionalized aryl azides with fully substituted o-alkyl substituents. The synthetic utility of our process was showcased using γ-lactam substrates to enable efficient construction of functionalized 3H-indoles after Staudinger reduction.

Associated Content

Supporting Information

Complete experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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