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

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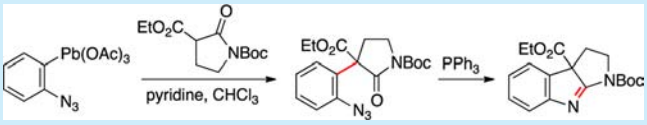
Supporting Information

ABSTRACT: The development of a lead-mediated α-arylation reaction between aryl azides and β-ketoesters or γ-lactams that facilitates the formation of 3*H*-indoles is disclosed. Twenty-five examples are included which demonstrate the generality of this reaction to access aryl azides bearing tetrasubstituted *o*-alkyl substituents. When paired with a Staudinger reduction, this reaction streamlines the synthesis of functionalized 3*H*-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.[1,2] 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,[3−5] the number of steps often required to access the aryl azide substrates diminished the overall efficiency of our *N*-heterocycle synthesis. In our intramolecular sp^2-C−H bond amination studies,[5b] seven linear steps were required to introduce the fully substituted *o*-alkyl substituent present in the aryl azide (e.g., **1**) (Scheme 1). This study underscored the need to streamline our substrate construction,[6] and we anticipated that a modular synthesis could be achieved if the aryl azide moiety was installed through an α-arylation of a carbonyl compound.[7−12] We were surprised, however, to find that no examples of this reaction existed with aryl azides.[13] Herein, we report the first α-arylation of β-ketoesters and γ-lactams with aryl azides and leverage this reaction to efficiently synthesize 3*H*-indoles.

While there are many catalyzed and noncatalyzed α-arylation reactions of carbonyl compounds,[7−13] our survey of popular methods and environmentally benign arylating reagents found them to be incompatible with the *o*-azide moiety.[14] The failure of these methods prompted us to examine the α-arylation of β-ketoesters using an aryllead as the electrophilic reagent. Although the use of these complexes is well-established,[11] there are no examples of using an aryl azide substituent (much less an *o*-azide) in the α- arylation processes. The requisite 2-azidoaryllead acetate was readily prepared from either the 2-azidoarylboronic acid pinacolate ester (**8**)[15] or analogous stannane using the conditions reported by Pinhey and co-workers without any decomposition of the azido group.[11b,c] With **4a** in hand, a variety of conditions were screened to find the optimal conditions for the α-arylation of β-ketoester **9a**

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

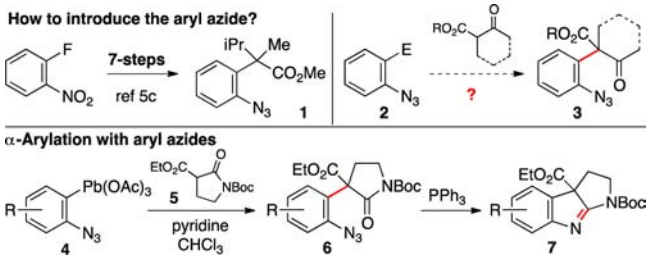
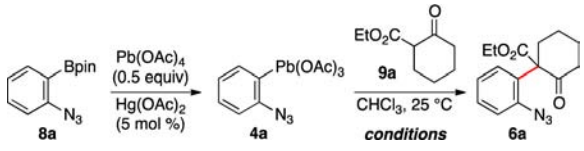


Table 1. Determination of the Optimal Conditions for α-Arylation



entry	base (equiv)	**4a** (equiv)	**9a** (equiv)	yield[a] (%)
1	none	1	5	90
2	none	1	3	89
3	none	1	1.05	59
4	dabco (3)	1	1.05	44
5	phenanthraline (3)	1	1.05	62
6	pyridine (3)	1	1.05	78
7	pyridine (3)	1	1.05	87[b]
8	pyridine (3)	1.05	1	83[b]
9	pyridine (3)	3	1	88[b]
10	pyridine (3)	1	1.05	45[c]

[a]As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b]Reaction performed at 50 °C. [c]Two-step yield from **8a**.

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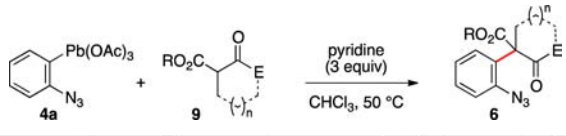
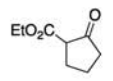
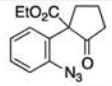
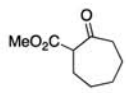
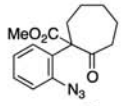
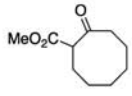
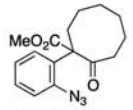
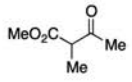
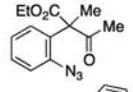
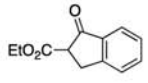
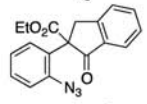
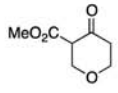
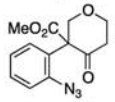
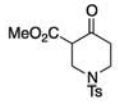
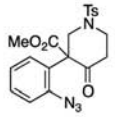
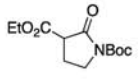
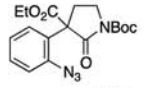
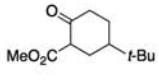
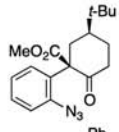
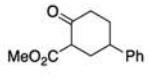
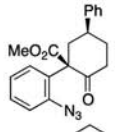
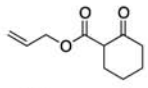
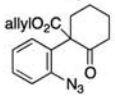
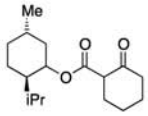
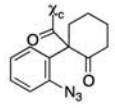
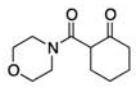
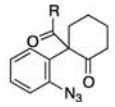
Table 2. Effect of Changing the Identity of the β-Ketoester

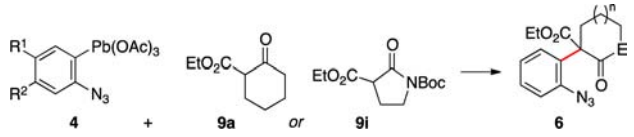


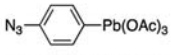
entry[a]	#	β-ketoester **9**	aryl azide **6**	%, yield[b]
1	b			89
2	c			97
3	d			97
4	e			79
5	f			75
6	g			53
7	h			86
8	i			79
9	j			79 d.r. 91:9
10	k			63 d.r. 91:9
11	l			89
12	m			54 d.r. 50:50
13	n			n.r.

[a]Reaction performed using 1 equiv of **4a**, 1.05 equiv of **9**, and 3 equiv of pyridine in $CHCl_3$ at 50 °C. [b]Isolated yield of **6** after silica gel chromatography; only product obtained.

(Table 1). 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

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



entry[a]	**4**	R^1	R^2	**9**	**6**	%, yield **6**[b]
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[c]
7	h			a	u	67
8	b	F	H	i	v	75
9	c	Cl	H	i	w	56
10	d	Me	H	i	x	52[c]
11	f	H	Me	i	y	89[c]
12	g	H	F	i	z	42[c]

[a]Reaction performed using 1 equiv of **4**, 1.05 equiv of **9**, 3 equiv of pyridine in $CHCl_3$ at 50 °C. [b]Isolated yield of **6** after silica gel chromatography; only product obtained. [c]3 equiv of **4** used.

(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**

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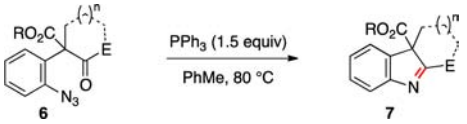
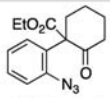
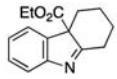
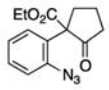
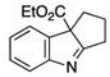
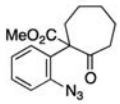
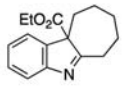
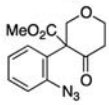
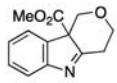
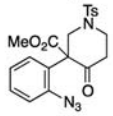
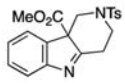
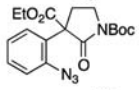
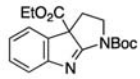
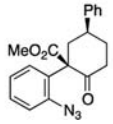
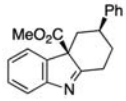
Table 4. Conversion of Aryl Azides to 3*H*-Indoles



6 7

entry	#	aryl azide **6**	3*H*-indole **7**	%, yield[a]
1	a			96
2	b			>95[b]
3	c			84
4	g			90
5	h			95
6	i			92
7	k			91

[a]Isolated yield of **7** after silica gel chromatography. [b]As determined using ^{1}H NMR spectroscopy; 3*H*-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 **9j** 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 carboxylate 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** or 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).[17] 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).[18] We found that exposure of aryl azides **6** to triphenylphospine produced 3*H*-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, 3*H*-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,[19] such as γ-carboline **7h** (entries 4 and 5). The Staudinger reaction could even be extended to γ-lactams to efficiently access 3*H*-pyrroloindole **7i** in nearly quantitative yield (entry 6), whose structure is ubiquitous in bioactive alkaloids.[20] Finally, submission of aryl azide **6k** to the reduction conditions furnished 3*H*-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 3*H*-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 3*H*-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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