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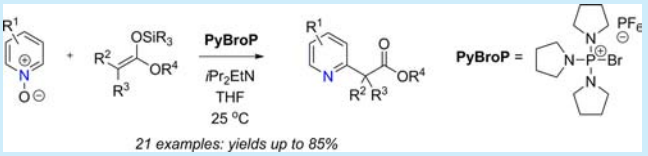
Expedient Synthesis of α-(2-Azaheteroaryl) Acetates via the Addition of Silyl Ketene Acetals to Azine-*N*-oxides

Allyn T. Londregan,* Kristen Burford, Edward L. Conn, and Kevin D. Hesp

Pfizer Worldwide Medicinal Chemistry, Eastern Point Road, Groton, Connecticut 06340, United States

Supporting Information

ABSTRACT: A new and expedient synthesis of α-(2-azaheteroaryl) acetates is presented. The reaction proceeds rapidly under mild conditions via the addition of silyl ketene acetals to azine-*N*-oxides in the presence of the phosphonium salt PyBroP. This procedure affords diverse α-(2-azaheteroaryl) acetates which are highly desirable components/building blocks in molecules of pharmaceutical interest but are traditionally challenging to synthesize via contemporary methods. The reaction optimization and mechanism as well as a novel electronically enhanced PyBroP derivative are described.

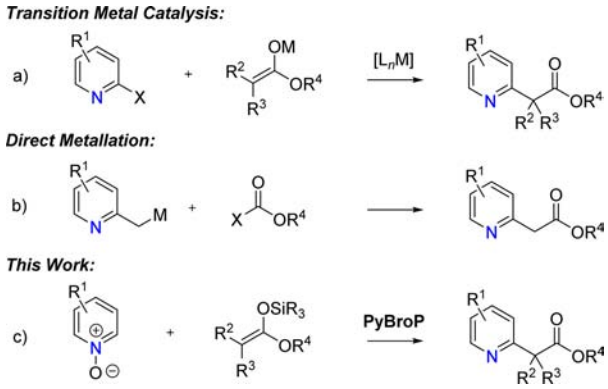


The α-aryl carbonyl moiety is a ubiquitous feature in molecules of pharmaceutical and biological interest. New synthetic methods for the direct α-arylation of carbonyl and enolate equivalents are important for strategic bond formation and the introduction of heterocyclic diversity into molecules. In recent years, there has been extensive research into the intermolecular, transition metal-mediated reaction of enolates with aryl halides to form the corresponding α-aryl carbonyl derivatives.[1] Palladium-catalyzed transformations are now perhaps the most widely used for this type of C−C bond construction. In their seminal works on the topic, Buchwald,[2] Hartwig,[3] and Miura[4] demonstrated the direct arylation of ketones with aryl iodides and aryl bromides in the presence of catalytic palladium. Since those reports, there have been continuous improvements made in yield, selectivity, and substrate compatibility. Additionally, reaction conditions can now be adapted to a variety of carbonyl reaction partners including, esters,[5] amides,[6] and aldehydes.[7] Despite these advancements, the substrate scope of the aryl halide reaction partner remains limited with respect to heterocyclic diversity. Reported examples of α-heteroaryl carbonyl adducts are infrequent and often low yielding.

During the course of our research, we required a facile synthesis of α-(2-azaheteroaryl) acetates (Scheme 1) for use as versatile synthetic intermediates. We found that these were among the most challenging substrates to synthesize via transition metal catalysis. Direct metalation[8] approaches are known but severely limit reactant scope and compatibility. Our laboratory was therefore interested in developing a new protocol for the synthesis of α-(2-azaheteroaryl) acetates, which would be more amenable to diverse heterocyclic substrates and overcome some of the inherent limitations of traditional methods.

In previous communications,[9] we described the addition of varied nucleophiles to azine-*N*-oxides with the phosphonium salt PyBroP.[10] We found that 1,3-dicarbonyl enolates[11] were suitable reaction partners in the transformation. Others have reported similar results,[11] but to our knowledge, no other

Scheme 1. Direct Syntheses of α-(2-Azaheteroaryl) Acetates



carbonyl enolates have been introduced with success onto azine-*N*-oxides in a C−C bond forming process. We rationalized that, with the use of the appropriate carbon nucleophile, our methodology might serve as an effective means to directly synthesize the requisite α-(2-azaheteroaryl) acetates in a single step under mild conditions.

We initiated a reaction optimization study with pyridine-*N*-oxide and commercially available methyl *tert*-butyldimethylsilyl ketene acetal **2** (Table 1). It was imperative to utilize either a relatively acidic[12] carbon nucleophile or an equivalent in neutral form, as anionic bases are incompatible with our PyBroP-based methodology. Using optimized conditions from our previous work (entry 1), we were pleased to observe the formation of desired product **3**, but the yield was poor (27%), and the product derived from overheteroarylation (**4**) was significant. With further experimentation, we determined that this transformation was remarkably sensitive to both solvent and base. The solvent/base pair of THF/*i*Pr$_2$EtN appeared optimal (entry 4). To diminish **4**, we assessed reaction concentration

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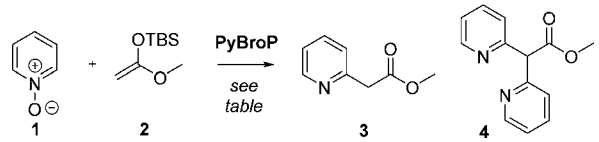
Table 1. Reaction Optimization for the Addition of Methyl *tert*-Butyldimethlysilyl Ketene Acetal to Pyridine-*N*-oxide[a]



entry	base	solvent	equiv 2	% yield[b]	3/4
1	iPr$_2$EtN	CH_2Cl_2	1.3	27	15
2	Et_3N	CH_2Cl_2	1.3	30	35
3	Et_3N	THF	1.3	60	10
4	iPr$_2$EtN	THF	1.3	80	8
5	$(Cy)_2MeN$	THF	1.3	55	8
6	iPr$_2$EtN	1,4-dioxane	1.3	45	13
7	iPr$_2$EtN	DMSO	1.3	<10	–
8	iPr$_2$EtN	DMF	1.3	20	–
9	iPr$_2$EtN	toluene	1.3	33	10
10[c]	iPr$_2$EtN	THF	1.3	55	20
11[d]	iPr$_2$EtN	THF	1.3	15	–
12[e]	iPr$_2$EtN	THF	1.3	89(67)	4
13	**iPr$_2$EtN**	**THF**	**2.0**	**89(81)**	**3(1)**
14	iPr$_2$EtN	THF	3.0	85	2

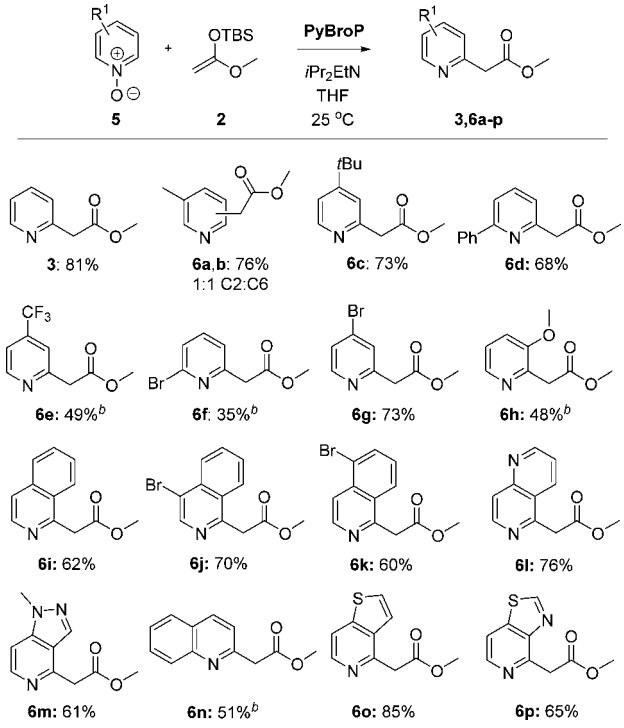
[a]Unless otherwise noted, all reactions were conducted in 2 dram vials at 0.20 M concentration with **1** (1.00 equiv), base (3.00 equiv), and PyBroP (1.10 equiv) at 25 °C for 15 h. [b]Yield determined by ^{1}H NMR using 2,6-dimethoxytoluene as internal standard with isolated yields in parentheses. [c]0.05 M concentration. [d]iPr$_2$EtN (1.00 equiv). [e]iPr$_2$EtN (5.00 equiv).

(entry 10), base equivalents (entries 11−12), and reagent addition order. None of these parameters, however, were effective. Ultimately, we determined that a second equivalent of silyl ketene acetal (**2**) reduced side-product **4** to almost undetectable levels, with a fortuitous increase in the yield of desired product. Under optimized conditions (entry 13), we were able to isolate **3** in 81% yield. Any impurities, including a trace amount of **4**, were easily removed by silica gel chromatography.

As shown in Scheme 2, we applied the optimized reaction conditions to a series of azine-*N*-oxides (**5**) and were pleased to obtain a diverse array of α-(2-azaheteroaryl) acetates (**6a−p**) in modest to high yields. The reactions were performed in capped 2-dram vials without atmospheric controls and were usually complete within 2 h at room temperature. For each example, we prepared a solution of **5** in THF and sequentially added iPr$_2$EtN, silyl ketene acetal **2**, and PyBroP. A slight exotherm and color change were usually noted after the addition of the PyBroP. In general, electron-neutral/-rich azine-*N*-oxides performed most effectively in the transformation. Certain reactions were sluggish and required gentle heating to ensure reaction completion.[13] Pleasingly, most bromide-containing substrates were well-tolerated under our reaction conditions (**6g**, **6j−k**). Substrates with polar functionality and multiple heteroatoms all performed acceptably. Interestingly, the majority of the reactions showed no evidence of over-heteroarylation, which we observed in our original optimization study with pyridine-*N*-oxide.

In accord with our previous reports on the addition of nucleophiles to azine-*N*-oxides activated by PyBroP, we propose intermediate **7** (Figure 1) as the key mechanistic feature in this transformation. The counteranion of the phosphonium salt appears to be crucial for successful reactivity

Scheme 2. Substrate Scope for the Addition of Methyl *tert*-Butyldimethlysilyl Ketene Acetal to Azine-*N*-oxides[a]



[a]Unless otherwise noted, all reactions were conducted in 2 dram vials at 0.20 M concentration with **5** (1.00 equiv), **2** (2.00 equiv), iPr$_2$EtN (3.00 equiv), and PyBroP (1.10 equiv) at 25 °C. [b] 45 °C for 2 h.

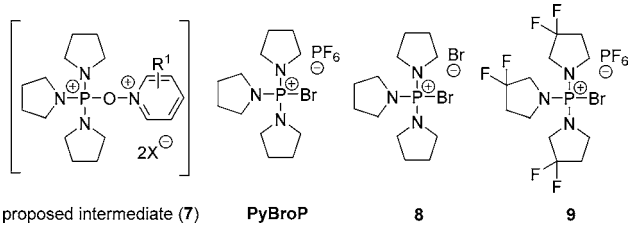


Figure 1. Proposed intermediate, PyBroP, and newly synthesized PyBroP derivatives.

with silyl ketene acetals. When we utilized PyBroP variant **8**, which contains a bromide counteranion, we observed no reactivity under our standard conditions. This suggests that the hexafluorophosphate counteranion of PyBroP is an important reaction component. Likely, equilibrium dissociation of fluoride from PF_6^- initiates silicon−oxygen cleavage for ketene acetal addition. In an effort to better understand the attenuated reactivity of certain azine-*N*-oxides, particularly those with electron-withdrawing groups, we prepared a novel PyBroP derivative (**9**) containing tris-3,3-difluoropyrrolidine and reassessed 4-trifluoromethylpyridine-*N*-oxide as a substrate (**6e**, from Scheme 2). As hypothesized, the enhanced electrophilic character of **9** significantly improved the yield of **6e** at room temperature when compared with PyBroP as the activator (51% vs 22% respectively).[14] This suggests that facile formation of intermediate **7** is critical to a robust outcome and that "designed" PyBroP-type reagents may be an effective means to enhance overall yields with substrates less inclined to form intermediate **7**.

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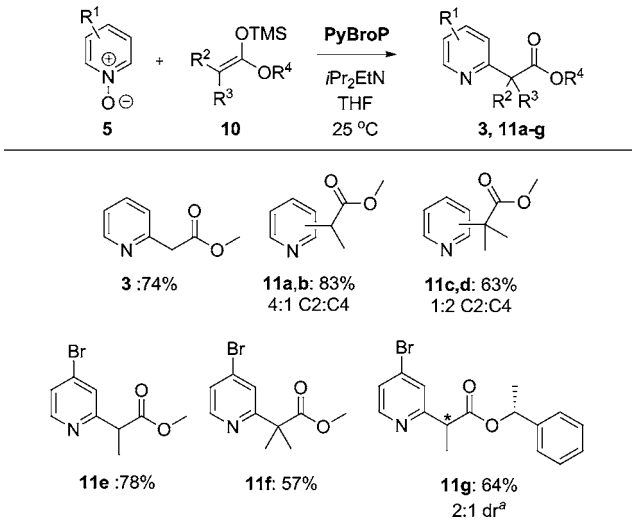
As shown in Scheme 3, we briefly assessed the competency of several trimethylsilyl ketene acetals with varied substitution

Scheme 3. Addition of Varied Trimethylsilyl Ketene Acetals to Azine-*N*-oxides[a]



[a]Unless otherwise noted, all reactions were conducted in 2 dram vials at 0.20 M concentration with **5** (1.00 equiv), **10** (2.00 equiv), *i*Pr$_2$EtN (3.00 equiv), and PyBroP (1.10 equiv) at 25 °C. [b] Determined by integration of ^{1}H NMR spectrum.

at the nucleophilic carbon. When R^2 and R^3 were equal to hydrogen and pyridine-*N*-oxide was utilized as a substrate, we obtained the expected product (**3**) in 74% yield. Surprisingly, when trimethylsilyl ketene acetals bearing methyl groups at the R^2 and R^3 position were utilized in the same transformation, we obtained a regioisomeric mixture of products (**11a−b** and **11c−d**), resulting from addition to both the 2- and 4-postion of pyridine-*N*-oxide. This loss of selectivity is contrary to the other examples reported here, as well as to those from our previous works, and is not fully understood. Nevertheless, these preliminary results suggest that steric bulk at the nucleophilic carbon may interfere with the critical charge association[15] we attribute to the usual regioselectivity. In further support of this hypothesis, when we compared the reactivity of analogous *tert*-butyldimethylsilyl ketene acetals (OTBS vs OTMS) in examples **11a−d**, we again obtained a mixture of isomers, albeit in lower yield. Azine-*N*-oxide substrates with substitution at the 4-position proceeded as expected and afforded single products (**11e−f**). Lastly, we determined if a silyl ketene acetal containing a chiral auxiliary might impart some degree of stereoselectivity if utilized in this transformation. Indeed, as demonstrated in example **11g**, we obtained a 2:1 diastereomeric ratio of products with an optically pure phenethyloxy-silyl ketene acetal.

In conclusion, we have presented a novel procedure for the synthesis of diverse α-(2-azaheteroaryl) acetates, which remains a challenge by contemporary methods. Our procedure is expedient, operationally simple, and tolerant of varied substrate functionality, including reactive bromides. This methodology should be of particular use in the synthesis of small molecule chemotherapeutics, where the incorporation of polarity is needed to control lipophilicity, increase beneficial drug/target interactions, and optimize drug-like properties. Our laboratory will continue to investigate the addition of silyl ketene acetals to azine-*N*-oxides with an emphasis on "designed" PyBroP alternatives and stereochemical induction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: allyn.t.londregan@pfizer.com.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(12) From our previous experimentation, we determined that competent nucleophiles were within a pK_a range of ∼10−20.
(13) Azine-*N*-oxide (<10%) by LCMS analysis.
(14) Although not shown in Scheme 2, example **6e** was prepared in 22% yield at room temperature utilizing PyBroP.
(15) A charge association of the incoming nucleophile with the distributed cationic charge and/or lone pairs of the tris-pyrrolidino moiety in **7** likely directs nucleophiles to the 2-position of the azine-*N*-oxide exclusively. See ref 9a.

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