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Samarium-Promoted Coupling of Pyridine-Based Heteroaryl Analogues of Benzylic Acetates with Carbonyl Compounds

Jeremy A. Weitgenant, Jonathan D. Mortison, and Paul Helquist*

Department of Chemistry and Biochemistry and Walther Cancer Research Center, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556

phelquis@nd.edu

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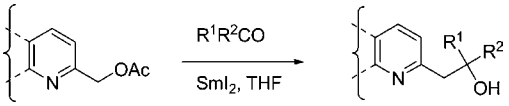
ABSTRACT



2-Substituted pyridine, quinoline, isoquinoline, bipyridine, and 1,10-phenanthroline analogues of benzylic acetates undergo SmI_2-promoted coupling with aldehydes and ketones to afford (2-hydroxyalkyl)heteroaromatics.

Simple one-step, metal-promoted coupling reactions represent a diverse set of synthetic methods for the construction of numerous classes of compounds. Among the many types of substrates that participate in these reactions are allylic esters.[1] Allylic acetates are especially commonly employed, due in large part to their facile, low-cost preparation. The participation of *allylic* acetates in coupling reactions is unique compared to ordinary *alkyl* acetates which show quite different patterns of reactivity mainly associated with nucleophilic acyl substitution and enolate chemistry. On the other hand, the special reactivity of allylic esters is due to electronic stabilizing influences on transition states and intermediates, commonly involving formation of η^3-allyl-metal complexes.

At least for certain types of reactions, parallel patterns of behavior are often seen in the reactivity of various types of allylic and benzylic systems, due to related stabilizing influences that operate in both systems. Although the more reactive benzylic halides are commonly employed in many types of reactions,[2] there is a dearth of reports on the use of benzylic esters in coupling reactions. Among their few uses are palladium-catalyzed coupling of benzylic carbonates with active methine compounds and amines,[3] Suzuki coupling with arylboronic acids,[4] Negishi coupling with arylzinc reagents,[5] Stille coupling with aryltin reagents,[6] hydroxy- or alkoxycarbonylation reactions,[7] and Heck olefination of benzyl trifluoroacetate.[8] In this paper, we report that certain heteroaryl analogues[3,c,e,4−6] of benzylic acetates undergo useful coupling reactions with aldehydes and ketones to give

(1) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163−3185.

(2) (a) Hamann-Gaudinet, B.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 6585−6588. (b) Bieber, L. W.; Storch, E. C.; Malvestiti, I.; da Silva, M. F. *Tetrahedron Lett.* **1998**, *39*, 9393−9396. Benzylic alcohols also undergo coupling with lanthanum metal in the presence of TMSCl, I_2, and CuI, most likely via formation of benzylic iodide intermediates: (c) Nishino, T.; Nishiyama, Y.; Sonoda, N. *Tetrahedron Lett.* **2002**, *43*, 3689−3691. (d) Nishino, T.; Nishiyama, Y.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 635−641. (e) Qian, M.; Neghishi, E.-i. *Tetrahedron Lett*. **2005**, *46*, 2927−2930. Benzyl ethers have also been activated for coupling: (f) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2004**, *45*, 3717−3720.

(3) (a) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509−2510. (b) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235−3246. (c) Legros, J.-Y.; Primault, G.; Toffano, M.; Rivière, M.-A.; Fiaud, J.-C. *Org. Lett.* **2000**, *2*, 433−436. (d) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104−12105. (e) Primault, G.; Legros, J.-Y.; Fiaud, J.-C. *J. Organomet. Chem.* **2003**, *687*, 353−364. (f) Legros, J.-Y.; Boutros, A.; Fiaud, J.-C.; Toffano, M. *J. Molecul. Catal. A−Chem.* **2003**, *196*, 21−25. (g) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545−3547.

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(6) Lindsey, C. C.; O'Boyle, B. M.; Mercede, S. J.; Pettus, T. R. R. *Tetrahedron Lett.* **2004**, *45*, 867−868.

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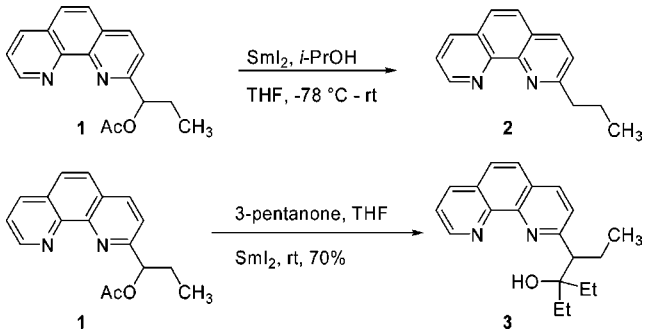
products having many potential synthetic uses. Among these products are pyridine and quinoline systems that are of interest in the natural products and pharmaceutical areas[9] and as ligands in metal coordination chemistry.[10]

One of the most versatile reagents for effecting a vast range of reductive transformations is samarium diiodide.[11] In its role as a single electron-transfer agent, SmI_2 has been employed in many different types of transformations, including couplings,[12] cleavages,[13] and cyclizations.[11i,12b,14]

Cleavages of suitably activated alkoxy groups are well-known, and Kato and co-workers have shown that 2- and 4-(1-acetoxyalkyl)pyridines are also cleaved when they are treated with SmI_2.[13h,l] Consistent with this precedent, we observed that when 2-(1-acetoxypropyl)phenanthroline (**1**) is treated with SmI_2, the acetate functionality is reductively cleaved yielding 2-propylphenanthroline (**2**) (Scheme 1).

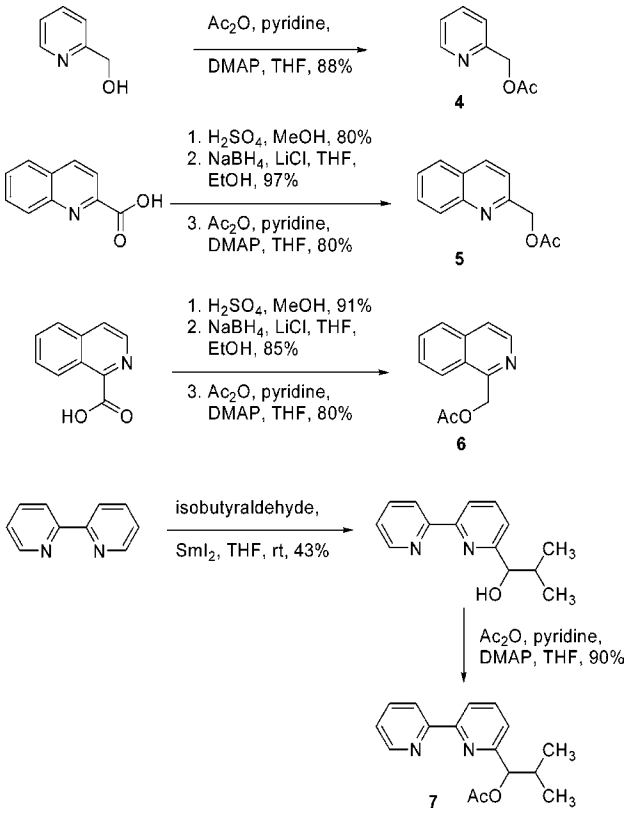
Scheme 1. SmI_2 Cleavage and Addition Reactions of a 1,10-Phenanthroline Derivative



However, when the same acetate **1** is treated with SmI_2 in the presence of a ketone, we have found that **1** undergoes a reductive coupling to give alcohol **3**.

Following this observation, we wished to perform a more thorough study to test the scope and limitations of this reductive coupling. We obtained the required substrates by either of two approaches (Scheme 2). In the simplest cases,

Scheme 2. Synthesis of Heterocyclic Acetates



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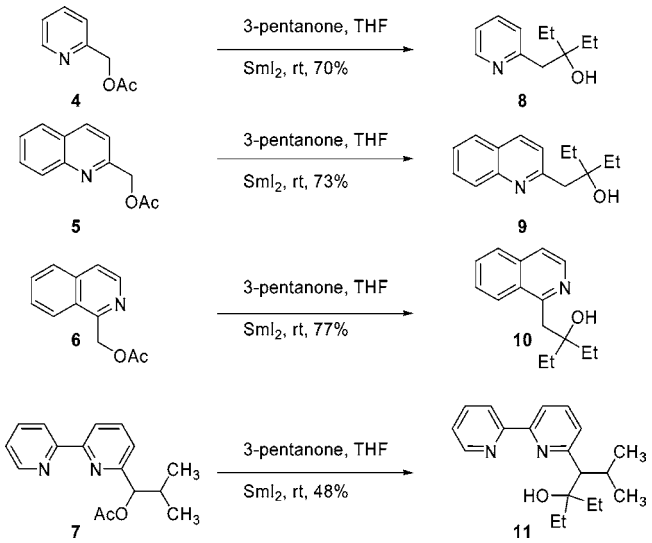
we began with conversion of commercially available pyridine-2-carbinol directly to the acetate derivative **4**, or by conversion of commercially available quinoline-2-carboxylic acid and isoquinoline-1-carboxylic acid into the corresponding ethyl esters followed by reduction with $NaBH_4$ and reaction of the resulting alcohols with acetic anhydride to give the acetates **5** and **6**.[15] In other cases, we extended our previously developed SmI_2-promoted coupling[16] of 1,10-phenanthroline with aldehydes and ketones to the analogous use of 2,2′-bipyridine. The resulting alcohol was then converted into acetate **7**.

Each of these heterocyclic benzylic acetates were then tested in the coupling reaction with aldehydes or ketones promoted by SmI_2. For instance, the corresponding pyridine derivative **4** was found to react with 3-pentanone to produce alcohol **8**. Likewise, the quinoline, isoquinoline, and bipyridine substrates all undergo the desired coupling reaction as shown by the formation of products **9** through **11** as representative examples in Scheme 3.

Scheme 3. Coupling Reactions with Heterocyclic Compounds

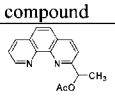
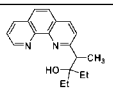
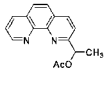
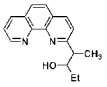
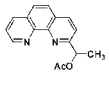
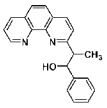
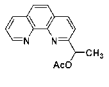
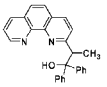
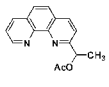
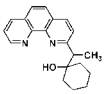
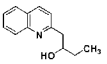
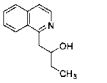
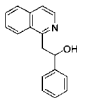


Several aldehydes and ketones were then used in coupling reactions with the various acetate substrates (Table 1). In certain cases, such as the coupling reactions using benzaldehyde (entries 3 and 8), pinacol coupling occurred as a competing reaction which led to lower yields of the desired products.

To determine whether these reactions are specific to compounds that have acetoxyalkyl groups adjacent to nitrogen in a heterocyclic system, a few other examples were tested. Treatment of 3-(acetoxymethyl)pyridine (**14**) with SmI_2 in the presence of 3-pentanone gave no coupled product, and the acetate was recovered unchanged (Scheme 4). Likewise, when 4-(acetoxymethyl)pyridine (**15**) was subjected to the same conditions, no coupling product was

(15) Oda, K.; Nishi, T. *J. Antibiot.* **1997**, 446−448.
(16) Weitgenant, J. A.; Mortison, J. D.; O'Neill, D. J.; Mowery, B.; Puranen, A.; Helquist, P. *J. Org. Chem.* **2004**, *69*, 2809−2815.

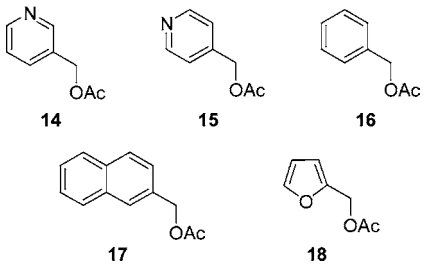
Table 1. Additional Examples of Coupling Reactions with Heterocyclic Compounds and Carbonyl Compounds

entry	carbonyl compound	heterocyclic compound	product	yield
1	3-pentanone			75%
2	propanal			86%[a]
3	benzaldehyde			50%[b]
4	benzophenone			26%
5	cyclohexanone			66%
6	propanal			52%
7	propanal			70%
8	benzaldehyde			25%

[a] This product was isolated as a mixture of diastereomers. [b] This product was isolated as a mixture of diastereomers as well as the cleavage product (Scheme 1).

observed. Treatment of benzyl acetate (**16**) with SmI_2 in the presence of 3-pentanone gave only starting material as well. Also, when 2-(acetoxymethyl)naphthalene (**17**) was subjected to the coupling reaction conditions, no product was observed. One final reaction was attempted using 2-furfuryl acetate (**18**) to see whether the reaction was specific to nitrogen-containing heterocycles, but a complex mixture of products resulted. This reaction must be investigated in more detail. From these results, we can conclude that the new coupling reaction is dependent upon the use of heteroaromatic systems having a benzylic acetate attachment point immediately adjacent to the heteroatom. Unlike some benzylic ester coupling reactions,[3−7] carbocyclic systems or heterocyclic

Scheme 4. Other Substrates Used in Attempted Coupling Reactions



systems having the heteroatom more remotely situated from the benzylic site are not suitable substrates. The reaction seems to be driven through chelation of samarium to the ring heteroatom and the acetate which allows it to compete effectively with pinacol coupling in most cases. This chelation effect may also be the reason that the 3- and 4-substituted pyridines are unsuitable substrates for the coupling reaction. Although 4-(1-acetoxyalkyl)pyridines have been cleaved with SmI_2, the coupling reaction using nonchelating 4-substituted substrates may not proceed effectively enough to compete with the pinacol coupling reaction.[13h,l]

These SmI_2-promoted couplings provide a very direct method for efficient functionalization of various heterocycles, including 2-substituted pyridines, quinolines, isoquinolines, bipyridines, and phenanthrolines with carbonyl compounds. These reactions should find wide application in heterocyclic chemistry in general, including alkaloid synthesis and the preparation of pharmaceutically important compounds. Good potential exists for developing catalytic and enantioselective versions of these reactions, for extending these reactions to imines and other substrates, and for using these reactions to produce ligands for use in metal-promoted reactions. Our ongoing investigations are focusing on these points.

Acknowledgment. We thank Procter & Gamble Pharmaceuticals and the University of Notre Dame for financial support of this research, and we acknowledge collaboration with the Walther Cancer Institute. J.D.M. thanks the Beckman Foundation for a research fellowship.

Supporting Information Available: Details for the preparation of compounds **1**−**11**, the products from Table 1 as well as their precursors and ^1H and ^{13}C NMR data for compounds **1**−**11**, and the products from Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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