Use of the Stille Coupling Reaction on Heteroaromatic Cations: Synthesis of Substituted Quinolizinium Salts

ORGANIC LETTERS 1999 Vol. 1, No. 4 545-547

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Received April 30, 1999

ABSTRACT



We describe the first efficient application of the Stille coupling reaction on heteroaromatic cations. In the presence of Pd(0)/Cul, the reaction of bromoquinolizinium salts and various tributylstannyl compounds proceeds in satisfactory yield under mild reaction conditions, affording different substituted quinolizinium salts.

The palladium-catalyzed cross-coupling reaction of organostannanes with organic electrophiles (usually halides or triflates), known as the Stille reaction,¹ has emerged as an extremely powerful tool for C–C bond formation.² Although this methodology has been applied to a variety of heterocyclic substrates,³ a cross-coupling route involving heteroaromatic cations such as azinium or quinolizinium salts has not been previously described.

As part of a project focused on the development of a novel class of DNA intercalators based on quinolizinium and azaquinolizinium-type systems 1,⁴ and subsequent transforma-

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10.1021/ol990626y CCC: \$18.00 © 1999 American Chemical Society Published on Web 07/22/1999

tion into bis-intercalators 2 with chromophores linked by chains with different length, rigidity, and functionality (see below), we examined the feasibility of using a palladium-



mediated catalyzed coupling reaction as a means of introducing different aryl/heteroaryl substituents and aliphatic side chains in 1 in order to improve their intercalating properties

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as well as their antitumor activity. In this Letter, we report our initial results on the transformation of some quinolizinium salts **3**, as simple models, into substituted quinolizinium derivatives **4** (Scheme 1) via the Stille coupling reaction.

Our efforts to achieve a cross-coupling route to quinolizinium derivatives focused on the 1- and 2-bromoquinolizinium salts. The bromo derivatives **3**, being accessible substrates to study the reactivity of the 1- and 2-bromoquinolizinium salts in various coupling processes, were prepared in several steps by standard procedures.⁵

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We initially examined the coupling process with 1-bromoquinolizinium salt **3a** and tributylvinylstannane to establish the best reaction conditions in the presence of 5 mol % of PdCl₂(PPh₃)₂ as the catalyst and in dimethylformamide (DMF) or tetrahydrofuran (THF) as the solvents at different temperatures. In all experiments, however, we found only extensive decomposition of the substrate. In addition, under the above conditions, the same procedure was tested in the presence of 3 equiv of LiCl⁶ in DMF, a solvent that can both solubilize lithium chloride and act as a ligand for palladium. The reaction products, however, contained only starting material. In the presence of 3 equiv of LiCl in DMF, the use of tetraphenylstannane instead of tributylvinylstannane produced homo-coupling of the heterocycle^{7,8} in a 44% yield after 12 h of heating at 85 °C.

After further experiments, the desired coupling reaction was reproducibly obtained from **3a** and tributylvinylstannane in the presence of 5 mol % of Pd(PPh₃)₄, in DMF at room temperature, and with the addition of 10 mol % of copper-(I) iodide as a cocatalyst. The reaction was completed in 17 h, producing 1-vinylquinolizinium (Table 1, entry 1) in a 55% yield, with CuI being essential for success of the reaction. The beneficial effect of the Cu(I) salts in cross-coupling reactions has been previously observed.⁹ Although the exact role of copper is not clear, transmetalation of the R groups has been suggested.⁹c

Starting with 3a, alkenyl, alkynyl, and heteroaryl groups on tin were all transferred in high yield (entries 1-3). By comparison, the same coupling of 2-bromoquinolizinium **3b** with tributylvinylstannane under optimized conditions¹⁰ produced the desired substituted compound, although in poor yield (entry 4). Similarly, coupling of **3b** with phenylethy-nyltributylstannane and 2-thiophenyl- and 2-furanyltributyl-stannane produced yields ranging from good (entry 6) to moderate (entries 7 and 8). On the other hand, heating (85 °C) was required in the coupling with tetraphenylstannane to obtain the 2-phenylquinolizininium salt (entry 5) in a 60% yield.

The method was further extended to tributylstannylpyridine, -thiazole, and -pyrazole, which were prepared according to previously reported procedures.¹¹ The results of the crosscoupling with 2-bromoquinolizinium was successful for the thiazole and pyrazole derivatives (entries 9 and 10) and, as anticipated, resulted in a lower yield with the more electrondeficient pyridine (entry 11).

The above methodology, however, is limited to the transfer of alkyl groups. Our experiments with tetramethylstannane were unsuccessful and it is generally accepted that an sp³ carbon directly attached to the metal is less reactive than carbons with lower hybridization in Pd-catalyzed reactions,^{1d} which likely accounts for the lack of reactivity observed.

In summary, a new and simple route to substituted heteroaromatic cations, with a bridgehead quaternary nitrogen, was developed involving palladium-catalyzed crosscoupling between bromoquinolizinium and various aryl, heteroaryl, vinyl, and ethynyl stannanes. This method expands the scope of the Stille reaction and provides a good alternative for substitution of quinolizinium derivatives, which are usually very unstable when in contact with nucleophilic species.

Acknowledgment. We wish to express our thanks for financial support to the Comisión Interministerial de Ciencia y Tecnología (CICYT, Project SAF98-0093).

OL990626Y

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