A Direct Synthesis of 6-Pyridinyl-2(1H)-quinolinones via Palladium-Catalysed Cross-Coupling Reaction

Andrew S. Bell, David A. Roberts, Keith S. Ruddock

Pfizer Central Research, Sandwich, Kent, England, CT13 9NJ

Pyridinylzinc chlorides were treated with 6-haloquinolinones in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to give the corresponding 6-pyridinylquinolinones in moderate to high yields.

Recently, we required a versatile synthesis of various pyridinyl-substituted 2(1H)-quinolinones as part of a programme designed to identify novel cardiac stimulants. Previous approaches to heterocyclic-substituted quinolinones involved inconvenient, separate construction of either the pendant heterocyclic ring, or the quinolinone system. Numerous examples of the application of palladium-catalysed cross-coupling methodology to the heterocyclization of pyridines have been reported; however, extension to pyridione or quinolinone systems has been limited to a single recent example but the reported yield was very low.
We now report the direct synthesis of 6-pyridinyl-2(1H)-quinolines 4 by palladium-catalysed cross-coupling of pyridinylzinc chlorides 2 with haloquinolines 3 (X = Br, I). Compounds 2 are readily obtained by transeuction of pyridinyllithium or pyridinylmagnesium halides (I) with zinc chloride.

Thus, treatment of quinololines 3 with a two-fold excess of pyridinylzinc reagent 2 in tetrahydrofuran at reflux under a nitrogen atmosphere in the presence of a catalytic amount of tetakis(triphenylphosphine)palladium gave products 4a-f (Table). An excess of the pyridinylzinc reagent is required, presumably because deprotonation of the acidic NH occurs initially. Consequently, the quinololine system is somewhat deactivated towards coupling, and iodo- rather than bromo-quinololines are preferred since reaction times are shorter and yields higher.

The reaction offers a versatile, regioslective synthesis of a wide range of pyridinyl-2(1H)-quinololines in a single step. The method has the advantage of experimental simplicity, ready accessibility of the reagents, and tolerance of ortho-substituents (products 4d–f). The scope of the reaction and extension to other heterocyclic systems is under investigation.

IR spectra were recorded with a Perkin-Elmer 983 infrared spectrophotometer. 1H-NMR spectra with a General Electric QE-300 NMR spectrometer.

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(1) Present address: ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, England.
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