Polysubstituted Pyridines via Re-Catalyzed Alkyne Insertion

Significance: Reported is a de novo synthesis of multisubstituted pyridines via a regioselective reaction of terminal or internal alkynes with N-acetyl β-enamino ketones catalyzed by Re₂(CO)₁₀. In this reaction, substituents (R¹ and R²) appear at the 3- and 4-positions of the pyridine products with regioselectivity. The proposed mechanism involves a cyclobutenone intermediate generated from oxidative cyclization (1) followed by reductive elimination (2). After C–C bond cleavage by a retro-aldol-type reaction (3), intramolecular cyclization (4), and elimination of acetic acid (5) leads to the pyridine product. A reasonable scope of substrates was investigated. For terminal alkynes, improved regioselectivity was observed when starting N-methoxy carbonyl β-enamino ketones (R⁶ = OMe) were employed.

Comment: Aside from the widely used classical Hantzsch synthesis of pyridine derivatives, many recent methods for highly substituted pyridine synthesis have been developed which involve reactions of transition-metal-catalyzed C–H activation followed by C–C bond formation (R. M. Martin, R. G. Bergman, J. A. Elman J. Org. Chem. 2012, 77, 2501). In these reactions, use of unsymmetrical alkynes as starting material often leads to a mixture of regioisomers. The present method is based on a previously reported Re-catalyzed terminal alkyne insertion into 1,3-dicarbonyl compounds developed in the same group (Y. Kuninobu, A. Kawata, K. Takai J. Am. Chem. Soc. 2006, 128, 11368) and provides a new regioselective synthesis of polysubstituted pyridines. The catalyst Re₂(CO)₁₀ is commercially available from Strem Chemicals Inc. at $248.00/5 g.