Category

Synthesis of Heterocycles

Key words

pyridones

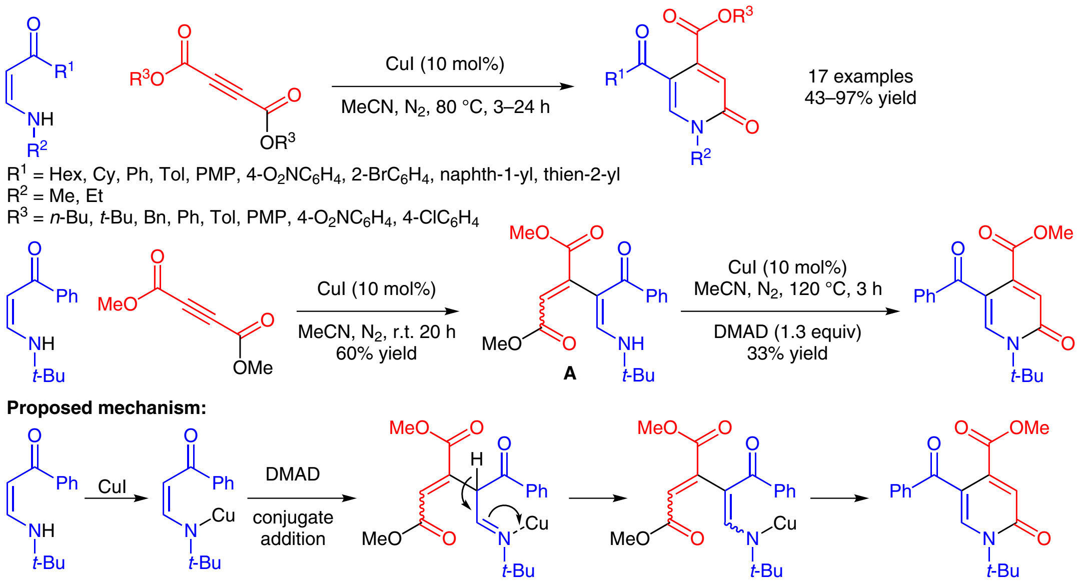
enaminones

alkynes

copper catalysis

Y. SHAO, W. YAO, J. LIU, K. ZHU, Y. LI* (EAST CHINA NORMAL UNIVERSITY, SHANGHAI, P. R. CHINA)
Copper-Catalyzed Selective Synthesis of Highly Substituted Pyridones by the Reaction of Enaminones with Alkynes
Synthesis **2012**, *44*, 3301–3306.

De Novo Synthesis of Pyridones From Enaminones and Alkynes



Significance: Reported is the copper-catalyzed synthesis of substituted pyridones from the reaction of dialkyl acetylenedicarboxylates with enaminones. Although simple dialkyl acetylenedicarboxylates (e.g. dimethyl acetylenedicarboxylate, DMAD) are commercially available, the enaminones must be synthesized. A method for their synthesis was not explicitly disclosed, but a quick search of the literature provides several different methods (e.g. a one-pot Sonogashira coupling of an acid chloride with ethynyltrimethylsilane followed by the addition of an amine and methanol; A. S. Karpov, T. J. J. Müller *Org. Lett.* **2003**, *5*, 3451). A mechanism for the reaction was proposed and studied through the isolation of intermediate **A**. This was re-subjected to the reaction conditions but did not generate product until more DMAD was added and the temperature was raised. This suggests that DMAD may be involved with the copper in generating a catalytically active species for the subsequent cyclization.

Comment: Pyridones are important building blocks for the synthesis of substituted pyridines and other heterocycles and also represent pharmacologically relevant structures in their own right (e.g. M. A. Ciufolini, B. K. Chan *Heterocycles* **2007**, *74*, 101). Thus, the current method should be a useful addition to the plethora of established synthetic routes as it operates under mild conditions and uses inexpensive and easily synthesized starting materials. The reaction was optimized with respect to catalyst, catalyst stoichiometry and solvent. In addition, it was found that the reaction must be conducted under inert atmosphere to avoid the formation of pyrrole byproducts. The substrate scope was modestly examined and showed that the yields are generally good for enaminones with electron-donating groups and good to moderate for enaminones with electron-withdrawing groups. The reaction was relatively insensitive to the electronics of the enaminone carbonyl unit.

SYNFACTS Contributors: Victor Snieckus, Johnathan Board
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