Copper(I)-Catalyzed Synthesis of 3-Amino-2-pyrones and 2,5-Dihydrofurans

Significance: Reported is a three-component reaction of propargyl alcohols, aldehydes, and amines under copper(I) catalysis to form 3-amino-2-pyrones and 2,5-dihydrofurans. It follows a previous report from the Ma laboratories in which the same components afforded allylic amines (Nat. Commun. 2014, 5, 3884). The difference appears to be that the aldehyde component is ethyl glyoxylate; there is little if any modification of the reaction conditions or the catalyst. Consideration of the readily derived mechanism of the reaction allows formulation of the 2-pyronone 1 as the expected product resulting from mild (silica gel) acidic treatment of isolated intermediate 2, R = OEt, which in turn results from an allene precursor. A rational consideration that EWG in the aldehyde component would encourage formation of the furan ring was confirmed by using glyoxal and the isolation of dihydrofurans 2, R = Ph. A reasonable mechanism is given which, although proceeding via isolated 2, lacks further definition especially in terms of graphical representation of copper involvement. Both processes were tested with at least ten examples each, thus sufficient to justify giving these new processes general status.

Comment: The significance of 2-pyrones and dihydrofurans as units possessing biological activity, selective COX-1 inhibition, and as structural units of bioactive natural and unnatural products, respectively, is noted. Fourteen optimization experiments established the best conditions as shown. Scope for R1 = alkyl, benzyl, aryl, and R2, R3 = substituted pyrrolidinyl, piperidinyl, and one case of dibutyl was established for the 2-pyronone synthesis, while mainly R2, R3 = piperidinyl derivatives for the dihydrofurans were obtained. In the glyoxal study, as expected, EWG = NO2 led to poor yields of product. Experiments were carried out in a flame-dried Schlenk tube under argon atmosphere. Significance of this work would have been increased if further transformation of products 1 and 2 would have been carried out or noted (for example, for 1, use for Diels–Alder chemistry).

R1 OH + HOOEt 1) CuBr (20 mol%) 1,4-dioxane, 4 Å MS 40 °C, 14 h 2) silica gel PhMe, 50 °C

31 examples 43–78% yield

n = 1, R = OEt, 55% yield
n = 2, R = Ph, 70% yield

n = 1, R = OMe, 52% yield >99% ee
n = 2, R = Bz, 44% yield

Category: Synthesis of Heterocycles
Key words: pyrones, dihydrofurans, C–H activation, copper catalysis, multicomponent reaction

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