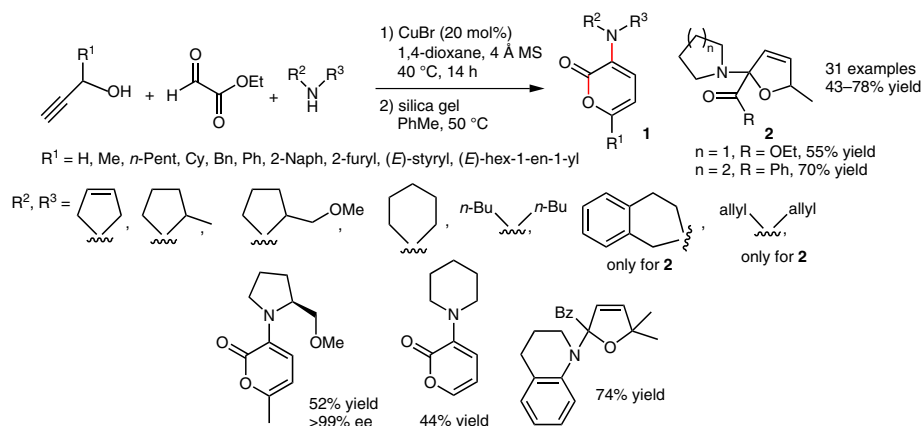


Copper(I)-Catalyzed Synthesis of 3-Amino-2-pyrones and 2,5-Dihydrofurans



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-pyrone **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.

SYNFACTS Contributors: Victor Snieckus
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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-pyrone 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 at 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).