Cu-Catalyzed Pyridine Annulation via Oxidative Reaction of Cyclic Ketones with Propargyl Amine

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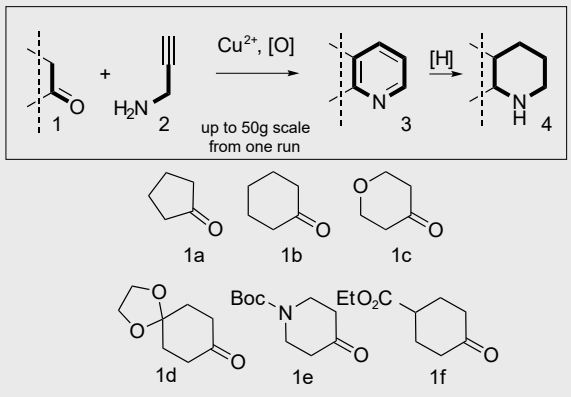
Introduction and Aim

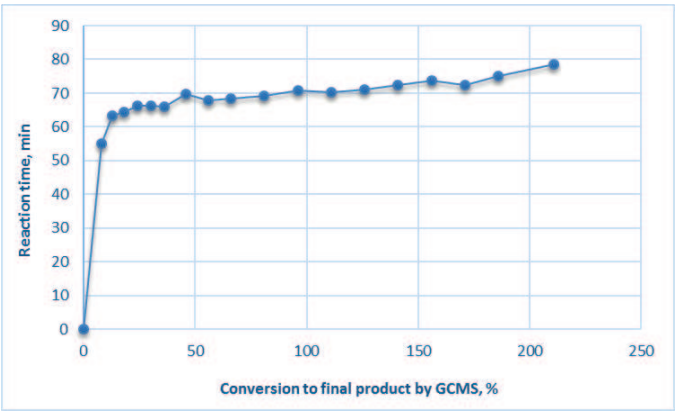
Since the discovery of gold-catalyzed one-step amination/annulation/aromatization reaction of carbonyl compounds and propargylamine by Abbiati *et. al* in 2003 this reaction has been widely used for synthesis of functionalized pyridines. This approach allows to prepare various compounds which are hardly accessible by other synthetic routes. At present the dominating majority of reported reactions of this type were performed at presence of Au^{III} compounds or Au nanoparticles. Development of reliable method to perform this reaction at presence of 3d metals is challenging task.

In this study we have shown that a series of cyclic ketones **1** reacted with propargylamine **2** at presence of Cu^{II} compounds ($CuCl_2$, $Cu(NO_3)_2$, $Cu_2(btc)_3$, where btc^{3-} is 1,3,5-benzenetricarboxylate) at ambient pressure upon heating with reflux.

The reaction mixtures were analyzed by HPCL and GC, while the products were identified by NMR and HPLC. It was found that $CuCl_2$ and $Cu(NO_3)_2$ as catalysts led to comparable results, while performance of $Cu_2(btc)_3$ was lower. In all cases aromatization of presumable dihydropyridine intermediate occurred due to reaction with air oxygen. The method proposed allowed to achieve 40-70 % yields of pyridines **3**. The methodology was suitable for multigram scale synthesis up to hundreds grams, which was shown on compounds **3d-f**. The scope and limitation of the reaction was determined. Compounds represented in the result section were synthesized in tens grams scale. The possibility of the reducing of the pyridine ring by catalytic hydrogenation was also demonstrated. The examples of appropriate piperidines was obtained in high yields.

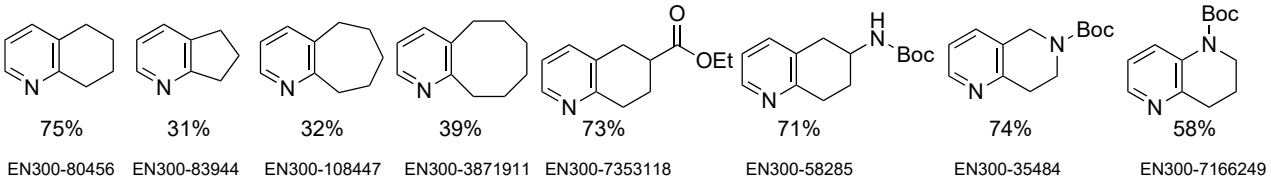


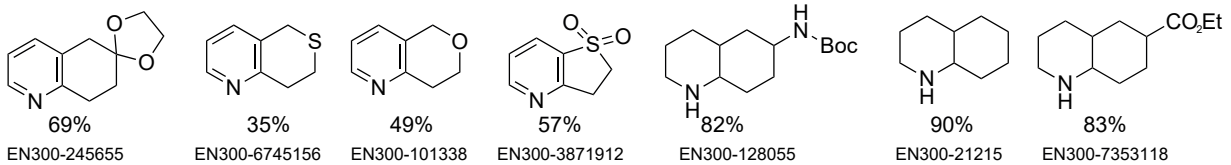
Optimization



reaction time, min	conversion by GCMS, %
0	0
8	54,98
13	63,39
18	64,37
24	66,15
30	66,15
36	66,08
46	69,6
56	67,96
66	68,42
81	69,11
96	70,88
111	70,25
126	71,07
141	72,27
156	73,79
171	72,42
186	75,17
211	78,6

Results





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