COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITION IN THE SYNTHESIS OF A TRIAZOLE-ANNULATED CYCLONONYNE

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Bioorthogonal chemical click-reactions are becoming more and more important nowadays. It is known that azido group is the excellent choice for bioorthogonal bioconjugation either through Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) [1,2] or Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC) [3], because neither azides nor alkynes present in natural biopolymers (glycans, proteins, nucleic acids).

SPAAC has several advantages over CuAAC "click" transformation, i.e. faster kinetics and avoiding of toxic affection of Cu(I) ion to cells and organisms [3]. However, CuAAC is known as the most convenient way for the synthesis of triazoles because of its superior regioselectivity and tolerance in the presence of many functional groups [2].

The main purpose of our work was to use CuAAC of iodalkynes [4] as a key step in the synthesis of new triazole-based SPAAC reagent **8**. The target triazole-fused cyclononyne **8** has two important structural features to maintain the optimal stability-reactivity balance: the fused triazole ring and the endocyclic nitrogen atom at the propargylic carbon atom.

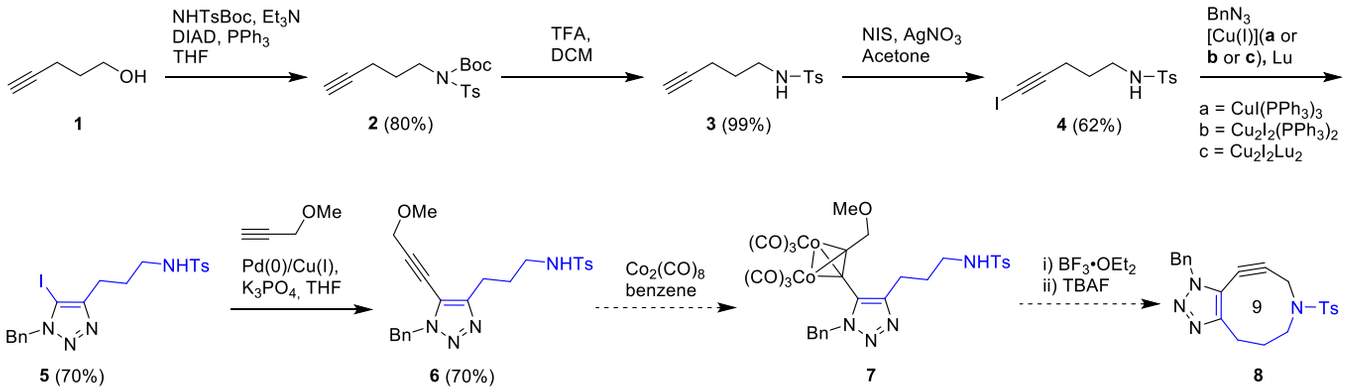

Figure 1. Supposed scheme of synthesis

The starting for CuAAC iodoalkyne **4** with the essential NHTs group was synthesized using standard chemical transformations (Fig. 1). CuAAC of iodoalkyne **4** was carried out using three different complexes of Cu(I) (**a-c**) in the presence of 2,6-lutidine (Lu) [5,6]. The highest yield of **5** was achieved using $CuI(PPh_3)_3$ catalyst. The absence of solvent and the presence of Lu was crucial; the yield of 5-iodotriazole **5** under solvent free conditions was 70%, while an attempt to carry out the reaction in THF gave only unconverted starting materials.

The next step of our research was to test whether the triazole **5** is suitable for the Sonogashira coupling. The Sonogashira reaction proceeded in high yield with the formation of desired alkyne for the further Nicholas-type cyclization, which is currently being studied.

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