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A robust and scalable synthesis of cis- and trans-fused octahydropyrrolo[2, 3-c]azepin-4(5H)-ones via aza-Cope-Mannichre arragement

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The aza-Cope rearrangements are examples of heteroatom versions of the Cope rearrangement, which is a [3, 3]-sigmatropic rearrangement that shifts single and double bonds between two allylic fragments. The most common and synthetically useful strategy couples the cationic 2-aza-Cope rearrangement with a Mannich cyclization. This tandem reaction is well fit for pyrrolidine compound array generations. The aza-Cope-Mannichtandem reaction is characterized by mild reaction conditions, diastereoselectivity, and a wide synthetic versatility. It provides easy access to acyl-substituted pyrrolidines, a structure commonly found in natural products such as alkaloids, and has been used in the synthesis of a number of them, notably strychnine and crinine. With cyclic amino alcohols substrates, this transformation leads to ring-enlarged pyrrolidine annulated products. Because of the restricted conformational freedom in the transition state, this variant of the aza-Cope-Mannich reaction occurs without loss of enantiomeric purity of the starting amino alcohol and usuallyleads to an excellent stereoselectivity. In a recent work, the author and his team have reported a case of a highly stereo-controlled synthesis of *trans*-fused octahydrocyclohepta[b]pyrrol-4(1H)-ones via the aza-Cope-Mannich rearrangement in either the racemic and enantiopure forms. In order to enlarge the medicinal chemistry reaction portfolio, we have evaluated the possibility of extending this technology for the synthesis of more complex ring systems such as 5, 7-fused heterocyclic systems and their pyrrolidine-based derivatives. There are 2 major drawbacks for these methods. The first one is the necessity of developing a robust synthetic method for the production of the starting amino alcohols to be used as substrates for the aza-Cope-Mannich reactions. The second drawback is linked to the correct stereoselectivity assessment. These drawback factors can be tackled by adjusting a synthetic methodology used for the synthesis of trans octahydropyrrolo[2, 3-c]azepin-4(5H)-ones, previously developed, which can be applied to this case just with minor modifications. The amine 6 was effectively synthesized in five steps with excellent overall yield of 60%. All steps were very handy to perform. Due to the robustness of the synthetic method developed and to its easy scalability, we manage to achieve the desired compound in gram quantities (>10g). In order to generate the required heterocyclic ketones, we have investigated the aza- Cope -Mannich reaction conditions of the starting alcohol and the formaldehyde by using a set of different solvents. This ultimately allowed us to synthesize a separable mixture of trans- and cis-products, with one isomer predominance. This work demonstrate the synthetic flexibility of our previous methodic and how well it can be used, just by minor variations, for the synthesis of complex cis and trans fused heterocyclic systems such the octahydropyrrolo[2, 3-c]azepin-4(5H)-ones.

Biography

Alexander V Kurkin received his PhD in Chemistry from the Lomonosov Moscow State University where he continued his academic carried by achieving a postdoc fellowship in the 2002, an Associate Synthetic Chemistry Professor position in 2004, eventually become Assistant Professor in 2007 and full Professor in 2010. He is currently holding a Deputy Dean position at the Moscow State Chemistry Department. With his group, he published over 40 international research publications on the synthesis of heterocyclic and natural product-like compounds, plus two chemistry books: Basic of Organic Chemistry (Binom 2010) and Drug Synthesis Principle (Binom 2010). He received several scientific awards among them the “Heterocyclic Chemistry Award 2009” and very recently the “Russian Foundation for Basic Research 2013 Award”. Since the 2005, he is a chemistry consultant for BASF Russia, and other Russian based chemistry organizations. In the 2008 founded and started EDASA Scientific, a Chemistry Service Driven Organization, where he is currently holding the CEO position.

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