Synthesis of cotinine and iso-cotinine analogs using an Ugi-4CR approach

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The nocive side effects that tobacco consumption has on human health continue to be the subject of numerous studies to better understand the relation between nicotine and its secondary metabolites with the central nervous system (CNS). Cotinine, the main metabolite of nicotine has proved to be less toxic than nicotine itself, apart from not having addictive or cardiovascular effects on humans, despite the structural similarity between both molecules. Pre-clinical studies have shown that cotinine facilitates the elimination of fear memories and improve attention and working memory in a model for Alzheimer disease (AD), reduce fear and anxiety of post-traumatic stress disorder (PTSD), as well as antipsychotic drug-like properties.

Despite the outstanding biological profile of cotinine, there is a lack of efficient synthetic methods that allow the preparation of this molecule and its derivatives, and the known procedures for their construction rely mainly on the C-H oxidation at C-2 from the corresponding nicotine analogs using highly toxic oxidants.

We present a convenient base-mediated two-step synthesis of cotinine analogs and a one-pot base-free synthesis of iso-cotinine derivatives featuring an Ugi-4CR/cyclization protocol.