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Efficient synthesis of pharmaceutical relevant *N*-nitrosamines under flow reaction conditions

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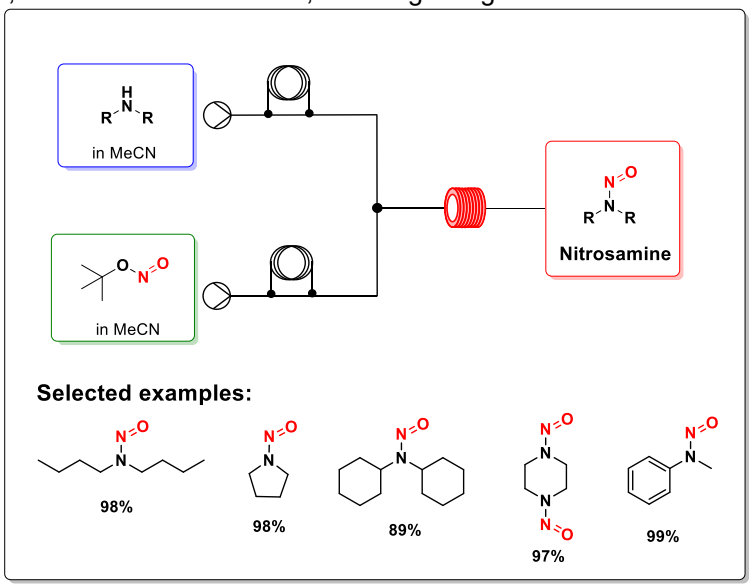
ABSTRACT

A detection of pharmaceutical impurities, such as nitrosamines, has become a significant concern in the industry since their presence was discovered in Sartan class medications around mid-2018. *N*-nitrosamines are nitroso compounds known for their carcinogenic potential in animals[1]. Traditionally, synthesizing these nitrosamines involves nitrous acid, generated in situ by reacting sodium nitrite with mineral acids[2]. In our study, we explored an alternative to this classic synthesis, using tert-butyl nitrite (TBN) as a nitrosating agent via continuous flow reactions (Scheme 1). TBN stands out for its competitive cost, good reactivity, and solubility in common synthetic solvents[3]. Additionally, its application in continuous flow processes is advantageous due to moderate volatility and the formation of tert-butanol as a benign by-product, facilitating its removal from the reaction medium[4]. This approach has demonstrated potential in synthesizing nitrosamine derivatives under solvent-free, metal-free, and acid-free conditions, ensuring straightforward isolation and high yields[5].



Scheme 1. Continuous flow reactions proposed in this work.

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