Reduction of variously functionalized nitroxides through catalytic flow synthesis

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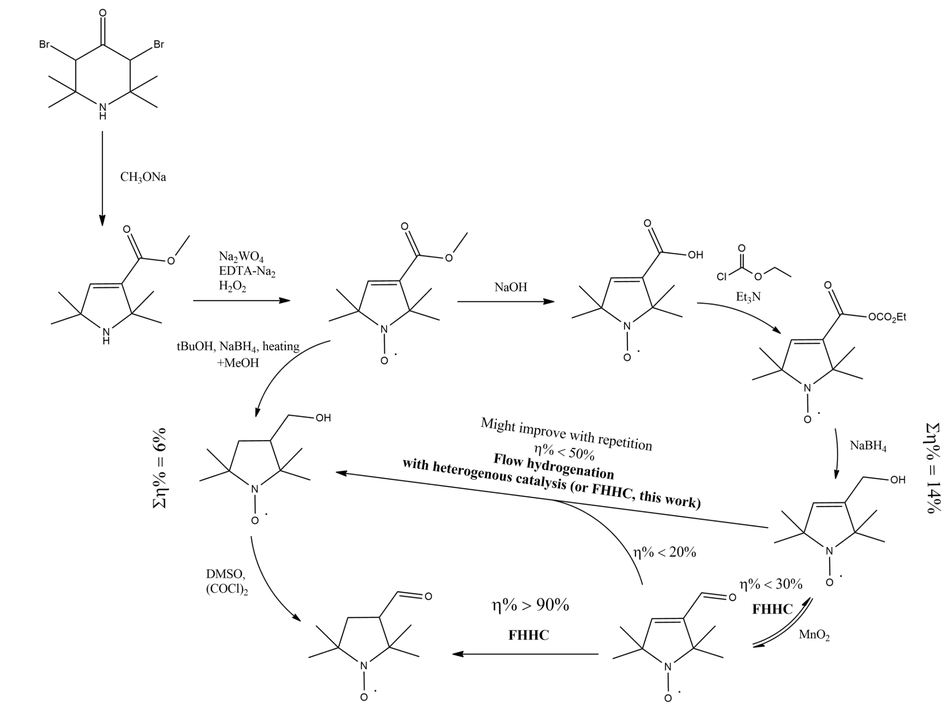
Abstract

Catalysed reduction reactions are important for many organic syntheses, its combination with flow synthesis results in efficient green chemistry processes. To our knowledge, its applicability in the presence of nitroxide stable free radicals has not been investigated. In this study we wanted to shed light on how reductions happen in the case of variously functionalized nitroxides, because the synthesis of saturated ring-containing nitroxides is more complex than that of their unsaturated analogues. As a second aim we investigated how the nitroxide group behaves under pressure and temperature changes in flow reductions. While the reduction of the nitroxide group was unavoidable we found that other functional groups are readily reducible under mild conditions. The reduction of nitroxide to amine is favoured by elevated in temperature, even at high pressure the nitroxide group is less affected, indicating that pressure can help control secondary group reductions. We hope that this work will prove to be helpful in the selective synthesis of pyrrolidine- and piperidine-type stable free radicals with a green methodology.

Introduction

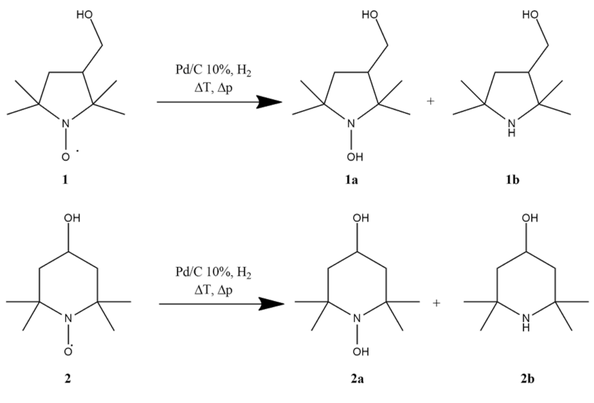
The synthesis of pyrrolidin and piperidine type nitroxides are generally more complex[1] and afford lower yields than their unsaturated counterparts, they are also desirable because of their better redox properties. Catalytic reduction of the endocyclic carbon–carbon double bond circumvents this limitation, and its implementation under heterogeneous flow conditions offers a more sustainable, green chemistry solution[2]. We used an H-Cube® Mini Plus reactor for the experiments



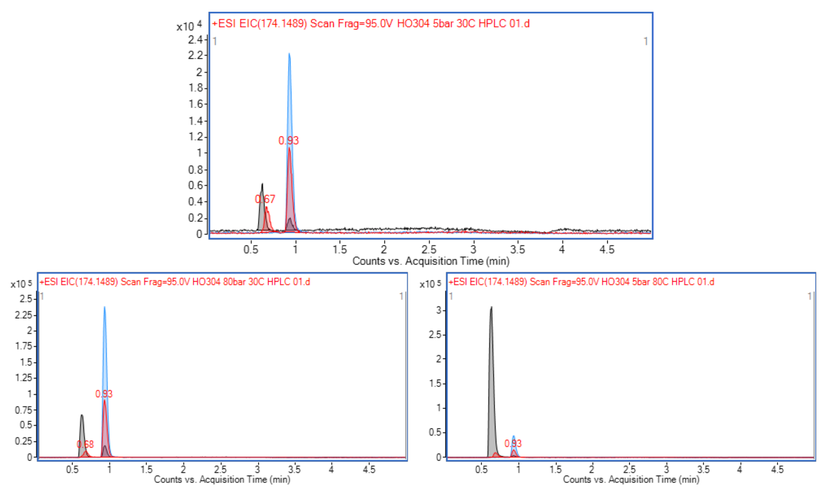
A general route of nitroxide synthesis

Results

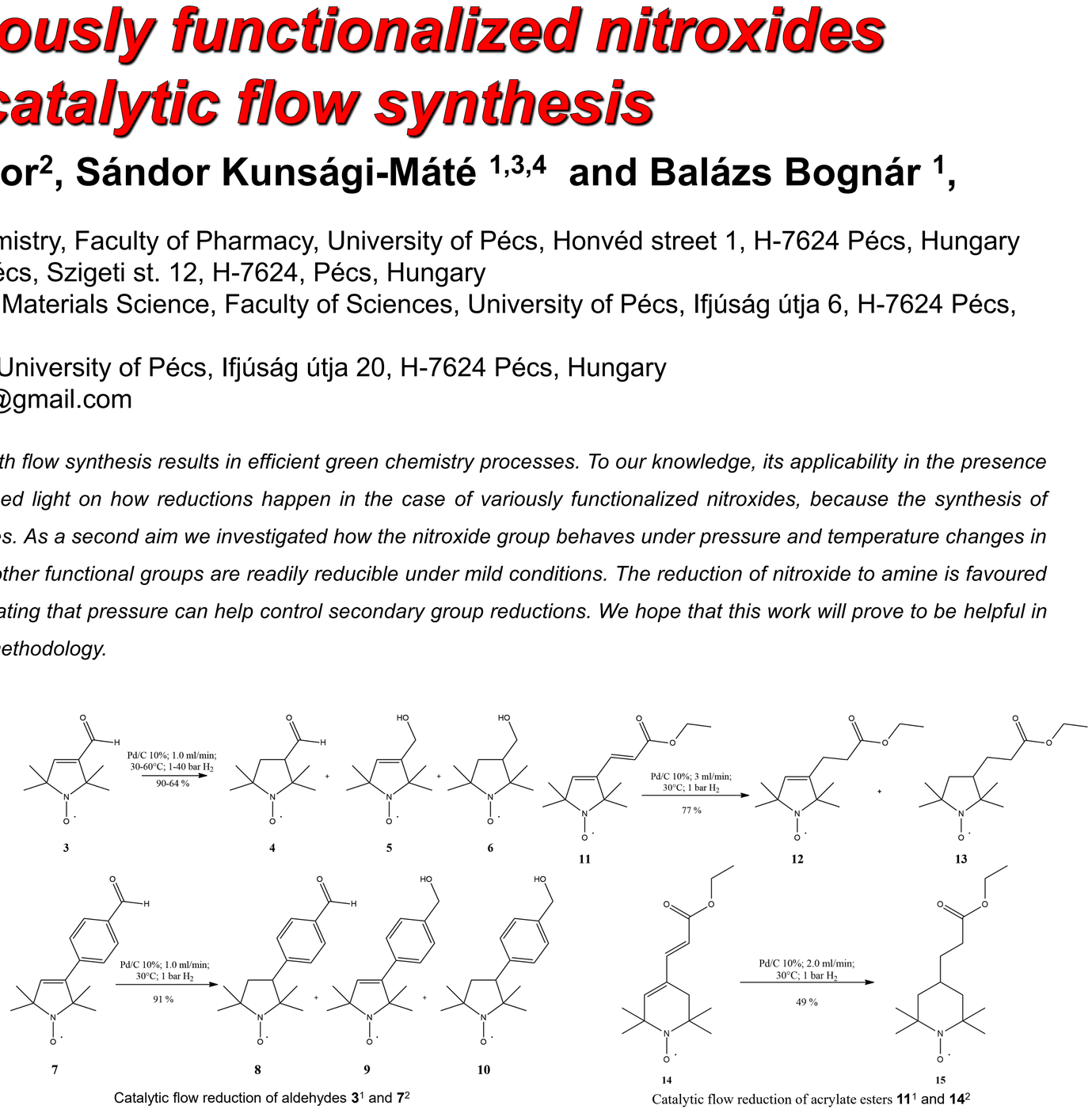
Nitroxides can take many redox states however the main ones in catalytic reduction are the amine and hydroxylamine. Paramagnetic pyrrolidine and piperidine alcohols (**1**, **2**) was chosen to investigate the ratio of amine-hydroxylamine/nitroxide ratio under various pressure and temperature conditions We found, that elevated temperature lead mainly to amine, while the increase of pressure results mostly in the corresponding hydroxylamine/nitroxide pair.



	1			2		
	5 bar, 30 °C	*80 bar*	*80 C°*	*5 bar, 30 °C*	*80 bar*	*80 C°*
NO%	93,43	88,16	19,47	93,54	94,26	33,68
NH%	6,57	11,84	80,53	6,46	5,74	66,32



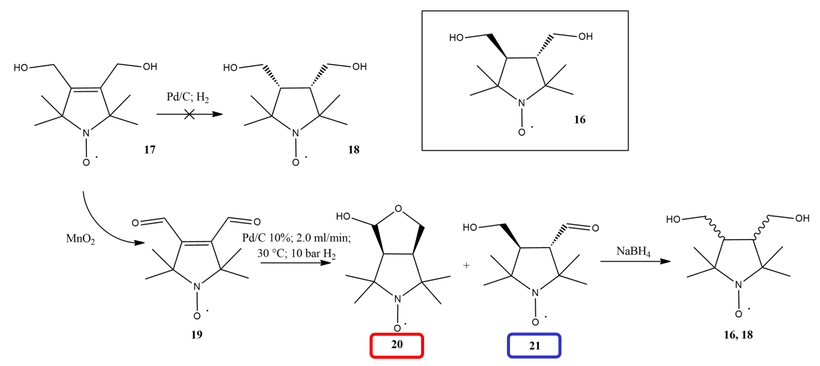
Overlaid extracted ion chromatograms (EICs) after the reduction of compund **1** of the three components: amine (**1b**, m/z 158.154, t_R = 0.63 min, gray coloured EIC), hydroxylamine (**1a**, m/z 174.149, t_R = 0.67 min, red coloured EIC), and nitroxide (**1**, m/z 173.141, t_R = 0.93 min, blue coloured EIC). In order of table above.

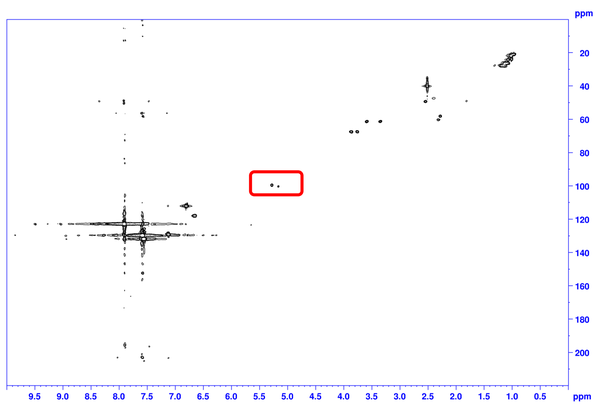


Catalytic flow reduction of aldehydes **3**[1] and **7**[2]

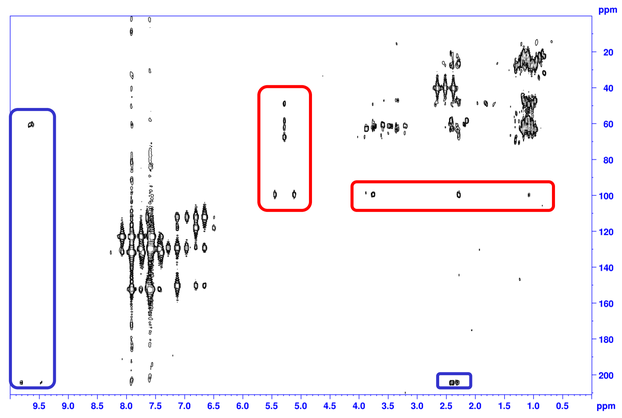
Catalytic flow reduction of acrylate esters **11**[1] and **14**[2]

We have synthesised the saturated analogues of several different nitroxides (**3**[1], **7**[3], **11**[4], **14**[4], **17**) through heterogeneous flow reduction. As **16**[5] has already been reported by Kálai et al. We aimed to make its cis diastereomer (**18**). In the case of **17** the reduction couldn't be carried out directly and had to be oxidized to **19**. From **19** the reduction proceeded normally and we got the mixture of compound **20** and **21**. We opened the ring and completed the reduction with $NaBH_4$ to afford **16** and **18**.





HSQC of mixture **20** and **21**



HMBC of mixture **20**and **21**

Conclusion

- We found that high temperature lead to overreduction of nitroxides in flow catalytic reductions. From this we conclude that pressure would be the main parameter to fine tune reactions.
- We have synthesised pyrrole and piperidine nitroxides from their unsaturated counterparts in a fast and efficient manner, sometimes achieving this selectively.
- The synthesis of meso 3,4-bis(hydroxymethyl)pyrrolidine nitroxide proved to be challenging, nevertheless the presence of **20** is proven by HSQC and HMBC 2D NMR from which we got compound **16**.

Acknowledgments

We are grateful to the Hungarian National Research, Development and Innovation Office under grants (NKFI K 137793) for financial support.

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