Progress towards labeling modafinil with [^{11}C]Cyanide

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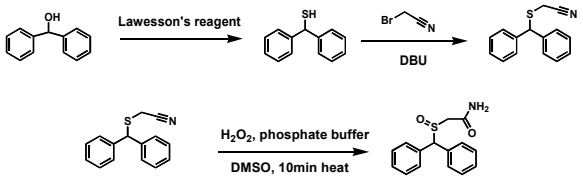
Introduction

Modafinil is a wake-promoting drug for the treatment of narcolepsy, a common disease in shift workers. Narcolepsy manifests itself in excessive day-time sleepiness, cataplexy (muscular weakness) and abnormal rapid eye movement during sleep phases[1]. The drug modafinil alleviates the indications and is FDA approved since 1998. The exact mechanism of action, however, is still unknown and should be explored by labeling modafinil with [^{11}C]-cyanide and consequently using it in PET (positron emission tomography) studies.

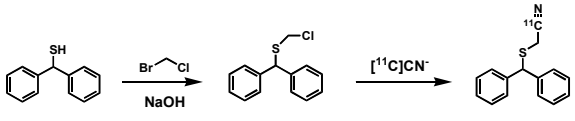
Results and discussions

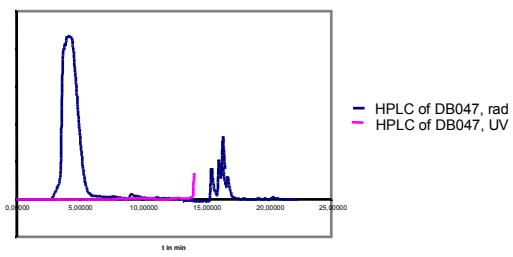
As a standard for TLC and HPLC we first synthesized non-radioactive modafinil in a three-step synthesis from Benzhydrol. This is a new and shorter synthesic route to modafinil and has not been reported before.



Scheme 1: synthesis of a modafinil standard

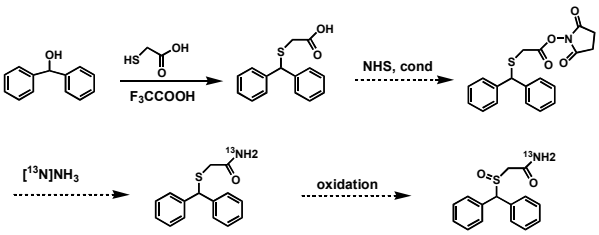
Originally, modafinil should be labeled with the positron-emitter carbon-11 due to its convenient half-life (21min) and the fact that the insertion of this isotope would not change the molecule in its stereochemistry. (Benzhydrylsulfanyl)methyl chloride was synthesized as a precursor for the "hot" reaction and the chloride was exchanged by [^{11}C]-cyanide in the following. While screening reactions by HPLC "cold", though, we often observed the formation of a side product with a retention time of 10.9min, which we could not further identify. This byproduct, together with others, also occurred in the "hot" reaction and thus made purification and characterization of the desired product tough.





Scheme 2: "hot" reaction, first step, and radio-HPLC

Although the oxidation reaction to modafinil had been performed "cold" with promising yields, it could not be attempted "hot" due to the above mentioned problems. A new approach now is to synthesize a reactive carbonyl precursor molecule which is then labeled with [^{13}N]-ammonia.



Scheme 3: new synthetic route to modafinil

Conclusions

A new synthesis for "cold" modafinil has been successfully developed. Efforts to synthesize [^{11}C]modafinil by using [^{11}C]KCN and (Benzhydrylsulfanyl)methyl chloride as starting material, however, did not lead to the desired product [^{11}C]-(Benzhydrylsulfanyl)methyl cyanide, which would have been then oxidized to modafinil. For this reason, current research focuses on labeling with nitrogen-13 as described above.

References

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[2] Prisinzano, T.; Podobinski, J.; Tidgewell, K.; Luo, M.; Swenson, D.; *Tetrahedron Asymmetry* 2004, 15, 1053-1058

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