SYNTHESIS OF INDOLE DERIVATIVES AS BUILDING BLOCKS IN ORGANIC AND MEDICINAL CHEMISTRY

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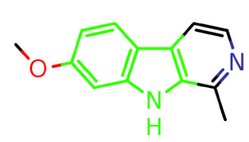
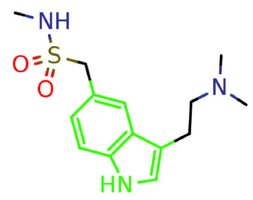
Motivation

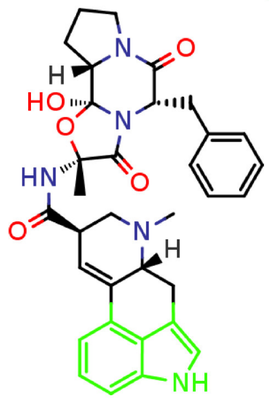
Indole is an exceptionally electron rich fused ring heterocycle. Is it among the most widely distributed scaffolds in nature. It is one of the most important building blocks in medicinal chemistry. The unusually high abundance of indole nucleus in ligands of different biological activity led to its classification as 'priviledged structure'.[1]



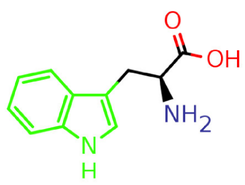
harmine – plant alkaloid, MAO inhibitor



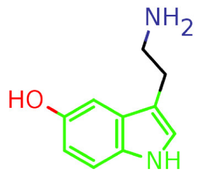
sumatriptan – migraine remedy



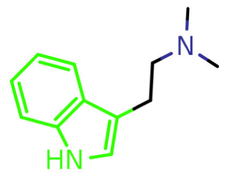
ergotamine - an important fungal alkaloid, anti-migraine agent and substrate to many semisynthetic drugs



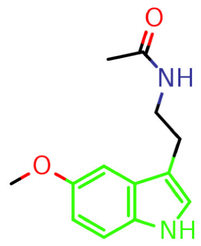
tryptophan – a natural aminoacid



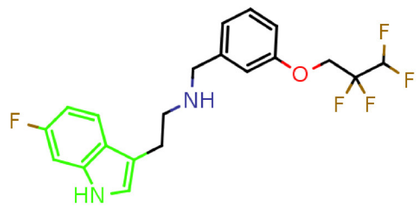
serotonin – one of the most important neurotransmitters



N,N-dimethyltryptamine – possibly responsible for near-death experiences



melatonin – circadian rhythm regulator



idalopirdine – incoming Alzheimer's disease medication

Background and output

In our search for indole based building blocks we were trying to synthesize compounds **1**-**4** (Fig. 1). Synthesis of **1** proved to be notoriously difficult as several independent synthetic paths failed. We were not able to reproduce a literature method – $LiAlH_4$ reduction of **5** (Fig. 2); in two separate trials tryptamine was obtained instead. Trials of hydrogenation of **5** over Pd/C were also unsuccesful. Despite our efforts we did not manage to synthesize this simple molecule. According to Reaxys database, we were the first to obtain **2** via mCPBA epoxidation of olefin **7**.[3] The olefin was synthesized in two ways: by Wittig reaction described in literature,[2] and by our own method: elimination of secondary alcohol **8**.
Synthesis of bromoketones **3** and **4** proved to be challenging (Fig. 3). Direct bromination in acetic acid or dichloromethane yielded tarry mixture instead of the desired product. We attempted a non-selective dibromination and selective debromination, again with no success.[4] Minuscule yield of **3** was obtained by bromination of **9** with copper(II) bromide.

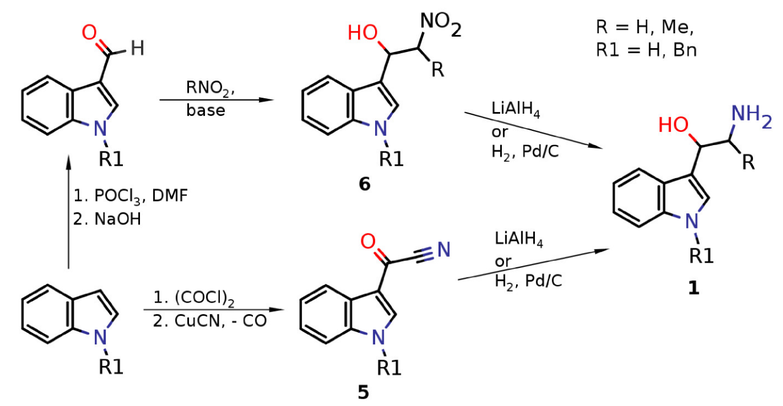


*Fig 1. Synthesis of **1***

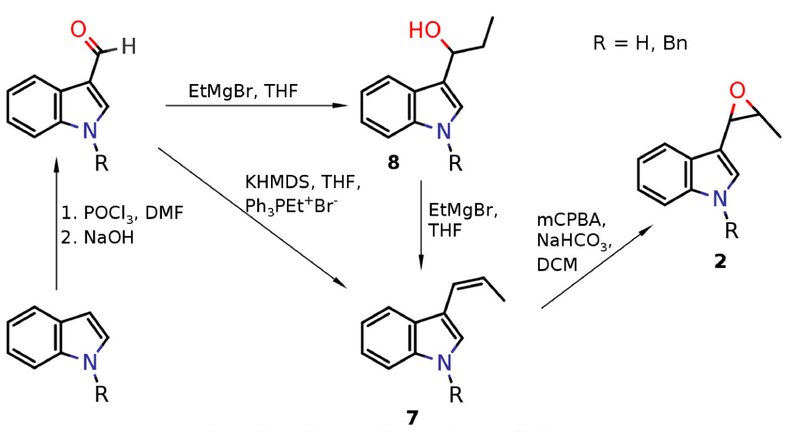


*Fig 2. Synthesis of **2***

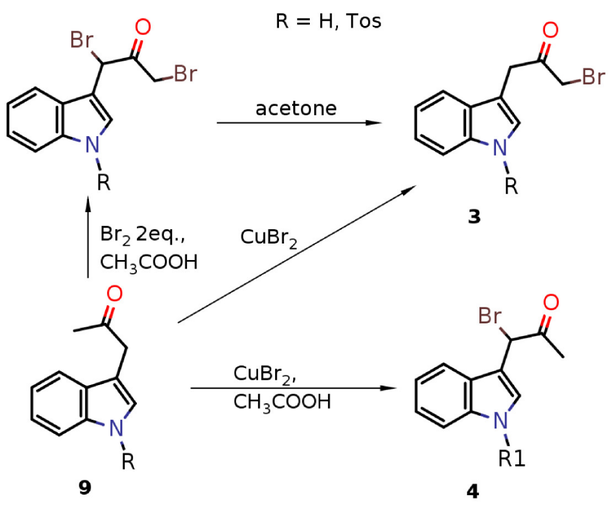


*Fig 3. Syntheses of **3** and **4***

Possible applications

Summary and outlook

Compounds **2**,**3**,**4** can be subjected to reactions with different nucleophiles, vicinal dinucleophiles, trichloroacyl derivatives and many others. Stereospecific opening of **2** enables obtaining specified diastereoisomers. Exemplary structures of achievable products are shown in Fig. 4. A large chemical space of compounds thus obtained might contain numerous bioactive scaffolds.

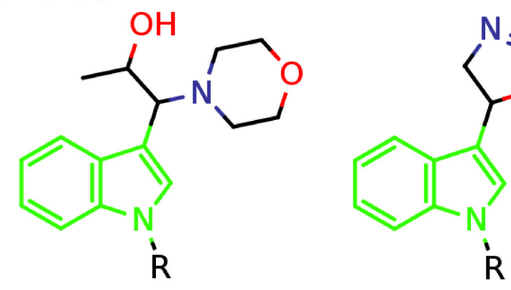


Fig. 4 Diverse available heterocycles

References

1. Evans, B., E.; Rittle, K., E.; Bock, M., G.; DiPardo, R., M.; Freidinger, R., M.; Whitter, W., L.; Lundell, G., F.; Veber, D., F.; Anderson, P., S. **1988** 'Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists', *J. Med. Chem.*, *31*: 2235-2246,
2. Terada, M.; Moriya, K.; Kanomata, K.; Sorimachi, K. **2011** 'Chiral Brønsted acid catalyzed stereoselective addition of azlactones to 3-vinylindoles for facile access to enantioenriched tryptophan derivatives', Angew. Chem. Int. Edit., 50(52): 12586-12590,
3. Imuta, M.; Ziffer, H. **1979** 'Convenient method for the preparation of reactive oxiranes by direct epoxidation', J. Org. Chem., 44:1351-1352,
4. Choi, H., Y.; Chi, D., Y. **2003** 'Nonselective bromination-selective debromination strategy: selective bromination of unsymmetrical ketones on singly activated carbon against doubly activated carbon', Org. Lett., 5(4): 411-414.

Acknowledgements

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