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Microwave-assisted methods for the synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecylamines

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Abstract

Efficient methodologies for the preparation of pentacyclo[5..4.0.0^{2,6}.03^{,10}.05,9] undecane (PCU) amine derivatives are described via microwave-assisted synthesis. The obtained results revealed that microwave-assisted synthetic procedures under controlled conditions (power, temperature and time) are very convenient, high yielding, efficient and low-cost methods for the preparation of PCU amine derivatives. The new methods show several advantages including operational simplicity, good performance, significant reduction in reaction time, less by-product formation and easier purification.

The synthesis, chemical and biological applications of saturated polycyclic hydrocarbon 'cage' compounds have, in recent years, become an intense area of research interest. The pharmacology and medicinal potential of these compounds were realized with the discovery that the cage-like molecule, 1-amino-adamantane or amantadine (1, Fig. 1), an antiviral agent, could be used as a symptomatic treatment option for Parkinson's disease patients.[1,2] The pharmacological mechanism of amantadine as an anti-Parkinson's agent, at least in part, has generally been attributed to its ability to increase extracellular dopamine (DA) levels via reuptake inhibition and DA release.[1,2] A distinct structural similarity (Fig. 1) exists between amantadine (1) and the polycyclic pentacyclo[5.4.0.0^{2,6}.03^{,10}.05,9]undecyl (PCU) amines 3 and 4.[3,4] PCU amines are derived from the Cookson's diketone cage structure (2; pentacyclo[5.4.0^{2,6}.03^{,10}.05,9]undecane-8,11-dione), which is obtained via the intramolecular photocyclization of the Diels Alder adduct of p-benzoquinone and cyclopentadiene.[5]

The first account of biological activity for PCU amines was published in 1986, detailing L-type calcium channel inhibition by 8-benzylamino-8,11-oxapentacycloundecane (NGP1-01, 8, Scheme 1).[6] Early on in the synthesis of 8, it was first assumed that the aza-derivative 9 was formed. However, two independent studies based on X-ray crystallographic data later showed that when the imine 7 was reduced with sodium borohydride ($NaBH_4$), the oxa-derivative 8 was formed, whereas reduction with sodium

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