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[E0008]

Microwave assisted synthesis of indoles: Madelung's Reaction

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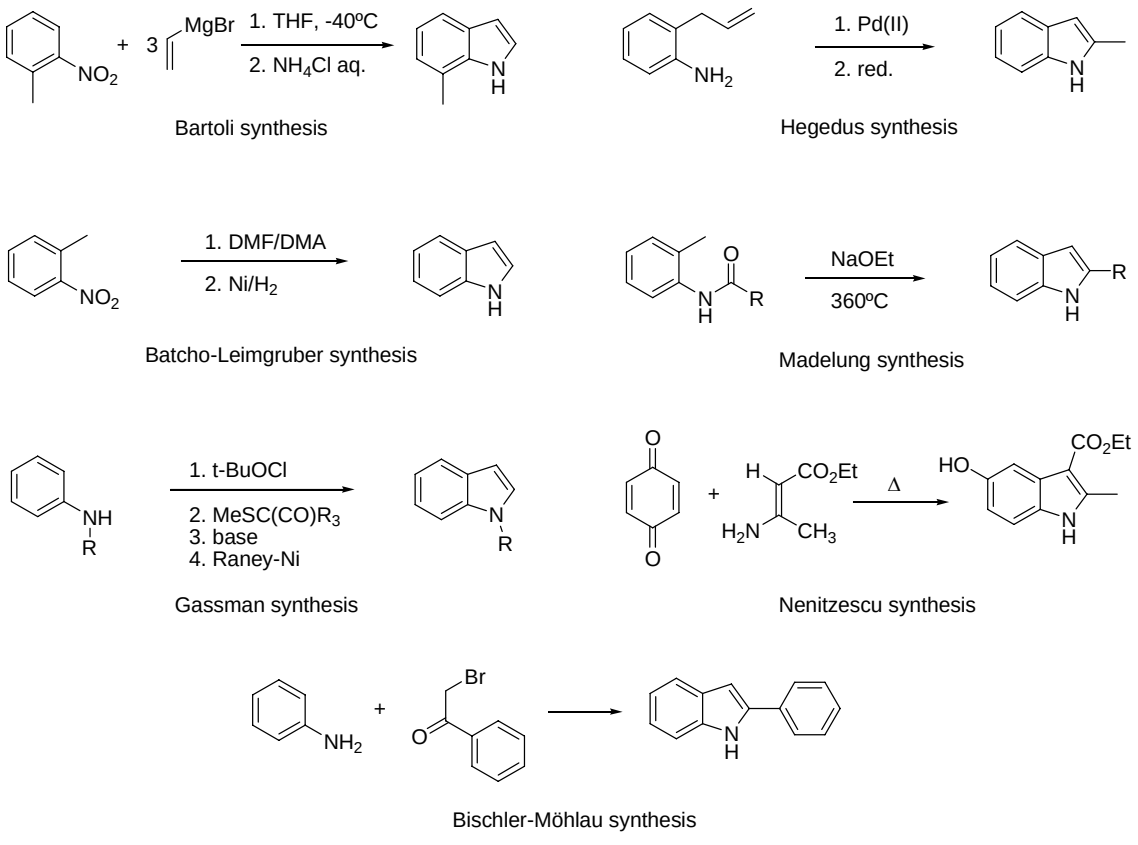
Abstract: Microwave assisted Madelung indole synthesis was achieved under solvent-free conditions using potassium tert-butoxide as base.

The synthesis of indole nucleus has been object of a great deal of studies, and there are several classic named reactions dedicated to the building of this ring: Fischer[1], Reissert,[2] Gassmann,[3] Batcho-Leimgruber,[4] Bischler-Möhlau,[5-8] Hegedus,[9] Nenitzescu[10;11] and Madelung,[12] are the most known (Scheme 1).



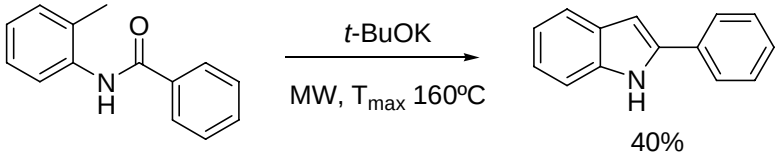
Scheme 1

Classically, Madelung indole synthesis is achieved treating *N*-benzoyl-*o*-toluidines with alkoxides at high temperatures (360-380ºC). The range of bases was increased by Verley,[11] however the harsh conditions used kept the reaction far from wide application. The use of n-butyllithium from 1981 introduced the possibility of using smoother conditions for Madelung's reaction.[13]

The usefulness of microwave irradiation to promote organic reactions is nowadays a fact out of discussion. Not only heating with microwaves is faster than conventional (with the consequent energy saving) but as well has more advantageous features like cleaner reactions and possibility of using solvent-free reaction conditions. There have been several previous reports on the use of MAOS (Microwave-Assisted Organic Synthesis) applied to different synthesis of indoles,[14-17] however to our knowledge none of them with Madelung's reaction. Since, mechanism proposed for the reaction involves several polar intermediates[18] which could be affected positively by the irradiation with microwaves,[19] we studied this possibility.

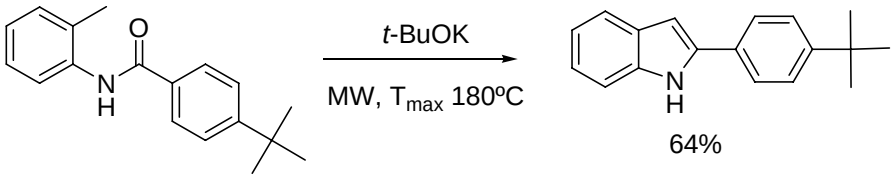
So, the conversion of *N*-*o*-tolylbenzamide into 2-phenyl-1*H*-indole was studied using potassium *tert*-butoxide as base, in several solvents: DMF, DMSO, 1,2-dichlorobenzene, BMIMCl and tetrahydronaphthalene, heating by microwaves at the boiling point of each solvent. However all results were unsuccessful.

These all temperatures were far from those employed in the classical conditions, thus solvent-less conditions were tried. Several basis were studied: DBU, sodium methoxide and potassium *tert*-butoxide. But, only the last one gave a reasonable conversion into 2-phenyl-1*H*-indole (40% yield, scheme 2).



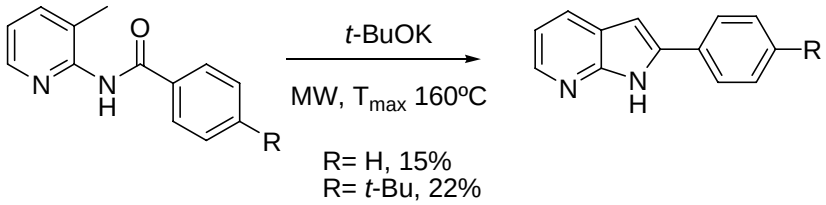
Scheme 2

This procedure was extended to the synthesis of other indole derivatives. Thus, 4-*tert*-butyl-*N*-*o*-tolylbenzamide yielded the corresponding indole after 20 minutes of irradiation at 1000W (64% yield).



Scheme 3

The influence in the reaction of a heteroatom in the aniline moiety of the amide was also studied. So, *N*-(3-methylpyridin-2-yl)benzamide and 4-*tert*-butyl-*N*-(3-methylpyridin-2-yl)benzamide were irradiated in the same conditions described above, but the temperature in the vessel did not surpass 160ºC (scheme 3).



Scheme 4

In summary, in this communication microwave assisted solvent-free Madelung reaction for the synthesis of indoles is presented as alternative to the classical conditions.

General Procedure

A mixture of 4-*tert*-butyl-*N*-*o*-tolylbenzamide (300 mg, 1.12mmol) and potassium *tert*-butoxide (268 mg, 2.8 mmol) were irradiated in a microwave oven (Milestone ETHOS D, power 1000W) for 20 minutes, reaching a maximum temperature of 330 ºC. The reaction mixture was dissolved in CH_2Cl_2 and washed successively with aq. 10% HCl (10 mL), aq. 10% NaOH (10 mL) and water (10 mL), dried with anhydrous sodium sulfate and evaporated to give 2-(4-*tert*-butylphenyl)-1*H*-indole (178 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H, NH), 7.76-7.10 (m, 8H, ArH), 6.81 (dd, 1H, N-C=CH, J=2.1, 0.9 Hz), 1.39 (s, 9H, $C(CH_3)_3$).

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