

OPTIMIZATION, SYNTHESIS AND N-ARYLATION OF AMIDES BY UNCONVENTIONAL WAY

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Introduction & Objectives: The amide bond is widely present in pharmaceutical intermediates and natural products, about 25% of the known clinical drugs contain at least one amide bond.¹ Thus, the thermal activated amidation of carboxylic acids with amines is a potential complementary procedure to eliminate some of the reported synthetic challenges. This reaction has been neglected for many years principally because of the long reaction times and high temperatures needed^{2,3}. Currently, microwave irradiation has proven to be efficient at reducing the reaction times in many organic transformations. Furthermore, previous work reported by Loupy and co-workers⁴ showed the first microwave-assisted synthesis of amides from carboxylic acids. For our part, and firstly, we optimized, by unconventional way, the N-acylation of aniline by acetic acid, secondly, the N-acylation was carried out on different aromatic amines. The N-arylation was performed on the different amides formed by pentavalent organobismuth. The proton and carbon 13 NMR as well as the melting point were the methods for characterizing the obtained products.

Methodology (Material and methods): All the chemicals and reagents used were lab grade material procured from Sd-fine. All solvents were purchased from commercial suppliers and used without further purification. Custom made microwave oven having magnetic stirring, power control, and condenser fixing facility was used. The melting points were determined by the open capillary method and are uncorrected. The FT-IR spectra recorded in Nicolet 5700 FT-IR spectrophotometer (Nicolet, Madison, WI, USA) using KBr pellet. ¹H and ¹³C NMR Spectra obtained in CDCl₃ on Bruker spectrometer at 400 MHz. The chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard.

Results and Discussion: First of all we carried out model reaction of acetic acid (10 mmol), and aniline (10 mmol) in a 10 mL pressure vial in a microwave at optimized 300W power at 100°C temperature for 30 min and 60 min. The best yield was obtained after 60 minutes. The amidation product was isolated in a 31% yield. The ratio of the equiv of acid to amine, reaction temperature, solvent, the used base were optimized as well. Performing the reaction under optimized MW conditions improve the conversion of acetanilide, final product was isolated after flash chromatography with 90% yield. The next objective that we want to establish in our undertaken work is reacting the obtained N-Phenylacetamide with different phenylation agents in order to have the corresponding arylamide. The N-arylation of the formed amide in the presence of pentavalent organic bismuth using a copper catalyst gave traces of N-phenylacetanilide.

Conclusion: The work we have undertaken is based on multiple objectives that we want to establish: The direct N-acylation of amides by microwave irradiation. The N-arylation of the formed amide in the presence of pentavalent organic bismuth.

Keywords: amine, acetic acid, N-acylation, unconventional way, N-arylation.

References

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