Rocío Gámez-Montaño et al., Organic Chem Curr Res 2017, 6:2 (Suppl)
DOI: 10.4172/2161-0401-C1-020

Synthesis of 2-tetrazolylmethyl-isoindolin-1-ones via a one-pot Ugi-azide/(n-acylation/exo-Diels−Alder)/dehydration process

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Isoindolin-1-one (oxoisoindoline) is the core of various natural and synthetic drugs, for example, pagoclone (antianxiolytic) and lenalidomide (anticancer). Additionally, 1,5 disubstituted tetrazoles (1,5-DS-T) are bioisosteres of the *cis*-amide bond of peptides, which are present in various drugs, such as latamoxeb (antibiotic). Moreover, 1,5-DST's have been used as MOF precursors, ligands, and chelating agents. We have recently reported MCR one-pot methods for the synthesis of a series of novel 1,5-DT's linked with a variety of heterocyclic moieties. There are no reports describing the synthesis of unsymmetrical *bis*-heterocycles containing an isoindolin-1-one core N-linked with 1,5-DS-T's using MCR one-pot methodologies or multistep methods. Thus, we now describe, for the first time, MCR one-pot synthesis of 2-tetrazolylmethyl isoindolin-1-ones N-linked with a 1,5-DS-T moiety (Fig 1). A series of 15 2-tetrazolylmethyl-isoindolin-1-one linked-type bis-heterocycles were synthesized in 10−76% yields under mild conditions via a one-pot Ugi-azide/(N-acylation/exo-Diels−Alder)/dehydration process from furan-2-ylmethanamine, aldehydes, isocyanides, azidotrimethylsilane, and maleic anhydride. Density functional theory calculations were performed using the polarizable continuum model (toluene)-M06-2X-D3/6-311+G(d)//M06-2X-D3/6-31G(d) level of theory to obtain the full energy profile when investigating over eight possible pathways. An anthracene containing analogue displayed a distribution of its highest occupied molecular orbital−lowest unoccupied molecular orbital throughout both cyclic moieties. The sustainable methodology described herein is the first MCR one-pot synthesis of bis-heterocycles containing isoindolin-1-one and 1,5-DS- moieties in a linked manner. This work is a contribution to the synthesis of linked-type unsymmetrical bis-heterocycles using Ugi-azide one-pot processes. DFT-based computational calculations gave us enough elements to propose the most plausible reaction mechanism among eight possible ones, which involves an Ugi-azide/(N-acylation/exo-DA)/dehydration sequence as the most thermodynamic and kinetically favored pathway. An anthracene-containing analogue displayed a very interesting distribution of HOMO−LUMO frontier orbitals throughout both of its cyclic moieties, which probably can be attributed to effective electron transfer.

Biography

Rocío Gámez-Montaño has got her PhD under guidance of Professor Raymundo Cruz-Almanza in UNAM, CDMX, México. After a Post-doctoral fellow under guidance of Professor Jieping Zhu at Gif-Sur-Yvette, France, she was incorporated to University of Guanajuato, México, where she is actually full-time Research-Professor (Class B). Her scientific interest includes design and developement of efficient synthesis of heterocycles and poly-heterocycles via MCR, *in vitro* and *in silico* studies of biological properties, applications in optics, as well as study of reaction mechanisms.

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