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Efficient Synthesis of Highly Functionalized Biologically Important Spirocarbocyclic Oxindoles via Hauser Annulation

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Abstract : The unique structural features of spiro-oxindoles with diverse biological activities have made them privileged structures in new drug discovery. The key structural characteristic of these compounds is the spiro ring fused at the C-3 position of the oxindole core with varied heterocyclic motifs. Structural diversification of heterocyclic scaffolds to synthesize new chemical entities as pharmaceuticals and agrochemicals is one of the important goals of synthetic organic chemists. Nitrogen and oxygen containing heterocycles are by far the most widely occurring privileged structures in medicinal chemistry. The structural complexity and distinct three-dimensional arrangement of functional groups of these privileged structures are generally responsible for their specificity against biological targets. Structurally diverse compound libraries have proved to be valuable assets for drug discovery against challenging biological targets. Thus, identifying a new combination of substituents at C-3 position on oxindole moiety is of great importance in drug discovery to improve the efficiency and efficacy of the drugs. The development of suitable methodology for the synthesis of spiro-oxindole compounds has attracted much interest often in response to the significant biological activity displayed by the both natural and synthetic compounds. So creating structural diversity of oxindole scaffolds is need of the decade and formidable challenge. A general way to improve synthetic efficiency and also to access diversified molecules is through the annulation reactions. Annulation reactions allow the formation of complex compounds starting from simple substrates in a single transformation consisting of several steps in an ecologically and economically favorable way. These observations motivated us to develop the annulation reaction protocol to enable the synthesis of a new class of spiro-oxindole motifs which in turn would enable the enhancement of molecular diversity. As part of our enduring interest in the development of novel, efficient synthetic strategies to enable the synthesis of biologically important oxindole fused spirocarbocyclic systems, We have developed an efficient methodology for the construction of highly functionalized spirocarbocyclic oxindoles through [4+2] annulation of phthalides via Hauser annulation. functionalized spirocarbocyclic oxindoles was accomplished for the first time in the literature using Hauser annulation strategy. The reaction between methyleneindolinones and arylsulfonylphthalides catalyzed by cesium carbonate led to the access of new class of biologically important spiro[indoline-3,2'-naphthalene] derivatives in very good yields. The synthetic utility of the annulated product was further demonstrated by fluorination Using NFSI as a fluorinating agent to furnish corresponding fluorinated product.

Keywords : Hauser-Kraus annulation, spiro carbocyclic oxindoles, oxindole-ester, fluoridation
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