Resources, Recycling and Waste Management

Extended Abstracts Vol 6, Iss 1

Citric acid Mediated One-pot Regioselective Synthesis of N-Alkylated Indazoles: An Efficient Green Strategy

Dr. Gangi Reddy NC*
Assistant Professor, Department of Chemistry Yogi Vemana University, Kadapa, India.
E-mail: ncgreddy@yogivemanauniversity.ac.in

ABSTRACT

Citric acid mediated green synthetic route has been demonstrated for the regioselective synthesis of N-alkylated indazoles in good to excellent isolated yields (~ 78-96%) from readily available starting materials 2-methylanilines (1), NaNO2 (2) and ethyl chloroacetate (3) via diazotization, intra molecular cyclization and followed by N-alkylation in the presence of 1:1 ratio of ethanol and water in one-pot. Notably, if the substrate (1) contains – NO2 group and is reduced to – NH2 in the presence of Fe, CaCl2 in the same pot at 60-65°C for 30-40 min. The remarkable advantages of this method include cleaner reaction profile, easy to perform, high yields of products and simple work-up procedure. Besides, the reaction is step-and atom-economic and is carried out in green catalytic medium.

Heterocyclic ring systems are frequently found in numerous naturally occurring compounds and they compose the core structures of many biologically active motifs as well as some industrial compounds [1]. Among them, indazoles represent an important class of nitrogen containing heterocycles and this nucleus (Figure 1) [2,3] is of great current interest as partial structure in many synthetic drugs or drug candidates with a broad range of pharmacological activities including anti-HIV [4], anti-inflammatory [5], anti-tumor [6,7], anti-depressant [8], analgesic and antipyretic [9], anti-leukemia [10], anti-convulsant activity [11], anti-cancer [12], anti-arthritic [13], anthelmintic [14] and anti-diabetes [15]. Indazole moiety is present only in three natural products such as Nigellicine, Nigeglanine and Nigellidine indicates their rare presence in nature.

Extensive literature survey revealed that a huge number of methods have been reported for the synthesis of substituted 1H-indazoles. One general route involves diazotization of o-alkylsubstituted anilines followed by acid promoted cyclization [18,19], functionalized sydnone, oxadiazole condensation/Boulton- Katritzky rearrangement [20], intramolecular dehydration from common arylamino oximes/ o-aminobenzoximes [21,22], condensation of arynes with nitrile imines/ diazomethane derivatives/diazo compounds/hydrazones [23,24], condensation of hydrazine to o-halo/o-alkoxy arylhydrazone [25,26]. In addition to the above methods, other intra molecular cyclizations are also reported for the synthesis of indazole derivatives, for example Pd-mediated ring closure of hydrazine and hydrazone based derivatives.

Results: n the present study, our initial efforts are focused on identifying the catalyst, solvent(s) for the construction of 1H-indazole followed by N-alkylation in a single step operation. For this purpose, the reaction of 2-methyl anilines (1a) with NaNO2 (2) and followed by treatment with ethyl chloroacetate (3) in onepot was chosen as a model reaction to optimize the reaction conditions and the obtained results are presented

Keywords: Citric acid; o-Toluidines; Ethyl chloroacetate; Regioselectivity;,N-Alkylated,Indazoles.