HL
http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 4: (3), 2014, 377-380

MICROWAVE ASSISTED SIMPLE SYNYHETIC ROUTE FOR THE SYNTHESIS OF MEDICINALLY IMPORTANT PYRAZOLE SCAFFOLDS

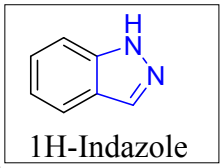
Pradeep Pant[a], Ajay Joshi[b,*]

[a]*Department of Chemistry, Indian institute of Technology, New Delhi, India*
[b,*]*Department of Energy, University of Petroleum and Energy Studies, Dehradun, India*
Corresponding author, Tel:+91-8010367099
E. mail: ajayjoshi037@gmail.com

ABSTRACT
Pyrazoles are one of the most important heterocyclic systems with vast spectrum of biological activities and indazoles are benzene fused pyrazole derivatives. In the present method we used microwave irradiation for the cleaner and simple synthesis of indazoles by condensation reaction of phenyl hydrazine derivatives with substituted salicyl aldehydes followed by intra-molecular cyclization in convenient experimental conditions.

KEYWORDS: Pyrazole, microwave, condensation, phenyl hydrazine, salicylaldehyde.

INTRODUCTION
Organic compounds incorporating heterocyclic ring systems continue to attract considerable attention from pharmaceutical industries due to their wide variety of biological activities[i]. The development of novel synthetic protocols for the preparation of such heterocyclic compounds is a major challenge in modern synthetic chemistry. Pyrazoles are doubly unsaturated five membered cyclic system having two nitrogen atoms adjacent to each other.The pyrazole ring is present as the core in a variety of leading analgesic, anti-inflammatory, antipyretic, anticonvulsant, antidiabetic, antibacterial and antitumor drugs[ii-vii]. Some of the most common pyrazole containing drug available in the market are celecoxib, lonazolac, crizotinib, tepoxalin, and surinabant. Since it rarely occurs in nature, there is a need to development a simple synthetic approach to such bioactive molecules and a pragmatic method to synthesize such compounds on a commercial scale. Pyrazoles are usually prepared by condensation between a hydrazine derivative and 1, 3-dicarbonyl compound or by 1, 3-dipolar cycloaddition of diazoalkanes or nitrile imines to olefins or acetylenes.This method is useful but has its limitation as it involves low yield problem with different functional group, long reaction time and requires sensitive reaction conditions.

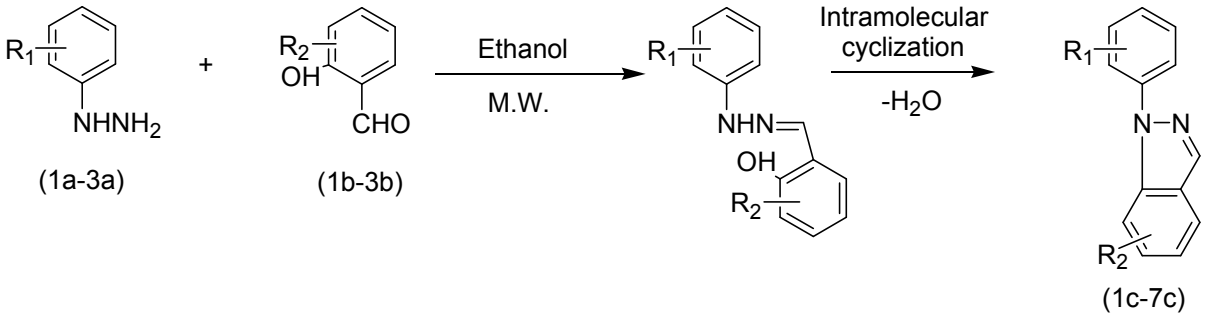


1H-Indazole

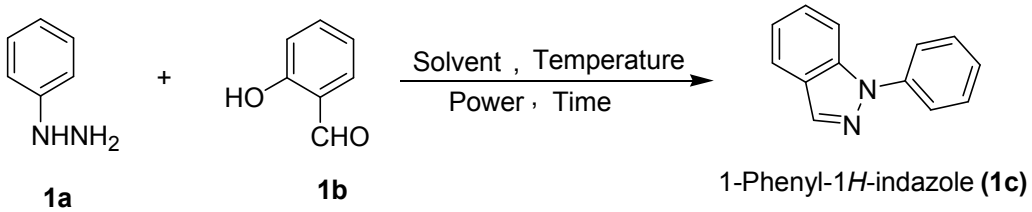
In recent years, the increase in the importance of microwave assisted method for synthesis of organic compounds was greatly observed not only because the method is fast and effective but it also reduces the side reactions thereby causing an increase in the product yield[viii-x]. In this paper we wish to report an efficient and simple technique for the synthesis of pyrazole scaffold. In the present

method, microwave assisted reaction of phenyl hydrazines with substituted salicylaldehyde in ethanol as a solvent gives a condensation product which immediately undergoes intramolecular cyclization to give moderate to high yields of indazoles.

Scheme 1: Synthesis of indazoles:



Results and Discussion:



Synthesis of 1-Phenyl-1H-indazole (**1c**)

The reaction of phenylhydrazine (**1a**) with salicylaldehyde(**1b**) was initially carried out in ethanol: water (1:1) system on a reflux condenser system at 100^0C in an oil bath. The progress of the reaction was checked by TLC and after 24 h, yield of the 1-Phenyl-1H-indazole (**1c**) so obtained was found to be ~60%. This observation clearly shows the possibility of the reaction outline in **scheme-1**. Changing conditions from conventional heating to microwave irradiation reduces the reaction time to 1 h only giving rise to high yield of **1c** (79%), thus it was decided to conduct further studies under MW irradiation.

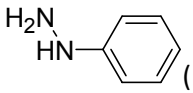
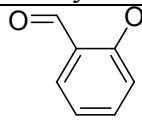
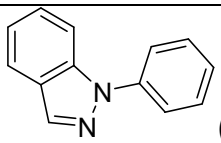
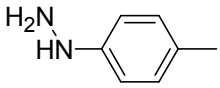
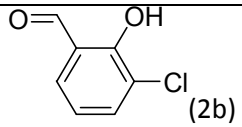
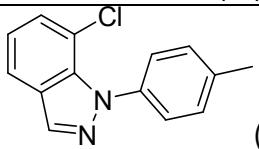
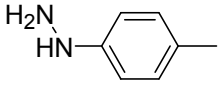
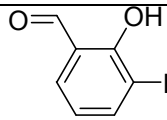
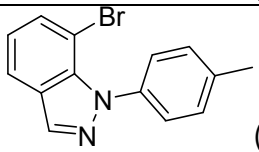
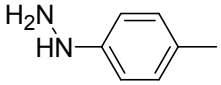
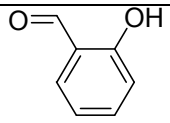
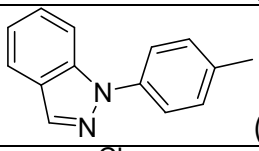
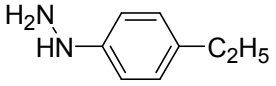
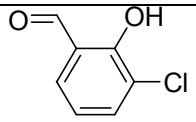
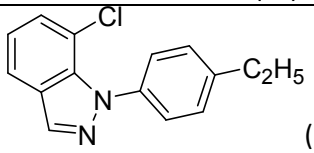
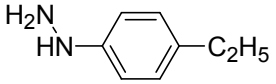
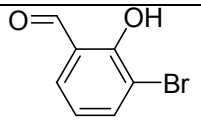
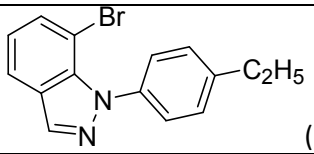
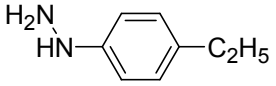
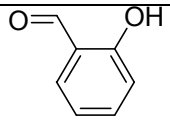
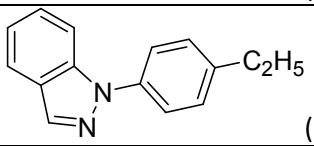
Optimization of solvent: The effect of solvent system change was studied in order to get maximum completion of the reaction. The use of different solvents revealed efficient reaction of **1a** with **1b** to give **1c** (~80% yield) inethanol. In the case of DMSO, yield of the product dropped significantly, while in H_2O, no desired product was obtained. The starting substrates were not consumed completely in the case of various THF/H_2O systems giving rise to low yield of the **1c**.

By stepwise investigation, the reaction parameter such as reagent stoichiometry, reaction time, temperature, and power were examined. The best results were obtained with (1:1) mole ratio of phenylhydrazine: salicylaldehyde for 35 minutes at 80^oC under 50 W of microwave irradiation. To check the scope of the **Scheme**-1, the reactions of phenylhydrazine (having electron donating substituents on the phenyl ring) with halo salicylaldehyde were carried out under the optimized conditions of stoichiometry of reactants, solvent, temperature, power, and time which gives moderate to high yields of the desired product (77-83%)(**Table 1**).

Conclusion:

We have developed an efficient and economical procedure that can bring about the synthesis of pyrazole derivatives in milder reaction conditions using MW. Use of MW has enabled in bringing down the reaction time from several hours to a few minutes promoting a much cleaner reaction and limiting the formation of other side products.

Table 1: Scope of scheme-1

Entry	Phenyl hydrazine	Salicylaldehyde	Product	%Yield
1	 (1a)	 (1b)	 (1c)	79
2	 (2a)	 (2b)	 (2c)	83
3		 (3b)	 (3c)	80
4			 (4c)	77
5	 (3a)		 (5c)	80
6			 (6c)	82
7			 (7c)	82

Reaction conditions: phenyl hydrazine: salicylaldehyde (1: 1), temperature = 80 ^{o}C, power = 50 W (MW), time = 35 min.

Experimental:

All chemicals were purchased from commercial sources and used without further purification. Solvents were purified by distillation according to the standard procedure available. All the reactions were done on the Microwave irradiation using CEM Discover system microwave. The products were purified by column chromatography on silica gel. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 MHz spectrometer (^{1}H 300 MHz, ^{13}C 75MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the international standard at room temperature.

General Procedure for the synthesis of 1-Phenyl-1H-indazole: Phenyl hydrazine (1 mmol) and salicylaldehyde (1 mmol) were taken in a microwave tube along with ethanol (3 ml) as a solvent. This mixture was exposed to microwave irradiations (50W) for 35 min at 80 ^{o}C. The reaction mixture was extracted with ethyl acetate (3x20mL). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography on silica gel afforded product.

Spectral data for selected compound (**4c**): ^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.33 (s, 1H), 7.79 (d, J = 8.49 Hz, 1H), 7.76 (d, J =8.15 Hz, 2H), 7.68 (d, J = 8.44 Hz, 1H), 7.30 (t, J = 6.47 Hz, 1H), 7.30 (d, J =8.36 Hz, 2H), 7.09 (t, J =7.48 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 149.8 (C), 138.4 (C), 138.0 (C), 130.2 (CH), 126.8 (CH), 122.8 (C), 122.4 (CH), 120.9 (CH), 120.5 (CH), 120.4 (CH), 118.0 (CH), 21.2 (CH_3); MS (ESI): m / z calculated for $C_{14}H_{13}N_2$ $(M + H)^+$: 209.10, found: 209.09.

ACKNOWLEDGEMENT: We thank University of Petroleum and Energy Studies for providing generous support of this research.

References:

i. C. A.Zificsak,D. J.Hlasta,Tetrahedron, 60, 8991(2004).
ii. M.Boyne,C.Stratton,F.Johnson,P.Tonge,ACS Chem Biol.,1, 43(2006).
iii. G. C.Rovnyak,R. C.Millonig,J. Schwartz,V.Shu,J. Med. Chem.,25, 1482(1982).
iv. E.Palaska,M. Aytemir,I. T.Uzbay,D. Erol,Eur. J. Med. Chem.,36, 539 (2001).
v. A. Sener, R.Kas□mogullar□, M. K. Sener, I. Bildirici, Y. Akcamur, J Heterocyclic Chem.,39, 869 (2002).
vi. X. H.Liu,P. Cui,B. A.Song,P. S.Bhadury,H. L.Zhu,S. F.Wang, Bioorg. Med. Chem.,16, 4075 (2008).
vii. E.Akbas, I.Berber,Eur. J Med Chem., 40, 401 (2005).
viii. D. Adam, Nature, 421, 571 (2003).
ix. R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, Tetrahedron Lett., 27, 279 (1986).
x. R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, Tetrahedron Lett., 27, 4945 (1986).

Received on June 10, 2014