Advancements in the Synthesis of 2H-Indazole: Focus on 2-Substituted Benzaldehyde Reactions

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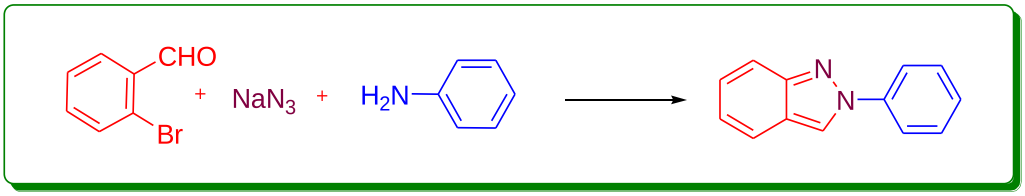
ABSTRACT

Several compounds has more than one nitrogen contained bicyclic heterocycles were important structural motifs found in numerous natural products and bioactive molecules. In recent years, the synthesis of bicyclic compounds possessing imidazole heterocycle as central core has been the focus of great interest. They are associated with diversified biological activities



I. INTRODUCTION

Heterocycles are broadly found in naturally occurring compounds and have an immense importance in the design and discovery of new compounds for pharmaceutical applications [1]. Among the numerous heterocycles, nitrogen containing heterocyclic skeleton show a key role in alkaloids chemistry. These alkaloid compounds are gaining a lot of importance and they have exhibit a broad spectrum of pharmacological and biological activities [2]. Over the past decades, a great deal of research interests has been devoted toward the synthesis of heterocyclic compounds because of their significant biological activities [3]. Indazole is a ten-π electron aromatic heterocyclic system in which pyrazole ring condensed with the benzene ring [4]. Indazole also called benzpyrazole or isoindazole is a heterocyclic aromatic organic compound. Comparable the pyrazole molecule indazole resembles both pyridine and pyrole and its reactivity reproduces this twofold activity [5]. The indazole ring has two nitrogen atoms and presents annular tautomerism with regards to the position of the NH hydrogen atom [6]. There are two tautomeric forms for indazole, the 1*H*- and 2*H*- form (**Figure 1**).

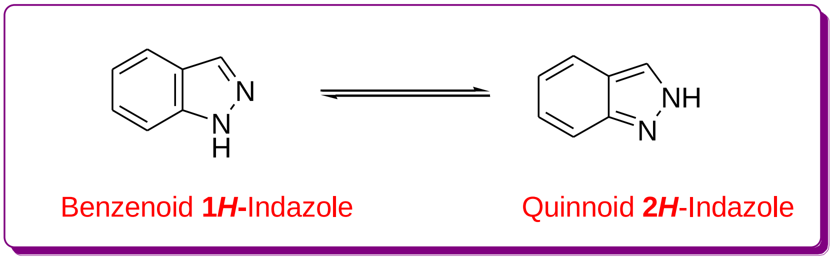
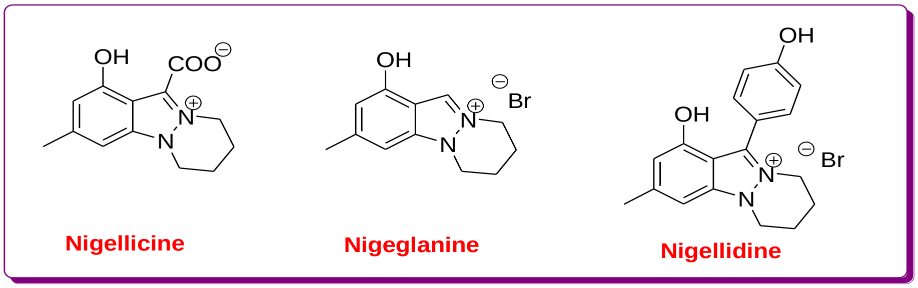


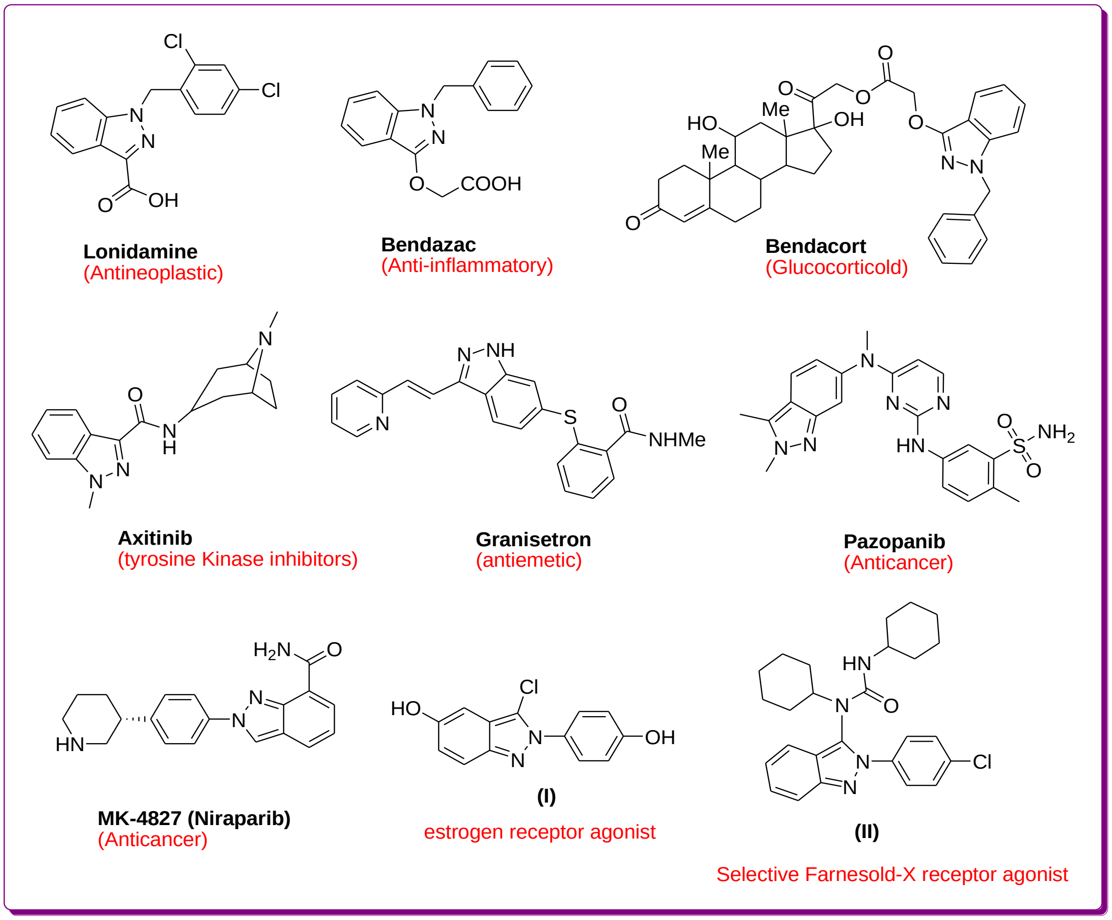
Figure 1: Tautomers of Indazole.

he synthesis of bicyclic pyrazole bearing heterocyclic compounds 2*H*-Indazole unit has been reorganized by a "privileged structure" and is an important pharmacophore in medicinal chemistry [7]. Indazoles are rare in nature and to date only three natural products possessing the indazole ring have been isolated are Nigellicine, Nigeglanine and Nigellidine (**Figure 2**) [8].



Nigellicine **Nigeglanine** **Nigellidine**

***Figure 2**: Natural products possessing the indazole ring*



Lonidamine (Antineoplastic)

Bendazac (Anti-inflammatory)

Bendacort (Glucocorticold)

Axitinib (tyrosine Kinase inhibitors)

Granisetron (antiemetic)

Pazopanib (Anticancer)

MK-4827 (Niraparib) (Anticancer)

(I) estrogen receptor agonist

(II) Selective Farnesold-X receptor agonist

Figure 3: The structure of approved drugs having indazole cores and their corresponding pharmaceutical properties.

Interestingly, in the field of drug discovery, the Indazole scaffolds received a lot of interest because they act as efficient bioisosters of indole and benzimidazole [7, 9].Molecules constitute 2*H*-Indazole skeleton are found the key subunit in various drug substances has been receiving significant attention due to its pronounced biological activities, including anti-inflammatory [10], anti-platelet [11], antidepressant [12], anticancer [13], anti-tumor [14], anti-HIV [15], antimicrobial [16] and anti-spermatogenic [17] activities. Some 2*H*-indazole derivatives are proved to have high affinity for the imidazoline I_2 receptor [18], potent affinity for estrogen β-receptor [19] and 5-HT$_{1A}$ receptors [20]. Some clinically approved important drugs such as lonidamine [21], bendacort [22], bendazac [23], granisetron [24], axitinib [25], pazopanib [26], nirapanib (MK-4827) [27], YC-1 [28], selective estrogen β-receptor (**Figure 3 (I)**)[19] and farnesold-X receptor agonist (**Figure 3 (II)**)[29] were known to involve the indazole and its related compounds have been manufactured and used worldwide (**Figure 3**). The indazole ring system is also present in many other compounds such as herbicides [30], dyes-pigments [31] and as optoelectronic chromophores used in fabrication of devices like OLEDs [32].

II. REVIEW OF LITERATURE

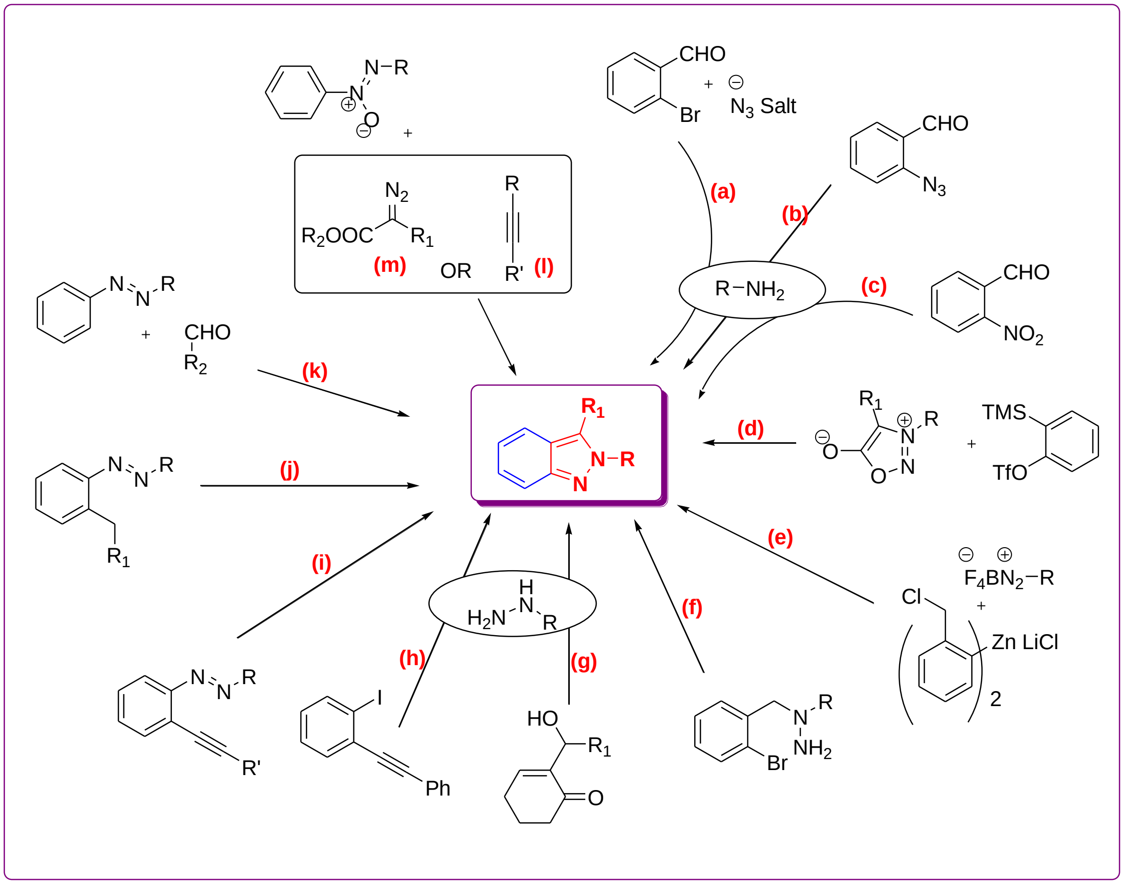
The tautomeric equilibrium between 1*H*- and 2*H*-indazole has been calculated by thermo-chemical and photo physical techniques. The results shows 1*H* tautomer more stable than 2*H* tautomer, for example 1-methyl-1*H*-indazole (3.2 kcal/mol) [33] more stable and stronger base [34] than 2-methyl-2*H*-indazole. Dipole moment of 2*H* tautomer is more than 1*H* tautomer [35]. (**Table 1**)

Table 1: Basicity and dipole moment comparison of indazole tautomers

Physical technique	1-methyl-1*H*-indazole	2-methyl-2*H*-indazole
Basicity (P^{kb})	0.42	2.02
Dipole moment (D)	1.50	3.4

The chemistry of 2*H*-indazoles has not been explored as well as the chemistry of 1*H*-indazoles. However, the discovery that *N*-2 substituted 2*H*-indazole compounds exhibit biological activities, which has produced recent interest in their simple and efficient preparation. Although a number of methods were known for the synthesis of Indazoles, amongst them most of the existing approaches are targeted 1*H*-Indazole or mixture of both 1*H*- and 2*H*-Indazoles. 2*H*-Indazoles are less studied as compared to 1*H*-Indazole; due to the difficulty in their preparation. Therefore the formation of 2*H*-Indazoles still remains a challenging task [7].

In past, few synthetic approaches have been developed for the synthesis of 2*H*-indazoles (**Scheme 1**), which can be achieved by the different synthetic methodologies viz. C-C and C-N bond formation using different catalysts through the one pot three-component condensation reaction of 2-bromobenzaldehyde, primary amine and salt of azide (**route a**)[36-42]. A copper catalyst plays the key role in both C-N bond formation between the aryl bromide and the azide and N-N bond formation between the imine and the azide. The condensation reaction of 2-azidobenzaldehyde with primary amine via formation of imine as intermediate in situ (**route b**) [43, 44].One traditional approach to yield 2*H*-indazole is intramolecular reductive *N*-hetero-cyclization of *N*-(2-nitrobenzylidene)anilines formed from 2-nitro benzaldehyde with primary amine (**route c**)[45-51].

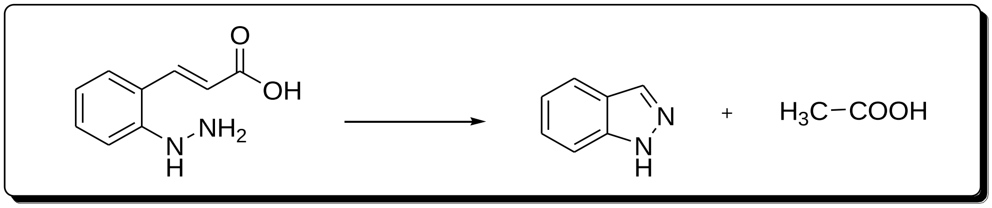


Scheme 1: Literature available methods for the synthesis of 2H-Indazoles.

In other way arynes with easily obtained sydnones by a sequence involving [3+2] dipolar cycloaddition reaction in presence of TBAF (1.6 equiv) (**route d**) [52]. Other methods involve the reaction of bis(2-chloromethylaryl)zinc reagents with aryldiazonium salt in THF:NMP (4:1) (**route e**)[53]. Song and Yee reports that the $Pd(OAc)_2$/dppf as homogeneous catalytic system and NaO^tBu as base through intramolecular amination reaction of *N*-aryl-*N*-(o-bromobenzyl)-hydrazines (**route f**)[54]. Kim and his research group reportedthe two step procedure for the synthesis of 2*H*-indazole via cross coupling reaction of aryl hydrazine with the Baylis-Hillman adduct (**route g**)[55]. In another reported process reactions of aryl hydrazine with2-halophenyl acetylenes (**route h**) [56]. Some reports are shows that palladium-catalyzed intramolecular C-N bond formation of *o*-alkyne azoarene (**route i**) [57] and iodine mediated intramolecular oxidative annulation of benzyl sp^3 C-H functionalization of o-alkylazoarenes (**route j**) [58]. Also Rh (III)-catalyzed direct addition of an azobenzene C−H bond to an aldehyde with subsequent cyclization and aromatization (**route k**) [59]. A Rh(III)-catalyzed tandem C−H alkylation as well as intramolecular decarboxylative cyclization of azoxy compounds with diazoesters (**route l**)[60] or alkynes (**route m**)[61] via a classic [4 + 1] annulation manner. The 2*H*-indazoles are synthesis by Davis-Beirut reaction from o-nitroso benzaldehyde and primary amines under both acid and base catalysis [62]. Base-catalysed reaction of 2-nitrobenzyl triphenylphosphonium bromide with Aryl isocyanate [63] and Fe-catalysed N-N bond formation of 2-azidophenyl ketoximes[64].

Some selected reactions for the synthesis of 2*H*-indazoles are described here.

Emil Fischer and Kuzel (1880) have reported the first synthesis of heterocycle containing an indazole ring by heating o-hydrazinocinnamic acid [7]. In an attempt to prepare the anhydride of *o*-hydrazinocinnamic acid, Fisher got many products, out of these products one of which was a new substance containing no oxygen. The analysis of the reaction mixture demonstrated the elimination of an acetic acid molecule and led to the conclusion that the structure of the new substance was a pyrazole ring condensed with a benzene ring which requires longer reaction time and low to moderate yield of product. Fischer and Kuzel described this transformation as "remarkable of the highest degree" and named the product "indazole" by analogy with the previously known indole (**Scheme 2**).

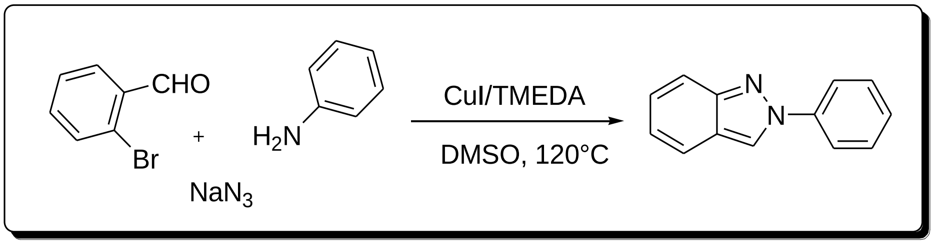


Scheme 2: First reported synthesis of Indazole

Synthesis of 2*H*-indazole from 2-substituted benzaldehyde (Route a-c):

1) M. R. Kumar *et al.* (2011) [36]

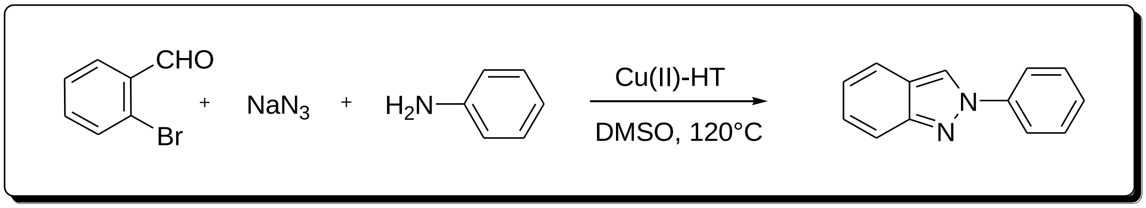
M. R. Kumar *et al*. have reported the synthesis of 2-aryl-2*H*-Indazoles through one-pot, three-component condensation reactions of 2-bromobenzaldehydes, primary amines, and sodium azide by using CuI (10 mol%)/TMEDA (10 mol%) as a homogeneous catalyst system in DMSO at 120°C for 12h resulted in good yields (**Scheme 3**).



Scheme 3

2) B. M. Reddy and co-workers (2013) [37]

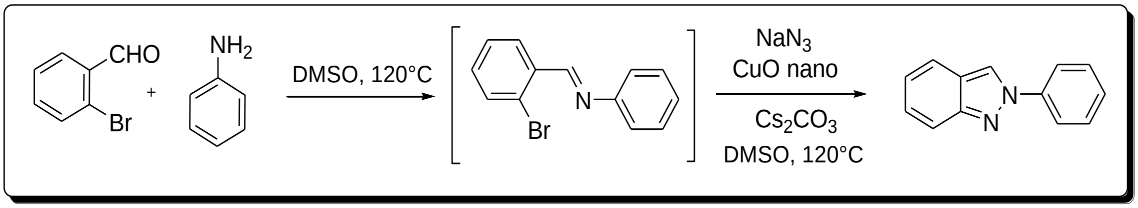
B. M. Reddy and co-workers described that a synthesis of 2*H*-indazoles was achieved from 2-bromobenzaldehydes, primary amines and sodium azide through consecutive condensation, C–N and N–N bond formations catalyzed by a heterogeneous Cu(II)–HT (20mg, Cu:Al ratio 3:1) catalyst in DMSO at 120°C temperature for 6 h (**Scheme 4)**. A series of 2*H*-indazoles were synthesised in good to excellent yields. Furthermore, the Cu(II)–HT catalyst can be reused for three runs without any significant loss of activity.



Scheme 4

3) N. Khatun*etal.* (2014) [38]

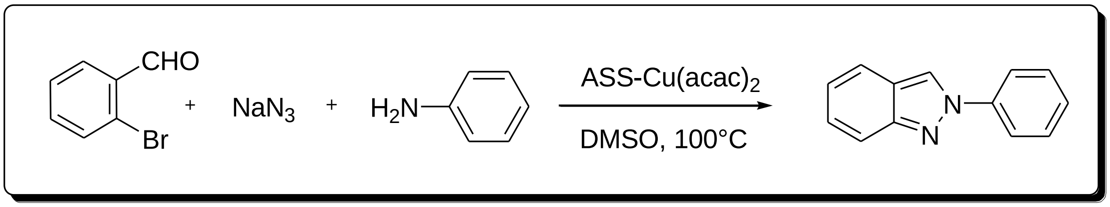
N. Khatun*etal.*have reported a CuO (2.5 mol%) nano catalysed one-pot synthesis of 2*H*-indazoles has been devised from 2-bromobenzaldehydes, primary amines and sodium azide with Cs_2CO_3 (2 equiv.) as base in DMSO at 120°C under ligand free conditions. This catalytic system gave the yield in the range of 40-84%. The catalyst can be recycled up to three times (**Scheme 5**).



Scheme 5

4) R. K. Sodhi*etal.* (2014) [39]

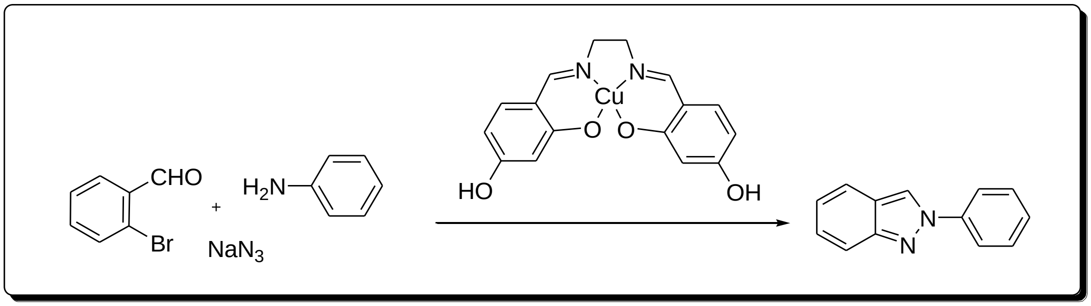
R. K. Sodhi*etal.*have reported the one pot multicomponent synthesis of 2*H*-indazole from 2-bromobenzaldehyde, primary amines and sodium azide through consecutive C-N and N-N bond forming reaction was carried out in the presence of different amine functionalized silica/starch-M(acac)n catalysts. ASS-Cu(acac)$_2$ (0.2 g, 1.1 wt% Cu) was turned out to be the best catalyst in DMSO at 100°C for the synthesis of 2*H*-indazoles (**Scheme 6**). It was found that ASS-Cu(acac)$_2$ could be recycled for four times.



Scheme 6

5) H. Sharghi*etal.* (2017) [40]

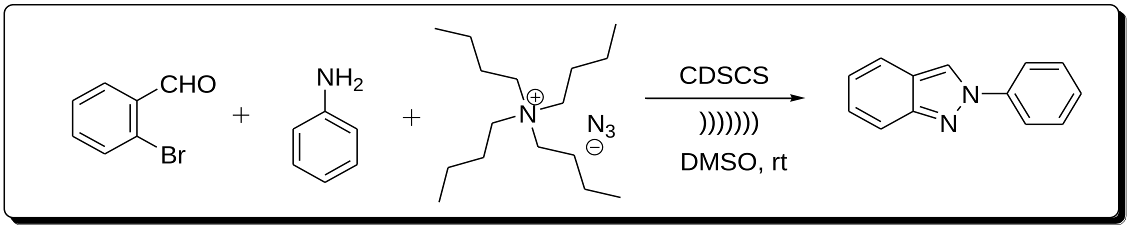
H. Sharghi*etal.*have reported the synthesis of 2*H*-indazole via one pot multicomponent condensation of 2-bromobenzaldehyde, primary amine with sodium azide by using salen. The support-free Cu(II)–salen complex (7 mol%) as a catalyst under nearly solvent-free conditions at 120°C (**Scheme 7**).



Scheme 7

6) M. N. Soltani Rad (2017) [41]

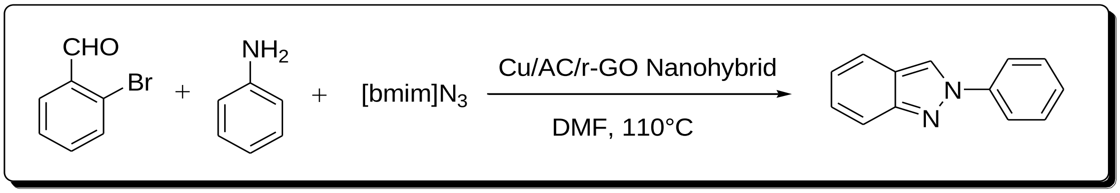
M. N. Soltani Rad has reported an ultrasonic promoted facile and convenient one-pot three-component reaction of 2-bromobenzaldehyde, primary amine and tetra-butyl ammonium azide (TBAA) used as an azide source in presence of copper-doped silica cuprous sulphate (CDSCS) in DMSO at room temperature furnishes 2*H*-indazoles in good yields (**Scheme 8**).



Scheme 8

7) S. Behrouz (2016) [42]

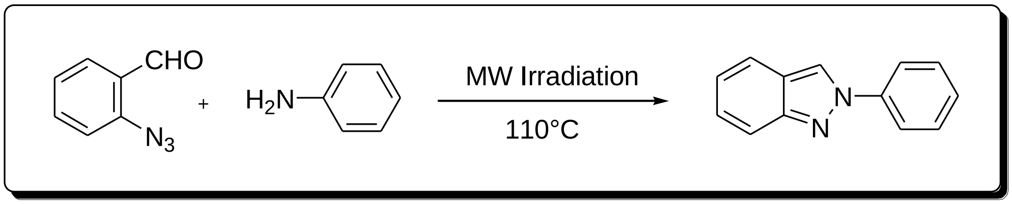
S. Behrouz reported the multicomponent synthesis of 2*H*-indazole from condensation of 2-bromobenzaldehyde, structurally diverse amines, and [bmim]$N_3$is used as an azide source in the presence of Cu/aminoclay/reduced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid) as heterogeneous catalyst in DMF at 110°C gave 2*H*-indazoles in good yields (**Scheme 9)**.



Scheme 9

8) D. S. Sharada and group (2014-2017) [43]

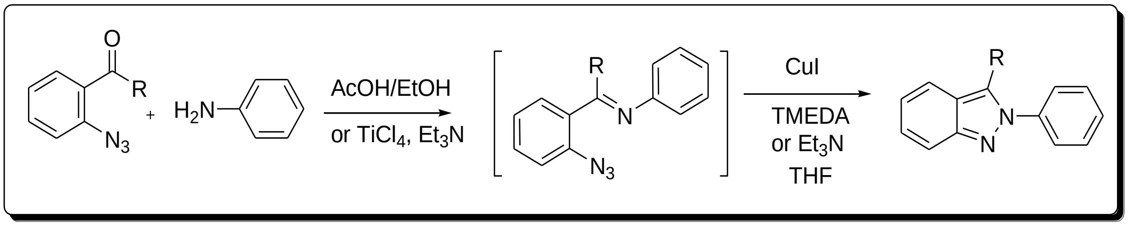
D. S. Sharada and group have described a catalyst-free, solvent-free (neat condition) and microwave-irradiated approach at 110°C for 50-60 min, to 2*H*-indazoles through consecutive formation of C=N and N=N bonds from 2-azidobenzaldehyde with various primary amines like aromatic, heteroaromatic, aliphatic and benzylic amines which offered wide range of 2*H*-indazoles in excellent yields (**Scheme 10)**.



Scheme 10

9) J. Hu *et al.*(2011) [44]

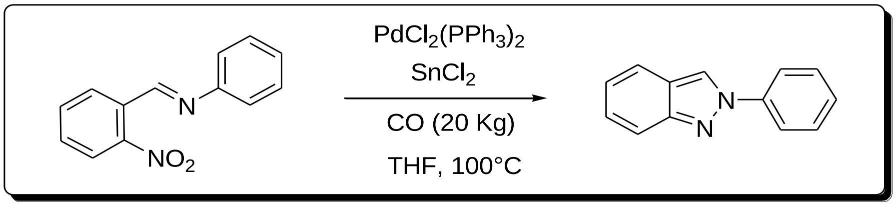
J. Hu *et al.* have developed an intramolecular amination reaction of 2-azidobenzaldehyde with primary amine under mild condition. By employing a combination of CuI (0.1 equiv.) with tertiary amines TMEDA or TEA (0.5 equiv.) which is homogeneous catalytic system in THF at rt for 4h or at 40°C for 2h used for the intramolecular N–N bond formation reaction (**Scheme 11**).



Scheme 11

10) Akazome*etal.* (1994) [45]

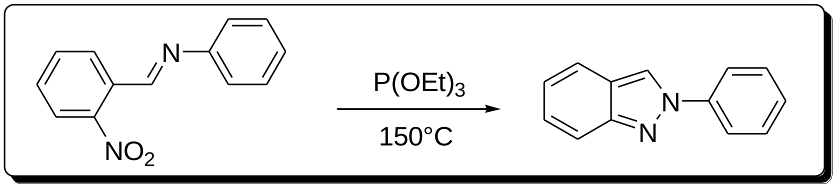
Akazome*etal.* demonstrated the palladium-catalyzed intramolecular reductive *N*-heterocyclization of (2-nitrobenzylidene) amines to give the corresponding 2*H*-indazoles. Reactions were conducted in a stainless reactor under 20 kg cm^{-2} of initial CO pressure in the presence of a $PdCl_2(PPh_3)_2$ (5 mol%) and $SnCl_2$ (50 mol%) at 100°C for 16h (**Scheme 12**). Carbon monoxide effectively worked as a deoxygenating agent of the nitro group which gave a nitrene intermediate. Also, it required high catalyst loading with no recyclability.



Scheme 12

11) J.I.G. Cadogan and R. K. Mackie (1968) [46]

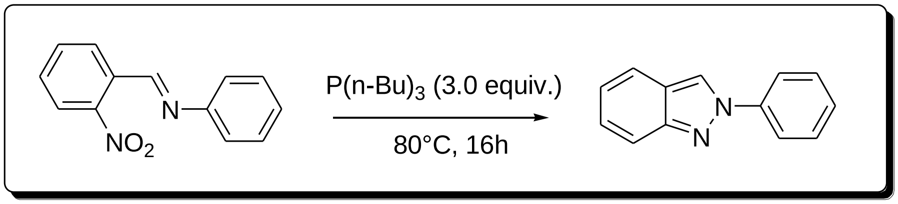
J.I.G. Cadogan and R.K. Mackie reported the new catalytic method for the synthesis of 2-aryl-2*H* indazole derivatives through reductive cyclocondensation of 2-nitrobenzaldehyde with aromatic primary amines in presence of $P(OEt)_3$ as catalyst at 150°C temperature by Cadogan reaction (**Scheme 13**).



Scheme 13

12) N. E. Genung*etal.* (2014) [47]

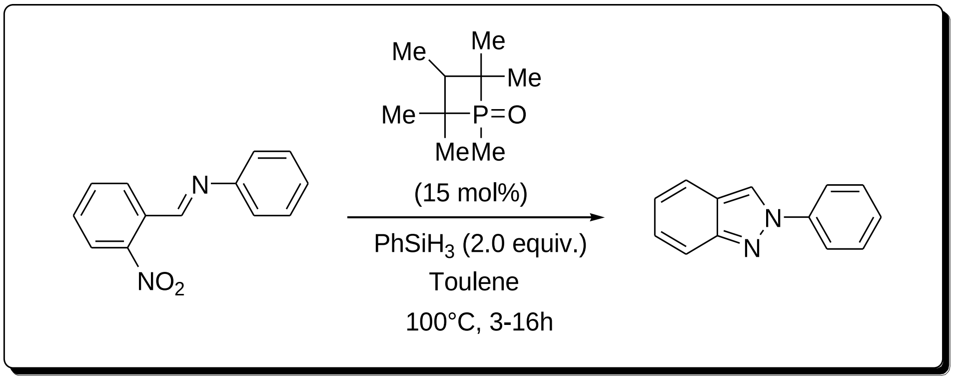
N. E. Genung*et al.* reported the synthesis of 2*H*-indazoles by one-pot condensation Cadogan reductive cyclization. As condensation of aryl aldehyde and aniline occurs readily in *iso*-PrOH at elevated temperature, it was envisioned that simply adding tri-n-butylphosphine after the condensation was completed, followed by heating, would afford the desired product without the complicating factor of isolating an *o*-iminonitrobenzene intermediate. Fortunately, this method proved effective as the one-pot process afforded indazole in 85% yield (**Scheme 14**).



Scheme 14

13) T. V. Nykaza*etal.* (2017) [48]

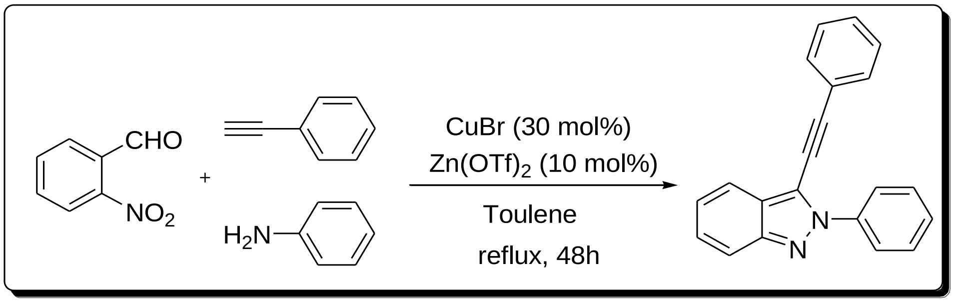
T. V. Nykaza*etal.*have reported a readily accessible phosphetane which was a suitable catalyst for the Cadogan indazole synthesis. A small-ring phosphacycle, 1,2,2,3,4,4-hexamethyl-phosphetane, was found to catalyze deoxygenative N-N bond-forming Cadogan heterocyclization of o-nitrobenzaldimines, o-nitroazobenzenes and related substrates in the presence of hydrosilane terminal reductant. The method provides a simple phosphacatalytic approach to a valuable N−N bond-forming mode (**Scheme 15**).



Scheme 15

14) A. K. Saikia*etal.* (2014) [49]

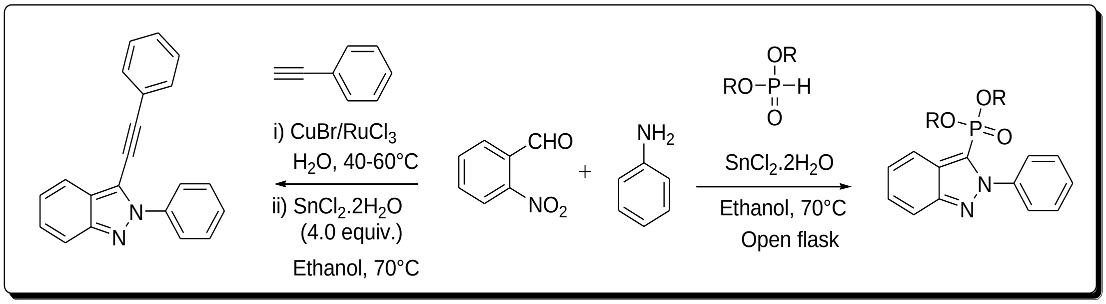
A. K. Saikia*etal.*have reported the effective synthesis of 3-(Arylethynyl)-2*H*-indazoles through one pot three component condensation using 2-nitroarylaldehydes, primary amines and alkynes co-catalyzed by copper(I) bromide and zinc(II) triflate in toluene refluxed for 24 to 48h (**Scheme 16**).



Scheme 16

15) N. Sudhapriya*etal.*(2014 & 2017) [50]

N. Sudhapriya*etal.* reported the synthesis of 3-Alkynyl-2-Aryl-2*H*-Indazole or 2-aryl-2*H*-indazole-3-phosphonates via $SnCl_2.2H_2O$ mediated A^3-coupling followed by reductive cyclization of 2-nitrobenzaldehyde, primary amine and phenyl acetylene or dialkyl phosphonates (**Scheme 17**). A rapid and efficient synthesis of indazole through N-N bond formation. This protocol proceeds wide substrate scope and good yields.



Scheme 17

III. CONCLUSION

In this review, we have reporting various methods for the synthesis of 2*H*-indazoleheterocyclic scaffoldthrough C-N bond formation reactions.

IV. ACKNOWLEDGEMENTS

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