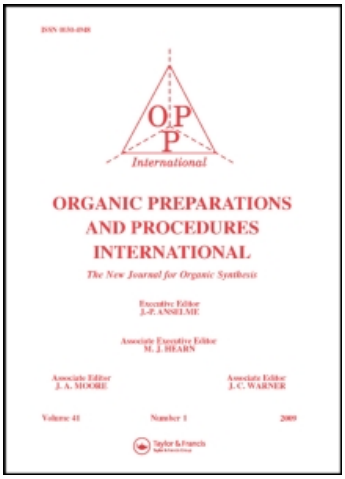


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# Recent Synthetic Approaches to 1*H*- and 2*H*-Indazoles. A Review

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# Recent Synthetic Approaches to 1*H*- and 2*H*-Indazoles. A Review

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## Introduction

This decade (2001–2010) witnessed an unprecedented explosion of research on the diverse biological properties of compounds sharing an indazole core. Interest in indazoles is demonstrated by the large number of published articles devoted to their biological activity. These studies include a wide range of characteristics connected with receptor interaction, enzyme inhibition, anti-proliferative effects, anti-fungal activity, *etc*. The pharmaceutical aspects of indazoles were summarized in a review published in 2005[1] and subsequently as a part of a review published in 2008.[2] During 2009, more than 150 articles were published describing biological effects connected with indazole derivatives, and more than 400 patents or patent applications issued to cover priority of indazole core-mediated biological effects.

Neuroprotective effects exhibited by fluorinated indazoles[3] illustrate one of the most interesting aspects of their biological activities. Some of the compounds reported in this article represent a promising strategy for nitric oxide synthase (NOS) selective inhibitors, especially because of selective inhibition of NOS-II. NOS are enzymes divided into neuronal (nNOS, type I), inducible (iNOS, type II) and endothelial (eNOS, type III) types which are responsible for generation of nitric oxide from L-arginine. Drugs with an efficiency to inhibit these enzymes have been developed to inhibit biological effects of nitric oxide with aim to recognize its role in nervous system and influence processes connected with pain perception, convulsive behavior, and memory. It was demonstrated that 4,5,6,7-tetrafluoro-3-perfluorophenyl-1*H*-indazole (**1**) was able to inhibit this enzyme to an 80% extent and leave NOS-I untouched (*Figure 1*).

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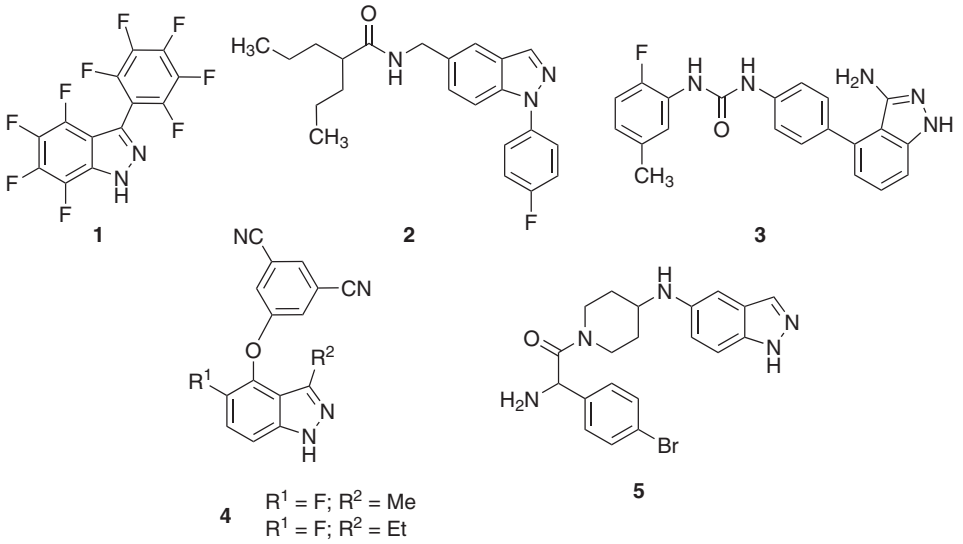



**Figure 1**



Implementation of high throughput screening (HTS) in the drug discovery process led to interesting lead compound **2** (*Figure 1*), effective as Smoothened antagonist and inhibitor of the Hedgehog pathway[4] which is originally responsible for proper development of embryo cells. (Smoothened is a G-protein coupled receptor-like protein involved in hedgehog signal transduction). Signaling proteins involved in this pathway such as Smoothened protein also play a significant role in adult age, because malfunctions of this pathway can result in diseases such as basal cell carcinoma. The pathway is also connected with stem cell regulation leading to regeneration of adult tissues. Subsequently, a chemical library of *N*-[(1-aryl-1*H*-indazol-5-yl)methyl]amides was synthesized and subjected to SAR studies to find antagonists with nanomolar activity.

Indazoles have been reported as effective agents to inhibit tyrosine kinase. One of the most recent examples includes *N*-(4-(3-amino-1*H*-indazol-4-yl)phenyl)-*N′*-(2-fluoro-5-methylphenyl) urea (**3**) (*Figure 1*) as a multi-targeted inhibitor of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinase family members.[5] VEGF is a chemical signal produced by cells that stimulates the growth of new blood vessels. Over-expression of VEGF can cause various vascular diseases and is responsible for supplying tumors with blood, enabling them to grow and metastasize. PDGF is particularly responsible for cell divisions during angiogenesis. Compound **3** reduced tumor growth in multiple preclinical animal models and in early clinical trials as well.

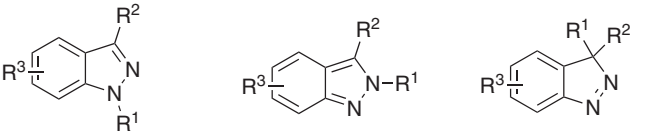
Furthermore, non-nucleoside inhibitors of reverse transcriptase, constituting a rapidly-growing area of biologically active compounds, includes the indazole structural motif. According to the latest results, some of these inhibitors seem to have both metabolic stability and resilience against mutations of this enzyme. The most effective agents were reported to be indazoles **4** (*Figure 1*).[6]

Indazoles were also reported as effective inhibitors of Rho kinase (ROCK)[7]—an enzyme implicated in many diseases ranging from glaucoma to central nervous system

disorders, such as Alzheimer's disease. The best inhibitor **5** exhibited the half maximal inhibitory concentration $IC_{50} = 13$ nM of inhibition activity (*Figure 1*).

A substantial effort has been made towards development of synthetic strategies to access indazoles during the last five years. Although a majority of drug-discovery syntheses used protocols several decades old, new approaches were developed that overcame failures and harsh reaction conditions of some of the existing methods, and have been focused at increasing the yields and development of chemical libraries through the use of solid-phase synthesis. The purpose of this review is to compare different approaches with emphasis on the practical design of the syntheses.

Indazoles can exist in three tautomeric forms (*Scheme 1*). The energy of 1*H* and 2*H* tautomers was calculated and it was concluded that the 1*H* tautomer is energetically more stable than the 2*H* tautomer;[2] 3*H*-Indazoles are not common.




**Scheme 1**
1*H*, 2*H*, and 3*H*-Indazoles.

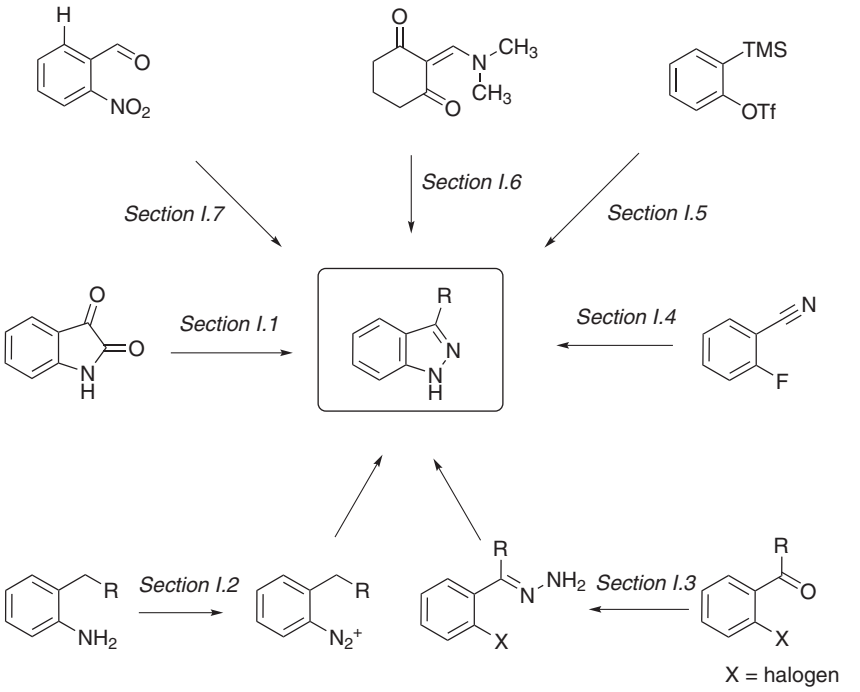


For the purpose of this review, synthetic methods are arranged according to the target indazole derivatives rather than the mechanism of indazole formation. The existence of tautomers resulted in two main classes of indazole derivatives, 1*H*- and 2*H*-indazoles. First, we describe routes for the syntheses of indazoles unsubstituted at nitrogen in *Section I* (*N*-H indazoles). *Section II* summarizes the syntheses of *N*-alkyl/aryl 1*H*-indazoles (*N*-R 1*H*-indazoles) with direct incorporation of the N-substituent during indazole core assembly. *N*-Alkyl/aryl 2*H*-indazoles (*N*-R 2*H*-indazoles) are covered similarly in *Section III*. *Section IV* deals with the *N*-alkylation of *N*-H indazoles.

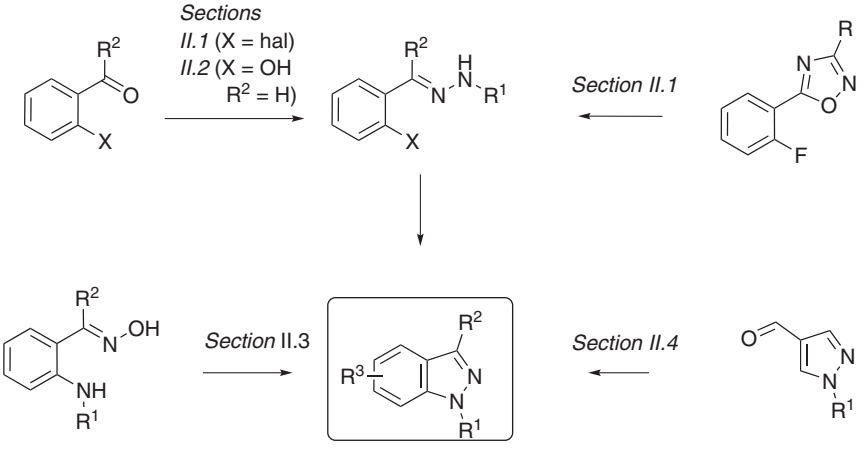
Irrespective of the final target structure, the five-membered pyrazole ring was typically constructed from suitable 1,2-substituted benzene derivatives. Two approaches for the synthesis of *N*-alkyl/aryl 1*H*- and 2*H*-indazoles were frequently reported in the literature. The first is based on the synthesis of *N*-H indazole, followed by *N*-alkylation. The second route introduced the *N*-substituent during assembly of the indazole five-membered ring.

Individual routes leading to *N*-H indazoles are summarized in *Scheme 2* and are described in detail in *Section I*. They can be generally divided into two main approaches. The first is based on ring closure by C–N bond formation, and the majority of indazoles were prepared by this methodology. Within this group of chemical transformations, synthons represented by 2-halo (fluoro, chloro, bromo) or OMs benzaldehydes were the most frequently used. Condensation with hydrazines closed the five-membered ring of the indazoles by consecutive formations of two C–N bonds reaction. An alternative route is based on cyclization by N–N bond formation.

*Scheme 3* summarizes direct routes to *N*-alkyl/aryl 1*H*-indazoles, where the *N*-substituent was introduced as a part of one building block (as opposed to *N*-alkylation of *N*-H indazoles).

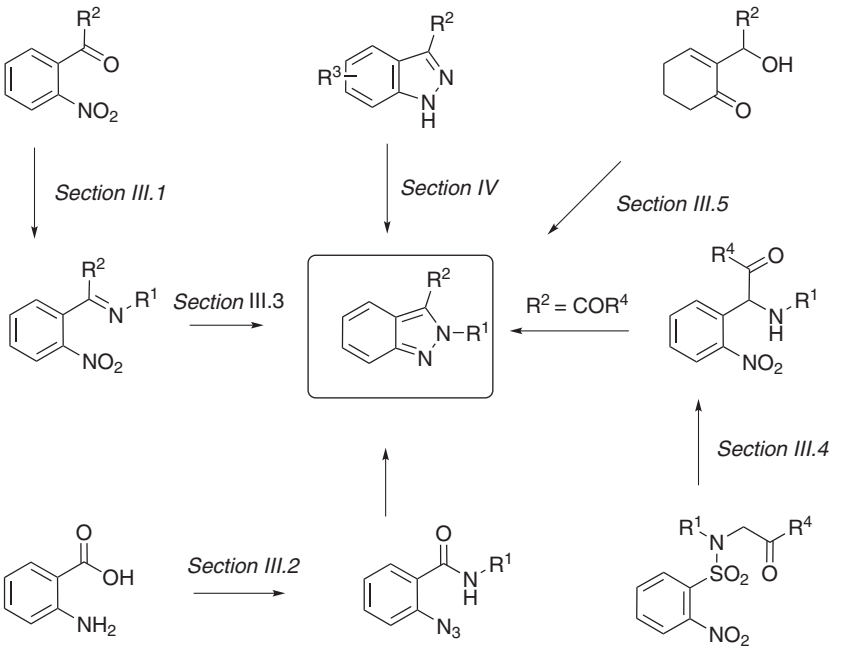



**Scheme 2**
Routes to *N*-H Indazoles.




**Scheme 3**
Routes to *N*-R 1*H*-Indazoles.

*N*-Alkyl/aryl (*N*-R) 2*H*-indazoles were typically prepared using chemical transformations that introduced the *N*-substituent during assembly of the five-membered ring (*Scheme 4*). Only a few examples of the preparation of 2-alkyl/aryl indazoles by *N*-alkylation of *N*-H indazoles have been reported.



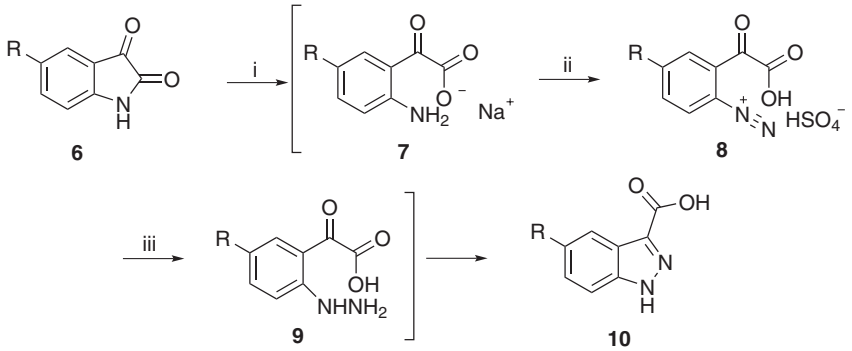

**Scheme 4**
Routes to *N*-R 2*H*-indazoles.



## I. Syntheses of *N*-H Indazoles

### *1. Synthesis of 1H-Indazole-3-carboxylic Acids from Isatin*

Isatin was used for synthesis of indazoles for the first time in 1952. The reaction sequence involves hydrolysis of the isatin to aminophenylglyoxylic acid **7**, followed by diazotization and subsequent reduction to a hydrazine intermediate **9**. Spontaneous cyclization afforded indazole-3-carboxylic acid **10** (*Scheme 5*).[8]

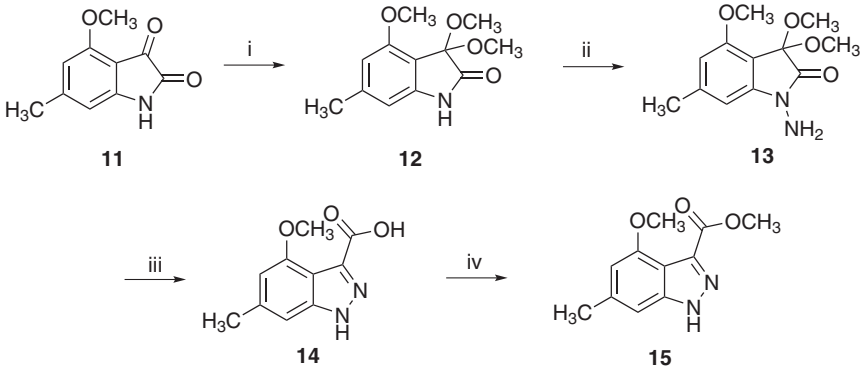



(i) NaOH; (ii) $NaNO_2$, $H_2SO_4$ conc; (iii) $SnCl_2.2H_2O$, HCl conc

**Scheme 5**

Recently, this protocol was successfully used for the synthesis of 5-methoxy- and 5-bromo derivatives[9] and 5-chloro and 5-fluoro derivatives[10] in good to excellent yields.

On the other hand, using the original reaction sequence,[8] Elliot *et al.*[11] reported a failed indazole synthesis from 4-methoxy-6-methylisatin. Therefore, they modified the route by initial protection of the reactive ketone functionality, deprotonation with sodium hydride and subsequent direct *N*-amination with *O*-(diphenylphosphinyl)hydroxylamine ($DppONH_2$) to yield derivative **13** (*Scheme 6*).[12] The intermediate **13** was then treated with aqueous sulfuric acid to afford unprotected 4-methoxy-6-methyl-1*H*-indazole-3-carboxylic acid **14**. This intermediate was used for the synthesis of nigellicine and nigeglanine hydrobromide. 4-Methoxy-6-methylisatin **11** was prepared from commercially available 2-chloro-5-methylphenol.[13]



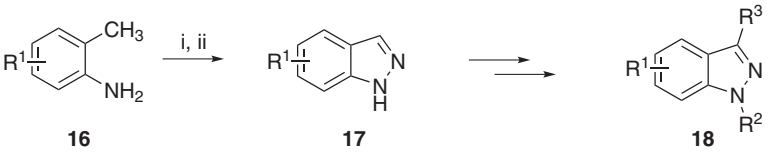

(i) $HC(OCH_3)_3$, *p*-TsOH, MeOH; (ii) NaH, then $DppONH_2$; (iii) $H_2SO_4$; (iv) $SOCl_2$, MeOH

**Scheme 6**



### *2. Synthesis of 1H-Indazoles from o-Toluidine*

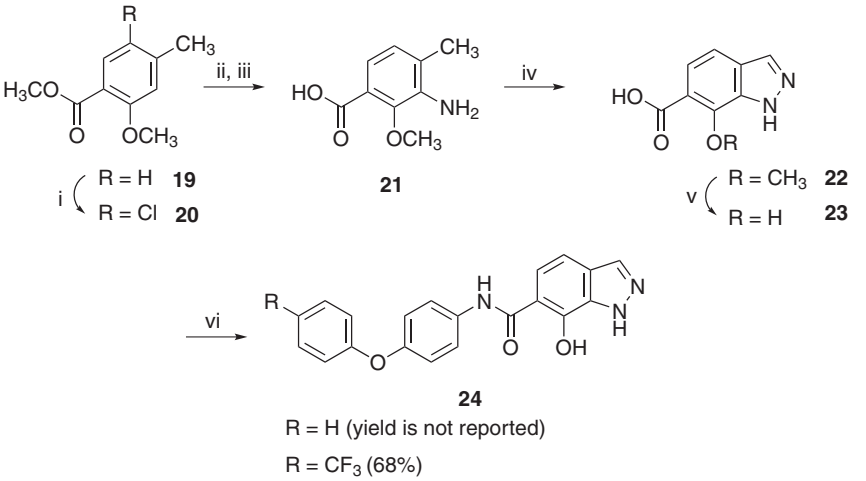
Syntheses utilizing *o*-toluidine as a starting material have been described several times. The reaction is based on diazotization of an amino group and subsequent coupling with the *ortho* methyl group. 1*H*-Indazoles have been studied as melanin-concentrating hormone receptor 1 antagonists for the treatment of obesity (*Scheme 7*).[14–16] Although diazotization surprisingly was performed in acetic acid at room temperature, the reported yields of 4-nitro- and 5-methoxy-1*H*-indazoles **18** were excellent.




(i) $NaNO_2$, AcOH, rt; (ii) TEA (if $R^1$ = 4-$OCH_3$)

**Scheme 7**

Bolgunas *et al.*[17] prepared 7-hydroxy-*N*-(4-phenoxyphenyl)-1*H*-indazole-6-carboxamide **24**, an inhibitor of the Qi site of the mitochondrial respiration complex



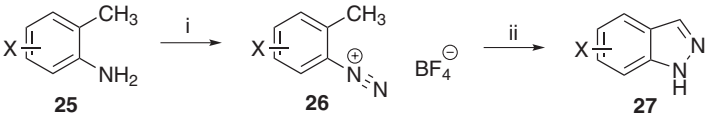

(i) NCS, DMF, 20 °C, 3 days; (ii) $HNO_3$, $Ac_2O$, AcOH, 25 °C, 18h; (iii) 50 psi $H_2$, $NEt_3$, $Pd(OH_2)/C$, EtOH, 20 °C, 8h; (iv) *i*-amyl nitrite, HOAc, 20 to 117 °C, 1h; (v) HBr concn, 80 °C, 18h (vi) EDC.HCl, HOBt, 4-(4R-phenoxy)phenylaniline, pyridine, 90 °C, 18h

**Scheme 8**



III. 7-Methoxy-1*H*-indazole-6-carboxylic acid **22** was obtained by treatment of 3-amino-2-methoxy-4-methylbenzoic acid **21** with isoamyl nitrite (*Scheme 8*). Subsequent demethylation in concentrated HBr led to 7-hydroxy-1*H*-indazole-6-carboxylic acid **23** which was coupled to a variety of anilines to yield target compound **24**. As an example for the synthesis of a starting material for indazole synthesis, methyl 2-methoxy-4-methylbenzoate **19** was protected in position 5 by chlorination, subsequently nitrated and then reduced to afford **21**.[18]

This approach was also used for the preparation of halogenated 1*H*-indazoles substituted at various positions on the benzene ring of indazole (*Scheme 9*).[19] Substituted *o*-toluidines **25** were converted to the corresponding *o*-methylbenzenediazonium tetrafluoroborates **26**, which were cyclized to the appropriate indazoles **27** in the presence of [18]crown-6. The yields of halogenated indazoles were in the range of 41–98%; 5- and 7-bromo-1*H*-indazoles were prepared in 80–91% yields while in contrast 6-bromo-1*H*-indazoles were obtained in only 41% yield. Interestingly, the yield of 6-chloro-1*H*-indazole was 98% whereas 5-chloro-1*H*-indazole was obtained in 51% yield. 5-Iodo-1*H*-indazole was isolated in 74% yield while 4-iodo-1*H*-indazole was formed in 49%.

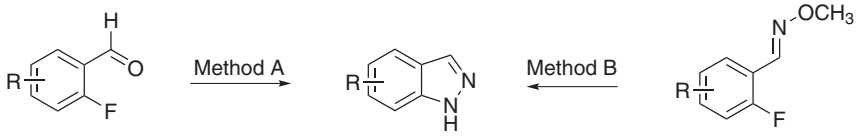



(i) $HBF_4$ aq 50%, then $NaNO_2$ aq, 0 °C; (ii) AcOK, [18]crown-6, $CHCl_3$, rt

**Scheme 9**

### *3. Synthesis of 1H-Indazoles from o-Halophenylalkan-1-one*

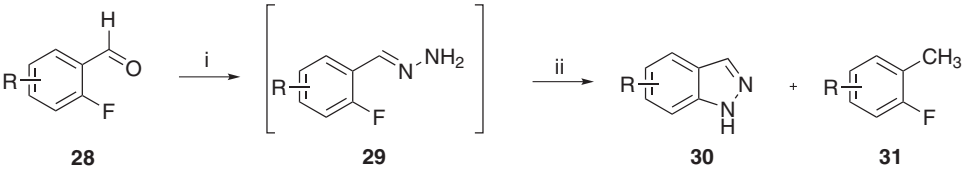
This frequently used method for syntheses of *N*-H as well as *N*-R 1*H*-indazoles involves the reaction of *o*-halobenzaldehydes/*o*-haloacetophenones with hydrazines. *N*-Unsubstituted 1*H*-indazoles were synthesized from *o*-fluorobenzaldehydes by two methods.[20] *Method A* included refluxing of *o*-fluorobenzaldehyde with an excess of hydrazine in dimethoxyethane (DME) for 15 hours and precipitation of the product from water (*Scheme 10*). *Method B* included heating of *o*-fluorobenzaldehyde with *O*-methylhydroxylamine hydrochloride and potassium carbonate in DME for 4–5 hours. After removing the precipitate formed, the filtrate containing the *O*-methyloxime intermediate was concentrated and refluxed with an excess of hydrazine (98%) for 5–25 hours. The yields were generally higher in ethereal solvents such as THF, DME, or dioxane and by using anhydrous hydrazine.




**Scheme 10**



One disadvantage of *Method A* was the competitive Wolf-Kishner reduction leading to *o*-fluorotoluene (*Scheme 11*). This undesirable reaction was further enhanced by the use of bases stronger than sodium bicarbonate. It was also noted that cyclization of the isolated hydrazones into 1*H*-indazole was markedly slower in comparison to the same hydrazone, formed *in situ*; even after three-days at 100°C, the starting material was present and the yield of target 1*H*-indazole was less than 10%.



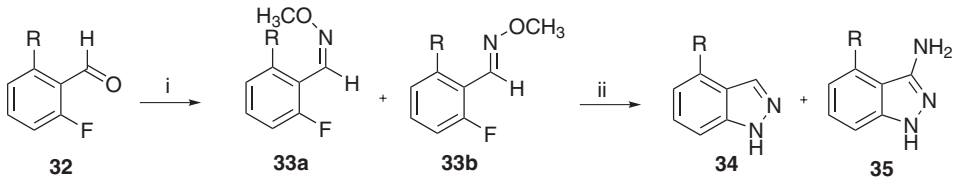

**28** **29** **30** **31**

(i) $NH_2NH_2$ (3 equiv); (ii) 100 °C

**Scheme 11**
Method A.

The overall yields of 1*H*-indazoles **30** formed by method A were 47–82%, with the exception of *o*-fluorobenzaldehydes bearing electron-donating groups at position 5, as well as unsubstituted *o*-fluorobenzaldehydes; in these cases the yields were only 0–45%. An advantage of *method B* was elimination of the Wolf-Kishner reduction (*Scheme 12*).

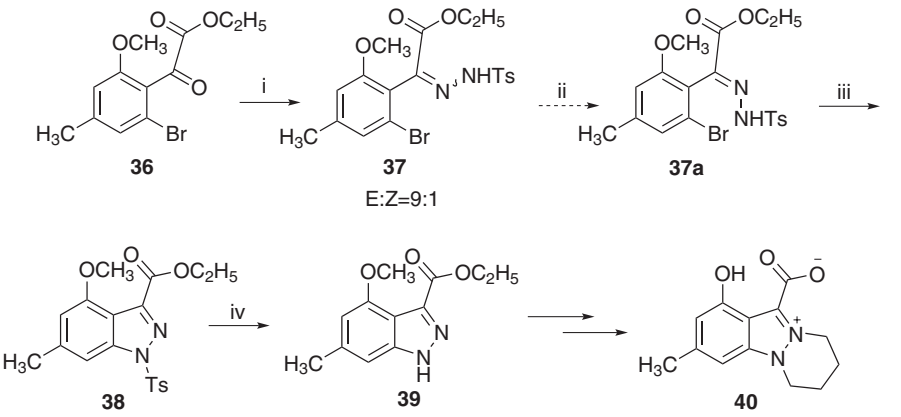
A side-product of this pathway, 3-amino-1*H*-indazole **35**, was observed in the experiments with oximes possessing relatively high levels of *Z*-isomers. The yields of the target 1*H*-indazoles were in the range of 69–94% with the exception of *o*-fluorobenzaldehyde bearing a methoxy group at position 6 (the yield in this case was only 5%). Synthesis of 1*H*-indazoles *via* hydrazone intermediates was also described by Inamoto *et al.*[21] for




(i) $NH_2OCH_3$; (ii) $NH_2NH_2$

**Scheme 12**
Method B.

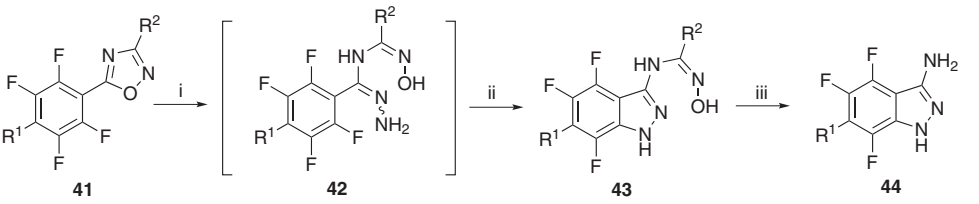
synthesis of nigellicine (**40**). Treatment of ethyl 2-(2-bromo-6-methoxy-4-methylphenyl)-2-oxoacetate **36** with *p*-tosylhydrazide in EtOH afforded hydrazone **37** as a mixture of *E*- and *Z*-isomers in the ratio 9:1 (*Scheme 13*) for cyclization to the pyrazole ring, only the *E*-isomer **37a** was suitable. Therefore, for the next step, isomers had to be separated by column chromatography. Nucleophilic substitution affording intermediate **38** was performed with use of $Pd(OAc)_2$ and 1,1′-*bis*(diphenylphosphino)ferrocene (dppf) as a catalyst, and lithium *bis*(trimethylsilyl)amide (LiHMDS) or $K_3PO_4$ as a base. The reaction was performed at room temperature, in 26 hours when $K_3PO_4$ was used as a base (45% yield), and in 66 hours when LiHMDS was used as a base (50% yield). The tosyl group was removed by tetrabutylammonium fluoride (TBAF) at low temperature (0°C) to afford ethyl 4-methoxy-6-methyl-1*H*-indazole-3-carboxylate (**39**) in 95% yield. Nigellicine (**40**) was then obtained in the next three steps.)




(i) $NH_2NHTs$, EtOH, 50 °C, 43h; (ii) column chromatography; (iii) LiHMDS or $K_3PO_4$, $Pd(OAc)_2$, dppf, dioxane, rt, 26-66h; (iv) TBAF, THF, 0 °C, 3h

**Scheme 13**

A different approach to 3-amino-1*H*-indazoles with various substituents at C(6) represents an ANRORC (**A**ddition of **N**ucleophile, **R**ing-**O**pening and **R**ing-**C**losure) rearrangement of 5-tetrafluorophenyl-1,2,4-oxadiazoles **41** with hydrazine (*Scheme 14*).[22] First, the C(5) carbon of the 1,2,4-oxadiazole ring underwent nucleophilic attack by hydrazine, followed by ring opening and subsequent cyclization leading to fluorinated intermediate



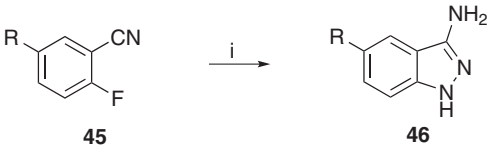

(i) $NH_2NH_2$, DMF, rt, 1h; (ii) -HF; (iii) EtOH/HCl

**Scheme 14**

**43**. Hydrolysis afforded the target 3-amino-1*H*-indazoles **44** in yields ranging 65–98%. The starting 5-tetrafluorophenyl-1,2,4-oxadiazoles **41** were prepared by a two-step synthesis in 90–96% yields.

### *4. Synthesis of 1H-Indazoles from o-Fluorobenzonitrile*

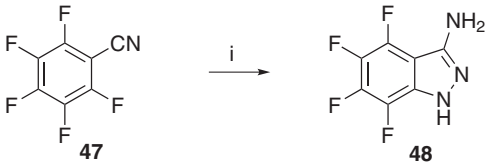
5-Substituted *o*-fluorobenzonitriles **45** were utilized as a starting material for the preparation of 5-substituted 3-amino-1*H*-indazoles **46** by reaction with hydrazine hydrate under reflux (*Scheme 15*).[14] The authors did not report yields for this reaction.




(i) $NH_2NH_2.H_2O$, *n*-BuOH, reflux, 4h

**Scheme 15**

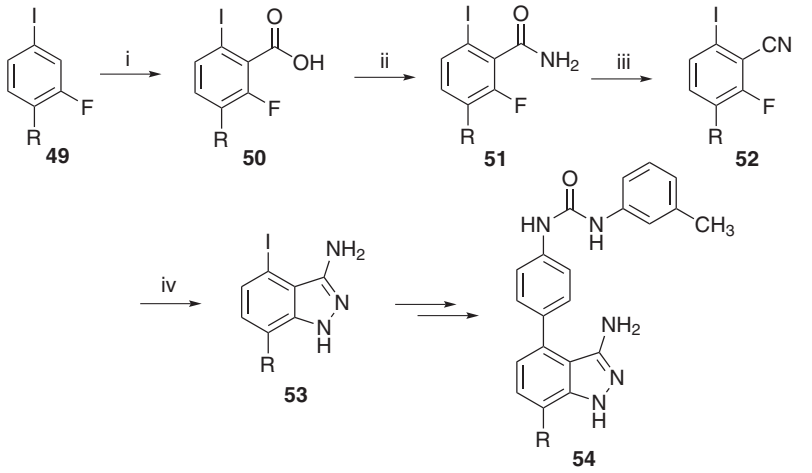
Later on, similar conditions were used for the synthesis of perfluorinated 3-amino-1*H*-indazole **48** from pentafluorobenzonitrile **47** in 25% yield (*Scheme 16*).[22]




(i) *t*-BuOK/MeOH; then $NH_2NH_2$

**Scheme 16**

Dai and co-workers[23] reported the synthesis of 3-amino-1*H*-indazoles **53** in good yields (80–90%) from *o*-fluorobenzonitrile and they were further transformed into coupled products **54**. A disadvantage of this approach was the preparation of 3-substituted 2-fluoro-6-iodobenzonitrile **52** from 1-fluoro-3-iodobenzene **49**. The three-step synthesis required low temperature (−78°C), high temperature (over 100°C), solid $CO_2$, and handling of phosgene (*Scheme 17*).



(i) LDA, THF, -78 °C, 1h, then solid $CO_2$, -78 °C to rt; (ii) $SOCl_2$, reflux, 2h or $(COCl)_2$, cat. DMF, rt, then $NH_4OH$ conc aq, THF, 0 °C to rt; (iii) $SOCl_2$, DMF, 115 °C; (iv) $NH_2NH_2.H_2O$, *n*-BuOH, 110 °C

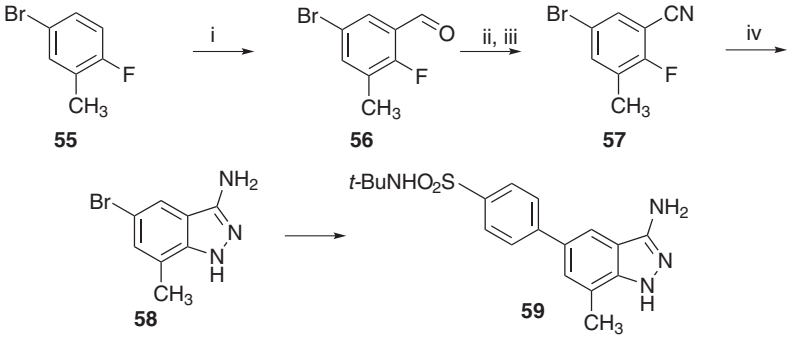
**Scheme 17**



A similar approach to 3-amino-1*H*-indazole was described by Antonysamy *et al.*[24] In order to obtain Janus kinase 2 (JAK-2) inhibitor **59**, 3-amino-1*H*-indazole **58** was prepared (*Scheme 18* ) and made to undergo Suzuki coupling. JAK-2 inhibitors are produced by genes found in leukemia patients. Mutations in these signaling proteins have been implicated in some myeloproliferative disorders. The yield of 5-bromo-7-methyl-1*H*-indazol-3-amine **58** was 81%. The method was applied to the synthesis of only one compound thus it is difficult to assess usefulness of this method for other derivatives. Moreover, working at −78°C is inconvenient.

### *5. Synthesis of 1H-Indazoles by 1,3-Dipolar Cycloaddition*

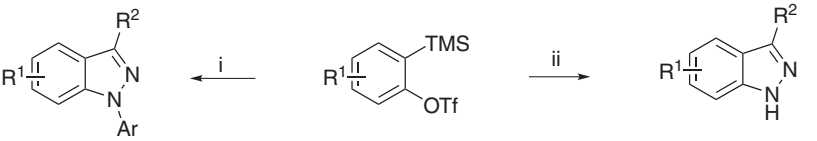
A general procedure for the synthesis of *N*-unsubstituted 1*H*-indazoles and 1-aryl indazoles was developed by Jin *et al.*[25] 1,3-Dipolar cycloaddition proceeded between arynes



(i) LDA, THF, -78 °C; DMF; (ii) $NH_2OH.HCl$, EtOH, NaOAc, rt; (iii) $Ac_2O$, 140 °C; (iv) $NH_2NH_2.H_2O$, EtOH, 120 °C

**Scheme 18**

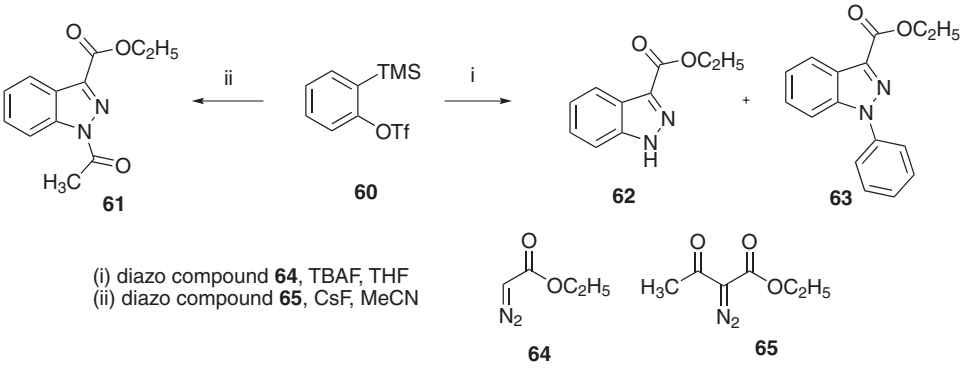
generated *in situ* from commercially available silylaryl triflates and various diazo compound. Depending on reaction conditions, the specific synthesis of either of the two products was possible (*Scheme 19*).




(i) $R^2CHN_2$ (0.5 equiv), CsF, MeCN, rt; (ii) $R^2CHN_2$ (1.2 equiv), KF/[18]crown-6, THF, rt

**Scheme 19**

A wide range of 1*H*-indazoles was prepared by the [3+2] cycloaddition of diazo compounds with *o*-(trimethylsilyl)aryl triflates in the presence of CsF or *n*-tetrabutylammonium fluoride (TBAF) at room temperature.[26] Benzyne generated *in situ* by treatment of *o*-(trimethylsilyl)aryl triflate (**60**) with CsF or TBAF reacted with the diazo compounds (*Scheme 20*) to afford the target indazoles. The outcome of the reaction was diazo compound dependent. While the cycloaddition of monosubstituted diazomethane derivatives **64** yielded a mixture of *N*-unsubstituted 1*H*-indazoles **62** and 1-aryl-1*H*-indazoles **63**, use of dicarbonyl containing diazo compound **65** afforded 1,3-disubstituted 1*H*-indazoles **61**. The authors optimized reaction conditions for the synthesis of individual derivatives.

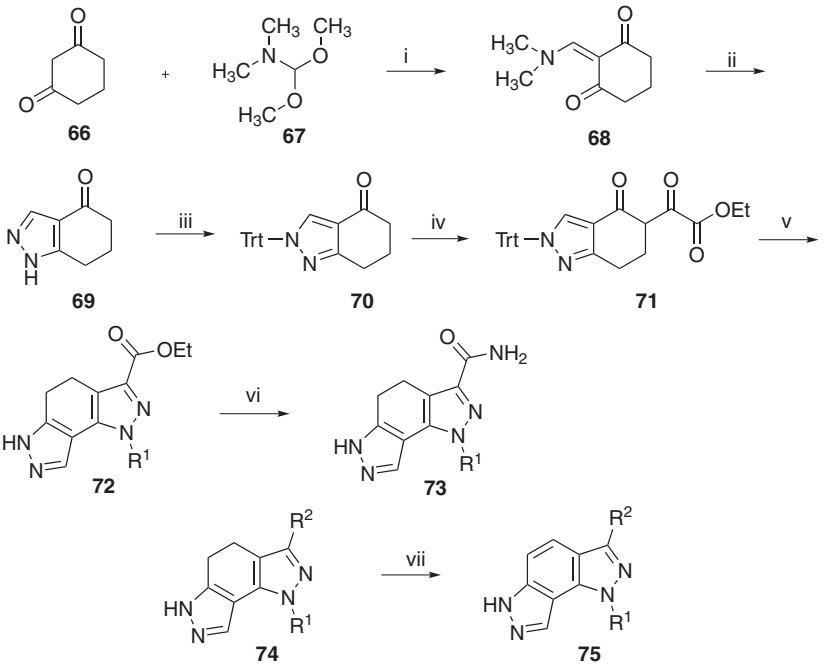



**Scheme 20**

### *6. Synthesis of 1H-Indazoles from Baylis-Hillman Adducts*

Tetrahydrobenzodipyrazoles were reported as a new class of potent cyclin-dependent kinase 2 (CDK2) inhibitors.[27] CDK2 has an influence on the G1 and S phase of the cell cycle, and is essential for the G1/S transition. Target compounds were synthesized from the Baylis-Hillman adduct of cyclohexane-1,3-dione **66** and 1,1-dimethoxy-*N*,*N*-dimethylmethanamine **67**[28] by a six-step synthesis (*Scheme 21*).

N-Protection of compound **69** with the trityl group reportedly afforded only one regioisomer **70** and deprotection occurred during the closure of the second pyrazole ring.




(i) reflux, 1h; (ii) $NH_2NH_2.2HCl$, NaOH/MeOH, reflux, 3h; (iii) TrCl/TEA, DCM; (iv) $(COOEt)_2$, $(Me_3Si)_2NLi$ (v) $NH_2NHR^1$, AcOH, 65 °C, 3h; (vi) $NH_4OH$/MeOH, 25-60 °C, 1-2 days; (vii) DDQ/dioxane, 100 °C, 2.5h

**Scheme 21**

Even though this is a multi-step synthesis, the intermediates were obtained in very good yields (75–98%) and in crystalline form. The ester or amide moiety at position 3 of compounds **72** and **73** could be converted into other functionalities. The last step, oxidation of tetrahydrobenzodipyrazoles **74** into dihydrobenzodipyrazoles **75**, was carried out by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in high yields (73–87%). The generality of this method was demonstrated by the preparation of more than forty derivatives and it appears to be robust.

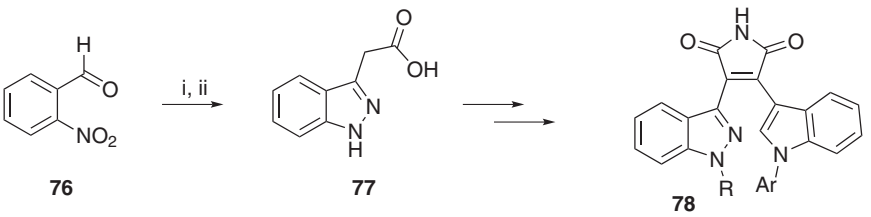
### *7. Synthesis of 1H-Indazoles from o-Nitrobenzaldehyde*

Zhang and co-workers described the synthesis of 3-substituted 1*H*-indazoles from *o*-nitrobenzaldehyde (**76**) by reaction of malonic acid in the presence of ammonium formate in EtOH.[29] Subsequent reductive cyclization in the presence of base gave 2-(1*H*-indazol-3-yl)acetic acid (**77**) in 54% yield, which was further transformed to afford the target indolylindazolylmaleimides **78** (*Scheme 22*).

## II. Syntheses of *N*-Substituted 1*H*-Indazoles

### *1. Synthesis of 1H-Indazoles from o-Halophenylalkan-1-one*

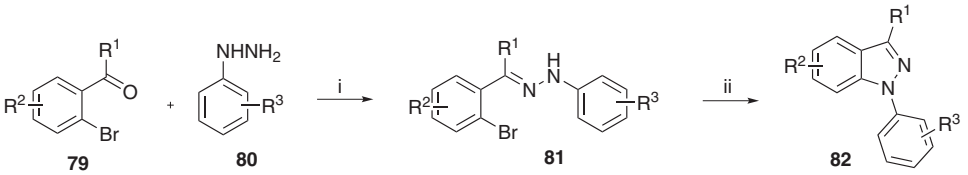
Reaction of *o*-bromobenzaldehydes/*o*-bromoacetophenones with arylhydrazines afforded the corresponding arylhydrazones, which were further cyclized to yield target




**76** **77** **78**

(i) $CH_2(CO_2H)_2$,$HCO_2NH_4$, EtOH; (ii) $N_2H_4$, Ra-Ni, aq NaOH

**Scheme 22**




**79** **80** **81** **82**

(i) for $R^1$ = H: MeOH, reflux, 30 min, then -30 °C, 12h; for $R^1$ = alkyl, aryl: dry ether, 40 °C, 140h;
(ii) $Pd(dba)_2$, DPEphos, $K_3PO_4$, toluene, 110 °C, 8h

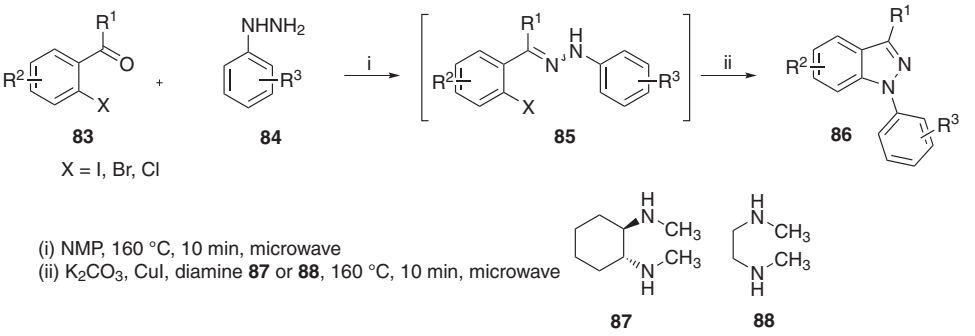
**Scheme 23**



1-aryl-1*H*-indazoles (*Scheme 23*). Synthesis of substituted 1-aryl-1*H*-indazoles using this strategy was studied in detail.[30]

*bis*(Dibenzylideneacetone)palladium ($Pd(dba)_2$) and chelating phosphines were tested as catalysts in the presence of $Cs_2CO_3$ or $K_3PO_4$ as a base. Racemic 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthyl (rac-BINAP), *bis*-(2-diphenylphosphinophenyl)ether (DPEphos), and dppf appeared to be the most effective ligands. In contrast, electron-rich, bulky ligands commonly used for intermolecular amination such as $P(t\text{Bu})_3$ and $o\text{-PhC}_6\text{H}_4\text{P}(t\text{Bu})_2$ were shown to be ineffective for cyclization. From the practical point of view, DPEphos was used for the synthesis, because it is much cheaper and more readily available than BINAP. The yields of hydrazones were dependent on the $R^1$ substituent. In general, the yields were in the range of 48–98% for $R^1 = H$; the yields dropped to 34–68% for $R^1 = CH_3$. Overall yields were 20–98%. The yields were also dependent on the purity of the starting hydrazones. The reaction temperature was 110°C and reaction time was generally 8 h. This method is supposed to be applicable for synthesis of variety of indazoles bearing electron-donating (Me, OMe) as well as electron-withdrawing ($NO_2$, $CF_3$) substituents.

A similar approach to 1*H*-indazoles is a Cu-catalyzed one-pot two-step microwave procedure.[31] Reaction of *o*-halobenzaldehydes or *o*-haloacetophenones with phenylhydrazines yielded arylhydrazones. In contrast to the previous synthesis (*Scheme 23*),[30] the arylhydrazones were not isolated and were cyclized *via* CuI/diamine-catalyzed *N*-arylation to afford 1-aryl-1*H*-indazoles (*Scheme 24* ). *N*-arylation was found to be the most effective (100% conversion) when 2 equiv of $K_2CO_3$, 5 mol% of CuI, and 10 mol% of diamine **87** were used at that step.

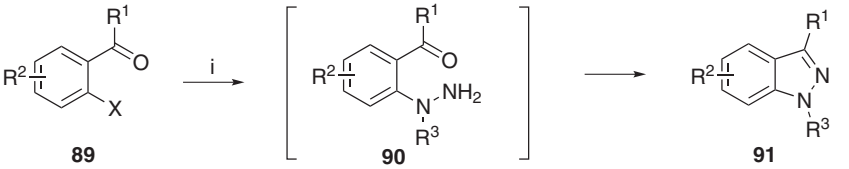



**Scheme 24**

The role of diamine ligand appears to be very important. When the diamine **87** was replaced by diamine **88**, the conversion dropped to 82%. Without any diamine, the conversion was less than 5%.

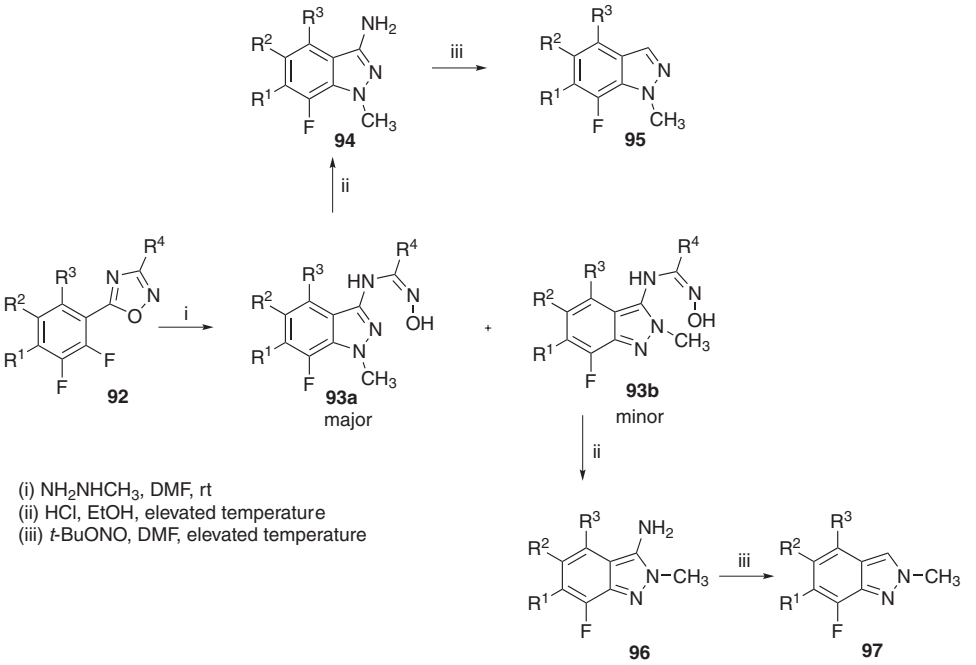
Replacement of $K_2CO_3$ by the more soluble $Cs_2CO_3$ had no influence on the conversion. Optimal temperature for the reaction was 160°C with a reaction time of 10 min. Higher temperatures promoted side-reactions, whereas lower temperatures led to incomplete conversion. *N*-Methyl-2-pyrrolidone (NMP) as a solvent proved to be the most effective in comparison with other solvents, such as toluene, dioxane, and DMF. Microwave-assisted heating was critical, as conventional heating required very long reaction times.

The versatility of the original methodology[30] prompted the search for the best reaction conditions. One-step regioselective synthesis of 1-alkyl-/1-arylindazoles was developed from 2-halobenzaldehydes/2-haloacetophenones/2-halocarboxylic acids *via* CuO-catalyzed amination catalyzed with 0.2 mol% of CuO in the presence of $K_2CO_3$, followed by intramolecular dehydration (*Scheme 25*).[32] Replacement of $K_2CO_3$ by $Cs_2CO_3$ surprisingly lowered yields, contrary to previously reported results.[31] The highest yields were obtained with 2-haloacetophenones and methylhydrazine (30–83%); coupling of 2-haloarylcarboxylic acids with methylhydrazine gave lower yields (16–54%) and coupling of fluoroarylketones with alkyl/arylhydrazines afforded 22–40% yields. The reaction time was 20 h and the reaction temperature was 110°C. A disadvantage of this method is the necessity of an inert atmosphere and to work in sealed tubes.




**Scheme 25**

As mentioned above, fluorinated 3-amino-1*H*-indazoles were formed as a result of an ANRORC rearrangement from 1,2,4-oxadiazoles (*Scheme 26* ).[33] 1,2,4-Oxadiazoles were treated with an excess of methylhydrazine to yield a mixture of fluorinated

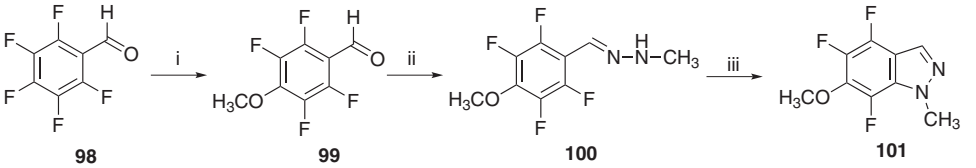



**Scheme 26**

*N*-methylindazole regioisomers with a preference for the *N*(1) isomer **93a**; nevertheless, the yields were poor in some cases (34–77%). Intermediate **93a** was then hydrolyzed to the corresponding 3-amino-1-methyl-1*H*-indazoles **94**. This step was carried out only with 4,5,7-trifluoro-6-methoxy-1-methyl-1*H*-indazol-3-amine to afford target 1-methyl-1*H*-indazole **95** in only 55% yield.

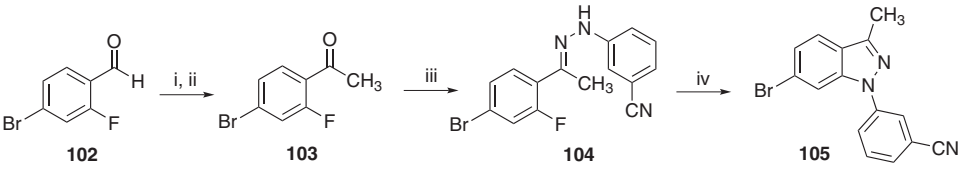
By this procedure, 2-methyl-2*H*-indazole **93b** was formed as well. Although the final step proceeded in 57% yield, the first two steps afforded very poor yields (4–38%).[34] For this reason, the method is not useful for the synthesis of 2*H*-indazoles.

The same authors also synthesized 1-methyl-1*H*-indazole by a different method. Pentafluorobenzaldehyde (**98**) was transformed into the 4-methoxy derivative **99**, which was condensed with methylhydrazine to yield the corresponding hydrazone **100** (60% yield). Cyclization to the target 1-methyl-1*H*-indazole **101** in pyridine at elevated temperature yielded only 22% of product (*Scheme 27*).




**Scheme 27**

Lee *et al.*[35] synthesized substituted 1-aryl-1*H*-indazoles using a similar protocol.[20,32] The corresponding non-fluorinated indazole analog was prepared in four steps in a similar fashion. Treatment of 4-bromo-2-fluorobenzaldehyde (**102**) with methylmagnesium bromide followed by oxidation with $CrO_3$ afforded 4-bromo-2-fluoroacetophenone (**103**); further treatment of **103** with arylhydrazine yielded the corresponding hydrazone **104** that was cyclized under basic conditions to afford target indazoles **105** (*Scheme 28*). This method is somewhat inconvenient as a Grignard reagent is used. The yield of the products was not reported.

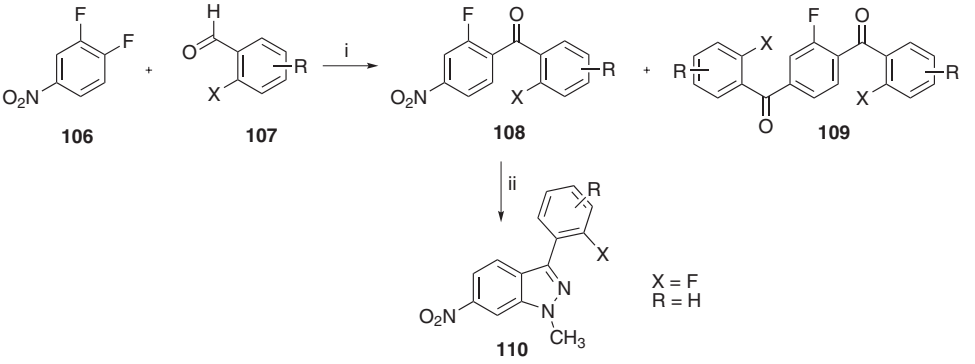



(i) $CH_3MgBr$, THF; (ii) $CrO_3$, DCM; (iii) EtOH, TSA; (iv) $K_2CO_3$, DMF, 100 °C, 2h

**Scheme 28**



An interesting route to 1*H*-indazoles was described by Suzuki and co-workers.[36] They synthesized indazoles *via* a *N*-heterocyclic carbene (NHC) catalyzed aroylation; imidazolidenyl carbene was used as a catalyst. The catalyst was generated *in situ* from 1,3-dimethylimidazolium iodide in the presence of NaH. 1,2-Difluoro-4-nitrobenzene **106** was treated with substituted *o*-halobenzaldehydes **107** catalyzed by NHC to afford benzophenones **108** in 27–70% yields; **109** was formed as a side-product. Substitution of fluorine with methylhydrazine and subsequent cycloaddition was carried out only with (2-fluoro-4-nitrophenyl)(2-fluorophenyl)methanone to form target indazole **110** in 40% yield (*Scheme 29*). In the first step, an argon atmosphere and low temperature (0°C) are required.

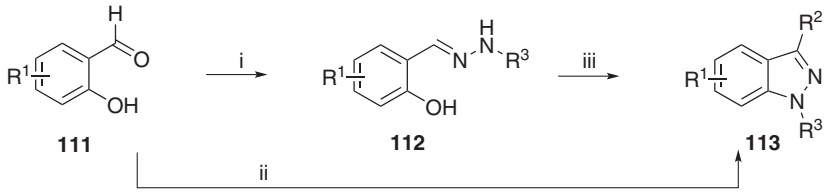



(i) 1,3-dimethylimidazolium iodide, NaH/DMF, 0 °C, 1h; (ii) $NH_2NHCH_3$, 1,4-dioxane, reflux, 12h

**Scheme 29**

### *2. Synthesis of 1H-Indazoles from o-Hydroxybenzaldehyde*

1,3,5,6,7-Substituted 1*H*-indazoles were prepared *via* arylhydrazones that were obtained by condensation of *o*-hydroxybenzaldehyde **111** with an excess of hydrazine hydrochloride under reflux in ethanol.[37] A set of compounds was synthesized with yields in the range of 70–92% (*Scheme 30*).




(i) $NH_2NHR^3$ . $H_2O$ (2 equiv), EtOH; (ii) $NH_2NHR^3$ . $H_2O$ (excess), EtOH; (iii) $H^+$/EtOH

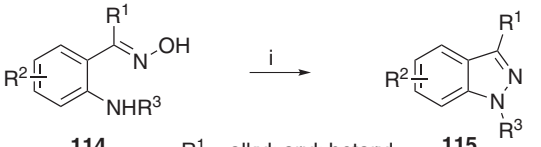
**Scheme 30**



The same authors also studied the effect of solvent on the yields. The use of DMF or DMSO gave the highest yields (85%, 92%), while in acidic ethanol slightly lower yields were obtained. The advantages of this method are availability of the starting materials, few reaction steps, and good yields. On the other hand, the method has some limitations; the presence of –OH group on the benzaldehyde at the *ortho* position was shown to be necessary for indazole formation; reaction of hydrazine hydrochloride with benzaldehydes without *o*-hydroxy group gave only hydrazones (reaction with *o*-methoxy-, *o*-allyloxy-, *o*-benzyloxy-, and *o*-halobenzaldehydes failed). Acidic conditions were also necessary for cyclization.

### *3. Synthesis of 1H-Indazoles from o-Aminobenzoximes*

*o*-Aminobenzaldehyde oximes can serve as starting materials for the synthesis of substituted 1*H*-indazoles.[38] Mesyl chloride appears to be a better activating agent for the hydroxy group than acetyl chloride, $Boc_2O$, methyl chloroformate, or tosyl chloride. Activated oximes **114** were then attacked by the amino group. The yields of target indazoles **115** were in the range of 35–87% (*Scheme 31*).




$R^1$ = alkyl; aryl; hetaryl
$R^2$ = H; 5,6-di$OCH_3$; 5-Cl
$R^3$ = H; alkyl; aryl; Ms; Ts

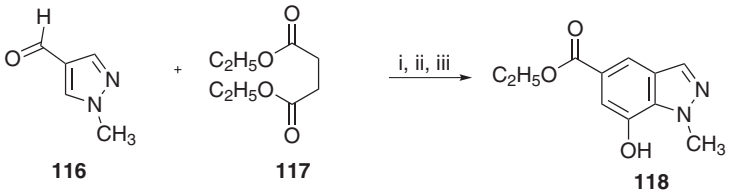
(i) MsCl (1.2 equiv), TEA (2.0 equiv), DCM, 0-23°C

**Scheme 31**

The influence of isomers on the reactivity has been also studied. It was found in agreement with previous work,[21] that the *E*-isomer afforded less than 5% of the target indazole. In contrast, an increasing amount of *Z*-isomer gave increasing yields (up to 86%). The starting oximes **114** were prepared from corresponding ketone and hydroxylamine hydrochloride with pyridine or NaOH as a base. The yields of oximes were in the range of 40–80%.

### *4. Synthesis of 1H-Indazoles from 1-Methyl-1H-pyrazole-4-carbaldehyde*

An unusual approach to indazoles was reported by Simoni *et al.*[39] A pyrazole derivative **116** was used as a starting material and the benzene core was created. During the last five years, this methodology was reported only for the synthesis of 1*H*-indazoles. The reaction is started by a Stobbe condensation of 1-methyl-1*H*-pyrazole-4-carbaldehyde **116** with ethyl succinate **117**, followed by acylation of the pyrazole ring at position 5 (*Scheme 32*). Ethyl 7-hydroxy-1-methyl-1*H*-indazole-5-carboxylate (**118**) was further converted into *combretastatin* analogs for evaluation of cytotoxicity on the bovine microvascular endothelial cell line (BMEC).




(i) *t*-BuOH, KOBu, reflux, 2h; (ii) $Ac_2O$, AcONa, reflux, 5h; (iii) $K_2CO_3$, EtOH, reflux

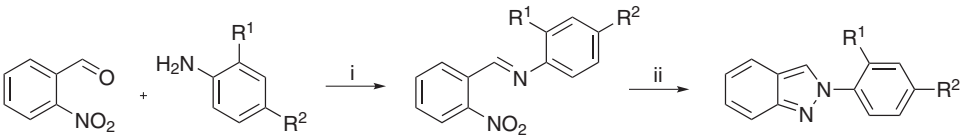
**Scheme 32**

## III. Syntheses of *N*-Substituted 2*H*-Indazoles

### *1. Synthesis of 2H-Indazoles from o-Nitrobenzaldehydes*

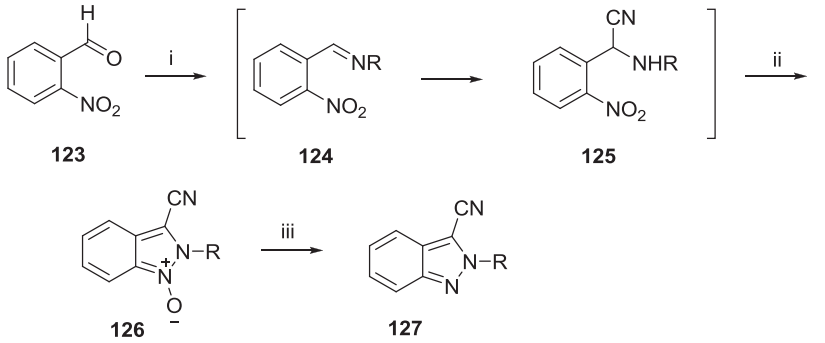
Synthesis of 2*H*-indazoles from *o*-nitrobenzaldehyde and suitably substituted anilines, described for the first time in 1962,[40] was modified for green chemistry.[41] For this purpose, "water-based biphasic reaction" was developed. Liquid reactants were mixed in a large amount of water to form a biphasic system from which Schiff bases **121** precipitated in pure form in about 90% yield. Reaction of the Schiff base with an excess triethyl phosphite under microwave irradiation, afforded 2*H*-indazoles **122** in 60–70% yields (*Scheme 33*). This convenient and effective route was supposedly applicable for small scale as well as multi-molar scale reactions. However, the authors reported the synthesis of only five 2*H*-indazoles.

In interesting work, Gerpe and colleagues[42] were inspired by an older preparation[43–45] of 2*H*-indazoles and their oxides from *o*-nitrobenzaldehyde and applied this to synthesis of 2-substituted 3-cyano-2*H*-indazole 1-oxides **126** (*Scheme 34*). The Schiff bases obtained from *o*-nitrobenzaldehyde and amines were treated with sodium cyanide to yield




(i) microwave, 2 min; (ii) $(EtO)_3P$ (excess), microwave, max 150°C

**Scheme 33**




(i) $NH_2R$, KCN, AcOH, rt; (ii) TEA, rt or $NaHCO_3$, rt or spontaneously; (iii) $PPh_3$, EtOH, reflux, 4-5h

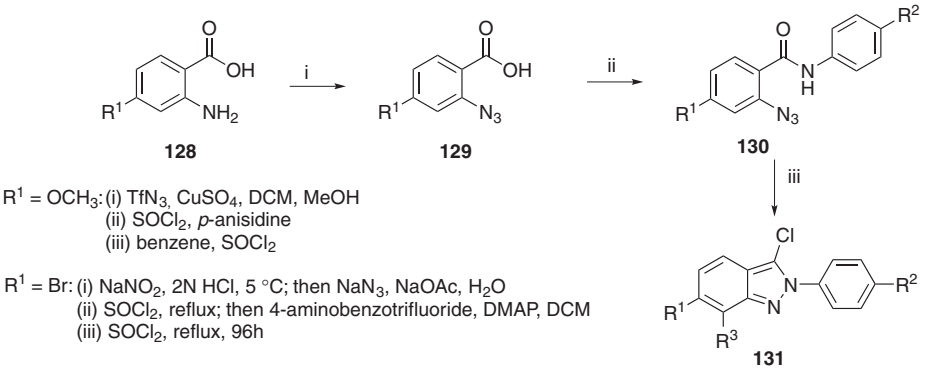
**Scheme 34**

$\beta$-aminonitrile derivatives **125**, which underwent base-mediated cyclization. Depending on the substituent on *N*(2), the cyclization proceeded in TEA, in the presence of $NaHCO_3$, or spontaneously to afford target 2*H*-indazole oxides **126** in yields of 15–75%. Three indazole oxides were deoxygenated using $PPh_3$ to afford 2*H*-indazoles **127** in yields 37–58%.

### *2. Synthesis of 2H-Indazoles from Anthranilic Acid Derivatives*

Recently, two research groups applied an old methodology[46] for the preparation of substituted 3-chloro-2*H*-indazoles (*Scheme 35*).[47,48] The aim was to transform the indazoles **131** into transient receptor potential vanilloid 1 (TRPV1) antagonists[48] as potential analgesics and highly selective ligands for the estrogen receptor $\beta$ (ER $\beta$)[47] as important pharmaceutical targets. In order to develop ER $\beta$ selective ligands, a series of non-steroidal compounds having a 2-aryl-2*H*-indazole core with different groups at C(3) were synthesized.[47] 2-Phenyl-2*H*-indazoles were shown to have a high affinity and good ER $\beta$ selectivity, especially those with polar and polarizable substituents at this site (halogen, $CF_3$, nitrile). The best of these compounds have affinities for ER $\beta$ comparable to estradiol.

The 2-aryl-2*H*-indazoles **131** were obtained in yields in the range of 35–85% and were transformed into indazolones as potent TRPV1 antagonists and into suitable 2-phenyl-2*H*-indazoles as compounds with high ER $\beta$ subtype affinity and potency selectivity.




$R^1$ = $OCH_3$: (i) $TfN_3$, $CuSO_4$, DCM, MeOH
(ii) $SOCl_2$, *p*-anisidine
(iii) benzene, $SOCl_2$

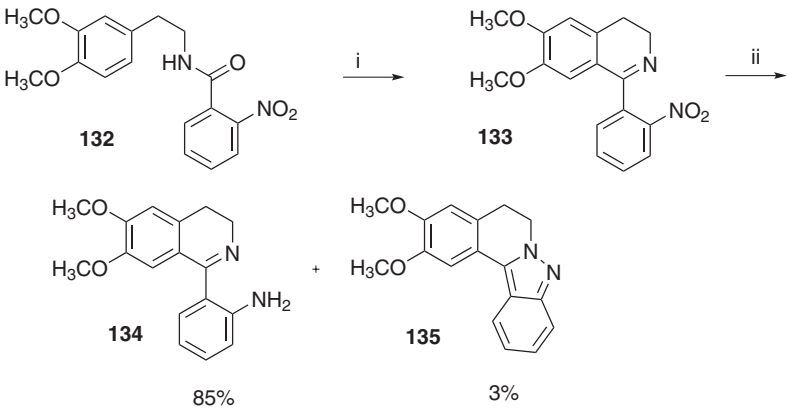
$R^1$ = Br: (i) $NaNO_2$, 2N HCl, 5 °C; then $NaN_3$, NaOAc, $H_2O$
(ii) $SOCl_2$, reflux; then 4-aminobenzotrifluoride, DMAP, DCM
(iii) $SOCl_2$, reflux, 96h

for $R^1$ = $OCH_3$; $R^2$ = $OCH_3$; $R^3$ = H (35%), $R^3$ = Cl (51%)
for $R^1$ = Br: $R^2$ = $CF_3$; $R^3$ = H (85%)

**Scheme 35**

### *3. Synthesis of 2H-Indazoles from o-Nitrobenzamides*

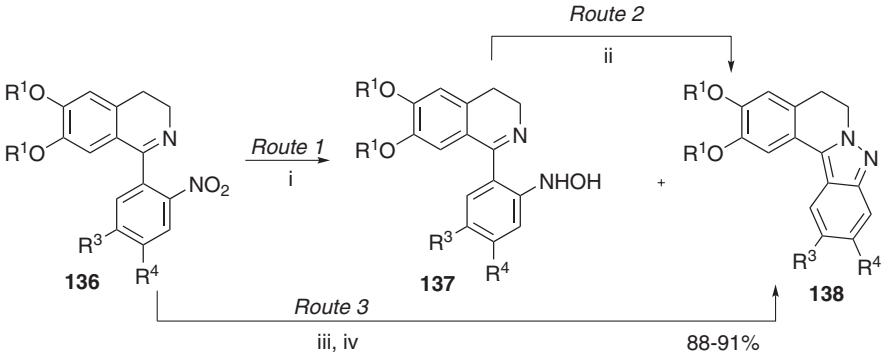
Unprecedented $SnCl_2$-mediated cyclization *via* N–N bond formation was described by Sawant *et al.*[49] The formation of 5,6-dihydroindazolo[3,2-*a*]isoquinoline (**135**) was observed during reduction of the nitro group of *o*-nitrobenzamide **133** using $SnCl_2{\cdot}2H_2O$ as a side-product in 3% yield (*Scheme 36*). The reaction probably involved a hydroxylamine intermediate that intramolecularly cyclized *via* N-N bond formation. Reduction with Pd/C or $(EtO)_3P$ did not afford any indazole. Interestingly, N-N bond formation between amino and nitro groups was used to synthesize indazole oxides, discussed in *Section 4*.




(i) $POCl_3$, $PhCH_3$, reflux; (ii) $SnCl_2.2H_2O$, MeOH

**Scheme 36**

The synthesis of 2*H*-indazoles was also carried out by using nitroarene substrates derived from dihydroisoquinolines **136** (*Scheme 37*). Reduction of the nitro group with $SnCl_2{\cdot}2H_2O$ in the presence of benzenethiol and TEA afforded hydroxylamine derivative **137** in 71% yield and 2*H*-indazole derivative **138** in 29% yield (*Route 1*). Cyclization



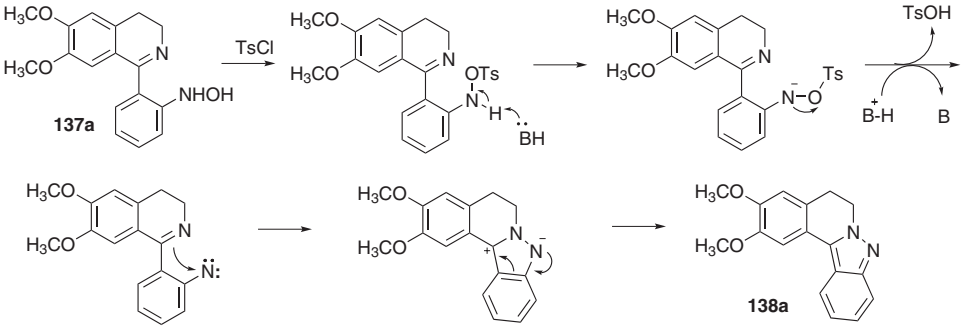

Route I: (i) $SnCl_2.2H_2O$, PhSH, TEA, MeCN, rt, 15 min
Route II: (ii) TsCl, MeCN, 10 min
Route III: (iii) $SnCl_2.2H_2O$, PhSH, TEA, MeCN, rt, 15 min; (iv) TsCl, 10 min

**Scheme 37**



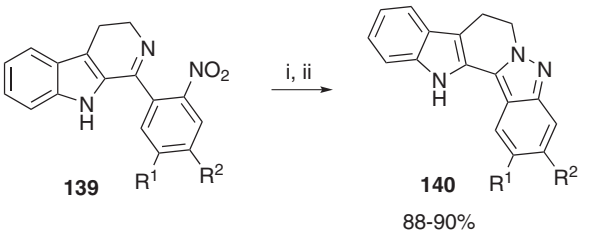
*via* hydroxylamine **137** to the 2*H*-indazole **138** may have occurred by the loss of a water molecule, which can be formed by the combination of a proton obtained from the protonated base and the hydroxyl anion departing from the hydroxylamine in **137**. In view of the poor nucleofugicity of the hydroxy group, it was converted to the tosyloxy group to facilitate the process (*Route* 2). The next, *Route 3*, represents a one-pot conversion of nitro compound **136** into 2*H*-indazole derivative **138** and subsequent tosylation of the hydroxy group. The final products achieved by *Route 3* reach to 88–91% yields.

A plausible mechanism for the intramolecular cyclization of arylhydroxylamine **137a** to dihydroindazoloisoquinoline **138a** could be *via* an electron-deficient nitrene intermediate (*Scheme 38*).




**Scheme 38**

The versatility of this methodology was also demonstrated on the nitroarene substrates derived from dihydro-$\beta$-carbolines **139** (*Scheme 39*). The yields reach to 88–90%.




(i) $SnCl_2.2H_2O$, PhSH, TEA, MeCN, rt, 15 min; (ii) TsCl, rt, 15 min

**Scheme 39**

### *4. Synthesis of 2H-Indazoles from Sulfonamide Ketones*

Up to now, indazoles were predominantly prepared in solution. Solid-phase synthesis of 2*H*-indazoles was first reported by Lopez and co-workers in 2000.[50] Recently, a very efficient tandem reaction was reported in solid phase.[51] The synthesis of substituted 2*H*-indazoles and their 1-oxides occurred under very mild conditions, with diversely substituted building blocks and high purity of products.

N-Alkylation of polymer-supported 2-nitrobenzenesulfonyl (2-Nos)-activated/protected amines by bromoketones provided $\alpha$-sulfonylamino ketones. Treatment of these 2-Nos derivatives with DBU led to tandem carbon-carbon bond-formation followed by nitrogen-nitrogen bond formation to produce indazole oxides of excellent purity (*Scheme 40*). To access the parent heterocycle, mesyl chloride in the presence of triethylamine[52] at ambient temperature turned out to be the reagent of choice for mild deoxygenation of indazole oxides **144** to indazoles **146**. A small combinatorial array of 2,3-substituted 2*H*-indazoles was prepared by using five resin-bound amines prepared from amino moiety substrates, two 2-Nos chlorides, and four bromoketones.

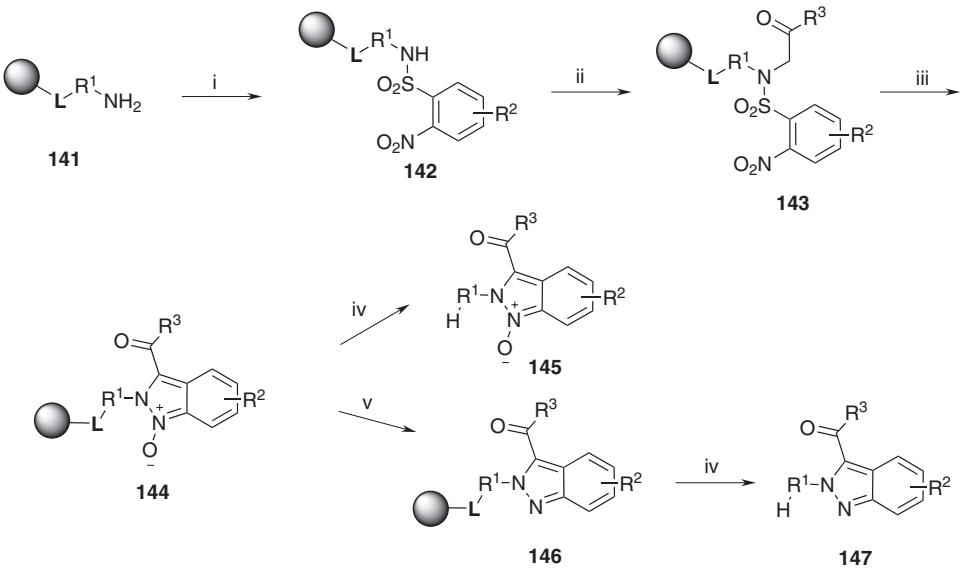
A tandem reaction of 2-nitrobenzenesulfonyl $\alpha$–aminoketones **143** leading to indazole **144** oxides involved two consecutive transformations, C–C bond formation followed by N–N bond formation. Unlike 4-nitrobenzenesulfonyl derivatives, the 2-Nos (2-nitrobenzenesulfonyl) group is not cleaved by treatment of the 2-nitro derivatives with mercaptoethanol and DBU (*Scheme 41*).

Instead, the 2-Nos group is removed by an internal C-nucleophile generated by DBU from the $\alpha$-ketosulfonamide. This transformation can be regarded as a variation of an S–C Smiles rearrangement involving an internal C-nucleophile. The 2-nitrobenzylamine intermediate underwent spontaneous cyclodehydration to form indazole oxides.

The presence of a carbonyl group at the side-chain of the substituent in position 2 allowed subsequent transformations of indazoles and formation of a fused pyrazine ring *via* an intramolecular nucleophile located on the $R^1$ side-chain, providing a route for pyrazino[1,2-b]indazoles **146a** (*Scheme 42*).[53]

### *5. Synthesis of 2H-Indazoles from Baylis-Hillman Adducts*

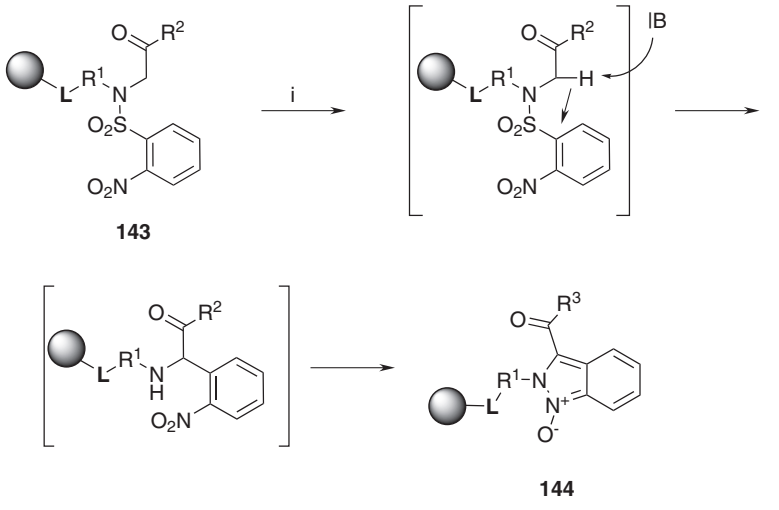
2,3-Disubstituted 2*H*-indazoles were synthesized from Baylis-Hillman adducts **149** prepared from cyclohex-2-en-1-one and aldehydes.[54] Subsequent transformation into




(i) 2-Nos chloride, lutidine, DCM, 16h; (ii) bromoketone or bromoacetate, DIEA, DMF, 16h
(iii) DBU, DMF, 30 min; (iv) 50% TFA in DCM, 30 min; (v) mesyl chloride, TEA, DCM, 16h

**Scheme 40**

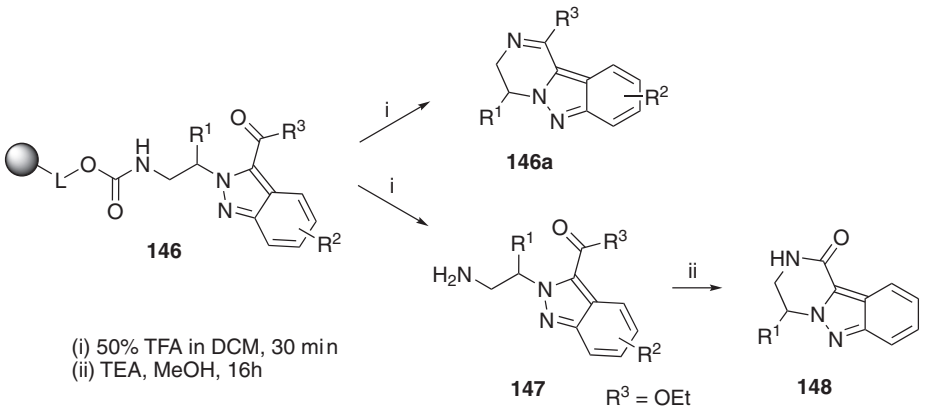




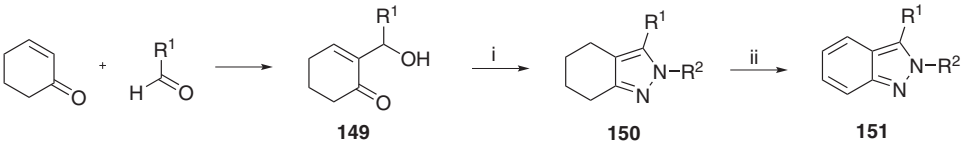

(i) mercaptoethanol, DBU, 30 min

**Scheme 41**

2,3-disubstituted 4,5,6,7-tetrahydro-2*H*-indazoles **150** proceeded by condensation with substituted hydrazines *via* the formation of hydrazone and spontaneous reaction with of the hydroxy group.[55] The cyclohexane moiety was then aromatized to the target indazoles **151** (*Scheme 43*). The oxidation was accomplished with 2 equiv of DDQ in benzene under reflux. The overall yields using DDQ were 69–80%; Pd/C and tetrachloro-1,4-benzoquinone




**Scheme 42**

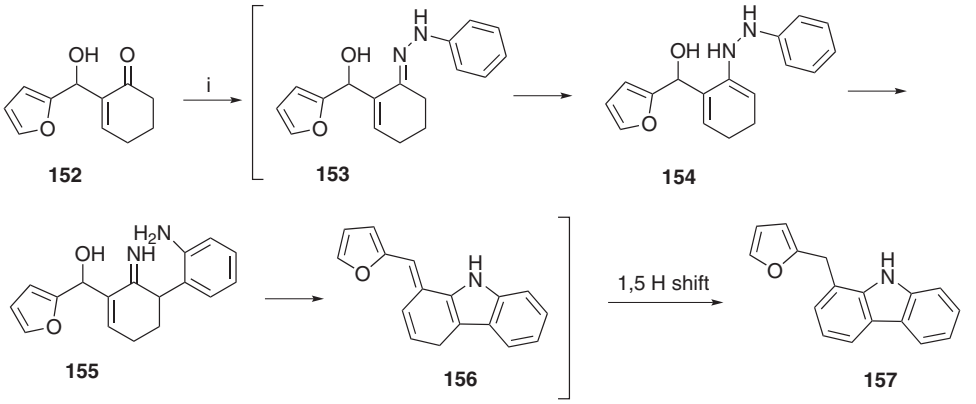



**Scheme 43**

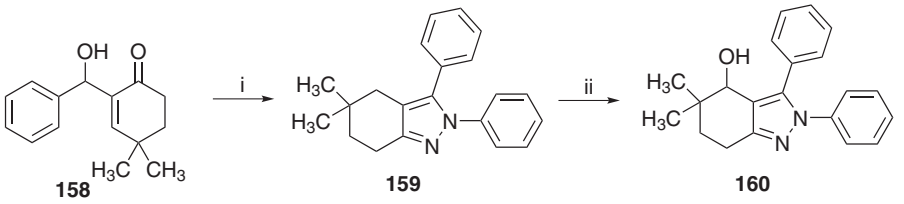


(*p*-chloranil) methods were not as effective. Cleavage of the *N*-substituent during oxidation was observed for indazoles with $R^2 = t$-Bu.

A limitation of this method is the formation of carbazole derivative **157** instead of the target 2*H*-indazole core for R = furanyl (*Scheme 44*). The hydrazone **153** was converted to the carbazole derivative *via* a mechanism analogous to the Fischer indole synthesis. Surprisingly, no pyrazole derivative was observed as an intermediate.




**Scheme 44**




(i) $PhNHNH_2$.HCl, DCE, reflux, 3 days; (ii) DDQ (2 equiv), benzene, reflux, 24h

**Scheme 45**

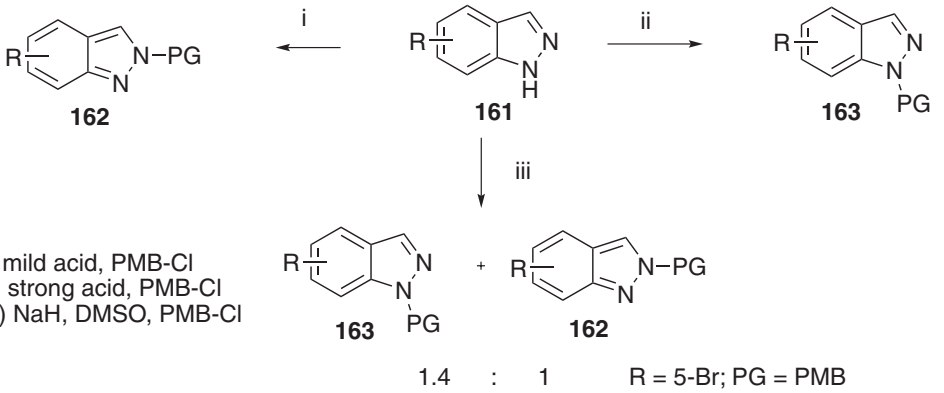
Another example of unexpected product formation was observed with the Baylis-Hillman adduct of 4,4-dimethylcyclohex-2-en-1-one with phenylhydrazine hydrochloride during oxidation with DDQ.[54] The authors reported formation of an alcohol derivative **160** without dehydrogenation of the cyclohexane moiety (*Scheme 45*).

## IV. Alkylation of 1*H*-Indazoles

Generally, the alkylation of *N*-H indazoles yielded a mixture of *N*(1) and *N*(2) regioisomers. Fine tuning the reaction conditions led to the regioselective alkylation and formation of either the *N*(1) or the *N*(2) isomer.[56] The energetically less favorable *N*(2) isomer was obtained under kinetically controlled conditions.

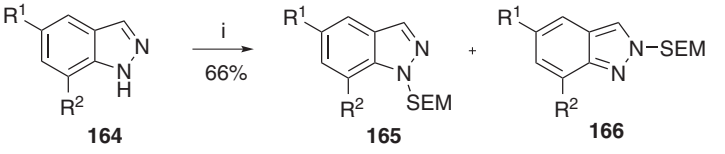
Alkylation of NaH-treated 1*H*-indazoles using alkyl bromides yielded *N*(1)-alkyl indazoles as the major products in 30–50% yield.[14,29] A mixture of regioisomers was obtained when alkylation was carried out in the presence of $K_2CO_3$, the alkylated 1*H*-indazoles being obtained after chromatography in 27–67% yield.[15]

1*H*-Indazoles were transformed into 2*H*-indazoles *via* regioselective alkylation of the *N*(2) position. Slade *et al.*[56] protected the nitrogen of the indazole in order to carry out other transformations. Protection with PMB-Cl (*p*-methoxybenzyl chloride) under mildly acidic conditions yielded the *N*(2) protected indazoles **162**, while strongly acidic conditions led to regioselective protection at *N*(1) (*Scheme 46*). In contrast, 1*H*-indazoles were unselectively protected under strongly basic conditions and afforded a mixture at *N*(1) and *N*(2) substituted indazoles.



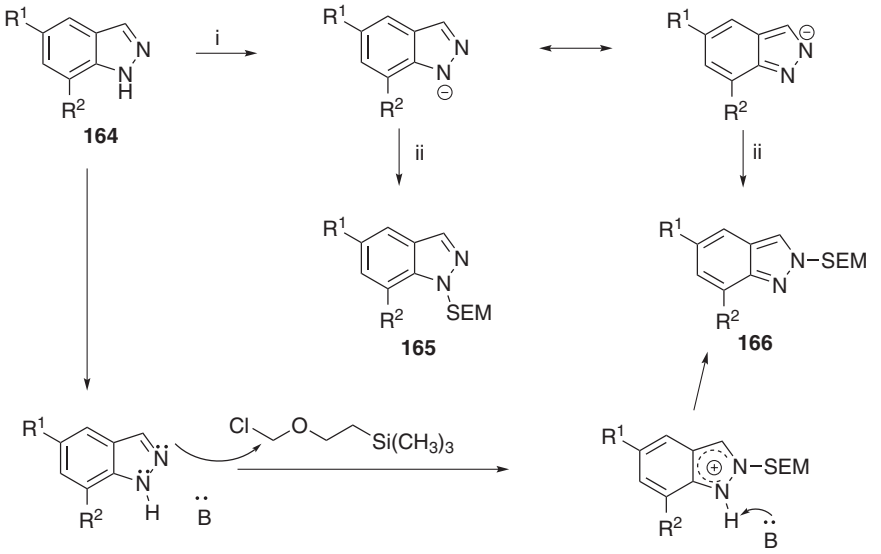

**Scheme 46**

The regioselectivity of alkylation was studied in detail by Luo and co-workers.[57] Alkylation of unsubstituted 1*H*-indazole **164** yielded both regioisomers **165** and **166** in good combined yield (66%) (*Scheme 47*). Under the same conditions, with 7-methyl-1*H*-indazole-5-carbaldehyde ($R^1$ = CHO, $R^2$ = Me) the ratio of the *N*(2) protected indazole, increased albeit in the same combined yield (66%).



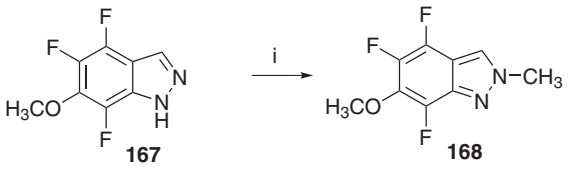

**Scheme 47**

An explanation of such reactivity is that after deprotonation of the 1*H*-indazole **164** by NaH, the resulting anion though preferring to remain localized on *N*(1) can apparently transfer to *N*(2) without much of an energy barrier. Therefore 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) reacts at both positions to afford the respective isomers (*Scheme 48*). When a non-deprotonating base is used, it should be the electron pair at *N*(2) that is the most nucleophilic and, thus, able to react with electrophiles such as SEM-Cl, because the electron pair on *N*(1) is part of the aromatic system. After cation formation, the N–H becomes sufficiently acidic to be deprotonated by the weaker base.




**Scheme 48**

Alkylation of unsubstituted 1*H*-indazole was also carried out by Piccionello *et al.*[33] Regioselective methylation was accomplished with $(CH_3)_3O^+ BF_4^-$ in EtOAc to afford the corresponding 2-methyl-2*H*-indazole **168** in 64% yield (*Scheme 49*).




(i) $(CH_3)_3O^+BF_4^-$, EtOAc

**Scheme 49**

## Conclusion

The last six years have witnessed considerable progress in methodologies for the preparation of indazoles. Most of these efforts focused on 1*H*-indazoles whereas syntheses of 2*H*-indazoles were studied less intensively. Since a plethora of compounds incorporating the indazole core were shown to have significant biological activity, substantial work was also devoted to find convenient and inexpensive synthetic routes compatible with diverse substitution patterns and employing easily accessible building blocks. This review article was devised with the practical point of view in mind.



## List of Abbreviations

| | |
|---|---|
| MeCN | Acetonitrile |
| BAL resin | 4-(4-Methylbenzyl)aminomethyl-3-methoxyphenoxy)butyric Acid Resin |
| BINAP | 2,2′-*bis*-(Diphenylphosphino)-1,1′-binaphthyl |
| BMEC | Bovine microvascular endothelial cell |
| CDI | 1,1′-Carbonyldiimidazole |
| CDK2 | Cyclin-dependent kinase 2 |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCE | Dichloroethane |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DIC | Diisopropyl carbodiimide |
| 2,4-diNos | 2,4-Dinitrobenzenesulfonyl |
| DME | Dimethoxyethane |
| DPEphos | *bis*-(2-Diphenylphosphinophenyl)ether |
| Dppf | 1,1′-*bis*(Diphenylphosphino)ferrocene |
| $DppONH_2$ | *O*-(Diphenylphosphinyl)hydroxylamine |
| EDC | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride |
| ER $\beta$ | Estrogen receptor $\beta$ |
| HOBt | *N*-Hydroxybenzotriazole |
| HTS | High throughput screening |
| $IC_{50}$ | Half maximal inhibitory concentration |
| iNOS | Inducible nitric oxide synthase |
| JAK-2 | Janus kinase 2 |
| LDA | Lithium diisopropylamide |

| | |
|---|---|
| LiHMDS | Lithium *bis*(trimethylsilyl)amide |
| NCS | *N*-Chlorosuccinimide |
| NHC | *N*-Heterocyclic carbenes |
| NMP | *N*-Methyl-2-pyrrolidone |
| nNOS | Neuronal nitric oxide synthase |
| NOS | Nitric oxide synthase |
| 2-Nos | 2-Nitrobenzenesulfonyl |
| $Pd(dba)_2$ | *bis*-(Dibenzylideneacetone)palladium |
| PDGF | Platelet-derived growth factor |
| PMB | 4-Methoxybenzyl |
| Py | Pyridine |
| SEM | 2-(Trimethylsilyl)ethoxymethyl |
| TBAF | Tetrabutylammonium fluoride |
| TRPV1 | Transient receptor potential vanilloid 1 |
| TEA | Triethylamine |
| VEGF | Vascular endothelial growth factor |



## Acknowledgement

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