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An efficient synthesis of 1-*H* indazoles

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Abstract—The reaction of substituted salicyaldehydes with hydrazine hydrochloride under different conditions gave the corresponding 1-*H* indazoles. However, the reaction of benzaldehydes with hydrazine hydrate under the same conditions yielded only hydrazones.
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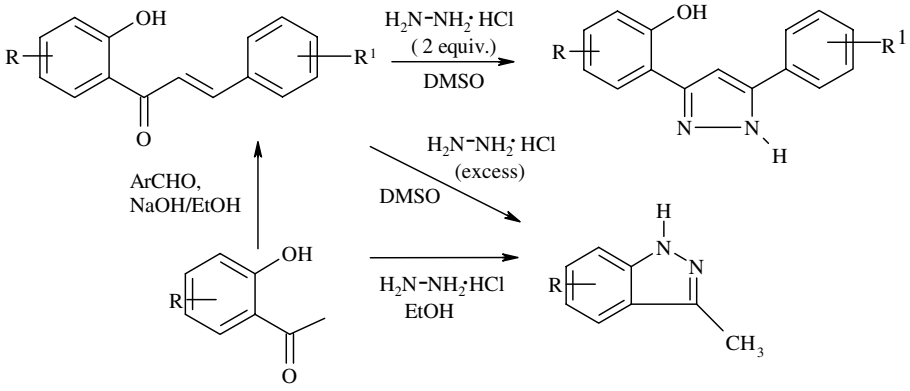
During the course of our work on the synthesis of pyrazoles from the reaction of 2′-hydroxychalcones with hydrazine hydrochloride[1] (Scheme 1) we noticed the formation of 3-methylindazole in low yields. Thus, we envisioned, that on reacting salicyaldehydes with excess hydrazine hydrochloride under reflux in ethanol the corresponding indazoles would be obtained. Indazole derivatives have been shown to possess a wide range of pharmacological activity including nitric oxide (NO) synthase inhibition,[2] analgesic,[3] antiinflammatory[4] and antiviral.[5] Indazoles also possess HIV protease inhibitory activity,[6] antifertility,[7] anticancer[8] and antispermatogenic activity.[9]

Syntheses of indazoles involving the cyclization of aryl hydrazones substituted with bromo,[10] chloro,[11] nitro,[12] fluoro[13] or mesylates[14] have been reported. There are several other methods reported on the synthesis of indazoles, which include reduction of protected azides[15] and cyclization of arylazosulphides.[16] In addition, diazotization and cyclization of substituted *o*-methylanilines[12] has been reported. However, the elevated temperatures required for indazole formation makes this approach impractical. These methods also have limitations from the point of view of yields, reaction conditions, availability of starting materials and generality.



Scheme 1. Formation of indazole from 2′-hydroxychalcones.

Keywords: Indazoles; Hydrazones; Salicyaldehyde; Hydrazine hydrochloride.
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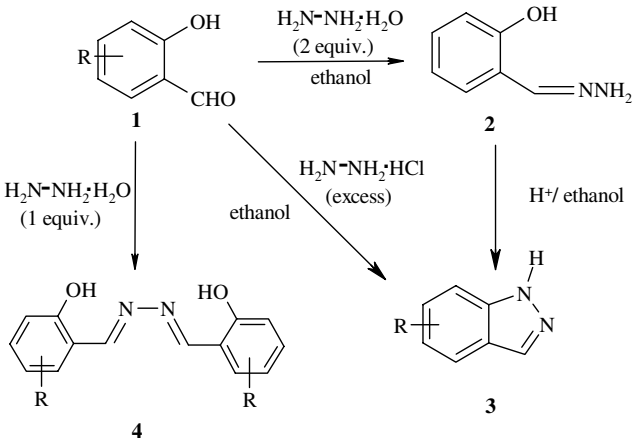


Scheme 2. Formation of indazole and other derivatives. Reagents and conditions: H_2N–NH_2·HCl, reflux,70%.

Our initial approach towards the synthesis of indazole from salicyaldehyde is shown in Scheme 2. On reaction of salicyaldehyde with hydrazine hydrochloride in acidic ethanol, indazole **3** was obtained in 92% yield. The use of acetic acid or hydrochloric acid was preferred. The use of aprotic solvents such as dimethylformamide and dimethylsulphoxide gave higher yields (Table 1). Other solvents did not have any significant effect on the yields of the product. In benzene, the corresponding hydrazine was usually formed in higher yield compared to the indazole. If the more nucleophilic hydrazine hydrate was used in excess, hydrazone **2** was formed exclusively. The hydrazones were fully characterized from spectral data. Reaction of two moles of salicyaldehyde with one mole of hydrazine hydrate gave dimer **4**.

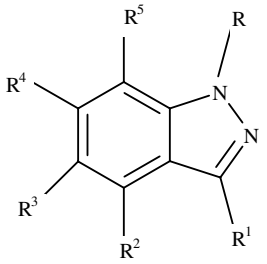
Various salicylaldehydes on refluxing with acidic ethanol gave the corresponding indazoles (Table 2). The formation of indazole using hydrazine has been reported in the literature.[1] The structures of all compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The reaction was then extended to the preparation of 3-methylindazoles under similar conditions. 2-Hydroxyacetophenones were refluxed with hydrazine hydrochloride in acidic ethanol to give 3-methylindazoles in quantitative yields (Scheme 1). Aryl hydrazines could also be used. The attempted acidic cyclization of 2-halosubstituted arylaldehydes in ethanol failed to provide the desired indazole.

Although the conversion of *o*-substituted benzaldehydes to the desired 1-*H*-indazole could be achieved by base,[6–11] 2-hydroxybenzaldehyde hydrazones did not undergo cyclization in practical yields when using base. The hydrazone of **1** gave only 20% of indazole when heated at 150 °C in *t*-butoxide/*t*-butanol.

Table 1. Effect of solvent on the yield of indazole

Entry	Solvent	Yield (%)
1	Dichloromethane	70
2	DMF	85
3	Toluene	66
4	IPA	71
5	Ethanol	78
6	Methanol	75
7	DMSO	92

Table 2. Synthesis of substituted indazoles ($R^2 = H$)

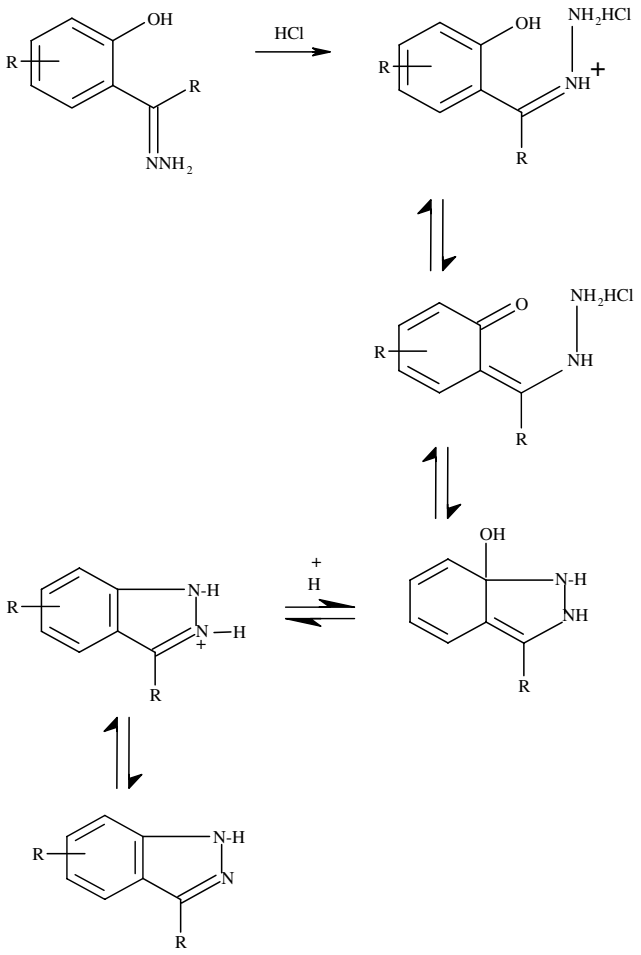


Entry	R	R^1	R^3	R^4	R^5	Mp (°C)	Yield (%)
1	H	H	H	H	H	Lit.[15]144	70
2	Ph	H	H	H	H	Lit.[17]78	90
3	H	H	NO_2	H	H	Lit.[15]144	85
4	Ph	H	NO_2	H	H	Lit.[17]180	92
5	H	H	H	H	NO_2	Lit.[12]187	78
6	Ph	H	H	H	NO_2	205	75
7	Ph	H	H	H	Cl	221	70
8	H	H	H	H	Cl	Lit.[15]134	80
9	H	H	CH_3	H	H	Lit.[15]111	85
10	Ph	H	CH_3	H	H	190	76
11	H	H	Cl	H	Cl	Lit.[18] 200	79
12	Ph	H	Cl	H	Cl	226	72
13	H	CH_3	H	H	H	Lit.[12]113	79
14	H	CH_3	CH_3	H	H	Lit.[19]	76
15	H	H	H	–NEt_2	H	102	70
16	Ph	H	H	–NEt_2	H	152	74

It is evident from Table 2 that the reaction can be carried out with a variety of electron rich or electron deficient salicylaldehydes and acetophenones with different substitution patterns. In all cases, we observed rapid conversion to the hydrazones, which underwent cyclization under acidic condition. The use of bases gave negligible yields for salicyaldehyde **1**. Cyclization was observed when 2,2′,4,4′-tetrahydroxybenzophenone was refluxed with hydrazine, phenyl hydrazine or methyl hydrazine at 200 °C.[11] As acidic conditions are an essential requirement, cyclization probably follows the Fischer-indole synthesis mechanism. Under acidic conditions the phenolic –OH group tautomerizes to a keto hydrazine, which undergoes cyclodehydration to afford the indazole as depicted in Scheme 3. Benzaldehydes without an *ortho*-hydroxy group gave only hydrazones in ethanol as was observed with acetophenones having no *ortho*-hydroxy group. Similarly *O*-methoxy, *O*-allyloxy and *O*-benzyloxy benzaldehydes yielded only hydrazones under similar conditions showing that the presence of –OH was necessary for indazole formation.

The significance of the present work lies in the availability of starting materials, fewer reaction steps, simplicity and good yields of products. This method allowed the synthesis of 7-methoxy- and 7-nitro-1-*H* indazoles, which are known NO synthase inhibitors.[2]

General procedure for the formation of indazoles: To a solution of salicylaldehyde **1** in ethanol (5 ml) was added hydrazine hydrochloride (in excess). The solution was



Scheme 3. Proposed mechanism for the synthesis of indazoles from substituted salicylaldehydes.

refluxed for 2–3 h and the solvent was distilled under reduced pressure. Purification of the residue by filtration through a pad of silica afforded indazole **3** as a yellow solid. The products were characterized from spectral data and melting points.[20]

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20. *^{1}H NMR data of new compounds:* (i) 5-(Diethylamino)-1-*H*-indazole (Table 2, entry 15), mp 102 °C ^{1}H NMR ($CDCl_3$) δ 8.01 (s,1H), 7.75 (s,1H), 7.58 (d, $J = 8.6$ Hz, 1H), 7.43 (dd, $J = 8.6$, 1.5 Hz, 1H), 5.2 (s, 1H), 3.2 (q, $J = 4$H), 1.03 (t, $J = 6$H); (ii) 5-(diethylamino)-1-phenylindazole (Table 2, entry 16), mp 152 °C ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.63 (s, 1H), 7.58 (d, 1H, $J = 8.6$ Hz, 1H) 7.52 (dd, $J = 8.6$, 1.5H), 7.42 (m, 5H), 3.2 (q, $J = 4$H), 1.03 (t, $J = 6$H).