Res Chem Intermed (2012) 38:1619–1628
DOI 10.1007/s11164-012-0488-y

Synthesis of 1H-indazole: a combination of experimental and theoretical studies

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Received: 23 November 2011 / Accepted: 11 January 2012 / Published online: 26 January 2012

Abstract A new practical synthesis of 1H-indazole is presented. A previous mechanism for the cyclization step is proved to be nonfeasible and a hydrogen bond propelled mechanism is proposed. The new mechanism is suitable for similar cyclization, and a new reaction is predicted.

Keywords Cyclization · 1H-indazole · DFT study

Introduction

Biologically active compounds containing an indazole fragment have been investigated and applied in producing HIV protease inhibitors, serotonin receptor antagonists, aldol reductase inhibitors, and acetylcholinesterase inhibitors [1, 2]. Various routes have been explored to synthesize indazole [3–8]. Among all these methods, cyclization of *ortho*-substituted benzylidenehydrazine using *ortho*-substituted benzaldehyde as starting material is a useful way. As shown in Eq. 1, utilizing nitro as a leaving group was first reported more than a century ago; then this method was developed by using 2-fluoro and 2-hydroxyl benzaldehyde. Lukin et al. [6] reported synthesis of indazole from 2-fluorobenzaldehyde and hydrazine, and Lokhande et al. [5] found that the reaction between 2-hydroxylbenzaldehyde and hydrazine can also produce indazole.

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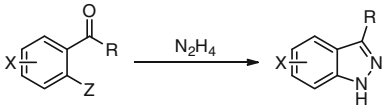


1a. Z=NO_2
1b. Z=F
1c. Z=OH

2

(1)

In our recent study, we found that the reaction between benzonitrile and hydrazine under certain conditions produces benzylidenehydrazine. This approach was expanded to the derivatives of benzonitrile with substitution on the benzene ring. We further investigated cyclization of various *ortho*-substituted benzylidenehydrazines and found that some of our experimental results indicate a different mechanism from that previously proposed by Lukin et al. [6]. To figure out the reaction details, we performed theoretical calculations using density functional theory (DFT). The results of our investigation led to a novel mechanism related to the synthesis of indazole.

Calculation method

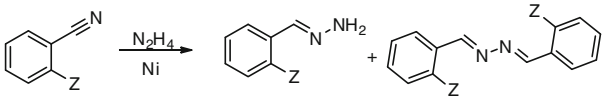
All the calculations were performed using the GAUSSIAN 03 software [9]. Hybrid DFT theory is applied to this problem with B3LYP method, which uses Becke's three-parameter hybrid functional [10], together with the non-local correlation provided by the LYP expression [11, 12], and VWN functional III [13] for local correlation. The basis set 6-311++G(d,p) was used. The polarized continuum (overlapping spheres) model (PCM) [14–16], which is based on a description of the solvent as a macroscopic continuum medium, was employed to estimate the solvent effect in aqueous reaction. Geometries of transition states (TS) were searched and optimized. Subsequent calculations, such as frequency calculation and the intrinsic reaction coordinates (IRC) [17, 18] calculation, were performed to confirm the TS. Frequency calculations on the optimized geometries were also used for the zero point energy (ZPE) corrections.

Results and discussion

Synthesis of *ortho*-substituted benzylidenehydrazine

Our initial investigation on the synthesis of *ortho*-substituted benzylidenehydrazine from *ortho*-substituted benzonitrile gave surprising results. The reactions were carried out at temperatures between 0 and 20 °C, and completed in 5 h with high yields of corresponding benzylidenehydrazine (higher than 85% of GC yields) under catalysis by Raney nickel (Eq. 2). In employing hydrazine hydrate, a dose of more than 2 eqv. per mole of **3** is needed. Organic solvent is not indispensable in this

process, and any strong base must be excluded from the reaction system. The yields of **4** are diminished even if a little strong base, such as NaOH, is added, and the resulting byproducts are substituted benzylamines. Though prolonging the reaction time gives a higher conversion of **3**, a too-long reaction time (longer than 10 h) causes the formation of dibenzylidenehydrazines **5**. The compound **4** can be separated from water through extraction by organic solvents. It is important that acid should be excluded from **4**, otherwise it can be fully converted to **5** (Eq. 3). The benzylidenehydrazines should be used for subsequent reactions shortly after they are prepared. The reaction mixtures are filtered and the filtrates are used for intramolecular cyclization.



3a. Z=F
3b. Z=Cl
3c. Z=OH
3d. Z=NH_3

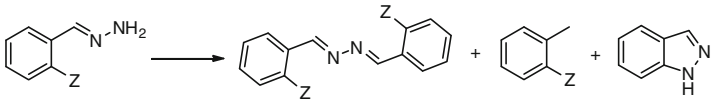
4a. Z=F
4b. Z=Cl
4c. Z=OH
4d. Z=NH_3

5a. Z=F
5b. Z=Cl
5c. Z=OH
5d. Z=NH_3

(2)

Cyclization of *ortho*-substituted benzylidenehydrazines

Heating the filtrates containing **4a** or **4c** to 100 °C results in 1H-indazole **7** (less than 30% yield), as well as the side products **5a**, **6a** and **5c**, **6c**, respectively. However, heating **4b** and **4d** only resulted in dibenzylidenehydrazines **5b**, **5d** and *ortho*-substituted toluene **6b**, **6d**. We decided to optimize the reaction conditions for intramolecular cyclization of the isolated benzylidenehydrazine **4a** and **4c** to indazole. Selection of the base used in the process is critical to minimizing the side products. Considerable amounts of *ortho*-substituted toluene **6a** and **6c** were observed in the presence of strong bases (e.g., sodium hydroxide and potassium carbonate), while the yield of **5a** and **5c** increased when a too-weak base was used. Actually, formation of the Wolff–Kishner reaction products **6b** and **6d** were inevitable. Only when ammonia or excess hydrazine was present could indazole be obtained with higher yields (see Table 1).



4a. Z=F
4b. Z=Cl
4c. Z=OH
4d. Z=NH_3

5a. Z=F
5b. Z=Cl
5c. Z=OH
5d. Z=NH_3

6a. Z=F
6b. Z=Cl
6c. Z=OH
6d. Z=NH_3

7

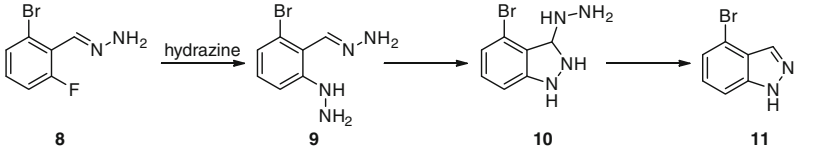
(3)

Lukin et al. [6] proposed that the formation of 4-bromo-1H-indazole **11** in the reaction of 2-bromo-6-fluorobenzaldehyde with hydrazine does not proceed via an intramolecular cyclization of 2-bromo-6-fluorobenzylidenehydrazine **8**. Instead,

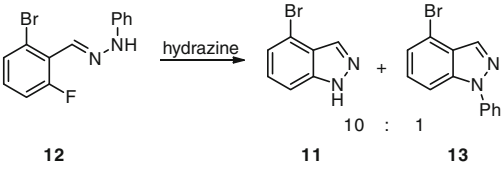
Table 1 Cyclization of *ortho*-substituted benzylidenehydrazines in the presence of different bases

Entry	Reactant	Base added	GC of **7** (%)
1	**4a**	NaOH	4
2	**4a**	Na_2CO_3	8
3	**4a**	KOH	<1
4	**4a**	$NH_3{\cdot}H_2O$	19
5	**4a**	$N_2H_4{\cdot}H_2O$	25
6	**4c**	NaOH	5
7	**4c**	Na_2CO_3	10
8	**4c**	KOH	<1
9	**4c**	$NH_3{\cdot}H_2O$	54
10	**4c**	$N_2H_4{\cdot}H_2O$	61

they proposed a mechanism that the reaction proceeds by substitution of the aryl fluoride of 2-bromo-6-fluorobenzylidenehydrazine with another molecule of hydrazine, followed by the cyclization of 3-bromo-2-(hydrazonomethyl)phenylhydrazine **9**, as shown in Eq. 4. To support the conclusion, they prepared benzyl-substituted benzylidenehydrazine and subjected it to the cyclization with hydrazine (Eq. 5). The major product, 4-bromo-1H-indazole **11**, seems to be proof of the fluoride-substitution mechanism. However, the singular result that no 4-fluoro-1H-indazole was formed made us doubt the proposed mechanism. As substitution of the bromo on benzene ring by hydrazine is more favorable than that of fluoro, the yield of 4-fluoro-1H-indazole should have been higher than that of 4-bromo-1H-indazole according to Lukin et al. We carried out comparative reactions between different benzene halides (fluoro-, chloro-, bromo- and iodo-benzenes) and hydrazine hydrate. For all four reactions, only a little phenylhydrazine was produced after 3 h under reflux; no obvious higher yield was detected in the reaction between fluorobenzene and hydrazine hydrate.



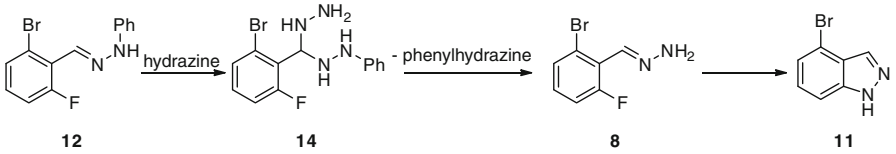
(4)



(5)

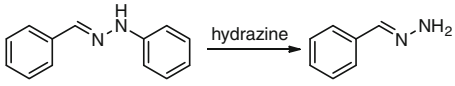
Considering the reaction result shown in Eq. 5, we proposed a reaction route which can give a reasonable explanation, as shown in Eq. 6. Reaction between

benzyl-substituted benzylidenehydrazine **12** and hydrazine yields 2-bromo-6-fluorobenzylidenehydrazine **8** directly, while subsequent cyclization gives 4-bromo-1H-indazole **11**. To prove our assumption, another reaction between benzyl-substituted benzylidenehydrazine **15** and hydrazine was carried out, and hydrazone **16** was obtained after reflux for 2 h. Carmeli et al. [19] have also reported a similar result. Thus, it can be concluded that the conversion from *ortho*-substituted benzylidenehydrazine to indazole does not follow the substitution–cyclization route (Eq. 4). It remains unknown why cyclization of hydrazone **4a** and **4c** occurs while the reactants **4b** and **4d** give no indazole at all. DFT investigation was further performed.



12 **14** **8** **11**

(6)



15 **16**

(7)

Geometries of *ortho*-substituted benzylidenehydrazine

Six *ortho*-substituted benzylidenehydrazines, 2-nitrobenzylidenehydrazine, 2-fluorobenzylidenehydrazine, 2-chlorobenzylidenehydrazine, 2-bromobenzylidenehydrazine, 2-hydroxylbenzylidenehydrazine and 2-aminobenzylidenehydrazine, were optimized. Each *ortho*-substituted benzylidenehydrazine has *cis*-(*E*)-, *cis*-(*Z*), *anti*-(*E*)- and *anti*-(*Z*) configurations related to different energies; only the *cis*-configurations are ready for intramolecular cyclization while the *anti*-benzylidenehydrazines need transition of configuration. The calculation results indicate that *cis*-(*E*)-configurations of 2-chlorobenzylidenehydrazine, 2-bromobenzylidenehydrazine, and 2-aminobenzylidenehydrazine have lower energies than the corresponding *cis*-(*Z*)-configurations, while *cis*-(*Z*)-configurations of 2-nitrobenzylidenehydrazine, 2-fluorobenzylidenehydrazine, and 2-hydroxylbenzylidenehydrazine have slightly higher energies than the corresponding *cis*-(*E*)-configurations. On comparing the *cis*-(*Z*)-configuration of each *ortho*-substituted benzylidenehydrazine, we found that a hydrogen bond forms between the terminal H atom and the *ortho*-group in 2-nitrobenzylidenehydrazine, 2-fluorobenzylidenehydrazine, and 2-hydroxylbenzylidenehydrazine (as shown in Fig. 1), so that the *cis*-(*Z*)-configuration is stabilized. We believe that the cyclization process is greatly affected by the hydrogen bond.

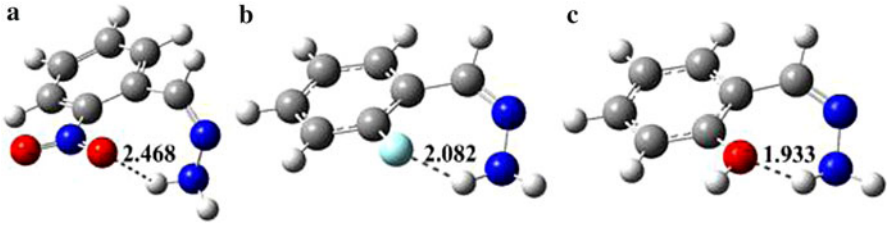


Fig. 1 Geometries of the *cis*-(*Z*)-configurations of 2-nitrobenzylidenehydrazine (**a**), 2-fluorobenzylidenehydrazine (**b**), and 2-hydroxylbenzylidenehydrazine (**c**)

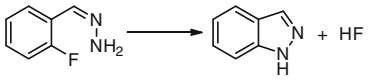
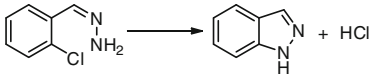
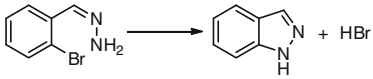
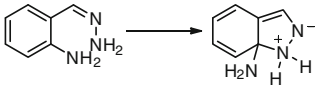
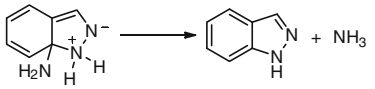
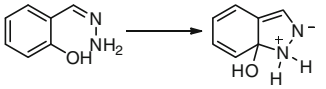
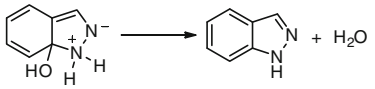
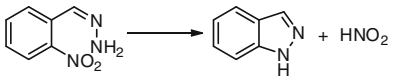
Calculation results for cyclization of *ortho*-substituted benzylidenehydrazine

Direct cyclization of *ortho*-substituted benzylidenehydrazines via substitution of the *ortho*-group by the terminal N atom was investigated. The reactants, products, and TS were located and optimized, and the corresponding reaction energies and barriers are shown in Table 2. It is clear in Table 2 that cyclization of 2-nitrobenzylidenehydrazine, 2-fluorobenzylidenehydrazine, and 2-hydroxylbenzylidenehydrazine have obviously lower barriers than those of the other *ortho*-substituted benzylidenehydrazines. The calculation results are in good agreement with our experiment. Relative TS structures are shown in Fig. 2.

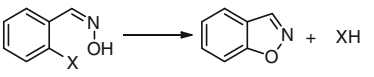
The lower barriers of reactions 1, 5, and 6 can be attributed to electron withdrawing from the *ortho* group to the terminal H atom. Effective electron attraction results in obvious increase of electron density around the *ortho* group and the terminal N atom, so both ionization of the *ortho* group and nucleophilic attack by the terminal N are favored. The question arises as to which group can give effective attraction? Comparative calculation on different *ortho* substituted benzylidenehydrazines indicates that only the hydrogen bond forms between the terminal H and the *ortho* group. Can the group give effective attraction? In other words, the *ortho* group must contain at least one atom of sufficient electronegativity. Considering the electron withdrawing effect of benzene ring, which decreases the electronegativity of the *ortho* amino, only 2-fluoro and 2-hydroxyl are available to form a hydrogen bond. We further calculated substitution of the fluorine in 2-fluorobenzylidenehydrazine by hydrazine, and compared it with direct cyclization. The calculated barrier of the substitution is 35.4 kJ/mol, considerably higher than that of direct cyclization. This can be further proof that the substitution–cyclization route is nonfeasible. Therefore, it can be concluded that cyclization of *ortho*-substituted benzylidenehydrazines is propelled by the hydrogen bond.

If the above approach is suitable for compounds of similar structures, *ortho*-substituted benzaldehyde oxime **17** can proceed via intramolecular cyclization when the *ortho* group is –F or –OH, as shown in Eq. 8. Strupczewski et al. [20] have reported intramolecular cyclization of 2-fluorobenzaldehyde oxime **17a**, and cyclization of 2-hydroxylbenzaldehyde oxime **17b** [21–23], with the same product benzo[*d*]isoxazole **18**. Other *ortho*-substituted benzaldehyde oximes, such as 2-chloro, 2-bromo, and 2-amino, have not been shown to be amenable for

Table 2 Reaction energies and barriers for direct cyclization of various *ortho*-substituted benzylidenehydrazines; both the barriers and the reaction energies, which have been corrected with ZPVE, are in kJ/mol

Reaction	Barrier	Reaction energy
1. 	19.5	−29.5
2. 	36.7	−27.1
3. 	30.0	−26.4
4a. 	36.1	20.7
4b. 	23.6	−50.2
5a. 	18.6	17.5
5b. 	11.4	−34.1
6. 	20.1	−25.3

intramolecular cyclization. Thus, the cyclization of *ortho*-substituted benzaldehyde oxime **17** lends support to the hydrogen bond propelling mechanism.



17a. X=F
17b. X=OH

18

(8)

It should be noticed that the N–O bond in *ortho*-substituted benzaldehyde oxime is active and easy to rupture. So the cyclization may proceed via dehydration if a hydrogen bond can form between the terminal O and an active H in the *ortho* group. Then, we speculated that cyclization of 2-aminobenzaldehyde oxime **17c** will give 1H-Indazole **7** (Eq. 9), although this reaction has not been reported. Full calculation was performed on this cyclization using the aforementioned methods. The calculated barrier for direct cyclization of *cis*-(*Z*)-2-aminobenzaldehyde oxime is 20.5 kJ/mol, which is comparable with that for cyclization of 2-nitrobenzylidenehydrazine, and

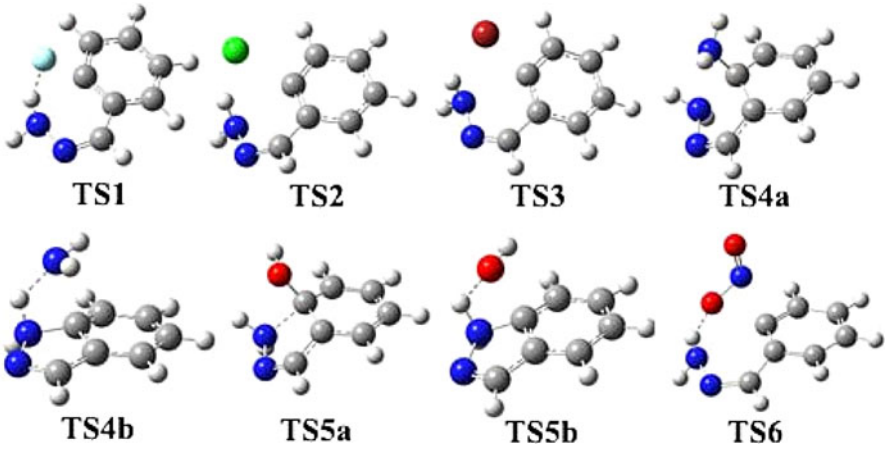
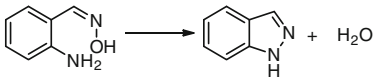


Fig. 2 TS structures of reactions 1–6 in Table 2

the reaction is also energetically favorable. Judging from the calculation results, we can conclude that synthesis of 1H-Indazole via cyclization of 2-aminobenzaldehyde oxime is probably feasible, but there is as yet no report on this and similar reactions.



(9)

Conclusion

We have presented a new practical synthesis of 1H-indazole. The intermediate *ortho*-substituted benzylidenehydrazines were obtained in high yields via reaction of *ortho*-substituted benzonitrile with hydrazine catalyzed by Raney nickel. The introduction of even a little acid or base into the reaction system can decrease the yield of *ortho*-substituted benzylidenehydrazine dramatically. Cyclization of 2-fluorobenzylidenehydrazine and 2-hydroxylbenzylidenehydrazine gave the final product, 1H-indazole; a previously proposed mechanism for the cyclization step was proved to be nonfeasible according to other literature and our experiment. To determine the details of cyclization, theoretical calculations using DFT were performed. The calculation results indicated that cyclization of *ortho*-substituted benzylidenehydrazine is propelled by the hydrogen bond between the terminal H on N and the *ortho* group. The reported cyclization of *ortho*-substituted benzaldehyde oxime proved that the hydrogen bond propelled mechanism is also suitable for cyclization of compounds with similar structures. Finally, we proposed the cyclization of 2-aminobenzaldehyde oxime to synthsize 1H-indazole, and theoretical calculation indicated that it is feasible. Further study is in progress.

Experimental section

Typical procedure for synthesis of *ortho*-substituted benzylidenehydrazine

Hydrazine (85%, 10 mL) was added into a solution of 2-fluorobenzonitrile (5 mmol) in toluene (10 mL). Raney nickel (0.2 g) was added. Then, the mixture was stirred for 3 h at 10–15 °C, giving 90% GC yield of 2-fluorobenzylidenehydrazine.

Typical procedure for cyclization of *ortho*-substituted benzylidenehydrazines

Hydrazine (85%, 5 mL) was added into the concentrated 2-fluorobenzylidenehydrazine solution (5 mmol). The mixture was refluxed for 5 h, giving 25% GC yield of 1H-Indazole.

*1H-indazole (**7**)*

^{1}H NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 7.11$ (t, 1H, $J = 7.6$ Hz), 7.35 (t, 1H, $J = 7.6$ Hz), 7.55 (d, 1H, $J = 8.3$ Hz), 7.79 (d, 1H, $J = 8.2$ Hz), 8.07 (s, 1H), 13.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): $\delta = 111.2$, 121.0, 121.4, 122.5, 126.6, 135.2, 141.3.

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