Tetrahedron Letters 55 (2014) 2480–2483

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mild method for the synthesis of 1*H*-indazoles through oxime-phosphonium ion intermediate

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ARTICLE INFO

Article history:
Received 5 February 2014
Revised 1 March 2014
Accepted 2 March 2014
Available online 11 March 2014

Keywords:
1*H*-Indazoles
Oxime-phosphonium ion intermediate
N–N bond formation
Mild reaction condition
Basic medium

ABSTRACT

The synthesis of 1*H*-indazoles from *o*-aminobenzoximes is achieved via N–N bond formation using triphenylphosphine, I_2, and imidazole. Selective formation of oxime-phosphonium ion intermediate in the presence of the amino group is the driving force for this reaction. The nucleophilicity of the arylamino group and electrophilicity toward the N–O bond of oxime also control the reaction. The reaction proceeds at a faster rate with good to excellent yield under this mild reaction condition and is amenable to scale-up.

Pharmacologically active 1*H*-indazole and its derivatives are widely used as drug in treating various human diseases including cancer, inflammation, cardiovascular, and others.[1–3] This has incited researchers in developing innovative methods toward their synthesis. The synthesis of substituted 1*H*-indazole has been already accomplished by various chemical methods, but only a few methods offer mild, transition-metal-free reaction condition.[4–9] Most of the reported transition-metal-free reaction methods such as diazotization or nitrosation of *o*-alkyl substituted anilines, condensation of hydrazine with *o*-halo- or mesylate-containing aldehydes or ketones, and cycloaddition of diazomethanes with benzynes require stringent or inconvenient conditions.[4–7] There have been ongoing efforts in recent years aimed at developing mild, transition-metal-free reaction protocols for the synthesis of substituted 1*H*-indazole with improved efficiency. Blom and co-workers recently reported a mild, base-catalyzed method for the synthesis of substituted indazoles through condensation of *o*-halo- substituted ketones and tosylhydrazone.[10] Among the other reported metal-free reaction processes, a study by Stambuli and co-workers to synthesize substituted indazoles via N–N bond formation caught our attention.[11] They reported that selective activation of the hydroxyl group of the oxime in the presence of the arylamino group is the key step for the synthesis of 1*H*-indazole under basic condition. Interestingly, Robles and co-workers, and our group reported the esterification process using the similar concept of selective activation of the alkyl or aryl acid group.[12,13] We hypothesized that selective activation of the hydroxyl group of the oxime by using triphenylphosphine, I_2, and base would produce a suitable leaving group in the presence of arylamine. The presence of mild base would then trigger an intramolecular nucleophilic attack by the arylamino group onto the activated oxime to produce the desired 1*H*-indazole.

For the initial screening and optimization of the reaction condition, oxime of *o*-amino benzophenone was chosen as substrate. For the N–N bond formation in the presence of Ph_3P/I_2, different bases and solvents were tested, and the reaction parameters (temperature, time) were altered. The best result was obtained with imidazole (3.3 equiv) as a base and CH_2Cl_2 as solvent at room temperature for 4 h (Table 1). However, lower amount of imidazole (<3.3 equiv) reduced the amount of 1*H*-indazole derivatives. The use of other bases including, tetrazole, Et_3N, pyridine, DBU, DIPA, and DMAP resulted poor or no yield, under the similar experimental condition. The use of other solvents including DMF, THF, and CH_3CN also produced poor yield. There was no significant improvement in the 1*H*-indazole formation for a longer time or even at a higher temperature.

It is reported that oximes undergo Beckmann rearrangement to produce amides or nitriles at ambient temperature.[14] However, we observed little or no Beckmann rearrangement product for the examined substrates (Table 2) under the optimized reaction conditions. This could be due to the basic reaction medium and stronger nucleophilicity of the arylamino group over the rearrangement process. It is also reported that oximes with α-proton can undergo

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http://dx.doi.org/10.1016/j.tetlet.2014.03.001
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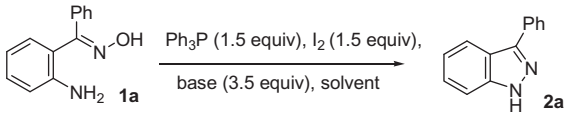
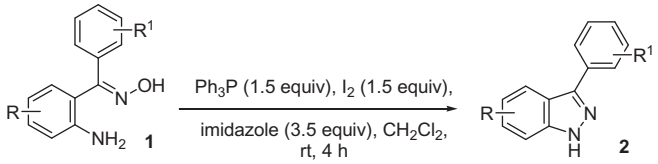
Table 1
Screening and optimization of the reaction conditions

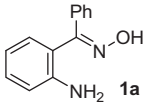
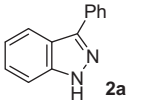
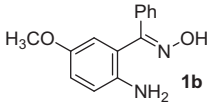
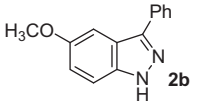
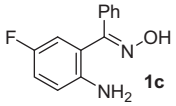
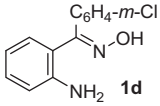
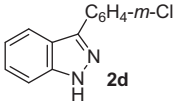
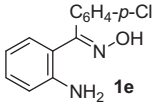
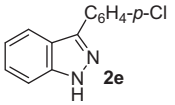
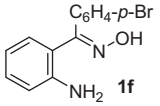
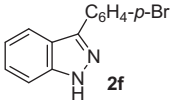
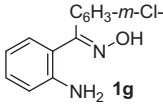
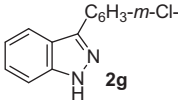
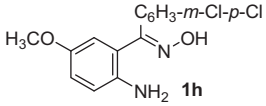
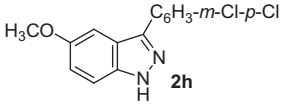
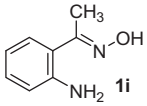
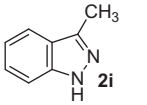


Entry	Phosphine/I_2	Base	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	Ph_3P/I_2	Imidazole	CH_2Cl_2	rt	4	72
2	Ph_3P/I_2	Et_3N	CH_2Cl_2	rt	4	N.R
3	Ph_3P/I_2	Diisopropylamine	CH_2Cl_2	rt	4	15
4	Ph_3P/I_2	Tetrazole	CH_2Cl_2	rt	4	30
5	Ph_3P/I_2	Imidazole	DMF	rt	4	10
6	Ph_3P/I_2	Imidazole	CH_3CN	rt	4	N.R
7	Ph_3P/I_2	Imidazole	THF	rt	4	N.R
8	Ph_3P/I_2	Imidazole	CH_2Cl_2	rt	10	74
9	Ph_3P/I_2	Imidazole	CH_2Cl_2	60	4	75

[a] Isolated yields.

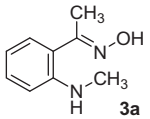
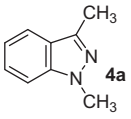
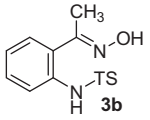
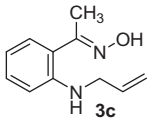
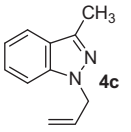
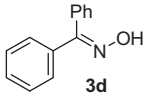
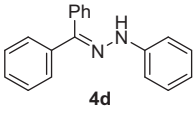
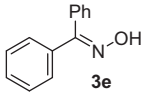
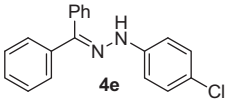
Table 2
Synthesis of 1*H*-indazoles from oximes



Entry	Oxime	Indazole	Yield[a] (%)
1			72
2			88
3		NR[b]	—
4			78
5			80
6			75
7			85
8			87
9			48

[a] Isolated yields.
[b] No reaction.

Table 3
Substrate scope of the optimized reaction conditions

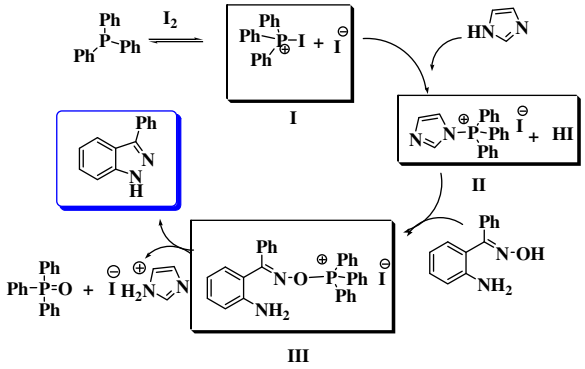
Entry	Oxime	Indazole	Yield[a] (%)
1	 **3a**	 **4a**	64
2	 **3b**	NR[b]	–
3	 **3c**	 **4c**	48
4	 **3d**	 **4d**	68
5	 **3e**	 **4e**	54

[a] Isolated yields.
[b] No reaction.

Neber rearrangement at this ambient temperature.[15] We did not observe any such rearrangement products for oximes with α-proton under the optimized reaction conditions (Table 2, entry 9). We hypothesized that mild basicity of the imidazole makes the arylamino group sufficiently strong nucleophile for the formation of N–N bond through oxime-phosphonium ion intermediate, without any migration product under these optimized reaction conditions. Therefore, the conversion of oximes to 1*H*-indazoles under these optimized reaction conditions is facile and avoids the Beckmann and Neber rearrangement products.

Encouraged by this excellent result, we decided to determine the scope of this methodology for the synthesis of several other substituted 1*H*-indazoles by analyzing the reactivity of various oximes of *o*-amino benzophenone using the optimized reaction conditions (Table 2). We also investigated the role of R and R^1 groups in 1*H*-indazole formation. The oximes with R as the electron-donating group produced the desired indazoles with excellent yields (88–87%). Whereas, oximes with R^1 as the electron-withdrawing group produced poor/no yield. The results clearly showed that the nucleophilicity of the arylamino group has a direct effect on the N–N bond formation under the optimized reaction conditions. Similarly, oximes with R^1 as the electron-withdrawing group produced the desired indazoles with excellent yields (75–87%). The presence of R^1 as the electron-withdrawing group could enhance the electrophilicity toward the N–O bond of the oximephosphonium ion intermediate and facilitate the nucleophilic attack of the arylamino group. This hypothesis was further supported by the excellent yield of compound **2h** (Table 2, entry 8), where R is electron-donating, and R^1 is the electron-withdrawing functional group.

We also tested secondary aniline oxime derivatives using the optimized reaction conditions. *N*-methylaniline oxime resulted in the corresponding 1*H*-indazole with moderate yield; however, other secondary aniline oximes produced the desired 1*H*-indazole with lower/no yield. This could be due to the bulkiness and nucleophilicity of the secondary aniline toward the formation of substituted 1*H*-indazoles (Table 3). We also determine the scope of this methodology for the intermolecular N–N bond formation by analyzing the reactivity of benzophenone-oxime and substituted anilines using these optimized reaction conditions. The benzophenone phenylhydrazones were obtained with moderate to good yield. A similar effect of the electron-withdrawing group was also observed for these compounds (Table 3).



Scheme 1. Plausible mechanistic pathway for the synthesis of 1*H*-indazoles through N–N bond formation.

It is also important to note that, the intramolecular nucleophilic substitution mechanism is only possible for the (*E*) isomer of the activated oxime. Meanwhile, complete conversion of *o*-aminobenzoximes to 1*H*-indazole clearly indicates the formation of only (*E*) isomer of the activated oxime, under the experimental conditions. This could be because of the formation of predominantly (*E*) isomer of the oxime from the corresponding benzophenone.

Based on the experimental results and previous mechanistic studies, we suggest the following mechanism (Scheme 1) for the synthesis of 1*H*-indazoles. The reaction between Ph_3P, I_2, and imidazole yielded the intermediate (**II**), and subsequent attack of oxime of *o*-amino benzophenone selectively generates the oxime-phosphonium ion intermediate (**III**). The intramolecular nucleophilic attack by the arylamino group onto the Sp^2-nitrogen center of the activated oxime (**III**) generates the desired 1*H*-indazole under basic media. This could be the rate-determining step for the synthesis of 1*H*-indazole through N–N bond formation. To obtain further understanding of the reaction mechanism, we also performed the reaction of oxime of benzophenone with aniline under the similar experimental condition. The formation of these proposed intermediates in the reaction mixture was studied by ^{31}P NMR spectroscopy (Fig. 1 and Fig. S1). The spectra were collected after

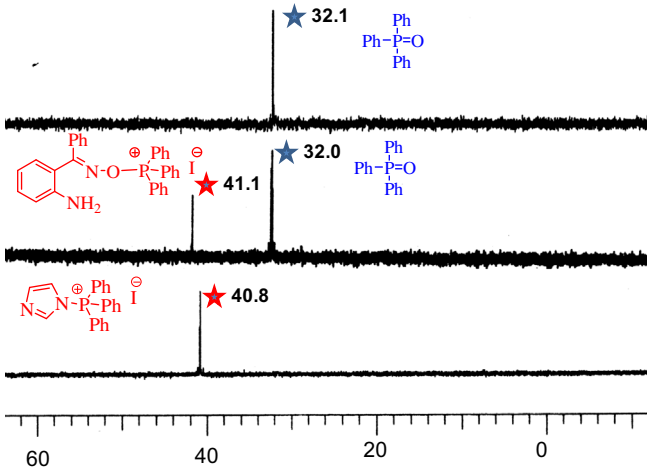


Figure 1. Monitoring the progress of reaction by ^{31}P NMR of *o*-amino benzophenone oxime in $CDCl_3$.

addition of each reagent with a sufficient time gap. The observed changes in their chemical shifts (Table S1) indicate the formation of intermediate **II** and **III**. The downfield shift of the ^{31}P NMR signal ($\Delta\delta$ = 0.22 ppm) after addition of oxime to the intermediate **II** indicates the formation of intermediate **III**. Although the chemical shift is very little, still in situ generation of triphenylphosphine oxide in the reaction media indicates the formation of intermediate **III**.

In conclusion, we report a mild reaction method for the synthesis of 1*H*-indazole derivatives in the presence of triphenylphosphine, I_2, and imidazole. In particular, we have demonstrated the formation of oximephosphonium ion intermediate during the formation of inter- and intramolecular N–N bond. We have also shown that the nucleophilicity of the arylamino group and electrophilicity toward the N–O bond of oxime play an important role in the synthesis of 1*H*-indazole derivatives. We believe this facile and efficient method will serve as a useful alternative to the existing methods for the synthesis of substituted 1*H*-indazoles.

Acknowledgments

The authors are thankful to the DST (SB/FT/CS-131/2012), Govt. of India, for financial support. We are thankful to CIF for instrumental support. Special thanks are due to Mr. Dipjyoti Talukdar for technical support.

Supplementary data

Supplementary data (experimental section, characterization of the unknown compounds, ^{31}P NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.001.

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