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Synthesis of *N*-aryl-3*H*-indazol-3-imine and *N*-aryl-1*H*-indazol-3-amine via Na_2WO_4/H_2O_2 mediated by intramolecular *N*—*N* coupling

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ABSTRACT

A fast and convenient method for synthesis of N-aryl-1H-indazol-3-amine and N-aryl-3H-indazol-3-imine compounds has been described via intramolecular oxidative cyclization of the 2-amino-N′-aryl-benzimidamide intermediates by Na_2WO_4/H_2O_2 in excellent yields. This procedure has several advantages such as mild reaction conditions, short reaction time, and excellent yields, making this methodology practical.

1. Introduction

N-heterocyclic compounds are of unique structural units and widely exist in the bioactive molecular and natural products [1]. Among them indazoles with a broad spectrum of pharmacological activities are very important. The biological and medicinal properties of indazoles have prompted immense research effort aimed at synthetic routes and medicinal functionalization of the nucleus [2]. Indazole derivatives have been has been known as anticancer [3], antibacterial [4], antiprotozoal [5], and anti-inflammatory agents [6], and as inhibitors of protein kinase [7], HIV protease [8], nitric oxide synthase [9], and monoamine oxidase [10]. Fig. 1 shows some typical biologically active compounds containing indazole scaffold that are used as core structures synthetic drugs such as Benzadac [11], Lonidamine [12], Granisetron [13] and 7-nitroindazole [14].

In the recent years, there has been great interest in the application of 3-aminoindazole as agents interacting with a variety of biological targets including kinase inhibitors [15], MCH receptor 1 antagonist [16], HIV protease inhibitors [17], factor XIa inhibitors and CB1 receptor inhibitors [18]. For example, Linifanib has been used as a structurally novel, potent inhibitor of receptor tyrosine kinases (RTK), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (Fig. 2).

Moreover, the 3-aminoindazoles are able to mimic the adenine nucleus of ATP for the design of ATP-competitive receptor tyrosine kinase inhibitors with potent antitumor activities [19]. There are various methods for the synthesis of 3-aminoindazole. For example, in 2008, Michael and et al. reported the synthesis of 3-aminoindazoles compounds in the presence of hydrazine with thioamides [20]. The methods for the preparation of these compounds typically involved the reaction of a 2-haloaryl nitrile with hydrazine to provide the 3-aminoindazole, the leaving group used for the reaction to succeed is mainly fluorine. The main drawback of these methods is the low yields and harsh conditions when fluorobenzonitriles are deactivated by an electron-donating group [18]. We required a general method for the preparation of 3-aminoindazoles which avoided the use of harshly acidic conditions, protecting groups, or metal catalysis while allowing for the incorporation of elaborated amines.

Amidines, in addition to being used in the synthesis of quinazoline compounds, can be used in the synthesis of heterocycle nitrogen-riched indazole by an oxidative N—N bond formation [21].

The formation of N—N bond has been recently utilized for the synthesis of heterocycles and azo compounds [22]. The advantages of this method include not need to leaving group on the heteroatom or pre-functionalization and avoided challenging to prepare

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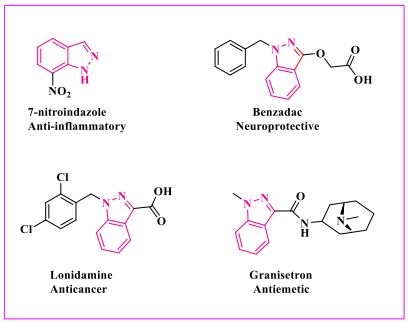


Fig. 1. Selected biologically active compounds with an indazole core.

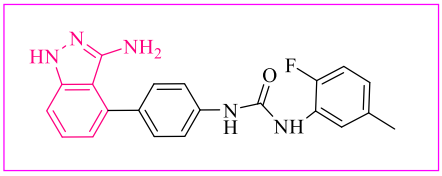
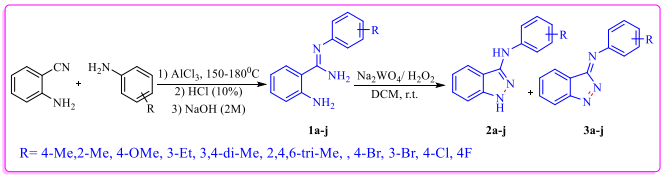


Fig. 2. Linifanib structure.



Scheme 1. Synthesis of N-aryl-1H-indazol-3-amine and N-aryl-3H-indazol-3-imine derivatives.

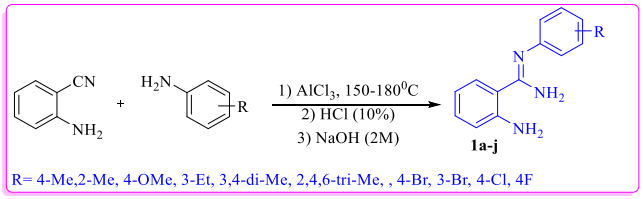
building blocks containing an N—N bond [23].

Many tungstate-based catalytic systems have been reported to be active for oxidation reactions with aqueous hydrogen peroxide solutions [24,25]. Newly tungsten peroxide, has been used for oxidation of alcohols to aldehydes or ketones as practical methodology. This oxidant is prepared from hydrogen peroxide (H_2O_2) and catalytic amount of sodium tungstate dihydrate ($Na_2WO_4{\cdot}2H_2O$. Also, attention has been especially attracted to a method of 'green' oxidation with use of tungsten peroxide [26,27]. In this way, oxidation of alcohol to ketone or aldehyde was carried out by using N,N-dimethylacetamide, hydrogen peroxide, and a catalytic amount of disodium tungstate dihydrate under neutral conditions as a green method.[28]Also, sodium tungstate are used as an active and highly selective catalyst to oxidation of various primary or secondary origin renewable alcohols by hydrogen peroxide as green oxidant [29].

Due to the above mentioned and in continues of our research for the synthesis of heterocyclic compounds with biological activity [30,31]. Herein, we report a Na_2WO_4/H_2O_2-mediated oxidative N—N bond formation reaction to produce N-aryl-1H-indazol-3-amine and N-aryl-3H-indazol-3-imine from 2-amino-N´-arylbenzimidamides (Scheme 1).

2. Results and discussion

For the synthesis of our target molecules, in the first, we synthesized 2-amino-N´-arylbenzimidamides derivatives (**1a-j**), from reaction of *o*-aminobenzonitrile and aniline derivatives in the presence of $AlCl_3$ at 150—180 °C according to the literature reported



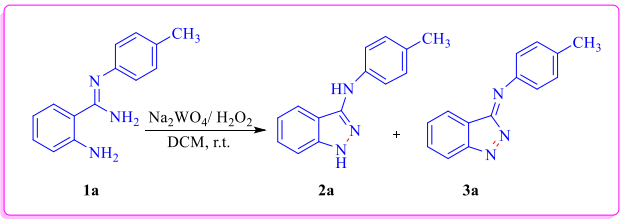
Scheme 2. Synthesis of 2-amino-N′-phenylbenzimidamide derivatives.

(Scheme 2) [32].

In continues of work, we carried out cyclization **1** in presents of different solvents and catalysts. To find the optimized conditions for synthesis *N*-aryl-1*H*-indazol-3-amine and *N*-aryl-3*H*-indazol-3-imine derivatives by an oxidative N—N bond formation, reaction of 2-amino-N'-(p-tolyl)benzimidamide (**1a**) was selected as a model reaction. Various catalysts, and solvents were used at ambient temperature. The results have been summarized in Table 1.

As shown on Table 1, in absent oxidant, at room temperature, CH_3OH as solvent and $Cu(OAc)_2$ or $Cu(NO_3)_2$ as catalyst, no desired product was observed, according to the TLC (n-Hexane: EtOAc 3:1) (Table 1, entries 1 and 2). Also, addition of H_2O_2 as an oxidant in presence different catalysts such as $CuBr_2$, $ZnSO_4$, TiO_2, ZnO and KI/I_2 not improved the yield of the desired product, in some cases these led to a complicated result, according to the TLC (n-Hexane: EtOAc 3:1) (Table 1, entries 3—9). When we used H_2O_2 in presence of Na_2WO_4 as catalyst in CH_3OH solvent at room temperature corresponding product was produced in good yields (60%) (Table 1, entry 10). To improve the yields, various solvents such as DMSO,

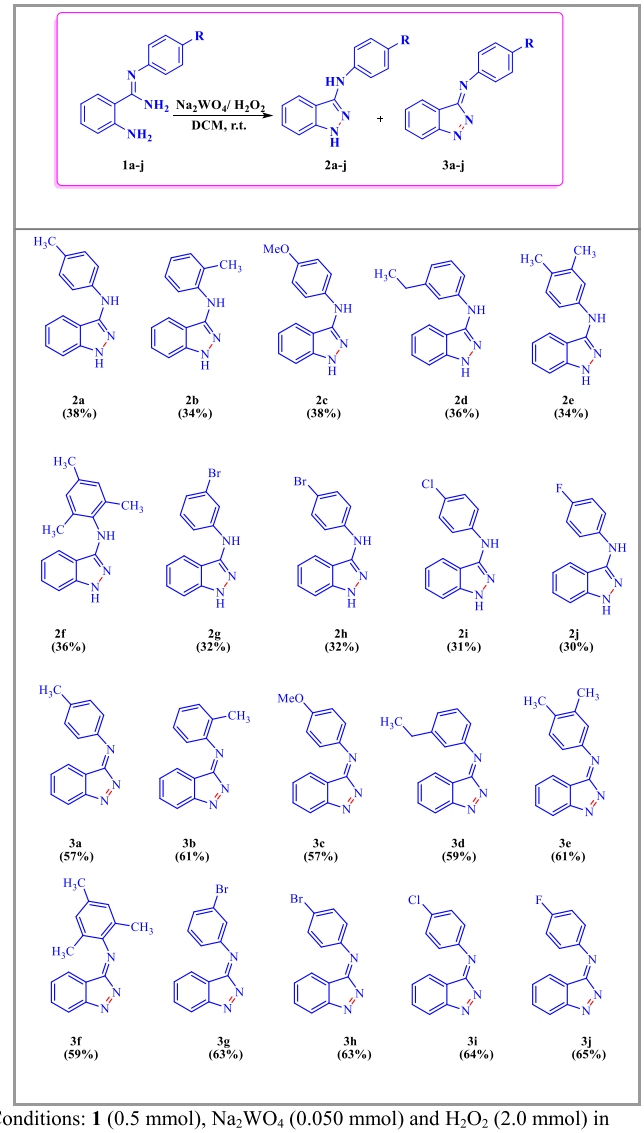
Table 1
Optimization of conditions for synthesis the N-(p-tolyl)-1H-indazol-3-amine and N-(p-tolyl)-3H-indazol-3-imine.[a].



Entry	Catalyst/Oxidant	Catalyst (mmol)	Solvent	Time (h)	Yield (%)	
					2	3
1	$Cu(OAC)_2$/-	0.025	MeOH	5	–	–
2	$Cu(NO_3)_2$/-	0.025	MeOH	5	–	–
3	$Cu(OAc)_2/H_2O_2$	0.025	MeOH	5	–	10
4	$Cu(NO_3)_2/H_2O_2$	0.025	MeOH	5	–	10
5	$CuBr_2/H_2O_2$	0.025	MeOH	5	–	10
6	$ZnSO_4/H_2O_2$	0.025	MeOH	5	5	10
7	TiO_2/H_2O_2	0.025	MeOH	5	–	10
8	ZnO/H_2O_2	0.025	MeOH	5	–	–
9	I_2/KI –	0.025	MeOH	5	–	–
10	Na_2WO_4/H_2O_2	0.025	MeOH	2	20	40
11	Na_2WO_4/H_2O_2	0.025	DMSO	4	–	–
12	Na_2WO_4/H_2O_2	0.025	DMF	4	–	10
13	Na_2WO_4/H_2O_2	0.025	THF	3	–	10
14	Na_2WO_4/H_2O_2	0.025	EtOH	3	–	10
15	Na_2WO_4/H_2O_2	0.025	Toluene	0.75	30	50
16	Na_2WO_4/H_2O_2	0.025	DCM	0.75	30	50
17	**Na_2WO_4/H_2O_2**	**0.050**	**DCM**	**0.5**	**38**	**57**
18	Na_2WO_4/H_2O_2	0.012	DCM	1	25	50
19	Na_2WO_4/H_2O_2	0.006	DCM	2	20	40

[a] Conditions: H_2O_2 (2.0 mmol).

Table 2
Synthesis of N-aryl-1H-indazol-3-amine and N-aryl-3H-indazol-3-imine derivatives under optimized conditions.[a].



[a]Conditions: **1** (0.5 mmol), Na_2WO_4 (0.050 mmol) and H_2O_2 (2.0 mmol) in DCM at room temperature. Isolated yield is shown.

DMF, THF, EtOH, toluene, and DCM were used. According to Table 1, DCM and toluene provide better yields within 0.5 h under same reaction conditions (Table 1, entries 11–16). Therefore, DCM was selected as solvent on the basis of economic costs and environmental safety. Also, the results show that the reaction efficiency increases with increasing the amount of catalyst (Table 1, entire 17).

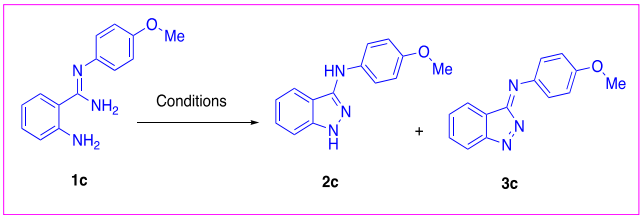
In the next set of experiments the influence of different amount Na_2WO_4 on the outcome of the model reaction were studied. Our finding indicates the best conditions reaction and oxidant for this reaction are 0.050 mmol Na_2WO_4 (Table 1, entries 17–19).

Thus, the optimized reaction conditions for the synthesis of N-disubstituted indazoles are 2-amino-N′-arylbenzimidamides (0.5 mmol), Na_2WO_4 (0.050 mmol) and H_2O_2 (2.0 mmol) in DCM at ambient temperature for 0.5 h.

In order to the investigation of electronic effect on the reaction time and yield, various amidine contains electron withdrawing and electron releasing groups, were used (Table 2). The reaction proceeds without significant differences in reaction time or yield. The structures of products confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra.

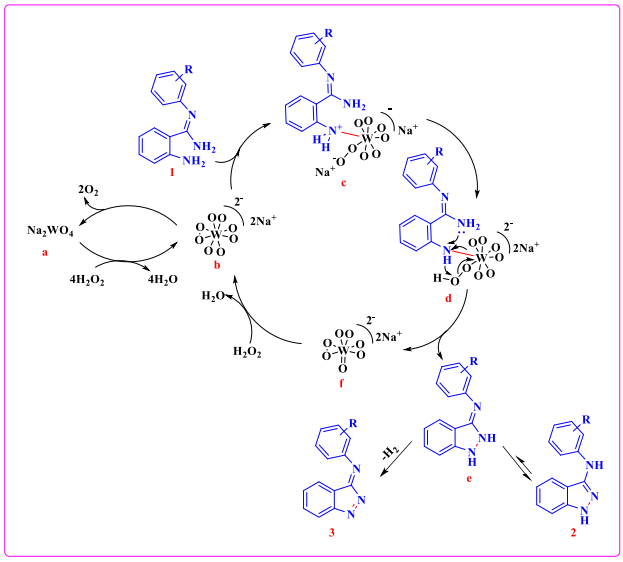
In the next step we tried to change the conditions reaction so that only one of the two products **2** and **3** are produced. We suggested if the time and amounts of oxidants were increased and also the reaction was carried out at the presence of O_2 the ratio compounds **2** and **3** can be changed. Therefore, for the testing of this hypothesis, the reaction cyclization of 2-amino-*N*'-(4-methoxyphenyl)benzimidamide was selected as a model (Table 3). At the first, we used H_2Wo_4/H_2O_2 with (0.05:2) ratio in the toluene solvent. In this case after 12 h the products **2c** and **3c** were obtained with ratios 30:63% (Entry 2, Table 3). When we used H_2Wo_4/H_2O_2 with (0.05:4) and (0.05:6) ratios, after 6 h the compound **2c** was not obtained, and only product **3c** was observed (75%) (Entry 3 and 4, Table 3). Also, we examined H_2WO_4/H_2O_2/KI, I_2 (0.05:2:0.025) as oxidant system, it is interesting, in these conditions we didn't observed any product. Finally, the reaction was carried out under O_2 atmosphere and H_2WO_4/H_2O_2 (0.05:2). In

Table 3
Optimization of conditions for synthesis the N-(4- methoxyphenyl)-3H-indazol-3-imine.[a].



Entry	Oxidants	Oxidant (mmol))	Solvent	Time (h)	Yield (%)	
					2c	3c
1	Na_2WO_4/H_2O_2	0.05/2	Toluene	0.25	16	34
2	Na_2WO_4/H_2O_2	0.05/2	Toluene	12	30	63
3	Na_2WO_4/H_2O_2	0.05/4	Toluene	6	–	75
4	Na_2WO_4/H_2O_2	0.05/6	Toluene	6	–	75
5	H_2WO_4/H_2O_2/KI, I_2	0.05/2/0.025	Toluene	6	–	–
6	$H_2WO_4/H_2O_2/O_2$	0.05/2	Toluene	5	–	86

[a] Conditions: H_2WO_4 (0.05 mmol).



Scheme 3. Proposed reaction mechanism using tetraperoxotungstate.

these conditions we didn't obtained compound **2c** as product and only compound **3c** was produced in 85% yield (entry 6, Table 3).

A possible mechanism for this reaction is proposed in Scheme 3.

At the first, Na_2WO_4 (**a**) and H_2O_2 give $Na_2[W(O_2)_4]$ (**b**). Although thermal cleavage of W–O bond occurs. The formation of intermediate **c** can be rationalized by the nucleophilic attack of amidine **1** with tetraperoxotungstate **b**. After formation of intermediate **d** the cyclization reaction occurs by an oxidative N–N bond formation and removing of the water molecule, the intermediate **e** was synthesized which can be tautomerized to product **2** or by further oxidation produce compound **3**.

3. Conclusions

In summary, we have successfully synthesized a new series of indazole derivatives in excellent yields via oxidative N–N bond formation reaction of 2-amino-N′-arylbenzimidamides derivatives. This method constitutes a fast, facile, and inexpensive route to obtain indazole derivatives which are of great importance in medicinal chemistry.

4. Experimental section

4.1. General information

All chemicals and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Melting points were obtained by a Bamslead Electrothermal 9200 apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Scientific, Nicolet iS10 Fourier transform IR spectrometer (Thermo Fisher Scientific, Waltham, MA) in KBr with absorption in cm^{-1}. All of the NMR spectra were recorded on a Varian model UNITYInova 500 MHz (^1H: 500 ^{13}C: 125 MHz) NMR spectrometer. Chemical shifts of ^1H and ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) Chemical shifts are given in ppm relative to TMS as an internal standard in DMSO-d_6 or $CDCl_3$ as a solvent, the coupling constants J are given in Hz and spectra were recorded in parts per million (ppm).

4.2. Synthetic procedures

4.2.1. General procedure for the synthesis of compounds *1*

A mixture of aryl amines (15 mmol) and o-aminobenzonitrile (10 mmol) were carefully heated until a homogenous melt. Anhydrous aluminium chloride (15 mmol) was added in many portions with swirling. The resulted mixture was then heated at 150–180 °C during 1 h. Then 10% hydrochloric acid (25 ml) was added, and after dissolving the post-reaction mixture, 2 M sodium hydroxide solution was added until PH = 6. The obtained solution was extracted with chloroform (3 × 10 ml). The aqueous layer was separated and basified with 2 M sodium hydroxide solution. The white precipitate was filtered off, washed with water until neutral reaction, air dried, and crystallized from a benzene–petroleum ether mixture.

*General procedure for the synthesis of compounds **2** or **3**.*

To a solution of 2-amino-N′-arylbenzimidamides 1 (0.5 mmol) in CH_2Cl_2 (2 mL), H_2O_2 (2 mmol, 35%) and $Na_2WO_4{\cdot}2H_2O$ (0.050 mmol) were added and the mixture stirred for 0.5 h at room temperature. Then, solvent was evaporated, water was added (10 mL) to the mixture, and then extracted with CH_3Cl (2 X 7 mL). The extracts were combined and dried over anhydrous Na_2SO_4, filtered, and purified using plate chromatography with EtOAc/n-Hexane (1:3) to afford the corresponding product 2 or 3.

*N-(p-tolyl)-1H-indazol-3-amine (**2a**)*

Yellow oil (38% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3346.48 (N–H), 1691.50 (C=N); ^1H NMR (500 MHz, DMSO d_6) δ = 11.87 (s, 1H, N–H), 8.68 (s, 1H, N–H), 7.92 (d, 1H, *J* = 8.5 Hz, H–Ar), 7.55 (d, 2H, *J* = 8.5 Hz, H–Ar), 7.34 (dd, 1H, *J* = 8.5 Hz, *J* = 1 Hz, H–Ar), 7.29 (td, 1H, *J* = 7.5 Hz, *J* = 1 Hz, H–Ar), 7.14 (d, 2H, *J* = 8.5 Hz, H–Ar), 6.99 (td, 1H, *J* = 7.5 Hz, *J* = 1 Hz H–Ar), 2.22 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 141.7, 139.3, 134.1, 129.6, 129.4, 127.6, 127.0, 120.4, 119.6, 118.5, 116.2, 114.7, 109.9, 20.7 (Me).

4.3. N-(o-tolyl)-1H-indazol-3-amine (*2b*)

Yellow oil (34% yield); ^1H NMR (500 MHz, DMSO d_6) δ = 7.69 (d, 1H, *J* = 8.5 Hz, H–Ar), 7.42–7.44 (m, 2H, H–Ar), 7.35–7.38 (m, 1H, H–Ar), 7.314 (d, 1H, *J* = 7.5 Hz, H–Ar), 7.20 (d, 1H, *J* = 8.5 Hz, H–Ar), 7.10 (td, 1H, *J* = 7.0 Hz, *J* = 1.0 Hz, H–Ar), 6.66–6.69 (m, 1H, H–Ar), 5.92 (s, 2H), 2.01 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 148.2, 142.0, 137.9, 135.9, 131.3, 129.5, 128.2, 127.1, 126.9, 121.8, 116.3, 115.9, 108.3, 17.6 (Me).

*N-(4-methoxyphenyl)-1H-indazol-3-amine (**2c**)*

Cream oil (38% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3450.19 (N–H),

1616.40 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.07 (dd, 1H, *J* = 7.5 Hz, *J* = 0.5 Hz, H−Ar), 8.03 (d, 1H, *J* = 9.0 Hz H−Ar), 7.83−7.87 (m, 3H), 7.75 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.67 (td, 1H, *J* = 8 Hz, *J* = 1 Hz, H−Ar), 7.03 (d, 1H, *J* = 9.0 Hz, H−Ar), 6.96 (d, 2H, *J* = 9.0 Hz H−Ar), 3.88 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 140.6, 135.6, 133.5, 132.9, 131.1, 130.0, 129.8, 125.8, 122.9, 115.3, 114.5, 114.3, 55.5 (OMe).

*N-(3-ethylphenyl)-1H-indazol-3-amine (**2d**)*

Cream oil (36% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1})**:** 3384.59 (N−H), 1610.45 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 11.92 (s, 1H, N−H), 8.70 (s, 1H, N−H), 7.93 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.51 (bs, 1H, H−Ar), 7.48 (dd, 1H, *J* = 8.7 Hz, *J* = 1.5 Hz, H−Ar), 7.35 (d, 1H, *J* = 8.5 Hz, H−Ar), 7.30 (td, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz, H−Ar), 7.13 (t, 1H, *J* = 8.0 Hz, H−Ar), 7.00 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 6.63 (d, 1H, *J* = 7.5 Hz, H−Ar), 2.56 (q, 2H, *J* = 7.5 Hz, CH_2), 1.90 (t, 3H, *J* = 7.5 Hz, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 145.4, 144.5, 132.9, 132.0, 129.0, 128.9, 127.0, 120.4, 118.7, 118.6, 115.5, 113.6, 110.0, 28.8 (CH_2), 14.3 (Me).

*N-(3,4-dimethylphenyl)-1H-indazol-3-amine (**2e**)*

White oil (34% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3449.98 (N−H), 1638.30 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 11.85 (s, 1H, N−H), 8.57 (s, 1H, N−H), 7.92 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.44 (s, 1H, H−Ar), 7.40 (dd, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, H−Ar), 7.33 (dd, 1H, *J* = 8.5 Hz, *J* = 1.0 Hz, H−Ar), 7.29 (td, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz, H−Ar), 6.99 (td, 2H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 2.18 (s, 3H, Me), 2.13 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 141.0, 136.3, 130.0, 129.8, 126.9, 120.5, 120.4, 119.7, 118.5, 117.6, 113.8, 111.7, 109.9, 20.2 (Me), 18.9 (Me).

4.4. N-mesityl-1H-indazol-3-amine (**2f**)

White oil (36% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3241.75 (N−H), 1617.64 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 11.43 (s, 1H, N−H), 7.54 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.41 (s, 1H, N−H), 7.21−7.23 (m, 2H, H−Ar), 6.86 (bs, 3H, H−Ar), 2.23 (s, 3H, Me), 2.11 (s, 6H, 2Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 148.3, 142.0, 137.3, 135.1, 133.9, 129.0, 128.9, 126.5, 120.5, 118.0, 114.1, 110.0, 1.9.9, 20.9(Me), 18.7 (2Me).

*N-(3-bromophenyl)-1H-indazol-3-amine (**2g**)*

White oil (32% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3431.77(N−H), 1620.37 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 12.11 (s, 1H, N−H), 9.11 (s, 1H, N−H), 8.08 (bs, 1H, H−Ar), 7.94 (d, 1H, *J* = 8.0, H−Ar), 7.54 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.39 (d, 1H, *J* = 8.5, H−Ar), 7.33 (t, 1H, *J* = 8.0 Hz, H−Ar), 7.19 (t, 1H, *J* = 7.5 Hz, H−Ar),7.04 (t, 1H, *J* = 7.5 Hz, H−Ar), 6.94 (d, 1H, *J* = 7.5 Hz, H−Ar); ^{13}C NMR (125 MHz, DMSO d_6) δ = 145.1, 144.7, 140.9, 130.9, 127.2, 122.3, 121.5, 120.2, 119.0, 118.2, 115.1, 114.8, 110.2.

*N-(4-bromophenyl)-1H-indazol-3-amine (**2h**)*

Cream solid (32% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3413.51 (N−H), 1619.14 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 12.05 (s, 1H, N−H), 9.02 (s, 1H, N−H), 7.92 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.64 (d, 2H, *J* = 9.0, H−Ar), 7.36−7.40 (m, 3H, H−Ar), 7.32 (t, 1H, *J* = 8.5 Hz, H−Ar), 7.03 (t, 1H, *J* = 7.0 Hz, H−Ar); ^{13}C NMR (125 MHz, DMSO d_6) δ = 144.9, 142.8, 140.9, 132.0, 131.7, 127.2, 124.0, 120.2, 118.9, 118.0, 114.7, 110.1, 110.0.

*N-(4-chlorophenyl)-1H-indazol-3-amine (**2i**)*

Cream solid (31% yield); ^{1}H NMR (500 MHz, DMSO d_6) δ = 12.04 (s, 1H, N−H), 9.01 (s, 1H, N−H), 7.92 (d, 1H, *J* = 7.5 Hz, H−Ar), 7.69 (dd, 2H, *J* = 9.0 Hz, *J* = 1.5 Hz, H−Ar), 7.37 (d, 1H, *J* = 8.5 Hz, H−Ar), 7.32 (t, 1H, *J* = 7.5 Hz, H−Ar),7.27 (dd, 2H, *J* = 9.0 Hz, *J* = 1.5 Hz, H−Ar), 7.02 (t, 1H, *J* = 8.0 Hz, H−Ar); ^{13}C NMR (125 MHz, DMSO d_6) δ = 141.0, 139.3, 134.9, 128.8, 127.2, 126.4, 120.2, 118.8, 117.8, 117.6, 116.3, 110.9, 110.1.

*N-(4-fluorophenyl)-1H-indazol-3-amine (**2j**)*

Cream oil (30% yield); IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 3449.34 (N−H), 1569.19 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.19 (s, 1H, N−H), 7.56 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.36−7.40 (m, 5H, H−Ar), 7.11 (td, 1H, *J* = 7.0 Hz, *J* = 2.0 Hz, H−Ar), 7.01 (t, 2H, *J* = 8.5 Hz, H−Ar), 6.21 (s, 1H, N−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 143.4, 137.9, 130.4, 127.5, 124.5, 119.9, 119.4, 118.1, 115.8, 115.4, 115.0, 114.3, 112.1.

*N-(p-tolyl)-3H-indazol-3-imine (**3a**)*

Red solid (57% yield); mp = 164−166 °C; ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.10 (d, 1H, *J* = 7.5 Hz, H−Ar), 7.96 (d, 1H, *J* = 7.5 Hz, H−Ar), 7.89 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.83 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.44 (d, 2H, *J* = 8.5 Hz, H−Ar), 7.28 (d, 2H, *J* = 8.5 Hz, H−Ar), 2.34 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 161.7, 155.8, 145.9, 138.3, 138.1, 134.2, 133.0, 130.0, 129.6, 126.2, 122.8, 116.0, 109.9, 21.2 (Me).

*N-(o-tolyl)-1H-indazol-3-amine (**3b**)*

Orange solid (61% yield); mp = 170−172 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1629.78 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.05 (d, 1H, *J* = 7.0 Hz, H−Ar), 7.85 (bs, 2H, H−Ar), 7.71 (bs, 1H, H−Ar), 7.62 (d, 1H, *J* = 7.5 Hz, H−Ar), 7.49 (d, 1H, *J* = 6.5 Hz, H−Ar), 7.44 (d, 1H, *J* = 6.5 Hz, H−Ar), 7.35 (t, 1H, *J* = 7.0 Hz, H−Ar), 2.69 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 153.3, 150.2, 139.4, 134.7, 134.5, 133.2, 132.1, 132.0, 127.2, 118.7, 117.2, 115.8, 112.1, 17.6 (Me).

*N-(4-methoxyphenyl)-3H-indazol-3-imine (**3c**)*

Red solid (57% yield); mp = 133−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.03 (d, 2H, *J* = 9.0 Hz, H−Ar), 7.87 (dd, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz, H−Ar), 7.81 (dd, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, H−Ar), 7.66 (td, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, H−Ar), 7.49 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.03 (d, 2H, *J* = 9.0 Hz, H−Ar), 3.91 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.3, 153.6, 146.9, 133.5, 133.2, 130.0, 125.8, 117.1, 116.9, 114.4, 113.8, 112.5, 109.9, 55.6 (OMe).

*N-(3-ethylphenyl)-3H-indazol-3-imine (**3d**)*

Orange solid (59% yield); mp = 120−122 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1618.75 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.11 (d, 1H, *J* = 7.5 Hz, H−Ar), 7.96 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.91 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.85 (td, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz, H−Ar), 7.36 (t, 1H, *J* = 7.5 Hz, H−Ar), 7.26 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.16 (d, 1H, *J* = 7.5 Hz, H−Ar), 2.64 (q, 2H, *J* = 7.5 Hz, CH_2), 1.20 (t, 3H, *J* = 7.5 Hz, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 147.7, 146.2, 1450.0, 134.3, 133.2, 132.2, 131.9, 129.2, 127.3, 124.8, 123.0, 122.7, 116.0, 28.4 (CH_2), 15.8 (Me).

*N-(3,4-dimethylphenyl)-3H-indazol-3-imine (**3e**)*

Orange solid (60% yield); mp = 142−144 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1616.68 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.08 (dd, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.95 (d, 1H, *J* = 7.5 Hz, H−Ar), 7.89 (t, 1H, *J* = 7.5 Hz, H−Ar), 7.83 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, H−Ar), 7.34 (s, 1H, H−Ar), 7.29 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H−Ar), 7.22 (d, 1H, *J* = 8.0 Hz, H−Ar), 2.26 (s, 3H, Me), 2.25 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 155.5, 145.8, 145.3, 137.3, 137.0, 134.2, 132.9, 130.4, 129.6, 127.3, 123.6, 122.7, 116.0, 19.8 (Me), 19.5 (Me).

*N-mesityl-3H-indazol-3-imine (**3f**)*

Red solid (59% yield); mp = 141−143 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1650.62 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.19 (d, 1H, *J* = 7.0 Hz, H−Ar), 7.93−7.97 (m, 2H, H−Ar), 7.90 (d, 1H, *J* = 8.5 Hz, H−Ar), 7.00 (s, 1H, H−Ar), 6.88 (s, 1H, H−Ar), 1.96 (s, 6H, 2Me), 1.92 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO d_6) δ = 157.8, 147.1, 145.1, 134.6, 134.0, 133.6, 129.4, 128.6, 126.2, 125.0, 124.0, 123.2, 116.3, 20.8 (Me), 18.5 (Me), 18.0 (Me).

*N-(3-bromophenyl)-3H-indazol-3-imine (**3g**)*

Orange solid (63% yield); mp = 100−102 °C; ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.07 (dt, 1H, *J* = 7.5 Hz, *J* = 1 Hz, H−Ar), 7.98−7.99 (m, 1H, H−Ar), 7.93 (d, 1H, *J* = 8.0 Hz, H−Ar), 7.85 (m, 1H, H−Ar), 7.83−7.84 (m, 1H, H−Ar), 7.79−7.82 (m, 1H, H−Ar), 7.73 (td, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, H−Ar), 7.59 (t, 1H, *J* = 8.0 Hz, H−Ar); ^{13}C NMR (125 MHz, DMSO d_6) δ = 153.1, 152.4, 135.5, 134.7, 134.5, 132.9, 132.1, 124.8, 123.7, 123.0, 117.6, 116.8, 112.4.

*N-(4-bromophenyl)-3H-indazol-3-imine (**3h**)*

Orange solid (63% yield); mp = 184–185 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1701.53 (C=N); ^{1}H NMR (500 MHz, DMSO d_6) δ = 8.11 (d, 1H, *J* = 7.0 Hz, H–Ar), 7.96 (d, 1H, *J* = 7.5 Hz, H–Ar), 7.91 (t, 1H, *J* = 7.0 Hz, H–Ar), 7.87 (dd, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz, H–Ar), 7.64 (d, 2H, *J* = 8.5 Hz, H–Ar), 7.38 (d, 2H, *J* = 8.5 Hz, H–Ar); ^{13}C NMR (125 MHz, DMSO d_6) δ = 158.0, 157.4, 148.1, 146.7, 134.4, 133.6, 133.4, 132.2, 127.2, 123.0, 120.6, 116.1, 115.7.

*N-(4-chlorophenyl)-3H-indazol-3-imine (**3i**)*

Orange solid (64% yield); mp = 179–180 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1592.42 (C=N);^{1}H NMR (500 MHz, DMSO d_6) δ = 8.12 (d, 1H, *J* = 7.5 Hz, H–Ar), 7.94 (d, 1H, *J* = 7.5 Hz, H–Ar), 7.91 (t, 1H, *J* = 7.5 Hz, H–Ar), 7.87 (d, 1H, *J* = 7.5 Hz, H–Ar),7.51 (d, 2H, *J* = 8.0 Hz, H–Ar), 7.47 (d, 2H, *J* = 8.0 Hz, H–Ar); ^{13}C NMR (125 MHz, DMSO d_6) δ = 157.3, 146.3, 146.2, 134.4, 133.4, 132.1, 129.3, 129.2, 127.0, 123.0, 121.3, 116.1, 109.9.

*N-(4-fluorophenyl)-3H-indazol-3-imine (**3j**)*

Cream solid (65% yield); mp = 181–184 °C; IR KBr($\bar{\upsilon}_{max}$, cm^{-1}): 1592.11 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05–8.08 (m, 2H, H–Ar),8.89 (d, 1H, *J* = 8.0 Hz, H–Ar), 7.85 (d, 1H, *J* = 7.5 Hz, H–Ar), 7.70 (td, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz H–Ar), 7.56 (t, 1H, *J* = 7.5 Hz, H–Ar), 7.25 (d, 1H, *J* = 8.0 Hz, H–Ar), 7.22 (t, 1H, *J* = 9.0 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.3, 162.4, 153.0, 149.8, 144.0, 133.6, 133.2, 130.8, 125.6, 125.8, 117.1, 116.4, 116.2.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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