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CuO nanoparticle catalysed synthesis of 2*H*-indazoles under ligand free conditions†

Nilufa Khatun, Anupal Gogoi, Pallabita Basu, Prasenjit Das and Bhisma K. Patel*

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A CuO nano catalysed one-pot synthesis of 2*H*-indazoles has been devised from easily accessible starting materials *viz.* 2-bromobenzaldehydes, primary amines and sodium azide under ligand free conditions. The nano CuO catalyst played an important role during the formation of the intermolecular C–N bond followed by the intramolecular N–N bond, providing 2*H*-indazoles. This method has a broad substrate scope with a high tolerance of a variety of functional groups. The catalyst can be recycled up to three times, however with slight decreases in the yields each time.

Introduction

Over the past decade due to the immense importance of derivatives of 2*H*-indazole in the field of modern drug discovery this moiety has attracted considerable attention. Molecules possessing an indazole skeleton are found to have a broad spectrum of biological activities such as anti-tumour,[1] anti-HIV,[2a] anti-microbial,[2b] anti-inflammatory,[2c] anti-depressant,[2d] anti-cancer,[2e] anti-platelet,[2f] and anti-contraceptive.[2g] Besides, indazoles are efficient bioisosters of indoles and benzimidazoles in pharmaceutical chemistry.[3] Bioactive compounds containing 2*H*-indazoles have been found to have potential activity towards the imidazoline I_2 receptor[4a] and 5-HT_{1A} receptors.[4b]

Some examples of biologically active molecules containing an indazole nucleus include a neuroprotective voltage-dependent sodium channel modulator, oxadiazolylindazole (**I**),[3b] a selective ligand for the estrogen receptor (**II**),[5a] the hybrid molecule (**III**), which is antitumor agent CC-1065,[1a] and an anti-HIV agent (**IV**)[5b] are shown in Fig. 1.

Due to numerous applications of 2*H*-indazoles in modern drug discovery, the development of novel methods for its synthesis is of great interest to synthetic chemists. Fewer methods have been reported in the literature for the synthesis of 2*H*-indazoles compared to 1*H*-indazoles as most of the attempts provide the thermodynamically controlled 1*H*-indazoles as the main product or a mixture of 1*H* and 2*H*-indazoles with low selectivity.[6,7] To overcome the problems of selectivity, some promising methodologies have been reported in the literature recently as shown in Scheme 1. Earlier efforts involve (a) Rh catalysed reductive *N*-cyclisation of (2-nitroarylidine),[8a] (b) a domino reaction of 2-halophenylacetylene with hydrazine in the presence of a palladium catalyst,[8b] (c) cycloaddition of arynes with sydnones, (d) reaction of 2-chloromethylaryl zinc reagents and aryldiazonium salts,[8c] (e) DDQ mediated reaction of Baylis–Hillman adducts and hydrazine,[8d] (e) iron catalysed N–N bond formation of 2-azidophnylketoxime.[8e] Most recently the CuI catalysed intramolecular reaction of 2-azidoimine[9a] (path f, when X = Ar) and an intermolecular N–N bond formation *via* a three component reaction[9b,c] (path g) for the synthesis of 2*H*-indazoles have been reported. Though some of the reported methods are efficient, the generation of a regio-isomeric mixture, requirement of pre-synthesised starting materials, use of ligands, high catalyst loading and longer reaction times make them unsuitable for large scale syntheses.

Recently metallic nanoparticles have been used extensively as an alternative catalyst in organic synthesis due to their high reactivity, easy recovery and often the recyclability of the catalyst. The high reactivities of nanoparticles are the result of their large surface area and they often exhibit different reactivities when dispersed down to a nanometer scale. Metal nanoparticle catalysed reactions are advantageous over conventional metal catalysed reactions in terms of low catalyst loading, high atom economy, better yields, shorter reaction times and recyclability of the catalyst. In addition, high dispersivity and better stability

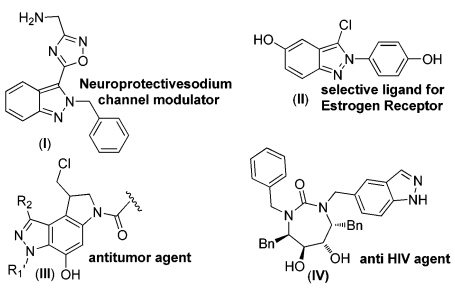

Fig. 1 Biologically active molecules having 2*H*-indazoles scaffolds.

Department of Chemistry, Indian Institute of Technology Guwahati, 781 039, Assam, India. E-mail: patel@iitg.ernet.in

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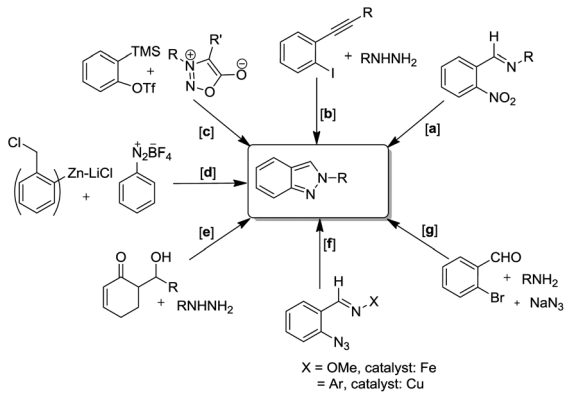


Scheme 1 Literature available methods for the synthesis of 2*H*-indazoles.

towards most chemical environments make nanoparticles a celebrated catalyst. Due to those features metal, especially copper salt, nanoparticles have been used successfully for C–N, C–O, C–S cross-coupling reactions.[10] Their efficacy in the formation of intramolecular C–S bonds even from inert sp^2 C–Cl and C–F illustrates their superiority over conventional catalysts.[11] The use of a CuO nano catalyst to form the N–N bond in organic reactions has not been reported till date. Herein we aspire to report a one-pot synthesis of 2*H*-indazoles from 2-bromobenzaldehyde, primary amines and sodium azide using a CuO nano catalyst.

Result and discussion

To execute our strategy the *in situ* generated imine obtained from the reaction of 2-bromobenzaldehyde (**1**, 1 equiv.) and aniline (**a**, 1 equiv.) in DMSO was first treated with CuO nano (5 mol%), KOH (2 equiv.) and sodium azide (NaN_3, 1.1 equiv.) at room temperature. No product formation was observed even after 24 h at room temperature but when the reaction mixture was heated at 90 °C, the imine decomposed to a multitude of inseparable products from which only a small amount of the expected 2*H*-indazoles (7%) could be isolated (Table 1, entry 1). An imine was generated *in situ*, which showed the presence of unreacted aniline (**a**). To consume this unreacted aniline (**a**), a slight excess of 2-bromobenzaldehyde (**1**) (1.1 equiv.) was used in the next reaction. The replacement of KOH with K_2CO_3, led to a cleaner reaction mixture, although a substantial amount of the imine remained unreacted even after 9 h at 90 °C. The product upon isolation (48% yield) and characterisation was found to be the expected 2*H*-indazole (Table 1, entry 2). The structure of the product (**1a**) has been unambiguously confirmed by X-ray crystallography as shown in Fig. 2. Under identical conditions increasing the reaction temperature to 120 °C gave an improved yield of 59% within 7 h. No further improvement in the yield was observed even when the reaction was continued up to 12 h. However when the quantity of NaN_3 was increased to 3.0 equiv. from 1.1 equiv. the yield improved up to 72% (Table 1, entry 4). Further substituting Cs_2CO_3 *in lieu* of K_2CO_3 provided the desired product in 85% yield with a shorter reaction time (2.5 h) (Table 1, entry 5). When the catalyst loading was reduced to 2.5 mol% from 5 mol% the yield practically remained unchanged although the reaction took longer (5 h) (Table 1, entry 6). Polar aprotic solvents such as DMF, DMSO (Table 1, entry 6) led to better efficacy than a nonpolar solvent like toluene (Table 1, entry 8). Taking a cue from our CuO nano catalysed intramolecular C–S bond formation in water,[11] when the present reaction was executed in water the

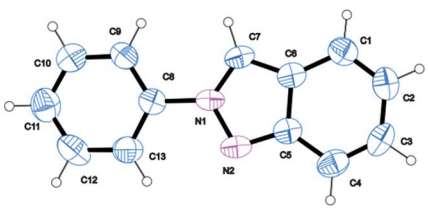
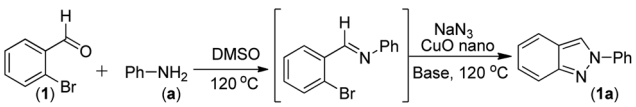


Fig. 2 ORTEP view of product (**1a**).

Table 1 Screening of reaction conditions[a]



Entry	Catalyst (mol%)	Base (equiv.)	Solvent	NaN_3 (equiv.)	Time (h)/T °C	Yield[b] (%)
1	CuO (5)	KOH (2)	DMSO	1.1	13/90 °C	7
2	CuO (5)	K_2CO_3 (2)	DMSO	1.1	9/90 °C	48
3	CuO (5)	K_2CO_3 (2)	DMSO	1.1	7/120 °C	59
4	CuO (5)	K_2CO_3 (2)	DMSO	3.0	6/120 °C	72
5	CuO (5.0)	Cs_2CO_3 (2)	DMSO	3.0	2.5/120 °C	85
6	CuO (2.5)	Cs_2CO_3 (2)	DMSO	3.0	5/120 °C	84
7	CuO (2.5)	Cs_2CO_3 (2)	DMF	3.0	6/120 °C	62
8	CuO (2.5)	Cs_2CO_3 (2)	Toluene	3.0	15/120 °C	<5
9	CuO (2.5)	Cs_2CO_3 (2)	Water	3.0	12/120 °C	—

[a] Reactions were monitored by TLC. [b] Isolated yield.

reaction was not at all effective. The use of normal CuO gave an inferior yield (37% after 12 h) compared to CuO nano (85%, after 5 h) under identical reaction conditions.

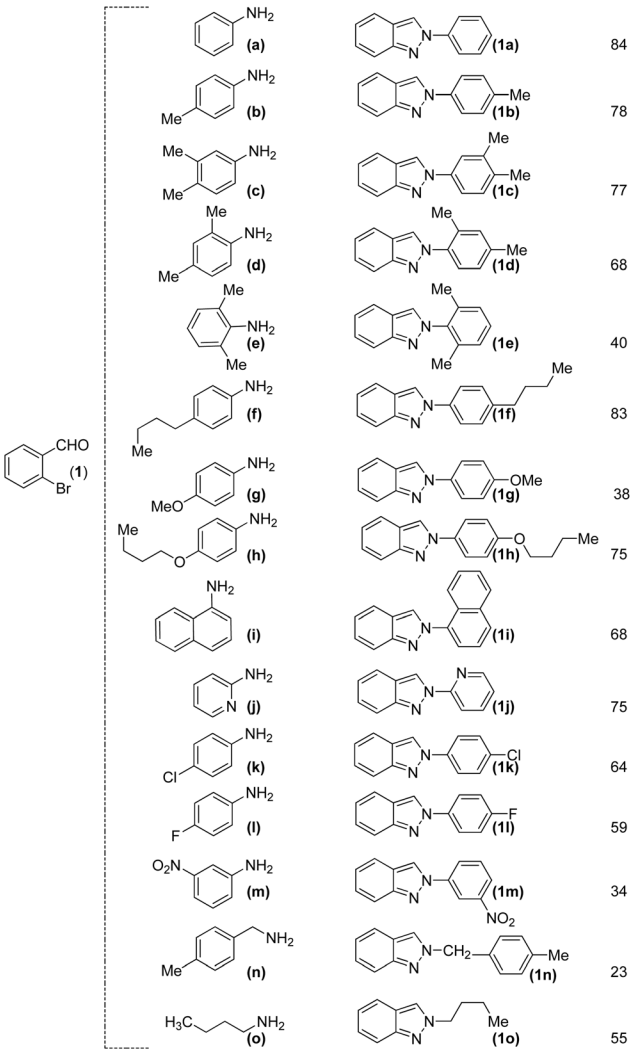
Thus 2-bromobenzaldehyde (**1**, 1.1 equiv.), aniline (**a**, 1.0 equiv.), NaN_3 (3.0 equiv.), Cs_2CO_3 (2.0 equiv.) and CuO nano (2.5 mol%) at 120 °C in DMSO was chosen as the optimised reaction conditions, which was applied for the ensuing reactions.

Thus having arrived at the optimised reaction conditions, the methodology was then applied to various aromatic, heteroaromatic and aliphatic primary amines. It was observed that all of these reactions proceeded smoothly providing the corresponding 2*H*-indazoles in good to excellent yields. Initially, the reactions of 2-bromobenzaldehyde (**1**) with various substituted primary amines were examined. The *in situ* generated imine obtained by the reaction of (**1**) and 4-methyl aniline (**b**) under the optimised conditions, produced a 78% yield of (**1b**) as shown in Table 2. Aromatic amines possessing a weakly activating substituent (–Me) on the aromatic ring as in 3,4-dimethyl aniline (**c**) and 2,4-dimethyl aniline (**d**) provided their expected 2*H*-indazoles (**1c**) and (**1d**) respectively in 77% and 68% yields. However, isomeric aniline such as 2,6-dimethyl anilines (**e**) yielded only 40% of product (**1e**). The poor yield obtained is because of the steric hindrance imparted by two *o*-methyl groups. 4-Butyl aniline (**f**) provided a good yield (83%) of the 2*H*-indazole (**1f**) when reacted with 2-bromobenzaldehyde (**1**) under the optimised reaction conditions. Surprisingly 4-methoxy aniline (**g**) gave only 38% yield of expected product (**1g**). The lower yield obtained is possibly due to the competitive hydrolysis of the *in situ* generated imine under the reaction conditions. Interestingly the analogous substrate 4-butoxy aniline (**h**) gave a good yield (75%) of its 2*H*-indazole (**1h**). The polycyclic aromatic amine, 1-napthyl amine (**i**) when reacted with 2-bromobenzaldehyde (**1**) under the present reaction conditions yielded product (**1i**) in 68% yield. Heteroaromatic amines such as 2-amino pyridine (**j**) produced the corresponding 2*H*-indazoles (**1j**) in good (75%) yield. The above optimised conditions were also successful for aryl amines possessing electron withdrawing substituents such as *p*-Cl (**k**), *p*-F (**l**) and *m*-nitro (**m**) groups giving corresponding 2*H*-indazoles (**1k**), (**1l**) (**1m**). In the case of *m*-nitroaniline (**m**) due to the presence of a strong electron withdrawing substituent ($-NO_2$) the imine formation with the aldehyde in the first step was not effective and a considerable amount of unreacted *m*-nitroaniline (**m**) and 2-bromobenzaldehyde (**1**) were found in the reaction mixture, which affected the ultimate yield.

Furthermore, the *in situ* generated imine derived from a benzyl amine such as 4-methyl benzyl amine (**n**) and 2-bromobenzaldehyde (**1**), gave a poorer (23%) yield of the corresponding 2*H*-indazole (**1n**), under the present reaction conditions. All other attempts to further improve the yield failed. The 2-bromobenzaldehyde (**1**) and butyl amine (**o**) derived imine provided a moderate yield (55%) of indazole (**1o**).

Encouraged by this one pot synthetic strategy of 2*H*-indazoles, we then attempted to explore the substrate scope of the reaction using substituted 2-bromobenzaldehyde (**2**). Accordingly, 2-bromo-5-flurobenzaldehyde (**2**) was then treated with various aryl amines and the results are summarised in Table 3.

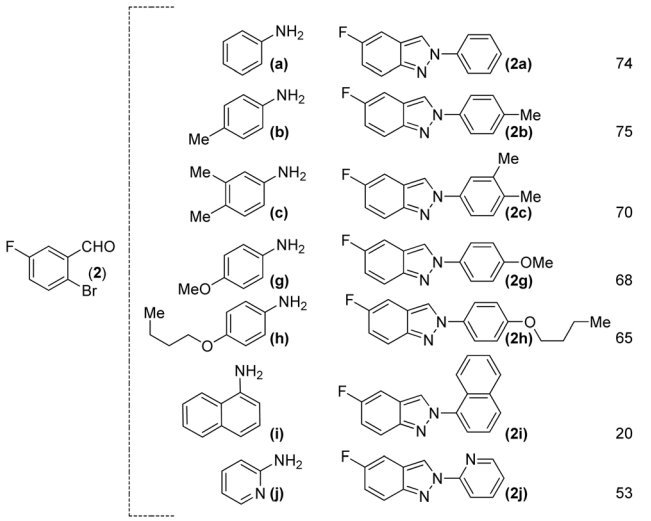
Table 2 CuO nano catalysed synthesis of 2*H*-indazoles from 2-bromobenzaldehyde[a]

Substrate(s)	Product[b]	Yield[c] (%)
		
	(a) → (1a)	84
	(b) → (1b)	78
	(c) → (1c)	77
	(d) → (1d)	68
	(e) → (1e)	40
	(f) → (1f)	83
	(g) → (1g)	38
	(h) → (1h)	75
	(i) → (1i)	68
	(j) → (1j)	75
	(k) → (1k)	64
	(l) → (1l)	59
	(m) → (1m)	34
	(n) → (1n)	23
	(o) → (1o)	55

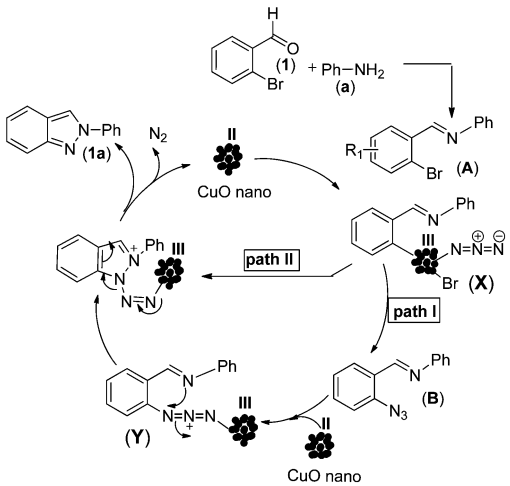
[a] Reactions were monitored by TLC. [b] Products characterised by IR and NMR. [c] Isolated yield.

All the reactions were found to be quite effective at providing 2*H*-indazoles in moderate to good yields. The *in situ* generated imine obtained by the reaction of (**2**) and aniline (**a**) under the reaction conditions, provided 77% yield of (**2a**). The imine generated by the reaction of (**2**) and aromatic amines containing weakly activating substituents such as *p*-Me (**b**) or 3,4-dimethyl (**c**) provided a good yield of products (**2b**) and (**2c**), respectively. Similarly, the aromatic amines containing activated substituents such as *p*-methoxy (**g**) and *p*-butoxy (**h**) gave similar yields of (**2g**) and (**2h**) as shown in Table 3. Surprisingly the polycyclic 1-napthyl amine, another activated amine (**i**) provided only 20% yield of (**2i**) however in Table 1 the same substrate (**i**) gave much better yields. Here as well no correlation between the yields of the product obtained and electronic effect of substituents could

Table 3 CuO nano catalysed synthesis of 2*H*-indazoles from substituted 2-bromobenzaldehyde[a]

Substrate(s)	Product[b]	Yield[c] (%)
		
	(a)	(2a) 74
	(b)	(2b) 75
	(c)	(2c) 70
	(g)	(2g) 68
	(h)	(2h) 65
	(i)	(2i) 20
	(j)	(2j) 53

[a] Reactions were monitored by TLC. [b] Products characterised by IR and NMR. [c] Isolated yield.



Scheme 2 Plausible mechanism for the CuO nano catalysed 2*H*-indazoles formation.

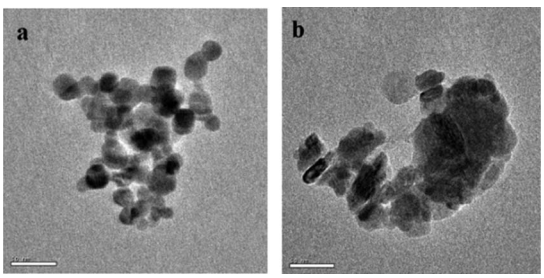


Fig. 3 TEM images of (a) fresh CuO nano catalyst and (b) CuO nano catalyst after the third cycle.

be found. Likewise heteroaromatic amine, 2-amino pyridine (**j**) under the reaction conditions gave a modest yield of (**2j**) as shown in Table 3.

A mechanism analogous to the one that has been proposed by Lee *et al.*[9b] can be envisaged for this transformation as well, as shown in Scheme 2. The *in situ* generated imine (**A**) obtained by the condensation of 2-bromoaldehyde (**1**) and aniline (**a**) first underwent an intermolecular coupling reaction with NaN_3 in the presence of the CuO nano catalyst to form the 2-azido intermediate (**B**). The formation of (**B**) is hypothesised to occur from the complex (**X**). The nano catalyst then activates the azide moiety through coordination to the N-atom terminus in intermediate (**B**) as shown in path I and results in the formation of another copper-azide complex (**Y**). The nucleophilic attack of the imine, N-atom, of complex (**Y**) to the activated azide moiety results in a N–N bond formation. Finally the expulsion of N_2 and dissociation of the copper nano catalyst yielded the expected 2*H*-indazole. The reaction involving path II cannot be ruled out where simultaneous azidation and product formation was considered. Separately prepared (**B**)[9a] when subjected to the present reaction conditions provides compound (**1a**) in 89% yield suggesting the intermediacy of (**B**) in the reaction.

The catalyst was then recovered from the reaction mixture by centrifugation and was washed successively with ethyl acetate, water and acetone. The catalytic efficiency of the recovered catalyst was then tested employing the *in situ* generated imine obtained from 2-bromobenzaldehyde (**1**) and aniline (**a**). In the first catalytic cycle, 93% (by GC) conversion was observed under the optimised reaction conditions. In the second and third run the yields obtained were 82% and 75% respectively (by GC). The morphologies of the catalyst after three cycles and fresh were compared by TEM (Fig. 3), which shows that the catalyst agglomerates during the course of the recycling process. Since the catalyst is cheap and only 2.5 mol% is needed for the reaction it is advised to use fresh catalyst for a better conversion.

Conclusion

We developed a novel method for the synthesis of 2*H*-indazoles under ligand free conditions using CuO nano as the catalyst. Low catalyst loading, high yields, shorter reaction time and broad substrate scope tolerating a wide variety functional groups such as methoxy, nitro, chloro *etc.* are attributes of the present methodology.

General procedure for the synthesis of 2-phenyl-2*H*-indazole (1a)

A mixture of 2-bromobenzaldehyde (**1**) (1.1 mmol) and aniline (**a**) (1 mmol) was stirred in DMSO (1.0 mL) at 120 °C for 1 h. A small aliquot of the *in situ* generated imine was then collected and the bulk portion was treated with CuO nano particles (2.5 mol%), Cs_2CO_3 (2 equiv.) and sodium azide (3 equiv.) at the same temperature. The progress of the reaction was monitored by TLC. After 4 h, the total conversion of the imine was observed by TLC. After cooling to room temperature, the reaction mixture

was then mixed with ethyl acetate and passed through a celite pad. This organic layer was then washed with water (3 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography eluting with (97 : 3: petroleum ether–ethyl acetate) to give pure product (**1a**) in 84% yield.

Acknowledgements

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