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ARTICLE TYPE

Regioselective one-pot, three-component synthesis of substituted 2*H*-indazoles from nitroarylaldehyde, alkyne and amine catalyzed by CuBr/Zn(OTf)$_2$ system

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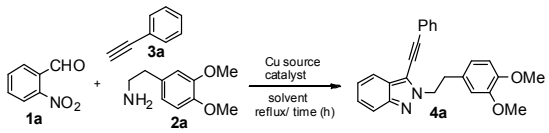
3-(Arylethynyl)-2*H*-indazoles can be effectively synthesized in one-pot using 2-nitroarylaldehydes, primary amines and alkynes co-catalyzed by copper (I) bromide and zinc (II) triflate. This method has a broad substrate scope with high to medium tolerance for a variety of functional groups.

The indazoles are important structural units found in many biologically active molecules.[1] The isomeric form of indazole, 2*H*-indazoles are gaining considerable interest due to their anticancer,[2] imidazole I_2 receptor,[3] 5-HT_{1A} receptor,[4] estrogen receptor β,[5] and antiangiogenic activities.[6] There are several methods for the synthesis of indazoles, but most of them are restricted to the thermodynamically favoured 1*H*-indazole or mixtures of 1*H*- and 2*H*-indazoles.[7] Methods for the regioselective synthesis of 2*H*-indazoles are limited due to the difficulty in their preparation. Therefore, selective preparation of 2*H*-indazoles remains challenging task in organic chemistry. Recently, several synthetic routes to 2*H*-indazoles have been developed,[8] but considering the bioactivities of 2*N*-substituted indazoles,[2b,5,6,9] the development of new strategies for the general and efficient synthesis of highly substituted 2*H*-indazoles is needed. Although there are several methods for the synthesis of 2*N*-substituted 2*H*-indazoles, methods for the direct synthesis of 2*N*,3*C*-substituted 2*H*-indazoles are rare.[8a,c,g,j,10] These methods suffer from drawbacks, such as multistep synthesis,[8c,j,10d] low selectivity,[10a] low yields and formation of side products.[10b] Multicomponent reactions are gaining importance in heterocyclic chemistry due to their ability to form a series of bonds in a single step.[11] Herein, we report a one-pot direct synthesis of 2,3-disubstituted 2*H*-indazoles using 2-nitroarylaldehydes, amines and alkynes co-catalyzed by CuBr and Zn(OTf)$_2$ in moderate to good yields.

Initially, we treated the 2-nitrobenzaldehyde **1a**, 2-(3,4-dimethoxyphenyl)ethanamine **2a**, and ethynylbenzene **3a** with CuBr (30 mo%) and In(OTf)$_3$ (10 mol%) in dry toluene at reflux and it led to the formation of 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2*H*-indazole **4a** in 40% yield (Table 1, entry 1). Similarly, under the same reaction conditions Sn(OTf)$_2$ gave 50% yield (entry 2). Zn(OTf)$_2$/CuBr system was found to be more reactive and yielded 83% (entry 3). When the amount of CuBr was increased to 1 equivalent, 80% of the product was isolated (entry 4). Other Lewis acids and copper salts were also screened and the results are shown in Table 1. It was observed that bismuth, scandium and silver triflates gave lower yields (entries 5-7). Other metal salts such as $FeCl_3$, $ZnCl_2$, $SnCl_2.2H_2O$ and

Table 1. Optimization of the reaction[a]



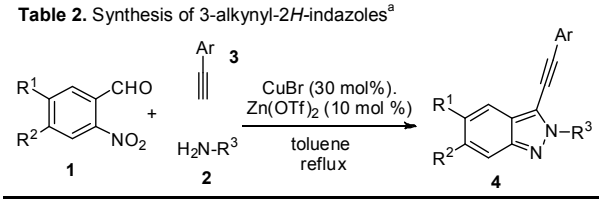
Sl. No	Cu Source (mol%)	Catalyst (mol%)	Solvent	Time/h	Yield (%)[b]
1	CuBr (30)	In(OTf)$_3$ (10)	Toluene	21	40
2	CuBr (30)	Sn(OTf)$_2$ (10)	Toluene	24	50
3	**CuBr (30)**	**Zn(OTf)$_2$ (10)**	**Toluene**	**18**	**83**
4	CuBr (100)	Zn(OTf)$_2$ (10)	Toluene	18	80
5	CuBr (30)	Bi(OTf)$_2$ (10)	Toluene	24	35
6	CuBr (30)	Ag(OTf) (10)	Toluene	24	37
7	CuBr (30)	Sc(OTf)$_2$ (10)	Toluene	24	32
8	CuBr (30)	$FeCl_3$ (100)	Toluene	24	33
9	CuBr (30)	$ZnCl_2$ (100)	Toluene	24	42
10	CuBr (30)	$SnCl_2.2H_2O$ (100)	Toluene	24	36
11	CuBr (30)	$InCl_3$ (100)	Toluene	24	12
12	CuBr (30)	P(Ph)$_3$ (100)	Toluene	24	---[c]
13	CuBr (30)	P(OEt)$_3$ (100)	Toluene	24	17
14	CuBr (30)	Zn(OTf)$_2$ (10)	Dioxane	24	---[c]
15	---	Zn(OTf)$_2$ (10)	Toluene	24	---[c]
16	CuBr (30)	---	Toluene	36	Trace
17	CuI (30)	Zn(OTf)$_2$ (10)	Toluene	24	28
18	CuCl (30)	Zn(OTf)$_2$ (10)	Toluene	24	63

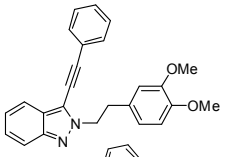
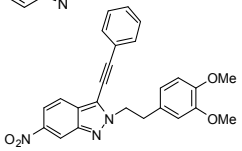
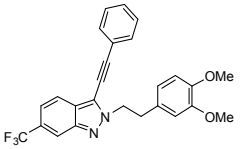
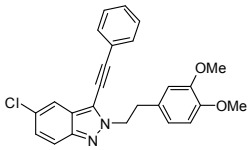
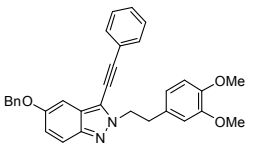
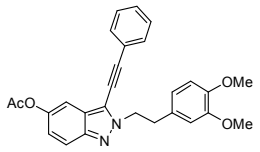
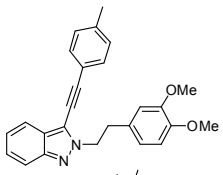
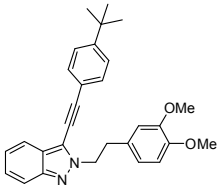
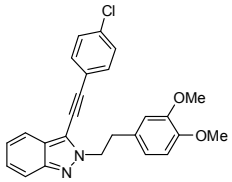
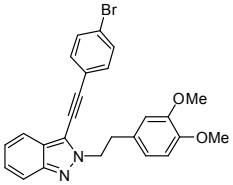
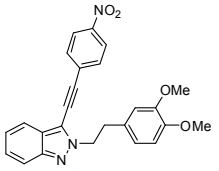
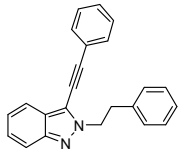
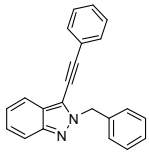
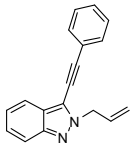
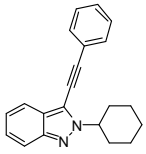
[a]Reaction conditions: aldehyde (0.5 mmol), amine (0.55 mmol), alkyne (1.0 mmol), solvent (8 mL).[b]Yield refers to isolated yield. [c]Corresponding imine was isolated.

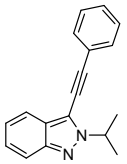
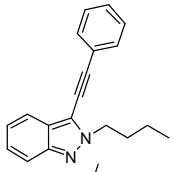
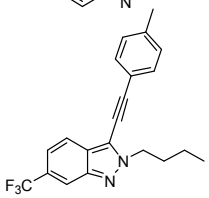
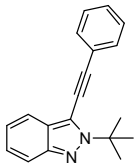
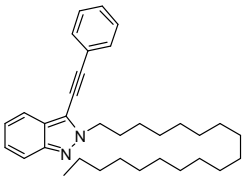
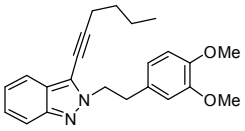
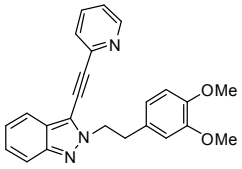
$InCl_3$ also found to be less effective (entries 8-11). In the case of phosphorous reagents, $P(Ph)_3$ produced only imine (entry 12), whereas $P(OEt)_3$ gave 17% of the desired product (entry 13). Reaction with $CuBr/Zn(OTf)_2$ in dioxane (entry 14) and $Zn(OTf)_2$ (entry 15) alone in toluene gave the corresponding imines, whereas CuBr alone gave trace amount of the desired product (entry 16). Other copper salts such as CuI and CuCl gave 28 and 63% yields, respectively (entries 17-18).

With the established optimal conditions in hand, the scope of this reaction was investigated, and the results are summarized in Table 2. 2-Nitroarylaldehydes having electron-withdrawing groups were transformed into 2*H*-indazoles in 60-79% yields (Table 2, entries 2-4, 18). Acetylenes with aromatic substituents containing electron-withdrawing or electron-donating groups were transformed in 57-81% yields (Table 2, entries 7-11, 18). On the other hand, acetylene having alkyl group (Table 2, entry 21) was unable to give desired product, but corresponding imine was recovered in 90% yield. Similarly, heterocyclic alkyne (entry 22) also gave imine in 85% yield. The scope of the reaction was also extended to primary amines. The reaction yielded moderate to good yields with variously substituted primary amines. The reaction with aromatic amines with 2-nitrobenzaldehydes and alkynes under the same reaction conditions gave quinolines.[12]

Table 2. Synthesis of 3-alkynyl-2*H*-indazoles[a]



Entry	Product	Time/h	Yield (%)[b]
1	 **4a**	18	83
2	 **4b**	24	75
3	 **4c**	36	79
4	 **4d**	48	71
5	 **4e**	48	30
6	 **4f**	48	35
7	 **4g**	36	60
8	 **4h**	48	57
9	 **4i**	36	62
10	 **4j**	36	65
11	 **4k**	24	81
12	 **4l**	48	78
13	 **4m**	36	48
14	 **4n**	24	59
15	 **4o**	24	66

16		**4p**	24	64
17		**4q**	24	70
18		**4r**	30	60
19		**4s**	24	51
20		**4t**	24	56
21		**4u**	72	0[c]
22		**4v**	72	0[d]

[a]Reaction conditions: aldehyde (0.5 mmol), amine (0.55 mmol), alkyne (1.0 mmol), CuBr (30 mol%), $Zn(OTf)_2$ (10 mol%), toluene (8 mL), reflux. [b]Isolated yield. [c]Imine was isolated in 90% yield. [d]Imine was isolated in 85% yield.

The reaction is highly regioselective and only 2*N*-substituted product could be obtained in high purity without any regioisomeric products as determined from ^{1}H and ^{13}C NMR analysis of crude product. The structure of the compounds was determined by X-ray analysis of compound **4a** (see the supporting Information).[13]

In summary, we have developed a practical and general one-pot procedure for the synthesis of 2*H*-indazoles from 2-nitroarylaldehydes, primary amines and alkynes catalyzed by CuBr and $Zn(OTf)_2$. The practical and highly versatile one-pot, three-component procedure is a novel approach for the synthesis of highly substituted 2*H*-indazoles. The mechanism of the reaction is not yet known. Efforts to determine the mechanism of this unusual reaction is under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, ^{1}H, ^{13}C and HRMS spectra of all new compounds]. See DOI: 10.1039/b000000x/

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13 The crystallographic data for the compound **4a** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC1008821.

Graphical Content

Regioselective one-pot, three-component synthesis of substituted 2*H*-indazoles from nitroarylaldehyde, alkyne and amine catalyzed by CuBr/Zn(OTf)$_2$ system

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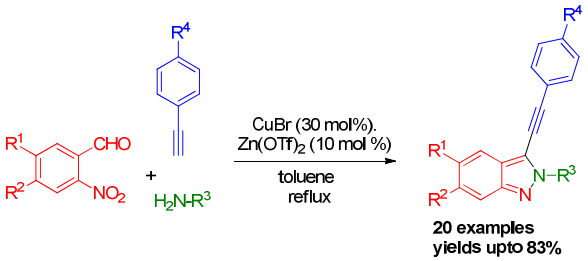

3-(Arylethynyl)-2*H*-indazoles are synthesized in one-pot using 2-nitroarylaldehydes, primary amines and alkynes catalysed by Zn(OTf)$_2$/CuBr system in moderate to good yields.