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COMMUNICATION

Four-component, three-stepcascade reaction: An effective synthesis of indazole fused triazolo[5,1-*c*]quinoxalines

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An efficient four component,three-step cascade reaction has been developed for the synthesis of indazole fused triazolo[5,1-*c*]quinoxalines from *o*-azido aldehyde, *o*-iodoaniline, phenylacetylene, and sodium azide. The methodology involves sequential formation of 2*H*-indazole then azide−alkyne cycloaddition followed by C−N coupling, and finally intramolecular cross dehydrogenative C−C coupling. Notable features of this protocol include simple starting materials, reduced synthetic steps and good yields.

In modern organic synthesis, chemical reaction sequencing by combining two or more distinct steps into a single transformation, thereby producing a sequential multi-component reaction which is one of the most important and economicstrategys.[1] Fused heterocyclic framework systems are one of the abundantly motifs in organic chemistry and have vast applications in medicinal[2] and material[3] chemistry. Among them, nitrogen-fused polycyclic compounds are widely distributed in pharmaceutical agents and natural products.[4] Therefore, continuing efforts have been devoted to explore efficient approaches for accessing nitrogen-heterocycles.[5]

2*H*-Indazoles are the integral part of several bioactive compounds for example, Pazopanib[6] (**A**) is a selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumour growth, Niraparib[7] (**B**), that inhibits poly(ADP-ribose)polymerase is useful for the potential treatment ovarian cancer and compound **C** is a viral polymerase inhibitor.[8] Triazoloquinoxalines, on the other hand, are considered as privileged structures in the area of drug discovery.[9-10] A series of 1,2,3-triazolo[1,5*a*]quinoxaline-4-ones (**D**) have shown good affinity toward the benzodiazepine receptor[10] (K_i 53-314 nM) whereas 1,2,4-triazolo[1,5-*a*]quinoxaline (**E**) is known to be useful as selective hA3 AR antagonists.[9a]

Thus combination of structural features of both 2*H*-indazole and triazolo quinoxaline in a single molecular entity represented by **F** (Fig. 1) was expected to provide a new hybrid chemical structure i.e. indazole fused triazolo[5,1-*c*]quinoxalines that might lead to the identification of novel molecules possessing pharmacological and photophysical properties.

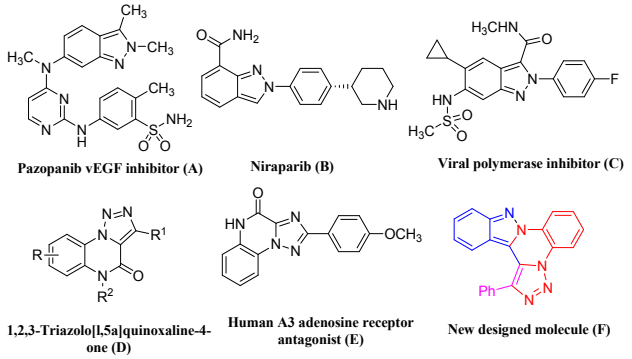
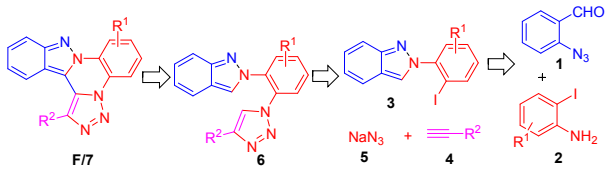


Fig. 1 Representative bio-active molecules (**A-E**) and our designed molecule (**F**).

One of the major goals and aim of the present work was to develop a one-pot and robust methodology for the consturction of fused heterocyclic framework as represented by **F** (Fig. 1).



Scheme 1 Strategy for the synthesis of indazole fused triazolo[5,1-*c*]quinoxalines.

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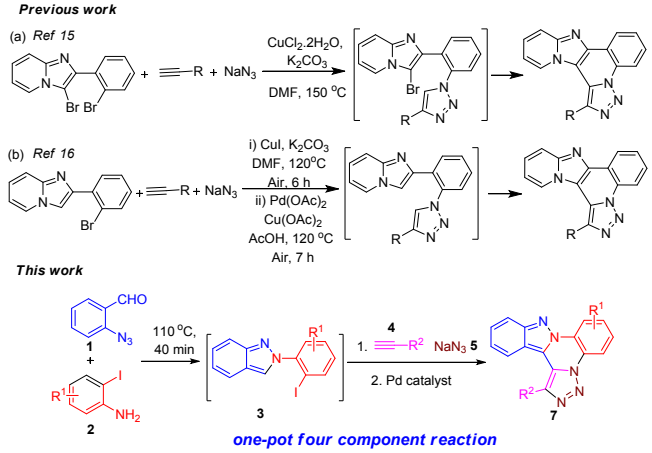
In continuation of our interest in the synthesis of fused heterocyclic compounds,[11] we envisioned that the sequential one-pot cascade synthesis of indazole fused triazolo[5,1-*c*]quinoxaline based on **F** *via* a *o*-azidoaldehyde and iodoaniline is resulting to form 2-(2-iodophenyl)-2*H*-indazole, followed by azide−alkyne cycloaddition would provide the 1,2,3-triazole. Later, C−N coupling between 1,2,3-triazole and aryl iodide, finally intramolecular cross dehydrogenative C−C coupling between 1,2,3-triazole and imidazo[1,2-*a*]pyridine would afford indazole fused with triazolo[5,1-*c*]quinoxaline (Scheme 1). This cascade approach would involve the formation of three new bonds i.e. C−N, N−N and C−C, resulting in the formation of three heterocyclic rings.

Metal-catalyzed reactions play a vital role in the synthesis of polycyclic aromatic and heteroaromatic compounds.[12] Azide−alkyne cycloaddition (CuAAC) followed by intramolecular cyclisation has become the most efficient method to generate the fused triazoles and is used extensively by different groups.[13-17] Kumar *et al*. reported copper-catalysed tandem synthesis of 1,2,3-triazole/quinoline-fused imidazo-[1,2-*a*]pyridines *via* azide-alkyne cycloaddition, Ullmann-type C-N coupling, and intramolecular direct arylation (Scheme 2a).[18] Recently, Fan *at al*. reported the one-pot construction of 1,2,3-triazole/quinoline-fused imidazo[1,2-*a*]pyridines through azide−alkyne cycloaddition followed by C−N coupling between 1,2,3-triazole and aryl bromide, finally, intramolecular cross-dehydrogenative C−C coupling between 1,2,3-triazole and imidazo[1,2-*a*]pyridine (Scheme 2b).[19] While the above methods are effective, but they require synthetically challenging starting meterials. Moreover, this strategy has not been explored for the synthesis of indazole fused triazolo[5,1-*c*]quinoxalines. We, therefore, decided to develop a practical and one-pot method for the synthesis of indazole fused triazolo[5,1-*c*]quinoxaline derivatives starting from commercially available simple materials.

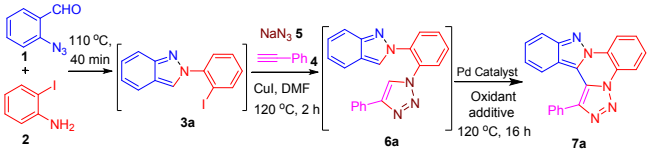


Scheme 2 Synthetic strategies towards the fused heterocycles *via* cascade azide−alkyne cycloaddition, C−N Coupling followed by intramolecular cyclisation.

Initially, we heated the *o*-azido aldehyde (**1a**) at 110 °C with *o*-iodoaniline (**2a**) to provide the intermediate 2*H*-indazole (**3a**) with satisfactory yields.[20] We next screened the synthesis of intermediate 2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-2*H*-indazole (**6**) with respect to catalyst, base, solvents and temperatures. After optimization of the conditions (see the Supporting Information for details), we found that the combination of CuI and K_2CO_3 in DMF at 120 °C under air for 2 h (see Table S1, entry 1, in the Supporting Information) is the the best condition for the synthesis of **6a.**

With these results in hand, we moved forward to study a three step, one-pot synthesis of 1-phenylindazolo[2,3-*a*][1,2,3]triazolo[5,1-*c*]quinoxaline (**7a**). Thus, the mixture of **1a** and *o*-iodoaniline (**2a**) was heated at 110 °C for 40 min. Then, **4a**, **5**, CuI and K_2CO_3 in DMF was added and the mixture was heated at 120 °C under air for 2 h to provide the intermediate 2*H*-indazole (**3a**). To this was added $Pd(OAc)_2$ and $Cu(OAc)_2$ and the resulting mixture was stirred at 120 °C for 16 h, to afford the targeted intramolecular cross dehydrogenative C−C coupling product **7a** in 21% yield. An improvement in the yield of **7a** was observed when AcOH (2 equiv.) was used as an additive (Table 1, entry 2). Interestingly, further increase in the amount of AcOH to 3 equiv. improved the yield of **7a** to 65% (Table 1, entry 3). However, the further increase of the AcOH (4 equiv.), did not improve the yield of **7a** (Table 1, entry 4) further. Increasing the loading of $Cu(OAc)_2$ up to 1.5 equiv provided an increase in the yield of **7a** (Table 1, entry 5) though further increase in $Cu(OAc)_2$ loading did not increase product yield (Table 1, entry 6). When the reaction was performed under O_2 in the presence of 1.5 equiv of $Cu(OAc)_2$, **7a** was obtained in highest yield (71%) (Table 1, entry 7). Notably, ommission of $Cu(OAc)_2$ decreased the yield of **7a** to 10% (Table 1, entry 8) whereas use of other oxidants e.g. $Cu(OTf)_2$, CuO or Ag_2CO_3 was less effective (Table 1, entry 9–11). The use of other additive e.g. Ac_2O, PivOH and PhCOOH (Table 1, entry 12-14) was also examined but found to be less effective. Furthermore, the use of other catalysts, e.g. $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ afforded the product **7a** but in low yield (Table 1, entries 15–16). The use of a lower quantity of Pd-catalyst decreased the product yield (Table 1, entry 17). The lowering or increasing the reaction temperature or time was also found to be less effective (Table 1, entry 18–20).

Table 1 Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant (equiv)	Additive (equiv)	% Yield[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	-	21
2	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	AcOH (2)	48
3	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	AcOH (3)	65
4	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	AcOH (4)	62
5	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5)	AcOH (3)	68
6	$Pd(OAc)_2$	$Cu(OAc)_2$ (2.0)	AcOH (3)	65
7	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	71

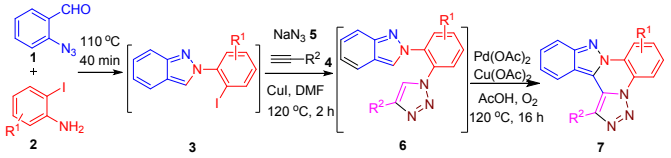
8	$Pd(OAc)_2$	O_2	AcOH (3)	10
9	$Pd(OAc)_2$	$Cu(OTf)_2$ (1.5), O_2	AcOH (3)	56
10	$Pd(OAc)_2$	CuO (1.5), O_2	AcOH (3)	57
11	$Pd(OAc)_2$	Ag_2CO_3 (1.5), O_2	AcOH (3)	55
12	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	Ac_2O (3)	28
13	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	PivOH (3)	55
14	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	PhCOOH (3)	38
15	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	48
16	$Pd_2(dba)_3$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	45
17[c]	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	37
18[d]	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	62
19[e]	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	68
19[f]	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	62
20[g]	$Pd(OAc)_2$	$Cu(OAc)_2$ (1.5), O_2	AcOH (3)	67

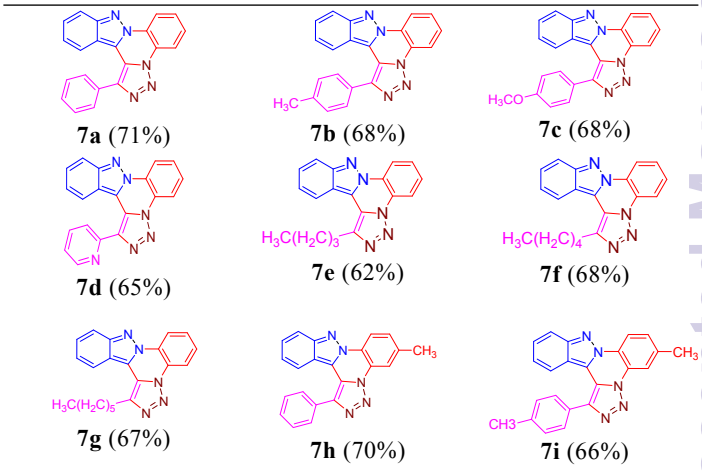
[a]Reaction conditions: **1a** (0.67 mmol) and **2a** (0.67 mmol) was heated at 110 °C, 40 min, and then added **4a** (0.67 mmol), **5** (0.67 mmol), CuI (10 mol%), K_2CO_3 (0.81 mmol), DMF (3 mL) and heated for , air, 2 h under air followed by addition of Pd catalyst (10 mol %), oxidant, additive and heating at 120 °C for 16 h. [b]Isolated yields. [c]5 mol % of $Pd(OAc)_2$ was used. [d]The reaction was carried out at 100 °C. [e]The reaction was carried out at 140 °C. [f]The reaction was stirred for 12 h. [g]The reaction was stirred for 18 h.

The substrate scope and generality of the present three step, one–pot cascade reaction was assessed by synthesizing a large number of indazole fused triazolo[5,1-*c*]quinoxaline derivatives (**7**) (Table 2). Variously substituted terminal acetylenes (**3a–g**) smoothly reacted under the optimized conditions to give desired indazole fused triazolo[5,1-*c*]quinoxalines in good yields. For example, aryl (**4a–c**) and heteroaryl (**4d**) substituents on the triple bond participated well in the reaction. Aliphatic alkynes (**4e–4g**) also efficiently participated in cascade reaction to give the corresponding indazole fused triazolo[5,1-*c*]quinoxalines. Similarly, various substituted iodoanilines (**2b-d**) containing a methyl and fluro on the aryl ring gave the corresponding indazole fused triazolo[5,1-*c*]quinoxalines (**7h–7v**) in good yields. The molecular structures of **7q** was confirmed by the single-crystal X-ray data analysis (Fig. 2).[21]

On the basis of these results and the literature precedents,[19-20] a tentative mechanism is proposed in Scheme 3. First, the *o*-azido aldehyde **1** reacts with amine **2** to give an imine intermediate **A**, followed by a subsequent intramolecular cyclization in the formation of 2*H*-indazole **3**. In the first catalytic cycle, Cu(I) catalyzed azide−alkyne cycloaddition between the azide **5** and terminal alkyne **4** afforded intermediate **C** *via* **B**. Followed by C−N coupling between the triazole (**C**) and 2*H*-

Table 2 One-pot synthesis of indazole fused triazolo[5,1-*c*]quinoxalines (**7**) *via* sequential cascade reactions





[a]Reaction conditions: **1a** (0.67 mmol) and **2a** (0.67 mmol) was heated at 110 °C, 40 min, and then added **4a** (0.67 mmol), **5** (0.67 mmol), CuI (10 mol%), K_2CO_3 (0.81 mmol), DMF (3 mL) and heated for 2 h under air followed by addition of Pd catalyst (10 mol %), $Cu(OAc)_2$ (1.01 mmol), AcOH (2.03 mmol) and heated at 120 °C for 16 hunder O_2. [b]Isolated yields.

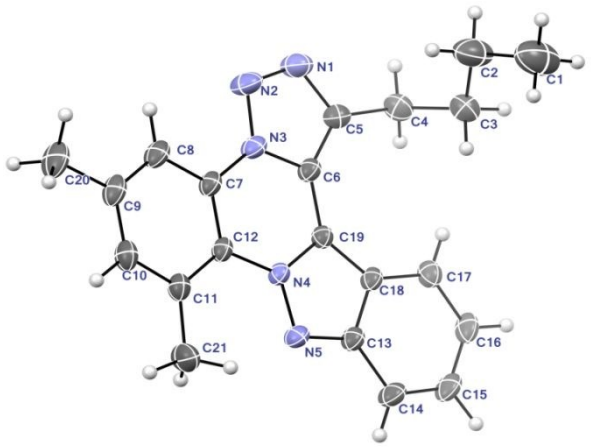
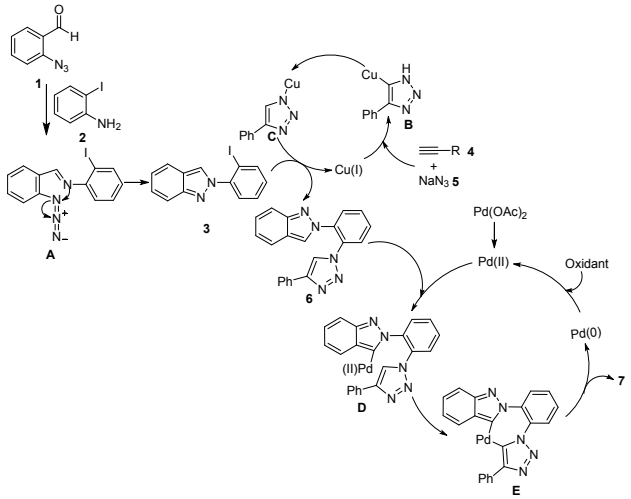


Fig. 2 X-ray crystal structure of **7q** (ORTEP diagram). Thermal ellipsoids are drawn at the 50% probability level.

Indazole **3** results in the formation of the key intermediate triazol-1-yl)phenyl)-2*H*-indazole (**6**)**.** In the second catalytic cycle, electrophilic palladiation occurs at C3-position of indazole that results in the formation of intermediate **D.** Further electrophilic palladation of trizole occurs to form seven-membered palladacycle intermediate **E**, which on reductive elimination generates the indazole fused triazolo[5,1-*c*]quinoxalines (**7**) together with Pd(0). Finally, palladium acetate was regenerated from Pd(0) under oxidant to complete the catalytic cycle.



Scheme 3 Plausible mechanism.

In conclusion, we have demonstrated a facile and efficient route for the synthesis of diverse indazole fused triazolo[5,1-*c*]quinoxalines through one-pot sequential cascade reaction of *o*-azido aldehyde, *o*-iodoaniline, phenylacetylene and sodium azide. The reaction proceeds *via* 2*H*-indazole formation, azide–alkyne cycloaddition followed by C−N coupling and intramolecular cross dehydrogenative C−C coupling. Overall, we have reported synthesis of privileged fused heterocyclic compounds from simple starting meterials.

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Conflicts of interest

The authors confirm that this article content has no conflict of interest.

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21. Crystal data of (**7q**): CCDC 1863988, Single crystals suitable for X-ray diffraction of **7q** DCM: EtOAc (1:1). Molecular formula = $C_{21}H_{21}N_5$, Formula weight = 343.43, Crystal system = Monoclinic, space group = 2/c, a = 12.2671(5)Å, b = 18.1570(8)Å, c = 15.9123(7)Å, V = 3523.8(3)Å3, T = 100(2) K, Z = 8, Dc = 1.295 Mg/m3, 54074 Reflections collected, 4570 unique reflections (R(int) = 0.0669).

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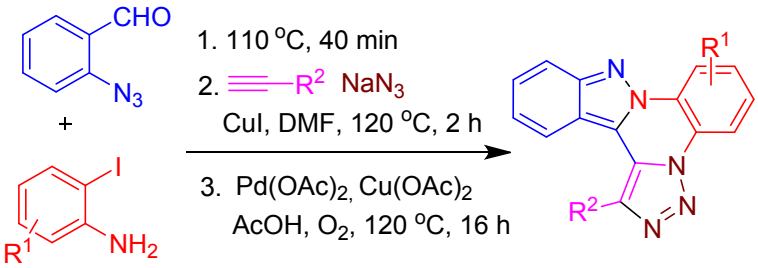
GRAPHICAL ABSTRACT

An efficient four component, three-step cascade synthesis of indazole fused triazolo[5,1-*c*]quinoxalines has been described. Notable features of this protocol include simple starting materials, reduced synthetic steps and good yields.



one-pot four component reaction