A ligand-free copper (1) catalysed intramolecular N-arylation of diazoaminobenzenes in PEG-water: an expeditious protocol towards regiospecific 1-aryl benzotriazoles†

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An efficient and highly versatile method for the synthesis of diverse regiospecific 1-arylbenzotriazoles being important medicinal scaffolds, by the copper (1) catalysed intramolecular N-arylation of diazoaminobenzenes of 2-haloaryldiazonium salts in PEG-water has been developed. A very simple reaction protocol, large number of substrate affordability and excellent yields are the main features of this methodology.

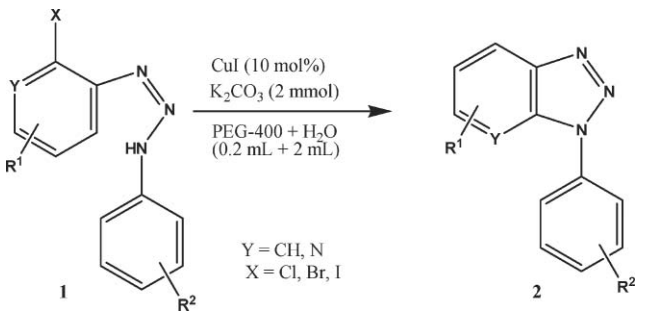
Introduction

Substituted benzotriazoles, one of the most privileged heterocyclic subunit display many interesting properties including anticancer, antifungal, anti-inflammatory, anti-depressant activities[1] and exhibit utility as synthetic auxiliaries.[2] Many methods have been developed to synthesize 1,2,3-benzotriazoles till date.[3] Traditionally, 1,3-dipolar cycloaddition of organic azides with terminal alkynes commonly known as click chemistry[4] proved to be a very useful and extremely applicable method.[5] However, the synthetic efficiency of this methodology is largely dependant on the steric and electronic properties of the alkynes and the regioselectivities of these reactions are normally low using unsymmetrical alkynes leading to the regioisomeric mixture of triazoles.[6] Again, the preparations of arynes as well as handling of low molecular weight azides are hazardous.[7] Therefore, it is extremely desirable to develop more efficient, eco-friendly methodologies for synthesizing this important heterocyclic nucleus particularly, the 1-aryl substituted ones by one-step procedure.

Although synthesis of various heterocycles from aryl halides with copper catalysts[8–20] has become one of the most popular synthetic methodologies in the last few decades, yet there is no report for the synthesis of 1-aryl benzotriazoles using this strategy. Moreover, all previous syntheses of 1-aryl benzotriazoles generally proceed by N-arylation of the simple benzotriazole.[3a,b] Recently, the synthesis of diverse organic compounds maintaining an environmentally benign pathway has emerged as a powerful alternative to the use of volatile, toxic and hazardous organic solvents.[21] PEG, a biologically acceptable polymer has been used as an inexpensive, thermally stable, recoverable and non-toxic reaction medium[22] as well as a solid-liquid phase transfer catalyst (PTC) with Cs_2CO_3 or K_2CO_3 as a base.[23] In addition, a probable complexation of PEG with copper(I) might result in the prevention of the hydrolysis of copper species.

Results and Discussion

In continuation of our search for the synthesis of biologically important heterocycles,[24] we, here for the first time, describe the synthesis of 1-aryl benzotriazoles by copper(I)iodide catalysed intramolecular N-arylation of diazoaminobenzenes of 2-haloaryldiazonium chlorides in PEG-water at moderate temperature in excellent yields (Scheme 1).



Scheme 1 Synthesis of 1-aryl benzo and pyridotriazoles.

Initially, the diazoaminobenzene (**1a**) (formed by the reaction of 2-iodobenzene diazonium chloride and aniline) was chosen as the model substrate (Scheme 1, X═I, Y═CH, R^1═R^2═H) in order to optimize the reaction conditions like the amount of bases, solvents, copper catalysts, reaction temperature *etc.* It was observed that in the absence of either the base or the copper source, the reaction failed completely (Table 1, entries 1–3). Bases such as K_2CO_3, Cs_2CO_3, K_3PO_4 were activated this reaction and K_2CO_3 (2 equivalents) proved to be the best (Table 1, entry 4) among them. Solvents such as DMF, DMSO, ACN, 1,4-dioxane, MeOH were investigated and it was found that the best results were obtained both in cases of DMF and DMSO (Table 1, entries 4, 5). Readily available copper salts such as CuI, CuCl, CuBr, $CuSO_4$, $Cu(OAc)_2$ were surveyed and CuI proved to be the best choice without any ligand (Table 1, entries 3–12). Next, we thought it worthwhile to see if the same reaction can be performed in water keeping in mind its green impact. We were rather disappointed to find that the reaction proceeded very poorly in water (Table 1, entry 11) which may be due to the poor solubility of the diazoaminobenzenes in aqueous

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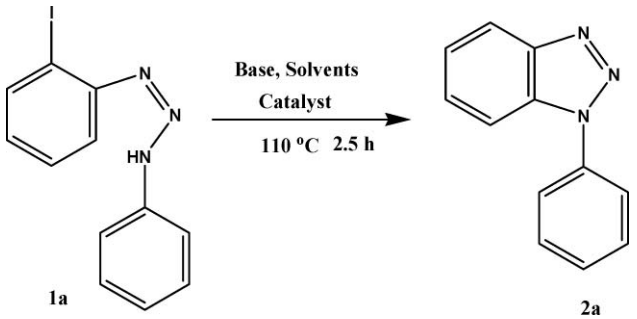
† Electronic supplementary information (ESI) available: Materials and methods, synthesis of diazoaminobenzenes, analytical data of compounds, NMR of compounds. CCDC reference numbers 773428–773429. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00177e

Table 1 Optimization of reaction condition for copper (1) catalyzed ligand-free intramolecular N-arylation of diazoaminobenzenes[a]



1a 2a

Entry	Base	Solvent	Catalyst (10 mol%)	Conversion (%)
1	none	DMF	none	nil
2	K_2CO_3	DMF	none	nil
3	none	DMF	CuI	nil
4	K_2CO_3	DMF	CuI	100
5	K_2CO_3	DMSO	CuI	100
6	Cs_2CO_3	DMSO	CuI	95
7	K_3PO_4	DMSO	CuI	85
8	K_2CO_3	1,4 – dioxane	CuI	70
9	K_2CO_3	ACN	CuI	60
10	K_2CO_3	MeOH	CuI	20
11	K_2CO_3	H_2O	CuI	05
12	K_2CO_3	H_2O - PEG – 400	CuI	100
13	K_2CO_3	H_2O - PEG – 400	CuCl	45
14	K_2CO_3	H_2O - PEG – 400	CuBr	75
15	K_2CO_3	H_2O - PEG – 400	$CuSO_4$	50
16	K_2CO_3	H_2O - PEG – 400	$Cu(OAc)_2$	60

[a] Reaction conditions: diazoaminobenzene 1a (1 mmol), CuI (0.1 mmol), base (2 mmol) in H_2O+PEG-400 (2 mL+0.2 mL) at 110 °C for 2.5 h.

medium. Therefore, we used a phase transfer catalyst (PTC) in water in order to enhance the solubility of diazoaminobenzenes in this solvent. Moreover, we tried several well known PTCs such as CTAB, TBAB, 18-Crown-6 and PEG-400. Among them, PEG-400 turned out to be the best. Using PEG-400 (0.2 mL) in water (2 mL), the desired product was obtained in excellent yield after 2.5 h (Table 1, entry 12) which was even better than in DMF or in DMSO. The great enhancement in yield using PEG compared to water must be surely due to the phase transfer catalytic properties of PEG.[23]

With the above optimizations in hand, the scope of this methodology was explored using different diazoaminobenzenes of 2-haloaryldiazonium chlorides and substituted anilines (Table 2). The results show that almost all the tested diazoaminobenzenes successfully produced the desired benzotriazoles in excellent yields. The reaction was also well tolerated using varieties of diazoaminobenzenes of quinoline amines. It was noteworthy that diazoaminobenzenes of less reactive 2-bromoanilines could successfully react under the present reaction condition to produce the desired benzotriazoles but in the case of diazoaminobenzenes of 2-chloroanilines which is obviously much less reactive, the temperature had to be elevated to 130 °C for 6–8 h (Table 2, entries 9–12, 15, 18–22) to obtain the best yields. In addition, the same protocol worked well for the diazoaminobenzenes from 3-amino-2-chloropyridine to produce the pyridotriazoles (Table 2, entries 18–22).

The final structure for **2e** has been confirmed by an X-ray crystallography of its single crystal and is shown below in Fig. 1.

Interestingly, in case of diazoaminobenzenes of anilines both possessing halogen atom (I, Br, Cl) at 2-position of the amines, we obtained the single product indicating the absence of tautomerism in diazoaminobenzenes under the present reaction conditions (Table 3).

The final structure for **2d** has been confirmed by an X-ray crystallography of its single crystal and is shown below in Fig. 2.

Conclusion

In summary, a simple, efficient and expeditious synthetic protocol, for the synthesis of benzotriazoles and pyridotriazoles through ligand-free copper(I) iodide catalyzed intramolecular N-arylation of diazoaminobenzenes of 2-halo anilines or 2-halo pyridoamines

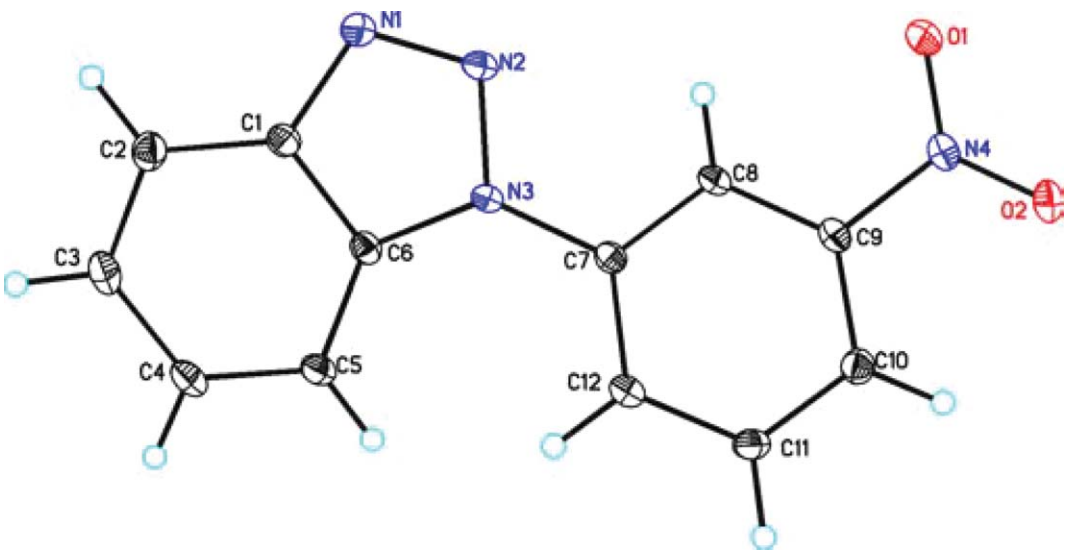
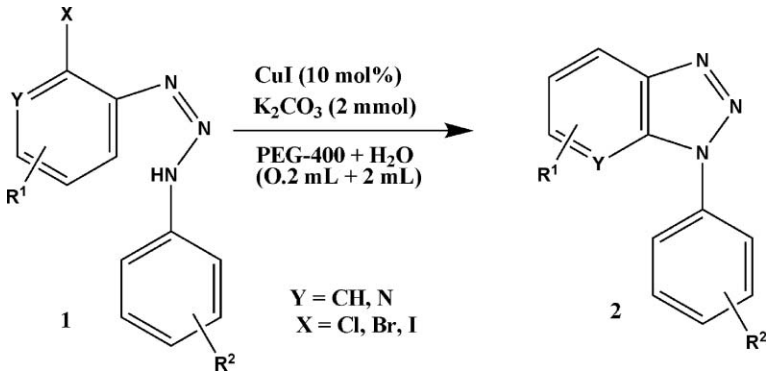


Fig. 1 Ortep plot of **2e** showing the crystallographic numbering (CCDC 773428).

Table 2 Investigation on the scope of diazoaminobenzenes of 2-haloanilines for the formation of benzotriazoles and pyridotriazoles



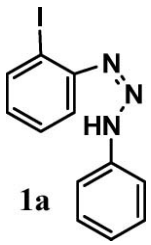
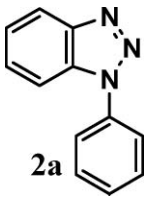
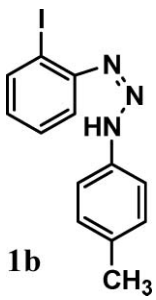
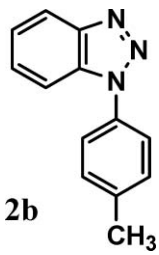
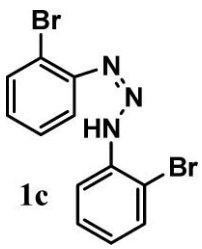
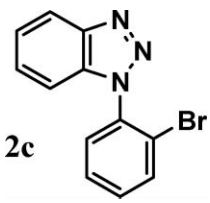
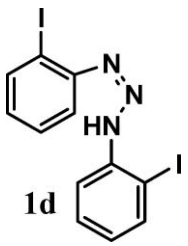
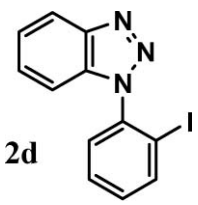
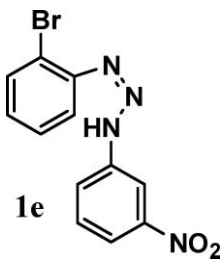
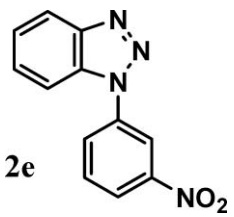
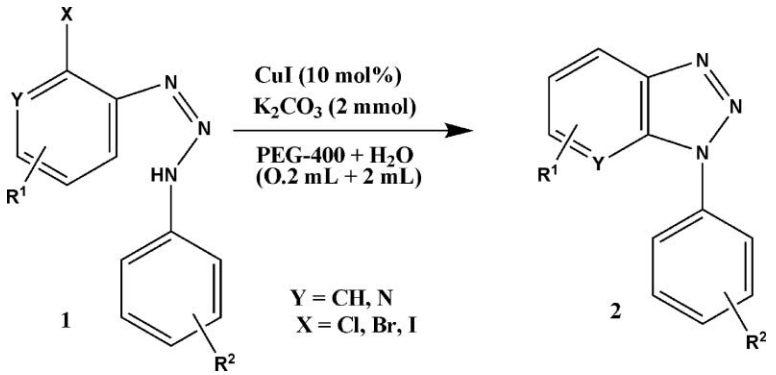
Entry	Diazoaminobenzene	Product	Time/h	Yields (%) (isolated)	Reference
1			2.5	92	3(c)
2			2.5	92	3(c)
3			3.0	90	3(c)
4			2.5	92	—
5			3	89	—

Table 2 *(Contd.)*



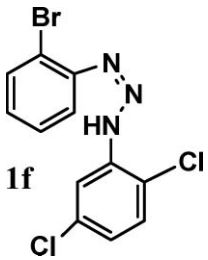
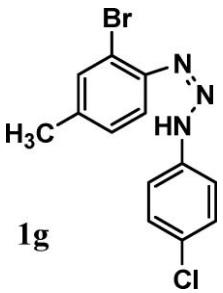
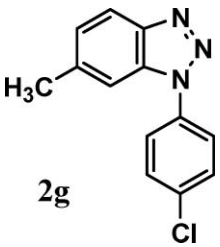
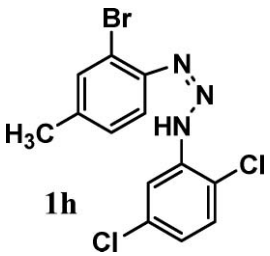
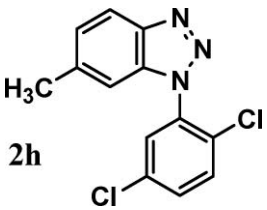
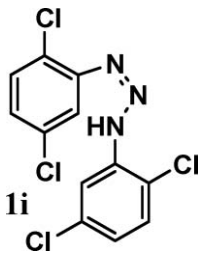
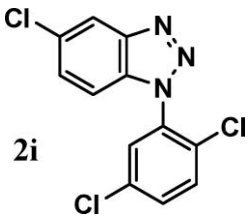
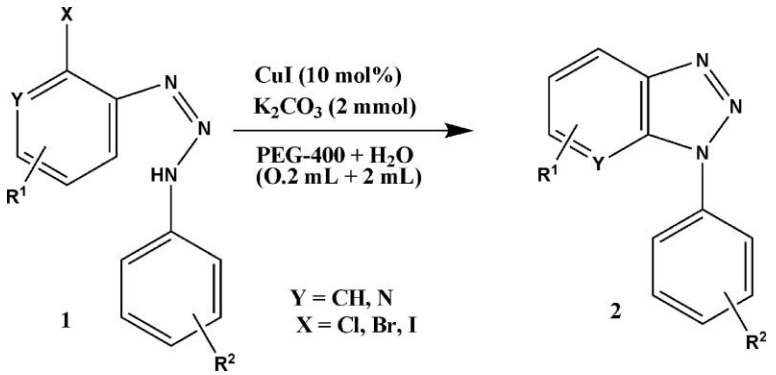
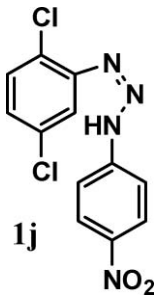
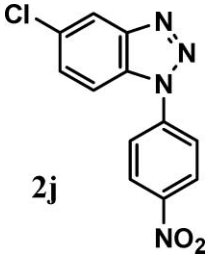
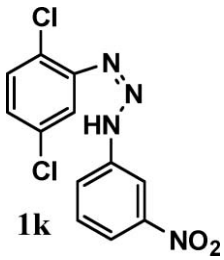
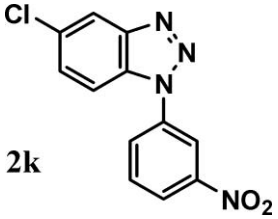
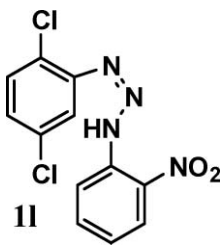
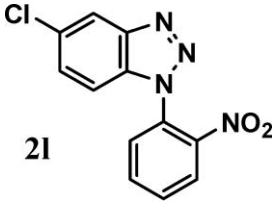
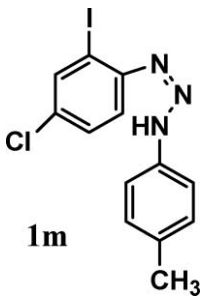
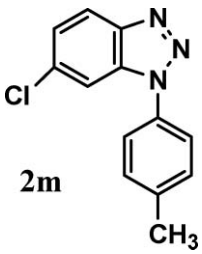
Entry	Diazoaminobenzene	Product	Time/h	Yields (%) (isolated)	Reference
6			3	90	—
7			2.5	92	—
8			3	91	—
9			6.0	91	—

Table 2 *(Contd.)*



Entry	Diazoaminobenzene	Product	Time/h	Yields (%) (isolated)	Reference
10			6.5	84	—
11			6.0	84	—
12			6.0	82	—
13			2.5	92	25

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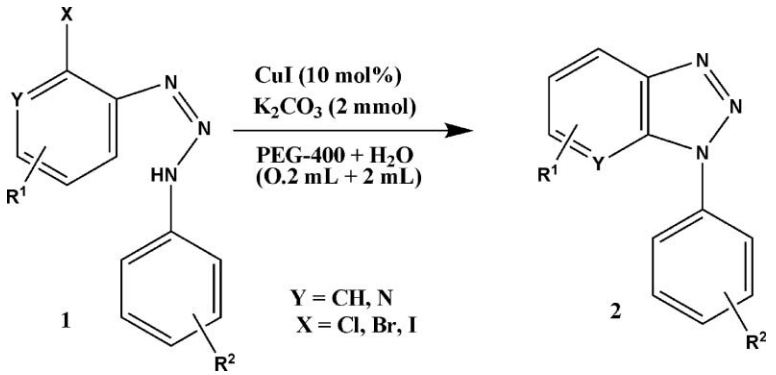
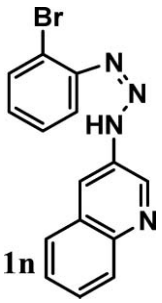
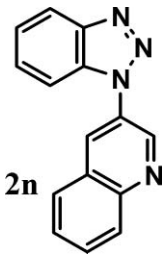
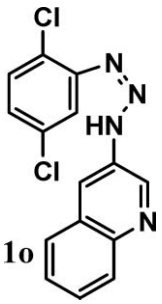
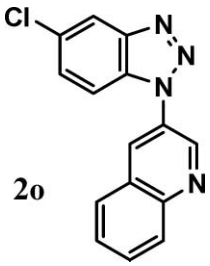
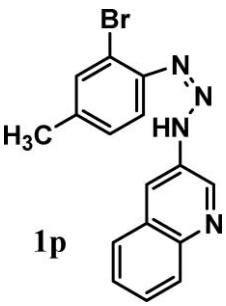
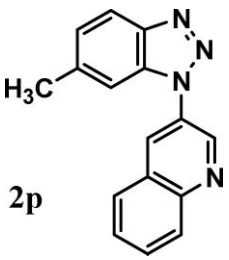
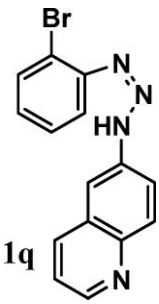
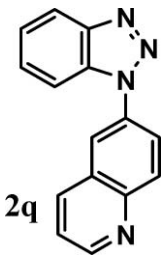


Entry	Diazoaminobenzene	Product	Time/h	Yields (%) (isolated)	Reference
14			3.0	82	26
15			6.5	88	—
16			3.0	90	—
17			3.0	75	—

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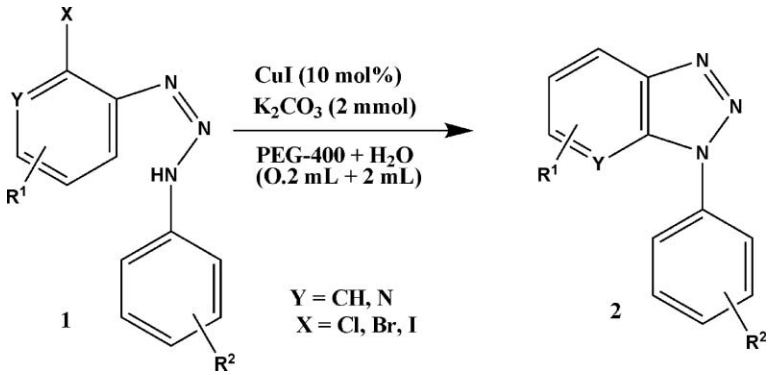


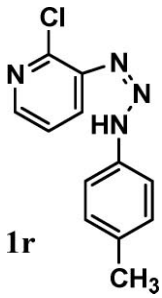
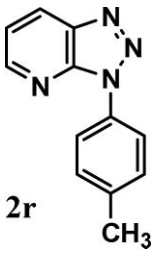
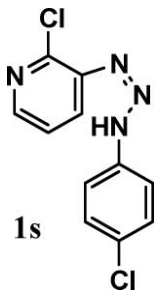
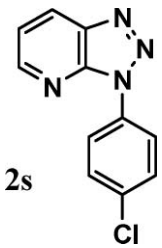
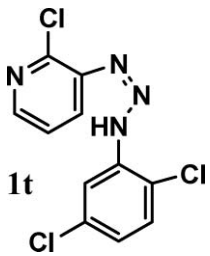
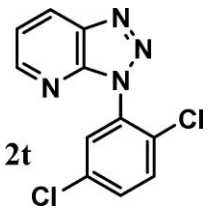
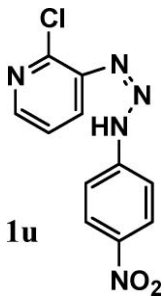
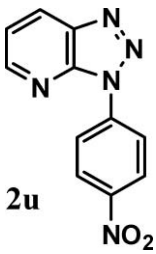
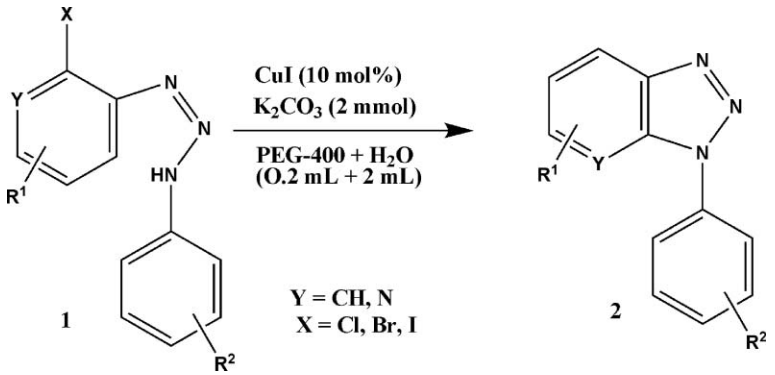
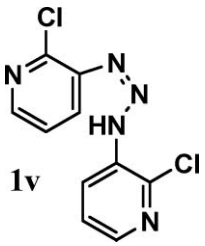
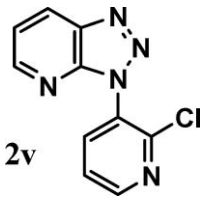
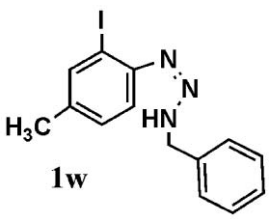
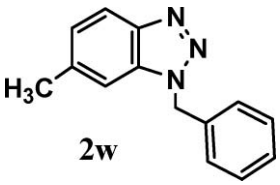
Entry	Diazoaminobenzene	Product	Time/h	Yields (%) (isolated)	Reference
18			6.0	86	27
19			6.0	88	27
20			6.0	88	—
21			6.5	75	—

Table 2 *(Contd.)*



Entry	Diazoaminobenzene	Product	Time/h	Yields (%) (isolated)	Reference
22			6.5	84	—
23			3.0	85	—

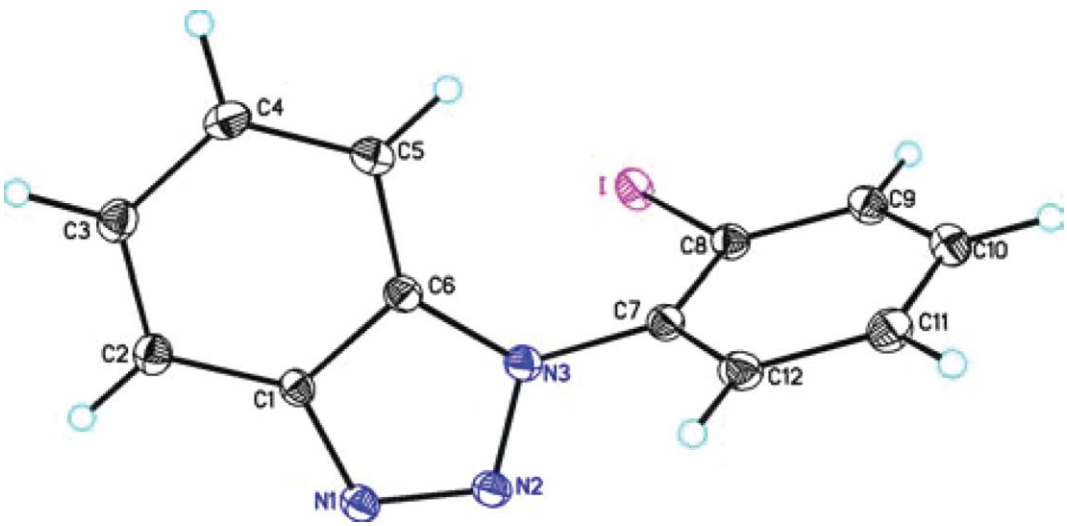
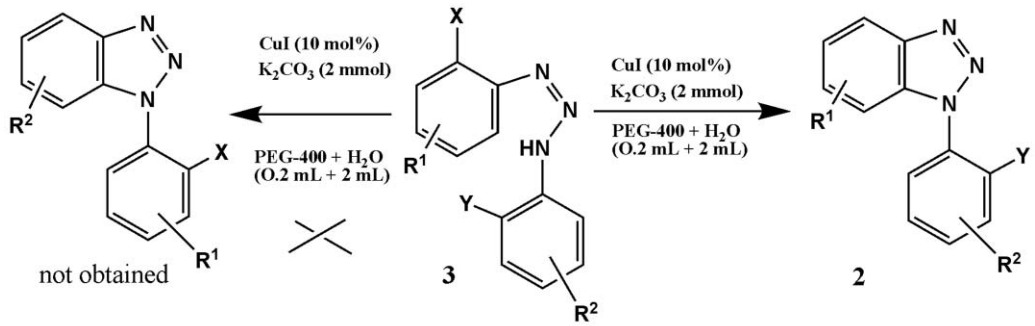
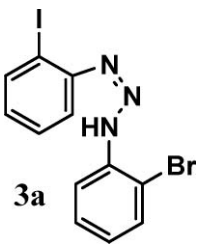
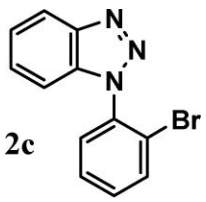
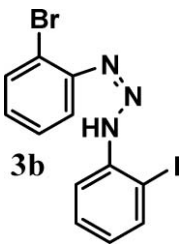
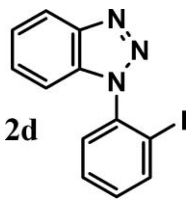
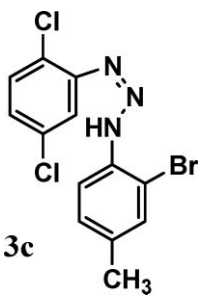
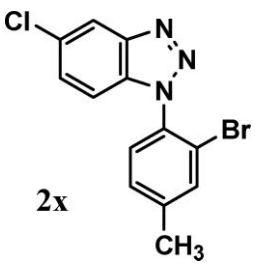
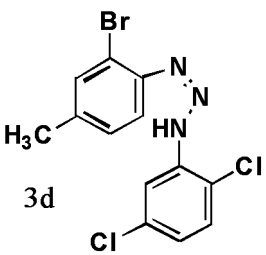
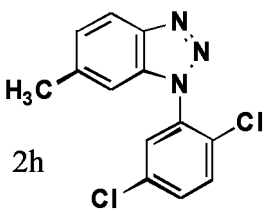


Fig. 2 Ortep plot of **2d** showing the crystallographic numbering (CCDC 773429).

in PEG-H_2O medium are described. The methodology worked well for all the diazoaminobenzenes of 2-iodo, 2-bromo, 2-chloro anilines. This synthetic strategy allows the construction of a wide range of different benzo and pyrido-triazoles both being important medicinal scaffolds in excellent yields maintaining a green protocol. We sincerely hope that this methodology should find great applications in the near future both in academia and in industry.

Table 3 Selective formation of 1-aryl benzotriazoles with the CuI catalyzed intramolecular N-arylation of diazoaminobenzenes of 2-halo anilines



Diazoaminobenzene	Product	References
 3a	 2c	3(c)
 3b	 2d	—
 3c	 2x	—
 3d	 2h	—

Experimental section

General procedure for the synthesis of 1-aryl benzotriazoles. Diazoaminobenzene (1 mmol), CuI (0.1 mmol), K_2CO_3 (2 mmol), PEG-400 (0.2 mL), H_2O (2 mL) were taken in an Erlenmayer flask and the resulting mixture was heated at 110 °C (130 °C for diazoaminobenzenes of 2-chloroanilines) until the disappearance of reacting materials (monitored by TLC). The reaction mixture was then cooled and poured into a beaker containing crushed ice. After stirring the mixture for 10 min with a glass-rod, it was

filtered and extracted through celite by EtOAc. The solvent was evaporated under reduced pressure and was further purified by column chromatography using silica gel (60–120 mesh) to obtain the pure products which were fully characterized by spectral and analytical data. The data for compounds **2d** and **2u** are given below while the data for all other compounds are given in the ESI.†

Compound 2d. White crystalline solid; mp: 148–150 °C; IR (KBr, cm^{-1}): 754, 1066, 1190, 1269, 1436, 1481, 1605, 1936, 2372, 3059 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.29 (2H, m), 7.64–7.40 (4H, m), 8.09 (1H, dd, J = 8.1 and 1.2 Hz), 8.17 (1H, td, J = 8.4 and 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.6, 110.5, 120.2, 124.2, 128.1, 128.9, 129.4, 131.7, 133.5, 139.2, 140.5, 145.7. EI-MS (*m*/*z*): 321 (M^+), 281, 207, 166, 140. Elemental analysis calculated for $C_{12}H_8N_3I$: C 44.88, H 2.51, N 13.09; Found: C 44.88, H 2.49, N 13.11%.

Compound 2u. White crystalline solid; mp: 146–148 °C; IR (KBr, cm^{-1}): ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.39 (1H, m), 7.51–7.47 (1H, m), 7.61–7.55 (2H, m), 8.46 (1H, d, J = 8.4 Hz), 8.70 (1H, d, J = 4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.3, 129.1, 129.2, 130.0, 131.4, 131.6, 133.3, 133.5, 136.5, 146.2, 151.2. EI-MS (*m*/*z*): 264 (M^+), 238, 236, 201, 174, 166. Elemental analysis calculated for $C_{11}H_6N_4Cl_2$: C 49.84, H 2.28, N 21.13; Found: C 49.80, H 2.30, N 21.15%.

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