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Graphical Abstract

One-pot ‘click’ reaction from *spiro*-epoxides catalyzed by Cu(I)-pyrrolidinyl-oxazole-carboxamide

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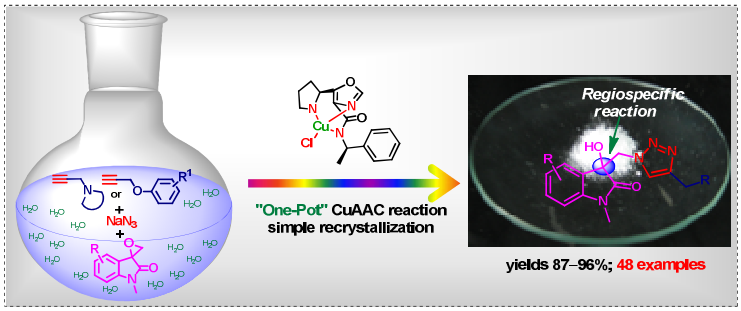
A sustainable green methodology for the ‘one-pot’ syntheses of 1,2,3-triazolo 3-hydroxy-2-oxindoles from isatin-epoxides has been employed *via* CuAAC reaction.



Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

One-pot 'click' reaction from *spiro*-epoxides catalyzed by Cu(I)-pyrrolidinyl-oxazole-carboxamide

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An efficient Cu(I)-pyrrolidinyl-oxazolo-carboxamide catalyst has been employed for the 'one-pot' synthesis of novel 3-substituted-1,2,3-triazolo-3-hydroxy-indolin-2-ones. This reaction involves an *in situ* azide generation from *spiro*-epoxide with concomitant 'click' reaction in aqueous media. This protocol has the advantage of avoiding the interim purification of toxic organic azide intermediates resulting in significant enhancement of overall yield with reduced reaction time. The regiospecificity of epoxide ring-opening has been unequivocally established on the basis of single X-ray crystallographic analysis and quantum chemical calculations. Moreover, this approach offers a broad scope to access diversely substituted indolino-*O/N*-linked 1,2,3-triazoles as novel privileged scaffolds.

Introduction

The nucleus 3-substituted-3-hydroxy-indolin-2-one is frequently found in natural products and continues to attract the interest of synthetic chemists as well as biologists.[1,2] A number of bioactive natural products and their derivatives have been constructed around this nucleus such as arundaphine,[3] maremycin B,[4] donaxaridine,[1a] 3-hydroxy-*N*-methyl welwitindolinone C,[1b] paratunamide D,[1e] and anisyl (*S*)-57[5] (Figure 1), having various biological profiles. Moreover, the synthetic derivatives *viz.* NSC635473 and YK-4-279[6] which blocks oncogenic protein EWS-FLI1 interaction with RNA helicase A, thereby inhibiting the growth of Ewing's sarcoma. Therefore, there is a strong impetus for the syntheses of this class of novel privileged scaffolds. The various drug discovery programs have now started to recognize their pharmacological importance such as anti-oxidant,[7] anti-cancer,[1a,4] anti-HIV,[8] neuroprotective,[9,10] and other related biological properties.[11] In this scenario, the development of highly efficient and regio- or stereoselective reactions under mild/greener conditions is an everlasting and tricky task for synthetic organic chemists.

In the new millennium, most of the pharmaceutical industries are now widely focusing on the concept of 'green chemistry' to protect the environment and human health.[12] Therefore, there has been increasing demand in exploiting eco-friendly, cost-effective, and high atom-economy protocols in both academia as well as industry.[13] As a result, the scientific communities are focusing their efforts to minimize the use of organic solvents or to develop new protocols using water as a reaction media or to develop more environmentally friendly alternatives.[14] However, recent reports indicates that the use of water as a solvent for the epoxide ring-opening provides a much cleaner reaction.[15] In addition, water has a remarkable accelerating effect on various organic reactions due to inherent property of the water–hydrophobic substance.[16]

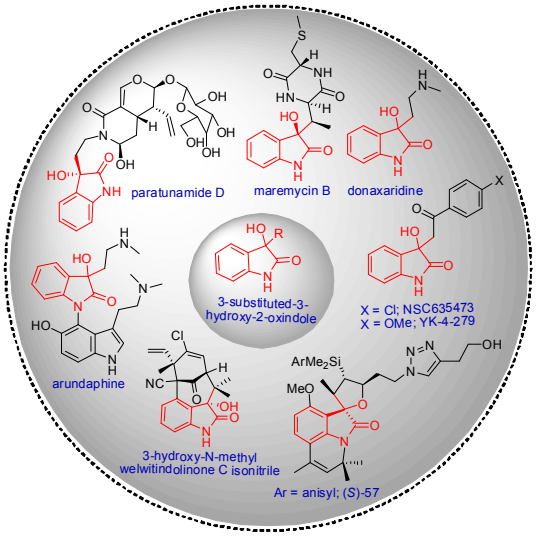


Fig. 1 Bioactive natural and synthetic products built around a 3-substituted-3-hydroxy-2-oxindole motif.

The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is a 'gold standard' reaction for the construction of 1,2,3-triazole (1,4-regioselectivity) motif, called as 'click' reaction, and the term was coined by Barry Sharpless in 2001.[17] The salient features of this reaction are high selectivity, yields and exceptional tolerance towards a wide range of functional groups which attracted tremendous attention throughout the chemical community.[18] A number of multi-component 'click' approaches were reported using the epoxides, but most of them were not regioselective upon ring-opening with NaN_3.[19] Moreover, the regiochemistry reported is not satisfactory as desired that usually leads to the formation of mixture of *β*-hydroxy azides followed by 1,2,3-triazole formation. In general, (*a*) monoalkyl-substituted

epoxides majorly give secondary *β*-hydroxy 1,2,3-triazoles by nucleophilic (azide ion) attack from less hindered side, and (*b*) monoaryl-substituted epoxides leads to primary *β*-hydroxy 1,2,3-triazoles, where the electronic factors predominates over the steric factors with exclusive attack of nucleophile from the more stable benzylic position.[20] Therefore, there is a need of particular attention towards disubstituted *spiro*-epoxide ring-opening reactions, which were not properly addressed hitherto and that may result in an incorrect assignment of the reaction products. In addition, a plethora of methods have been successfully developed around this reaction. However, many of these methods suffer from one or more reaction constraints such as the indispensability of additives *viz.* reducing/stabilizing agents, the difficulty in catalyst/product(s) separation, reuse of catalysts, etc. Moreover, the handling of organic azides is not safe because of their hazardous nature and explosive property. Keeping in view of these limitations, we have developed a safe, mild, eco-friendly, and step-economic protocol. To the best of our knowledge, the H_2O-mediated "one-pot" *in-situ* azide generated "CuAAC" reaction from *spiro*-epoxide with Cu(I) catalyst has never been acomplished.

Results and discussion

One-pot synthesis of 1,2,3-triazoles from *spiro*-epoxides

In continuation of our earlier efforts devoted towards the synthesis of biologically interesting pharmacophoric scaffolds connected with 1,2,3-triazoles,[21] we have herein explored the possibility of *in-situ* generation of organic azides from suitable *spiro*-epoxides followed by "click" reaction to yield the corresponding novel privileged compounds **3a**–**z**, **3aa**, **3ab**, and **4a**–**t**.

In CuAAC reactions, a mixture of $CuSO_4.5H_2O$ and sodium ascorbate has been traditionally used as a catalytic system which generates the required active Cu(I) species in the reaction media.[22] Later, it has been discovered that *N*-containing polydentate ligands not only stabilize Cu(I) center but also dramatically accelerate the global catalytic process and this allowed the direct use of Cu(I) salts as catalysts.[23] Furthermore, a variety of homogeneous and heterogeneous catalysts have been reported to be active for the 1,3-dipolar cycloaddition.[24] It is important to note that in all examples the active species were generated *in situ* upon mixing of a copper source and the *N*-based ligand and that, to the best of our knowledge, no well-defined copper system with these ligands has been applied to catalysis to date.

The search of well-defined catalysts for CuAAC reactions, prompted us to explore the various *N*-containing organocatalysts as ligands for this transformation. Interestingly, the 'pyrrolidinyl-oxazole-carboxamide' (**9**) organocatalyst[25] worked out to be a highly efficient ligand for this process. To our delight, significant increase in the rate of reaction was observed when 5 mol% of free ligand **9** was added to the reaction mixture containing 5 mol% of CuCl (81%, entry 6, Table 1). These findings inspired us to overcome the existing shortcomings by synthesizing metal–organic frameworks. We envisioned that, the Cu(I)-pyrrolidinyl-oxazole-carboxamide derivative could be a highly stable catalyst for CuAAC reaction. Thus, the catalyst **10** was synthesized from pyrrolidinyl-oxazole-carboxamide and screened for *spiro*-epoxide ring-opening tandem CuAAC strategy in order to develop a facile protocol. Gratifyingly, this new catalyst turned out to be air and moisture stable, which allows the reactions to be performed in air and aqueous media, precludes either oxidation or disproportionation, which are generally associated with Cu(I) catalysts. The use of pre-formed Cu(I) complex avoids the need of any reducing agent. Furthermore, facile use of the catalyst in this transformation accelerated *spiro*-epoxide ring-opening by azide nucleophile allowing the mild reaction conditions. Practically, this "one-pot" method avoids any interim purifications of potentially unstable organic azide intermediates.[26] In addition, these *spiro*-epoxides are very active intermediates and versatile starting materials due to their highly strained structure (ring) as well as excellent electrophilic nature. Moreover, epoxides are playing the role of synthetic equivalents of hazardous organic azides. The initial screening of the reaction was carried out not only on the basis of high yield, but also by considering the green reaction conditions.

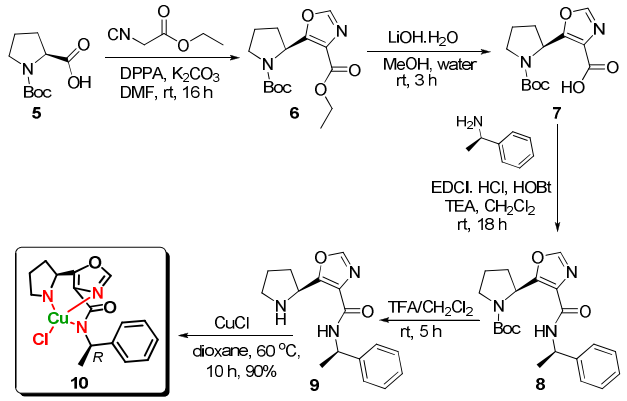
At first, 1-methyl*spiro*[indoline-3,2'-oxiran]-2-one (**1a**) was chosen as the model substrate to test our hypothesis. The **1a** was reacted with NaN_3 followed by 1,2,3-trimethoxy-5-(prop-2-ynyloxy)benzene *via* 1,3-dipolar cycloaddition under different reaction conditions. A series of experiments varying the mol% of catalyst, time, temperature and solvents for the representative reaction were carried out. The results are summarized in Table 1. Since it is the three component one-pot reaction, the reaction sequence would be first epoxide opening with azide nucleophile followed by triazole ring formation. The isatin epoxide derivatives were prepared by *in-situ* generated sulfoxonium ylide reagent,[27] and these substituted isatin building blocks were directly synthesized from commercially available anilines employing Sandmeyer procedure.[28] All alkyne building blocks were prepared from the corresponding phenols as well as amines by reaction with propargyl bromide.

Preparation of catalyst 10

The 'catalyst' **10** was prepared by the reaction of pyrrolidinyl-oxazole-carboxamide derivative **9** with CuCl as shown in Scheme 1.[29] The pyrrolidinyl-oxazole-carboxamide derivatives were synthesized from the commercially available *N*-Boc-$_L$-proline. The reaction of **9** with CuCl afforded the Cu(I) complex with the Cu/L ratio of 1:1. A FT–IR spectrum of catalyst **10** shows the adsorption band of the Cu–N bonds $\nu_{Cu\text{-}N}$ at 446, 407 cm^{-1} (see ESI†). The weight percentage of copper was estimated by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis. In fact, theoretical calculations were also performed for Cu(I) complex **10** by using 'B3LYP/LANL2DZ'. The optimized distances of Cu–N bonds have values of $Cu\text{-}N_{(py)}$ 2.041 Å, $Cu\text{-}N_{(ox)}$ 2.023 Å, $Cu\text{-}N_{(am)}$ 1.941 Å, and Cu–Cl optimized distance is 2.276 Å (Figure 2).

Optimization study

To demonstrate the generality of this method, initially we have investigated this 'one-pot' protocol using different solvents such as H_2O, H_2O:*t*-BuOH, EtOH, MeOH, DMF, CH_3CN, and THF with the aim to increase the yields, selectivity, shorten the reaction time, and to obtain clean products. To our delight, **10**



Scheme 1 Synthesis of Cu(I)-pyrrolidinyl-oxazole-carboxamide catalyst.

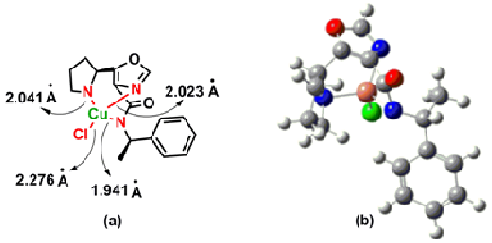
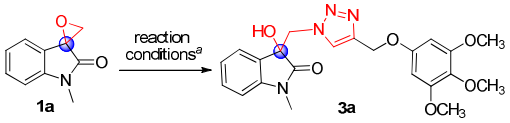


Fig. 2 (a) Schematic representation of Cu(I)-pyrrolidinyl-oxazole-carboxamide complex **10** (b) DFT (B3LYP/LANL2DZ)-optimized geometries of the **10**.

Table 1 Investigation of various solvents effect on the "one-pot" reaction



Entry	Solvent	Catalyst**10** (mol%)	Conversion (%)[c]	Time (h)	Yield (%)[d]
1	CH_3CN	2	30	12	28
2	MeOH	2	42	12	37
3	EtOH	2	20	10	15
4	DMF	2	0	10	0
5	THF	2	0	10	0
6	H_2O	5[b]	85	5	81
7	**H_2O**	**2**	**100**	**4**	**96**
8	H_2O	1	>95	8	93
9	H_2O	0.5	>90	24	89
10	H_2O:*t*-BuOH (4:1)[b]	2	70	8	67

[a] The reaction was performed with epoxide (**1a**, 0.2 mmol), sodium azide (0.2 mmol), alkyne (1,2,3-trimethoxy-5-(prop-2-ynyloxy)benzene, 0.2 mmol), in the presence of catalyst **10** *via* a three-component 'one-pot' protocol. [b] 5 mol% of ligand 'pyrrolidinyl-oxazole-carboxamide (**9**) was used in combination with 5 mol% of CuCl in H_2O at room temperature. [c] Reaction progress and regioselectivity of the reaction was monitered by GC analysis. [d] Isolated yields.

exhibited significant catalytic activity, particularly when water was used as a reaction media. Due to the hydrogen-bond donor and acceptor properties, H_2O enhance the electrophilicity of the epoxide ring through hydrogen-bonding. In addition, the hydrogen bond driven electrophilic-nucleophilic dual activation[30] by water might also assist the epoxide ring-opening by azide nucleophile as well as 1,3-dipolar cycloaddition reaction. However, the coordination of the oxygen of epoxide ring with metal center in this catalytic transformation could not be excluded, since it may also play an important role in the ring-opening process.[31]

Notably, using H_2O as solvent in the presence of 2 mol% of catalyst **10**, the best conversion (100%) and yield (up to 96% after recrystallization, entry 7, in Table 1) was obtained at room temperature in 4 h. The solvents CH_3CN, MeOH, and EtOH gave poor to moderate reaction yields (28, 37, 15%, entry 1, 2, 3, Table 1). The reactions did not proceed in solvents, such as DMF and THF (entry 4, 5, Table 1). However, H_2O:*t*-BuOH (4:1) solvent system also gave significant conversion (70%) and yield (67%, entry 10, Table 1) with 2 mol% of catalyst. Hence, the regiospecificity of the epoxide ring-opening with concomitant 1,2,3-triazole ring formation process is more efficient in H_2O alone rather than H_2O:*t*-BuOH (4:1). Since, *in situ* generated organic azide, a very weakly coordinating ligand, needs access to the metal center, therefore solvent coordination plays an important role in the reaction.[23a] However, the efficiency of these solvents based on conversions and yields decreases in the order H_2O>H_2O:*t*-BuOH (4:1)>MeOH>CH_3CN>EtOH. Of note, Cu(I) complex **10** provided the best catalytic results compared to free pyrrolidinyl-oxazole-carboxamide ligand **9** showing the advantage of preformed catalysts over *in situ* generated Cu(I) species. In fact, reactions were fast at elevated temperature in the sole presence of water, with catalyst loading of 1.0 mol% (93%, entry 8, Table 1). Interestingly, catalyst loading could be further reduced to 0.5 mol%, affording excellent yield of **3a** within 24 h (89%, entry 9, Table 1). These results suggest that the sufficient steric effect of side chain '1-phenylethyl' must be present to create a favorable environment around a copper center which might help in decomplexation of final product from copper center after completion of the reaction.[23a,32]

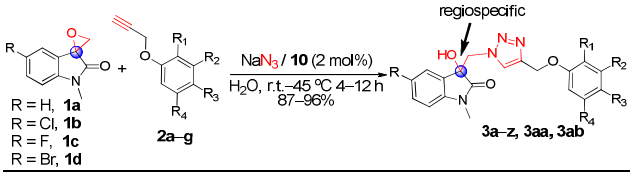
Synthesis of 3-substituted *O*/*N*-linked-1,2,3-triazolo-3-hydroxy-indolin-2-ones

The precursors **1a–d** underwent ring-opening with NaN_3 (0.2 mmol) and tandem "CuAAC" reaction by using different terminal acetylenes **2a–n** (0.2 mmol) in the presence of catalyst **10** (2 mol%) in water (3 mL) within 4–12 h, and all the final products **3a–z**, **3aa**, **3ab**, and **4a–t** were obtained regiospecifically. In case of **1d** (R = Br), the reactions took longer time (10–12 h) to produce the required products (**3v–z**, **3aa** and **3ab**, Table 2) which might be attributed due to less reactivity as compared with other substrates **1a–c**.

In most of the cases, the final desired products were hardly water-soluble; therefore, a simple filtration of reaction mixture followed by recrystallization with a little amount of hot ethyl acetate furnished the products in a pure form. The purity of the final compounds were estimated by HPLC.[33] ICP-AES analysis of the final product showed that there was no copper species were detected by leaching of the copper ions from the catalyst into the product. Under these optimized reaction conditions, this protocol gave the best regiospecificity and yields (87–96% Table 2 and 3). Regardless of the substitution pattern, this "one-pot" reaction tolerated both electron-withdrawing as well as electron-donating groups alike, proceeded uniformly for all *o*-, *m*-, and *p*-substituted alkynes to accomplish the final products. Moreover, this

methodology is highly compatible with a variety of functional groups, such as fluoro, chloro, bromo, nitro, methoxyl, allyl, phthalyl, naphthyl, tetrahydroquinoline, pyridyl-piperazine, and cyclopropylcarbonyl-piperazine as shown in Table 2 and 3.

Table 2 "One-pot" process for the synthesis of a library of new 3-substituted *O*-linked-1,2,3-triazolo-3-hydroxy-indolin-2-ones[a]



Entry	R	R_1	R_2	R_3	R_4	Time (h)	Yield (%)[b]
3a	H	H	OCH_3	OCH_3	OCH_3	4	96
3b	H	OCH_3	H	allyl	H	4	93
3c	H	H	OCH_3	H	OCH_3	5	93
3d	H	H	H	OCH_3	H	6	90
3e	H	OCH_3	H	H	H	6	90
3f	H	H	NO_2	NO_2	H	7	88
3g	H	H	H	Cl	H	7	90
3h	F	H	OCH_3	OCH_3	OCH_3	6	95
3i	F	OCH_3	H	allyl	H	6	94
3j	F	H	OCH_3	H	OCH_3	7	92
3k	F	H	H	OCH_3	H	7	92
3l	F	OCH_3	H	H	H	7	92
3m	F	H	NO_2	NO_2	H	8	87
3n	F	H	H	Cl	H	8	88
3o	Cl	H	OCH_3	OCH_3	OCH_3	6	95
3p	Cl	OCH_3	H	allyl	H	6	95
3q	Cl	H	OCH_3	H	OCH_3	7	93
3r	Cl	H	H	OCH_3	H	8	92
3s	Cl	OCH_3	H	H	H	8	92
3t	Cl	H	NO_2	NO_2	H	8	88
3u	Cl	H	H	Cl	H	8	89
3v	Br	H	OCH_3	OCH_3	OCH_3	10	92
3w	Br	OCH_3	H	allyl	H	10	90
3x	Br	H	OCH_3	H	OCH_3	11	90
3y	Br	H	H	OCH_3	H	12	88
3z	Br	OCH_3	H	H	H	11	89
3aa	Br	H	NO_2	NO_2	H	12	87
3ab	Br	H	H	Cl	H	12	88

[a] The reactions were performed with epoxides (0.2 mmol), sodium azide (0.2 mmol), alkynes (0.2 mmol), in the presence of catalyst **10** (2 mol%) in H_2O (3 mL) as reaction media. [b] Isolated yields after recrystallization.

Similarly, this "one-pot" procedure was also applied for the synthesis of a series of 3-substituted *N*-linked 1,2,3-triazolo-3-hydroxy-indolin-2-ones **4a**–**t** and afforded excellent yields 87–95% as depicted in Table 3. However, in case of **4a**–**c**, **4e**–**g**, **4i**–**l**, **4n**, and **4q**–**s**, the reactions proceeded sluggishly even after 24 h. Then, we performed the same reactions at 60 °C, based on the substrate scope the corresponding products could be acquired completely within 4–12 h. It is our keen observation that the reactions of phthalyl and naphthalimide containing alkyne building blocks proceeded at 60–65 °C and afforded the yields ranging from 87–92%. Next, the cyclopropylcarbonyl-piperazine, pyridyl-piperazine, and tetrahydroquinoline building blocks smoothly participated in the reaction at room temperature and achieved the excellent yields (91–95%). Although, the previous research suggests that bulkier alkynes are relatively unfavorable substrates in the 'CuAAC' reaction under mild reaction conditions, resulting in low yields.[34] Therefore, we have successfully employed this 'one-pot' sustainable green approach to chemical synthesis by emphasizing the features as follows: (i) mild reaction conditions, (ii) operational simplicity, (iii) cleaner reaction profile: regiospecific reaction which avoids the formation of other by-products, (iv) easy work-up and isolation, (v) eco-friendly, inexpensive material, high yields, and (vi) reusable catalyst.

Regiochemistry

It could be delighted that the multi-component synthesis of 3-substituted-1,2,3-triazolo-3-hydroxy-indolin-2-ones catalyzed by Cu(I) complex in aqueous media was regiospecific with regard to both azidolysis of the epoxide and 1,3-dipolar cycloaddition with terminal alkynes. However, we have used racemic isatin-epoxides as substrates for azidolysis which resulted in racemic products and moreover no enantiomeric excess was observed. Although our results differ considerably from reported aryl-substituted epoxides (styrene epoxide),[20] it could nevertheless be that the regiospecificity in isatin *spiro*-epoxide ring-opening arises from the steric restriction prevalent in the structure. The epoxide ring opened from Cβ side of isatin derivatives affording the products regiospecifically. The more electrophilic nature of amide functionality makes the benzylic carbon less stable, which favours the attack of azide nucleophile from other side. It was also speculated that water enhances the electrophilicity of the epoxide-ring through hydrogen-bonding and facilitating the nucleophilic attack of the azide. The dipolar bonding between azide and oxygen (amide carbonyl) may provide additional stabilization and allowing the epoxide to be opened specifically from the less-hindered side. However, the Cu(I) catalyst might also play an important role in the fate of regioselectivity due to the addtional coordination of the epoxide ring oxygen with metal center,[31] since it was observed to accelerate the azidolysis of epoxide ring. Moreover, the regiochemistry of this reaction was confirmed by single X-ray crystallographic study which shows the exclusive formation of one regiospecific isomer (**3s**) as shown in Figure 3.[35]

Quantum chemical calculations

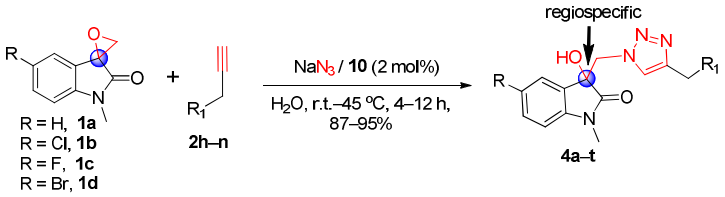
Herein, we have employed a quantum chemical method to support the experimentally observed regiospecificity for epoxide ring-opening reaction. The energetic basis and possible reaction pathway for isatin-epoxide ring-opening was explored for the first time. In this context, we have studied the hydrogen-bond driven *spiro*-epoxide ring-opening process by excluding catalyst interaction. The results suggest that the product β is more stable than the product α by 4.25 kcal/mol, and are in agreement with the experimentally observed regiospecificity. The dipolar interaction between azide and amide carbonyl favours a more stable 6-membered Transition State (TS) *via* Cβ compared to strained 5-membered TS *via* Cα (Figure 4). The activation energy barriers ($\Delta^{\ddagger}G°$) for the formation of TSs α and β are 34.37 and 29.33 kcal.mol^{-1} respectively, which represents the lower $\Delta^{\ddagger}G°$

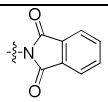
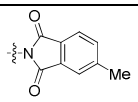
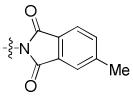
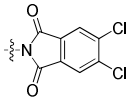
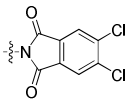
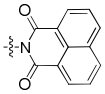
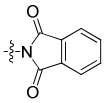
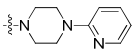
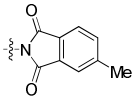
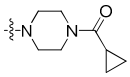
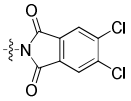
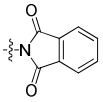
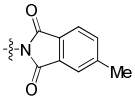
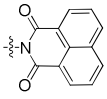
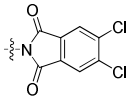
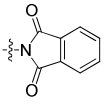
value in case of product β. This indicates that the formation of the regiospecific product β is kinetically and thermodynamically favored. Moreover, it was observed that in the TSβ, the breaking bond Cβ–$O_{epoxide}$ elongates from 1.433 Å to 1.993 Å, whereas the forming bond Cβ–N_{azide} shortens from 2.012 Å to 1.479 Å.

Recyclability study

For practical applications of the catalyst, the lifetime of the catalyst and its level of reusability are very significant factors. To shed light on this study, a set of experiments was established for the one-pot cycloaddition reaction of *spiro*-epoxide **1a**, sodium azide and terminal alkyne with 2 mol% of catalyst **10**. After the completion of the reaction, product **3a** was obtained by simple filtration process. After each cycle, the aqueous reaction mixture was washed by using ethyl acetate to eliminate the remaining traces of other impurities. This aqueous solution containing the catalyst was directly used for the next reaction. The same procedure was followed for consecutive recycling of the catalyst **10**. The catalyst could be used at least four times without any appreciable loss of activity in an aqueous medium with the fourth run giving 90% isolated yield of **3a** as shown in Figure 5.

Table 3 "One-pot" process for the synthesis of a library of new 3-substituted *N*-linked-1,2,3-triazolo-3-hydroxy-indolin-2-ones[a]



Entry	R	R_1	Time (h)	Yield (%)[b]	Entry	R	R_1	Time (h)	Yield (%)[b]
4a	H		4	89[c]	**4k**	Cl		10	87[c]
4b	H		6	90[c]	**4l**	Cl		10	88[c]
4c	H		6	90[c]	**4m**	Cl		8	94
4d	H		4	95	**4n**	Cl		12	87[c]
4e	F		6	90[c]	**4o**	Cl		8	95
4f	F		8	92[c]	**4p**	Cl		8	93
4g	F		8	92[c]	**4q**	Br		11	87[c]
4h	F		7	95	**4r**	Br		12	88[c]
4i	F		12	87[c]	**4s**	Br		12	88[c]
4j	Cl		9	89[c]	**4t**	Br		9	91

[a] The reactions were performed with epoxide (0.2 mmol), sodium azide (0.2 mmol), alkynes (0.2 mmol), in the presence of catalyst **10** (2 mol%) in H_2O (3 mL) as reaction media. [b] Isolated yields after recrystallization. [c] Reactions were carried out at 60 °C.

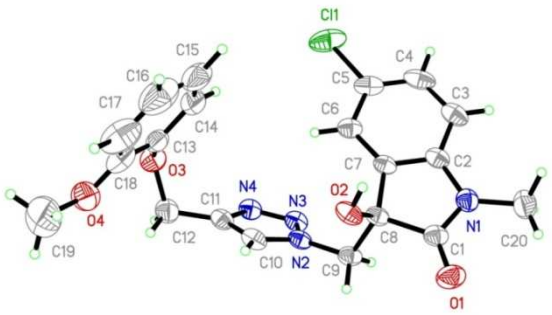


Fig. 3 ORTEP diagram of compound **3s**.

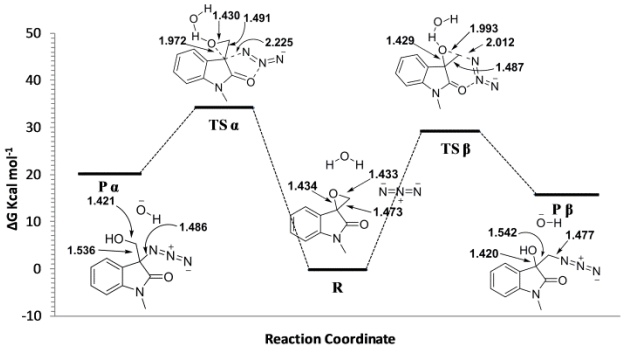


Fig. 4 Reaction profile for the epoxide ring-opening of **1a** calculated at the B3LYP level by using the 6-311++g(d,p) basis set by utilizing the integral equation formalism polarisable continuum (IEFPCM) model in water (ε = 78.3553) using the Gaussian 09 computational package (298.15 K and 1 atm); R = reactant, TS = transition state, P = product.

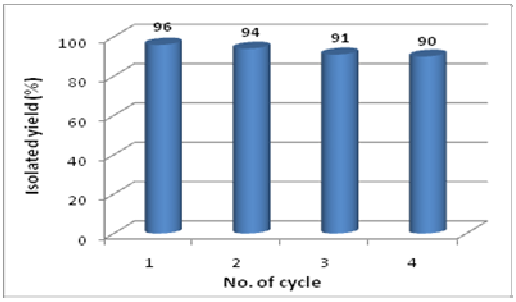


Fig. 5 The recyclability chart of compound **3a**.

Conclusions

In conclusion, we have developed a sustainable 'one-pot' click protocol by employing Cu(I)-pyrrolidinyl-oxazole-carboxamide as a catalyst. It involves the multi-component reaction between *spiro*-epoxides, terminal alkynes and sodium azide towards the synthesis of a library of novel 1,2,3-triazolo-3-hydroxy-indolin-2-ones. This method provides a significant advantage by avoiding the isolation and handling of hazardous organic azide intermediates. The reaction offers regiospecificity, high yields, cost-effective, and easy isolation of final products including broad substrate scope. The overall modularity of this "one-pot" sequence is greener and noteworthy. The biological evaluation of these new molecules, particularly as regards their anticancer potential and the mechanism of action, is in progress.

Experimental section

General Methods

All the starting materials and other reagents were commercially available of the best grade and were used without further purification. TLC was performed on 0.25 mm silica gel 60-F_{254} plates. Spots were visualized by UV light. All melting points were taken and are uncorrected. FT-IR spectra for all the compounds were recorded by using KBr disk as well as ATR method. ^{1}H and ^{13}C NMR spectra were recorded on 200, 300, 400, and 500 MHz spectrometers using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Spin multiplicities are described as s (singlet), brs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported in hertz (Hz). HRMS analyses were acquired on single quadruple and carried out in the ESI techniques at 70 eV. Wherever required column chromatography was performed using silica gel of 60-120 µm with hexane and ethyl acetate as eluent.

Syntheses

Pyrrolidinyl-oxazole-carboxamide derivative (9). *N*-((*R*)-1-phenylethyl)-5-((*S*)-pyrrolidin-2-yl)-oxazole-4-carboxamide (**9**) was prepared according to the literature procedure and the experimental data was matched with the reported data.[25]

Cu(I) complex of *N*-((*R*)-1-phenylethyl)-5-((*S*)-pyrrolidin-2-yl)oxazole-4-carboxamide (**10**). In a round bottom flask, ligand **9** (1.0 mmol) was dissolved in dioxane (10 mL). CuCl (1.0 mmol) was added, and the reaction mixture was heated up to 60 °C for 10 h. Then, the solvent was removed under reduced pressure, and the residue was dissolved in 2 mL dichloromethane and precipitated with 20 mL of hexane. After filtration, the pale greenish complex **10** was obtained. Greenish solid; yield 90%; purity: >99.5%, t_R = 0.81 min.; mp: 148–150 °C; $C_{16}H_{17}ClCuN_3O_2$ (382): calcd. C 50.26, H 4.48, N 10.99; found C 50.23, H 4.49, N 10.98; FT-IR (ATR): 1625, 1118, 701, 446, 407 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-$_{d6}$, 1:1 *v/v*): δ 1.57 (d, 3H, J = 6.8 Hz), 1.76–1.97 (m, 3H), 2.07–2.19 (m, 1H), 2.93–3.06 (m, 2H), 4.84 (t, 1H, J = 6.8 Hz), 5.16–5.25 (m, 1H), 7.22–7.39 (m, 5H), 7.84 (s, 1H); MS (MALDI): *m/z* for $C_{16}H_{17}N_3O_2Cu$, 346.

Catalytic studies

General procedure for the "one-pot" synthesis of 3-substituted-1,2,3-triazolo-3-hydroxy-indoline-2-ones (**3a–z**, **3aa**, **3ab**, and **4a–t**). The *spiro*-epoxide (**1a–d**, 0.2 mmol), NaN_3 (0.2 mmol), and terminal alkynes (**2a–n**, 0.2 mmol) were added to a solution of **10** (2.0 mol %) in water (3 mL). The reaction mixture was stirred at room temperature (at heating 60 °C, wherever required) for 4–12 h until the disappearance of the starting material, as indicated by TLC. Later, the water (10 mL) was added to the resulting mixture followed by filtration. The residue, thus obtained was air dried and washed twice with EtOAc:Hexane (20:80, 5 mL) and recrystallized to obtain the products **3a–z**, **3aa**, **3ab**, and **4a–t** in pure form as well as good yields (87–96%).

Gram-scale procedure for the "one-pot" synthesis of 3-Hydroxy-1-methyl-3-((4-((3,4,5-trimethoxyphenoxy)methyl)-

1*H*-1,2,3-triazol-1-yl)methyl)indolin-2-one (3a). The *spiro*-epoxide (**1a**, 1.0 g 5.7 mmol), NaN_3 (0.371 g, 5.7 mmol), and terminal alkyne (1,2,3-trimethoxy-5-(prop-2-ynyloxy)benzene, 1.27 g, 5.7 mmol) were added to a solution of **10** (43 mg, 2.0 mol %) in water (20 mL). The reaction mixture was stirred at room temperature for 4 h. Later, the water (20 mL) was added to the resulting mixture followed by filtration. The residue, thus obtained was recrystallized to obtain the pure white solid **3a**, (2.41 g, 96%).

Catalyst recyclability. The reaction was carried out as mentioned above using **1a** (1.0 mmol), sodium azide (1.0 mmol), 1,2,3-trimethoxy-5-(prop-2-ynyloxy)benzene (1.0 mmol) and **10** (2 mol %) in water (10 mL). After completion of reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The recovered aqueous layer containing the catalyst (catalyst was soluble in aqueous layer) was then directly used as the solvent for the next run of the catalyst recyclability experiment by addition of fresh reactants. The same procedure was followed for consecutive recycling. The combined organic phase obtained in each run was concentrated under reduced pressure. The crude compound of each recycle was recrystallized and isolated yields were calculated.

Quantum chemical calculations

Geometry optimization and frequency calculations for the structures corresponding to the reactants, probable transition states and the products were performed, with DFT methods at the B3LYP level using the 6-311++g(d,p) basis set[36] by utilizing the Integral Equation Formalism Polarisable Continuum (IEFPCM) Model[37] in water using the Gaussian 09 computational package.[38] The Synchronous Transit-guided Quasi-Newton (STQN) method was used to locate the transition states and substantiate the observed experimental results. All the stationary points were located and characterized as minima with real frequencies or transition states with one imaginary frequency by vibrational frequency calculations at the same level of theory and these data are used for calculation of activation free energies (298.15 K and 1 atm). Intrinsic reaction coordinate (IRC) calculations were performed at the same level of theory to verify that the transition structures connect the reactants and products. The Cu(I) complex was optimized by DFT calculations at B3LYP/LANL2DZ level.

X-ray analysis of compound 3s

X-ray data for the compound **3s** was collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71073Å) with ω-scan method.[39] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames.

Integration and scaling of intensity data was accomplished using SAINT program. The structure was solved by direct methods using SHELXS97 and refinement was carried out by full-matrix least-squares technique using SHELXL97.[40] Anisotropic displacement parameters were included for all non-hydrogen atoms. The O-bound H atom was located in difference Fourier maps and their positions and isotropic displacement parameters were located and refined. All other H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å and $U_{iso}(H) = 1.2U_{eq}(c)$ for H atoms].

Acknowledgements

K.R.S., P.S. and S.N., are thankful to DoP, Ministry of Chemicals & Fertilizers, Govt. of India, New Delhi, for the award of NIPER fellowship.

Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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