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A ligand-free approach to substituted (*Z*)-3-methyleneisoindolin-1-ones via Cu (I) catalyzed regio- and stereo-selective assembly of 2-iodo benzamide and terminal alkyne

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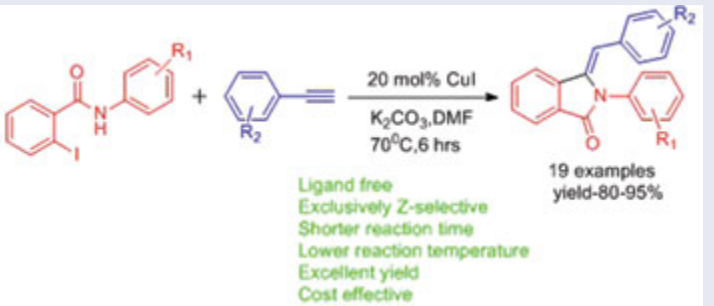
ABSTRACT

A ligand-free and cost-effective synthesis of substituted 3-methyleneisoindolin -1-ones from 2-iodobenzamide and terminal alkyne under copper (I)-catalyzed condition was accomplished. The reaction affords excellent yield of the product at a relatively lower temperature and exclusive *Z*-selectivity was observed in the title compound. By varying the substitution pattern on N-atom of benzamide or aromatic core of the alkyne system, a large array of substituted 3-methyleneisoindolin-1-one derivatives could be accessed employing this method.

GRAPHICAL ABSTRACT



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Domino reaction; ligand free; 3-methyleneisoindolin-1-one; regio- and stereo-selective cross coupling; *Z*-selectivity

Introduction

Substituted 3-methyleneisoindolin-1-ones are important structural subunits frequently encountered in naturally occurring substances and medicinally valuable compounds. These natural products include different aristolactam alkaloids such as piperolactam,[1a] lennoxamine (an isoindolobenzazepine alkaloid),[1b] pazinaclone,[1c] AKS 186 (a phenylethyledine derivative),[1d] fumaridine (a secophthalide isoquinoline lactam),[1e] magallanesine (an isoindolobenzazocine alkaloid)[1f] to name a few. Some important natural products and medicinally significant molecules decorated with 3-methyleneisoindolin-1-

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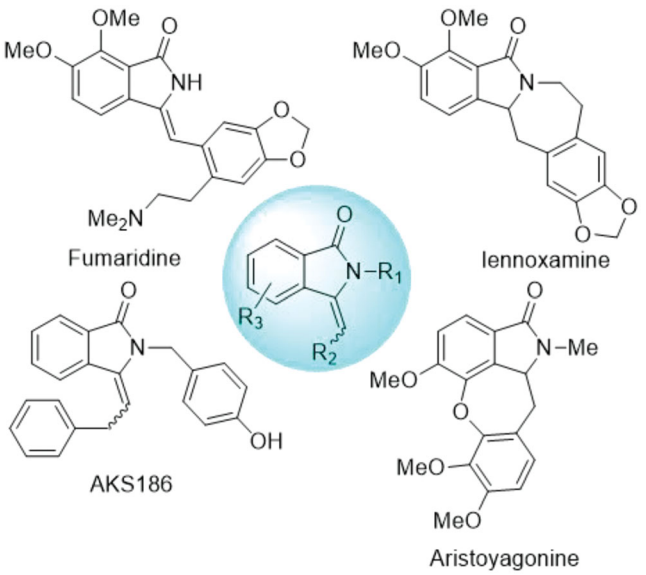


Figure 1. Natural products and biologically important molecules embellished with 3-methyleneisoindolin-1-one framework.

one structural backbone are listed in Figure 1. Apart from their diversified structural features, substituted 3-methyleneisoindoline-1-one derivatives are also important from the therapeutic point of view. Amongst various biological activities of 3-methyleneisoindolin-1-one containing compounds, local anesthetic activity,[2] sedative activity,[3] antiviral,[4] anti-hypertensive,[5] and anti-leukemic[6] activities are worth mentioning. Some 3-methyleneisoindolin-1-one derivatives are also known to be useful for the treatment of a psychotic disorder.[7] Apart from medicinal significance, different functionalized materials are also synthesized from 3-methyleneisoindolin-1-one moiety and find application in material chemistry.[8] Due to their diversified structural architecture and biological significance, a couple of total synthesis of isoindolin-1-one containing natural products have been surfaced in the literature.[9,10a] As an obvious consequence, several novel synthetic routes have been developed to construct the 3-methyleneisoindolin-1-one core structure. Traditionally, 3-methyleneisoindolin-1-one was accessed via aryne cyclization and Homer–Wadsworth–Emmons type reaction of o-(and m-)halogeno-N-phosphoryl-methylbenzamide derivatives.[10b] 3-Methyleneisoindolin-1-one may also be synthesized from phthalimide via photochemical reaction,[11a] electroreductive intermolecular coupling of aldehyde,[11b] photodecarboxylative addition of carboxylates,[11c] anionic cycloaromatization of 2-alkynylbenzonitrile.[12] Larock et al. demonstrated the synthesis of isoindoline-1-one via electrophilic cyclization of preformed 2-alkynylbenzamide.[13] Electrophilic cyclization of hydrazides of 2-alkynylbenzoic acid led to the formation of differently substituted 3-methyleneisoindolin-1-one derivatives.[14] However, all the above-mentioned methods are associated with their own drawback such as poor regioselectivity for unsymmetrical substrate, low yield, longer reaction time, extra synthetic steps, etc. To overcome these shortcomings, transition metal-mediated coupling reactions have emerged as an efficient tool for the synthesis of title compounds. Alper et al. developed palladium-catalyzed Sonogashira coupling-carbonylation-

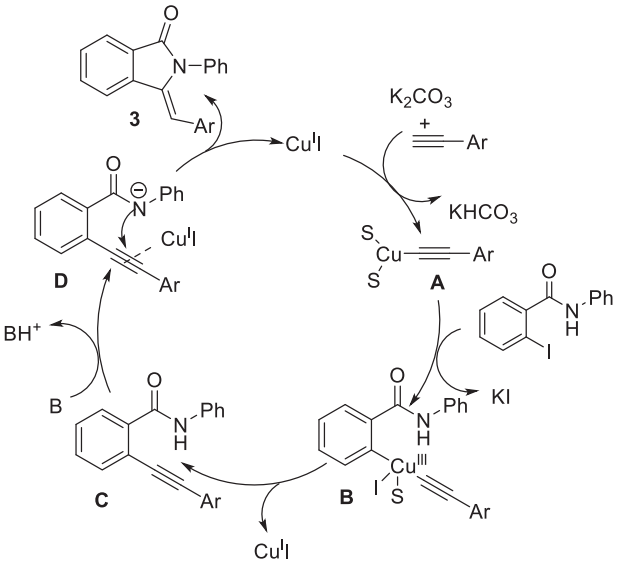
hydroamination reaction sequence to afford 3-methyleneisoindolin-1-one derivatives.[15] Cossy and coworkers demonstrated that 3-methyleneisoindolin-1-one derivative could be synthesized from ynamides and boronic acids via Pd-catalyzed Heck–Suzuki–Miyaura domino reaction.[16]

Apart from Alper and Cossy's work, there are many more examples of Palladium promoted synthesis of 3-methyleneisoindolin-1-one under diversified reaction conditions including sonochemical condition, microwave condition and even in an aqueous micellar medium.[17a–j]

Another elegant strategy toward 3-methyleneisoindolin-1-one was developed by Lee[18a] and Patel[18b] via decarboxylative cross-coupling of 2-halobenzamide and aryl alkynyl acids under Cu-catalyzed condition. Cu (II) mediated oxidative alkynylation and intramolecular annulation is another prominent entry to 3-methyleneisoindolin-1-one synthesis by You et al.[19] However the substrate scope of arene was restricted to N-(quinolin-8-yl) benzamide only. Another Cu (II) catalyzed, ligand assisted synthesis of the title compound was reported by Zeng et al.[20a] though the reaction time was sufficiently prolonged. Recently Surya Praksh and his coworkers[20b] reported a Cu (I) catalyzed tandem desilylation-hydroamination strategy for the synthesis of isoindoline. Though, the method required higher temperatures and costly starting materials. Other noteworthy copper-catalyzed methods offering 3-methyleneisoindolin-1-one derivatives were reported by Phukan,[20c] Yao,[20d] and Kumar[20e] with their own merits and drawbacks. Though many metal-free and transition metal-catalyzed methods are already known to access 3-methyleneisoindolin-1-one derivatives, issues like regioselectivity (5-*Exo* vs 6-*endo* cyclization) and chemoselectivity (due to nucleophilicity of O- and N-atom of amide moiety) are not fully resolved. In fact, a mixture of compounds was obtained in several cases due to regio- and chemoselectivity issues.[21] Herein, we report a copper(I) promoted, ligand-free approach to access (*Z*)-3-methyleneisoindolin-1-one derivatives with complete regio- and stereo-selectivity.

Results and discussion

Transition metal-catalyzed approaches toward 3-methyleneisoindolin-1-one are mainly restricted to palladium and copper. And more commonly, a suitable ligand or additives were used in all the methods reported earlier. According to the reported literature, a plausible mechanism of this domino reaction (Described in Scheme 1) consisted of Sonogashira cross-coupling between 2-halobenzamide and terminal alkyne or alkynyl acid (via copper (l)-acetylide intermediate A, oxidative addition B, and reductive elimination C), followed by base mediated amide deprotonation. Finally, nucleophilic attacks of amide anion D on transition metal-alkyne complex complete the intramolecular cyclization to afford 3-methyleneisoindolin-1-one derivatives. Though, a variety of ligands such as L-proline, *N,N*-dimethylglycine, pipecolinic acid, 2-picolinic acid, 1,10-phenanthrene, TMEDA, DMEDA, SPhos, XantPhos, and other phosphine based ligands have been used in different transition metal assisted approaches, the evidence for the beneficial effect of ligands are not mentioned elsewhere. We anticipated that this domino reaction may proceed equally well without using any ligand or additive if we start with the iodoarene substrate. Iodide might play a dual role as Sonogashira coupling partner



Scheme 1. Plausible mechanism of the formation of 3-methyleneisoindole-1-one derivatives under ligand-free conditions.

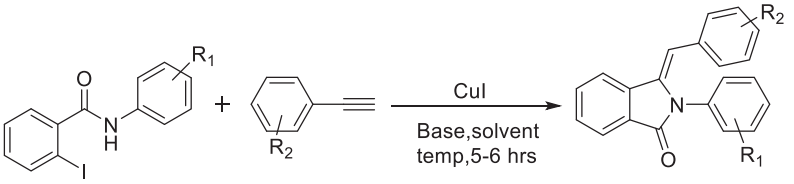
as well as a ligand in the catalytic cycle as shown in Scheme 1. Therefore we chose 2-iodobenzamide **1** and phenylacetylene **2** as our model substrate and the reaction was carried out with 20 mol% of CuI, K_2CO_3 as the base in DMF as solvent by heating at 70 °C. It was our delight to see that it results in fairly clean conversion only within 6 h and excellent yield of 3-methyleneisoindole-1-one **3a** was obtained after column chromatography purification.

To find out the optimum reaction condition, we also carried out the reaction in different solvents like toluene and acetonitrile at the same or elevated temperature but practically no product was found (Table 1, Entries 1–3,). Ag_2CO_3 was tested as an alternative base keeping the other reaction parameter unaltered (Table 1, Entry 4) but we ended up with inferior yield. To optimize the temperature, the reaction was performed under different temperature and we found that 70 °C is the ideal temperature to consume the starting material completely within 6 h. On the other hand, if the temperature is elevated up to 100 or 120 °C, the yield started decreasing with the formation of undetected more polar compounds (Table 1, Entries 7–8). Decreasing catalyst loading to 10 mol% under identical reaction condition, furnished lower yield (Table 1, Entry 9). Further lowering of catalyst loading to 5 mol%, resulted in incomplete conversion after 6 h heating at 70 °C (Table 1, Entry 10).

Since the reaction was found to be most effective in DMF and non-coordinating solvents were not suitable, the participation of DMF as ligand may not be ruled out.

Being inspired by our preliminary observation, we wanted to examine the substrate scope of this reaction under ligand-free conditions. Initially, we prepared differently substituted 2-iodo-*N*-phenyl benzamide (substitution on amide phenyl group) and they were subjected to Sonogashira cross coupling-intramolecular cyclo-amination reaction protocol with phenylacetylene. In all the cases, the reaction went smoothly and we obtained 3-methyleneisoindol-1-one derivatives **3b–3d** with excellent isolated yield and

Table 1. Optimization of following coupling reaction by Cu (I) under different condition.[a]



3a

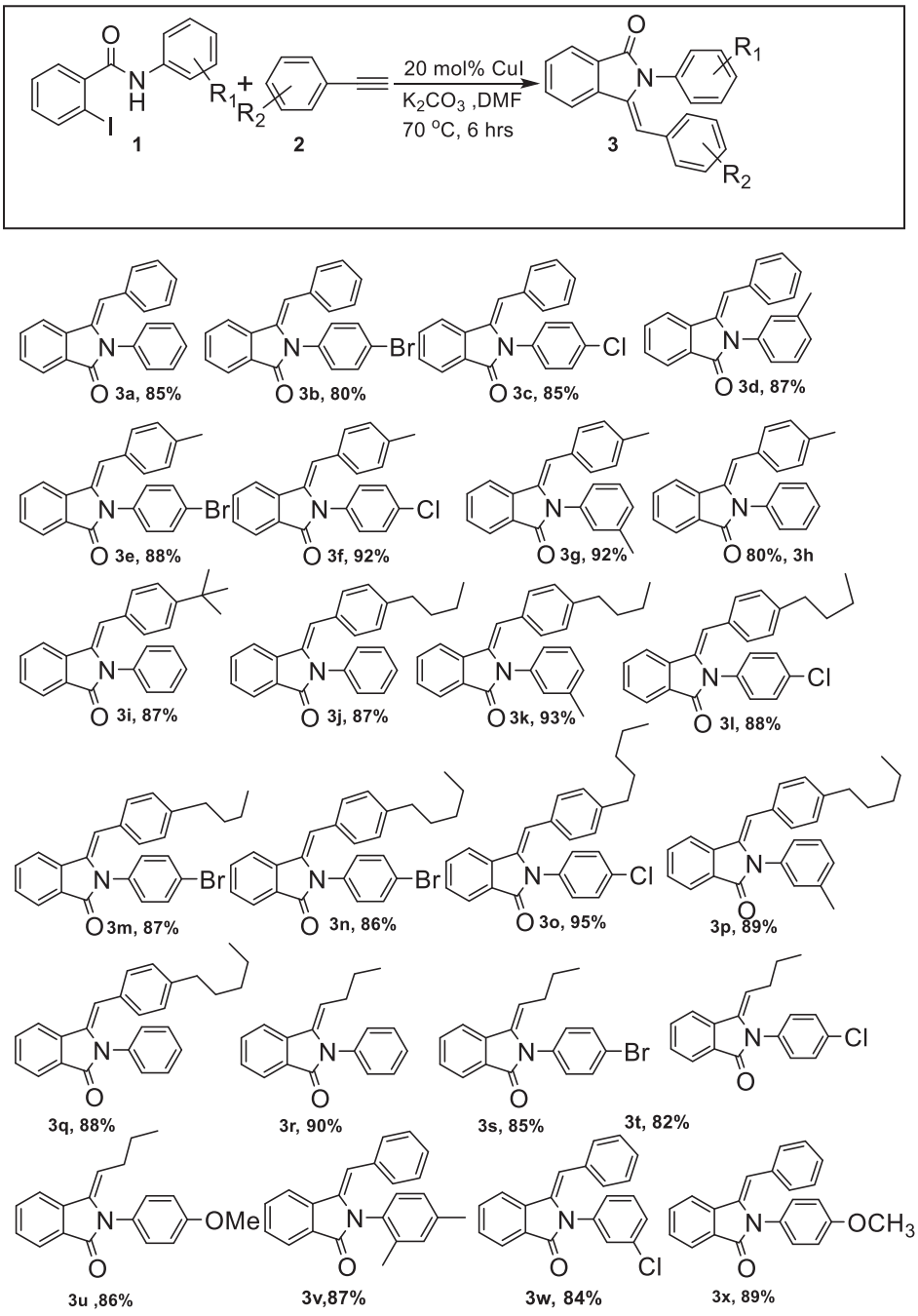
Entry	CuI(mol%)	Base	Solvent	Temp (°C)	Yield (%)
1	20	K_2CO_3	Toluen	110	Trace
2	20	K_2CO_3	Acetonitrile	80	ND
3	20	Ag_2CO_3	Acetonitrile	80	ND
4	20	Ag_2CO_3	DMF	80	60[b]
5	20	K_2CO_3	DMF	90	85
6	**20**	**K_2CO_3**	**DMF**	**70**	**85**
7	20	K_2CO_3	DMF	100	70
8	20	K_2CO_3	DMF	120	60
9	10	K_2CO_3	DMF	70	65
10	5	K_2CO_3	DMF	70	45[c]

[a]Reaction condition: 0.3 mmol of **1**, 2.0 equiv.of K_2CO_3, 1.2 equiv. of alkyne and solvent (2 ml under N_2), 6 h; [b]time 8 h; [c]based on starting material recover.

much shorter reaction time. Similarly, *p*-tolyl acetylene and 4-*tert*-butylphenylacetylene were tested as the terminal acetylene source and corresponding 3-methyleneisoindol-1-one derivatives **3e–3i** (Scheme 2) were isolated with very good-to-excellent yield. Long-chain substituted phenylacetylene such as 4-*n*-butylphenylacetylene and 4-*n*-pentylphenylacetylene were also found to be an excellent partner for this Sonogashira coupling-cycloamination reaction. Therefore, they were readily coupled under standard reaction conditions with a variety of 2-iodo-*N*-phenylbenzamide to afford 3-methyleneisoindol-1-one derivatives **3j–3q** (Scheme 2) with comparable isolated yields. To the best of our knowledge, compounds **3j–3q** are new and are accessible via our ligand-free approach with superior yield compared to similar compounds. 1-pentyne which was never tested before as potential terminal alkyne counterpart was found to be an outstanding candidate for this domino reaction protocol.

Toward this end, 1-pentyne was treated with different 2-iodobenzamide to afford corresponding 3-methyleneisoindole-1-one derivatives **3r–3 u** (Scheme 2) respectively with excellent yield. To extend the substrate scope further, phenyl acetylene was once again, subjected to react under optimum reaction condition with differently substituted 2-iodobenzamide derivatives to get title compounds **3v–3x** (Scheme 2) with comparable isolated yields.

All the compounds obtained from this reaction are solid and we were interested to have the crystal structure of any of them for structural confirmation. Compound **3a** was crystallized from 20% ethyl acetate in hexane and we were able to pick up a white crystal suitable for X-ray analysis. Crystallographic analysis [CCDC 1849593] established the structure and stereo-chemistry unambiguously, Figure 2.



Scheme 2. Substrate scope of methyleneisoindole-1-one derivatives. Yields of isolated (By column chromatography) products have been reported.

Conclusion

In conclusion, we have developed a simpler way of making (Z)-3-methyleneisoindole-1-one derivatives exclusively starting from 2-iodo-*N*-phenylbenzamide and terminal alkyne under

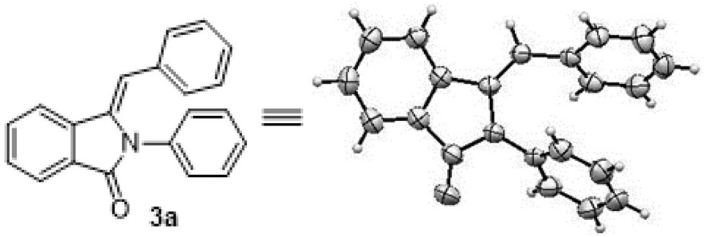


Figure 2. ORTEP diagram of compound **3a** with 50% probability.

mild ligand-free condition. The reaction proceeds via Sonogashira cross-coupling followed by 5-*exo-dig* heteroannulation. In this transformation, aliphatic alkyne may also be employed as an alkyne counterpart which was not used before in a similar reaction. Excellent yield and shorter reaction time are the other attractive features of this method.

Experimental

To an oven-dried 25 ml round bottom flask fitted with a reflux condenser containing 2-Iodo *N*-phenyl benzamide(1.0 mmol) in dry DMF (2.0 ml) was added potassium carbonate (2.0 mmol) and copper iodide (20 mol%) with stirring at room temperature under nitrogen atmosphere. A solution of aryl acetylene (1.2 mmol) in DMF was added to the reaction mixture and the flask was placed in an oil bath at 70 °C for 5–6 h. After starting material was fully consumed (TLC monitoring), the reaction mixture was cooled to room temperature and diluted with ethyl acetate and water. The compound was extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with brine solution (5 ml) and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by silica gel chromatography (Ethylacetate:pet ether = 4:1) to obtain the desired product.

Acknowledgments

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