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Facile synthesis of diverse isoindolinone derivatives via Ugi-4CR followed by Cu-catalyzed deamidative C(sp^2)–C(sp^3) coupling

Vikas Tyagi, Shahnawaz Khan, Prem M. S. Chauhan *

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow 226 001, India

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ABSTRACT

The present work highlights a synthetic approach to the diverse isoindolinone derivatives using Ugi-4CR followed by a Cu-catalyzed deamidative C–C coupling reaction.

This two-step sequence tolerates a broad range of amines, aldehydes, and isocyanides as starting materials for Ugi-4CR products to provide medicinally relevant isoindolinone derivatives in moderate to good yields.

Isoindolinone derivatives are valuable building blocks for the synthesis of various drugs and natural products and are of significant interest due to their broad range of biological activities such as antihypertensive, antipsychotic, antiinflammatory, anesthetic, and antiulcer activities.[1] Additionally, the substituted isoindolinone scaffold is also found in a great variety of natural products and biologically active compounds such as isoindolobenzazepine alkaloid lennoxamine (**1**), antiproliferative agent (**2**), anxiolytic drug pagoclone (**3**), and a potent dopamine D4 ligand (*S*)-PD172938 (**4**) (Fig. 1).[2]

In fact, several common methods are available for the synthesis of isoindolinone derivatives, but most of these traditional approaches suffer from low yields and/or poorly accessible precursors and take place under harsh reaction conditions.[3] In view of their broad range of biological activities, isoindolinone derivatives are an attractive synthetic target and a concise method involving commercially available and cheap starting materials is still required for their practical synthesis.

In this context, numerous transition metal catalyzed protocols for the synthesis of substituted isoindolinone derivatives have received considerable attention.[4] Thus, Zhu et al. reported the synthesis of isoindolinone via Rh catalyzed C–H olefination of *N*-benzoylsulfonamides with internal alkenes, Massa and co-workers reported the first organocatalytic asymmetric synthesis of 3-substituted isoindolinone and Gu and co-workers reported the synthesis of *N*-substituted isoindolinone using Pt nanowires as catalyst.[5]

In the recent past, isocyanide-based multicomponent reactions (IMCRs) followed by other synthetic transformations have emerged as an approach to introduce a large degree of diversity into final heterocyclic scaffolds in an atom economical fashion.[6] For example, Andreana and co-workers reported the synthesis of spiro-2,5-diketopiperazines via a cascade Ugi/6-exo-trig Aza-Michael reaction, Riva et al. described the synthesis of tricyclic *N*-heterocycles using an Ugi reaction with a tandem S_N2-Heck double cyclization reaction and Hulme's group developed a strategy for

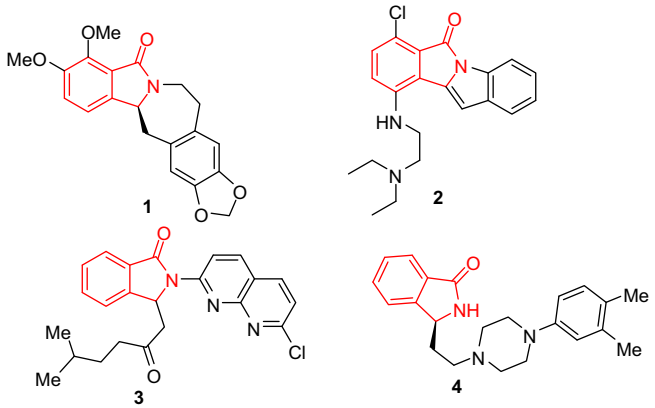

Figure 1. Biologically active compounds containing the isoindolinone scaffold.

* Corresponding author. Tel.: +91 522 2262411x4470; fax: +91 522 2623405.
E-mail addresses: premsc58@hotmail.com, prem_chauhan_2000@yahoo.com (P.M.S. Chauhan).

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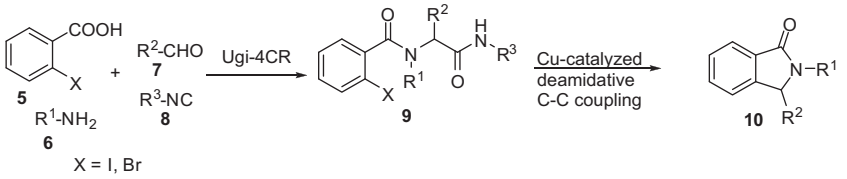
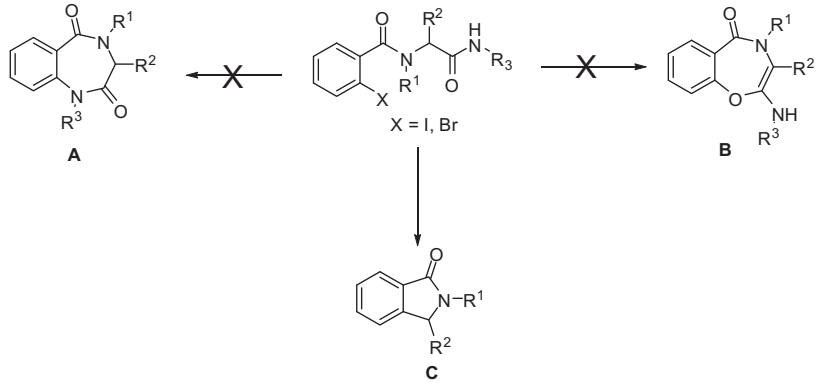
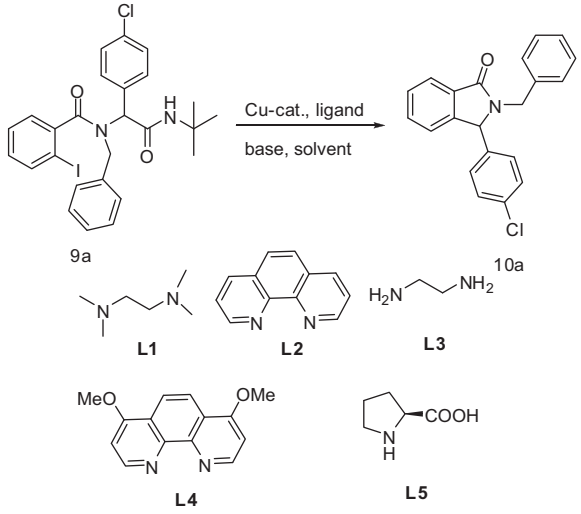


Scheme 1. General strategy for the synthesis of substituted isoindolinone.



Scheme 2. Three possible structures in two-step sequence.

Table 1
Investigation of the reaction conditions for Cu-catalyzed deamidative C–C coupling[a]



Entry	Catalyst	Ligand	Base	Yield[b] (%)
1	—	—	KO^{t}Bu	0[c]
2	CuTC	L2	KO^{t}Bu	19
3	CuI	L1	KO^{t}Bu	41
4	CuBr	L2	KO^{t}Bu	34
5	CuI	L2	NaO^{t}Bu	54
6	CuI	L2	KO^{t}Bu	79
7	CuI	L3	KO^{t}Bu	60
8	CuI	L4	KO^{t}Bu	32
9	CuI	L5	KO^{t}Bu	11
10	CuI	L2	KO^{t}Bu	23
11	CuI	L2	KO^{t}Bu	48[d]
12	CuI	L2	K_2CO_3	12
13	CuI	L2	—	0[e]

[a] Reaction conditions: substrate **9a** (1 mmol), catalyst (10 mol %), ligand (10 mol %), base (4 mmol), solvent (2 mL) under nitrogen atmosphere, reaction temperature (80 °C), reaction time (2 h).
[b] Isolated yield.
[c] No addition of catalyst and ligand.
[d] Loading of catalyst (5 mol %).
[e] No addition of base.

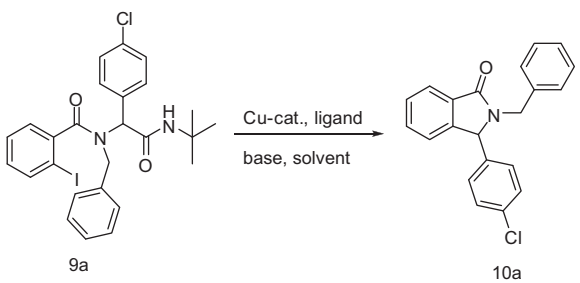
the synthesis of 2,4,5-trisubstituted oxazoles using Ugi/Robinson–Gabriel reactions.[7] Recently, we have also reported the synthesis of *N*-fused polycyclic heterocycles and isoquinolin-1(2*H*)-one scaffolds using IMCR-synthesized precursors.[8]

In our ongoing efforts to develop new strategies for the diversity oriented synthesis of biologically important heterocycles,[9] we report herein the synthesis of diverse isoindolinone derivatives via Ugi-4CR followed by Cu-catalyzed deamidative C–C coupling. To the best of our knowledge, it is the first report of the synthesis of diverse isoindolinones using this approach.

The general strategy for the synthesis of substituted isoindolinone derivative **10** is shown in Scheme 1. 2-Halo benzoic acids **5** were reacted with various amines **6**, aldehydes **7,** and isocyanides **8** in the Ugi-4CR to prepare the corresponding products,[10] which were used as starting materials for a Cu-catalyzed deamidative C–C coupling reaction.

As depicted in Scheme 2, there are three possible products **A**, **B**, and **C** from reaction under Cu-catalyzed conditions. ^{1}H NMR, ^{13}C NMR, and mass spectral data of compounds confirmed that the products have the general structure **C**.

Table 2
Screening of solvent for coupling reaction

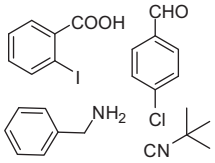
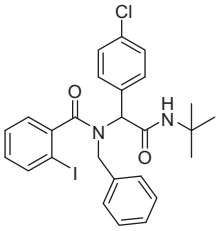
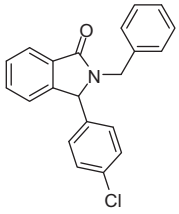
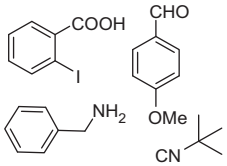
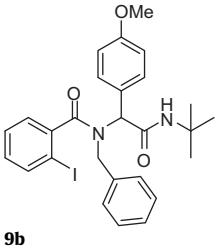
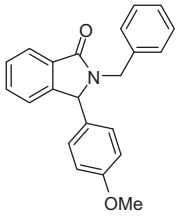
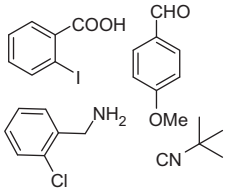
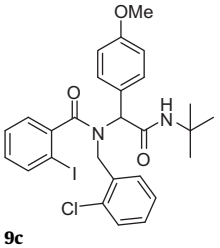
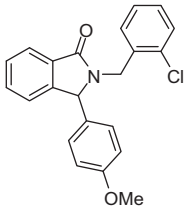
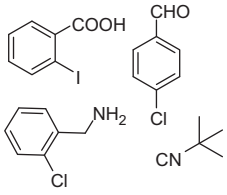
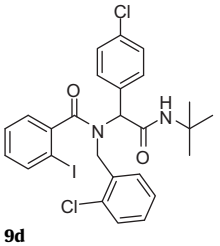
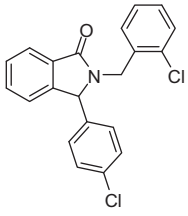
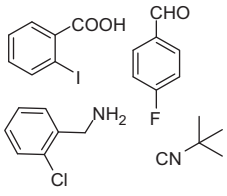
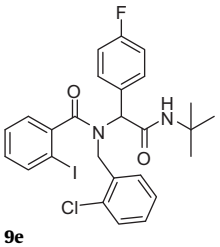
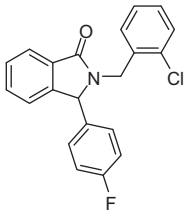
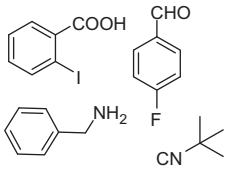
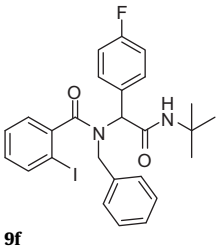
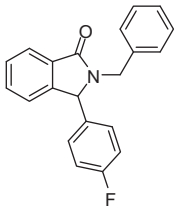


Entry	Solvent	Yield (%)
1	Benzene	71
2	Dioxane	63
3	DMF	57
4	NMP	52
5	Toluene	79

In the initial phase of the investigation, Ugi-MCR synthesized product **9a** was used as the model substrate for the optimization of metal catalyzed deamidative C–C coupling reaction conditions including different catalysts, bases, ligands, and solvents.

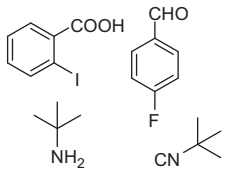
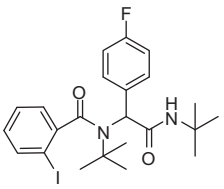
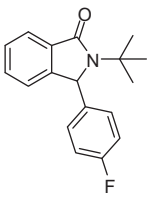
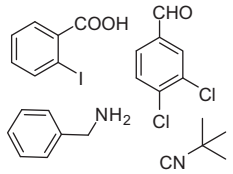
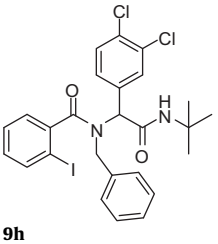
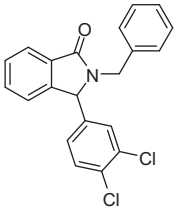
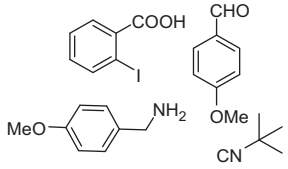
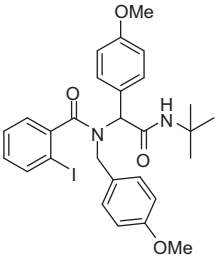
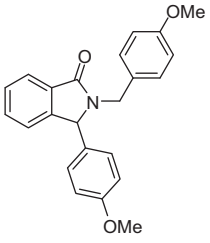
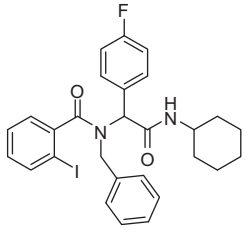
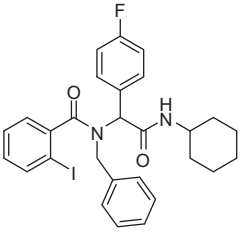
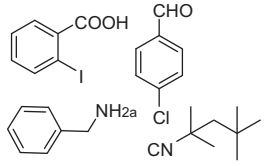
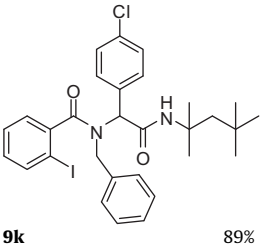
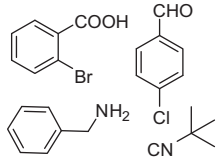
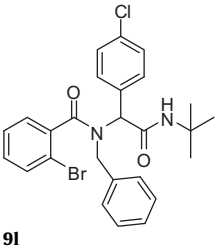
As shown in Table 1, the reaction failed when copper salt was excluded (Table 1, entry 1). Among the three copper catalysts (CuI, CuBr, CuTC) used, CuI was the best catalyst and provided product **10a** in 79% yield (Table 1, entry 6). Switching the Cu salt

Table 3
Scope of two-step procedure[a]

Entry	Starting material	IMCR products (**9**) yield[b] (%)	Coupling products (**10**) yield[b] (%)
1		 **9a** 91%	 **10a** 79%
2		 **9b** 85%	 **10b** 72%
3		 **9c** 88%	 **10c** 67%
4		 **9d** 79%	 **10d** 69%
5		 **9e** 91%	 **10e** 67%
6		 **9f** 89%	 **10f** 63%

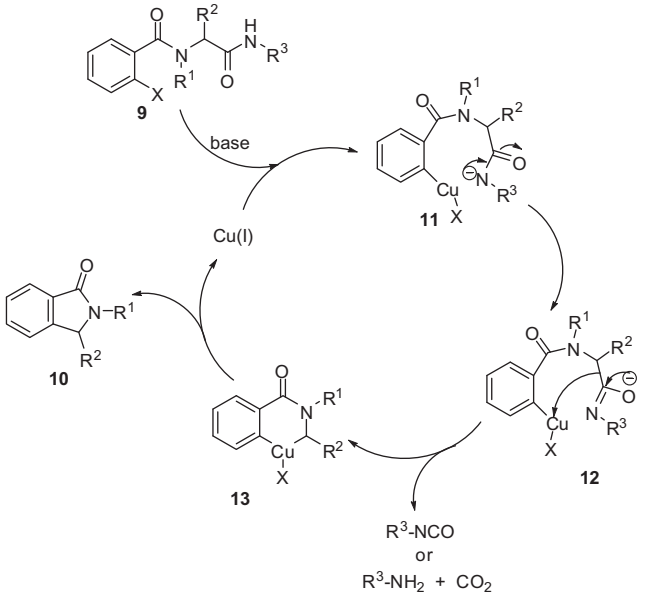
(*continued on next page*)

Table 3 (*continued*)

Entry	Starting material	IMCR products (**9**) yield[b] (%)	Coupling products (**10**) yield[b] (%)
7		 **9g** 72%	 **10g** 68%
8		 **9h** 79%	 **10h** 72%
9		 **9i** 81%	 **10i** 78%
10		 **9j** 94%	**10f** 56%
11		 **9k** 89%	**10a** 72%
12		 **9l** 90%	**10a** 68%

[a] Reaction conditions: under nitrogen atmosphere, substrate 9 (1 mmol), CuI (10 mol %), L2 (10 mol %), KO^{t}Bu (4 mmol), toluene (2 mL), 80 °C, 2–4 h.
[b] Isolated yield.

from CuI to CuBr or CuTC (copper(I) thiophene-2-carboxylate) did not improve the yield of product **10a** (Table 1, entries 2 and 4). Further, various ligands were also investigated; 1,10-phenanthroline (L2) was found to be the most efficient ligand using CuI as catalyst (Table 1, entry 6). However, ligands L1 and L3 also provided the product **10a** but in lower yield, while ligands L4 and L5 were inefficient ligands in the reaction (Table 1, entries 3 and 7–9). Next, to test the effect of base, NaO^{t}Bu, KO^{t}Bu, K_2CO_3, and K_3PO_4 were



Scheme 3. Proposed mechanism of the reaction.

screened; KO^{t}Bu was found to be the most effective base using CuI as catalyst and 1,10-phenanthroline as ligand (Table 1, entry 6). When the catalyst loading was decreased from 10 to 5 mol %, the efficiency of the transformation was affected (Table 1, entry 11). In addition, the reaction was unsuccessful when base was omitted from the reaction mixture (Table 1, entry 13). The effect of solvent was also investigated, and toluene was found to be the best solvent at 80 °C using CuI as the catalyst and KO^{t}Bu as the base, while using benzene, DMF, NMP, and dioxane under the same conditions produced **10a** in lower yield (Table 2).

With this standard protocol in hand, we extended it to the synthesis of various substituted isoindolenone derivatives (**10a**–**i**) via different Ugi-MCR synthesized products (**9a**–**l**) in moderate to good yields (Table 3). Very good yields were observed for the *t*-butyl isocyanide based IMCRs **9a**–**i**,[12] whereas moderate yield of product was obtained in the case of cyclohexyl isocyanide based IMCRs **9j** (Table 3, entry 10). In addition, the reaction took longer time to reach completion. Moreover, when 2-bromobenzoic acid was used in Ugi-MCR, the cyclized product **10a** was observed in lower yield (Table 3, entry 12).

Although the exact mechanism of this reaction is not clear, a probable mechanism for the synthesis of an isoindolinone of type **10** is depicted in Scheme 3.[11] Initially, the Cu(I) catalyst oxidatively adds to the Ugi-4CR synthesized precursor **9** to give metal complex **11**. Intermediate **11** subsequently undergoes deamidation through intermediate **12** leading to C–C bond formation in a new Cu-complex **13**, which undergoes reductive elimination to afford final product **10**.

In conclusion, we have reported an efficient methodology for the synthesis of biologically important isoindolinone derivatives via Ugi-MCR followed by a Cu-catalyzed deamidative C–C coupling reaction. This strategy allows the synthesis of diverse isoindolinone derivatives for combinatorial chemistry and medicinal chemistry using a broad range of amines, aldehydes, and isocyanides as starting materials for Ugi-MCR products.

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Supplementary data

Supplementary data (copies of ^{1}H and ^{13}C NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.091.

References and notes

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12. *Procedure for the synthesis of* ***10a****:* CuI (10 mol %), 1, 10-phenanthroline (10 mol %), KO^{t}Bu (4 mmol), Ugi-4CR product **9a** (1 mmol) and toluene (2 mL) were added to a dry Schlenk tube under nitrogen. The reaction mixture was stirred and heated at 80 °C for 2–4 h. After completion of the reaction as indicated by TLC, the resulting mixture was cooled down to room temperature, filtered through a pad of celite, and the celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc) affording the corresponding isoindolinone derivatives **10a** in 79% yield. *Characterization data of* ***10a****:* Semi-solid, Yield 79%, FT-IR (neat) ν (cm^{-1}): 3441, 2926, 2108, 1683, 1490, 1285, 1016, 766, 706; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.97 (m, 1H), 7.55–7.49 (m, 2H), 7.38–7.30 (m, 5H), 7.22–7.14 (m, 2H), 7.12–7.11 (m, 1H), 7.06 (d, J = 8.1 Hz, 2H), 5.46 (d, J = 14.7 Hz, 1H), 5.26 (s, 1H), 3.79 (d, J = 14.7 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.4, 145.8, 136.8, 135.3, 134.6, 132.0, 131.2, 129.4, 129.1, 128.7, 128.5, 128.4, 127.7, 123.9, 123.0, 62.8, 43.8 ppm, HRMS (ESI) Calcd for $C_{21}H_{17}ClNO$ $[M+H]^+$ 334.0999 Found: 334.0983.