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Synthesis of polysubstituted 1,2-dihydroisoquinolines via a CuI-catalyzed arylation/condensation cascade process

Yangyang Wu [a], Yihua Zhang [a,*], Yongwen Jiang [b,*], Dawei Ma [b,*]

[a] Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, China
[b] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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ABSTRACT

CuI-catalyzed reaction of 1-(2-bromophenyl)-propargylamines **4** with β-keto esters in *i*-PrOH/H_2O (3:1) at 50 °C provides polysubstituted 1,2-dihydroisoquinolines. The transformation involves a cascade intermolecular C–C bond formation and intramolecular condensation process.

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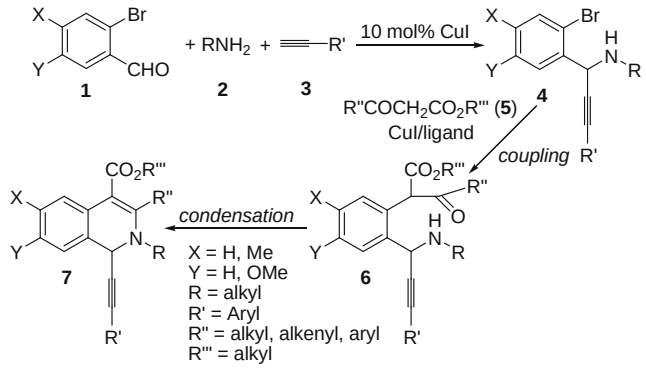
The 1,2-dihydroisoquinoline skeleton is an integral part of many naturally occurring substances and pharmaceutically important compounds.[1] The development of its facile synthesis has been an important issue.[1] Generally, addition of nucleophiles to activated isoquinolinium salts is a reliable method for the synthesis of 1,2-disubstituted dihydroisoquinolines.[2,3] Both acyl chlorides and chloroformates could be used for activation of isoquinolines. But for diversity-orientated synthesis, a drawback behind this method is that the source of substituted isoquinolines is limited. In 2005, Asao and coworkers reported the AgOTf-catalyzed synthesis of 1,2-dihydro-isoquinolines by a direct addition of nucleophiles to *o*-alkynylaryl aldimines.[4] Subsequently, different Lewis acid and nucleophiles were examined and they were found to give a great diversity of 1,2-dihydroisoquinolines.[5] Further investigations indicated that a straight three-component reaction of 2-alkynylbenaldehyde, amine, and nucleophiles could take place under the catalysis of Lewis acids,[6] thereby providing a convenient method for assembly of 1,2-dihydroisoquinolines.

Recently, we have revealed that some amino acids could promote typical Ullmann-type reactions, leading to these coupling reactions occurring under mild conditions.[7] For example, CuI/L-proline-catalyzed coupling of aryl halides and activated methylene compounds could occur at rt to 50 °C.[8] Taking this advantage we have developed some cascade processes for elaboration of heterocycles, which include benzofurans,[9] benzimidazoles,[10] benzimidazole-2-ones,[11] substituted indoles,[12] and substituted isoquinolines.[13,14] As an extension of this work, in this Letter, we explore the possibility of using the coupling reaction of substituted *o*-bromobenzylamines **4** with β-keto esters **5** and subsequent intramolecular condensation to elaborate polysubstituted 1,2-dihydroiso-quinolines **7** (Scheme 1). Herein, we wish to discuss our results.



Scheme 1.

As outlined in Scheme 1, the required substituted *o*-bromobenzylamines **4** could be assembled via a known three-component reaction of 2-bromobenzaldehydes, 1-alkynes, and primary amines.[15] Since this is another copper(I)-catalyzed reaction, we initially tried adding β-keto esters and ligands to this reaction system in order to develop a four-component reaction to polysubstituted 1,2-dihydroiso-quinolines. Unfortunately, we failed to obtain the desired products in reasonable yields under various conditions. Therefore, a stepwise manner was examined.

To explore the optimized reaction conditions, coupling of **4a** with methyl acetoacetate was selected as a model reaction. It was found that this reaction occurred at room temperature under the action of 10 mol % CuI, 20 mol % L-proline and K_2CO_3 in *i*-PrOH to give 1,2-dihydro-isoquinoline **7a** (Table 1, entry 1). However, the combined yield was low mainly because of poor conversion. Increasing reaction temperature to 50 °C gave a similar result (entry 2). After some experimentation, we were pleased to find that adding some water could improve the yield greatly (entry 3), although the reason is not clear. In this case the amino acid was

* Corresponding authors.
E-mail address: madw@mail.sioc.ac.cn (D. Ma).

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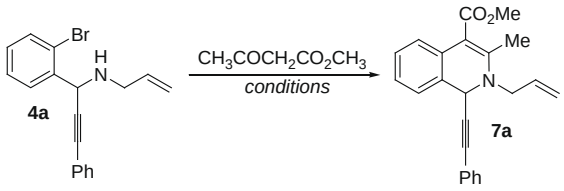
Table 1
Modifications of reaction conditions for the CuI-catalyzed cascade process[a]



Entry	Base	Solvent	Yield of **7a**[b] (%)
1	K_2CO_3	*i*-PrOH	22
2[c]	K_2CO_3	*i*-PrOH	25
3	K_2CO_3	*i*-PrOH/H_2O (3:1)	63
4[d]	K_2CO_3	*i*-PrOH/H_2O (3:1)	66
5[d]	K_2CO_3	*i*-PrOH/H_2O (1:1)	38
6[d]	K_2CO_3	*i*-PrOH/H_2O (6:1)	42
7[d]	Cs_2CO_3	*i*-PrOH/H_2O (3:1)	53
8[d]	K_3PO_4	*i*-PrOH/H_2O (3:1)	45
9[d]	Na_2CO_3	*i*-PrOH/H_2O (3:1)	Trace
10[c,d]	K_2CO_3	*i*-PrOH/H_2O (3:1)	66

[a] Reaction conditions: **4a** (0.5 mmol), methyl acetoacetate (1.0 mmol), CuI (0.05 mmol), L-proline (0.1 mmol, for entries 1–3), base (1.5 mmol), solvent (2.4 mL), rt, 24 h.
[b] Isolated yield.
[c] 50 °C, 12 h.
[d] L-Proline was not used.

found unimportant as evident from that a similar result was obtained in the absence of L-proline (entry 4). Probably β-keto ester itself may serve as a promoter for this transformation.

Further investigation revealed that the ratio for water and *i*-PrOH could influence the reaction process because either more or less than 1:3 of H_2O/*i*-PrOH gave poor yields (entries 5 and 6). Switching base from K_2CO_3 to Cs_2CO_3, K_3PO_4, or Na_2CO_3 also provided **7a** with relatively low yields (entries 7–9), indicating that the base played an important role for this reaction. Moreover, heating the reaction mixture was found to be able to shorten the reaction time although the reaction yield was not improved (entry 10). Accordingly, we carried out the reaction at 50 °C in the subsequent studies.

The optimized reaction conditions[16] were tested by varying *o*-bromobenzylamines and β-keto esters and the results are summarized in Table 2. Two substituted *o*-bromobenzylamines worked well to give **7b** and **7c** in good yields (entries 1 and 2), indicating that variation at the aromatic ring is possible. Changing substituents of alkyne moiety had little influence to the reaction process, as evident from that 1,2-dihydroisoquinolines **7d**–**g** were obtained in 52–74% yields (entries 3–6). Next, we explored the possibility to vary the N-substituents, and were pleased to observe that several other alkyl groups are suitable for this process (entries 7–10). However, switching methyl acetoacetate to methyl 3-oxohept-6-enoate gave the corresponding products **7k**–**n** with considerable lower yields (entries 11–13). In case of ethyl 3-oxo-3-phenylpropanoate as a substrate, no desired product was isolated (entry 14). These results could be rationalized by steric effect of the β-keto esters.

In conclusion, we have developed a cascade coupling/condensation process to polysubstituted 1,2-dihydroisoquinolines. The starting material could be easily assembled via a CuI-catalyzed three-component reaction of 2-bromobenzaldehydes, 1-alkynes, and primary amines. This advantage allows elaboration of functionalized 1,2-dihydroisoquinolines in a convenient manner.

Acknowledgments

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References and notes

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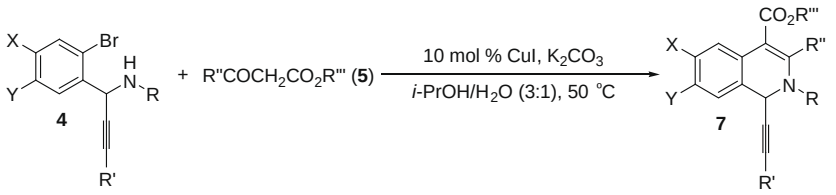
Table 2
Synthesis of polysubstituted 1,2-dihydroisoquinolines via a CuI-catalyzed cascade process[a]



Entry	X	Y	R	R′	R″	R‴	Yield (%) of **7**[b]
1	H	OMe	Allyl	C_6H_5	Me	Me	**7b** (59)
2	Me	H	Allyl	C_6H_5	Me	Me	**7c** (70)
3	H	H	Allyl	4-MeC_6H_4	Me	Me	**7d** (60)
4	H	H	Allyl	4-MeOC_6H_4	Me	Me	**7e** (52)
5	H	OMe	Allyl	4-MeC_6H_4	Me	Me	**7f** (74)
6	Me	H	Allyl	4-MeOC_6H_4	Me	Me	**7g** (65)
7	H	H	*n*-Bu	C_6H_5	Me	Me	**7h** (68)
8	H	H	*n*-Bu	4-MeOC_6H_4	Me	Me	**7i** (64)
9	H	H	C_3H_6OTBS	C_6H_5	Me	Me	**7j** (70)
10	H	H	Bn	C_6H_5	Me	Me	**7k** (39)
11	H	H	Allyl	4-MeC_6H_4	But-3-enyl	Me	**7l** (43)
12	H	OMe	Allyl	C_6H_5	But-3-enyl	Me	**7m** (37)
13	H	H	Allyl	C_6H_5	But-3-enyl	Me	**7n** (39)
14	H	H	Allyl	C_6H_5	Ph	Et	—

[a] Reaction conditions: **4** (0.5 mmol), β-keto ester (1.0 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), *i*-PrOH (1.8 mL), water (0.6 mL), 50 °C.
[b] Isolated yield.

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16. *Typical procedure for copper-catalyzed cascade process*: An oven-dried Schlenk tube was charged with CuI (0.05 mmol), potassium carbonate (1.5 mmol), and 1-(2-bromophenyl)-propargylamine **4a** (0.5 mmol). The tube was evacuated and backfilled with argon, methyl acetoacetate **5a** (1.0 mmol) was added into the tube followed by *i*-PrOH–H_2O (3:1, 2.4 mL). The reaction mixture was stirred at 50 °C. After 12 h, the mixture was cooled, then partitioned between ethyl acetate and brine. The organic layer was isolated, and the water phase was extracted with ethyl acetate. The assembled organic phase was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **7a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.83 (s, 3H), 4.14 (dd, J = 5.7, 16.8 Hz, 1H), 4.23 (dd, J = 4.5, 16.8 Hz, 1H), 5.23–5.32 (m, 2H), 5.33 (s, 1H), 5.84–5.96 (m, 1H), 7.12–7.18 (m, 2H), 7.23–7.28 (m, 4H), 7.35–7.38 (m, 2H), 7.67 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.96, 51.15, 52.47, 53.91, 85.26, 87.08, 102.87, 117.97, 122.87, 124.06, 124.88, 125.22, 127.08, 128.08, 128.43 (2*C), 128.62, 131.86, 132.10 (2*C), 133.72, 152.67, 169.29; ESI-MS m/z 344.1 $(M+H)^+$, 365.9 $(M+Na)^+$; EI-HRMS cacld for $C_{23}H_{21}NO_2$ $(M)^+$ requires 343.1572, found 343.1578.