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Assembly of Isoquinolines via CuI-Catalyzed Coupling of β-Keto Esters and 2-Halobenzylamines

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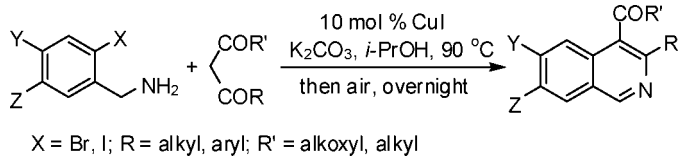
ABSTRACT



X = Br, I; R = alkyl, aryl; R' = alkoxyl, alkyl

CuI-catalyzed coupling of 2-halobenzylamines with β-keto esters or 1,3-diketones in *i*-PrOH under the action of K_2CO_3 produced 1,2-dihydroisoquinolines as the coupling/condensative cyclization products, which underwent smooth dehydrogenation under air atmosphere to afford substituted isoquinolines.

Isoquinoline ring systems have been found in numerous natural alkaloids that display a wide range of biological activities.[1] Common approaches to assemble these ring systems are highly dependent on Bischeler−Napieralski,[2] Pictet−Spengler,[3] or Pomeranz−Fritsch reactions.[4] They normally require harsh conditions (in the presence of strong acid), which prevent the elaboration of some sensitive isoquinolines. Consequently, considerable effort has been devoted to the assembly of substituted isoquinolines by employing metal-catalyzed reactions. Initial studies were carried out by Widdowson,[5] Pfeffer,[6] and Heck.[7] They found that substituted isoquinolines could be obtained via annulation of internal alkynes by cyclopalladated *N*-*tert*-butylarylaldimines,[5] cyclopalladated *N*,*N*-dimethylbenzylamine complexes,[6] or cyclopalladated *N*-*tert*-butylbenzaldimine tetrafluoroborates, respectively.[7] However, these syntheses suffered from the use of stoichiometric amounts of palladium salts, which prompted Larock and co-workers to explore a catalytic approach. They achieved this goal using the *tert*-butyl imine

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of 2-iodobenzaldehyde and internal alkynes as annulation substrates.[8] Subsequently a series of methods for preparing substituted isoquinolines based on palladium-catalyzed reactions were reported.[9] Recently, Cheng and co-workers reported that the annulation of 2-iodobenzaldimines with alkynes to substituted isoquinolines could be catalyzed by a relatively inexpensive nickel complex.[10] One major drawback for these catalytic processes is the use of phosphine ligands, which severely complicate product purification. Additionally, for some unsymmetrical alkynes poor regioselectivities were observed.

A recent advance in Ullmann-type reactions provided the opportunity for the development of new methodologies to assemble heterocycles.[11–15] Taking advantage of the mild conditions applied in amino acid-promoted Ullmann-type reactions, our group has recently established some cascade processes for the elaboration of heterocycles, which include benzofurans,[12] benzimidazoles,[13] benzimidazole-2-ones,[14] and substituted indoles.[15] Continuing our efforts in this area, we became interested in the coupling reaction of 2-bromobenzylamine (**1**) with β-keto esters and 1,3-diketones. We envisioned that, if the copper-catalyzed coupling between aryl bromides and these activated methylene compounds proceeded smoothly, the resulting coupling products **3** would undergo an intramolecular condensation followed by dehydration to afford 1,2-dihydroisoquinolines **5**, which should be easily oxidized to 3,4-disubstituted isoquinolines **6** (Scheme 1).

With this idea in mind, we investigated the reaction of 2-bromobenzylamine (**1**) and ethyl acetoacetate under the catalysis of 10 mol % CuI and 20 mol % L-proline at 60 °C in dioxane. After the scheduled reaction time a mixture of dihydroisoquinoline **5a** and isoquinoline **6a** was detected, indicating that the reaction took place in the desired manner. The formation of **6a** demonstrated that dehydrogenation of **5a** might occur spontaneously under air atmosphere. To prove this assumption we stirred the coupling mixture under air overnight and found that only **6a** was isolated in 48% yield (Table 1, entry 1). Considering that the poor yield most probably resulted from incomplete conversion in the coupling step, we next tried to optimize the conditions for this step to improve the overall transformation. Switching the ligand to *N*,*N*-dimethylglycine or omitting the ligand both gave similar results (entries 1−3), which illustrated that the ligand might be unnecessary for this process. This result is consistent with our previous report on the synthesis of benzofurans.[12] Increasing the reaction temperature gave a higher yield (entry 4), while further improvement was achieved by using *i*-PrOH as solvent (entry 5). Other solvents like THF, DMSO, or DMF gave worse results (entries 6−8). We were pleased to find that **6a** was obtained in 88% yield (entry 9) after decreasing the amount of K_2CO_3 from 4 equiv to 3 equiv. Under the same conditions, other bases such as K_3PO_4 or Cs_2CO_3 provided lower yields (entries 10 and 11).

These optimized reaction conditions were applied to a variety of aryl halides and activated methylene compounds; the results are summarized in Table 2. Ethyl propionylacetate worked well to provide the corresponding isoquinoline in 90% yield (entry 1). However, ethyl isobutyrylacetate only gave 53% yield (entry 2), indicating that the steric bulk of

Scheme 1

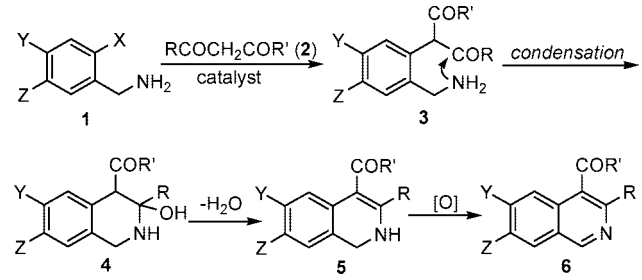
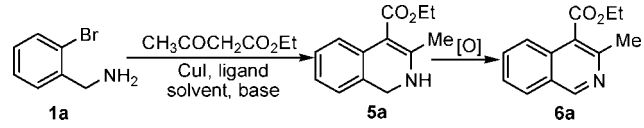


Table 1. Conditions Screened for the Coupling of 2-Bromobenzylamine (**1a**) with Ethyl Acetoacetate[a]



entry	ligand[b]	base	solvent	temp (°C)	yield (%)[c]
1	A	K_2CO_3	dioxane	60	48
2	B	K_2CO_3	dioxane	60	47
3	no	K_2CO_3	dioxane	60	51
4	no	K_2CO_3	dioxane	90	66
5	no	K_2CO_3	*i*-PrOH	90	76
6	no	K_2CO_3	THF	90	33
7	no	K_2CO_3	DMSO	90	50
8	no	K_2CO_3	DMF	90	36
9	no	K_2CO_3[d]	*i*-PrOH	90	88
10	no	K_3PO_4[d]	*i*-PrOH	90	54
11	no	Cs_2CO_3[d]	*i*-PrOH	90	42

[a] Reaction conditions: 2-bromobenzylamine (0.5 mmol), ethyl acetoacetate (1 mmol), CuI (0.05 mmol), ligand (0.1 mmol), base (2 mmol), *i*-PrOH (1.5 mL), 24 h, then stirring under air, rt, 12−24 h. [b] Ligand: A, L-proline; B, *N*,*N*-dimethylglycine. [c] Isolated yield for **6a**. [d] 1.5 mmol of base was used.

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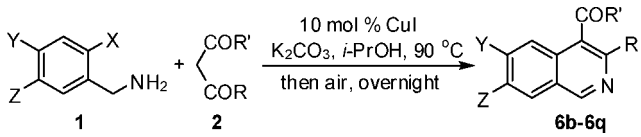
Table 2. Synthesis of Isoquinolines via CuI-Catalyzed Coupling of 2-Halobenzylamines with β-Keto Esters and 1,3-Diketones[a]



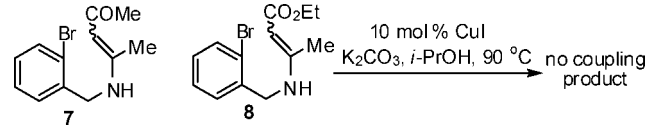
entry	X	Y	Z	R	R′	yield (%)[b]
1	Br	H	H	Et	OMe	90
2	Br	H	H	*i*-Pr	OMe	53
3	Br	H	H	But-3-enyl	OEt	80
4	Br	H	H	Bn	OMe	59
5	Br	H	H	Ph	OEt	74
6	Br	H	H	4-ClC_6H_4	OMe	51
7	Br	H	H	4-ClC_6H_4	OMe	73[c]
8	Br	H	H	4-$NO_2C_6H_4$	OEt	53
9	Br	H	H	4-$NO_2C_6H_4$	OEt	72[c]
10	Br	H	H	4-(EtCONH)-C_6H_4	OMe	79
11	Br	H	H	4-$MeOC_6H_4$	OMe	83
12	Br	H	OMe	Me	OEt	73
13	I	Cl	H	Me	OEt	76
14	Br	OCH_2O		Me	OMe	72
15	Br	OCH_2O		4-$MeOC_6H_4$	OMe	76
16	Br	H	H	$(CH_2)_3$		61
17	Br	H	H	$CH_2C(CH_3)_2CH_2$		51
18	Br	H	H	Me	Me	23

[a] Reaction conditions: aryl halide **1** (0.5 mmol), β-keto ester (1.0 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), *i*-PrOH (1.5 mL), 90 °C, 24 h, then stirring under air, rt, 12−24 h. [b] Isolated yield. [c] 2 mmol of β-keto ester was used.

the β-keto ester is unfavorable for the process. But-3-enyl, benzyl, and phenyl groups could be introduced in the 3-position of isoquinolines by choosing suitable β-keto esters (entries 3−5). When γ-(4-chlorophenyl)- or γ-(4-nitrophenyl)-substituted β-keto esters were used, the reaction yields were only moderate (entries 6 and 8). However, good yields were still observed when two γ-aryl-β-keto esters bearing electron-donating groups were employed (entries 10 and 11). These results demonstrated that the electronic nature of the aryl moiety has an influence on this transformation; an electron-rich aryl group can significantly enhance the nucleophilicity of the β-keto esters. Noteworthy is that satisfactory yields were obtained by increasing the amount of β-keto ester to 4 equiv for γ-aryl-β-keto esters bearing electron-withdrawing groups (entries 7 and 9).

Several substituted 2-halobenzylamines with both electron-donating and electron-withdrawing groups were compatible with the present process, providing polysubstituted isoquinolines in good yields (entries 12−15). Two cyclic 1,3-diketones also worked for this process, affording tricyclic compounds in moderate yields (entries 16 and 17). However, when acetoacetone was utilized the desired isoquinoline was isolated in only 23% yield (entry 18). The major side product was found to be imine **7** (Scheme 2) in this case. This phenomenon implied that first the coupling reaction must occur in an intermolecular manner as depicted in Scheme 1, but not go through the condensation/coupling process. Further evidence came from the fact that the CuI-catalyzed coupling reaction of imine **8** (formed by condensation of **1a** with ethyl acetoacetate at 60 °C) did not afford any coupling products.

Scheme 2



In conclusion, we have developed a CuI-catalyzed cascade process for the assembly of substituted isoquinolines from *o*-halobenzylamines and β-keto esters. A number of functional groups in both the benzylamine and the β-keto ester moieties are tolerated by the reaction conditions. Thus, our process provides a versatile access to substituted isoquinolines and a useful tool for the synthesis of biologically active molecules.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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