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Copper-catalyzed Meerwein carboarylation of alkenes with anilines to form 3-benzyl-3-alkyloxindole

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A simple and direct route for double C–C bond formation by copper-catalyzed Meerwein carboarylation process has been developed. In the presence of CuI (5 mol%), *tert*-butyl nitrite and anilines, a wide variety of *N*-arylacrylamides underwent tandem Meerwein arylation/C–H cyclization to produce pharmaceutically important 3-benzyl-3-alkyloxindole in moderate to good yield.

radical reaction, C–H cyclization, Meerwein arylation, oxindole, copper-catalyzed

1 Introduction

The clean and uncomplicated construction of multiple C–X (X = carbon and heteroatom) bonds in a cascade process is a continuing topic of interest for organic chemists [1]. In this regard, the Meerwein arylation of alkenes with aryl diazonium salts has gained increasing attention in recent years [2]. In these transformations, the alkyl radicals derived from oxidative addition of aryl radicals onto alkenes would trap various nucleophilic ions or groups to provide C–X (X = N [3], O [4], S [5], CN [6], CF_3 [7], etc.) bond and C–C bond in a single step. On the other hand, direct C–C formation by coupling a aryl radical generated from aryl diazonium salts with an aromatic C(sp^2)–H bond has been achieved recently which has gained increasing importance [8]. Therefore, we envisaged that a twofold C–C bond formed by the coupling of alkyl radical generated from addition of aryl radical onto alkene with an intermolecular aromatic C(sp^2)–H bond is possible in the Meerwein arylation of alkenes (Figure 1). However, such a protocol has, to the best of our knowledge, rarely met success except for a newly reported reaction using expensive $[Ru(bpy)_3]Cl_2$ catalyst under light irradiation [9]. Use of inexpensive and abundant metal complexes such as copper and iron instead of Ru for this coupling reaction is still in great demand. In addition, given the simplicity of preparation and handling as well as easy availability of starting material, the anilines; the transformations using aryl diazonium salts by *in situ* diazotization of anilines with alkyl nitrite are undoubtedly of huge concern [7, 10]. In this paper, we want to demonstrate a direct pathway for copper-catalyzed carboarylation of alkenes with anilines by a tandem Meerwein arylation/C–H cyclization process to construct 3,3-disubstituted oxindoles. More importantly, the 3,3-disubstituted oxindoles are common structural motifs in pharmaceutical agents and natural products (Figure 2), and their synthesis have attained increasing attention [11]. It is to be noted that significant progress has currently been achieved in the construction of these scaffolds through radical difunctionalization of *N*-arylacrylamides [12]. However,

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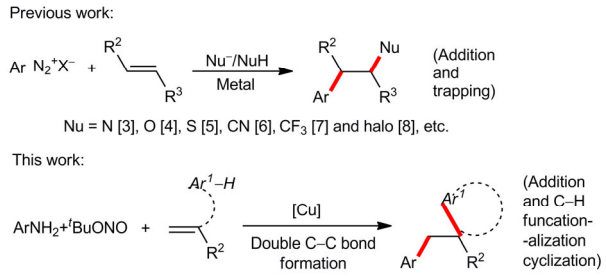


Figure 1 Meerwein arylation of alkenes.

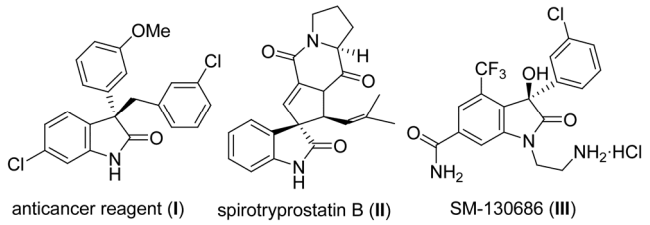


Figure 2 Several bioactive compounds containing the 3,3-disubstituted oxindole skeleton.

the reaction conditions are usually unfavourable owing to the use of expensive metal catalyst, elevated temperature and excess oxidant. Therefore, the development of practically feasible copper-catalyzed carboarylation of *N*-arylacrylamides with anilines to furnish 3-benzyl-3-alkyloxindoles under mild conditions is still of great interest, providing an alternative pathway to construct the family of 3,3-disubstituted oxindoles.

2 Experimental

2.1 Materials and methods

All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ: 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Column chromatographical purifications were performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) and *n*-hexane/ethyl acetate combination was used as the eluent. Commercially available starting materials and solvents were purchased and used without any further purification. *N*-arylacrylamides were prepared according to previously published procedures [11e].

2.2 Synthesis of 3,3-disubstituted oxindoles

To a mixture of *N*-arylacrylamide (**1**, 0.3 mmol), aniline (**2**, 3–4 equiv.), CuI (5 mol%) in CH_3CN (2 mL) was added ^{t}BuONO (3–4 equiv.) dropwise at 55 °C, and then the resulting solution was stirred 5 h. The solvent was evaporated under reduced pressure and the resulted mixture was filtered through a Florisil pad, diluted with Et_2O, and washed with water and brine successively. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to obtain the desired 3,3-disubstituted oxindoles.

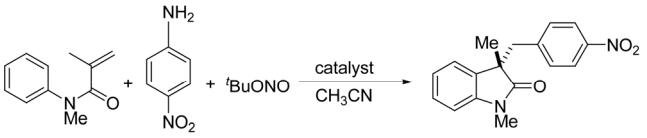
The characterizations of compounds **3a**–3**v** were shown in the Supporting Information online.

3 Results and discussion

In the course of our research project aiming at the production of 3,3-disubstituted oxindoles by carboarylation of alkenes with anilines, the reaction between *N*-methyl-*N*-phenylacrylamide **1a** and 4-nitroaniline **2a** was employed as the model reaction whose conditions were alsooptimized (Table 1). In the initial experiment it was observed that, even in absence of any catalyst the above mentioned reaction yielded as much as 26% of the desired cyclization product **3a** (Table 1, entry 1). On the basis of the preceding result, a number of metallic salts (e.g. Cu, Fe, Mn, Co, Ag) were subsequently used as the initiator for enhancing the yield (entries 2–12) [2b]. Among them, the copper iodine was found to be the most effective, producing **3a** with a yield of 75%. It was seen that decrease of CuI loading retarded the reaction to some extend (entry 14). Sequential screening of solvents revealed CH_3CN to be the best suited. The effect of temperature was investigated, and a lower temperature retarded the reaction to some extend (entry 20). *i*-AmONO instead of ^{t}BuONO gave an inferior yield (entry 18).

After optimization of the reaction conditions, the scope of *N*-arylacrylamides in the carboarylation reaction using 4-nitroaniline **2a** as aryl diazonium source was investigated (Table 2). Initial screening revealed that *N*-substituents of acrylamides have obvious effect on the reaction. For example, *N*-arylarylamides with a methyl or ethyl group on the N-atom were found to be well compatible with the reaction conditions, whereas unprotected *N*-arylacrylamide (R^2 = H) was less efficient in the cyclization as a consequence of getting easily decomposed under the reaction conditions (**3c**). Next, the substitution effect on the *N*-aryl moiety in the reaction was examined. Remarkably, a wide array of substituents, Me, MeO, Cl, Br, CN and F, at the 4-, 3- or 2-position of the aromatic ring displayed good reactivity [13], and the reactive order was: poor electron-withdrawing group and electron donating > strong-withdrawing groups, which was in consensus with the previous reports [12c]. Interesting, the halo groups, such as Cl, Br and F group were intact in the C–H functionalization process, thereby

Table 1 Screening of reaction conditions [a]

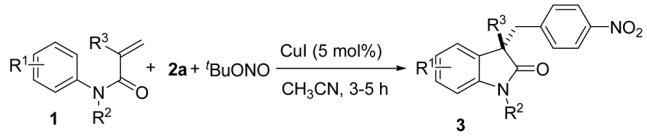


1a 2a 3a

Enrty	Metal (mol%)	Ratio (**1a**:**2a**:^{t}BuONO)	Solvent	Yield (%) [b]
1	none	1:3:3	CH_3CN	26
2	CuCl (5)	1:3:3	CH_3CN	56
3	CuBr (5)	1:3.3	CH_3CN	62
4	CuI (5)	1:3:3	CH_3CN	75
5	CuCN	1:3:3	CH_3CN	23
6	Cu	1:3:3	CH_3CN	19
7	$FeSO_4{\cdot}7H_2O$ (5)	1:3:3	CH_3CN	68
8	$FeCl_2{\cdot}7H_2O$	1:3:3	CH_3CN	57
9	$Fe(NH_4)_2(SO_4)_2{\cdot}6H_2O$	1:3:3	CH_3CN	71
10	$Mn(Oac)_2{\cdot}4H_2O$ (5)	1:3:3	CH_3CN	36
11	$CoCl_3.6H_2O$ (5)	1:3:3	CH_3CN	37
12	$AgNO_4$	1:3:3	CH_3CN	32
13	CuI (2)	1:3:3	CH_3CN	59
14	CuI (5)	1:3:3	toluene	4
15	CuI (5)	1:3:3	EtOAc	35
16	CuI (5)	1:3:3	EtOH	46
17 [c]	CuI (5)	1:3:3	CH_3CN	41
18 [d]	CuI (5)	1:3:3	CH_3CN	<10

a) Reaction conditions: **1a** (0.3 mmol), **2a** (2–4 equiv.), ^{t}BuONO (2–4 equiv.), initiator (5–10 mol%), and solvent (2 mL) at 55 °C for 5 h. ^{t}BuONO = *tert*-butyl nitrite, *i*-AmONO = isoamyl nitrite; b) yield of the isolated product; c) 30 °C; d) *i*-AmONO instead of ^{t}BuONO.

Table 2 Scope of *N*-arylacrylamines [a]



1 3

Enrty	$R^1/R^2/R^3$	Product	Yield (%) [b]
1	H/Me/Me	**3a**	81 [c]
2	H/Et/Me	**3b**	71
3	H/H/Me	**3c**	< 5
4	*p*-Cl/Et/Me	**3d**	75
5	*p*-F/Et/Me	**3e**	71
6	*p*-OMe/Et/Me	**3f**	45
7	*p*-Me/Et/Me	**3g**	51
8	*p*-CN/Et/Me	**3h**	43
9	*o*-Br/Et/Me	**3i**	72
10	2-methyl-4-chloro/Et/Me	**3j**	39
11	*o*-OMe/Me/Me	**3k**	< 5
12	3-pyridyl/Me/Me	**3l**	55
13	H/Me/Ph	**3m**	41
14	H/Me/CH_2OH	**3n**	42
15	H/Me/CH_2OOAc	**3o**	61
16	H/Me/H	**3p**	< 5

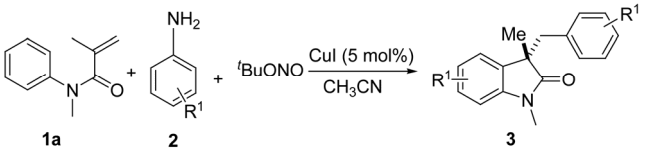
a) Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), ^{t}BuONO (0.9 mmol), CuI (5 mol%), and CH_3CN (2 mL) at 55 °C for 5 h; b) yield was given for isolated product after column chromatography; c) Run on a 3 mmol scale.

facilitating additional modifications at halogenated positions. However, low yield or only trace amount of product was obtained for the *ortho*-substituted *N*-arylacrylamide. The results might attribute to steric hindrance of *ortho*-substituent. Expectedly, the pyridyl ring was observed to be perfectly stable under the optimal conditions, providing the desired oxindoles **3m** in a yield of 58%. Sequential investigations revealed that several groups, Ph, CH_2OH, CH_2OAc at the 2-position of the acrylamide moiety were compatible to the optimal conditions for producing **3m**, **3n** and **3o**, respectively, whereas *mono*-substituted olefin (R^3 = H) was inert for the carboarylation process.

The scope of anilines in the presence of *N*-methyl-*N*-phenylacrylamide **2a**, CuI and ^{t}BuONO was explored (Table 3). It was noteworthy to find that, the carboarylation process was compatible with various other anilines bearing different substituents on the aromatic ring, such as Cl, F, Br, OEt, MeO. Interesting, 4-fluoroaniline gave a higher yield when the reaction was conducted in the absence of initiator CuI. Sequentially, it was found that 3-aminopyridine was suitable aryl diazonium source, and underwent the C–H cyclization smoothly to introduce a pyridyl mioety into desired oxindole. With this, the generality of C–H cyclization protocol was examined.

To elucidate the mechanism of this tandem Meerwein arylation/C(sp^2)–H cyclization process, the inter- and intramolecular kinetic isotope control experiments were performed as shown in Scheme 1, where little kinetic isotope effect ($k_{H/D}$ = 1.0) was observed, suggesting the compatibility of C–H functionalization cyclization step with either the SEAr mechanism or the free radical mechanism [14]. Notably, the free radical mechanism was supported by the control experiment: a stoichiometric amount of TEMPO (4 equiv.), a well-known radical inhibitor, was used in the reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with 4-nitroaniline (**2a**) and CuI, and the formation of the desired disubstituted oxindole was suppressed considerably.

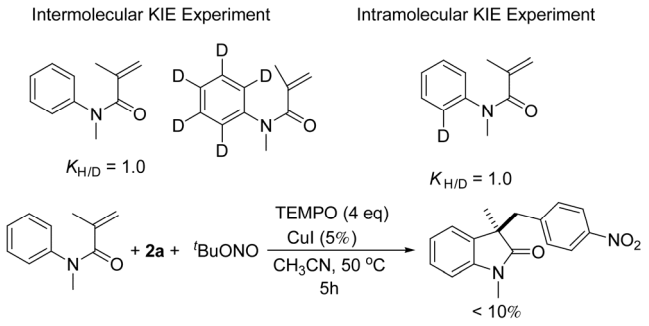
Table 3 Scope of anilines [a]



1a 2 3

Enrty	R^1	Product	Yield (%) [b]
1	*p*-Cl	**3q**	51
2 [c]	*p*-F	**3r**	43
3	*o*-Br	**3s**	55
4	*p*-OEt	**3t**	43
5	*o*-OMe	**3u**	58
6	3-pyridyl	**3v**	53

a) Reaction conditions: **1** (0.3 mmol), **2** (1.2 mmol), ^{t}BuONO (1.2 mmol), CuI (5 mol%), and CH_3CN (2 mL) at 55 °C for 5 h; b) yield was given for isolated product after column chromatography; c) in the absence of CuI.

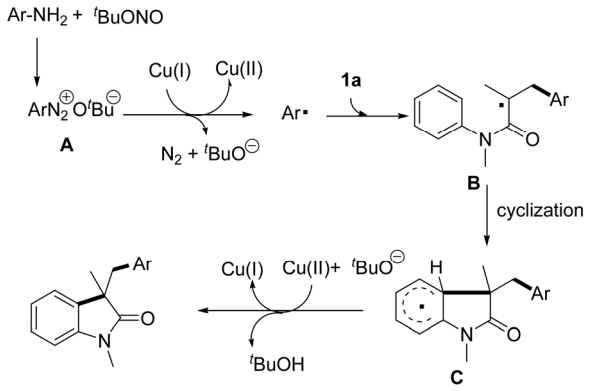


Scheme 1 Control experiments on carboarylation of alkenes with anilines.

Consequently, a possible mechanism was proposed as outlined in Scheme 2 for this carboarylation process of *N*-arylacrylamides on the basis of the preceding results and previously reported mechanism [2–8, 10–12]. Firstly, *in situ* diazotization of aryl amines with ^{t}BuONO generated aryl diazonium salt **A**. In the presence of CuI, the resulted diazonium alcoholate easily decomposed to give aryl radical [15], which was followed by its addition onto the carbon-carbon double bond of *N*-methyl-*N*-phenylacrylamide (**1a**) to yield an alkyl radical **B**. Intramolecular cyclization of intermediate **B** with a aryl ring formed radical intermediate **C**, proceeded by abstraction of an aryl hydrogen in radical intermediate **C** to yield the desired 3-benzyl-3-alkyloxindoles.

4 Conclusions

In summary, we have demonstrated a copper-catalyzed carboarylation reaction of alkenes and anilines via a radical C–H cyclization to produce pharmaceutically important 3,3-disubstituted oxindole scaffold. Notably, this protocol proceeds through a radical process and eliminates the requirement of expensive metal catalyst, excess of oxidant, and elevated temperature. Importantly, it provides an alternative pathway for the synthesis of pharmaceutical interest 3-benzyl-3-alkyloxindole through a direct and practical process. The detailed mechanism and the application of the novel reaction for more complex targets are currently being explored in our laboratory.



Scheme 2 Proposed mechanism process for carboarylation of alkenes with anilines.

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13 The configuration and structures of the products **3e** were unambiguously assigned by X-ray analysis. See Figure S3 in Supporting Information.

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