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Carbonylative Coupling of *N*-Chloroamines with Alcohols: Synthesis of Esterification Reagents

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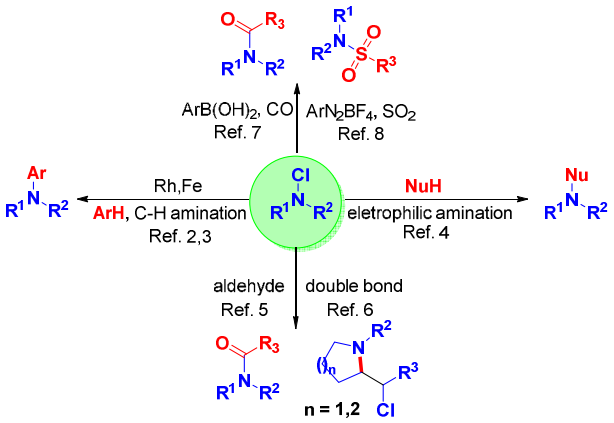
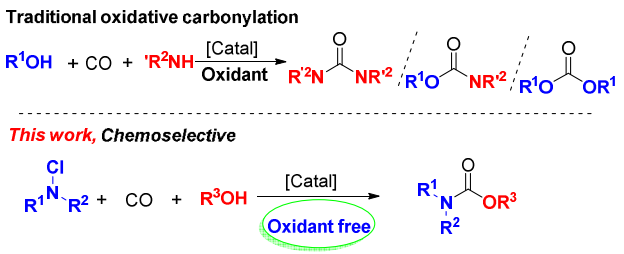
ABSTRACT: Herein we report a new method for the carbonylative synthesis of carbamates. Started from *N*-chloroamines and alcohols, with copper or Pd/C as the catalyst, the corresponding carbamates were produced in moderate to good yields. No additional oxidant or base is needed in this system. Notably, the produced benzotriazole-carboxylates can be used as esterification reagent.

The chemistry of *N*-chloroamines recently has attracted a great deal of attention, since it is an important building block for the synthesis of different nitrogen containing compounds (Scheme 1).[1] For example, the research groups led by Glorius and Yu reported a rhodium catalyzed intermolecular C-H amination reaction of arenes with *N*-chloroamines, independently.[2] In 2014, Nakamura's group developed the *ortho*-amination of aromatic carboxamides in the presence of an iron/diphosphine catalyst.[3] Besides, electrophilic amination catalyzed by nickel, copper or cobalt was also reported by Jarvo's, Murakami's and Gosmini's groups respectively, which gives an efficient method for the construction of carbon-nitrogen bonds.[4] Furthermore, nitrogen radical generated from *N*-chloroamines can react with different functional groups such as, aldehyde[5] or intramolecular double bond[6] were also reported. Our group studied the carbonylative coupling of aryl boronic acids with *N*-chloroamines as well.[7a,7b] Benzamides can be produced in an efficient manner. Simandi's group reported a palladium-catalyzed carbonylation of alkali metal salts of *N*-chloroarylsulfonamides with R'XH (X=O, S, NR') to give arylsulfonylcarbamic acid esters, thioesters, and amides.[7c] Very recently J. Wu and co-workers reported a copper catalyzed coupling reaction of aryl diazonium salts, SO_2 and *N*-chloroamines to produce aromatic sulfonamides.[8]



Scheme 1. *N*-Chloroamines based organic reactions.

On the other hand, oxidative carbonylation reactions are an efficient method to produce various carbonyl derivative products from two nucleophiles.[9] Generally, besides catalysts and additives, the process is consisted by two nucleophiles and an oxidant. Concerning the oxidants, organic compounds or inorganic salts, including benzoquinone (BQ), potassium persulfate ($K_2S_2O_8$), copper and silver salts, and air or oxygen are commonly applied. However, the selectivity of oxidative carbonylation reactions usually is problematic, especially when the two nucleophiles are different. Therefore, it is interesting to continual to develop new and selective oxidative carbonylation procedures. Among the various possibilities, *N*-chloroamine is an ideal choice which can be used as both the substrate and oxidant. In this manner, a selective carbonylation procedure without additional oxidant can be established (Scheme 2).



Scheme 2. Oxidative carbonylation reactions.

The reaction was initially performed using 1-chloro-1*H*-benzo[*d*][1,2,3]triazole **1a** as the model substrate to establish the reaction conditions. The first reaction was conducted

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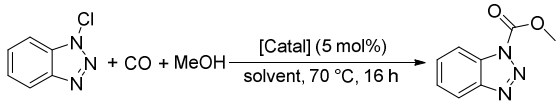
with **1a** (2.0 equiv.) and methanol (1.0 equiv.) in CH_3CN in the presence of $CuCl_2$ (5 mol%) under 50 bar CO pressure at 70 °C. To our delight, the reaction yielded 13% of the desired product (Table 1, entry 1). Then different catalysts were screened, the yield was increased to 64% when bromo(1,10-phenanthroline)(triphenylphosphine)copper(I) was applied as the catalyst (Table 1, entry 8). In the testing with $Fe_2(CO)_8$ and Pd/C (Table 1, entries 5-7), 68% of the desired product can be produced with Pd/C and tetra-*N*-butylammonium bromide (TBAB) as the catalytic system (Table 1, entry 7). Based on our previous experience with *N*-chloroamines,[7] the addition of base might can improve the reaction outcome. We therefore added 1 equivalent of base in the reaction mixture. However, only trace product was detected in the GC (Table 1, entries 9 and 10) which suggests that *N*-chloroamines might be unstable under basic conditions.[10] Finally, the yield was improved to 85% (Table 1, entry 11; 80% isolated yield) when CuCl(iPr) (5 mol%) [(iPr)CuCl = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) chloride] was utilized as the catalyst for this reaction. Reducing the loading of catalyst or **1a**, decreasing the yield to 76% and 56% respectively (Table 1, entries 12-13). Alternative solvents, including THF, DMF, toluene, DCE and H_2O were tested subsequently (Table 1, entries 14-18), all of these solvents are inferior to CH_3CN. The reaction efficiency slightly dropped with lower temperature or CO pressure (Table 1, entries 19-20). The final optimized conditions were found to be: CuCl(iPr) (5 mol%) at 70 °C which gave **2a** in 80 % isolated yield (Table 1, entry 11).

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

Entry	Catalysts	Solvent	Yield[b]
1	$CuCl_2$	MeCN	13%
2	CuI	MeCN	30%
3	$Cu(OAc)_2$	MeCN	12%
4	Cu(TC)	MeCN	14%
5	$Fe_2(CO)_8$	MeCN	14%
6	Pd/C	MeCN	52%
7	Pd/C, TBAB (5 mol%)	MeCN	68%
8	$CuBr(PPh_3)$(1,10-Phen)	MeCN	64%
9	$CuBr(PPh_3)$(1,10-Phen)	MeCN	Trace[c]
10	$CuBr(PPh_3)$(1,10-Phen)	MeCN	7%[d]
11	**[(iPr)CuCl]**	MeCN	**85%** **80%[e]**
12	[(iPr)CuCl]	MeCN	76%[f]
13	[(iPr)CuCl]	MeCN	56%[g]
14	[(iPr)CuCl]	THF	0%
15	[(iPr)CuCl]	DMF	trace
16	[(iPr)CuCl]	Toluene	15%
17	[(iPr)CuCl]	DCE	31%
18	[(iPr)CuCl]	H_2O	0%
19	[(iPr)CuCl]	MeCN	79%[h]
20	[(iPr)CuCl]	MeCN	80%[i]

[a] Reaction scale: catalyst (5 mol%), 1 mmol **1a** (2 eq.), 0.5 mmol MeOH, 50 bar CO, solvent (1.0 mL), 70 °C, 16 hours. [b] GC yields were determined by using hexadecane as the internal standard. [c] 1.0 eq $NaHCO_3$ was added. [d] 1.0 eq pyridine was added. [e] Isolated yield. [f] [(iPr)CuCl] (2.5 mol%). [g] 1.5 eq **1a** instead of 2.0 eq **1a**. [h] 30 bar CO. [i] 60 °C. [(iPr)CuCl] = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) chloride. THF = Tetrahydrofuran. DMF = dimethylformamide. DCE = 1,2-dichloroethane.

Having determined the best conditions, we next examined the scope of this reaction with a range of alcohols and *N*-chloroamines. As show in Table 2, we first examined the substrate of alcohols with 1-chloro-1*H*-benzo[*d*][1,2,3]triazole **1a**. Various benzotriazole-carboxylates were formed in moderate to good yields. A series of alcohols including ethanol, butanol and 3-phenylpropanol were well tolerated under the optimal conditions (Table 2, entries 2, 3 and 6). Remarkably, cyclobutylmethanol and cyclohexylmethanol were also successfully delivered the desired products in 55% and 68% yield, respectively (Table 2, entries 8 and 9). Benzyl alcohol and secondary alcohol were failed to generate the desired product as they are easier to be oxidized (Table 2, entries 10 and 11).

Table 2. Scope of alcohols and *N*-chloroamines.[a]

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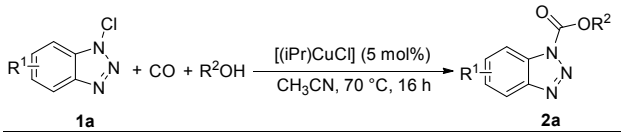


1a 2a

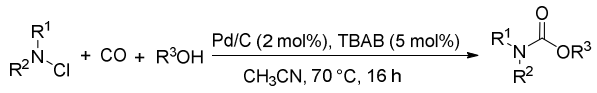
Entry	Substrate	Product	Yield
1 2 3	1a + ROH	2a	2a R = Me 80% 2b R = Et 79% 2c R = n-Bu 72%
4	1a + HO	2d	73%
5	1a + HO Ph	2e	67%
6	1a + $C_6H_5(CH_2)_3OH$	2f	83%
7	1a + $C_6H_5(CH_2)_4OH$	2g	66%
8	1a + HO	2h	55%
9	1a + HO	2i	68%
10	1a + HO Ph	2j	0%
11	1a + HO Ph	2k	0%
12	1b / 1b' + MeOH	2l / 2l'	70%
13	1c / 1c' + MeOH	2m / 2m'	77%

[a] Reaction scale: **1a-1c** (1.0 mmol, 153 mg), [(iPr)CuCl] (5 mmol%, 12 mg), R^2OH (0.5 mmol), 50 bar CO, solvent (2.0 mL), 70 °C, 16 hours, isolated yield.

Furthermore, various 1-chloro-1*H*-benzo[*d*][1,2,3]triazole bearing halogen substitutes on the aromatic rings engaged in this reaction efficiently,[11] potentially providing a synthetic handle for further synthetic modifications (Table 2, entries 12 and 13). Here the mixture of two products is due to the substrates were prepared as a difficult to separate mixture and were used directly.

Additionally, other types of secondary *N*-chloroamines were also tested. As shown in Table 3, various *N*-chloroamine substrates were synthesized according to the reported procedure and reacted smoothly.[12] It is noteworthy that Pd/C is a more efficient catalyst in this reaction compared with copper catalyst (45% yield of product under the above conditions). Various carbamate products were obtained in moderate to good yields. In addition, except for methanol, other alcohols, such as 3-phenylpropanol and 2,2,2-trifluoroethanol were also participated successfully, leading to the desired products in moderate yields (Table 3, entries 3-5).

Table 3 Scope of *N*-chloroamines.[a]



Entry	Substrate	Product	Yield
1	1d + MeOH	2n	60%
2	1e + MeOH	2o	53%
3[b]	1f + $C_6H_5(CH_2)_3OH$	2p	66%
4[b]	1g + $C_6H_5(CH_2)_3OH$	2q	49%
5	1d + CF_3CH_2OH	2r	56%

[a] Reaction scale: Pd/C (2 mol%, 21.2 mg), TBAB (5 mol%, 16.3 mg), **1d**, **1e** (1.0 mmol), R^3OH (10 mmol), 50 bar CO, MeCN (2.0 mL), 70 °C, 16 hours, isolated yield. [b] Pd/C (2 mol%, 21.2 mg), TBAB (5 mol%, 16.3 mg), **1f, 1g** (1.0 mmol), ROH (2 mmol), 50 bar CO, MeCN (2.0 mL), 70 °C, 16 hours. TBAB = tetra-*N*-butylammonium bromide.

Next, we turned our attention to investigate the application of our produced benzotriazole-carboxylates. According to the literature reported by Cava and co-workers, they used their prepared 1*H*-benzo[*d*][1,2,3]triazole-1-carbonitrile as a cyanation reagent to react with arylacetonitrile anions to give the corresponding arylmalonitriles products.[13] Therefore, we hypothesize that our benzotriazole-carboxylates can be used as an alkoxycarbonylation reagent (esterification reagent) as well. Delightfully, after using **2a** to react with phenylacetonitrile in the LDA/THF condition, the desired product methyl (*S*)-2-cyano-2-phenylacetate was formed in 74% yield

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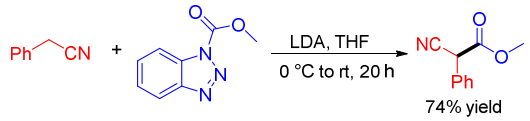
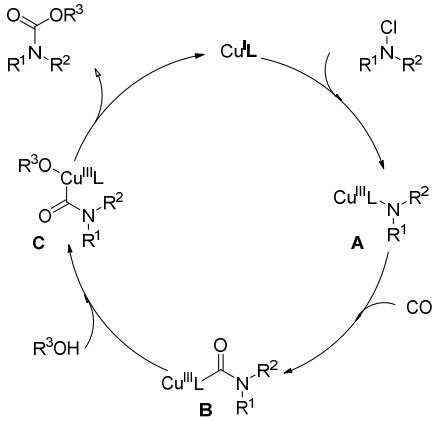
(Scheme 3). This method definitely will afford a new choice for the synthesis of medical and natural products related ester containing compound by later stage functionalization.



Scheme 3. Synthetic application.

Based on previous reports,[2-8] a possible reaction mechanism is proposed (Scheme 4). Firstly, dialkylaminyl copper **A** is generated by oxidative addition from the *N*-choro dialkylamine to the Cu(I). Under high pressure of carbon monoxide, CO is inserted into the dialkylaminyl copper intermediate to form carbamoyl copper **B**, which undergoes X ligand transfer with alcohols to form the product-releasing intermediate **C**. Then intermediate **C** affords the final carbamate products after reductive elimination while the active Cu(I) species is regenerated for the next catalytic cycle.



Scheme 4. Proposed mechanism.

In conclusion, a novel and versatile protocol for carbonylative transformation of *N*-chloroamines with alcohols have been developed. With copper or palladium on carbon as the catalysts, various benzotriazole-carboxylates and carbamates were produced in moderate to good yields with excellent functional group tolerance. Notably, the obtained products can be applied as an esterification reagent.

Conflict of interest
The authors declare no conflict of interest.

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