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Copper-catalyzed formylation of alkenyl C-H bonds using BrCHCl₂ as a stoichiometric formylating reagent†

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The first example of copper-catalyzed direct formylation of alkenyl C-H bonds for the facile synthesis of α,β -unsaturated aldehydes has been developed. This transformation has demonstrated high reactivity, mild reaction conditions and a broad substrate scope. BrCHCl2 is expected to be developed as an efficient stoichiometric C1 building block in organic synthesis.

Introduction

Developing novel methods for the synthesis of complex molecules in an efficient and expeditious manner still remains a major challenge in organic synthesis. Accordingly, many novel strategies for the quick construction of complex molecular skeletons have been developed and used for the total synthesis of complex compounds. 1,2 Among all of these strategies, domino reactions are emerging as efficient reactions in the facile synthesis of key intermediates. Of significant interest are cascade reactions that provide access to fundamental building blocks in a chemoselective manner from readily available starting materials in a step-economical fashion.3 As a key material used in cascade transformations, especially in organocatalyzed domino reactions, α,β-unsaturated aldehydes have been used in a broad range of unconventional transformations to make complex molecules or key intermediates.4 Thus, considerable efforts have been devoted to developing novel methods for the facile synthesis of α,β -unsaturated aldehydes from readily available simple raw materials in efficient and quick ways.5

As they are produced on a large scale industrially and have served as an important feedstock for the petrochemical industry, simple alkenes have long been realized as one of the most widely used raw materials for a great variety of organic transformations.6 The direct formylation of simple alkenes thus offers the most economical and efficient method for the facile construction of α,β-unsaturated aldehydes (Scheme 1). Indeed, the Vilsmeier-Haack reaction has long been developed as a useful approach to introduce a formyl group into alkenes.7 On the other hand, using the Grubbs II catalyst as the radical initiator succeeded in the atom transfer radical addition (ATRA) of styrene, which afforded alkenyl aldehyde via the subsequent elimination of

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hydrochloric acid under strong acid conditions or a stoichiometric amount of silver salts at high temperature.8 Apart from this interesting progress, both known methods still suffer from a limited scope of alkenes and the requirement for a large amount of poisonous reagents (POCl₃ as a precursor of the Vilsmeier reagent or CHCl3 as the solvent), which have definitely hampered their practical application in organic synthesis. Herein, we report a novel copper-catalyzed formylation of alkenyl C-H bonds for the facile synthesis of α,β-unsaturated aldehydes, in which high reactivity, mild conditions and a broad substrate scope have been demonstrated. The key to success is the use of commercially available BrCHCl2 as a stoichiometric formylating reagent instead of CHCl3, which is normally used as a solvent in such reactions. Alkenyl aldehydes were then furnished by the bifunctionalization of alkenes via a carbocation process and subsequent dehydration.

Results and discussion

Our initial investigation commenced with 4-methoxystyrene (1a) as the model substrate, and bromodichloromethane as the

a) Vilsmeier-Haack reaction

$$R^{1}$$
 H $DMF, POCl_{3}$ R^{2} CHO

b) Ru-catalyzed ATRA followed by elimination of HCI (only one example)

c) This work: Copper-catalyzed formylation of alkenes

$$\begin{array}{c|c}
R^2 \\
R^1 \\
\hline
R^3 \\
\hline
R^3 \\
\hline
Carbocation process
\end{array}$$

$$\begin{bmatrix}
CCI_2H \\
R^2 \\
R^3
\end{bmatrix}$$

$$\begin{bmatrix}
CCI_2H \\
R^3
\end{bmatrix}$$

$$\begin{bmatrix}
R^2 \\
R^3
\end{bmatrix}$$

$$\begin{bmatrix}
R^3 \\
R^3
\end{bmatrix}$$

$$\begin{bmatrix}
R^3 \\
R^3
\end{bmatrix}$$

Scheme 1 Facile synthesis of α,β -unsaturated aldehydes from alkenes

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stoichiometric formylating reagent in the presence of a catalytic amount of a copper catalyst (10 mol%) and 1.0 equiv. of PMDTA (1,1,4,7,7-pentamethyl-diethylenetriamine) in CH₃CN at 40 °C (Table 1). Unfortunately, none of the desired product 2a was obtained when CuBr was used as the catalyst. Considering that halogen atom exchange may improve the reactivity of CHBrCl₂, to our delight, the addition of 1.0 equiv. of KI into the reaction system afforded 2a successfully, albeit with a relatively low yield (23%, entry 2). A careful examination of copper catalysts was next performed, which indicated that Cu(OH)2 gave the best result with a 31% yield (entry 4). Meanwhile, further investigation into various solvents gave no improvement in yield and CH₃CN was still the best choice. When a trace amount of the bifunctionalized alcohol 2aa was isolated as a byproduct, it was conjectured that water acted as the hydroxyl source for this bifunctional reaction. As we expected, up to a 28% yield of 2aa was obtained along with a 24% yield of 2a when water was used directly as the solvent. To further improve the yield, co-solvents were investigated and CH₃CN/H₂O (1/1) gave the dichloromethylated alcohol 2aa in 74% vield along with the aldehyde 2a in 7% yield. After a simple work-up without purification and further dehydration with T3P, 2a was finally furnished in 80% yield (entry 8). Considering the key role that PMDTA played in this transformation,10 other bases were also screened instead of PMDTA, but they did not give the desired product 2a (Table 1, entries 11-13). Notably, by the replacement of KI with NaI, the

Table 1 Copper-catalyzed formylation of 4-methoxystyrene: optimization of conditions^a

Entry	[Cu]	Solvent(v/v)	Base	2a/2aa yield (%) ^b
1 ^c	CuBr	CH ₃ CN	PMDTA	0
2	CuBr	CH_3CN	PMDTA	23/2
3	CuO	CH_3CN	PMDTA	0
4	$Cu(OH)_2$	CH_3CN	PMDTA	31/2
5	$Cu(OH)_2$	THF	PMDTA	0
6	$Cu(OH)_2$	H_2O	PMDTA	24/28
7	$Cu(OH)_2$	DMSO	PMDTA	5/57
8	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	PMDTA	$7/74(80)^d$
9	$Cu(OH)_2$	$CH_3CN/DMSO(4:1)$	PMDTA	8/72
10	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	_	0
11	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	Et_3N	0
12	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	TMEDA	0
13	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	DMEDA	0
14^e	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	PMDTA	$10/72(82)^d$
15^f	$Cu(OH)_2$	$CH_3CN/H_2O(1:1)$	PMDTA	$9/85(90)^d$

^a Reaction conditions: 1a (0.2 mmol, 1.0 equiv.), CHBrCl₂ (3.0 equiv.), Cu catalyst (10 mol%), PMDTA (1.0 equiv.) and KI (1.0 equiv.) in $\rm CH_3CN$ (1 mL) at 40 °C for 24 h. b Isolated yield by 1 H NMR analysis. ^c KI was not added. ^d The mixture of **2a/2aa** was dehydrated by T3P (1-propanephosphonic acid cyclic anhydride, 50% in ethyl acetate). The yield in the parentheses was the isolated yield of 2a. e TBAI was used instead of KI. f NaI was used instead of KI. PMDTA: 1,1,4,7,7pentamethyl-diethylenetriamine.

yield of 2a was further improved to 90% after this two-step formylation of 4-methoxystyrene (entry 15). Finally, control experiments indicated that none of the desired product was obtained without the addition of a copper catalyst or base (for details, see the ESI†).

With the optimized conditions in hand, we next investigated the scope of the alkene (Table 2). Initially, the study of the substituent effect on the aryl rings of the styrene derivatives showed that both electron-donating groups, such as 4-methoxy, 4-phenoxy, 4-methyl and 4-methylthio (1a-d), and weak electron-withdrawing groups, such as fluorine, chlorine and

Table 2 Substrate scope^a

^a General conditions: 1 (0.2 mmol), Cu(OH)₂ (10 mol%), CHBrCl₂ (3.0 equiv.), PMDTA (1.0 equiv.) and NaI (1.0 equiv.) in CH₃CN/H₂O (v/v = 1:1, 1 mL) at 40 °C for 24 h, then dehydration with T3P (3.0 equiv.) in ÉtOAc at 100 °C; for 2x-y, 1 (0.2 mmol), Cu(hfacac)₂·xH₂O (10 mol%), CHBrCl₂ (3.0 equiv.), PMDTA (1.0 equiv.) and KI (1.0 equiv.) in CH₃CN (1 mL) at 80 °C for 24 h, and aldehydes 2x-y were obtained directly. Isolated yields are reported. 80 °C.

bromine (1f-h), were all compatible with this catalytic system and were able to furnish the desired products in moderate to high yields. Not surprisingly, the substrates with electron-withdrawing groups installed on the aryl rings typically gave lower yields and required relatively high reaction temperatures (2f-h). Meanwhile, a variety of styrene derivatives with *ortho*-and *meta*- as well as *para*-substituents were smoothly formylated to afford the corresponding α,β -unsaturated aldehydes 2i-k in acceptable yields.

The ortho-chloro- and meta-methyl-substituted styrenes (1g and 1k, respectively), styrene (1e) and 2-vinylnaphthalene (1l) also required a much higher temperature and gave moderate yields. Although the ortho- and meta-methoxystyrene (1i and 1j, respectively) did not need high temperatures, the yields of the reactions were only moderate. Of interest to us was that heteroarene-derived styrene substrates, including 2-vinylthiophene 1p and 3-vinylbenzothiophene 1q, were also well-tolerated in this novel transformation with synthetically useful yields (2p, 63%; 2q, 75%). Just as expected, 1,1-diphenylethenes 1r-t normally worked as better radical trappers than styrene, and generated tri-substituted unsaturated aldehydes 2r-t in relatively high yields (Table 2, 2r-t). Of note was that the formylation of tri-substituted internal styrene 1u also proceeded smoothly to give the corresponding tetra-substituted vinyl aldehyde with a fairly good yield (2u, 83%). Importantly, the subjection of 1,2-dihydronaphthalene 1v to the optimized conditions resulted in the successful formylation of a C-H bond that was part of the cyclic double bond system. It was also noteworthy that the conjugated alkene 1w underwent the reaction efficiently, with an acceptable yield (2w, 50%) and a good E/Z selectivity (8:1). To our satisfaction, N-vinyl substrates could also be directly formylated at the end of terminal alkenes to afford β-aminoacrylaldehydes in moderate yields, by simply altering the conditions to a combination of $Cu(hfacac)_2 \cdot xH_2O$, KI and CH₃CN.14

To gain some insights into the mechanism of this transformation, a series of control experiments were then performed accordingly (Scheme 2). First, the reaction was completely quenched when 1.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the standard conditions. Meanwhile, the addition of 1.0 equivalent of butylated hydroxytoluene (BHT) to the standard conditions afforded the corresponding dichloromethyl adduct 3 in 58% yield. Both results indicated that this transformation may proceed *via* a radical path. To further test this theory, the well known radical clock 1-(1-cyclopropylvinyl)-4-methoxybenzene 4 was synthesized and added into this catalytic system, furnishing the ring-opened product 5 in 65% yield, strengthening the hypothesis of the dichloromethyl radical ('CCl₂H) being involved in the catalytic cycle.

As alcohol **2aa** was isolated as the key intermediate along with the vinyl aldehyde **2a** in the model reaction (eqn (4), Scheme 2), it was suggested that a carbocation process was possibly involved in the catalytic cycle. Indeed, the replacement of H_2O with methanol as the cation scavenger afforded the corresponding bifunctional product **2ab** in 72% yield, which further strengthened this possibility.¹¹

Scheme 2 Mechanistic studies. a For details of the isolation of 2aa, see the ESI. †

On the basis of our preliminary results and previous reports, 12 a plausible mechanism involving a 'CHCl2 radical is proposed as shown in Scheme 3. The copper salt is reduced to generate a low-valent Cu complex, which can transfer a single electron to CHBrCl2 and then produce the free radical compound 'CHCl2 (B), and the radical subsequently reacts with the styrene. The 'CHCl₂ addition-compound **D** can be oxidized by a high-valent Cu complex to the cationic intermediate E. Finally, the high-valent Cu complex is reduced to a low-valent Cu complex to complete the catalytic cycle. There are two possible pathways for the sequential transformation of cation E to vinyl aldehyde F: Path a, which consists of deprotonation to regenerate the C=C bond, and F is obtained by the subsequent hydrolysis of the dichloromethyl group to the aldehyde; or Path b, where the cation E is captured by H₂O to give the alcohol intermediate G, followed by dehydration with T3P and subsequent hydrolysis of the dichloromethyl group to afford F.13

To demonstrate the synthetic potential of this transformation, we applied this two-step transformation to the late-

Scheme 3 Proposed mechanism.

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Scheme 4 Formylation of the estrone derivative 6.

stage formylation of complex biologically active molecules. As shown in Scheme 4, the estrone-derived aryl alkene 6, which was synthesized from estrone in two steps, was transformed to the desired vinyl aldehyde 7 in a 50% yield. This outcome clearly showed the great potential of this methodology as a facile strategy for the synthesis of various analogues or intermediates in drug discovery and screening.

Conclusions

In summary, we have developed a novel copper-catalyzed formylation of alkenyl C–H bonds for the facile synthesis of α,β -unsaturated aldehydes. This transformation has demonstrated high reactivity, mild conditions and a broad substrate scope. An important point is that commercially available BrCHCl₂ was used as a stoichiometric formylating reagent instead of CHCl₃. Mechanistic studies indicated that alkenyl aldehydes were furnished by bifunctionalization of alkenes \emph{via} a carbocation process and subsequent dehydration. Further applications of this method for the modification of bioactive molecules and the use of BrCHCl₂ as an interesting C1 building block in organic synthesis are still underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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