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A novel construction of acetamides from rhodium-catalyzed aminocarbonylation of DMC with nitro compounds†

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Dimethyl carbonate (DMC), an environment-friendly compound prepared from CO_2, shows diverse reactivities. In this communication, an efficient procedure using DMC as both a C1 building block and solvent in the aminocarbonylation reaction with nitro compounds has been developed. $W(CO)_6$ acts both a CO source and a reductant here.

Dimethyl carbonate (DMC) is a non-toxic and biodegradable compound, which is well-known as a green solvent in organic synthesis.[1] Many methods have been explored for the preparation of DMC during these years,[2] and one of the most significant and attractive strategies is using CO_2 as a feedstock,[3] by insertion of CO_2 into oxirane and then reaction with methanol. Meanwhile, DMC plays an important role as a versatile and appealing reactant in industry and fine chemistry for multiple applications. DMC can act as a methoxycarbonylating and methylating reagent with various nucleophiles.[4] Generally, diazomethane, methyl iodide, methyl tosylate, methyl triflate, and dimethyl sulfate are commonly used methylation reagents. Most of them suffer from several disadvantages such as being explosive, toxic/corrosive, expensive and so on. Besides, in these methylation reactions, a stoichiometric amount of base is usually required, affording the corresponding inorganic salts that have some disposal issues. In this perspective, DMC could be used as a safe and environmentally benign alternative without special cautions for conventional toxic dimethyl sulfate and expensive methyl iodide.[5,6] It does not produce undesired inorganic salts compared to methylation with dimethyl sulfate or methyl iodide.

On the other hand, since the pioneering work of Heck and co-workers,[7] the transition-metal-catalyzed carbonylation reaction experienced impressive progress during the last few decades, and has drawn much attention in both academic and industrial fields.[8] This reaction has been extensively applied as one of the most powerful and direct protocols for the production of carbonyl-containing compounds. The model case is the Monsanto process for the industrial manufacturing of acetic acid, an efficient rhodium-catalyzed carbonylation reaction of methanol.[9] In this process, HI is used as a cocatalyst that usually causes some serious equipment corrosion problem. Recently, Han, Liu and their co-workers demonstrated a new route for carbonylative synthesis of aryl acetates from aryl methyl ethers catalyzed by $RhCl_3$ in the presence of LiI and $LiBF_4$.[10] Moreover, the investigation of a new protocol for the construction of carbonyl-containing compounds is highly desired. In our continuous study of DMC in the transition-metal-catalyzed carbonylation reactions,[11] we herein wish to describe the first example based on the use of DMC as both a *C*1 building block and solvent in the rhodium-catalyzed aminocarbonylation reaction for the synthesis of acetamides with abundant and more stable nitro compounds as a nitrogen surrogate. To our knowledge, nitro compounds combined with DMC as a carbon coupling partner in the aminocarbonylation reaction remain unexplored. The integration of DMC in rhodium-catalyzed aminocarbonylation reactions would open a novel and sustainable pathway for the construction of acetamides.

To probe the catalytic system of DMC with nitro compounds, nitrobenzene was used as an initial substrate for establishing this aminocarbonylation reaction (Table 1). The reaction was performed in DMC with $Rh_2(CO)_4Cl_2$ as catalyst, DPPP as a ligand, NaI as an additive, $Mo(CO)_6$ as the CO source, and Na_3PO_4 as base in the presence of H_2O at 120 °C for 24 h. To our delight, the desired acetamide product **2b** was obtained in 75% yield (Table 1, entry 1). We next studied the catalyst effects, and the use of $Rh_2(OAc)_4$ and $[Cp^*RhCl_2]_2$ afforded acetamide in lower yields (Table 1, entries 2 and 3). However, compared to rhodium catalysts, $Pd(OAc)_2$ and $Ni(OTf)_2$ had very low efficiency on this catalytic system, only a trace amount of the target product

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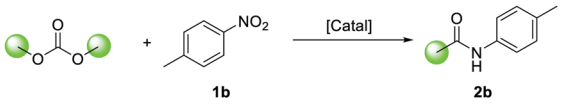
Table 1 Screening of reaction conditions[a]

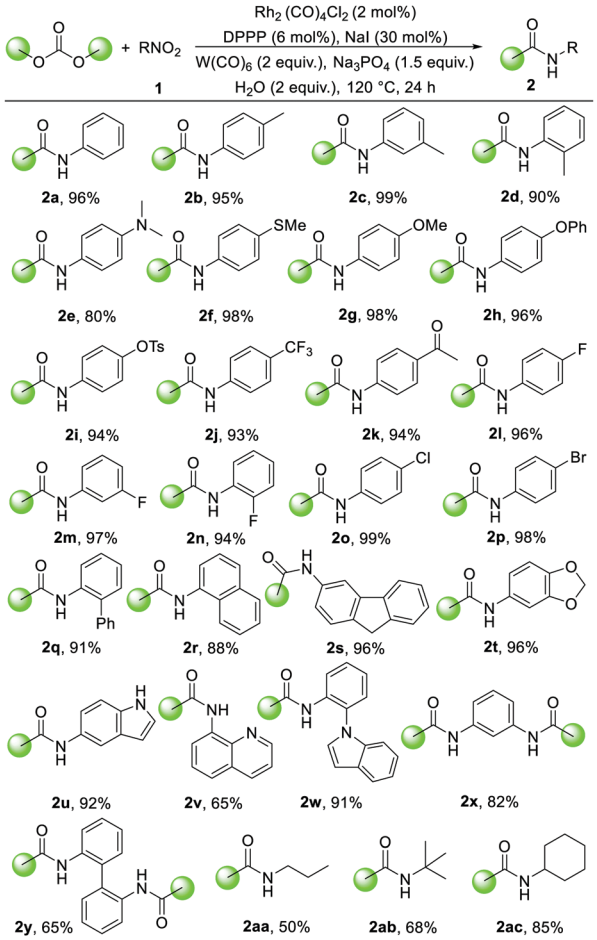


Entry	Catalyst (mol%)	DPPP (mol%)	Base (equiv.)	NaI (mol%)	Yield (%)
1	$Rh_2(CO)_4Cl_2$ (5)	10	Na_3PO_4 (1)	30	75
2	$Rh_2(OAc)_4$ (5)	10	Na_3PO_4 (1)	30	70
3	$[Cp^*RhCl_2]_2$ (5)	10	Na_3PO_4 (1)	30	55
4	$Pd(OAc)_2$ (10)	10	Na_3PO_4 (1)	30	<1
5	$Ni(OTf)_2$ (10)	10	Na_3PO_4 (1)	30	<1
6	$Rh_2(CO)_4Cl_2$ (5)	15	Na_3PO_4 (1)	30	80
7	$Rh_2(CO)_4Cl_2$ (5)	20	Na_3PO_4 (1)	30	70
8	$Rh_2(CO)_4Cl_2$ (5)	15	K_3PO_4 (1)	30	<1
9	$Rh_2(CO)_4Cl_2$ (5)	15	Na_2HPO_4 (1)	30	20
10	$Rh_2(CO)_4Cl_2$ (5)	15	Na_3PO_4 (1.5)	30	85
11	$Rh_2(CO)_4Cl_2$ (5)	15	Na_3PO_4 (2)	30	84
12	$Rh_2(CO)_4Cl_2$ (5)	15	Na_3PO_4 (1.5)	0	0
13	$Rh_2(CO)_4Cl_2$ (5)	15	Na_3PO_4 (1.5)	20	75
14	$Rh_2(CO)_4Cl_2$ (5)	15	Na_3PO_4 (1.5)	50	84
15	$Rh_2(CO)_4Cl_2$ (2)	6	Na_3PO_4 (1.5)	30	78
16[b]	$Rh_2(CO)_4Cl_2$ (2)	6	Na_3PO_4 (1.5)	30	81
17[c]	$Rh_2(CO)_4Cl_2$ (2)	6	Na_3PO_4 (1.5)	30	89
18[d]	$Rh_2(CO)_4Cl_2$ (2)	6	Na_3PO_4 (1.5)	30	96

[a] Reaction conditions: nitrobenzene **1a** (0.5 mmol), DMC (1.5 mL), catalyst (5 mol%), DPPP (10 mol%), NaI (30 mol%), $Mo(CO)_6$ (1.5 equiv.), Na_3PO_4 (1 equiv.), H_2O (1 equiv.), 120 °C, 24 h. GC yield, with hexadecane as the internal standard. [b] H_2O (2 equiv.). [c] $W(CO)_6$ (1.5 equiv.). [d] $W(CO)_6$ (2 equiv.).

could be detected (Table 1, entries 4 and 5). Notably, a higher yield could be observed with 15 mol% of DPPP (Table 1, entry 6), while when using 20 mol% of DPPP, the yield dropped (Table 1, entry 7). Next, different bases were checked, resulting in product **2a** in much lower yields when K_3PO_4 and Na_2HPO_4 were employed as base (Table 1, entries 8 and 9). By increasing the amount of Na_3PO_4 to 1.5 and 2 equivalents, the corresponding product was produced in 85% and 84% yields (Table 1, entries 10 and 11). Remarkably, NaI played an important role in this aminocarbonylation system, and a methyl iodide molecule could be detected in GC, suggesting that DMC might transform into CH_3I with the assistance of NaI. However, no aminocarbonylation reaction occurred in the absence of NaI (Table 1, entry 12). Further screening showed that 30 mol% of NaI seemed to be the best (Table 1, entries 10 *vs.* 13 and 14). Subsequently, when the catalyst loading was decreased to 2 mol% along with 6 mol% of DPPP, a slightly lower yield of **2b** was obtained (Table 1, entry 15). Considering the price of rhodium catalysts, 2 mol% loading was further employed, and a better result was achieved by using 2 equivalents of H_2O (Table 1, entry 16). Finally, it should be mentioned that the CO surrogate affected the yield significantly; **2b** with 89% and 96% yield was formed by using $W(CO)_6$ as the CO source (Table 1, entries 17 and 18). And lower yield was obtained when CO gas (1 bar) was applied.

With the best reaction conditions in hand, we next turn our attention to the substrate scope of this aminocarbonylation reaction towards various nitro compounds. As illustrated in Scheme 1, a wide range of nitro compounds were tolerated well under the standard reaction conditions, and most of the

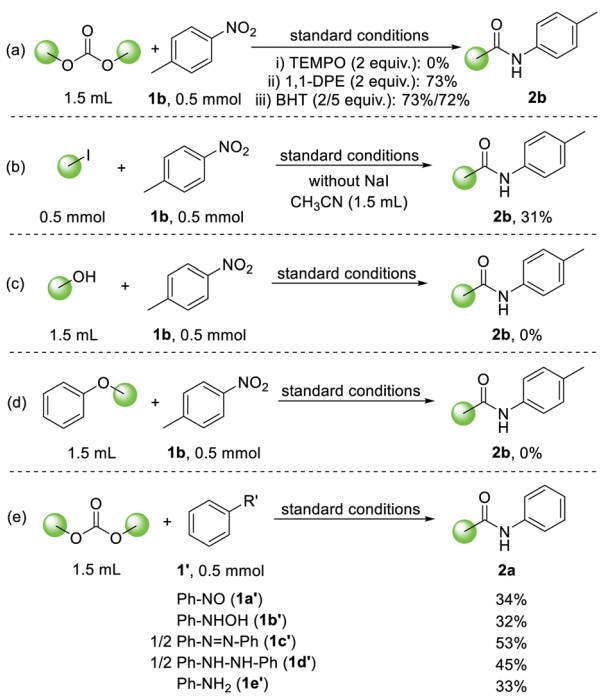


Scheme 1 Substrate scope of nitro compounds.[a] [a]Reaction conditions: nitro compounds (0.5 mmol), DMC (1.5 mL), $Rh_2(CO)_4Cl_2$ (2 mol%), DPPP (6 mol%), NaI (30 mol%), $W(CO)_6$ (2 equiv.), Na_3PO_4 (1.5 equiv.), H_2O (2 equiv.), 120 °C, 24 h. Isolated yield.

desired products were produced in more than 90% yields. Nitroarenes with electron-donating groups, including methyl, *N*,*N*-dimethyl, thiomethyl, methoxy, phenoxy, and tosylate groups afforded the acetamide products in good to excellent yields (**2b–2i**). Those substrates with *ortho*-substitution resulted in the product with lower yield compared to *para*- and *meta*-substitution probably due to the steric effects (**2d** *vs.* **2b**, **2c**). Electron-withdrawing groups such as trifluoro and acetyl groups were also well compatible in this aminocarbonylation reaction; the corresponding acetamides were successfully obtained in 93% and 94% yields (**2j** and **2k**). Moreover, nitroarenes with halo groups, involving fluoro, chloro, and bromo groups were well tolerated to provide the target products in excellent yields (**2l–2p**). 2-Nitro-1,1′-biphenyl, 1-nitronaphthalene, and 3-nitro-9*H*-fluorene substrates were further studied, and the desired amide products were isolated in 91%, 88%, and 96% yields (**2q–2s**). In addition, this catalytic system could work smoothly with heteroaryl groups, and the corresponding acetamides were obtained in good to excellent yields (**2t–2w**). Remarkably, substrates with two nitro groups, for examples, 1,3-dinitrobenzene and 2,2′-dinitro-1,1′-biphenyl, were still reactive,

delivering the diacetamide products in good yields (**2x** and **2y**). It is noteworthy that besides nitroarenes, aliphatic nitro compounds were shown to be suitable nitrogen sources as well. Those substrates with propyl, *tert*-butyl, and cyclic groups reacted smoothly with DMC and gave the acetamide products in moderate to high yields (**2aa–2ac**).

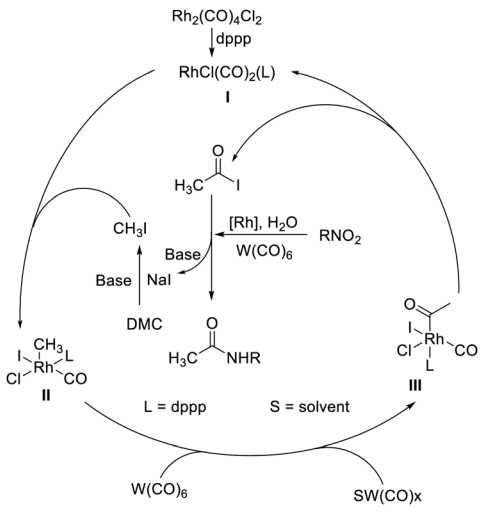
In order to gain more insight into the reaction mechanism for acetamide synthesis, several control experiments were conducted (Scheme 2). First, when TEMPO (2,2,6,6-tetramethylpiperidinooxy, 2 equiv.) was used as a radical scavenger under the standard reaction conditions, no target product **2b** could be observed (Scheme 2, eqn (a)). However, employing 1,1-DPE (1,1-diphenylethylene, 2 equiv.) and BHT (2,4-di-*tert*-butyl-4-methylphenol, 2/5 equiv.) as the radical-trapping reagents, the desired product **2b** was obtained in 73%, and 73%/72% yields (Scheme 2, eqn (a)), which indicate that a free radical pathway might not be involved. When methyl iodide and methanol were further treated with **1b** under the standard conditions, the final product **2b** was detected in 31% and 0% yield (Scheme 2, eqn (b) and (c)), suggesting that methyl iodide might be the key intermediate in this catalytic system. Here, it is important to note that methyl iodide can be detected in our optimization process when the yield of amide was low. When anisole was also used as a methyl source, no expected acetamide **2b** was produced (Scheme 2, eqn (d)). The reduction of nitro compounds can generate several nitrogen-containing intermediates.[12] To get more information about the nature of nitro compounds in this catalytic system, nitrosobenzene (**1a′**), *N*-phenyl hydroxylamine (**1b′**), azobenzene (**1c′**), 1,2-diphenyl hydrazine (**1d′**), and aniline (**1e′**) were reacted with DMC under the standard reaction conditions (Scheme 2, eqn (e)). The acetamide product **2a** was formed in 32–53% yields, which demonstrated that **1a′–1e′** are possible nitrogen intermediates in this aminocarbonylation reaction, and $W(CO)_6$ acts both a CO source and a reductant.



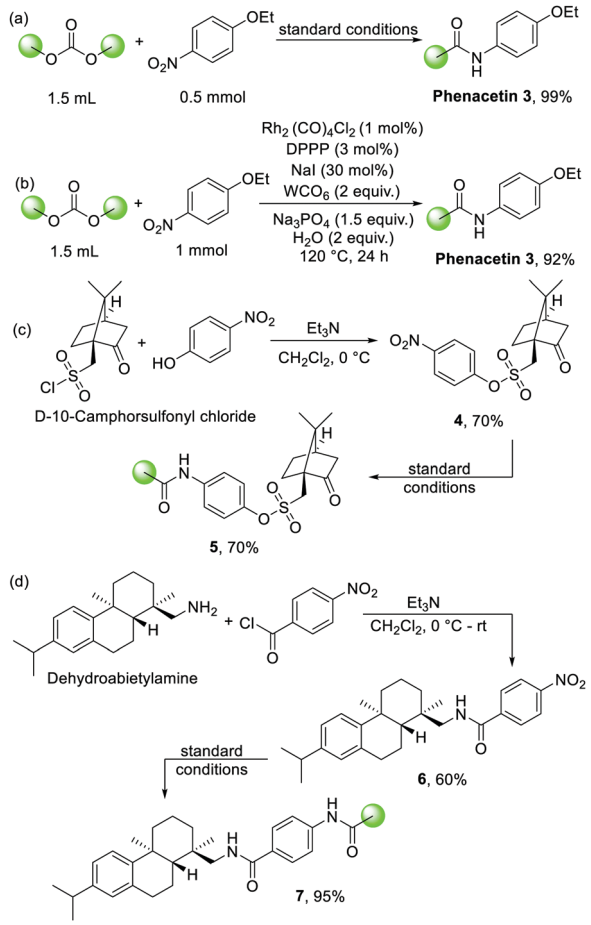
Scheme 2 Mechanistic studies.[a] [a]GC yields, with hexadecane as the internal standard.

Based on the above results and previous literature report,[9,10] a plausible reaction mechanism is proposed in Scheme 3. First, in the presence of a base, NaI will react with the soft electrophilic methyl group of DMC to give CH_3I, which further underwent an oxidative addition with $RhCl(CO)_2$(dppp) **I** to afford complex **II**, followed by the CO coordination and insertion to produce acetyl intermediate **III**. Acetyl iodide is then formed and the active rhodium species **I** will be released upon reductive elimination from complex **III**. Afterwards, a nucleophilic attack of amine (generated from nitro compounds) to the acetyl iodide molecule gave the final acetamide products.

To further reveal the potential utility of this aminocarbonylation protocol, an active pharmaceutical compound was synthesized. Under the standard reaction conditions, the non-steroidal anti-inflammatory drug Phenacetin was prepared in almost quantitative yield from the corresponding 1-ethoxy-4-nitrobenzene (Scheme 4, eqn (a)), which provides a new synthetic route for Phenacetin. Moreover, the reaction for Phenacetin synthesis in one mmol-scale catalyzed by lower loading of $Rh_2(CO)_4Cl_2$ (1 mol%) still worked very well to produce the Phenacetin product in 92% yield (Scheme 4, eqn (b)). Additionally, to extend the scope of this aminocarbonylation reaction, the late-stage modification of natural molecules was carried out. By using D-10-camphorsulfonyl chloride and dehydroabietylamine as starting materials, followed by the reaction with 4-nitrophenol and 4-nitrobenzoyl chloride, respectively; the resulting intermediates **4** and **6** reacted smoothly *via* the present pathway under standard reaction conditions to give the corresponding acetamide derivatives **5** and **7** in 70% and 95% isolated yields (Scheme 4, eqn (c) and (d)). These positive outcomes shed light on the potential application of this method in drug synthesis and discovery.



Scheme 3 Proposed reaction mechanism.



Scheme 4 Synthetic utility of the present protocol.[a] [a]Isolated yields.

In summary, a new route for the synthesis of acetamides has been developed *via* a general and practical rhodium-catalyzed aminocarbonylation reaction of DMC with nitro compounds. In this aminocarbonylative transformation, DMC acted as not only a *C*1 building block but also a reaction medium, whereas NaI served as a cocatalyst to promote the conversion of DMC to CH_3I. With $W(CO)_6$ as the CO source and reductant, a wide range of nitro compounds could be efficiently transferred to the corresponding acetamide derivatives in very good yields. Moreover, Phenacetin synthesis and last-stage modification of natural products were achieved *via* this aminocarbonylation strategy. This work provides a new synthetic pathway for the preparation of acetamides and highlights the application of DMC as both an active reagent and solvent in carbonyl-containing compound construction.

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Conflicts of interest

There are no conflicts to declare.

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