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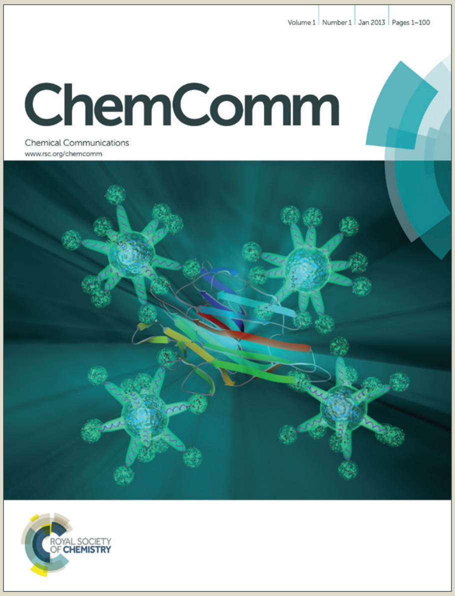

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Copper-catalyzed formal O-H insertion reaction of α-diazo-1,3-dicarbonyl compounds to carboxylic acids with the assistance of isocyanide

Zikun Wang,[a] Xihe Bi,[b] Yongjiu Liang,*[a] Peiqiu Liao,[b] Dewen Dong*[a]

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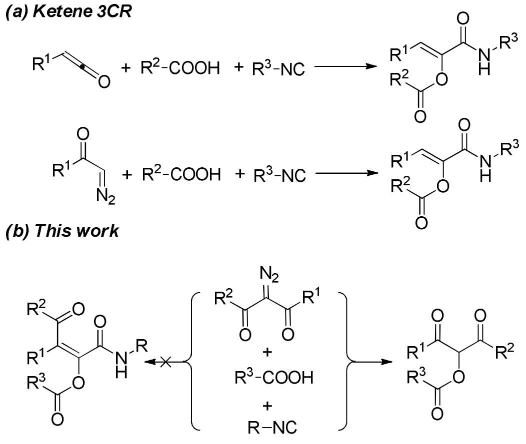
A novel copper-catalyzed formal O-H insertion of *α*-diazo-1,3-dicarbonyl compounds to carboxylic acids has been developed, providing a straightforward synthetic method for *α*-acyloxy-1,3-dicarbonyl compounds, in which the activation of carboxylic acids by isocyanide plays a crucial role.

α-Diazocarbonyl compounds have proved to be versatile precursors of carbenes under thermolytic, photolytic, or transition metal-promoted reaction conditions.[1] Owing to their ease of preparation and handling,[2] a diverse range of *α*-diazocarbonyl compounds have been employed in the cyclization,[3] ylide transformation,[4] the Wolff rearrangement [5] and X-H insertion (X = O, N, S, C or Si) [6] reactions for the synthesis of complex organic molecules.

Recently, Basso and co-workers developed a Passerini-like 3-component reaction of a carboxylic acid, an isocyanide and a ketene or an *α*-diazocarbonyl compound to access stereodefined captodative olefins, which was defined as K-3CR (Scheme 1).[7] During the course of our studies on the utilization of *α*-diazo-*β*-oxoamides in organic synthesis, we achieved the synthesis of 1,2,3-triazoles and pyrrol-3(2*H*)-ones in the presence of different catalysts.[8] It was worth noted that *α*-diazo-*β*-oxoamides could be transformed into ketene intermediates catalyzed by copper(II). Inspired by this finding, we envisaged that captodative olefins might be synthesized from *α*-diazo-*β*-oxoamides, isocyanides and carboxylic acids (Scheme 1). After a series of experiments, we found that a formal O-H insertion product of *α*-diazo-1,3-dicarbonyl compound to carboxylic acid instead of captodative olefin was obtained (Scheme 1).



Scheme 1 The isocyanide-based 3-component reactions.

α-Acyloxycarbonyl compounds as significant building blocks in synthetic organic chemistry are traditionally prepared by the substitution reaction of *α*-halodicarbonyl compounds with alkaline carboxylates,[9] the direct oxidative coupling of carbonyl compounds with acids mediated by hypervalent iodine reagents[10] or toxic heavy metal oxidants,[11] such as $Pb(OAc)_4$,[12] $Tl(OAc)_3$,[13] and $Mn(OAc)_3$,[14] or the formal O-H insertion reactions of *α*-diazocarbonyl compounds to carboxylic acids.[15] Among these methods, the latter has displayed outstanding advantages with regards to fabricating the *α*-acyloxycarbonyl compounds including (1) mild reaction conditions; (2) highly chemo-selectivity; (3) inexpensive and readily available starting materials. However, it is a challenge to synthesize the close related *α*-acyloxy-1,3-dicarbonyl scaffolds with this method due to the relative unstability of *α*-diazo-1,3-dicarbonyl compounds,[1,16] and expensive catalysts based on Pd or Rh are necessary to decompose the diazo group in most cases.[15g,h] In the present work, we wish to describe a straightforward procedure accessing to *α*-acyloxy-1,3-dicarbonyl compounds *via* copper-catalyzed formal O-H insertion reaction of *α*-diazo-1,3-dicarbonyl compounds to carboxylic acids with the assistance of isocyanide.

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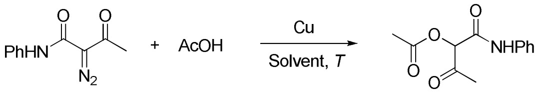
Table 1 Condition screening.[a]

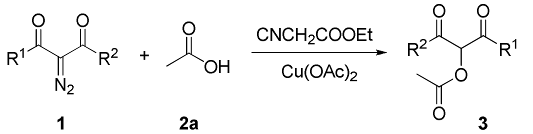


1a **2a** **3a**

Entry	Cu	Isocyanide (equiv.)	Solvent	*T* (°C)	Time (h)	Yield[b] (%)
1	$Cu(AcO)_2$	$CNCH_2Ts$ (1.0)	None	100	5	77
2	$Cu(AcO)_2$	none	None	100	10	N.R.
3	$Cu(AcO)_2$	$CNCH_2COOEt$ (1.0)	None	100	5	84
4	$\mathbf{Cu(AcO)_2}$	$\mathbf{CNCH_2COOEt}$ (0.5)	**None**	**100**	**5**	**83**
5	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.3)	None	100	5	71
6	$CuSO_4$	$CNCH_2COOEt$ (0.5)	None	100	6	46
7	$Cu(acac)_2$	$CNCH_2COOEt$ (0.5)	None	100	7	43
8	$CuBr_2$	$CNCH_2COOEt$ (0.5)	None	100	4	Unidentifed mixture
9	CuI	$CNCH_2COOEt$ (0.5)	None	100	4	Unidentifed mixture
10	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.5)	None	80	10	Trace
11[c]	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.5)	DMF	100	10	N.R.
12[c]	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.5)	Ethyl acetate	Reflux	10	N.R.

[a] Reagents and conditions: **1a** (1.0 mmol), **2a** (4.0 mL), copper salts (0.1 mmol). [b] Isolated yields. [c] AcOH (5.0 mmol) was added.

Table 2 Synthesis of α-acyoxycarbonyl compounds **3** from α-diazo-1,3-dicarbonyl compounds and acetic acid.[a]

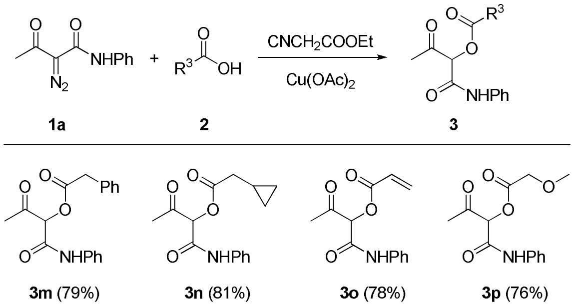


1 **2a** **3**

Entry	1	R^1	R^2	3	Yield[b]/%
1	**1b**	Me	$4\text{-}MeC_6H_4NH$	**3b**	82
2	**1c**	Me	$2\text{-}MeC_6H_4NH$	**3c**	77
3	**1d**	Me	$4\text{-}ClC_6H_4NH$	**3d**	81
4	**1e**	Me	$2\text{-}ClC_6H_4NH$	**3e**	79
5	**1f**	Me	$4\text{-}CF_3C_6H_4NH$	**3f**	75
6	**1g**	Me	$2,4\text{-}Me_2C_6H_3NH$	**3g**	73
7	**1h**	*n*-Pr	C_6H_5NH	**3h**	86
8	**1i**	Ph	C_6H_5NH	**3i**	78
9	**1j**	Me	OEt	**3j**	83
10	**1k**	Ph	OEt	**3k**	69
11	**1l**	Ph	Me	**3l**	74

[a] Reagents and conditions: **1** (1.0 mmol), **2a** (4.0 mL), $Cu(OAc)_2$ (0.1 mmol), ethyl isocyanoacetate (0.5 mmol), 100 °C, 4.0-5.0 h. [b] Isolated yields.

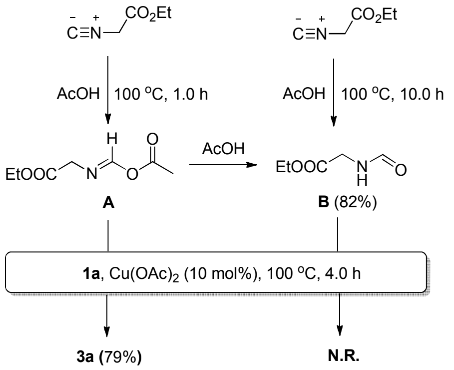
With the optimized conditions at hand, a series of reactions of *α*-diazo-*β*-oxoamides **1b-i** bearing varied alkyl and aryl groups R^1 and aryl amide groups R^2 with acetic acid were carried out. As shown in Table 2, all the reactions proceeded smoothly to afford the corresponding *α*-acyloxy carbonyl compounds **3b-3i** in good to high yields (entries 1-8). The synthetic efficiency was evaluated by performing *α*-diazo-*β*-dicarbonyls **1j**, **1k** and **1l** with ketone and ester groups (COR^2) and acetic acid under the identical conditions (entries 9-11). Next, we examined the reactions of miscellaneous carboxylic acids with *α*-diazo-*β*-oxoamide **1a**, and some of the results are summarized in Scheme 2. The *α*-acyloxy carbonyl compound synthesis was proved to be suitable for the saturated and unsaturated carboxylic acids.



[a] Reagents and conditions: **1a** (1.0 mmol), **2** (4.0 mL), $Cu(OAc)_2$ (0.1 mmol), ethyl isocyanoacetate (0.5 mmol), 100 °C, 4.0-5.0 h.

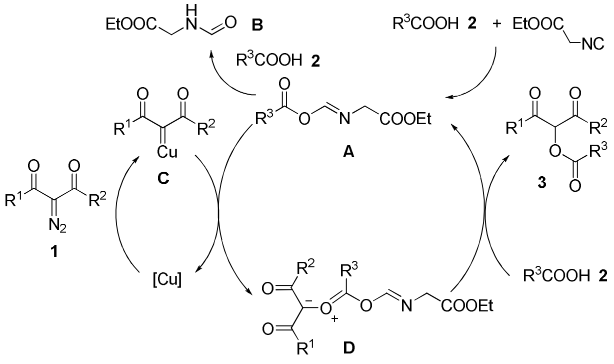
Scheme 2 The O-H insertion reactions of α-diazo-β-oxoamide **1a** with different carboxylic acids.

As previously mentioned, substrate **1a** failed to react with acetic acid in the absence of isocyanides, demonstrating that an isonitrilic specie is crucial for the success of the process. To further investigate the effect of isocyanides, some experiments were conducted. Firstly, 2-isocyanoacetate (0.5 mmol) and acetic acid (4.0 mL) was mixed under stirring and kept at 100 °C for 1.0 h. The H^1 NMR analysis of the resulting mixture indicated that ethyl isocyanoacetate was consumed, and an actively intermediate **A** seemed to be formed (Scheme 3). It was worth noting that **3a** could be obtained in 79% yield when **1a** (1.0 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) were added to the above mixture and stirred at 100 °C for 4.0 h. In another experiment, after the solution of ethyl isocyanoacetate (0.5 mmol) in acetic acid (4.0 mL) was run at 100 °C for 10 h, formamide **B** was obtained in 82% yield. It is interesting to note that no desired **3a** was obtained when **1a** (1.0 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) were added to the mixture or treated with **B** (0.5 equiv.) in acetic acid at 100 °C. Actually, the reaction of isocyanides and carboxylic acids had ever been reported *via* microwave irradiation or thermolytic activation to form formamides and anhydrides.[17]



Scheme 3 Probing the effect of isocyanide

On the basis of all the results obtained and the literature, a plausible mechanism for the formal O-H insertion reaction of α-diazo-1,3-dicarbonyl compounds to carboxylic acids is proposed.[18] As shown in Scheme 4, the reaction of carboxylic acid and isocyanide takes place to form the intermediate **A**. In the presence of $Cu(AcO)_2$ at high temperature, a Cu-carbene **C** is generated from α-diazo-1,3-dicarbonyl compound **1**, which then reacts with **A** to give an ylide intermediate **D**.[19] Then, intermediate **D** takes a proton from carboxylic acid **2** and undergoes a nucleophilic addition-elimination reaction with the carboxylate to afford α-acyloxy-1,3-dicarbonyl compound **3** along with the regeneration of **A**.



Scheme 4 A plausible reaction mechanism.

In conclusion, a novel Cu(II)-catalyzed and isocyanide-assisted formal O-H insertion reactions of α-diazocarbonyl compounds to carboxylic acids has been developed, which provides a straightforward synthetic access to α-acyloxycarbonyl compounds and describes an unprecedented reaction pattern in the chemistry of O-H insertion.

Notes and references

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[b] *Department of Chemistry, Northeast Normal University, Changchun, 130024, China*

† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, and spectra copies of all compounds. See DOI: 10.1039/b000000x/

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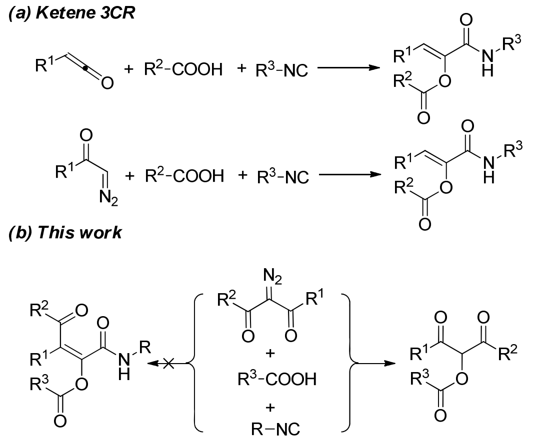

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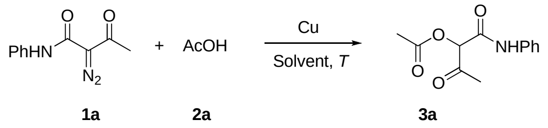

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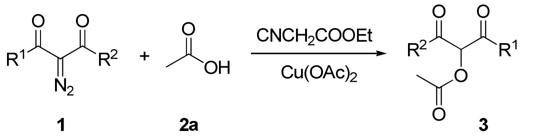
10	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.5)	None	80	10	Trace
11[c]	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.5)	DMF	100	10	N.R.
12[c]	$Cu(AcO)_2$	$CNCH_2COOEt$ (0.5)	Ethyl acetate	Reflux	10	N.R.

[a] Reagents and conditions: **1a** (1.0 mmol), **2a** (4.0 mL), copper salts (0.1 mmol). [b] Isolated yields. [c] AcOH (5.0 mmol) was added.

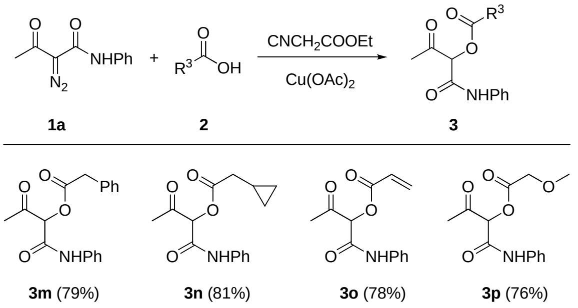
Table 2 Synthesis of α-acyoxycarbonyl compounds **3** from α-diazo-1,3-dicarbonyl compounds and acetic acid.[a]



Entry	1	R^1	R^2	3	Yield[b]/%
1	**1b**	Me	$4-MeC_6H_4NH$	**3b**	82
2	**1c**	Me	$2-MeC_6H_4NH$	**3c**	77
3	**1d**	Me	$4-ClC_6H_4NH$	**3d**	81
4	**1e**	Me	$2-ClC_6H_4NH$	**3e**	79
5	**1f**	Me	$4-CF_3C_6H_4NH$	**3f**	75
6	**1g**	Me	$2,4-Me_2C_6H_3NH$	**3g**	73
7	**1h**	*n*-Pr	C_6H_5NH	**3h**	86
8	**1i**	Ph	C_6H_5NH	**3i**	78
9	**1j**	Me	OEt	**3j**	83
10	**1k**	Ph	OEt	**3k**	69
11	**1l**	Ph	Me	**3l**	74

[a] Reagents and conditions: **1** (1.0 mmol), **2a** (4.0 mL), $Cu(OAc)_2$ (0.1 mmol), ethyl isocyanoacetate (0.5 mmol), 100 °C, 4.0-5.0 h. [b] Isolated yields.

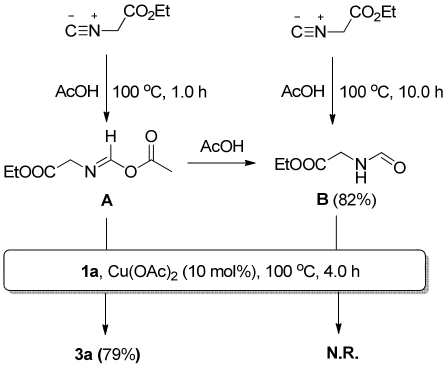
With the optimized conditions at hand, a series of reactions of *α*-diazo-*β*-oxoamides **1b-i** bearing varied alkyl and aryl groups R^1 and aryl amide groups R^2 with acetic acid were carried out. As shown in Table 2, all the reactions proceeded smoothly to afford the corresponding *α*-acyloxy carbonyl compounds **3b-3i** in good to high yields (entries 1-8). The synthetic efficiency was evaluated by performing *α*-diazo-*β*-dicarbonyls **1j**, **1k** and **1l** with ketone and ester groups (COR^2) and acetic acid under the identical conditions (entries 9-11). Next, we examined the reactions of miscellaneous carboxylic acids with *α*-diazo-*β*-oxoamide **1a**, and some of the results are summarized in Scheme 2. The *α*-acyloxy carbonyl compound synthesis was proved to be suitable for the saturated and unsaturated carboxylic acids.



[a] Reagents and conditions: **1a** (1.0 mmol), **2** (4.0 mL), $Cu(OAc)_2$ (0.1 mmol), ethyl isocyanoacetate (0.5 mmol), 100 °C, 4.0-5.0 h.

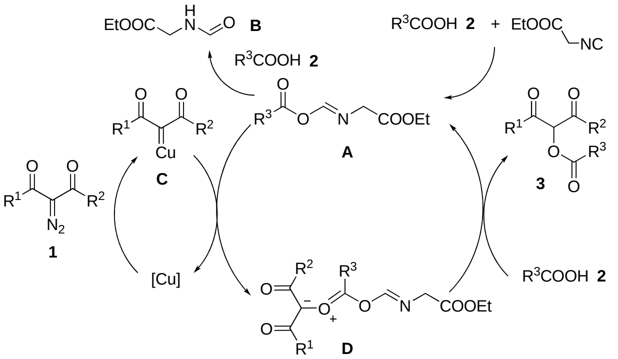
Scheme 2 The O-H insertion reactions of α-diazo-β-oxoamide **1a** with different carboxylic acids.

As previously mentioned, substrate **1a** failed to react with acetic acid in the absence of isocyanides, demonstrating that an isonitrilic specie is crucial for the success of the process. To further investigate the effect of isocyanides, some experiments were conducted. Firstly, 2-isocyanoacetate (0.5 mmol) and acetic acid (4.0 mL) was mixed under stirring and kept at 100 °C for 1.0 h. The H^1 NMR analysis of the resulting mixture indicated that ethyl isocyanoacetate was consumed, and an actively intermediate **A** seemed to be formed (Scheme 3). It was worth noting that **3a** could be obtained in 79% yield when **1a** (1.0 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) were added to the above mixture and stirred at 100 °C for 4.0 h. In another experiment, after the solution of ethyl isocyanoacetate (0.5 mmol) in acetic acid (4.0 mL) was run at 100 °C for 10 h, formamide **B** was obtained in 82% yield. It is interesting to note that no desired **3a** was obtained when **1a** (1.0 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) were added to the mixture or treated with **B** (0.5 equiv.) in acetic acid at 100 °C. Actually, the reaction of isocyanides and carboxylic acids had ever been reported *via* microwave irradiation or thermolytic activation to form formamides and anhydrides.[17]



Scheme 3 Probing the effect of isocyanide

On the basis of all the results obtained and the literature, a plausible mechanism for the formal O-H insertion reaction of *α*-diazo-1,3-dicarbonyl compounds to carboxylic acids is proposed.[18] As shown in Scheme 4, the reaction of carboxylic acid and isocyanide takes place to form the intermediate **A**. In the presence of Cu(AcO)$_2$ at high temperature, a Cu-carbene **C** is generated from *α*-diazo-1,3-dicarbonyl compound **1**, which then reacts with **A** to give an ylide intermediate **D**.[19] Then, intermediate **D** takes a proton from carboxylic acid **2** and undergoes a nucleophilic addition-elimination reaction with the carboxylate to afford *α*-acyloxy-1,3-dicarbonyl compound **3** along with the regeneration of **A**.



Scheme 4 A plausible reaction mechanism.

In conclusion, a novel Cu(II)-catalyzed and isocyanide-assisted formal O-H insertion reactions of *α*-diazocarbonyl compounds to carboxylic acids has been developed, which provides a straightforward synthetic access to *α*-acyloxycarbonyl compounds and describes an unprecedented reaction pattern in the chemistry of O-H insertion.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, and spectra copies of all compounds. See DOI: 10.1039/b000000x/

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