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Cu(II)-catalyzed cyclization of α-diazo-β-oxoamides with amines leading to pyrrol-3(2*H*)-ones†

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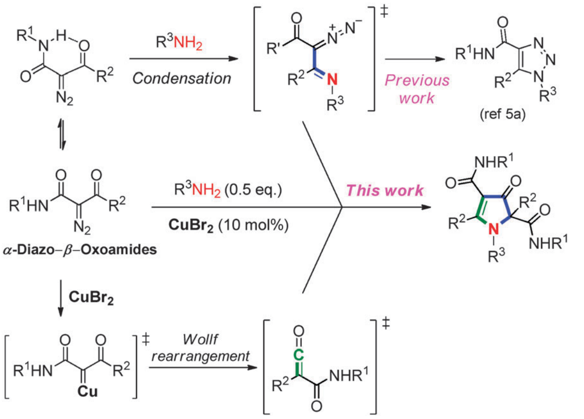
A novel Cu(II)-catalyzed cyclization of α-diazo-β-oxoamides with amines has been developed, constituting a straightforward method to construct pyrrol-3(2*H*)-one rings. The intramolecular hydrogen bonding effect in α-diazo-β-oxoamides plays an essential role in this reaction. A plausible reaction mechanism involving divergent generation and subsequent [2 + 3] cyclization of ketene and α-diazoimine intermediates was proposed.

The readily available α-diazocarbonyl compounds are distinguished by their unique reactivity through the generation of carbenoid species, induced thermally, photochemically, or by transition metal catalysis.[1] One important transformation of carbenoids is the Wolff rearrangement to yield ketenes that are useful in [2 + 2] and [2 + 4] cycloadditions, nucleophilic and rearrangement reactions.[2] On the other hand, the condensation of α-diazocarbonyls with amines promoted by Lewis or Brønsted acids generates α-diazoimine intermediates capable of undergoing further reactions such as 1,2-alkyl migration, 1,3-dipolar cycloaddition and ring-closure reactions.[3,4] However, to our knowledge, a reaction between ketenes and α-diazoimine intermediates remains unknown, probably due to the difficulty of generating both of them in one reaction system. We have previously realized the first catalytic Wolff 1,2,3-triazole synthesis *via* the cyclocondensation of α-diazo-β-oxoamides with amines due to the intramolecular hydrogen bonding effect (Scheme 1).[5a,6] As part of our continuing interest in developing new reactions based on functionalized β-oxoamides,[5] we herein wish to describe an unprecedented copper-catalyzed cyclization of α-diazo-β-oxoamides with amines that afforded pyrrol-3(2*H*)-ones through formal [2 + 3] cycloaddition of *in situ* generated ketene and α-diazoimine intermediates (Scheme 1).[7,8] Divalent copper catalyst plays a dual role in this reaction by inducing both the Wolff rearrangement and the condensation.[9] Also observed was the effect of intramolecular hydrogen bonding in the cyclization of α-diazo-β-oxoamides essential for this cyclization reaction.



Scheme 1 Cyclizations of α-diazo-β-oxoamides with amines in the presence of different catalysts.

Pyrrol-3(2*H*)-one belongs to a class of interesting heterocycles extensively studied by Smith and Hirschmann *et al.* that constitutes the key heterocyclic structural core in polypyrrolinone nonpeptidomimetics.[10] However, the construction of stable pyrrol-3(2*H*)-one rings is still challenging because of the keto–enol equilibrium with 3-hydroxyl pyrrole.[11] So far, this difficulty has been addressed by use of a quaternary carbon centre or exocyclic double bond to block the 2-position of pyrrol-3(2*H*)-ones. Hitherto, only a few synthetic methods are available, including (i) cyclocondensations of α-amino esters with aldehydes,[12] vicinal tricarbonyls with enamines or amines,[13] and amidines with acetylenic esters,[14] (ii) [2 + 3] cycloaddition reaction of cyclopropenones with imines,[15] (iii) hypervalent iodine reagent-mediated cyclization reaction of enaminones,[16] (iv) intramolecular alkylation reaction of 3-hydroxypyrrole-2-carboxylates,[17] and (v) ring-closure reactions.[18] Invariably, some of these methods suffer from serious drawbacks such as multi-step operations, non-readily available reactants and/or lower product yields. These shortcomings thus appeal the development of novel and efficient synthetic methods for pyrrol-3(2*H*)-ones.

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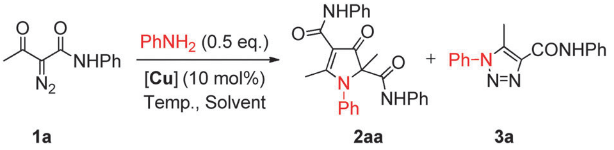
Table 1 Condition screening



Entry	[Cu]	T (°C)	Solvent	Time (h)	Yield^a (%) 2aa	Yield^a (%) 3a
1	CuCl$_2$	90	DMF	8	42	16
2	CuSO$_4$	90	DMF	7	54	13
3	Cu(OAc)$_2$	90	DMF	7	76	Trace
4	Cu(acac)$_2$	90	DMF	6	81	Trace
5	**CuBr$_2$**	**90**	**DMF**	**5**	**83**	Trace
6^b	CuBr	90	DMF	4	0	0
7^b	CuI	90	DMF	4	0	0
8	CuBr$_2$	60	DMF	10	0	21
9	CuBr$_2$	110	DMF	4	71	0
10	CuBr$_2$	90	DMSO	5	77	Trace
11	CuBr$_2$	90	EtOH	10	Trace	36
12	CuBr$_2$	90	Toluene	20	nr	nr
13^c	CuBr$_2$	90	H$_2$O	15	Trace	43

^{a} Isolated yields. ^{b} Unidentified mixture was formed. ^{c} Tetrabutyl ammonium bromide (TBAB) (10 mol%) was added.

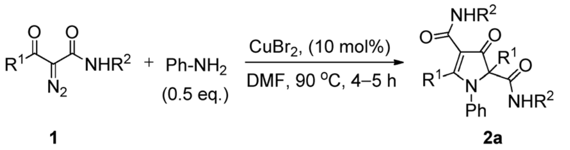
Our procedure described in this communication provided a straightforward method to construct pyrrol-3(2*H*)-one rings with simultaneous formation of a quaternary carbon center at the 2-position.

Initial survey on reaction parameters, including copper catalyst, temperature and solvent, was carried out with the reaction of α-diazo-β-oxoamide **1a** and aniline as a model. Some key results are summarized in Table 1. At 90 °C in DMF, treatment of the model substrates with CuSO$_4$ and CuCl$_2$ all resulted in a mixture of pyrrol-3(2*H*)-one **2aa** and 1,2,3-trizaole **3a**, albeit the ratio of **2aa** being a little higher (entries 1 and 2). The structure of **2aa** was unambiguously confirmed by X-ray diffraction (CCDC 911645). Other divalent copper salts such as Cu(OAc)$_2$, Cu(acac)$_2$ and CuBr$_2$ under the same conditions produced **2aa** in high yields with only trace amount of **3a** (entries 3–5). However, CuBr$_2$ was much more robust, offering 83% yield of the target within 5 h. On the contrary, cuprous catalysts such as CuBr and CuI under identical conditions afforded unidentified mixtures (entries 6 and 7). The reaction temperature also remarkably influenced the yield of products. For instance, when the reaction temperature was reduced to 60 °C, poor yield of triazole **3a** (21%) was obtained without formation of **2aa** (entry 8), while a higher temperature of 110 °C exclusively generated **2aa** in 71% yield (entry 9). Further, solvent screening disclosed that except for DMSO (entry 10), other solvents such as toluene, EtOH and H$_2$O were inappropriate (entries 11–13). The poor solubility of substrate **1a** in these solvents may account for these observations. As a result, the reaction conditions listed in entry 5 were optimal and hence selected for further investigation.

In the presence of a catalytic amount of CuBr$_2$ (10 mol%), a range of α-diazo-β-oxoamides with varying R^1 and R^2 groups were prepared and utilized in the cyclization reaction with aniline. As shown in Table 2, these substrates all smoothly reacted with aniline to give corresponding pyrrol-3(2*H*)-ones **2ab–2aj** in moderate to good yields. It is worth noting that the electronic effect of the substituent on the phenyl ring (R^2) played no significant role in the reactions.

The scope of the amines was examined in the reaction with α-diazo-β-oxoamide **1a** and the results are summarized in Scheme 2.

Table 2 Cyclization of different α-diazo-β-oxoamides with aniline

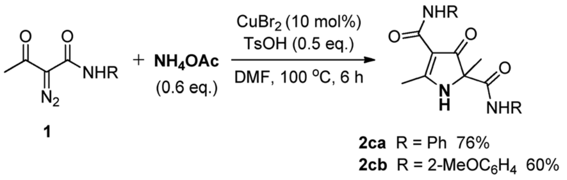


Entry	1	R^1	R^2	2a	Yield^a (%)
1	**1b**	Me	2-MeC$_6$H$_4$	**2ab**	72
2	**1c**	Me	4-MeC$_6$H$_4$	**2ac**	78
3	**1d**	Me	2-MeOC$_6$H$_4$	**2ad**	63
4	**1e**	Me	4-MeOC$_6$H$_4$	**2ae**	78
5	**1f**	Me	2-ClC$_6$H$_4$	**2af**	60
6	**1g**	Me	4-ClC$_6$H$_4$	**2ag**	77
7	**1h**	Me	2,4-Me$_2$C$_6$H$_3$	**2ah**	71
8	**1i**	Me	4-CF$_3$C$_6$H$_4$	**2ai**	70
9	**1j**	*n*-Pr	C$_6$H$_5$	**2aj**	73

^{a} Isolated yields.

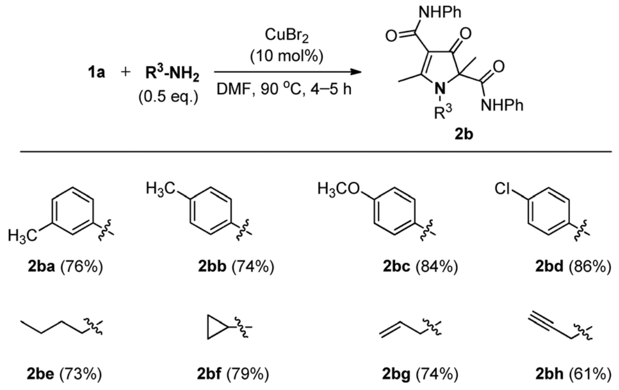
Several aromatic amines bearing different substituents on the phenyl ring were subjected to reactions with α-diazo-β-oxoamides and afforded products **2ba–2bd** in good to high yields. Similarly, aliphatic amines such as *n*-butylamine, cyclopropylamine, allylamine also displayed conformity to this cyclization by furnishing the corresponding *N*-functionalized pyrrol-3(2*H*)-ones **2be–2bh** in moderate to good yields.

Ammonium acetate (NH$_4$OAc) as the amine source was also explored with regard to assembling *N*-unsubstituted pyrrol-3(2*H*)-ones. Under slightly modified conditions, corresponding *N*-unsubstituted pyrrol-3(2*H*)-ones such as **2ca** and **2cb** were obtained in good yields (eqn (1)). The presence of 0.5 equivalent of *p*-toluenesulfonic acid (TsOH) was pivotal for an efficient transformation, which was ascribed to assisting the condensation of α-diazo-β-oxoamides **1** with ammonium acetate.[4]

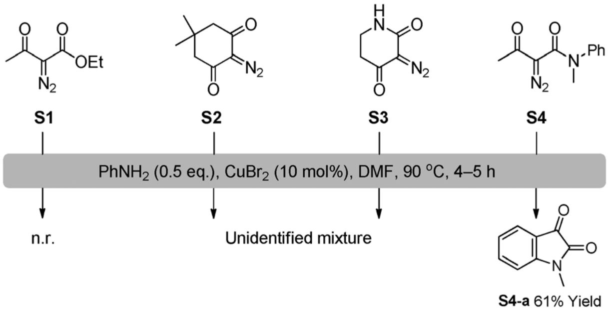


(1)

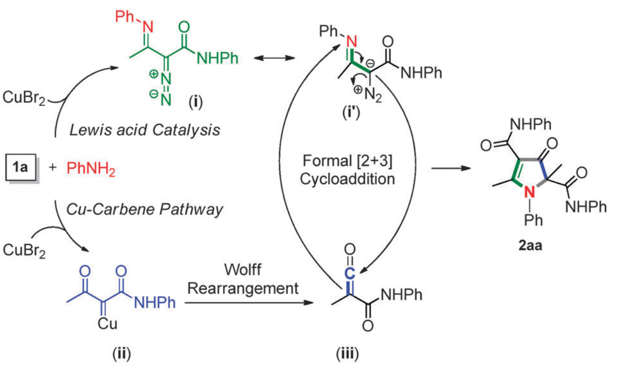
Further, in order to probe the effect of the intramolecular hydrogen bonding in α-diazo-β-oxoamides **1** several α-diazocarbonyl



Scheme 2 Cyclization of α-diazo-β-oxoamide **1a** with different amines.



Scheme 3 Probing the effect of hydrogen bonding.



Scheme 4 A plausible reaction mechanism.

compounds (**S1–S4**) were prepared and subjected to the standard reaction conditions (Scheme 3). Interestingly, we observed that α-diazocarbonyl **S1** was unreactive and compounds **S2** and **S3** resulted in an unidentified mixture, while that compound **S4** afforded an unexpected isatin derivative **S4-a** in 61% yield, for which a copper carbenoid aromatic C–H insertion might be involved.[6,9] These observations are consistent with our previous study[5a] in that the intramolecular hydrogen effect in α-diazo-β-oxoamides **1** is also necessary in the current Cu(II)-catalyzed cyclization, probably aiding the generation of the α-diazoimine intermediate under the catalytic conditions.

Two possible reactive precursors, α-diazo-β-imine and ketene, can be generated through retrosynthetic disconnection of pyrrol-3(2*H*)-one **2aa.** Consequently, a Lewis acid-catalyzed condensation and a Cu–carbene pathway should take place simultaneously in the cyclization of α-diazo-β-oxoamide **1a** with aniline; otherwise **2aa** would be difficult to be formed. On the basis of the above results and analysis, a plausible reaction mechanism is proposed and depicted in Scheme 4. Firstly, condensation of **1a** with aniline first occurs in the presence of $CuBr_2$, which acts as a Lewis acid catalyst, to generate intermediate **i** that tautomerizes to **i′**. Simultaneously, a Cu–carbene intermediate **ii** is formed *via* reaction of **1a** with $CuBr_2$ followed by the subsequent loss of N_2 and further transformation of this intermediate into ketene **iii** through Wolff rearrangement.[9] Finally, a formal [2 + 3] cycloaddition of intermediates **iii** and **i′** occurs leading to pyrrol-3(2*H*)-one **2aa.**[19] However, the exact ring-closure mechanism in the last step, concerted or stepwise, still remains unclear at the present time.

In conclusion, a novel Cu(II)-catalyzed cyclization of α-diazo-β-oxoamides with amines has been developed, providing a straightforward method to construct pyrrol-3(2*H*)-one rings. Although α-diazocarbonyl compounds have been widely studied over hundred years,[1,3] the reaction described in this communication represents an unprecedented reaction pattern in the chemistry of α-diazocarbonyls.

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