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# Silver-Catalyzed Nucleophilic Substitution of Aminals with Ethyl Diazoacetate: A New Entry to $\beta$ -Amino- $\alpha$ -Diazoesters

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A novel silver-catalyzed nucleophilic substitution of aminals with ethyl diazoacetate producing  $\beta$ -amino- $\alpha$ -diazoesters has been developed. A series of aminals with different amino moieties and substituents were successfully incorporated in this reaction, which delivered a wide range of  $\beta$ -amino- $\alpha$ -diazocarbonyl compounds in the presence of lower catalyst-loading in 2 hours.

#### Introduction

 $\alpha$ -Diazocarbonyl compounds are significant starting materials and have been widely applied in transition-metal-catalyzed X-H (X = N, O, S, B, Si, et al) insertion,<sup>1</sup> and coupling reactions owing to their unusual properties and versatile reactivities.<sup>2-3</sup> As a result, considerable efforts have been devoted to discovering simple and efficient approaches for the construction of such molecules.<sup>4</sup> The traditional strategies for the synthesis of  $\alpha$ -Diazocarbonyl compounds could be realized via primary amine diazotization, decomposition of hydrazones and diazo transfer reaction (Scheme 1).5-7 However, such reactions could not be utilized for synthesis of  $\beta$ -amino- $\alpha$ diazoesters, which not only are the most important precursors for the synthesis of  $\alpha$ -substituted  $\beta$ -amino acids, <sup>3a,b,f</sup> but also are attractive building blocks for chemical synthesis.<sup>8</sup> Over the Scheme 1. Strategies for preparation of  $\alpha$ -diazocarbonyl compounds



past several years, the base-mediated or Lewis acid-catalyzed

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nucleophilic addition of ethyl diazoacetate to activated imines, bearing strong electron-withdrawing groups (N-SO<sub>2</sub>R, N-COAr, N-Boc, N-Cbz, et. al) at the nitrogen atom, has been emerged as a powerful method for the synthesis of  $\beta$ -amino- $\alpha$ diazocarbonyl compounds with the retention of the diazo functionality (Scheme 2, (1)).<sup>9</sup> However, these elegant methods are limited to activated imines only, which significantly reduced the appeal of these methods. Although other significant routes to  $\beta$ -amino- $\alpha$ -diazo compounds were also reported, such as nucleophilic addition of diazo compounds to enamines (2),<sup>10a</sup> iminium salts,<sup>10b</sup> imines<sup>10c</sup> and oxidative coupling of tertiary amines (3)<sup>10d</sup> with diazo compounds, this protocol we disclosed here provided a new and efficient way to prepare  $\beta$ -amino- $\alpha$ -diazo compounds employing easily prepared aminals and commercial available diazoacetate.

## Scheme 2. Ag-catalyzed nucleophilic substitution of aminals with ethyl diazoacetate

Previous work





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Aminals have long been recognized as surrogates of imines and widely used as electrophiles in metal-catalyzed nucleophilic substitution/addition reactions.<sup>11</sup> The C-N bond in these molecules is easily cleaved under mild conditions to generate an iminium ion together with a basic amino anion. Inspired by this unique feature and on the basis of our work about aminals,<sup>12</sup> we envisaged that aminal might be used as a surrogate of imine to react with diazoacetate for furnishing the  $\beta$ -amino- $\alpha$ -diazoester, in which one amino moiety contained in the aminal could act as the inner base to abstract a proton to complete the transformation. Herein, we report a Ag-catalyzed nucleophilic substitution reaction of aminals with ethyl diazoacetate that provides an alternative access to  $\beta$ -amino- $\alpha$ diazoesters.

Table 1. Optimization of the reaction conditions <sup>a</sup>

	) + H <sup>N2</sup> 2a	[M] (5 mol%) 100 °C, solvent, 2 h	COOEt N2 3a
entry	[M]	solvent	yield <b>3a</b> (%)
1	Sc(OTf) <sub>3</sub>	THF	trace
2	Al(OTf) <sub>3</sub>	THF	trace
3	Zn(OTf)2	THF	trace
4	Cu(OTf)2	THF	0
5	Cu(TFA) <sub>2</sub>	THF	0
6	Ag(TFA)	THF	47
7	Ag(OTf)	THF	65
8	AgClO <sub>4</sub>	THF	66
9	$AgBF_4$	THF	74
10	$AgBF_4$	toluene	49
11	AgBF <sub>4</sub>	CH <sub>3</sub> CN	51
12	$AgBF_4$	anisole	62
13	$AgBF_4$	DCM	68
14	AgBF <sub>4</sub>	DMF	37
15	-	THF	0

<sup>&</sup>lt;sup>a</sup>Reaction conditions: **1a** (131.0 mg, 0.5 mmol), **2a** (114.0 mg, 1.0 mmol), [M] (5.0 mol%), solvent (1.5 mL) at 100  $^{\circ}$ C for 2 h, isolated yield.

#### **Results and discussion**

At the outset of our studies, we explored the viability of the process with 4,4'-(phenylmethylene)dimorpholine 1a and ethyl diazoacetate 2a as the model substrates. The reaction was performed at 100 °C in THF for 2 h. First, several typical Lewis acids, such as  $Sc(OTf)_3$ ,  $Al(OTf)_3$ ,  $Zn(OTf)_2$ ,  $Cu(TFA)_2$  and Cu(OTf)<sub>2</sub> were found to be ineffective catalysts for the desired reaction (Table 1, entries 1-5). When Sc(OTf)<sub>3</sub>, Al(OTf)<sub>3</sub> or Zn(OTf)<sub>2</sub> was employed as a catalyst, the starting materials were remained giving trace amount of the desired product (detected by TLC). If Cu(TFA)<sub>2</sub> or Cu(OTf)<sub>2</sub> was introduced into the reaction system, 2a was decomposed completely providing the dimerization product of 2a (detected by GC-MS analysis). To our delight, the corresponding product ethyl 2-diazo-3morpholino-3-phenylpropanoate 3a was obtained in 47% yield when Ag(TFA) was employed as the catalyst (entry 6). Inspired by this result, we then investigated a series of silver salts.

When AgBF<sub>4</sub> was introduced into the reaction system, the reaction proceeded well to give **3a** in 74% isolated yield while other silver salts didn't give better results (entries 7-9). To maximize the efficiency of this reaction, a variety of organic solvents were screened. As a result, THF proved to be the best solvent. If the solvent was switched to DCM, CH<sub>3</sub>CN, anisole, toluene or DMF, the yields of **3a** were reduced (entries 10-14). Finally, control experiment demonstrated that the desired product **3a** was not formed at all in the absence of a catalyst (entry 15). Trace amount of ethyl 3-morpholino-3-phenylacrylate was detected when Ag(I) was employed as the catalyst. It might be stemmed from the reaction of **3a** which can undergo the corresponding Bamford–Stevens-Shapiro reaction in the presence of Ag(I).<sup>13</sup>

Table 2. Substrate scope of aminals



<sup>a</sup>Reaction conditions: **1** (0.5 mmol), **2a** (114.0 mg, 1.0 mmol), AgBF<sub>4</sub> (5.0 mol %), THF (1.5 mL) at 100  $^{\circ}$ C for 2 h, isolated yield. <sup>b</sup>AgBF<sub>4</sub> (1.0 mol %), **2a** (68.4 mg, 0.6 mmol).

With the optimized reaction conditions identified, the scope of various aminals 1 were explored with ethyl diazoacetate 2a at 100 °C by using AgBF<sub>4</sub> as the catalyst. As illustrated in Table 2, aminals synthesized from both paraformaldehyde and aromatic aldehydes with a diverse set of substituents, such as methyl (3g-3i), chloride (3j-3l) on the phenyl ring, were well tolerated to give the desired products with good yields. Generally, aminals bearing electron-donating groups on the phenyl ring give higher yields than those with electronwithdrawing groups, as shown for products 3g-3l. Besides, reactions with aminals bearing electron-withdrawing groups (-Cl) underwent smoothly, giving the corresponding products up to 62% yield (3j-3l). In addition, aminals derived from naphthaldehydes were also compatible with this transformation, generating the corresponding products (3m and 3n) in 77% and 82% yield, respectively. After the exploration of the reaction scope of aminals above, we turned our attention to more challenging substrates derived from furaldehyde and pyridylaldehyde. The furaldehyde derived aminal 10 was tolerable in the present reaction to give the desired product 30 in 40% isolated yield. However, under the Published on 20 October 2016. Downloaded by Cornell University Library on 21/10/2016 07:11:37

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present reaction conditions, only 13% yield of **3p** was observed when 4-pyridylaldehyde derived aminal was employed as a coupling partner. N,N,N',N'-tetrabenzyl-1phenylmethanediamine **1q** proceeds current reaction giving the desired product **3q** in 78% yield. The solid state structures of **3g** and **3j** were confirmed by single-crystal X-ray analysis (Figure 1).<sup>14</sup>

#### Figure 1. X-ray structures of 3g and 3j.



X-ray structure of 3g

X-ray structure of 3j

On the basis of the results we obtained here and literature reports,  $^{9,10,11}$  a plausible reaction pathway for the present C-C bond formation reaction was proposed as shown in Scheme 3. First, the electrophilicity of the aminal would be enhanced by the AgBF<sub>4</sub> via coordination, which was then nucleophilic attacked by ethyl diazoacetate to give the desired product. It is likely that the one amino moiety in the aminal serves as an inner base to abstract the proton to deliver the desired product with the formation of a new C-C bond.

Scheme 3. Proposed reaction pathway



#### Conclusions

In summary, we have developed a novel silver-catalyzed direct implanting of ethyl diazoacetate into aminals to produce diverse donor-acceptor diazo-compounds through nucleophilic substitution reaction. Various  $\beta$ -amino- $\alpha$ -diazoacetates with different amino moieties were efficiently constructed by cleavage of C-N bond of aminals under mild and neutral reaction conditions. This strategy not only enlarges the application of ethyl diazoacetate in organic synthesis, but also provides an alternative synthetic method to prepare  $\beta$ -amino- $\alpha$ -diazoacetates. The practical advantage of the present protocol is that it could transform the simple available starting materials (ethyl diazoacetate and aminals) into complex  $\beta$ -amino- $\alpha$ -diazoacetates. Further investigations to apply this strategy to other reactions are currently underway.

#### Acknowledgements

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