The Catalytic Synthesis of Carboniolamide: The Role of sp^3 Hybridized Oxygen

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Received: 19.07.2014; Accepted after revision: 18.08.2014

Abstract: A catalytic synthesis of carboniolamide has been reported. The strategy was straightforward with aldehyde and amide as starting materials. The products can be isolated as precipitates from the reaction mixture. The factor that stabilizes the labile functionality of hemiaminal was elucidated as a sp^3 hybridized oxygen.

Key words: catalysis, amide, aldehyde, phosphate, nucleophilic addition

Hemiaminal bears unusual *gem*-N,OH functionality and has been supposed to be an unstable intermediate in the organic chemistry. The half-life of the trapped hemiaminal is about 30 minutes as reported by Rebek.[1] On the other hand, carboniolamide, the acylated hemiaminal, does occur naturally in the marine macrolide (–)-zampanolide (Figure 1).[2] The (–)-zampanolide showed outstanding anticancer potency against ovarian, breast, lung, prostate and colorectal cancer cell lines.[3] The backbone of zampanolide, named as dactylolide, shows reduced inhibitory activity than that of zampanolide with additional hemiaminal group. Recently, a study conducted by Steinetz and his co-workers revealed that the carbinolamide side chain plays an important role in the anticancer profile due to its unique hydrogen bonding ability.[4]

The synthesis of *gem*-diheteroatom functionality has advanced in the last decade with organo- and organometallic catalysis. In 2005, Antilla reported the first enantioselective intermolecular *N*,*N*-aminal synthesis.[5] Later on, the intramolecular aminal syntheses were achieved by List,[6] Rueping,[7] Toste,[8] Tian,[9] Kurth,[10] Masson,[11] and Lin.[12] Highly related N,OR chiral centers were constructed with similar protocols in both intermolecular[13] and intramolecular manners.[14] Meanwhile, several *O*,*O*-acetal syntheses were also presented by List,[15] Nagorny,[16] Gong,[17] and Aponick.[18] Despite these progresses, the synthesis of carboniolamide was somehow challenging due to its labile free hydroxyl group. In the pioneer work of total synthesis of zampanolide by Smith group, the carboniolamide group was derived from PMB-protected hemiaminal.[19] In this case, during the course of deprotection, epimerization happened spontaneously to give a mixture of diastereoisomers. Another strategy towards the carboniolamide utilized the amide preorganized with stochiometric aluminum[20] or boron[21] reagent. Toste demonstrated the enantioselective synthesis of α-fluoro carbinolamide with enamide as substrate, where excellent enantioselectivity was obtained.[8] In comparison, the direct addition of amide to aldehyde is a straightforward, atom-economic, and ideal synthesis.[22] In 2009, Tanaka and his co-workers reported the *p*-TsOH-catalyzed addition of amide to aldehyde in their total synthesis of (–)-zampanolide, where carboniolamide was generated as a minor product along with the bisamide as the major outcome.[23] The only example of chemoselective direct addition of amide to aldehyde is presented by Ghosh employing chiral phosphate as catalyst.[24] So far the factor that stabilized the carboniolamide instead of its overreaction to bisamide is not clear.[20,25]

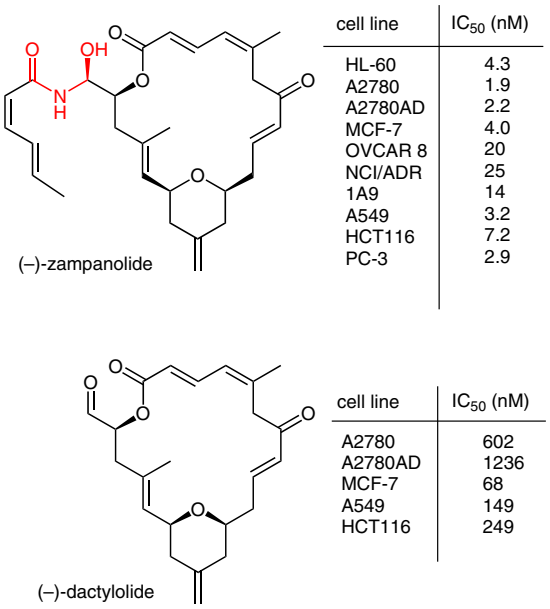
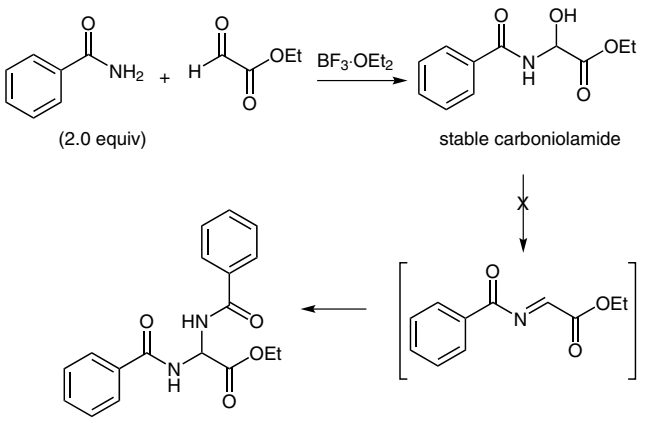


Figure 1 Marine macrolide with carboniolamide side chain

As a part of our ongoing research on the reaction between amide and aldehyde, we found that the ethyl glyoxylate reacted with amide (2.0 equiv), yielding the carboniolamide instead of commonly observed bisamide products (Scheme 1).[26] Herein, we report our study on the catalytic addition of amide to aldehyde as well as the stabilizing factor for carboniolamide.

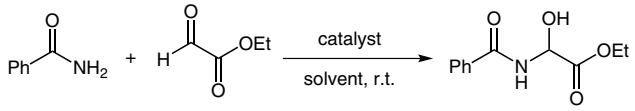
SYNLETT 2014, 25, 2644–2648
Advanced online publication: 17.09.2014
DOI: 10.1055/s-0034-1379101; Art ID: st-2014-w0612-l



Scheme 1 Unexpected carboniolamide synthesis

Our initial reaction was carried out with ethyl glyoxylate and benzamide as starting materials in the presence of 10 mol% boron trifluoride diethyl etherate (Table 1). Soon it turned out that the diphenyl phosphate could give superior reactivity (entries 1–3). So we chose the diphenyl phosphate as standard catalyst, and screened different solvents at room temperature. To our delight, diethyl ether, a relatively green solvent, facilitated the conversion by precipitating the target molecule as the only product, which drove the reaction to the high conversion instead of reaching equilibriums as observed in other solvents such as acetone, ethyl acetate and CH_2Cl_2. The purity of precipitate was satisfying in the absence of either chromatography or recrystallization.[27]

Table 1 Optimization Conditions for the Addition of Amide to Glyoxylate[a]

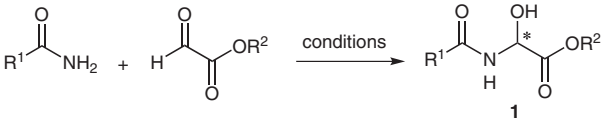


Entry	Catalyst	Solvent	Yield
1	$BF_3{\cdot}OEt_2$	acetone	50%[b]
2	AcOH	acetone	20%[b]
3	$(PhO)_2POOH$	acetone	60%[b]
4	$(PhO)_2POOH$	EtOAc	40%[b]
5	$(PhO)_2POOH$	CH_2Cl_2	35%
6	$(PhO)_2POOH$	Et_2O	85%

[a] Reaction conditions: ethyl glyoxylate (1.0 equiv), benzamide (1.0 equiv), catalyst (10 mol%), 0.25 M in solvents, r.t., 12 h; the product was obtained as precipitate.
[b] The product was obtained after chromatography.

With the optimized conditions in hand, we tested different amides with several glyoxylate derivatives (Table 2).[28] With the commercially available ethyl glyoxylate as starting material, different amides were evaluated in the presence of 10 mol% of diphenyl phosphate. The adducts of aliphatic amides gave the corresponding carboniolamides as white precipitate (**1a**–**1c**) in good yield. The aromatic products could be obtained efficiently as well (**1d–i**). The α,β-unsaturated amide such as cinnamide and acrolamide gave the desired product **1j** and **1k**, respectively, without any significant side reaction. Meanwhile, the heterocyclic compound **1l** was prepared in good yield. Besides these amides, the carbamates, such as Cbz-NH_2 and Fmoc-NH_2, worked in the same way to give the respective adducts **1m** and **1n**. When the different glyoxylates were adopted as the electrophiles, similar reactivities along with easy workup were retained for both amides and carbamates (entries 15–21).

Table 2 Substrate Scope of the Addition of Amide to Glyoxylate[a]



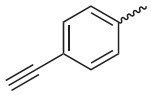
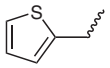
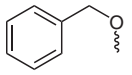
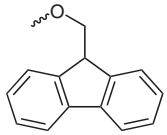
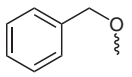
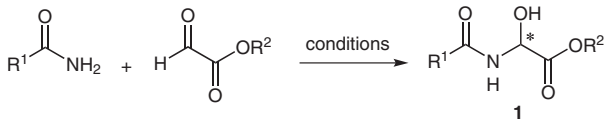
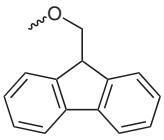
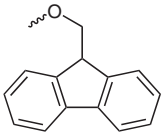
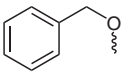
Entry	1	R^1	R^2	Yield (%)
1	**1a**	Me	Et	85
2	**1b**	*i*-Pr	Et	83
3	**1c**	Bn	Et	81
4	**1d**	Ph	Et	84[b]
5	**1e**	4-$MeOC_6H_4$	Et	84
6	**1f**	4-FC_6H_4	Et	91
7	**1g**	4-ClC_6H_4	Et	80
8	**1h**	4-$F_3CC_6H_4$	Et	80
9	**1i**		Et	73
10	**1j**	styrenyl	Et	81
11	**1k**	vinyl	Et	81
12	**1l**		Et	83
13	**1m**		Et	80
14	**1n**		Et	90
15	**1o**	Ph	*i*-Pr	80
16	**1p**		*i*-Pr	80

Table 2 Substrate Scope of the Addition of Amide to Glyoxylate[a] (continued)

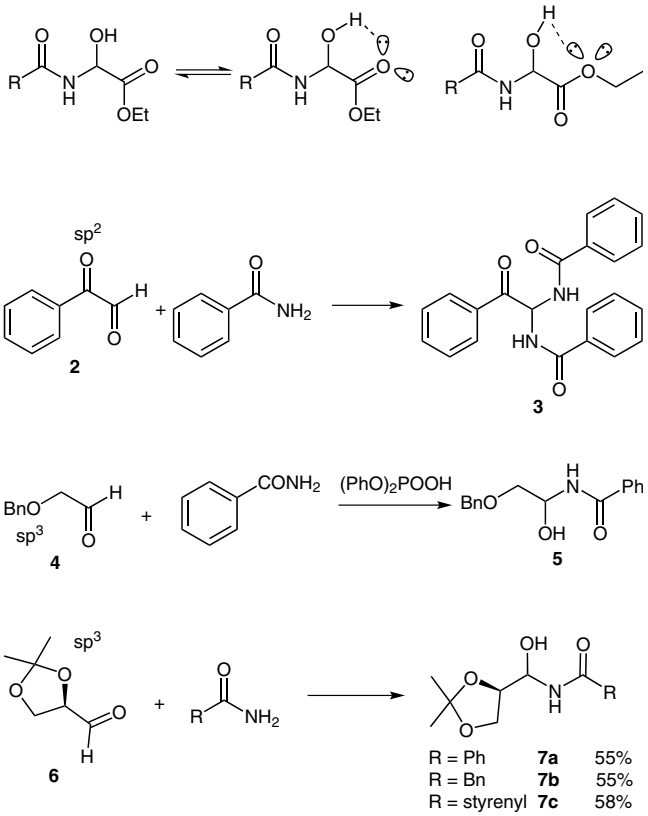


Entry	1	R^1	R^2	Yield (%)
17	**1q**		*i*-Pr	85
18	**1r**	4-MeC_6H_4	Bn	78
19	**1s**	3-thienyl	Bn	80
20	**1t**		Bn	88
21	**1u**		Bn	60

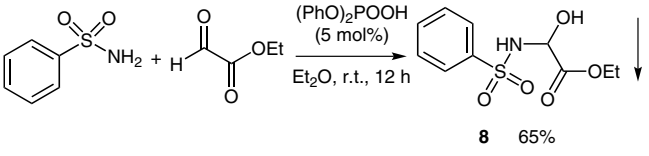
[a] Reaction conditions: glyoxate (1.0 equiv), amide (1.0 equiv), 0.25 M in Et_2O, diphenyl phosphate (10 mol%), r.t., 8–24 h. The precipitate was collected by filtration.
[b] Amount of amide used was 2.0 equiv.

It was noteworthy that even with 2.0 equivalents of benzamide as starting material the reaction gave the carboniolamide as the only product without any overaddition to bisamide (Table 2, entry 4). In contrast to the common bisamide condensation reactions, this phenomenon suggested that the product is too stable to undergo dehydration to give the imine intermediate. We presumed that the additional oxygen atom provided by the glyoxylate molecule could stabilize the hydroxyl group along with the carbonyl group from the amide part. So in turn, it was needed to be found which oxygen (sp^2 or sp^3) accounted for the major effect (Scheme 2). Thus, substrate **2** with only sp^2 α-oxygen and **4** with only sp^3 α-oxygen atom were subjected to the phosphate-catalyzed reactions using one equivalent of benzamide. The distinct chemoselectivity was observed in that bisamide **3** was the only product from dicarbonyl compound **2**, and carboniolamide **5** generated specifically from **4**. We reasoned that sp^3 oxygen is the effective hydrogen bonding acceptor for the formed hydroxyl group and prevents the further collapse of carboniolamide. We explored additional aldehydes such as dioxolane aldehyde **6** and the target molecules **7a**–**c** were obtained as mixtures of diastereoisomers.

In contrast to the known mode of hydrogen bonding network focused on the NH···OC,[25] an interaction also exists in the bisamide, and the present results suggested that the OH·OR interaction plays a unique role in surviving the hemiaminal. With the rationale of hydrogen bonding system, we assumed that sulfonamide, where the sulfonyl adopted tetrahedron configuration instead of planar triangle of carbonyl in amide,[29] could fit this protocol as well. Thus, a reaction between the benzenesulfonamide and ethyl glyoxylate was established with the standard conditions. The desired molecule **8** was obtained as the single product in the form of a white precipitate with the yield of 65% (Scheme 3). The compound was inert under the ambient condition and could be manipulated in the same manner.



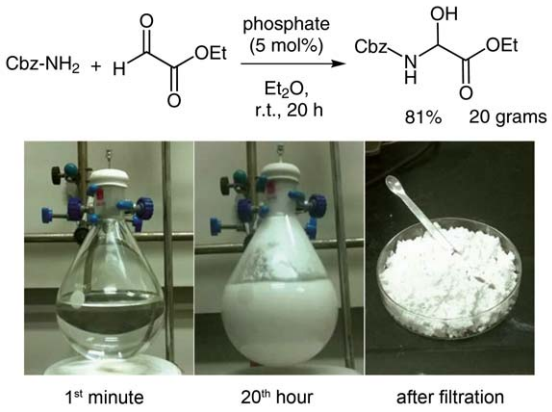
Scheme 2 The different behavior of aldehydes bearing α-oxygen. Note: 10 mol% diphenyl phosphate, aldehyde and amide, 0.25 M in Et_2O, r.t., 12 h. The products were collected as single products with filtration.



Scheme 3 The reaction between benzenesulfonamide and ethyl glyoxylate

In order to take the full advantage of the convenient filtration, the preparation of **1m** was set up at 0.1-mol scale (Scheme 4). At the beginning of the reaction, a mixture of glyoxylate, Cbz-NH_2, and diphenyl phosphate was obtained as a clear solution. After 20 hours, the desired product was obtained as a white crystalline solid by

spontaneous precipitation. At this point, no further purification such as recrystallization or chromatography was required, and the yield remained at the same level.



Scheme 4 The catalytic synthesis of carboniolamide on a 20-gram scale

In summary, we have discovered that Brønsted acid can catalyze the nucleophilic addition of amide to the aldehyde to form the carboniolamide as a stable compound where α-oxygen adopting sp^3 hybridization is necessary to stabilize the generated hydroxyl group. The chemistry can be extended to sulfonamide. This simple procedure could be scaled up to 20 grams. We are now working on the enantioselective construction of carboniolamide.

Acknowledgment

This work was supported by the National Science Fund for Talent Training in Basic Science (Grant No. J1103310), the Ph.D. Programs Foundation of Ministry of Education of China (Grant 20130091120047), and NSFC key Program (Grant 21332005). A scholarship for Z.Y. (SRTP Grant G1310284037) is highly appreciated.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(28) **General Procedure for the Synthesis of the Carboniolamide**: To a reaction vial charged with amide (1.0 mmol), glyoxylate (1.0 mmol), and diphenyl hydrogen phosphate (25.0 mg, 0.1 mmol) was added Et_2O (4 mL). Then the sealed reaction mixture was stirred at r.t. for the specified time. The obtained slurry was then filtered, and the precipitate was washed with a minimum amount of cold Et_2O to give the compound as a white powder.
1g: mp 106.2–108.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.46 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 6.63 (d, *J* = 6.1 Hz, 1 H), 5.64 (t, *J* = 6.9 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.26, 165.43,

137.01, 132.72, 129.93, 128.92, 72.44, 61.25, 14.49. IR (thin film): 1015, 1033, 1102, 1155, 1239, 1312, 1345, 1487, 1536, 1598, 1649, 1655, 1746, 3304, 3402 cm^{-1}. MS (ESI): *m*/*z* [M + Na^+] calcd for $C_{11}H_{12}ClNO_4Na$: 280; found: 280. HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{11}H_{12}ClNO_4Na$: 280.0353; found: 280.0356.

1n: mp 125.3–127.1 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.43 (d, *J* = 8.6 Hz, 1 H), 7.90 (d, *J* = 7.5 Hz, 2 H), 7.74 (t, *J* = 8.1 Hz, 2 H), 7.32–7.45 (m, 4 H), 6.50 (s, 1 H), 5.29 (d, *J* = 8.6 Hz, 1 H), 4.20–4.36 (m, 3 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.04, 155.92, 144.24, 144.14, 141.18, 128.14, 127.54, 125.83, 125.76, 120.59, 73.73, 66.34, 61.25, 46.94, 14.47. IR (thin film): 740, 758, 1042, 1093, 1224, 1267, 1331, 1449, 1530, 1703, 1721, 1753, 3328 cm^{-1}. MS (ESI): *m*/*z* [M – H^+] calcd for $C_{19}H_{19}NO_5$: 340; found: 340. HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{19}H_{19}NO_5Na$: 364.1161; found: 364.1163.

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