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Direct carbinolamide synthesis

Sezgin Kiren, Ning Shangguan and Lawrence J. Williams*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, United States

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Abstract—Carbinolamides were prepared by treatment of aldehydes with carboxamides in the presence of dicyclohexylboron chloride and triethylamine. All carbinolamide products were stable to isolation, purification and routine handling.

A part of our program to advance new preparative methods for complex amide synthesis has focused on the problem of the carbinolamide.[1] The carbinolamide and the corresponding amido ether represent synthetically challenging structural motifs present in small molecule natural products (e.g., **1**[2]), and constitute the defining structural element of N-linked glycosylated proteins and peptides (**2**, Fig. 1). Moreover, the reactive nature of such functionality could be used in certain substrates to leverage access to other nitrogen containing targets. Preliminary findings are presented here that demonstrate that the carbinolamide is readily obtained from amide and aldehyde.

Although direct addition of amides to electron deficient aldehydes is known, most approaches to other carbinolamides require multi-step sequences.[3] Several creative approaches to this class of complex amides have been developed in the context of the pederins, where an O-alkylated carbinolamide constitutes the central synthetic challenge of each active member of this natural product class[4] (e.g., **3**[5] and **4**[6], Fig. 2). Among the most successful methods are those of Matsumoto,[7] Roush,[8] Hoffmann,[9] and more recently, Huang.[10]

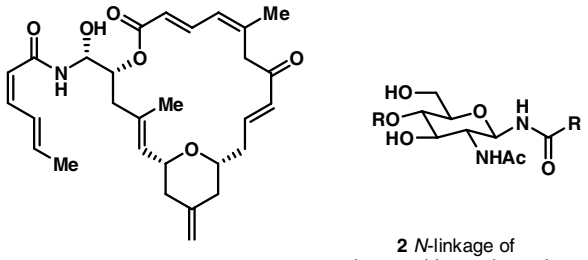

Figure 1. Carbinolamide and O-alkylated amides.

Our interest in carbinolamide synthesis was piqued by the structure of psymberin (**3**). We reported an approach to psymberin whereby **10** was prepared from pyran **6** by way of **5**[11] (Schemes 1 and 2). Stereochemical assignments were made based on the correlation of **6** and **10** to the natural product. The structure of **5** was correlated to the core of mycalamide A, as shown (**5**→**8**).[12]

Ideally, the carbinolamide of **3** would be prepared by direct addition of **9** to **10** (Scheme 2). To investigate the feasibility of this union, we examined the preparation

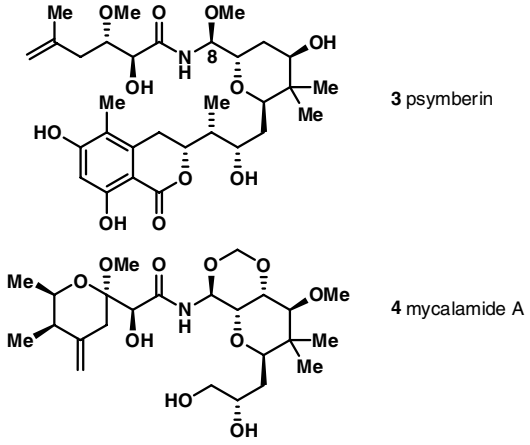

Figure 2. Two pederin-type natural products.

Keywords: Amide synthesis; Carbinolamide; Pederin; Mycalamide; Psymberin.
* Corresponding author. E-mail: ljw@rutchem.rutgers.edu

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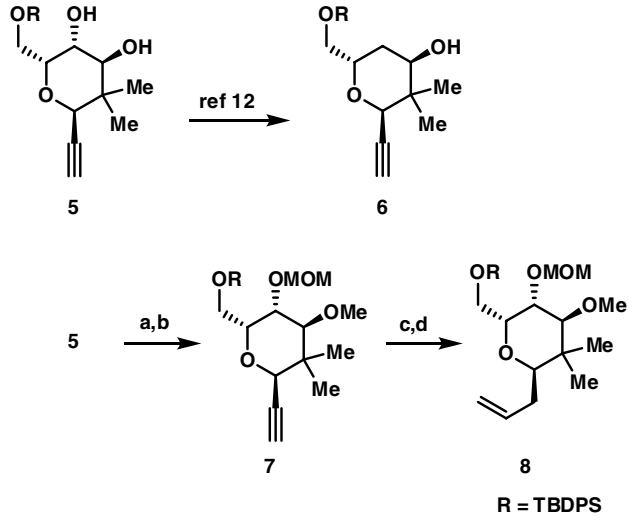
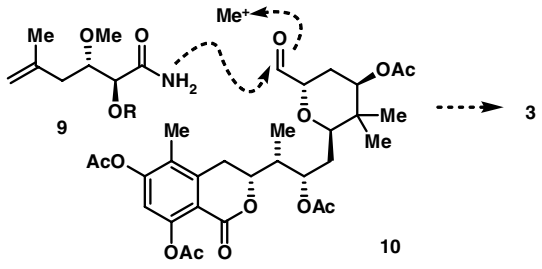
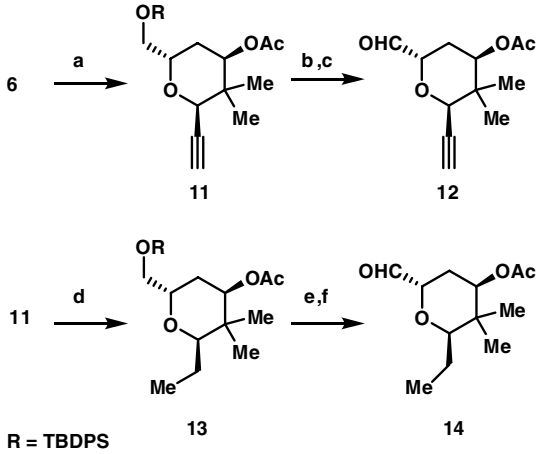


Scheme 1. Reagents and conditions: (a) NaH, MOMCl, THF, 60%; (b) NaH, CH_3I, THF, 98%; (c) BH_3·THF, 2-methyl-2-butene, then H_2O_2, NaOH, 82%; (d) Ph_3PCH_2, 75%.

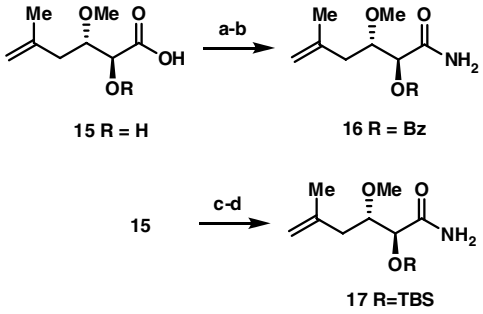


Scheme 2. Synthetic plan.

of carbinolamides from commercial and synthetic aldehydes and amides (e.g., **12**, **14**, **16** and **17**). Aldehydes **12** and **14** were obtained as shown in Scheme 3. Amides **16** and **17** were prepared from **15**[13] as shown in Scheme 4. The aldehydes and amides correspond to, in varying degrees, the structural features of **3** and **4**.

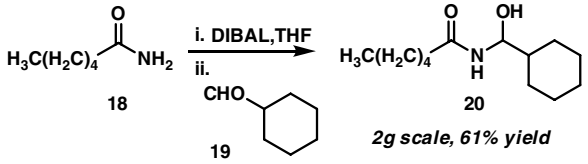


Scheme 3. Reagents and conditions: (a) Ac_2O, pyr 98%; (b) TBAF, THF, 95%; (c) $(COCl)_2$, DMSO, 80%; (d) Pd/C, H_2, 98%; (e) TBAF, THF; (f) DMP, 50% (two steps).



Scheme 4. Reagents and conditions: (a) BzCl, pyridine, 80%; (b) $(COCl)_2$, cat. DMF then NH_3, 80%; (c) AcCl, MeOH, then NH_3, 45%; (d) TBSCl, Im, DMAP, 96%.

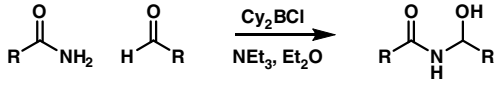
Initially, we attempted to use aluminum imidates. Hoye employed an aluminum imidate to give the carbinolamide of **1**.[14] The generality of this addition had not been reported. One rationale for the success of this addition focused on possible stabilization of the product by a hydrogen bond network.[14a,15] To test this, we examined the coupling of **18** to **19**, which was accomplished by treatment of the amide with 1 equiv of DIBAL, and then addition of 1 equiv of the aldehyde (Scheme 5). The reaction was conveniently run on a 2 g scale, and the product was isolated after aqueous workup and purified by column chromatography to give **20** as a white solid in 61% yield. DIBAL (13.0 mL, 1.0 M in hexane) was added slowly at room temperature to a solution of hexanamide (1.35 g, 13 mmol) in THF (12 mL). The reaction mixture was stirred at room temperature for 1 h, and then cyclohexylcarboxaldehyde (1.5 g, 13.0 mmol) was added slowly to the mixture. The reaction mixture was stirred for 1 h, quenched with saturated Rochelle's salt solution, and then extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:1.5) to give **20** (1.80 g, 61%) (mp 99–101 °C uncorrected). ^{1}H NMR (300 MHz, $CDCl_3$) 6.28 (d, 1H, $J = 7.8$ Hz), 5.06 (dd, 1H, $J = 7.8$, 7.5 Hz), 4.27 (br, 1H) 2.16 (t, 1H, $J = 7.5$ Hz), 0.98–1.89 (m, 17H), 0.87 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 174.5, 77.7, 42.5, 37.1, 31.8, 28.5, 28.4, 26.6, 26.1, 26.0, 25.6, 22.7, 14.3; IR ν_{max} (KBr pellet, cm^{-1}) 3246, 3068, 1645, 1553, 1026; *m/z* (ESIMS) calculated for $C_{13}H_{25}NO_2Na$ $[MNa]^+$ 250.18, found: 250.2. Unfortunately, this reaction proved capricious. Boron imidates, which apparently have not been the subject of study, were investigated as an alternative and found to add reliably to aldehydes.

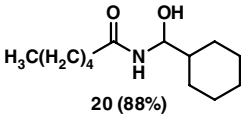
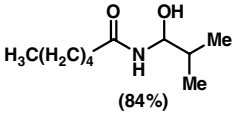
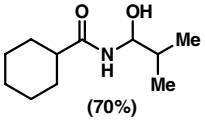
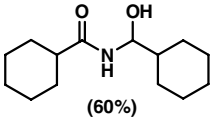
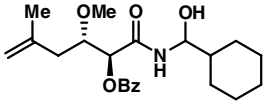
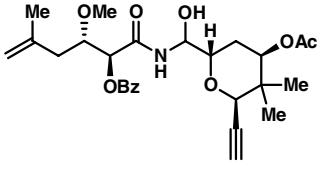
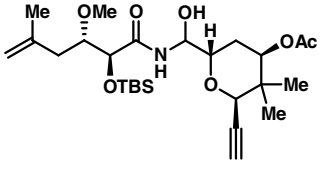
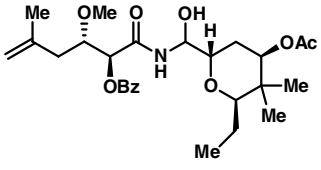


Scheme 5.

The results are shown in Table 1. The reaction conditions are based on the findings of Patterson et al.[16] for aldol addition of boron enolates. Thus, the amide (1.2 equiv) was taken up in diethyl ether (0.2 M), NEt_3 (2.0 equiv) was added, the mixture was cooled to 0 °C, and to this boron chloride (1.3 equiv, 1.0 M in hexane) was added dropwise. The heterogeneous mixture was stirred for 15 min, and then the aldehyde (1.0 equiv) was added. After 30 min the reaction was quenched with a mixture of MeOH/phosphate buffer (pH = 7.40)/H_2O_2 (30%). Isolation and purification gave the carbinolamide. Presumably, the boron imidate is formed under the reaction conditions and then adds to the aldehyde. Protected amides **16** and **17** add to the simple aldehyde of entry 5 as well as to pyran aldehydes related to **3** (entries 6–8). At present, there is no significant stereoselectivity in the addition reaction. Nevertheless, the yield appears to be independent of silyl or ester protection, and the pyran side chain does not significantly influence the efficiency of the reaction.

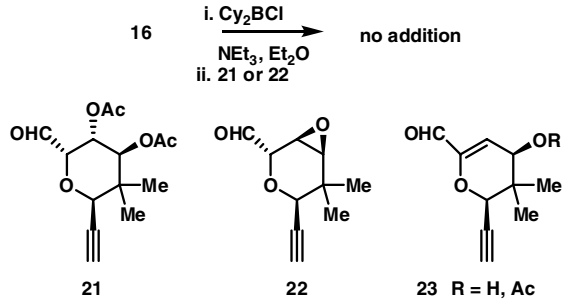
Table 1. Carbinolamide formation



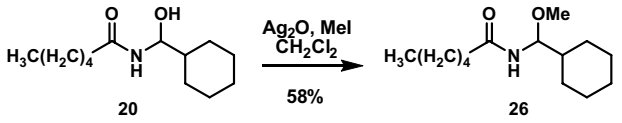
Entry	Amide	Aldeyhde	Carbinolamide (yield)
1	**18**	**19**	 20 (88%)
2	**18**	*i*-PrCHO	 (84%)
3	$CyCONH_2$	*i*-PrCHO	 (70%)
4	$CyCONH_2$	19	 (60%)
5	**16**	**19**	 (66%, dr 1:1)
6	**16**	**12**	 (40%, dr 1:1)
7	**17**	**12**	 (39%, dr 1:1)
8	**16**	**14**	 (40%, dr; 2:1)

The boron imidate conditions proved ineffective for carbinolamide formation for pyran aldehydes **21** and **22** (Scheme 6).[17] In these instances, decomposition of the aldehydes took place instead of addition, for example, β-elimination (→**23**). These findings are similar to the observations made by Rawal[18] and likely reflect the side reactions promoted by excess boron reagent.

We find that carbinolamides are not as intrinsically unstable as earlier reports suggest. Indeed in all cases, the carbinolamides of this study were stable to the reaction conditions, and accommodated aqueous workup, flash column chromatography, routine handling, and storage. It has been proposed that an appropriately positioned heteroatom may serve as an intramolecular hydrogen bond acceptor and that this interaction accounts for unexpected stability of such carbinolamides (e.g., **24**).[15a] The presence of an interaction has experimental support from related systems (**25**, Fig. 3).[15b] However, in light of the results presented here, particularly entries 1-4 of Table 1, the notion that carbinolamides are unstable in the absence of a hydrogen bond network must be reevaluated. Although the extended hydrogen bond networks interaction has been observed,[15b] it has not been established that such networks are *necessary* to render a carbinolamide stable to isolation without special precautions.[19] Importantly, carbinolamide O-alkylation is a known transformation.[20] Such alkylation reduces potential hydrogen bonding interactions, and yet, the products exhibit significant stability. An additional example is shown in Scheme 7. Carbinolamide **20** was smoothly converted to the methyl derivative **26**. The data suggest that carbinolamides are intrinsically stable enough to be isolated, characterized, and manipulated, even in the absence of an extended hydrogen bond network.[21]



Scheme 6.



Scheme 7.

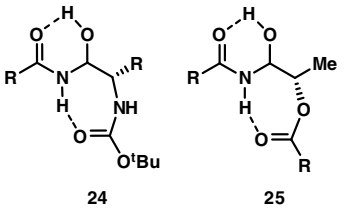


Figure 3. Previous proposed hydrogen bonded networks.

Acknowledgements

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19. This rationale has been invoked to account for the stability of zampanolide (**1**); see Ref. 14a.
20. For an example relevant to zampanolide (**1**), see Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.
21. There is a twofold proviso, however. The reaction conditions used to generate the carbinolamide must be compatible with isolation, and the other functionality must not facilitate decomposition.