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Solvent-free synthesis of monoacylaminals from the reaction of amides and aminals as precursors in carbinolamide synthesis

Matthew F. Sansone, Takaoki Koyanagi, David E. Przybyla, Richard W. Nagorski *

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA

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ABSTRACT

A solvent-free method of generating monoacylaminals by heating the amide and aminal starting materials in the presence of one another has been developed. Yields were generally between 45% and 65% with the monoacylaminal being isolated, needing no further purification after drying under high vacuum.

Carbinolamides are a functional group generated by the nucleophilic attack by an amide on an aldehyde followed by a proton shift.[1] Under neutral aqueous conditions, the compounds are very stable with their breakdown being catalyzed by both acids and hydroxide.[2,3] The compounds themselves have a long history, with reports appearing in the literature as early as the 1870's.[4] More recently, carbinolamides have been found to be involved in biological processes that have both postive[5,6] and negative[7] outcomes for the host. In addition, their synthesis has been the focus of increasing attention with the discovery of a growing number of compounds with interesting biological properties that possess either a carbinolamide moiety or the O-alkylated derivative.[8–10] Examples such as azaspirene (**1**)[9a,10] and psymberin (**2**)[11] are shown in Figure 1. Given the growing number of compounds being discovered that incorporate carbinolamides or its derivatives, there are surprisingly few routes leading to their generation (see below). One method, that we have found to be particularly versatile for the synthesis of carbinolamides, involves the generation of a monoacylaminal precursors which are subsequently hydrolyzed to the carbinolamide target.[12] Reported here are the details of the development of a solvent-free method of generating monoacylaminals from the amide and aminal precursors.

Our long standing interest in probing the reactivity of carbinolamides in aqueous solution[3] has led to the investigation of many methods of synthesizing this functionality. The traditional method involved simply mixing the amide and aldehyde, in solution, with the product precipitating out of solution or being isolated from the reaction mixture (see Scheme 1: method A).[1] This method has proved to be useful with highly electrophilic aldehydes such as formaldehyde and chloral but produced complex mixtures with less electrophilic aldehydes.[1]

More recently, Williams and co-workers developed a method of synthesizing carbinolamides from a broader range of amide and aldehyde starting materials utilizing dicyclohexylboron chloride and triethylamine in diethyl ether/hexane solution (see Scheme 1: method B).[13] This method has proved to be very useful in the direct synthesis of carbinolamides incorporating alkyl aldehydes.[13] In addition, a process for the direct synthesis of the *N*-(methoxyalkyl)amides has been developed by Lokensgard et al. utilizing acyl chlorides and imidates.[14]

The primary means we have utilized, in the synthesis of carbinolamides, has been to first generate the monoacylaminal precursor which was then solvolyzed to yield the target compound.[12] The literature process involved mixing equimolar amounts of the amine, amide, and aldehyde in methanol followed by addition of water and cooling (see Scheme 2).[2d] This procedure worked very well

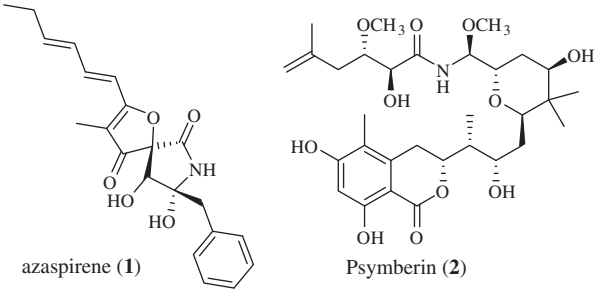

Figure 1. Carbinolamide and derivative containing compounds.

* Corresponding author. Tel.: +1 309 438 8978; fax: +1 309 438 5538.
E-mail address: rnagor@ilstu.edu (R.W. Nagorski).

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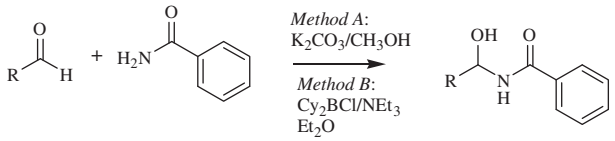
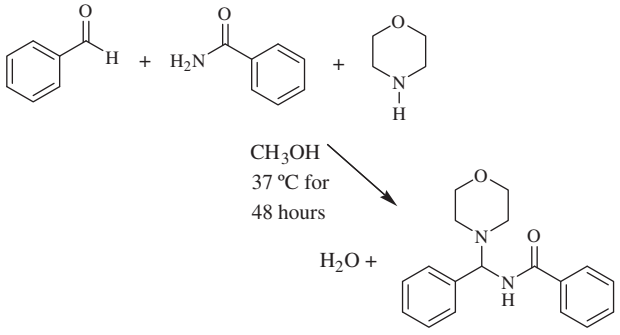


Scheme 1. Two methods of carbinolamide synthesis.

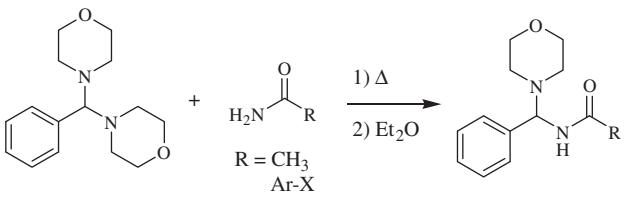


Scheme 2. Direct monoacylaminal synthesis.

for the production of the monoacylaminal generated from benzamide, benzaldehyde, and morpholine.[2d,15] However, as substituents were added to the amide/aldehyde or acetamide was used as the starting amide, the major product isolated via this procedure became the aminal.

Attempts to find other methods of synthesizing monoacylaminals yielded a paper by Sakai and Sekiya.[16a] In this paper, a method was mentioned wherein the pyrrolidine aminal of benzaldehyde was heated at 85–90 °C in the presence of an amide for several hours, yielding the monoacylaminal.[16a] Attempts to repeat this work, using the conditions described, with the morpholine aminal of benzaldehyde and acetamide, yielded limited quantities of the desired monoacylaminal. However, modifications to the procedure were developed that consistently produced the target monoacylaminals incorporating a variety of amides (see Scheme 3, Tables 1 and 2).

The general procedure used for all the monoacylaminal syntheses reported involved first mixing the aminal and amide in an Erlenmeyer flask (in all cases described here, both were solids). Using a Bunsen burner, the flask containing these materials was gently heated until the materials had melted, thus ensuring a homogenous mixture.[17] After the solids had melted, heating was continued with the solution reaching temperatures of ~185–220 °C. The period of heating was variable; however, in general, heating was continued for 5–10 min. Following cessation of heating, the flask was allowed to cool until it was hot to the touch but could be safely handled (~30–40 °C). At this point a small amount of ether was added to the reaction mixture, which completed the cooling and initiated crystallization upon agitation.



Scheme 3. Solvent-free synthesis of monoacylaminals.

Table 1
Yields and melting points for the synthesis of monoacylaminals from morpholine aminals of benzaldehyde derivatives and acetamide

Amide	Aminal	Yield[a] (%)	Melting point[b] (°C)	Lit. Mpt. (°C)
CH_3CONH_2	H	56	151–2	151–2[c]
CH_3CONH_2	4-CH_3	64	150–1	—
CH_3CONH_2	4-Cl	50	181–3	—
CH_3CONH_2	4-CN	71	157–8	—
CH_3CONH_2	4-$N(CH_3)_2$	56	144–7	—
CH_3CONH_2	4-NO_2	53	181–3	—
CH_3CONH_2	4-OCH_3	41	143–4	—
CH_3CONH_2	4-CF_3	66	188–9	—
CH_3CONH_2	3-Cl	51	129–30	—
CH_3CONH_2	3-NO_2	51	130–1	—

[a] Based upon 1–3 independent determinations.
[b] All melting points were determined using a commercial apparatus and are uncorrected.
[c] Refs. 16a and 16b.

The resulting mixture was cooled and the crystalline product collected by vacuum filtration.

In the case of the acetamide derivatives, the solvent-free reactions were performed with a 2:1 molar ratio of the amide to aminal (see details in Supplementary data). This procedure resulted in the crude monoacylaminal product being contaminated with excess acetamide. However, the acetamide could easily be removed by washing the crude product with water during vacuum filtration. While the total yield of the monoacylaminal product (yields were between 40% and 70%) was diminished using this method, it was found that the monoacylaminal obtained needed no further purification (see Table 1; yields are based upon 1–3 independent experiments).

For the benzamide derivatives (see Table 2), the solvent-free reactions were performed using a 0.99:1 molar ratio of the amide to aminal (see details in Supplementary data). When larger than equimolar amounts of amide were used, it became difficult to separate the monoacylaminal product from the excess amide. The most efficient means to overcome this problem was to use a slight excess of the aminal which would therefore limit the amount of benzamide starting material remaining in the reaction mixture. Any residual amide could be removed by washing the crystals isolated by vacuum filtration with ice cold ether and/or 95% ethanol. As with the acetamide derivatives, these compounds were pure upon drying under vacuum.

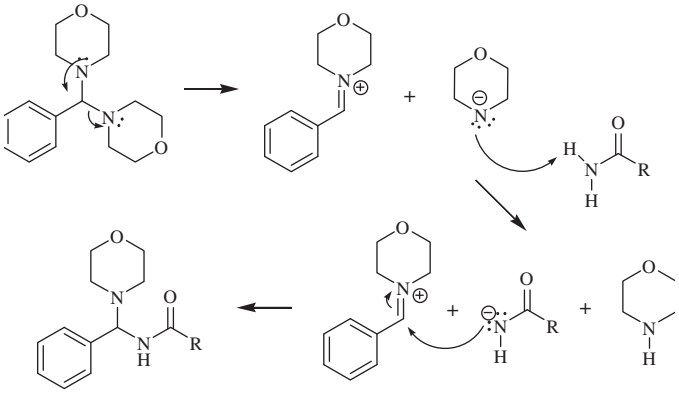
Shown in Scheme 4 is the proposed mechanism for the formation of the monoacylaminal under the solvent-free conditions of the reactions. In the proposed mechanism, the first stage involves the generation of an iminium ion and the anion of morpholine. The morpholine anion then deprotonates the amide, to generate morpholine and an amidate. This thermodynamically favored acid/base reaction[18] was further assisted by the morpholine boiling from the reaction solution as generated, leaving the amidate and iminium ion remaining in the reaction vessel. Condensate at the neck of the Erlenmeyer flask that formed during heating was collected and ^{1}H NMR showed it to be morpholine. Nucleophilic attack by the amidate on the carbon of the iminium ion resulted in the formation of the monoacylaminal.

Presented here is a method for the production of monoacylaminals via thermal initiation of a reaction between an aminal and an amide in the absence of solvent. The method provides good to modest yields of the target compounds having a variety of substituents on both the amide and aminal starting materials. Using the methods described herein, the products can be obtained directly from the reaction in a pure form. In our hands, the monoacylaminals have proved to be versatile intermediates that can be solvolyzed, under acidic conditions, to produce a variety of carbinolamides and their O-alkylated derivatives.[12]

Table 2
Yields and melting points for the synthesis of monoacylaminals from morpholine aminals of benzaldehyde derivatives and benzamide derivatives

Benzamide	Aminal	Yield[a] (%)	Melting point[b] (°C)	Lit Mpt. (°C)	Benzamide	Aminal	Yield[a] (%)	Melting point[b] (°C)	Lit. Mpt. (°C)
H	3-NO_2	64	165–6	—	4-NO_2	4-CH_3	59	116–8	—
4-NO_2	4-SCH_3	89	158–60	—	4-Cl	4-CH_3	57	154–6	—
4-Cl	4-SCH_3	61	235–8	—	3-Cl	4-CH_3	35	148–9	—
H	4-SCH_3	56	152–3	—	H	4-CH_3	78	158–60	—
4-NO_2	4-Cl	69	132–6	—	4-CH_3	4-CH_3	27	140–2	—
3-NO_2	4-Cl	37	176–9	—	3-CH_3	4-CH_3	49	143–6	—
4-Cl	4-Cl	50	158–9	—	4-NO_2	3-CH_3	66	105–8	—
H	4-Cl	97	159–61	—	3-NO_2	3-CH_3	36	139–42	—
4-CH_3	4-Cl	47	148–52	—	4-Cl	3-CH_3	41	98–100	—
3-CH_3	4-Cl	47	132–4	—	H	3-CH_3	32	136–8	—
4-NO_2	3-Cl	69	114–20	—	3-CH_3	3-CH_3	40	161–3	—
4-CF_3	3-Cl	24	161–2	—	4-NO_2	4-OCH_3	67	135–8	—
4-Cl	3-Cl	49	165–6	—	4-Cl	4-OCH_3	65	140–2	—
H	3-Cl	50	150–1	—	3-Cl	4-OCH_3	25	140–2	—
3-CH_3	3-Cl	33	171–3	—	H	4-OCH_3	44	132–4	—
4-NO_2	H	62	161–4	—	4-CH_3	4-OCH_3	32	145–6	—
3-NO_2	H	43	113–5	—	3-CH_3	4-OCH_3	43	125–8	—
4-Cl	H	49	140–3	—	4-Cl	3-OCH_3	51	171–3	—
4-CH_3	H	34	134–6	—	H	3-OCH_3	60	151–2	—
3-CH_3	H	54	166–8	—	H	H	67	160–2	166–7[c]

[a] Based upon 1–3 independent determinations.
[b] All melting points were determined using a commercial apparatus and are uncorrected.
[c] Ref. 16a.



Scheme 4. Proposed mechanism of the solvent-free monoacylaminal formation.

Acknowledgments

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Supplementary data

Supplementary data (synthetic methods and characterization of all monoacylaminals) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.043.

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12. (a) Unpublished work. (b) The reactions producing the carbinolamides were performed at room temperature with the monoacylaminals being hydrolyzed in a weakly acidic solution (pH maintained between 4 and 5 using 0.1 M HCl). Reaction progress was followed by monitoring the pH of the solution with the solvolysis being deemed complete when no further changes in pH occurred. The product precipitated during formation but the reaction solution was cooled, in an ice bath, prior to collection of the product by vacuum filtration.
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17. (a) All reactions were performed in a fume hood due to the evaporation of morpholine from the reaction mixture during the course of the procedure. (See Scheme 4 and discussion of the proposed mechanism.) (b) All flames were extinguished prior to the addition of ether to the Erlenmeyer flask.
18. (a) Although limited, available data suggests that benzamide derivatives will have pK_a's greater than 19 and as low as 16 for 4-nitrobenzamide (see Refs. 18b and 18c). Amines are expect to have a much higher pK_a and are therefore excellent organic bases (see Ref. 17d).; (b) Hine, J.; Hine, M. *J. Am. Chem. Soc.* **1952**, *74*, 5266–5271; (c) Homer, R. B.; Johnson, C. D. *The Chemistry of Amides*; Interscience Publishers: New York, 1970; (d) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442–3443.