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# A facile synthesis of stable β-amino-*N*-/*O*-hemiacetals through a catalyst-free three-component Mannich-type reaction

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ABSTRACT

A practical, straightforward and one-step procedure for the synthesis of novel and stable β-amino-*N*-/*O*-hemiacetals (i.e. γ-aminoalcohols) is provided. The title compounds were obtained in good to excellent yields through an uncatalyzed three-component reaction by treatment of secondary amines with polyformaldehyde and electron-rich alkenes in acetonitrile as solvent at ambient temperature. The reactions proceeded with the formation of iminium ions, through a Mannich-type reaction, as the key intermediates for the generation of the target products. Single crystal X-ray analysis of derivative **4l** confirmed unequivocally the structure and stability of the obtained compounds.



## Introduction

Contemporary research in organic synthesis focuses on atom economy.[1] Indeed, the efficiency of a synthetic sequence is dependent upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created. Therefore, devising reactions that achieve multibond formation in one operation is becoming one of the major challenges in searching for step-economic synthesis. Multicomponent reactions (MCR's) are processes in which three or more reactants are combined in a single chemical step to afford products that incorporate substantial fragments of all the components.[2a–e] Indeed, many important reactions such as Strecker (1850),[2f] Hantzsch (1882),[2g] Biginelli (1891),[2h] Mannich (1912),[2i] Passerini (1921),[2j] Ugi (1959),[2k] among others, are all multicomponent.

The γ-aminoalcohols are valuable building blocks in organic synthesis,[3a,b] in particular, because they are important precursors in the preparation of a variety of natural occurring products and compounds of biological interest.[3c–i] Thus, Venlafaxine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class,[4a] Haloperidol is a potent dopamine antagonist,[4b,c] while considerable attention has been focused on the opiate-agonists Tramadol and analogues[4d] (Fig. 1).

Hemiacetals are commonly formed when an equivalent of alcohol adds to the carbonyl carbon of an aldehyde.[5] Reaction proceeds in an equilibrium and contrary to the stability displayed by their five-/six-membered intramolecular cyclic analogues (called lactols),[5a,b] in the most cases, the open chain hemiacetals are intrinsically unstable and the equilibrium tend to favor the parents aldehyde and alcohol.[5c,d] There are just few examples of

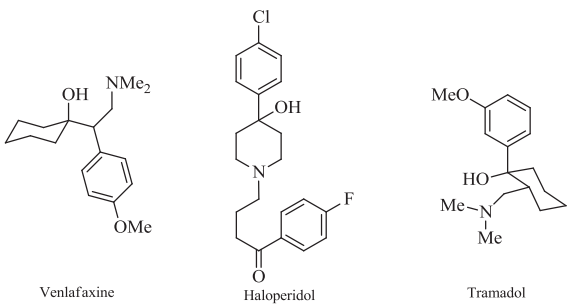


**Fig. 1.** Some representative examples of biologically active γ-aminoalcohols.

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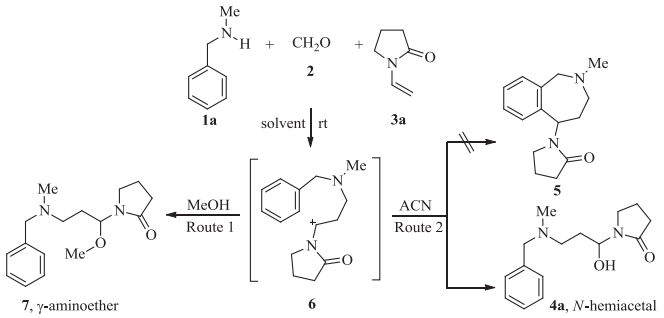



**Scheme 1.** Synthesis of the novel β-amino-*N*-hemiacetal **4a**.

stable and isolable open chain hemiacetals, especially from aldehydes bearing electron-withdrawing groups,[6] particularly, several of them derived from chloral.[6e–h]

Attempts have been made in the past to improve methodologies based on direct or indirect Mannich-type reactions involving nucleophiles such as enolates, enol ethers, and enamines.[7] These processes were found to be extremely substrate- and conditions-dependent, long reactions time and often required the use of an appropriate catalyst such as organocatalysts,[8] transition metal-based Lewis acids,[9] and Brønsted acid/bases.[10] Therefore, the development of new versions of the Mannich-type reaction working under mild conditions have been declared a subject of great importance.

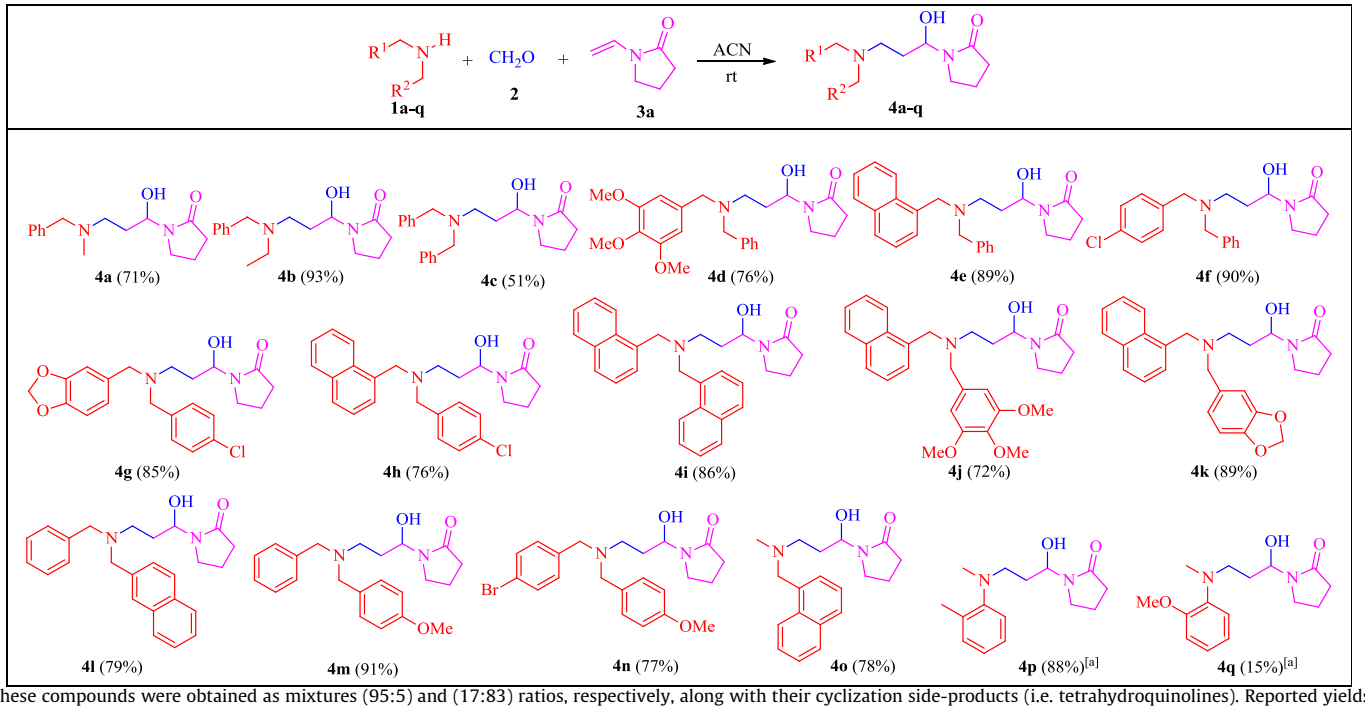
In connection with our current program on the synthetic utilization of benzylamine derivatives for multiple bond-forming reactions,[11] herein, we wish to report our results on the unplanned, catalyst-free and highly efficient synthesis of novel and stable β-amino-*N*-/*O*-hemiacetals (γ-aminoalcohols), through a three-component Mannich-type approach.

## Results and discussion

In an attempt to obtain the novel 2-benzazepine derivative **5** (Scheme 1), a scaffold of high synthetic and biological interest,[12] we considered that through a three-component Mannich-type reaction/intramolecular electrophilic aromatic substitution sequence would be possible to obtain the desired product **5** by stirring at room temperature a mixture of benzylmethylamine **1a** (1 equiv), polyformaldehyde **2** (1.2 equiv) and *N*-vinyl-2-pyrrolidone **3a** (1 equiv) in methanol (MeOH) as protic solvent. After analysis by spectroscopic techniques, we noticed that the formation of the desired product **5** did not occur and instead the unexpected γ-aminoether **7** was obtained as unique product (Scheme 1, route 1). This finding indicated that MeOH acted not only as the solvent but also as the nucleophile, trapping the carbocationic species **6** before the expected intramolecular cyclization process could occur.[11c] According to this result, we decided to repeat the same experiment but using an aprotic an non nucleophilic solvent (i.e. dry acetonitrile, ACN) instead of methanol in order to avoid the competition by the cation **6** and address the reaction toward the desired product **5**. After 72 h of stirring (TLC control), a dense oily material was obtained and purified by column chromatography on silica gel using a mixture $CHCl_3$:MeOH (15:1) as eluent. After analysis by spectroscopic techniques, we confirmed that the formation of the expected product **5** did not occur again, and instead the unexpected β-amino-*N*-hemiacetal (also γ-aminoalcohol) **4a** was obtained as the sole product in 71% isolated yield, (Scheme 1, route 2).

The main spectroscopic features of the structure of compound **4a** correspond to the presence of O—H, C=O and C—O absorption bands at 3411, 1682 and 1107 $cm^{-1}$, respectively, in the IR spectrum. A $NCH_3$ signal at 2.22 ppm, six methylenic signals between 1.57 and 3.64 ppm and a doublet of doublets integrating for 1H at 5.62 ppm (dd, $J$ = 9.0, 3.4 Hz) assigned to the new aza-hemiacetal proton (NC**H**-OH), along with five (but not four if product **5** had

**Table 1**
Three-component synthesis of novel and stable β-amino-*N*-hemiacetals **4a–q**.




[a]These compounds were obtained as mixtures (95:5) and (17:83) ratios, respectively, along with their cyclization side-products (i.e. tetrahydroquinolines). Reported yields are after isolation from column chromatography.

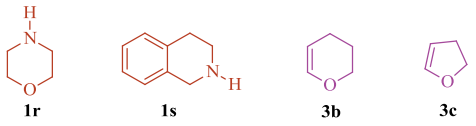



**Fig. 2.** Additional amines **1r,s** and cyclic vinyl ethers **3b,c** employed as reagents for the synthesis of a further family of β-amino-*N*-/*O*-hemiacetals **4**.

been obtained) aromatic protons are the most relevant signals in the $^{1}$H NMR spectrum. The signal corresponding to the hydroxyl proton (O—H) is not observed due to a rapid chemical proton exchange. The presence of six methylene carbon atoms at 18.1, 29.5, 31.8, 41.8, 54.6 and 62.5 ppm, the $NCH_3$ signal at 41.6 ppm, the signal of the aza-hemiacetal carbon atom (N**C**H-OH) at 76.5 ppm, three aromatic CH signals at 127.4, 128.4, 129.1 ppm and two quaternary carbon atoms at 137.5 and 175.0 (C=O) ppm in the $^{13}$C NMR spectrum, are in agreement with the proposed structure for compound **4a**. A molecular ion peak with *m*/*z* 262, also confirmed its structure.

Although, the aza-hemiacetal **4a** in principle, was not our expected product, owing to the practical usefulness of its structural parents γ-aminoalcohols,[3,4] we decided to explore in more detail this process. Then, in order to determine the reproducibility of this experiment, a chemset of diversely substituted secondary amines **1a–q** was evaluated, Table 1. Particularly, the commercially unavailable amines **1d–n** were synthesized from a one-pot reductive amination of primary benzylamines with arenealdehydes, involving the pre-formation of their respective imines followed by reduction with $NaBH_4$ in methanol at room temperature (see Supplementary data).[11a]

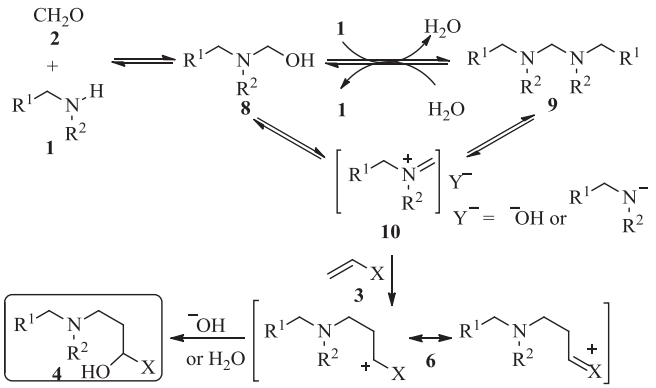
Thus, applying this multicomponent methodology to the further amines **1b–q** with *N*-vinyl-2-pyrrolidone **3a** under the established conditions (i.e. $(CH_2O)_n$, ACN, room temperature and stirring for 72 h), to our satisfaction, the corresponding β-amino-*N*-hemiacetals **4b–q** were obtained as shown in Table 1. In all cases reactions proceeded with the same behavior and yields in the range of 51–93%, except for compound **4q** (see Table 1 foot note).

Additionally, to increase the scope of this protocol, heterocyclic amines **1r,s** and the cyclic vinyl ethers **3b,c**, (Fig. 2), were assayed under the established reaction conditions.

Satisfactorily, all reactions afforded the desired products **4r–w** in good yields (Table 2). In general, all products **4** were obtained as colorless or pale yellow oily materials except for compounds **4c** and **4l** which were obtained as white solids.

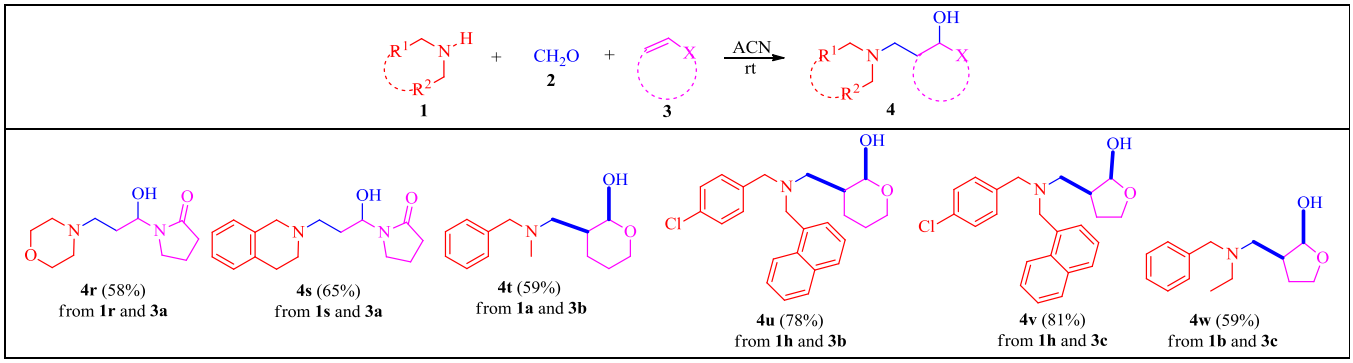
Most compounds **4** were obtained as air and light stable oily materials (only **4c** and **4l** were solids). Particularly, **4a–s** were isolated as racemic mixtures due to the chirality of the carbon atom of their aza-hemiacetal functionalities (N**C**H-OH) formed. While, compounds **4t–w** (bearing two chiral carbon atoms), were obtained as mixtures of their corresponding *cis* and *trans* diastereomers, being the *trans* isomer the main component for **4t** (i.e. d.r = 48:52 *cis*:*trans*) and **4u** (i.e. d.r = 33:67 *cis*:*trans*). In contrast, the *cis* isomer was the main component for **4v** (i.e. d.r = 71:29 *cis*:*trans*) and **4w** (i.e. d.r = 79:21 *cis*:*trans*). The diastereomeric ratios (d.r) were calculated from the $^{1}$H NMR spectra of their crudes. Although the signal corresponding to the hydroxyl proton in the $^{1}$H NMR spectra should be an important structural feature, only compounds **4b**, **4j**, **4k**, **4p**, **4q** and **4s** showed a broad singlet in the range of (4.97–6.12 ppm) for this functionality. A rapid chemical proton exchange should explain this outcome.

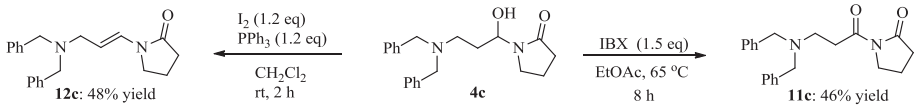
According to the results, it may be suggested that the synthesis of the hemiacetals **4** commenced with the formation of a hemiaminal **8** from the reaction of the secondary amine **1** and formaldehyde **2**, which should be simultaneously in equilibrium with the aminal **9** and the iminium ion **10** (its counter ion Y = $OH^-$ if comes from **8** or $(R^1CH_2)R^2N^-$ if comes from **9**), as shown in Scheme 2. In all cases during the course of the reactions, we detected by TLC the partial transformation of the secondary amines **1** into aminals type **9** although they were completely re-consumed during the reaction. Particularly, the aminal **9a** ($R^1$ = Ph, $R^2$ = $CH_3$) was isolated and thoroughly characterized (see Supplementary data). Moreover, treatment of aminal **9a** (1 equiv) with polyformaldehyde **2** (0.7 equiv) and alkene **3a** (2 equiv) under the established reaction conditions also afforded the expected product **4a**; so confirming its presence as an intermediate in this three-component reaction.




**Scheme 2.** Proposed mechanistic sequence for the formation of the β-amino-*N*-/*O*-hemiacetals **4** via the iminium ion **10**.

**Table 2**
Additional examples of β-amino-*N*-/*O*-hemiacetals **4** obtained from the chemset of amines **1r,s** and cyclic ethers **3b,c**.






**Scheme 3.** Oxidation and dehydration reactions over the *N*-hemiacetal **4c**.

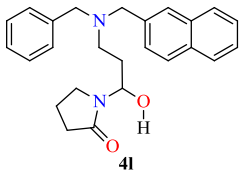
Subsequently, the iminium ion **10** should be trapped by the alkene **3** *via* a Mannich-type reaction leading to the carbocationic species type **6** (stabilized by a resonant effect with the free electronic pair of the X-substituent), through an irreversible process affording the new C—C bond. Formation of the proposed hydroxyl species **10** (a tightly ionic pair) from **8** and **9**, should be the key intermediate and source of the $OH^-$ ions for the synthesis of the isolated hemiacetals **4**. The intermolecular attack of the hydroxyl counter ion or a water molecule over the species **6** should led the isolated β-amino-*N*-/*O*-hemiacetals **4**.

Albeit, all compounds **4** showed in their IR spectra broad bands in the range of (3325–3517 $cm^{-1}$) associated with the O—H stretching vibration of the hydroxyl functionality, some of them were not observed in their $^1H$ NMR spectra. For a further confirmation of the presence of this functionality, we performed a couple of derivatization reactions involving such functional group. Thus, the oxidation of **4c** with *o*-iodoxybenzoic acid (IBX) afforded the corresponding solid amide **11c** isolated in moderate 46% yield as shown in Scheme 3. The following experiment consisted in the conversion of the *N*-hemiacetal **4c** into the alkene **12c** in 48% yield, *via* a dehydration process by treatment with triphenylphosphine and iodine.[13] In consequence, the chemical transformation of **4c** into both oxidation and dehydration products **11c** and **12c**, respectively, confirmed the presence of the hydroxyl functionality in structures **4**.

In addition to the above experiments and in order to confirm unequivocally the presence of this functionality and the stability of these compounds, after several attempts, we finally could grow single crystals suitable for X-ray diffraction of compound **4l** in ethyl ether at room temperature. As shown in Fig. 3 (and Supplementary data), there is no doubt that the obtained compounds **4** effectively corresponds to the hemiacetal structures proposed in Scheme 1 and Tables 1 and 2.

At this stage, remarkable features of our methodology are the facts that it does not involve the use of any catalyst, three new bonds are formed in sequence during the process and the reaction proceeds smoothly at room temperature. Moreover, the OH source for the last step of the process depicted in Scheme 2 corresponded to the $H_2O$ ($OH^-$) released from the formation of **9** or **10**, respectively. In consequence, the starting compounds **1**, **2** and **3** are consumed stoichiometrically in the formation of products **4** without releasing by-products. These findings are in agreement with the atomic economy concept providing also an environmentally friendly character to this three-component procedure.

In summary, we have implemented an efficient and straightforward approach for the synthesis of novel and stable β-amino-*N*-/*O*-hemiacetals (γ-aminoalcohols) **4** in good to excellent yields from an uncatalyzed three-component Mannich-type reaction at ambient temperature. The fact that all three precursors (i.e. amine, formaldehyde and alkene), were stoichiometrically consumed in the course of the reactions and three new bonds (i.e. C—O, C—N and C—C) were formed in only one-step without producing by-products, provide an outstanding bond-forming efficiency and environmentally friendly quality to this approach. Further studies oriented to increase of the scope of this methodology (i.e. try with primary amines, superior aldehydes instead of $CH_2O$ and other activated alkenes), as well as, the variation of the reaction conditions attempting to force the reaction toward the cyclized benzazepinic systems **5**, are currently in progress.



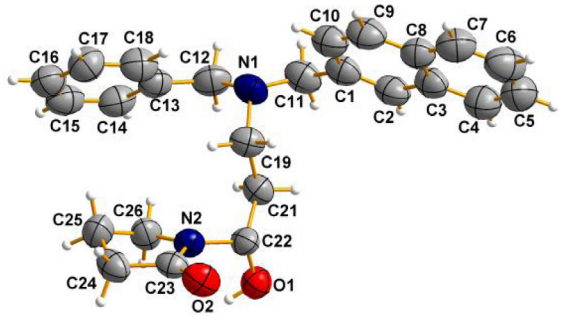




**Fig. 3.** ORTEP drawing of the asymmetric unit for the *N*-hemiacetal **4l**; ellipsoids are displayed at the 50% probability level.

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.02.084.

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