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Efficient Catalyst-Free Four-Component Synthesis of Novel γ-Aminoethers Mediated by a Mannich Type Reaction

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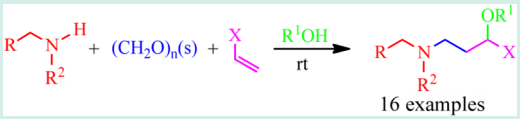
Supporting Information

ABSTRACT: Herein, it is provided an efficient and one-pot procedure for the synthesis of novel and diversely substituted γ-aminoethers in good yields through a four-component process by treatment of benzylamines with polyformaldehyde and activated alkenes in aliphatic alcohols acting both as solvent and as etherificant agents. Reactions proceeded via a Mannich-type reaction, where the formation of iminium ions and aminals was identified as the key intermediates to obtain the target products.



KEYWORDS: *Mannich-type reaction, alkylbenzylamines, multicomponent reactions, etherification reaction, γ-aminoethers*

INTRODUCTION

Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product,[1a−d] (e.g., Mannich,[1e] Strecker,[1f] Hantzsch,[1g] Ugi,[1h] Biginelli,[1i] Passerini,[1j] and Willgerodt−Kindler[1k] reactions). In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. Applications of MCRs in all areas of applied chemistry are very popular because they offer a wealth of products, while requiring only a minimum of effort. As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one pot. Unlike the usual stepwise formation of individual bonds in the target molecule, the defining attribute of MCRs is the inherent formation of several bonds in one operation without isolating the intermediates (referred to as the bond-forming efficiency, BFE),[2] changing the reaction conditions, or adding further reagents.

Amino ethers are valuable building blocks in organic synthesis, in particular, because they are important precursors in the preparation of a wide variety of pharmaceutical products.[3] In the past years, a series of selective serotonin (5-HT)-reuptake inhibitor (SSRI) antidepressants (e.g., fluexetine and paroxetine) and selective norepinephrine (NE)-reuptake inhibitor antidepressants (e.g., tomoxetine and viloxazine), have been developed.[4] Structural examination of such compounds revealed that several of them contain the γ-amino ether functionality in their structures, Figure 1, which could be related with the biological activity displayed by such compounds.

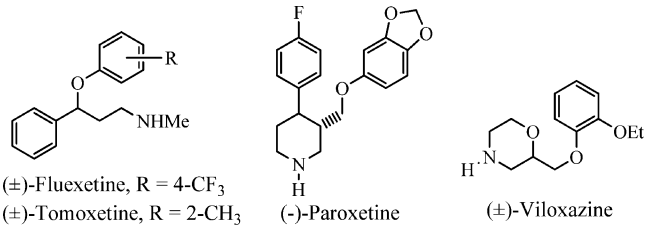


Figure 1. Some γ-aminoethers of biological interest.

RESULTS AND DISCUSSION

Continuing with our studies on the synthetic utility of benzylamine derivatives,[5] herein, we report a highly efficient synthesis of novel γ-aminoethers in good to excellent yield starting from secondary benzylamines through a four-component strategy mediated by a Mannich-type reaction.

As a result of our recent reports on the benzylamine derivatives,[5] we envisioned the possibility to obtain novel 2-benzazepine derivatives **5**,[6] by the treatment of benzylamine **1**{*1*} (1 equiv), polyformaldehyde (1.2 equiv), *N*-vinyl-2-pyrrolidone **2**{*1*} (1 equiv) in methanol **3**{*1*} as solvent and in the presence of L-proline (20 mol %) as organocatalyst. The experiment afforded a light and a dense oily material after 24 h of stirring, which was purified by column chromatography on silica gel using a mixture CH_2Cl_2/MeOH (20:1) as eluent. After analysis by spectroscopic techniques, we noticed that formation of the desired product **5** did not occur but the unexpected γ-aminoether **4**{*1,1,1*} was obtained as the sole product, Scheme 1. According to this result formation of aminoether **4**{*1,1,1*} involved the consumption of the methanol used as solvent.

The most relevant spectroscopic features to confirm the structure proposed for compound **4**{*1,1,1*} corresponded to the presence of C═O and C−O absorption bands at 1692 and

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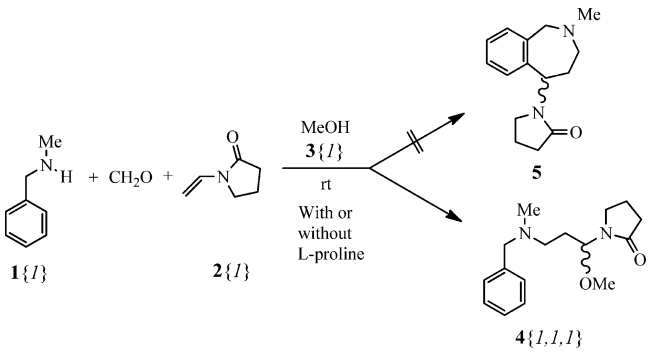
Scheme 1. Synthesis of the Novel γ-Aminoether 4{1,1,1} from the Benzylmethylamine 1{1}



(1207, 1077) cm^{-1}, respectively, in the IR spectrum. A NCH_3 signal at 2.20 ppm, six methylenic signals between 1.69 and 3.51 ppm, a singlet integrating for 3H at 3.22 ppm assigned to the OCH_3 functionality and a tiplet integrating for 1H at 5.21 ppm (t, J = 6.6 Hz) assigned to the new aza-methylacetal proton (NCH−O), along with five (but not four if product **5** were been formed) aromatic protons are the most relevant signals in the ^1H NMR spectrum. The presence of six methylene carbon atoms between 18.2−62.6 ppm, a NCH_3 signal at 42.3 ppm, a methoxy group at 55.6 ppm, a signal of the aza-methylacetal carbon atom (NCH−O) at 81.1 ppm, three aromatic CH, two quaternary Cq carbon atoms and the (C═O) at 176.0 ppm in the ^{13}C NMR spectrum, are in agreement with the proposed structure for compound **4**{*1,1,1*}. Finally, a molecular ion with m/z 276 and a base peak with m/z 91 (tropylium cation), also confirmed its structure.

Since compound **4**{*1,1,1*} possesses an asymmetric carbon atom (i.e., the aza-acetal one), a sample of the product was analyzed by polarimetry and HPLC using a chiral column to determine if an asymmetric process occurred by the presence of L-proline in the reaction media. Regrettably, product **4**{*1,1,1*} was optically inactive affording a racemic mixture, Figure 2. The reaction was repeated without adding L-proline, and the results were similar indicating L-proline did not participate in the synthetic process.

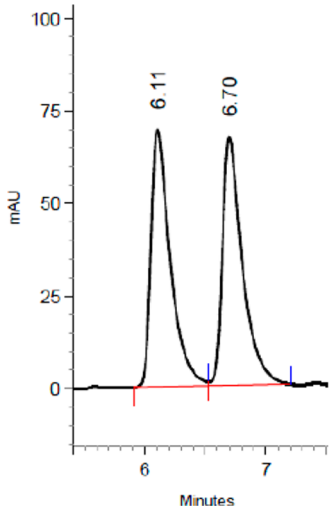


Figure 2. Chromatogram of the racemic mixture of compound **4**{*1,1,1*} separated by HPLC using a chiralpack column.

On the basis of this unexpected γ-aminoether product **4**{*1,1,1*}, we decided to test the scope of this synthetic methodology with benzylamines chemset **1**{*1−4*}, terminal alkenes chemset **2**{*1−4*}, and alcohols chemset **3**{*1−5*}, Figure 3, to determine the generality of this multicomponent methodology.

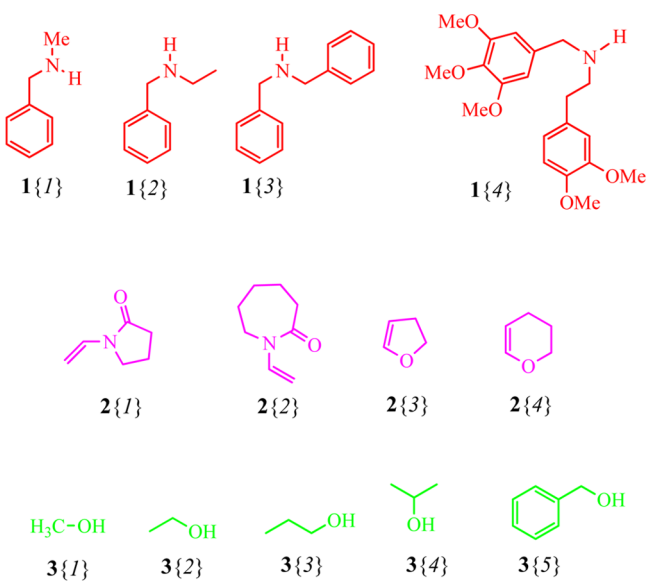
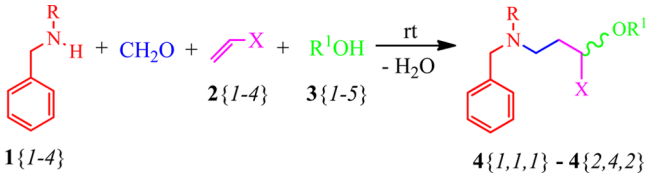


Figure 3. Employed diversity benzylamines **1**, terminal alkenes **2**, and alcohols **3** reagents for the synthesis of products **4**.

To our satisfaction a set of diversely substituted γ-aminoethers **4**{*1,1,1*} through **4**{*2,4,2*} was obtained as shown in the Scheme 2. The reaction proceeded similarly

Scheme 2. General Approach for the Synthesis of the Novel γ-Aminoethers 4



with yields in the range of 61−91%. Their structures were also confirmed by complete spectroscopic analysis (see Supporting Information). Table 1 summarizes the obtained results for compounds **4**{*1,1,1*} through **4**{*2,4,2*}.

The presence of the aza-acetalyc functionality (NCH−O) was the determinant structural feature in compounds **4**{*1,1,1*} through **4**{*4,1,1*} which appeared in the range of (5.14−5.66 ppm) and (77.3−83.2 ppm) in the ^1H and ^{13}C NMR spectra respectively. Meanwhile this functionality corresponds to an acetal (OCH−O) properly for compounds **4**{*2,3,1*} through **4**{*2,4,2*} and appears in the range of (4.35−4.85 ppm) and (98.3−108.5 ppm), respectively.

The general character of this approach was confirmed by using not only primary alcohols **3** (MeOH {*1*}, EtOH {*2*}, PrOH {*3*} and BnOH {*5*}) but also secondary (*i*PrOH {*4*}) aliphatic alcohols, although reaction does not proceeded when the tertiary *tert*-BuOH was used. The reaction worked well not only with the enamines (*N*-vinyl-2-pyrrolidinone **2a** and *N*-vinylcaprolactam **2b**) but also with the cyclic vinyl ethers (2,3-

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Table 1. Synthesis of the Novel γ-Aminoethers 4{1,1,1}−4{2,4,2}

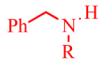
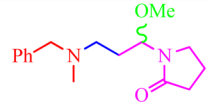
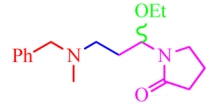
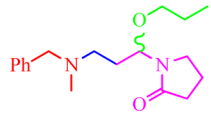
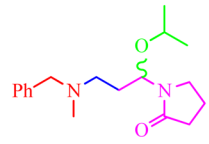
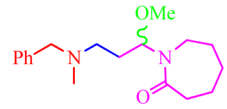
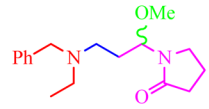
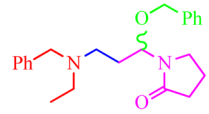
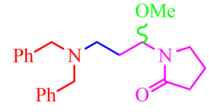
Entry	 **1**	 **2**	R^1OH 3	 4	Yields (%)[a]
1	**1**{*1*}	**2**{*1*}	**3**{*1*}	 **4**{*1,1,1*}	81
2	**1**{*1*}	**2**{*1*}	**3**{*2*}	 **4**{*1,1,2*}	78
3	**1**{*1*}	**2**{*1*}	**3**{*3*}	 **4**{*1,1,3*}	70
4	**1**{*1*}	**2**{*1*}	**3**{*4*}	 **4**{*1,1,4*}	61
5	**1**{*1*}	**2**{*2*}	**3**{*1*}	 **4**{*1,2,1*}	86
6	**1**{*2*}	**2**{*1*}	**3**{*1*}	 **4**{*2,1,1*}	73
7	**1**{*2*}	**2**{*1*}	**3**{*5*}	 **4**{*2,1,5*}	81
8	**1**{*3*}	**2**{*1*}	**3**{*1*}	 **4**{*3,1,1*}	74

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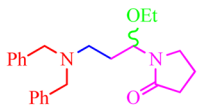
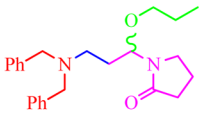
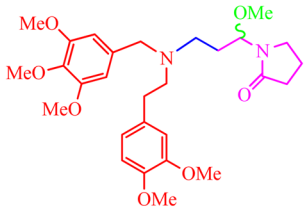
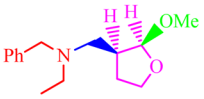
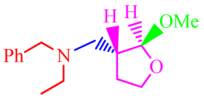
Table 1. continued

9	**1**{*3*}	**2**{*1*}	**3**{*2*}	 **4**{*3,1,2*}	68
10	**1**{*3*}	**2**{*1*}	**3**{*3*}	 **4**{*3,1,3*}	64
11	**1**{*4*}	**2**{*1*}	**3**{*1*}	 **4**{*4,1,1*}	63
12	**1**{*2*}	**2**{*3*}	**3**{*1*}	 ***cis*-4**{*2,3,1*}  ***trans*-4**{*2,3,1*}	65 26
13	**1**{*2*}	**2**{*4*}	**3**{*2*}	 **4**{*2,4,2*}	78

[a]Isolated yield.

dihydrofuran **2c** and 3,4-dihydropyran **2d**). No limitation was found for any of the secondary amines used. The reaction proceeded smoothly with sterically less hindered benzylmethylamine **1a** but also with the sterically most hindered dibenzylamine **1d**.

Compounds **4**{*2,3,1*} through **4**{*2,4,2*} (entries 12 and 13, Table 1), were obtained as mixtures of their corresponding cis and trans diastereomers with the *cis* isomer the main component for **4**{*2,3,1*} (i.e., 71:29 cis/trans ratio). In contrast, the trans isomer was slightly favored for **4**{*2,4,2*} (i.e., 47:53 cis/trans ratio). In both cases the ratios were calculated from the ^{1}H NMR spectra of their crudes. In the case of product **4**{*2,3,1*} we were able to separate the mixture of the two diastereomers (91% overall yield), by column chromatography on silica gel by using a $CHCl_3$/MeOH (30:1) mixture as eluent. Figure 4 shows the ^{1}H NMR signals of the acetalyc OCH−O protons of both cis (J = 0.75 Hz) and trans (J = 4.5 Hz) isomers, respectively. It confirms not only their formation and ratio (part a) but also their separation in pure components (part b) and (part c), respectively.

It is worth mentioning that this developed protocol is strongly dependent on the high concentration of alcohol **3**. Four alternative experiments were performed to demonstrate it. The first one consisted in repeat the reaction described in Scheme 2 but using a mixture 1:1 mL of MeOH/ACN as solvent. In this case, product **4**{*1,1,1*} was isolated in 56% yield after 24 h of stirring. Unreacted starting materials were detected. When reaction was carried out using a mixture 0.5:1.5 mL of MeOH/ACN product **4**{*1,1,1*} was isolated just in 25% yield after 24 h. Unreacted starting materials were also detected along with other minor components. In a third experiment a mixture of 1 equiv of MeOH in ACN (2 mL) was used as solvent. From this approach a complex mixture was obtained after 24 h of stirring, including product **4**{*1,1,1*} along with unreacted aminal **7**, as well as, other unidentified components. In the fourth experiment only ACN (2 mL) was used as solvent. In this case reaction was incomplete after 24 h of stirring, being the aminal **7** the main product. Unreacted alkene **2**{*1*} and other unidentified components were detected. These finding confirms that the best reaction

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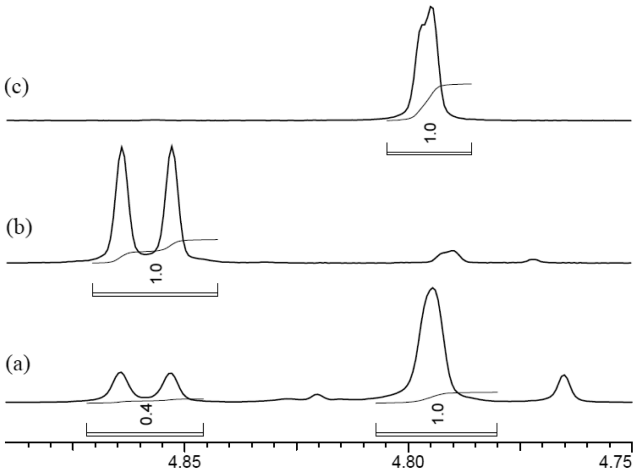


Figure 4. ^{1}H NMR expansion of the signals for the acetalyc OCH−O protons of the mixture of diastereomers of compound **4**{*2,3,1*}. (a) Crude mixture of both isomers. (b) Pure trans isomer. (c) Pure cis isomer.

conditions to efficiently afford products **4** should involve an excess of pure alcohols **3** acting both as solvent and as reagent.

On the basis of the literature[7] and our experimental observations, it may be suggested that synthesis of the γ-aminoethers **4** started with the formation of the well-known iminium ion type **6** from the reaction of the secondary amines **1** with polyformaldehyde. This species is then trapped by the electron-rich alkene **2** via a Mannich-type reaction affording a new cationic species **8** (stabilized by a resonant effect with the free electronic pair of the X (N, O) atoms). Finally, the nucleophilic intermolecular attack of the hydroxyl group of the alcohol R^1OH over species **8** afforded the γ-aminoether derivatives **4**, Scheme 3. Moreover, formation of aminals type **7** was detected in the reaction mixture but they were consumed in the course of the reaction. A hydrolytic process toward the iminium ion **6** may explain that. Particularly aminal 7{*3*} (R = $-CH_2Ph$) was isolated and characterized (see Supporting Information).

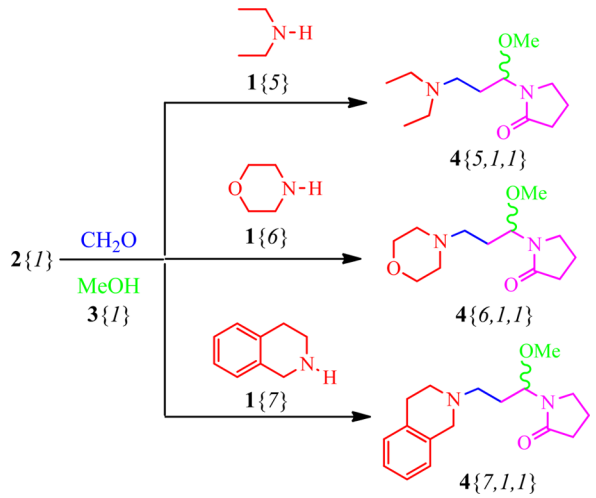
Although, initially we expected an intramolecular cyclization process (ring closure), involving the *ortho*-carbon atom of the Ph-ring in the intermediate species **8** to afford the 2-benzazepinic framework **5**, see Scheme 1, such product was not formed. This fact may indicate that the intermolecular nucleophilic attack of the hydroxyl group of the respective R^1OH over the species **8** proceeded faster than the intramolecular ring closure. Steric and conformational factors should be determinant features in this process.

It is also remarkable, that in this one-pot protocol three new bonds were formed in sequence during the process. This finding is in agreement with the atomic economy and bond-forming efficiency (BFE) concepts, which characterizes a multicomponent reaction.[2] Moreover, in the overall process only a molecule of water is removed as byproduct which provide also an environmentally friendly character to this four-component procedure.

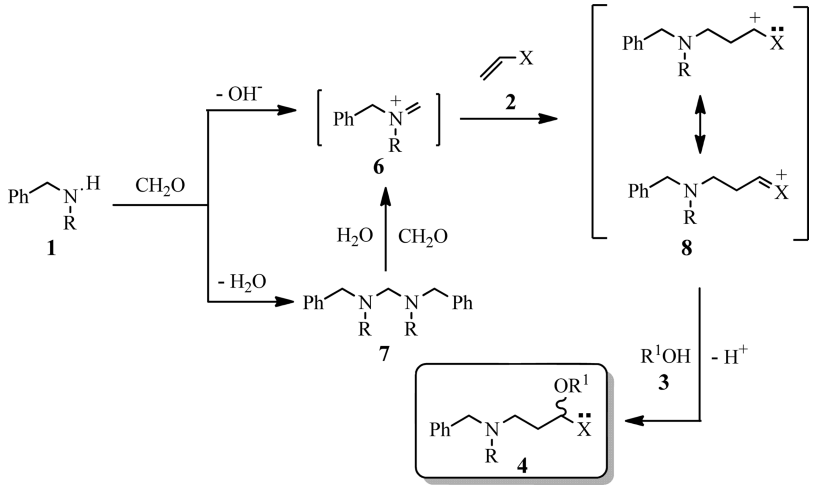
The interesting results obtained from Scheme 3 encouraged us to investigate a variation of the protocol in order to explore a broadest and scope of this methodology.

Our objectives were to extend the procedure to other amines chemset **1**{*5*−*7*} and phenolic derivatives chemset **3**{*6*−*9*}, as shown in Schemes 4 and 5 respectively. Thus, applying our

Scheme 4. Synthesis of the Novel γ-Aminoethers 4{*5*−*7,1,1*} from Diethylamine 1{*5*}, Morpholine 1{*6*}, and 1,2,3,4-Tetrahydro-isoquinoline 1{*7*}, Respectively



Scheme 3. Proposed Mechanistic Sequence for the Formation of the Products 4 via the Iminium Ion 6



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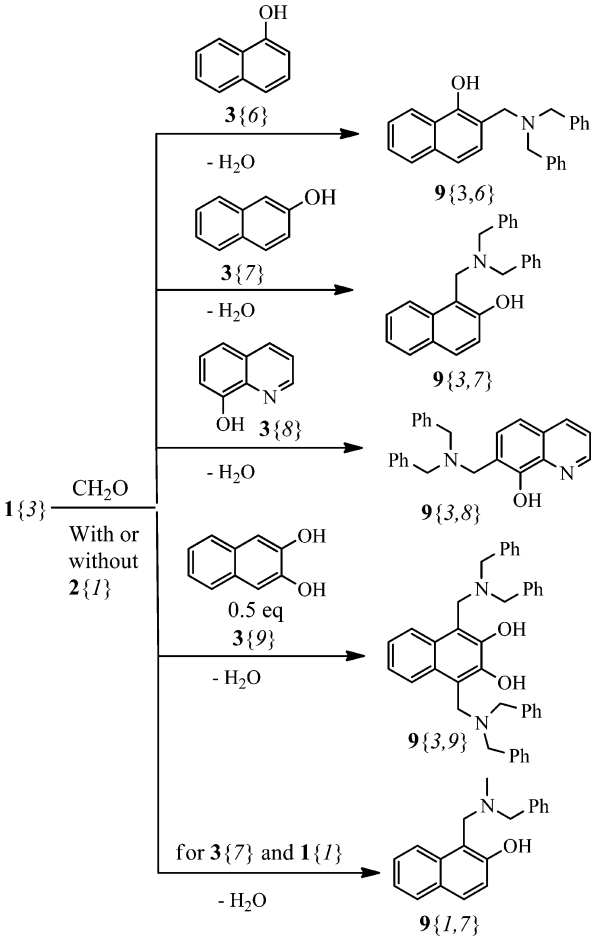
Scheme 5. Tricomponent Synthesis of the Aminals 9 from Phenolic Derivatives 3{6−9}



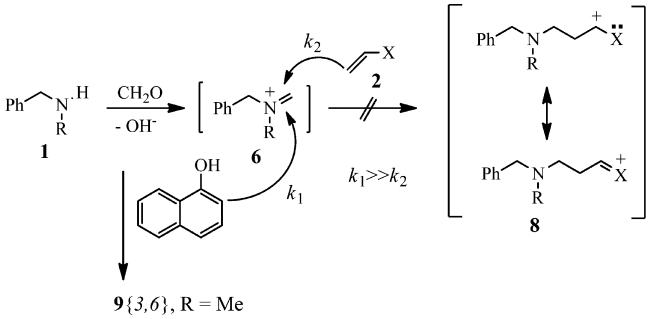
procedure to diethylamine **1**{*5*} and the heterocyclic amines morpholine **1**{*6*} and 1,2,3,4-tetrahydro-isoquinoline **1**{*7*} instead of benzylamine **1**{*1*} in MeOH **3**{*1*}, successfully afforded the corresponding γ-aminoethers **4**{*5,1,1*}, **4**{*6,1,1*}, and **4**{*7,1,1*} in 74%, 81%, and 63% isolated yields, respectively, Scheme 4 (see Supporting Information).

In the case of the phenolic derivatives **3**{*6*−*9*}, Scheme 5, the reaction was initially tried with amine **1**{*3*}, polyformaldehyde, alkene **2**{*1*} and 1-naphthol **3**{*6*} instead of methanol **3**{*1*}, in ACN as an aprotic solvent.

Reaction was monitored by TLC and although a new product was formed, consumption of alkene **2**{*1*} was not observed. After purification of the crude by column chromatography and spectroscopic analysis, the obtained product corresponded to the new aminal **9**{*3,6*} in 91% yield, but not to the expected naphthyl γ-amino ether derivative **4**{*3,1,6*}. Repetition of this reaction without alkene **2**{*1*} afforded the same product **9**{*3,6*} in similar yield. An extension of this result to 2-naphthol **3**{*7*}, 8-hydroxyquinoline **3**{*8*}, 2,3-dihydroxynaphthalene **3**{*9*} and the amine **1**{*1*} instead of **1**{*3*}, showed the same behavior affording the corresponding aminals **9**{*3,7*}, **9**{*3,8*}, the 2:1 adduct **9**{*3,9*} and **9**{*1,7*} in 89%, 92%, 73% and 89% yield, respectively, Scheme 5.

Formation of aminals **9** suggests that the relative nucleophilicity of the phenolic derivatives **3**{*6*−*9*} toward the iminium species **6** was higher than that for the activated alkene **2**{*1*} (i.e., $k_1 \gg k_2$, Scheme 6). The iminium ion **6** was trapped as soon as it was formed, via an *ortho*-C alkylation process as showed in Scheme 6.

Scheme 6. Proposed Mechanistic Sequence for the Formation of Aminals 9



The above results confirm that the *ortho*-carbon atoms of the phenolic derivatives **3**{*6*−*9*} possess a much higher nucleophilic character not only than the terminal alkenes **2** but also than their hydroxyl functionality of themselves. For that reason the C-alkylation proceeded instead of the O-alkylation in all entries of the Scheme 5. Resonant effects in the phenolic structures should support this finding.

A further exploration of the scope and limitations of this methodology consisted in trying the reaction with secondary anilines **1**{*8*−*9*} (instead of secondary benzylamines) and benzyl thiol **3**{*10*} (instead of alcohols) and using the pyrrolidone **2**{*1*} as the electron-rich alkene, as showed in Scheme 7. In the first case (entry 1), reactions were carried out in MeOH and stirred for 10 days. In both cases reactions were much slower than when benzylamines are used (see Supporting Information). For aniline **1**{*8*}, the reaction was not complete after this time and a difficult to separate mixture of unreacted starting materials along with several products was obtained. The ^{1}H, ^{13}C NMR, and DEPT spectra of the crude allowed us to identify the expected γ-amino ether **4**{*8,1,1*} as a minoritary product in 18% yield approximately (see Supporting Information). For aniline **1**{*9*} reaction was complete after this time but a mixture of products was obtained again. After performing a careful column chromatography to this crude, it was possible to isolate the tetrahydroquinoline **10** in 16% yield but not the corresponding γ-amino ether. Possible formation of product **10** should be explained through an aza-Diels−Alder type cycloaddition (Povarovs reaction)[8] between the iminium ion type **6** (R = −Ph) and the alkene **2**{*1*} without participation of MeOH. Alternatively an intramolecular cyclization of the carbocation type **8** (R = −Ph) could also afford the product **10**. Preferred formation of the six-member ring should be the driving force in this process.

In the case of the reaction of benzylamine **1**{*1*} with benzyl thiol **3**{*10*} (entry 2), regrettably, this approach does not afforded the desired γ-aminothioether **4**{*1,1,10*}. Although reaction proceeded faster that when alcohols were used (about 18 h, see Supporting Information), the *N,S*-acetal **11**[9] was obtained as the main component (about 42% isolated yield) of a mixture of products. Selective formation of this side-product could be explained by the fact that the trapping of the iminium ion **6** by the benzyl thiol occurred preferentially to the alkene **2**{*1*}. Higher nucleophilicity of the −SH function in **3**{*10*} over the double bond of alkene **2**{*1*} should support this finding.

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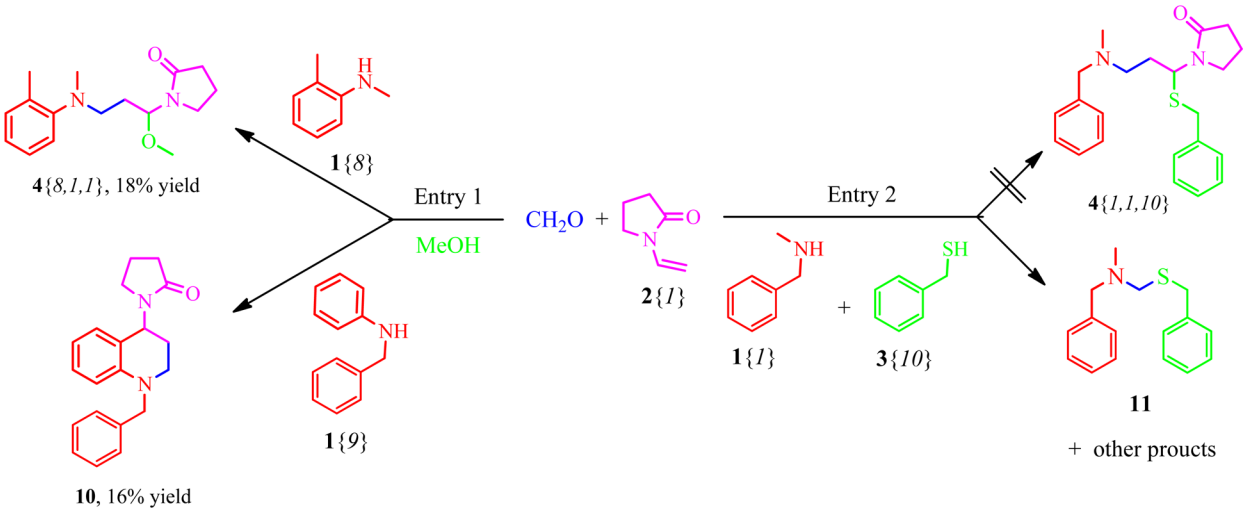
Scheme 7. Exploration of the Reactivities of Anilines and Thiols toward the Synthesis of Other Product 4 Analogs



In summary, as a consequence of an unplanned reaction we have implemented an efficient and multicomponent approach for the synthesis of the novel and diversely substituted γ-aminoethers **4** in good to excellent yields from a one-pot four-component procedure. This approach involved the trapping of the iminium ion **6** (formed *in situ*) by an activated alkene **2** through a Mannich-type reaction. The subsequent attack of the corresponding alcohol **3**{*1*−*5*} used as solvent toward the new carbocation species formed **8** afforded the isolated products **4**. In the case of phenolic derivatives **3**{*6*−*9*} aminals **9** were obtained instead of the corresponding γ-aminoethers **4**. The fact that three new bonds were formed in only one step and the releasing of water as the unique byproduct, gives to this approach an outstanding bond-forming efficiency, as well as a remarkable environmentally friendly quality.

EXPERIMENTAL PROCEDURES

General. Melting points were determined on a Büchi melting point B-450 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer in KBr disks and films. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 400 and 100 MHz, respectively, and Bruker AC 300 operating at 300 and 75 MHz respectively, and using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Mass spectra were run on a SHIMADZU-GCMS 2010-DI-2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Low resolution mass spectra (MS) were recorded on ion trap Bruker Esquire 6000, equipped with an electrospray source (ESI). Solvent used is methanol (Sigma Aldrich, chromasolv for HPLC). Microanalyses were performed on an Agilent elemental analyzer and the values are within ±0.4% of the theoretical values. Silica gel aluminum plates (Merck 60 F_{254}) were used for analytical TLC. The starting amines **1**{*1*−*3*,*5*−*9*}, alkenes **2**, polyformaldehyde, alcohols **3**{*1*−*5*}, thiol **1**{*10*}, and naphthol derivatives **3**{*6*−*9*} were purchased from Aldrich, Fluka, and Acros (analytical reagent grades) and were used without further purification. Owing to amine **1**{*4*} is commercially unavailable, it was synthesized by a reductive amination from 3,4-dimethoxyphenethylamine and 3,4,5-trimethoxybenzaldehyde, following a similar procedure as described previously.[5a]

General Procedure for the Synthesis of the γ-Aminoethers 4. A mixture of amine **1** (0.200 mg of each), polyformaldehyde (1.5 mmol), and the activated alkene **2** (1.1 mmol) was dissolved in the corresponding alcohol (R^1OH) **3** (2 mL). The solution was stirred at room temperature for 24 h until the starting amine **1** was not detected by TLC (revealed with an ethanolic solution of vanillin-sulfuric acid). After the excess of solvent was removed under reduced pressure, the oily material obtained was purified by column chromatography on silica gel, using a mixture of CH_2Cl_2/MeOH (20:1) as eluent.

Synthesis of the Aminals 9. A mixture of dibenzylamine **1**{*3*} (150.0 mg, 0.76 mmol), polyformaldehyde (34.0 mg, 1.13 mmol), the corresponding phenolic compound **3**{*6*−*9*} (0.76 mmol), and alkene **2**{*1*} (0.76 mmol or without it) was dissolved in ACN (2 mL). The solution was stirred at room temperature for 12 h until the starting amine **1**{*3*} was not detected by TLC. The solvent was removed under reduced pressure and the crude was purified by column chromatography on silica gel using a $CHCl_3$/MeOH (30:1) mixture as eluent. In the case of product **9**{*1*,*7*} it was used amine **1**{*1*} instead of **1**{*3*}. For the bis-aminal **9**{*3*,*9*}, the reaction was optimized by using a mixture of 2,3-dihydroxynaphthalene **3**{*9*} (1 equiv), dibenzylamine **1**{*3*} (2 equiv), and polyformaldehyde (2.5 equiv).

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, compound characterization data, and ^{1}H, ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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