

Mannich synthesis of acetylenic amino alcohols in aqueous ionic liquids

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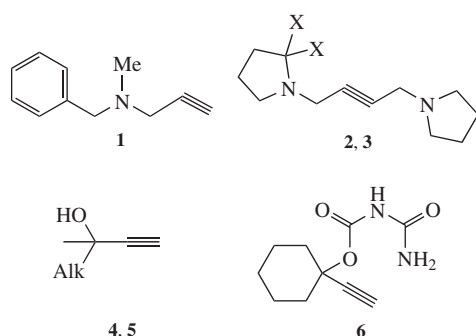
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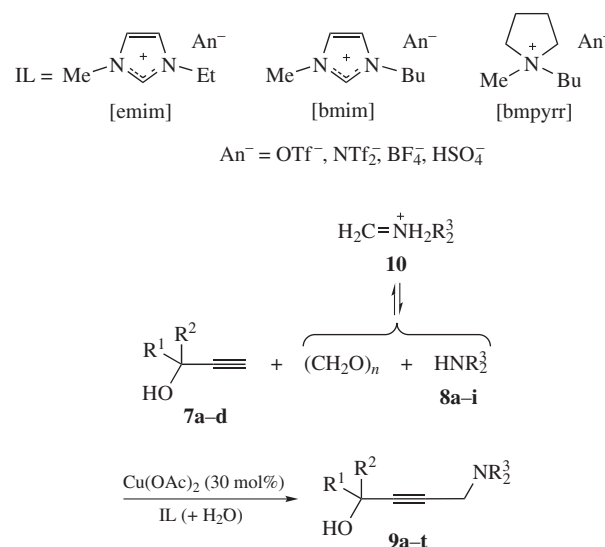
Terminal alkynols react with formaldehyde and secondary amines in aqueous ionic liquid [emim]HSO₄[−] in the presence of Cu(OAc)₂ to afford the corresponding 1-(α-hydroxyalkyl)- or 1-(β-hydroxyalkyl)-2-(aminomethyl)acetylenes in better yields in comparison with the reaction in conventional organic solvents. The catalytic system can be easily recovered and recycled.

Propargylamine derivatives exhibit valuable biological activities, in particular, antibacterial,¹ anticancer,^{2–4} antihistamine,^{5–7} and may act as enzyme inhibitors.⁸ Some of them are used in practical medicine: pargyline (**1**) – for curing of hypertension and depression, tremorine (**2**, X = H) or oxotremorine (**3**, X = O) – as cholinergic drugs.⁹ Acetylene-derived alcohols are another pharmacologically important family of organic substances: methylpentynol (**4**, Alk = Me) and repocal (**5**, Alk = Et) are used in the medications of psychotropic diseases; ethynylcyclohexyl allophanate (**6**) – as a soporific agent.¹⁰ It can be anticipated that 1-(hydroxyalkyl)-2-(aminomethyl)acetylenes containing both amino and hydroxy groups, would possess valuable biological properties.^{8,11}



These compounds have been prepared in moderate to high yields by Cu^{II}-catalyzed three-component condensation of terminal (hydroxyalkyl)acetylenes with aldehydes and amines (the Mannich reaction) in organic solvents^{12–20} and ionic liquids (ILs).^{21–28} However, the broad application of ILs in organic synthesis^{29,30} is limited by their relatively high price. Recently, it was shown³¹ that in some cases the consumption of hydrophilic ILs as reaction media can be reduced by dilution with water without negative influence on the reaction outcome. Importantly, the system reagents–IL–water remains homogeneous over a wide range of components ratio. Herein, we applied this approach to Cu^{II}-catalyzed three-component reaction of alkynols with formaldehyde and secondary amines and developed a useful procedure for the synthesis of 1-(hydroxyalkyl)-2-(aminomethyl)acetylenes. Typically, Mannich reaction in aqueous medium requires rather drastic conditions or microwave activation,^{24,32–34} which can be attributed to poor solubility of acetylenes in water.

At first, we studied Cu(OAc)₂-catalyzed interaction between 1-ethynylcyclohexanol **7a**, piperidine **8a** and paraformaldehyde (model reaction, Scheme 1) in molten salts medium composed of 1,3-dialkylimidazolium or 1,1-dialkylpyrrolidinium cations and



Scheme 1 For substituents R¹–R³, see Table 1.

various inorganic or organic anions.[†] The experiments were carried out with molar ratio **7a**:**8a**:**10**:IL of 1.0:1.2:3.0:3.0; Cu(OAc)₂ loading was 30 mol%. In all cases 1-[3-(piperidin-1-yl)-prop-1-ynyl]cyclohexanol **9a** was obtained as the major product. The yield of **9a** reached 80% if the reaction was performed in 1-alkyl-3-methylimidazolium triflates and was somewhat lower (65%) in [emim]HSO₄ medium. Furthermore, a higher reaction temperature (50 °C) was required in the experiments where rather viscous [emim]HSO₄ was used.

Surprisingly, addition of water to [emim]HSO₄ accelerated the reaction and improved the yield of product **9a**, the best yield (80%) being achieved in the case of 3:1 [emim]HSO₄–H₂O mixture. This reaction medium was less viscous than [emim]HSO₄ itself and could be well stirred at 40 °C. However, further raising of water content (to 50%) negatively influenced the yield of the product, presumably by causing a partial hydrolysis of **9a** in aqueous environment.

The [emim]HSO₄–H₂O (2:1) reaction medium was then extended on a variety of functionalized hydroxyalkylacetylenes (see Scheme 1, Table 1).[‡] Linear and cyclic amines **8a–i**, and natural alkaloids anabasine **8f** and cytosine **8g**, served as amino-component to afford corresponding products **9a–u**. Typically, yields of compounds **9a,f,i,q** in [emim]HSO₄–H₂O as reaction media were higher than those in organic solvents (Table 1) whereas

[†] For optimization data, see Table S1 in Online Supplementary Materials.

Table 1 Synthesis of 1-(α -hydroxyalkyl)-2-(aminomethyl)acetylenes **9a–t** in the [emim]HSO₄–H₂O (2:1) solvent system.

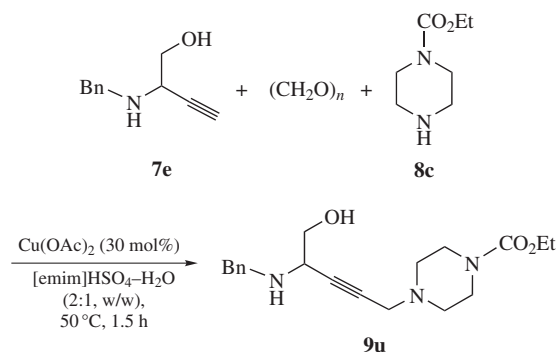
Entry	Alkynol	R ¹ , R ²	Amine	R ³ , R ³	T/°C [lit.]	t/h [lit.]	Product	Yield (%) (recycle) [lit. data]
1	7a	–(CH ₂) ₅ –	8a	–(CH ₂) ₅ –	40 [101 ^{14(b)}]	2.5 [24 ^{14(b)}]	9a	80 (1), 82 (2), 85 (3) [50 ^{14(b)}]
2	7a	–(CH ₂) ₅ –	8b	<i>c</i> -C ₆ H ₁₁ , <i>c</i> -C ₆ H ₁₁	50	3	9b	80 (1), 81 (2), 85 (3), 82 (4), 85 (5)
3	7a	–(CH ₂) ₅ –	8c	–(CH ₂) ₂ N(CO ₂ Et)(CH ₂) ₂ –	50	3	9c	77 (1), 80 (2), 81 (3), 81 (4), 80 (5)
4	7a	–(CH ₂) ₅ –	8d	–(CH ₂) ₂ N(Me)(CH ₂) ₂ –	50	2.5	9d	80 (1), 84 (2), 83 (3)
5	7a	–(CH ₂) ₅ –	8e	<i>i</i> -C ₅ H ₁₁ , <i>i</i> -C ₅ H ₁₁	30	3	9e	80 (1), 82 (2)
6	7a	–(CH ₂) ₅ –	8f	HNR ₂ ³ = anabasine ^a	50 (70 ²⁵)	3.5 (8 ²⁵)	9f	83 (1), 83 (2), 87 (3) [86 ²⁵]
7	7a	–(CH ₂) ₅ –	8g	HNR ₂ ³ = cytosine ^b	50	2.5	9g	83 (1), 86 (2), 85 (3)
8	7b	Me, Me	8d	–(CH ₂) ₂ N(Me)(CH ₂) ₂ –	50	2	9h	83 (1), 83 (2), 83 (3)
9	7b	Me, Me	8h	–(CH ₂) ₂ O(CH ₂) ₂ –	30	2	9i	82 (1), 84 (2)
10	7b	Me, Me	8i	Bn, Bn	30	2	9j	90 (1), 91 (2), 90 (3)
11	7b	Me, Me	8e	<i>i</i> -C ₅ H ₁₁ , <i>i</i> -C ₅ H ₁₁	30	3	9k	70 (1), 72 (2)
12	7b	Me, Me	8f	HNR ₂ ³ = anabasine ^a	50 (70 ²⁵)	3(8 ²⁵)	9l	72 (1), 73 (2) [67 ²⁵]
13	7b	Me, Me	8g	HNR ₂ ³ = cytosine ^b	30	2.5	9m	77 (1), 80 (2)
14	7c	Me, Et	8d	–(CH ₂) ₂ N(Me)(CH ₂) ₂ –	40	2	9n	87 (1), 90 (2), 90 (3)
15	7c	Me, Et	8i	Bn, Bn	30	3	9o	73 (1)
16	7c	Me, Et	8e	<i>i</i> -C ₅ H ₁₁ , <i>i</i> -C ₅ H ₁₁	40	3	9p	86 (1), 87 (2), 87 (3)
17	7c	Me, Et	8f	HNR ₂ ³ = anabasine ^a	50 (70 ²⁵)	3 (8 ²⁵)	9q	78 (1), 80 (2) [72 ²⁵]
18	7c	Me, Et	8g	HNR ₂ ³ = cytosine ^b	40	3	9r	83
19	7d	Me, 3-pyridyl	8c	–(CH ₂) ₂ N(CO ₂ Et)(CH ₂) ₂ –	50	2.5	9s	73 (1), 76 (2)
20	7d	Me, 3-pyridyl	8d	–(CH ₂) ₂ N(Me)(CH ₂) ₂ –	50	3	9t	71 (1), 73 (2)

^aAnabasine is 2-(3-pyridyl)piperidine. ^bCytosine is (1*R*,5*S*)-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one.

the required temperature (30–50 °C) and reaction time (1.5–3.5 h) were lower than those under water-free conditions. Presumably, the polar IL–water system efficiently promoted a reversible formation of active iminium intermediates **10** from formaldehyde and amines **8** in the Mannich reaction³⁵ and accelerated condensation process. Moreover, the use of the IL–water system simplified the isolation of the final product. Evaporation of the solvent, acidic treatment and neutralization of the reaction mixture is no more required. Condensation products **9f,g,l,m,q,r** having anabasine or cytosine fragments in the structure are optically active. Specific optical rotation values ($[\alpha]_D$) of the compounds **9f** (–198), **9l** (–172) and **9q** (–217) prepared according to described protocol³⁵ were in agreement with reported data.^{18(a)} This indicated that stereo-centres remained untouched. In the case of substrate **7e** with secondary amino group, this group remained intact in the presence of piperazine substrate **8c** (Scheme 2).

The catalytic system Cu(OAc)₂–[emim]HSO₄–H₂O can be easily recovered and reused. After extraction of the product with diethyl ether from the reaction mixture, fresh portions of starting compounds were added to the residue and the reaction was re-performed. This procedure can be repeated up to 5 times without any decrease in the reaction rate or in the yield of the products (Table 1, entries 2, 3). Moreover, the yield is slightly improved in the second and further runs in the recycled catalytic system probably due to the saturation of reaction media with the final product.

Summing up, we have developed a convenient synthesis of 1-(α -hydroxyalkyl)- and 1-(β -hydroxyalkyl)-2-(aminomethyl)-acetylenes by three-component condensation of terminal hydroxy-

**Scheme 2**

alkylacetylenes with formaldehyde and secondary amines catalyzed with the Cu(OAc)₂ in the [emim]HSO₄–water solvent system which can be easily recovered and reused several times. Invented method is based on the use of commercially available and inexpensive ionic liquid [emim]HSO₄. This procedure is remarkable for mild reaction conditions and high yields of the products. Proposed approach to minimize IL–consumption by its dilution with water may be useful to reduce the costs by industrial applications of ionic liquids.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.11.013.

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* *Typical procedure.* A mixture of hydroxyalkylacetylene **7** (1.0 mmol), secondary amine **8** (1.2 mmol), paraformaldehyde (3.0 mmol), Cu(OAc)₂ (0.3 mmol), IL (3.0 mmol) and corresponding amount of water was stirred under the conditions specified in Tables 1 and S1. The reaction mixture was extracted with Et₂O (3×5 ml). The combined extracts were passed through a silica gel or neutral (Brockman) Al₂O₃ pad, the solvent was evaporated *in vacuo* (15 Torr) and the residue was crystallized or purified by column chromatography on silica gel (Acros, 40–60 mm; eluent, light petroleum–Et₂O–EtOAc). Fresh starting compounds **7**, **8** and (CH₂O)_n were added to the recycled catalytic system which remained in the vessel after extraction of the products. The reaction was performed again according to the conditions specified in Table 1.

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