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Rapid and efficient synthesis of five- to eight-membered cyclic aminals under ultrasound irradiation

María A. Ramírez, Gisela Ortiz, Gustavo Levín, Walter McCormack, María M. Blanco, Isabel A. Perillo, Alejandra Salerno *

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956 (1113), Buenos Aires, Argentina

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ABSTRACT

A simple, efficient, and green procedure has been developed for the synthesis of cyclic aminals from alkylenediamines and aqueous formaldehyde under ultrasound irradiation. Applying this methodology a series of five-to eight-membered 1,3-dibenzyl substituted aminals were synthesized in excellent yields after short reaction times. Results were compared to thermal conventional method. All novel compounds were identified and characterized by ^{1}H and ^{13}C NMR spectra.

Aminals are the nitrogen equivalents of acetals.[1] In particular, cyclic aminals (**1**) (1,3-diazacycloalkanes) are more stable than their acyclic counterparts and have attracted researchers' interest. Among them, imidazolidines (tetrahydroimidazoles) (**1**, $n = 0$) and hexahydropyrimidines (**1**, $n = 1$) have been the most studied compounds either due to the wide ranging biological activities they have shown[2] or their value in organic synthesis as intermediates,[3] chiral auxiliaries,[4] or protecting groups.[5] In addition, some members have been employed as carriers of biologically active diamines,[6] polyamines,[7] or carbonyl compounds.[8]

Bioactivity of the above aminals appears to be closely related to their substitution patterns. In particular, 2-substituted 1,3-dibenzyl derivatives are compounds of pharmacological interest since they have shown a variety of activities such as anti-inflammatory,[9] analgesic,[9a,b] antibacterial,[9a] and antitumor.[10] Antiparasitic activities such as anti-*Trypanosoma cruzi*,[11] antimalarial,[12] antileishmanial,[2] and antiamebic[13] have also been reported.

As opposed to compounds mentioned above, hexahydro-1,3-diazepines (**1**, $n = 2$) and octahydro-1,3-diazocines (**1**, $n = 3$) have been barely explored. Properly N-substituted derivatives were synthesized and proposed as prodrugs for N-secondary alkyl 1,4- and 1,5-diaminoalkanes in a patent dated in 1976.[14] More recently 2-substituted 1,3-dibenzyl-hexahydro-1,3-diazepines and the homologous imidazolidines and hexahydropyrimidines were proposed as drugs for the treatment of cancer and other hyperproliferative diseases.[10]

The classical method of preparing cyclic aminals **1** involves the condensation of adequately substituted 1,*n*-diamines with aldehydes under conditions that remove water in order to shift the equilibrium to the product side. Drying agents, such as potassium carbonate, calcium sulfate, and boric anhydride have been used. Acid catalysts or removal of water by azeotropic distillation with benzene has also been employed. In the last decade, Wilhelm et al. reported a method in pure water without the presence of a catalyst.[15]

Ultrasound irradiation has emerged as an efficient technique for reagent activation in organic reactions. It has been considered as a clean and useful methodology in organic synthesis for the last years, in accordance with green chemistry requirements.[16] Remarkable advantages of this methodology are the simple experimental procedures, high yields of products, short reaction times, mild conditions, and easy work-ups. In this context, a large number of organic reactions can be carried out under ultrasonic irradiation and compared with classical synthetic procedures.[17] Especially, in heterocyclic chemistry, Cella and Stefani published an important review concerning the use of ultrasound in the synthesis of three- to seven-membered rings by heterocyclization.[18] However, so far, cyclic aminals have never been synthesized under ultrasound irradiation.

According to the references[9–13] some cyclic aminals (**1**, $n = 0,1,2$) 1,3-dibenzyl-2-substituted have been synthesized and explored. However, to the best of our knowledge, the

* Corresponding author. Tel./fax: +54 114 964 8250.
E-mail address: asalerno@ffyb.uba.ar (A. Salerno).

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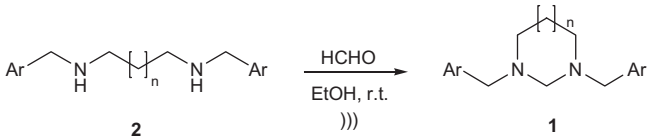
Table 1
Synthesis of acyclic aminals **1a–s** under ultrasound and conventional conditions



2 **1**

Compound **1**	Ar	*n*	Conventional (EtOH, reflux)		Ultrasonic irradiation (EtOH, rt)			
					Bath (LIU)		Sonicator (HIU)	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
a	C_6H_5	0	120	78	7	95	1	96
b	3-ClC_6H_4	0	110	78	7	96	1	97
c	4-ClC_6H_4	0	100	81	7	95	1	98
d	3,4-$Cl_2C_6H_3$	0	90	83	7	90	1	95
e	C_6H_5	1	150	69	7	85	1	97
f	3-ClC_6H_4	1	100	73	9	87	1	98
g	4-ClC_6H_4	1	80	71	8	92	2	98
h	2,3-$Cl_2C_6H_3$	1	90	68	8	85	2	95
i	3,4-$Cl_2C_6H_3$	1	120	59	9	88	2	95
j	C_6H_5	2	130	58	7	87	1	94
k	3-ClC_6H_4	2	120	60	7	87	2	92
l	4-ClC_6H_4	2	150	58	8	89	2	96
m	2,3-$Cl_2C_6H_3$	2	130	54	9	91	2	94
n	3,4-$Cl_2C_6H_3$	2	130	55	8	90	2	92
o	C_6H_5	3	>360	–	7	80	2	95
p	3-ClC_6H_4	3	>360	–	7	83	2	96
q	4-ClC_6H_4	3	>360	–	7	80	2	98
r	2,3-$Cl_2C_6H_3$	3	>360	–	7	85	2	97
s	3,4-$Cl_2C_6H_3$	3	>360	–	7	88	2	97

corresponding 2-unsubstituted derivatives and the eight-membered compounds (**1,** $n = 3$) have been barely studied.

In previous work we synthesized a series of 1,3-dibenzylimidazolidines (**1**, $n = 0$) in good yields by reaction of the corresponding *N*,*N*′-disubstituted ethylenediamine and aldehydes or aqueous formaldehyde (37%, excess) in ethanol under reflux for 1–2 h.[11] In this context, and continuing our ongoing work in the use of green chemistry tools[19] for heterocyclic chemistry, we report herein the ultrasound promoted synthesis of a series of 2-unsubstituted 1,3-dibenzylimidazolidines (**1**, $n = 0$), hexahydropyrimidines (**1**, $n = 1$), hexahydro-1,3-diazepines (**1**, $n = 2$), and octahydro-1,3-diazocines (**1**, $n = 3$).

The compounds synthesized in this work are shown in Table 1. They were obtained by the reaction of *N*,*N*′-dibenzylalkylenediamines **2** and aqueous formaldehyde.

The required diamines **2** were synthesized by our improved method involving the reaction of the corresponding alkylenediamine with formaldehyde under microwave irradiation and subsequent reduction with sodium borohydride.[3b]

We first examined the cyclodehydration of diamines **2** ($n = 0–3$) with aqueous formaldehyde in ethanol under conventional heating, following the process described in the literature for the five membered ring.[11,20] Under these conditions the reaction proceeded with different yields (Table 1). Imidazolidines **1a–d** were obtained in good yields (79–83%) and required 90–120 min for complete consumption of the starting materials, hexahydropyrimidines **1e–i** were obtained in moderate to good yields (59–73%) after 80–150 min, and hexahydro-1,3-diazepines **1j–n** showed low yields (<60%) and required 120–150 min. On the other hand, when *N*,*N*′-dibenzylcadaverines (**2**, $n = 3$) were utilized as precursors, no products were detected after 360 min. under reflux and starting materials were recovered without transformation. It is known that medium-sized rings are generally most difficult to prepare than their lower counterparts. The synthetic strategies are hampered by unfavorable transannular interactions leading to large enthalpies of activation.[21]

In order to optimize the reactions described above and widen the scope of the method to the synthesis of eight-membered cyclic aminals (octahydro-1,3-diazocines **1**, $n = 3$), we explored the use of US irradiation as a promoting agent.

The reactions were carried out at room temperature under low intensity ultrasonic (LIU) laboratory cleaning bath (which is more economic) and high intensity ultrasonic (HIU) probe system. It is well known that LIU from an ultrasonic cleaner has considerably less power and energy of ultrasound radiation is not uniformly available when compared to a LIU equipment. In all cases, the experimental results show that the yields of compounds **1a–n** improved under ultrasound and the reaction times decreased dramatically if compared to conventional heating (Table 1). In addition, this methodology allowed us to synthesize eight-membered cyclic aminals (octahydro-1,3-diazocines **1o–s**) in good yields and short reaction times.

Reactions were methodologically easy using both ultrasonic instruments, however excellent yields in shorter reaction time with reproducible results were achieved using a sonicator (HIU) (1–2 min, 92–98%) as compared to the ultrasonic bath (LIU) (7–9 min, 80–96%).

In conclusion, we have developed a simple and efficient procedure for the synthesis of five- to eight-membered cyclic aminals under ultrasound irradiation at room temperature. If compared to the conventional method, this approach has several and important advantages including milder conditions, shorter reaction times, and higher yield, and provides biologically interesting nitrogen containing heterocycles in good yields. To our knowledge, this is a general method for the preparation of cyclic aminals from the corresponding diamines and the first that uses US as a promoting agent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.061.

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