Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A hydrogen bond and strong electron withdrawing group lead to the formation of surprisingly stable, cyclic hemiaminals

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ARTICLE INFO

Article history:
Received 23 October 2019
Accepted 25 October 2019
Available online xxxx

Keywords:
Hemiaminal
Stable
Hydrogen bond
Computation

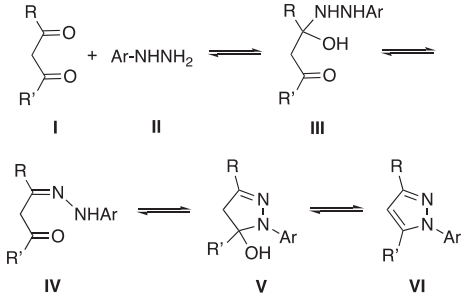
ABSTRACT

Hemiaminals are rarely stable, and usually arise during imine formation in the absence of acid using polar, aprotic solvents. Here, stable, cyclic hemiaminals from acidic or neutral ethanolic solutions are obtained. Using four 1,3-diketones (**a–d**) and four aromatic hydrazine derivatives (**1**–**4**), a hydrogen bond and strong electron withdrawing group (trifluoromethyl) are judged to be the two critical contributors to stability. Using resistance to dehydration as a surrogate for stability, these hemiaminals appear to be the most stable reported surviving in ambient, neat glacial acetic acid for long periods of time and requiring reflux for conversion to the corresponding pyrazole.

Introduction

The accepted mechanism for the addition of an amine nucleophile to a carbonyl group proceeds through the formation of a short-lived, tetrahedral intermediate called a hemiaminal or carbinolamine. From studies with semicarbazone and substituted benzaldehydes, Cordes and Jencks concluded that nucleophilic attack proceeds without protonation of the carbonyl. Instead, proton transfer and nucleophilic addition is concerted [1]. The rate-determining step depends on pH [2,3]. Under acidic conditions, nucleophilic attack is rate-limiting. Under neutral conditions, the acid-catalyzed dehydration is rate-limiting. Because these reactions often occur spontaneously under mild conditions, we were interested in their use for drug delivery using a well-explored triazine (dendrimer) platform [4,5]. To this end, the stability of single carbonyl condensation products with hydrazine-substituted triazines were explored [6,7]. Our interest in tuning the stability of such conjugates led us to explore 1,3-diketones.

When applied to an aromatic hydrazine (I) and a 1,3-diketone (II), the expectation (Scheme 1) is that concerted condensation yields a hemiaminal (III). Dehydration yields the expected imine (IV). Intramolecular nucleophilic attack within IV yields a second hemiaminal (V). Subsequent dehydration yields a pyrazole ring (VI) which, unsurprisingly, proves to be stable over a range of pH values. Surprisingly, however, is that in some cases, dehydration is not facile: Instead of yielding the pyrazole ring, a markedly stable hemiaminal (V) is produced.



Scheme 1. General scheme for the addition of an aromatic hydrazine to a 1,3-diketone and the expected, unstable hemiaminal intermediates that are formed.

In general, however, hemiaminals are uncommon. They have been reported in natural products and degradates [8–10] and observed transiently in metal-organic frameworks [11] and molecular receptors [12]. Most derive from reactions in neutral conditions, are unstable in acidic solutions and/or engage in hydrogen-bonded networks in the solid state [13–19].

In this paper, we report the design criteria for the synthesis of cyclic hemiaminals from aromatic hydrazines and 1,3-diketones (Chart 1). They are derived from neutral or acidic solutions and remain stable in both for long periods of time. The studies focus on four aromatic hydrazines (**1**–**4**) and four commercially available 1,3-diketones: 2,4-pentanedione (**a**), 1,1,1-trifluoro-2,4-pentandione (**b**), 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**c**) and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**d**). The stabilities of these molecules were examined as a function of temperature and pH.

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https://doi.org/10.1016/j.tetlet.2019.151334
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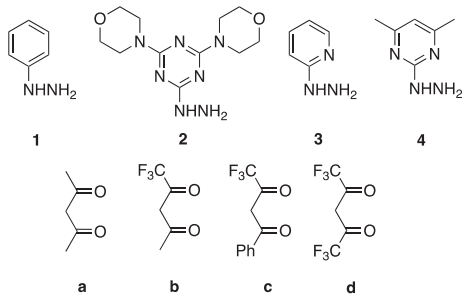

Chart 1. Aromatic hydrazines and 1,3-diketones used in this study.

Results & discussion

Nomenclature

To facilitate discussion, compounds are named to reflect whether a hemiaminal, **H**, or pyrazole, **P**, derivative forms from the respective starting materials. That is, **2** and **b** could yield hemiaminal **H-2b** and/or a pyrazole **P-2b**. Because both **b** and **c** are asymmetric, we distinguish the asymmetric pyrazole products as **P-2b** and **P-2b′** to reflect a difference in the regioisomers that result. A similar convention is adopted for **c.** In the cases of **b** and **c** (and not **b′** and **c′**), the CF_3-group is geminal to the hydroxyl group of the hemiaminal.

The numbering system employed for the diketones reflects the relative stability of the resulting hemiaminals (**a** < **b** < **c** < **d**). Compared with **1**, hemiaminals from **2, 3**, and **4** hydrazines are more stable. The relative stability of hemiaminals derived from **2**, **3**, and **4** is supported by computation (vide infra).

Synthesis

Aromatic hydrazines **1, 3** and **4** are commercially available. The triazine derivative, **2**, was synthesized in two steps by reacting cyanuric chloride with two equivalents of morpholine followed then by an excess of hydrazine monohydrate.

For conditions designated as neutral, the reagents are dissolved in absolute ethanol. In some cases a few drops of acetonitrile are added to enhance solubility. For conditions designated as acidic, the reagents were dissolved in neat glacial acetic acid, except for **1** which utilized drops of HCl in absolute ethanol. These acidic conditions could be described as 'dehydrating' presumably favoring pyrazole formation.

Distinguishing fingerprints for characterization

Hemiaminals and pyrazoles are readily distinguished. Using mass spectrometry, the hemiaminal has a molecular mass that is 18 a.m.u. higher the pyrazole. The ^{1}H NMR also shows diagnostic lines. The methylene protons of the five-membered ring typically appear as two doublets between 2.8 and 3.8 ppm with a coupling constant of around 18 Hz. The aromatic proton of the pyrazole, in contrast, is markedly downfield between 6.0 and 7.3 ppm. The broader range of chemical shifts is due in part to the substitution of the diketone. In some cases, the hydroxyl proton of the hemiaminal is apparent. Hydroxyl protons appearing between 8.0 and 9.0 ppm are suggestive of a strong hydrogen bond, while those between 3.0 and 4.0 ppm, an indicative of a weak or absent hydrogen bond.

Differences between the hemiaminal and pyrazole are also evident in the ^{13}C NMR spectra. The carbon atom of a hemiaminal attached to $-CF_3$ appears between 90 and 95 ppm as diagnostic quartet with coupling constant between 35 and 40 Hz. In contrast, the same C-atom in pyrazole derivatives appears downfield between 130 and 145 ppm as quartet.

Hemiaminals or pyrazoles

Table 1 summarizes the results of our studies wherein a '+' indicates formation of the corresponding product. Table 2 provides yield data. Quick inspection of Table 1 reveals a host of hemiaminals (green) that are stable in neutral solutions indefinitely and in neat glacial acetic acid at room temperature. In some cases (blue), hemiaminals are observed, but not considered stable (even if isolable as are **H1-c** and **H1-d**) because they dehydrate to the corresponding pyrazole over time at room temperature.

To elaborate, reactions of **a**–**d** with **1** yield pyrazoles in acidic conditions. Interestingly, under neutral conditions, reaction of **1** and **b** yields **P-1b** and **P-1b′** leading us to conclude that attack at either sp^2 center occurs. Neutral conditions also yield a mixture of the **H-1c** and **P-1c′** which is separable by conventional silica gel chromatography. The hemiaminal corresponding to **H-1c′** is

Table 1
Product distribution of hemiaminals (H) and/or pyrazoles (P) for reactions of **1**–**4** with **a-d** from either neutral or acidic conditions.

			Neutral		Acidic	
			H	P	H	P
1	a	R=R'=Me		+		+
	b	R=CF_3 R'=Me		+		+
	b'	R=Me R'=CF_3				+
	c	R=CF_3 R'=Ph	+			+
	c'	R=Ph R'=CF_3		t		
	d	R=R'=CF_3	+	t		+
2	a	R=R'=Me	+	+		
	b	R=CF_3 R'=Me	+		+	
	b'	R=Me R'=CF_3				
	c	R=CF_3 R'=Ph	+		+	
	c'	R=Ph R'=CF_3				
	d	R=R'=CF_3	+		+	
3	a	R=R'=Me				
	b	R=CF_3 R'=Me	+		+	
	b'	R=Me R'=CF_3				
	c	R=CF_3 R'=Ph	+		+	
	c'	R=Ph R'=CF_3				
	d	R=R'=CF_3	+		+	
4	a	R=R'=Me				
	b	R=CF_3 R'=Me	+		+	
	b'	R=Me R'=CF_3				
	c	R=CF_3 R'=Ph	+		+	
	c'	R=Ph R'=CF_3				
	d	R=R'=CF_3	+		+	

Key: + product observed; t trace; unstable hemiaminal; stable hemiaminal

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Table 2
Yields of hemiaminals, chemical shifts of the hydroxyl proton (ppm) and the conditions required for conversion to the pyrazole (time, temperatures and % conversion as determined by ^{1}H NMR).

H-#	Yield	δ OH	Conditions	Time	Temp. (°C)	%
1c	45	3.18	Neutral	30 days[a]	25	100
1d	21	3.48	Neutral	30 days[a]	25	93
2a	38[b]	5.90	NA	NA	NA	NA
2b	69[c]	8.16	Gl. AcOH	3	118	100
2c	94	8.21	Gl. AcOH	10	118	100
2d	72	7.95	Gl. AcOH	24	118	75
3b	91	8.75	Gl. AcOH	3	118	100
3c	64[d]	8.73	Gl. AcOH	12	118	100
3d	65	8.47	Gl. AcOH	24	118	75
4b	88	8.19	Gl. AcOH	12	118	100
4c	48[e]	8.48	Gl. AcOH	12	118	100
4d	25[f]	8.18	Gl. AcOH	72	118	65

[a]Immediate conversion in acid. [b]Hemiaminal **H-2a** could not be isolated.
[c-f]Modified conditions gave higher yield: [c]77%, [d]91%, [e]78%, [f]69%.

not observed presumably because the CF_3-group is not positioned to stabilize it, and accordingly, dehydration is facile yielding trace (indicated 't') amounts of **P1-c′.** For reactions of **1** and **d**, a mixture **H-1d** and **P-1d** is observed.

Under neutral conditions, reaction of **2** with **a** yields an inseparable mixture of **H-2a** and **P-2a** at a ratio of **P-2a**:**H-2a** of 1.6:1. Hemiaminal **H-2a** can be converted to **P-2a** with time or by the addition of a small amount of HCl. Under acidic conditions only **P-2a** is observed. Corresponding hemiaminals are not observed with **a** and **3** or **4**, only pyrazoles **P-3a** and **P-4a** are seen regardless of conditions.

For the remaining condensations using either acidic or neutral conditions, the reactions of **2**–**4** with **b**–**d** yield stable hemiaminals and not pyrazoles (save a trace of **P-3c′** under neutral conditions).

The notable absence of stable hemiaminals when a CF_3-group is absent (products of **a**) and when the hydrazine donor does not provide a hydrogen-bond acceptor (products of **1**) underscore the importance of both features as design criteria.

Stability

Our metrics for relative stability are the time and conditions required to convert the hemiaminal derivative into its pyrazole derivative. The data in Table 2 shows a trend for both the hydrazine donor and the 1,3-diketone. We surmise that hemiaminal stability increases from those derived from **a** < **b** < **c** < **d**. Using the **d** series, we are led to hypothesize that stability increases with hemiaminals derived from **1** < **2** < **3** < **4**. There is a notable difference in stability between hemiaminals derived from either **1** or **a** which lack a hydrogen-bond acceptor and CF_3 group, respectively. Those hemiaminals not bound by these contraints (**2**–**4**, **b**–**d**) were found to be stable at room temperature in acidic ethanolic solutions (HCl, glacial acetic acid, *p*TSA, and H_2SO_4). Refluxing hemiaminals for three hours in solutions of diisopropylethylamine or pyridine led to no change.

Design criteria for the preparation of stable hemiaminals

The studies performed suggest two design criteria for the preparation of stable hemiaminals; a hydrogen bond involving the OH of the hemiaminal, and a CF_3 group. These criteria will be addressed separately in the scope of literature precedent.

The role of hydrogen bonding

In the majority of reports (although not exclusively), hemiaminals derive from neutral conditions, in polar aprotic solvents, are unstable in the presence of acid, and form networks of intermolecular hydrogen bonds in the solid state [13–19]. Amongst those reported, the heminaminal derived from di-2-pyridyl ketone and 4-cyclohexyl-3-thiosemicarbazide is stabilized by an adjacent pyridine ring in a manner analogous to what is observed here with the OH hydrogen bonding to the *N*-heterocycle [18]. The stability of this molecule is not described. Other hemiaminals showing this hydrogen bond also derive from neutral conditions, but form the Schiff base over time in organic solvent [19]. This behavior would lead us to apply the moniker 'unstable' using the definition advanced by this manuscript.

Hydrogen-bonding in our system is observed in the x-ray crystal structures (Fig. 1) wherein the hydroxyl proton forms a hydrogen bond to the nitrogen in the aromatic ring hydrazine donor (pyridine, pyrimidine, or triazine). Crystal structures were obtained for hemiaminals **H-1c**, **H-2c, H-3c**, **H-4c**, and **H-4d** and pyrazoles **P-1c′**, **P-2c**, **P-3c**. Details are provided in the Supporting information.

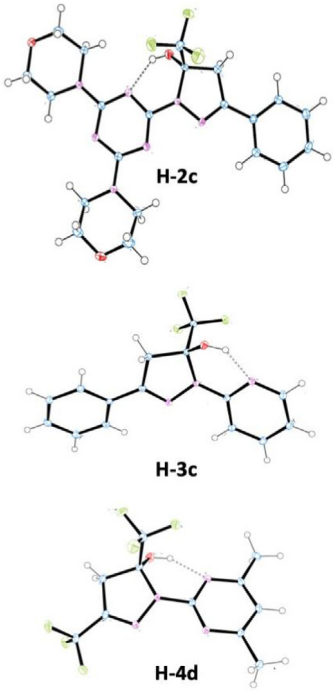

Fig. 1. Crystal structures of hemiaminal **H-2c**, **H-3c** and **H-4d** showing a hydrogen bond implicated in stability. The thermal ellipsoids are drawn at 30% probability.

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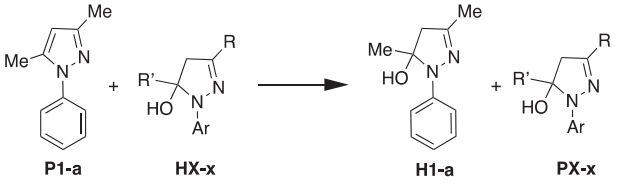
Table 2 also summarizes the chemical shifts observed for the OH groups in $CDCl_3$. We hypothesize that the downfield chemical shifts reported for the OH in the ^1H NMR are consistent with a similar hydrogen bond forming in solution. Indeed, there are no other hydrogen bond donors available to assign these shifts to, although the magnitude of the affect that the CF_3 group has could be considerable.

The role of the CF_3 group

In our studies, resistance of the hemiaminal to conversion to the pyrazole derivative from the requisite hemiaminal reveals the critical role of the CF_3 group. In the absence of a CF_3 group, conversion to the pyrazole happens rapidly at room temperature. Hemiaminals with a single CF_3 group (derived from **b** or **c**) convert more rapidly to the pyrazole than those with two CF_3 groups (**d**).

Computational modelling

Computational models underscore the importance of both the hydrogen bond and electron withdrawing trifluoromethyl group in stabilizing the observed hemiaminals. DFT calculations (M06-2X/6–311++G(2d,2p)) using the isodesmic reaction shown in equation 1 compliment the experimental findings [20–23]. Compared with **1**, hemiaminals from **2**, **3** and **4** exhibit overall higher stability. Table 3 summarizes these results and adopts the common coloring scheme with stable hemiaminals shown in green, observed but unstable hemiaminals shown in blue, and those species unobserved shown in black. The dotted line is intended to guide the eye and approximates a threshold for stability.



(1)

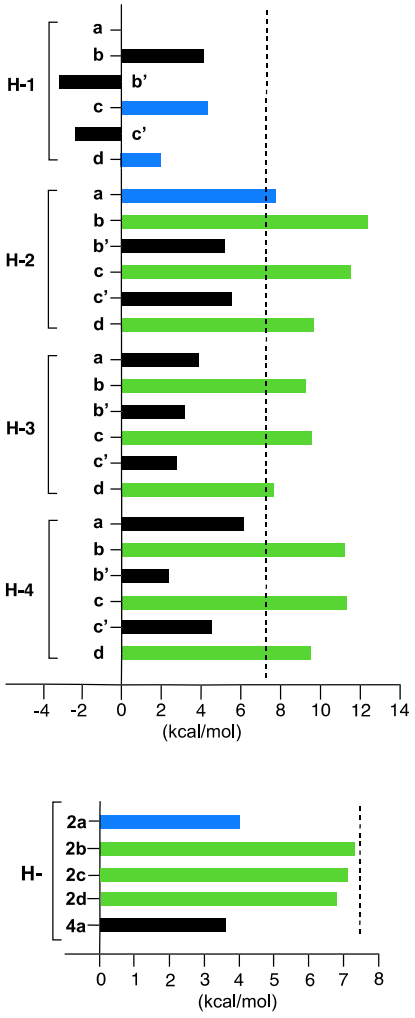
The data also shows that the location of CF_3 groups significantly effects the stability of the hemiaminal. Compounds derived from **a** or isomers wherein the CF_3 is ***not*** located on carbinol carbon (**b**′ and **c**′) show lower stability than the others (**b**, **c** and **d**) across the series.

The contribution of the hydrogen bond to stability was calculated for hemiaminals **2a–2d** and **4a** using at the M06-2X/6–311++g(2d,2p) level. In general, the hydrogen bond contributes 60–70% of the stabilizing energy for hemiaminals observed. We infer that the additional stabilization derives from the CF_3 group (s). The hydrogen bonds in hemiaminals obtained from **a** are ~3.5 kcal/mol lower in energy compared to those obtained from other 1,3-diketones, further supporting the fundamental role CF_3 group in promoting the hydrogen bond.

Conclusions

In conclusion, the work described expands the number of examples of stable hemiaminals and reinforces design criteria that have emerged from different reports. While the literature shows that hemiaminal formation is favored primarily by neutral conditions as well as apolar aprotic solvents, here, the observation of hemiaminals derived from reactions in ethanol and under acidic conditions underscore the influence of adopting both an strong electron withdrawing group and a hydrogen bond acceptor as design criteria. Using either neutral or acidic conditions, most hemiaminals are available in greater than 70% yield. To the best of our knowledge, the hemiaminals reported here are the most stable reported to date. Stability at room temperature across a range of pH values as well is in neat glacial acetic acid suggests that these structures might have general utility in a range of applications.

Table 3
Hemiaminal stability relative to H-1a (top) and more positive values correspond to a more stable hemiaminal. Stable hemiaminals are shown in green. Unstable hemiaminals are shown in blue. Hemiaminals that were not observed experimentally are shown in black. Bottom: The contribution of the hydrogen bond to stability. The color coding is preserved. The dotted lines are intended as a guide for the eye. In both panels, the dotted line approximates 7.5 kcal/mol.



Acknowledgment

We thank the Robert A. Welch Foundation (P-0008) and Texas Christian University for support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151334.

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