A New Thiazolium Salt-Catalyzed Synthesis of α-Aminoketones from Aldehydes and Iminium Salts

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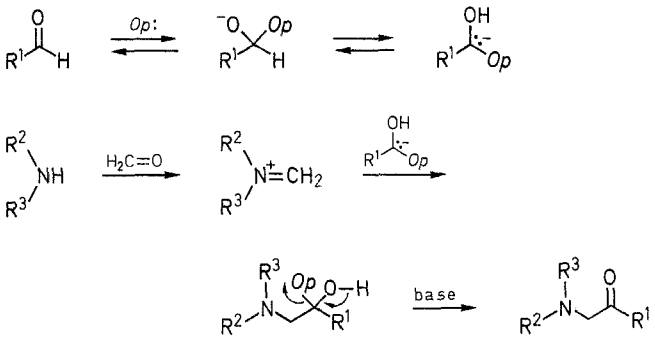
A new reaction, closely related to both the classical Mannich reaction and the benzoin condensation, affords α-aminoketones from aldehydes and *in situ* prepared *N*-methylenemorpholinium or *N*-methylenepiperidinium salts.

In recent years, several reactions related to the classical benzoin condensation[1,2] have been described. Such reactions are the catalyzed addition of aldehydes to double bonds,[3] the oxidative benzoin reaction,[4] the formoin reaction,[5] and the synthesis of hydroxymethyl ketones from formaldehyde and others aldehydes,[6] an extension of the formoin reaction.

Without regard to the catalytic species,[7,8] the rationale for all of the above reactions implies "umpolung" of an aldehyde carbonyl group (Scheme **A**) with formation of an active species (an acyl anion equivalent) which then attacks the pertinent electrophile. Electrophiles used up to now are characterized by the presence of a C=O double bond. We here describe a new reaction in which the receptor electrophile is an iminium salt formed *in situ* (Scheme **A**) and the product is an α-aminoketone.



Op = Catalytic species or "umpolung" operator

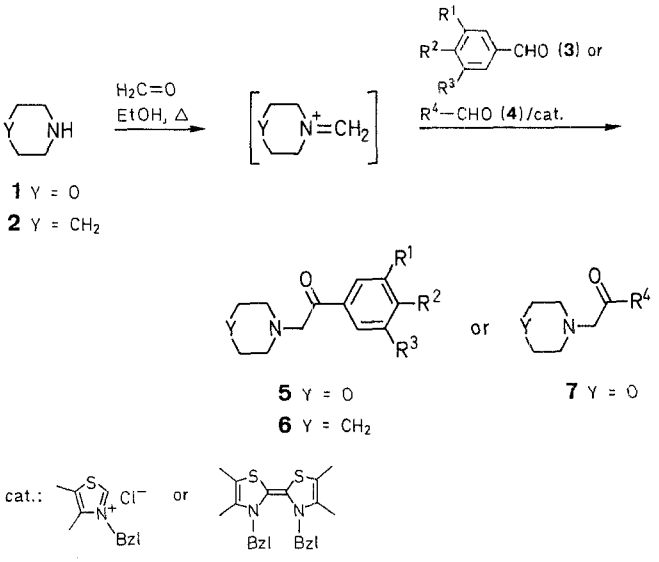
Scheme **A**

The new reaction can be viewed as a juxtaposition of a Mannich reaction and a benzoin condensation; both aspects of it should be disscussed.

The first step of the process (Scheme **B**) is, as in the classical Mannich reaction,[9] the reaction between a secondary amine and formaldehyde giving rise to an iminium cation, the desired aza analog of an activated carbonyl group. Morpholine and piperidine gave much better results than diethylamine. Various reaction conditions (temperature, solvent, pH) were tested, the best results being obtained in boiling ethanol without the addition of an acid; higher-boiling solvents such as dimethylformamide and dioxane did not afford better results.

As in all benzoin condensations, at least two aspects have to be considered in the second step of the reaction leading to α-aminoketones: the catalyst and the aldehyde which undergoes "umpolung".

Cyanide ion, the classical benzoin condensation catalyst,[1] cannot be used in our reaction because the irreversible formation of an aminonitrile overrides any other possible role of that ion. Fortunately, a variety of other chemical species directly or indirectly related to thiazolium cation have meanwhile been



	Y	R^1	R^2	R^3		Y	R^4
5a	O	H	H	H	**7a**	O	*i*-C_3H_7
5b	O	H	OCH_3	H	**7b**	O	*n*-C_7H_{15}
5c	O	OCH_3	OCH_3	H			
5d	O	OCH_3	OCH_3	OCH_3			
6b	CH_2	H	OCH_3	H			

Scheme **B**

found to be good alternative benzoin condensation catalysts. Good catalytic activity has been observed under two frequently used conditions: (a) addition as catalyst of a 2-unsubstituted thiazolium salt plus an auxiliary non-nucleophilic base (typically, triethylamine); (b) addition as catalyst of a bis(thiazolin-2-ylidene).[7]

As in earlier related reactions,[3] aliphatic or aromatic aldehydes can be used as starting materials. The behavior of the different types of aromatic aldehydes in the new reaction, as compared with that in symmetrical and unsymmetrical benzoin condensations, can be rationalized on the basis of the high electrophilicity of the receptor species, i.e., the iminium cation. Accordingly, formation of α-aminoketones takes place: (a) with "normal" unsubstituted aldehydes such as benzaldehyde and furfural; (b) with aldehydes having electron-donor substituents, (methoxy, amino, etc.) which give rise to highly nucleophilic, reactive intermediates but which are poor carbonyl electrophiles; (c) (with low yields) with aldehydes with electron-withdrawing substituents such as 2,6-dichlorobenzaldehyde, which give rise to reactive intermediates of very low nucleophilicity.

The reaction temperature plays an important role, in particular, when aliphatic aldehydes are used. In fact, at 25°C in ethanol, the yields of α-aminoketones range from acceptable to good but in boiling ethanol, the main isolated product is the corresponding acyloin, the yields of aminoketone being very low: ~1% when the catalyst is a thiazolium salt plus base and ~10% when

Table. Aminomethyl Ketones **5**, **6**, and **7** Prepared

Product[a]	Yield[b] (%)	mp (°C)[c] (acetone)	Molecular Formula[d]	MS (70 eV)[e] *m/z*	IR (KBr)[f] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$)[g] δ, *J*(Hz)
5a	33 (47)	222–225	$C_{12}H_{15}NO_2 \cdot HCl$ (241.7) (free **5a**: 205.25)	205 (M^+, 0.3), 105 (7), 100 (100)	1695	2.5 (m, 4H); 3.7 (m, 4H); 3.8 (s, 2H); 7.4 (m, 2H); 7.9 (m, 2H)
5b	30 (61)	195–197	$C_{13}H_{17}NO_3 \cdot HCl$ (271.7) (free **5b**: 235.3)	235 (M^+, 1), 135 (8), 100 (100)	1680	2.6 (m, 4H); 3.8 (m, 6H); 6.7 (d, 2H, J = 8); 7.6 (d, 2H, J = 8)
5c	33 (71)	167–170	$C_{14}H_{19}NO_4 \cdot HCl \cdot 2H_2O$ (337.8) (free **5c**: 265.3)	265 (M^+, 0.2), 165 (3), 100 (100)	1675	2.6 (m, 4H); 3.7 (m, 6H); 3.9 (s, 3H); 6.8 (d, 1H, J = 8); 7.6 (d, 1H, J = 8)
5d	25 (50)	226–230	$C_{15}H_{21}NO_5 \cdot HCl \cdot H_2O$ (349.8) (free **5d**: 295.3)	210 (14), 100 (100)	1690	3.2–3.8 (m); 3.6 (s); 4.7 (s); 6.9 (s)
6b	38 (50)	194–197	$C_{14}H_{19}NO_2 \cdot HCl$ (269.8) (free **6b**: 233.3)	233 (M^+, 0.7), 135 (3.4), 98 (100)	1690	1.5 (m, 6H); 2.4 (m, 4H); 3.6H (s, 2H); 3.8 (s, 3H); 6.8 (d, 2H, J = 8); 8.0 (d, 2H, J = 8)[f]
7a	47 (61)	180–183	$C_9H_{17}NO_2 \cdot HCl \cdot 0.5H_2O$ (216.7) (free **7a**: 171.2)	171 (M^+, 0.2), 100 (100), 71 (1)	1725	1.1 (s, 6H); 2.3 (m, 4H); 2.4 (s, 2H); 3.5 (m, 4H); 9.4 (s, 1H)
7b	~20 (48)	hygroscopic			1735	1.5–0.67 (m, 13H); 4.1–2.7 (m, 12H); 9.6 (s, enol form)

[a] All products are new compounds.
[b] Yields of isolated hydrochlorides or hydrochloride hydrates. (In brackets: yields calculated from the ^{1}H-NMR spectra of the crude reaction mixture).
[c] mp of hydrochloride or hydrochloride hydrate.
[d] The microanalyses of the hydrochlorides or hydrochloride hydrates showed the following maximum derivations from the calculated values: C ±0.22, H ±0.4, N ±0.05, Cl ±0.4.
[e] MS spectra recorded with the hydrochlorides or hydrochloride hydrates.
[f] Spectra of the hydrochlorides or hydrochloride hydrates.
[g] Spectra of the free aminoketones.

the catalyst is a bis(thiazolin-2-ylidene). The observed influence of the temperature can be explained by assuming that aminoketones and acyloins are the kynetically and thermodynamically controlled reaction products, respectively.

Secondary amine, formaldehyde, aldehyde, and catalyst are typically used in the mole ratio 1:1:2:0.1. Particularly important is the relative amount of aldehyde, because yields decrease strongly when less aldehyde is used whereas higher amounts of aldehyde do not improve the results. The table lists a series of representative examples.

Melting points were determined on a Büchi (Dr. Tottoli) apparatus and are uncorrected. Microanalyses of α-aminoketone hydrochlorides were satisfactory (absolute error less than 0.4%) for the expected structures. Mass spectra were recorded on a Hewlett-Packard 5988A mass spectrometer, IR spectra on a Perkin-Elmer 681 Infrared spectrometer, and ^{1}H-NMR spectra on a 60 MHz Hitachi Perkin-Elmer R-24 spectrometer.

Commercial aldehydes and bases were used; if necessary, they were purified by distillation (particularly, to remove acids from oxidation of the aldehydes). 3-Benzyl-4,5-dimethylthiazolium chloride was used as catalyst in all reactions listed in the Table.

Catalyst tested are: sodium cyanide (57 mg, 0.117 mmol); 3-benzyl-4,5-dimethylthiazolium chloride (280 mg, 0.117 mmol) plus triethylamine (11.8 mg, 0.117 mmol); bis(3-benzyl-4,5-dimethylthiazolin-2-ylidene), prepared from an equivalent amount of the above thiazolium salt (see below).

Bis(3-benzyl-4,5-dimethylthiazolin-2-ylidene):
A solution of 3-benzyl-4,5-dimethylthiazolium chloride (57 mg, 0.117 mmol) in dry MeOH (2 mL) is passed through a 2.7 × 30 cm chromatography column charged with IRA-401 anion-exchange resin (OH^- form) previously washed to neutral pH with MeOH and thermostatized at 0 °C. The eluate is collected in a flask, at 0 °C under an inert gas, containing 3 Å molecular sieves; elution is continued until the eluate is colorless. The solvent is removed under vacuum at low temperature. The residual bis(3-benzyl-4,5-dimethylthiazolin-2-ylidene) is used as catalyst without further manipulation.

Aminomethyl Ketones (α-Aminoketones 5, 6, and 7); General Procedure:
The secondary amine **1** or **2** (1.17 mmol), paraformaldehyde (35.1 mg, 1.17 mmol), and dry EtOH (5 mL) are placed in a 50 mL flask fitted with reflux condenser and magnetic stirrer. The mixture is boiled until the paraformaldehyde has dissolved (~ 30 min). The aldehyde **3** or **4** (2.34 mmol), the catalyst (0.117 mmol), and more dry EtOH (10 mL) are then added. The mixture is stirred at room temperature (aliphatic aldehydes) or at 70 °C (aromatic aldehydes) for 20 h. The solvent is removed at low pressure and the residue is dissolved in $CHCl_3$ (15 mL). This solution is washed with H_2O (15 mL fractions) until the water layer is neutral. The $CHCl_3$ solution is extracted with 5N HCl (3 × 15 mL). The aqueous extract is neutralized with NH_3/H_2O and extracted with $CHCl_3$ (3 × 15 mL). This $CHCl_3$ extract is dried (Na_2SO_4), the solvent is removed *in vacuo*, and the oily residue is distilled at low pressure. The distilled α-aminoketone **5**, **6**, or **7** is dissolved in dry Et_2O and precipitated as the hydrochloride by adding a solution of HCl in Et_2O. The isolated solid is recrystallized from dry acetone.

This work was supported by the "Comisión Asesora de Investigación Científica y Técnica" (Grant No. 575/84).

Received: 23 September 1987; revised: 30 November 1987

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