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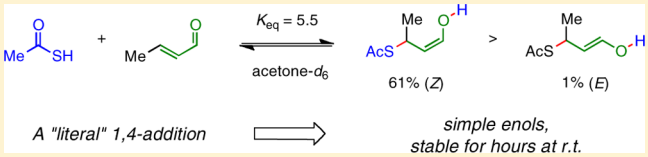
Reversible Generation of Metastable Enols in the 1,4-Addition of Thioacetic Acid to α,β-Unsaturated Carbonyl Compounds

Lukas Hintermann* and Aleksej Turočkin

Department Chemie, Technische Universität München, Lichtenbergstrasse 4, 85748 Garching b. München, Germany

Supporting Information

ABSTRACT: Addition of thioacetic acid to reactive α,β-unsaturated carbonyl compounds like acrolein or crotonaldehyde in acetone-d_6 generates metastable (*E*)- and (*Z*)-1-alkenols, which tautomerize slowly at ambient temperature. The 1,4-addition of thioacetic acid and crotonaldehyde to (*Z*)-3-(acetylsulfanyl)-1-propen-1-ol is reversible with K_{eq} = 5.5 ± 0.5 L/mol. A concerted, cyclic 1,4-addition mode is proposed to explain the preferred (*Z*)-stereoselectivity in lower polarity, nonprotic solvents.



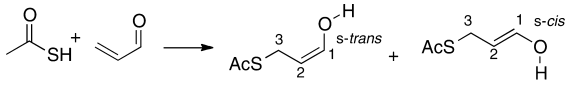
Simple enols[1] lacking steric or electronic stabilization are only a minute fraction in the tautomeric equilibrium with their parent aldehydes or ketones. The enol content of ethanal, for example, amounts to merely 0.00006%.[2] Nevertheless, excess concentrations of metastable enol solutions have been obtained by photoelimination[3,4] or careful hydrolyses of enol orthoesters.[1,5,6] Chin[7] and Bosnich[8] described elegant transition-metal-catalyzed isomerizations of allylic alcohols to enols,[9] which are stable for minutes to hours at ambient temperature and a stable enol, 2-methyl-1-propen-1-ol, has even been obtained at low temperatures (−20 °C).[7b] Still, simple enols remain unusual, and few NMR or reactivity studies are available. We now report that metastable enols are generated in the conjugate hydrothiolation of α,β-unsaturated aldehydes or vinyl ketones with thioacetic acid.[10] Solutions with 0.3−0.5 mol/L of simple enols are obtained straightforwardly by mixing commercially available starting materials in several solvents with no precautions. The enols have been studied by NMR spectroscopy for hours at ambient temperature. The mechanism of addition of the reaction involves a reversible 1,4-addition to an enol, followed by rate-limiting tautomerization.

The addition of thioacetic acid (**1**; 2 equiv) to a solution of acrolein (**2a**) in acetone-d_6 at ambient temperature (Scheme 1) generated a solution consisting mainly of enols (*Z*)-**3a** (69 mol %) and (*E*)-**3a** (15 mol %).[11] Compound **2a** was largely consumed (≤2 mol %) according to NMR spectra recorded after 15 min. For the major product isomer, the chemical shift of the enolic OH-hydrogen (δ_{OH} = 7.67 ppm)[12] and its coupling to H-1 ($^3J_{HOCH}$ = 6.9 Hz) are well resolved in acetone-d_6.[13] They correspond closely to those previously observed in (*Z*)-1-propen-1-ol (δ_{OH} = 8.07 ppm,[12] J_{HOCH} = 5.9 Hz at −80 °C).[6b] The values are consistent with an *s-trans* arrangement around the O−C-1 single bond in (*Z*)-**3a**,[6b] excluding an intramolecular hydrogen bond as a potential stabilizing factor. Similarly, the NMR data of the minor isomer (*E*)-**3a** ($^3J_{HCOH}$ = 9.1 Hz, δ_{OH} = 7.54 ppm) are consistent with the *s-cis* conformation, as also seen in (*E*)-1-propen-1-ol (δ_{OH} = 7.99 ppm, $^3J_{HCOH}$ = 9.5 Hz at −80 °C).[6b] It follows that the acetylsulfanyl group has no specific effect on structure and bonding of (*E*)-**3a**[14] and (*Z*)-**3a**, which are truly *simple enols*.[1] The ^{1}H,^{13}C-HSQC NMR experiment recorded at ambient temperature correlates the characteristic ^{13}C resonances of the enol carbons C-1 (δ = 144.2/146.7 ppm) and C-2 (δ = 99.3/99.9 ppm) with H-1 (δ = 6.44/6.57 ppm) and H-2 (δ = 4.35/4.79 ppm) in (*Z*)- and (*E*)-**3a**, respectively (Figure 1).

An analogous experiment with crotonaldehyde (**2b**) as substrate in acetone-d_6 gave similar results, with two notable changes: first, the metastable enol **3b** was almost exclusively formed as the (*Z*)-**3b** isomer, whose spectral characteristics are comparable to (*Z*)-**3a** (δ_{OH} = 7.70 ppm, $^3J_{HCOH}$ = 6.6 Hz; *s-trans*); second, **2b** was not completely consumed by an excess of thioacetic acid. The composition of the reaction mixture relative to the initial concentration of **2b** (0.38 mol·L^{-1} = 100 mol %) over the course of several days is shown in Table 1.

Preferential generation of the less stable[8] (*Z*)-enol in this uncatalyzed 1,4-addition could hint at a hydrogen-bond assisted mechanism (Scheme 2). It appears that thioacid **1** is not sufficiently strong to fully protonate the substrate carbonyl group, but instead undergoes a concerted, cyclic 1,4-addition to the *s-cis* isomer of **2** (Scheme 2). In the case of acrolein (**2a**) as a particularly strong electrophile, competitive addition to the *s-trans* conformer of **2** by a neutral or ionic mechanism could account for generation of some (*E*)-**3a**. The proposal of

Scheme 1. Simple Enols from the 1,4-Addition of Thioacetic Acid to Acrolein



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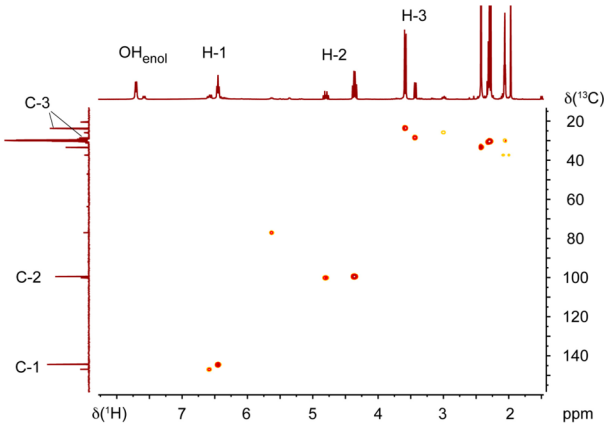
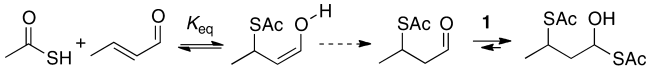


Figure 1. ^{1}H,^{13}C-HSQC of an acrolein/thioacetic acid mixture. ^{1}H,^{13}C-HSQC (500 MHz, acetone-d_6, 295 K) of a freshly prepared mixture of acrolein and thioacetic acid (2 equiv). Main signals are due to (*E*)-**3a** and (*Z*)-**3a**; minor signals are due to a hemithioacetal follow-up product, vide infra.

Table 1. Time-Dependent Composition of a Thioacetic Acid (1)/Crotonaldehyde (2b) Mixture in Acetone-d_6[a]

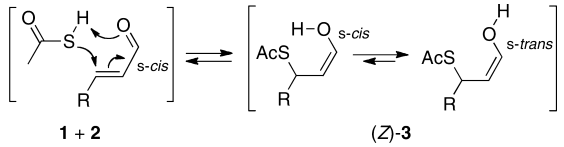


1 **2b** (*Z*)-**3b** **4b** **5b**

	time (h)					
	0	0.3[b]	1	5	35	60
2b	100	36	26	22.5	15	5.1
1	208	105[b]	112	105	64	33
(*Z*)-**3b**		51	61	50	20	3.4
(*E*)-**3b**		0.4	1.3	0.8	0.1	
4b		0.4	0.4	1.0	3.9	10.6
5b		4.3	7.2	21	55	75.3
K_{eq}[c]		3.6	5.5	5.6	5.5	5.3

[a]Reaction in acetone-d_6 at 295 K with 2.08 equiv of **1**. Molar composition in mol % relative to initially added **2b** (100 mol % = 0.38 mol/L) from ^{1}H NMR peak integrations relative to internal standard (see the Supporting Information). [b]Values from a separate experiment with only 2.0 equiv of **1**. [c]Equilibrium constant for generation of (*Z*)-**3b**; see eq 1. Units are L·mol^{-1}.

Scheme 2. Concerted 1,4-Addition of Thioacetic Acid as a Possible Explanation of the Selective Generation of (*Z*)-Enols 3



1 + **2** (*Z*)-**3**

Scheme 2 recommends itself for evaluation by in silico methods.

Even though **1** and **2b** react to 60−70% conversion within the first 15 min of mixing, the reaction levels off and remaining **2b** is only slowly consumed over several hours (Table 1).[15,16] This is due to the existence of a fast *private* equilibrium in the 1,4-addition reaction of **1** and **2b** to (*Z*)-**3b**.[17] The equilibrium constant for this reaction is defined by eq 1:

$$K_{eq} = [(Z)\text{-}\mathbf{3b}]/[\mathbf{1}]\cdot[\mathbf{2b}] = 5.5 \pm 0.5\ \text{L}\cdot\text{mol}^{-1} \quad (1)$$

Values for K_{eq} have been obtained by converting the mol % composition of species **1**, **2b**, and (*Z*)-**3b** from Table 1 to concentrations and insertion in eq 1. In spite of large changes of the individual concentrations, the value of K_{eq} is constant over most of the observation range, as expected for a true equilibrium constant;[18] only the value obtained after 20 min is low, indicating incomplete equilibration.

Generation of metastable enols and the existence of equilibria analogous to eq 1 has also been established with other unsaturated carbonyl substrates (Table 2). The extent to which enol is formed depends on the reactivity of the carbonyl acceptor, which in turn, reflects its ground-state stabilization.[19] The concentration of the most reactive acceptor acrolein (**2a**) was too small to allow reliable calculation of K_{eq}. Similar to crotonaldehyde (**2b**), (*E*)-2-hexenal (**2c**) underwent fast initial addition to (*Z*)-**3c**, accompanied by a small amount of (*E*)-**3c**. After 3 h, the product ratio for **3c** had changed to (*Z*/*E*)-**3c** ≈ 2:1, which means that (*E*)-**3c** is generated but also tautomerizes more slowly than (*Z*)-**3c**. The K_{eq} value for 1,4-addition to give (*Z*)-**3c** calculated after 20 min was low (1.2 L·mol^{-1}) but further rose and remained constant at 3.3 L·mol^{-1} after 1 day. A (*Z*)-enol **3d** was also detected in the conjugate addition to methyl vinyl ketone (**2d**) after 20 min, but it had largely disappeared within 1 h, when close to 99% of the tautomerized 1,4-addition product **4** was present.

With the least reactive ketone, 3-penten-2-one (**2e**), a small amount (*Z*)-enol **3d** was detected after 20 min, but none remained after 3 h, when the usual thia-Michael addition had gone to completion. The K_{eq} values listed in Table 2 for generation of (*Z*)-**3c** and (*Z*)-**3d** are probably low relative to the true equilibrium constants because tautomerization competes with equilibration of the initial 1,4-addition. Similarly, 1,4-addition of substrates **1** + **2** to form the stereoisomeric enols (*E*)-**3** is slow relative to the tautomerization (*E*)-**3**→**4**, and equilibration with (*E*)-enols is not established. The generation of enols from acrolein (**2a**) was also realized in other solvents including $CDCl_3$, C_6D_6, DMSO-d_6, and MeOH-d_4. In DMSO-d_6, the major enol observed after 20 min was (*E*)-**3a** (70%, besides 12% (*Z*)-**3a**), as was the case in MeOH-d_4 (47% (*E*)-**3a**, 27% (*Z*)-**3a**). The results point to a disruption of the concerted transition state (Scheme 2) by strong donor or protic solvents. Enols were even obtained in an aqueous medium consisting of D_2O/MeOH-d_4 (1:2):[20] after 15 min, 46% of (*E*)-**3a** and 3% of (*Z*)-**3a** were detected. Subsequent tautomerization was completed after 4 h.

Other Michael acceptors have not been included in Table 2, since enols were not observed in their 1,4-additions. These include cinnamaldehyde (3-phenyl-2-propenal) and mesityl oxide (4-methyl-3-penten-2-one), which slowly gave only the usual thia-Michael addition products (mesityl oxide: $t_{50\%}$ = 20 h and cinnamaldehyde: $t_{50\%}$ = 96 h, where $t_{50\%}$ denotes time to 50% conversion of starting materials). Neither were enol intermediates observed in conjugate additions of the cyclic enones 2-cyclopenten-1-one and 2-cyclohexen-1-one, though they reacted markedly faster ($t_{50\%}$ = 1 h).[21]

The fate of the reaction mixtures deserves some comment: in conjugate additions with a *2-fold excess* of thioacetic acid (**1**) to aldehydes **2a**−**c** in either acetone-d_6, C_6D_6, or $CDCl_3$, the final reaction products (>80%) are hemithioacetals **5a**−**c** in equilibrium with regular thia-Michael addition products **4a**−**c** (Scheme 3a). Whiting and co-workers have previously observed these *anti Erlenmeyer compounds*[22] as intermediates in thia-Michael additions of **1**,[15] and Böhme has isolated distillable

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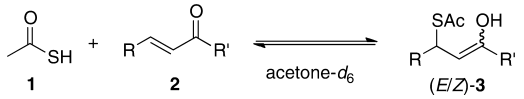
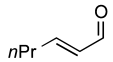
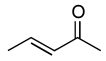
Table 2. Time-Dependent Generation of Metastable Enols from Thioacetic Acid and Various Acceptors in Acetone-d_6[a]

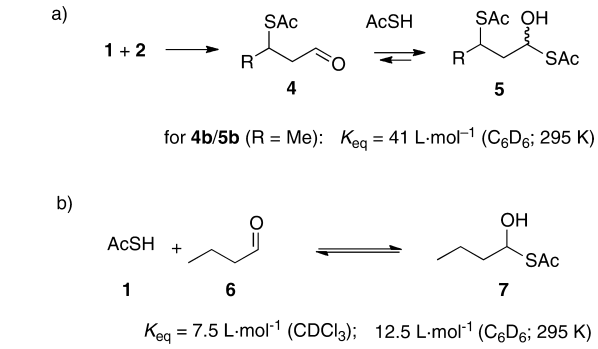


1 2

entry	reactant	enol	t = 0.3 h [%][b]	t = 1–3 h [%][c]	K_{eq}[d] [L·mol^{-1}]
1	 **2a**	(*Z*)-**3a**	69	54 (2 h)	>50
		(*E*)-**3a**	15	8 (2 h)	
2	 **2b**	(*Z*)-**3b**	51	61 (1 h)	5.5[e]
		(*E*)-**3b**	0.4	1.3 (1 h)	
3	 **2c**	(*Z*)-**3c**	44	25 (3 h)	3.3[f]
		(*E*)-**3c**	3	13 (3 h)	
4	 **2d**	(*Z*)-**3d**	27	0.5 (1 h)	9
		(*E*)-**3d**	-	-	
5	 **2e**	(*Z*)-**3e**	7	-	0.5
		(*E*)-**3e**	-	-	

[a]Reactions were performed in acetone-d_6 at 295 K with 2 equiv of **1**. [b]Mol% of enol relative to initially added **2** (100 mol % = 0.4–0.6 mol/L) after ca. 20 min. [c]Mol % of enol after the time indicated in brackets. [d]K_{eq} was calculated from species concentrations after 20 min reaction time or later as defined in eq 1. [e]K_{eq} after 1 h. [f]K_{eq} after 3 h. See the Supporting Information for additional data.

Scheme 3. Hemithioacetals of Aldehydes and Thioacetic Acid



hemithioacetals of lower aldehydes with **1**.[23] A quantification of the representative equilibria **1** + **4b** = **5b** (Scheme 3a) and **1** + **6** = **7** (Scheme 3b) was readily achieved by ^{1}H NMR spectroscopy. The hemithioacetalization constant for **4b** + **1** = **5b** is the sum of two individual constants (23 and 18 L·mol^{-1}) for the two diastereomers of **5b**. Interestingly, no 1,2-addition of thioacetic acid to the carbonyl groups of substrates **2** has been observed. This process may be kinetically and thermodynamically disfavored relative to 1,4-addition, since it would break off conjugation in the unsaturated aldehydes.

The generation of an enol as the initial product by ionic 1,4-addition of a heteronucleophile to an acceptor alkene (hetero-Michael addition) can be expected on the basis of the kinetically faster protonation of enolates at oxygen rather than at carbon.[2a,24,25] However, such enols are hardly ever observed because of fast tautomerization under reaction conditions. Nevertheless, from the conjugate addition of thioacetic acid (**1**) to carbonyl acceptors **2** it is possible to obtain and study solutions of metastable *simple enols* by mixing readily available starting materials at ambient temperature. The remarkable stability of the simple enols under the conditions of this experiment is apparently due to the weakly acidic character of the reaction medium, which suppresses tautomerization via ionization of the enol. At the same time, the acidity level is too

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low to induce acid-catalyzed tautomerization. A notable aspect of these reactions is the presence of an equilibrium **1** + **2** = (*Z*)-**3**, which is established in spite of the metastable character of product (*Z*)-**3**. Stereoselective generation of (*Z*)-enols in weakly hydrogen bonding solvents can be explained by assuming a concerted addition mechanism via hydrogen-bonding activation (Scheme 2). The rate-limiting step in these thia-Michael additions is tautomerization of enols **3** to regular thia-Michael products **4**.[25]

EXPERIMENTAL SECTION

General Procedure for Generating Metastable Enols. A solution of the Michael acceptor and CH_2Cl_2 (internal standard) in deuterated solvent was analyzed by ^1H and ^{13}C NMR spectroscopy. Thioacetic acid was then added by microsyringe and the reaction mixture monitored by NMR spectroscopy.

Generation of a Solution of 3-Acetylsulfanyl-1-propen-1-ol (3a). In an NMR tube, freshly distilled acrolein (**2a**; 17 μL, 0.25 mmol, 100%) and CH_2Cl_2 (internal standard, 16 μL) were dissolved in 400 μL of acetone-d_6 at ambient temperature. Thioacetic acid (**1**; 37 μL, 0.52 mmol, 208 mol %) was added, the NMR tube closed, and the tube thoroughly shaken. NMR spectra (^1H, ^{13}C) were recorded in regular time intervals. The following components (mol % relative to **2a**) were detected after 20 min: **1** (76%), **2a** (2%), (*E*)-**3a** (15%), (*Z*)-**3a** (69%), **4a** (1%), **5a** (9%), and acetic acid (23%). The analytical recovery of compounds derived from **2a** is 96% (**2a** + (*E*)-**3a** + (*Z*)-**3a** + **4a** + **5a**). The total enol concentration was 84% = 0.45 mol·L^{-1}.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for various reaction mixtures and species. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lukas.hintermann@tum.de.

Notes

The authors declare no competing financial interest.

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(9) For a highly efficient catalyst based on bifunctional ruthenium complexes, see: Larsen, C. R.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2012**, *134*, 10357−10360.
(10) While preparing the manuscript we became aware of a precedent where thiobenzoic acid was added to α-benzylacrolein over 7 days at −18 °C in CH_2Cl_2 to generate a (*Z*)-enol, which was then tautomerized to aldehyde with asymmetric induction. No spectral data or yields had been reported, however. A related observation (with thioacetic acid) from a doctoral thesis was mentioned: Henze, R.; Duhamel, L.; Lasne, M.-C. *Tetrahedron: Asymmetry* **1997**, *8*, 3363−3365.
(11) The ratio of (*E*)-**3a** and (*Z*)-**3b** isomers varied to some extent with the concentration and the quality of the thioacetic acid sample used; this observation could point to a competing, minor radical addition pathway.
(12) The chemical shift $\delta(^1H)$ of OH depends on concentration and temperature, causing minor deviations from Capon's data.[6b]
(13) The $^3J_{HOCH}$ coupling is not resolved in C_6D_6 or $CDCl_3$.
(14) An intramolecular hydrogen bridge is impossible in (*E*)-**3**.
(15) Ilyashenko, G.; Whiting, A.; Wright, A. *Adv. Synth. Catal.* **2010**, *352*, 1818−1825.
(16) Similar behavior was also observed but differently interpreted by Whiting and co-workers.[15] Their reaction conditions were slightly different; thus, their explanation might also be valid.
(17) The term *private equilibrium* specifies an equilibration between a set of starting materials and one specific among several possible reaction products. We thank Johannes Schlüter for suggesting the presence of an equilibrium in the conjugate addition reaction.
(18) 2D EXSY and selective 1D irradiation experiments have been performed with an intent to study this equilibrium. However, since $t_{50\%}$ for equilibration of **1** + **2** = (*Z*)-**3** at rt is in the order of minutes for the forward reaction, exchange kinetics are too slow for obtaining meaningful results for the reverse reaction. We thank Dr. Wolfgang Eisenreich, Technische Universität München, for assistance with these NMR experiments.
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(20) Reactions in D_2O were inhomogeneous.
(21) Since cyclic enones are fixed in the *s-trans* conformation; they cannot undergo a concerted addition such as displayed in Scheme 2.
(22) Referring to the Erlenmeyer rule, which states that compounds of the general form $R_2C(YH)(X)$ will decompose to $R_2C{=}Y$ and HX (X, Y = heteroelements); a discussion of the origin and scope of this rule is in preparation (L.H.).
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