Regioselective Reduction of 5-Substituted 2-Alkylidene-4-Oxothiazolidines by Metal Hydrides

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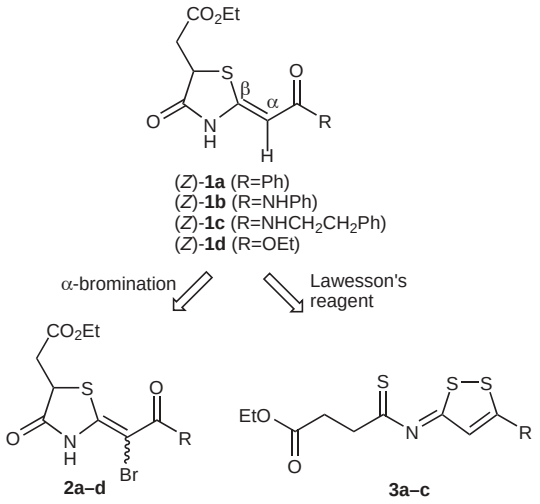
Abstract: Thiazolidine β-enamino derivatives possessing a 5-substituted acetate substituent were chemoselectively reduced to corresponding alcohols, or new condensed 2-alkylidenethiazolidines. The method is based on the resistance of an enaminone fragment to reduction by metal hydrides.

Key words: thiazolidine, reductions, hydrides, regioselectivity, ring closure

(*Z*)-4-Oxothiazolidines **1** (Scheme 1) bearing a trisubstituted exocyclic double bond at C(β) constitute a class of typical exocyclic β-enaminocarbonyl compounds. They are generally recognized as useful precursors in organic synthesis.[1] In particular, we have shown that the regiospecific bromination of the enaminone-type heterocycles **1** leads to α-bromo-α,β-unsaturated compounds **2**,[2] which are valuable α-acylvinyl anion equivalents.[3]

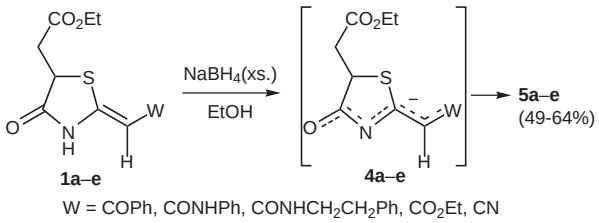


Scheme 1

More recently, we described a novel and highly efficient 4-oxothiazolidine-1,2-dithiole rearrangement induced by Lawesson's reagent (Scheme 1).[4]

The specific interest in exploring the reduction reactions of (*Z*)-4-oxothiazolidines **1** and other functionalized β-enamines is based on the presence of the prochiral exocyclic double bond[5] and an ester functionality.[6] Lhommet et al.[7] described recently the synthesis of chiral pyrrolidine β-amino esters by diastereoselective catalytic hydrogenation of chiral pyrrolidine tetrasubstituted β-enamino esters. Sodium triacetoxyborohydride in HOAc has been employed for the chemoselective reduction of homochiral β-enamino esters to biologically active β-amino esters.[8] Reductions of acyclic and cyclic β-enamino ketones to synthetically important γ-aminoalcohols have also been reported with various levels of diastereoselectivity.[9] Palmieri et al.[10] described the regioselective reduction of cyclic and acyclic *N*-acylenamino ketones to the β-hydroxyenamides using $NaBH_4$ in MeOH.

We present here results on the chemoselective reduction of 4-oxothiazolidines **1** by metal hydrides. Initial reductions of enamino ketone **1a** and *N*-methyl analogue **1f**, aimed at assessing the reactivity of enaminone moiety, were carried out in EtOH by adding increasing amounts of $NaBH_4$ (1–5 mol equiv) at 0 ºC to room temperature. In contrast to the literature results (vide ante) in the case of **1a**, only starting material was recovered, even after 24 h. However, reduction of **1a** under more vigorous conditions (a tenfold molar excess of $NaBH_4$, EtOH, reflux, 2 h) proceeded cleanly, affording 5-(2-hydroxyethyl)thiazolidine **5a** in 64% yield (Table 1, entry 1). Surprisingly, *N*-methyl substituted lactam **1f** was converted, via a reduction-ring closure sequence at room temperature, employing 2 mol equivalents of $NaBH_4$, to a not easily accessible new fused heterocycle, i.e. (*Z*)-(*N*-methyltetrahydrofuro[2,3-*d*]thiazol-2-ylidene)-1-phenylethanone (**6f**) (Table 1, entry 6). In general, we found that the regioselective reduction of other thiazolidines **1b**–**e** with excess $NaBH_4$ proceeded smoothly in refluxing EtOH giving rise to alcohols **5b**–**e** in moderate yields (49–64%).[11] The key step responsible for an inhibition of the enaminone moiety in **1** toward chemical and catalytic reduction as well (Table 1, entry



Scheme 2

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Table 1 Synthesis of (*Z*)-5-(2-Hydroxyethyl)-2-alkylidene-4-oxothiazolidines **5** and Condensed Thiazolidines **6**

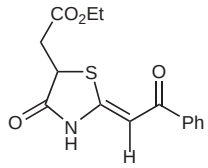
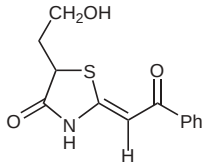
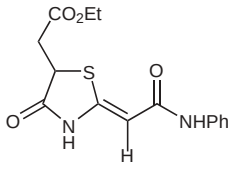
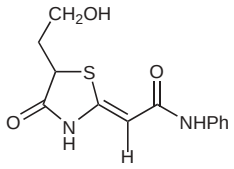
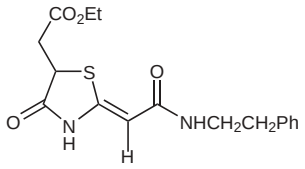
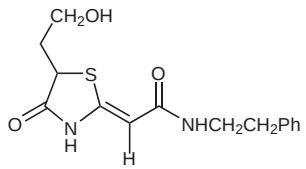
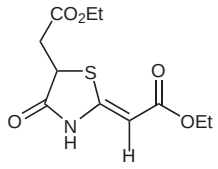
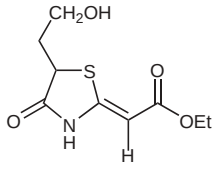
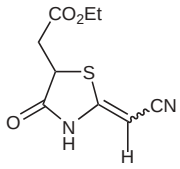
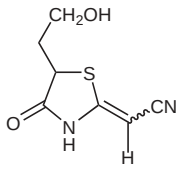
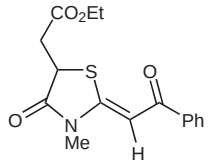
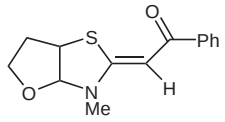
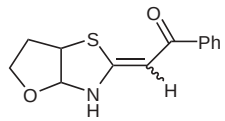
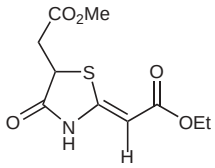
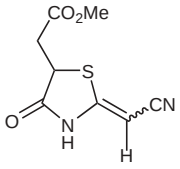
Entry	Substrate	Reducing reagent (mol equiv)–solvent	Product	Yield (%)[a]	Mp (°C)
1	 (*Z*)-**1a**	$NaBH_4$ (10)–EtOH[b]	 (*Z*)-**5a**	64	158–159
2	 (*Z*)-**1b**	$NaBH_4$ (10)–EtOH[b]	 (*Z*)-**5b**	49	223–224
3	 (*Z*)-**1c**	$NaBH_4$ (10)–EtOH[b]	 (*Z*)-**5c**	49	156–158
4	 (*Z*)-**1d**	$NaBH_4$ (10)–EtOH[b]	 (*Z*)-**5d**	64	110–111
5	 **1e** (*Z*/*E* mixture)	$NaBH_4$ (10)–EtOH[b]	 **5e** (*Z*/*E* mixture)	54	119–120
6	 (*Z*)-**1f**	$NaBH_4$ (2)–EtOH[c]	 (*Z*)-**6f**	21	121–122
7	(*Z*)-**1a**	$LiBH_4$ (10)–THF[c]	 **6a** (*Z*/*E* mixture)	19	Dec.

Table 1 Synthesis of (*Z*)-5-(2-Hydroxyethyl)-2-alkylidene-4-oxothiazolidines **5** and Condensed Thiazolidines **6** (continued)

Entry	Substrate	Reducing reagent (mol equiv)–solvent	Product	Yield (%)[a]	Mp (°C)
8	(*Z*)-**1d**	$NaBH_4$ (10)–MeOH[b]	 (*Z*)-**12d**	83	134–135
9	**1e** (*Z*/*E* mixture)	$NaBH_4$ (10)–MeOH[b]	 **12e** (*Z*/*E* mixture)	76	146–148
10	(*Z*)-**1a**	H_2 (3 atm)–PtO_2	NR		

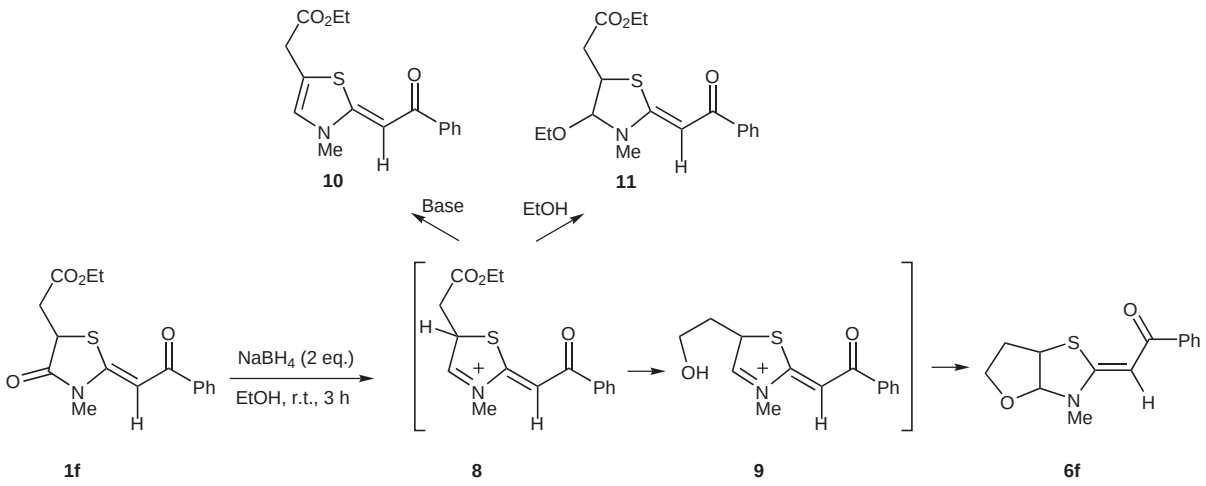
[a] Isolated yields following column chromatography on silica gel.
[b] Reflux.
[c] Room temperature.

10), is the formation of the highly stabilized anion **4** (Scheme 2).[1d,6b,12,13]

This is evidenced by the vigorous evolution of hydrogen upon addition of the thiazolidine **1** to the reducing agent during the initial stage of the reaction (10–15 min, r.t.). In the next step $NaBH_4$ selectively reduces the side-chain acetate group,[14] whereas the strongly deactivated W function and C=C bond of the conjugated enaminone moiety remain unaffected.

The formation of the bicyclic product **6f** is ascribed to the presence of the methyl group at the nitrogen atom in the starting thiazolidine **1f** (Scheme 3). Based on the literature precedent[15] that $NaBH_4$ in pyridine can reduce primary and tertiary amides to the corresponding nitriles and amines, respectively, we postulated the iminium ion **8** as a key intermediate. Obviously, the electrophilicity of the ester carbonyl is enhanced in the iminium ion **8**, allowing the reducing agent to become increasingly reactive even at room temperature.

The reduction step affords alcohol **9**, that subsequently cyclizes to new bicyclic tetrahydrofurothiazolidine **6f**, albeit in a small yield (21%). The detection of the heterocyclic derivatives **10** and **11**, which have been also isolated and characterized, supports the proposed mechanism.[16] Thus, an abstraction of the C(5)-hydrogen from the intermediate **8** by an excess base affords **10** (18%), and addition of EtOH to the same transient species leads to the traces of compound **11**. As shown in entry 7 of Table 1, the enaminone **1a** undergoes the same reduction-cyclization transformation in the presence of the stronger reducing reagent, such as $LiBH_4$ in THF. To the best of our knowledge, the formation of condensed thiazolidines **6**[17]



Scheme 3

Table 2 Comparisons of the ^{13}C NMR Chemical Shifts (ppm) of Olefinic Carbon Atoms in Thiazolidine Derivatives **1** and **6**

Entry	Compound	C(β)	C(α)	$\Delta\delta_{C(\beta)C(\alpha)}$
1	(*Z*)-**1a**[a]	161.56	94.94	66.62
2	(*Z*)-**6a**[a]	168.78	87.24	81.54
3	(*E*)-**6a**[a]	168.02	85.02	82.44
4	(*Z*)-**1f**[a]	161.48	95.50	65.98
5	(*Z*)-**6f**[b]	165.72	87.47	78.28

[a] DMSO-d_6.
[b] $CDCl_3$.

achieved through cyclization involving the 4- and 5-positions of thiazolidines **1** was not observed before.

The selected ^{13}C NMR shift differences between the olefinic carbon atoms, i.e. $\Delta\delta_{C(\beta)C(\alpha)}$ values in compounds **1** and **6** are worth noting (Table 2), since they indicate an increase of charge separation of C=C bond within the condensed thiazolidines **6**, relative to the corresponding precursors **1**.[18]

Larger $\Delta\delta_{C(\beta)C(\alpha)}$ values (78–82 ppm) in the bicyclic derivatives **6** (Table 2, entries 2,3 and 5) versus $\Delta\delta_{C(\beta)C(\alpha)}$ values (66–67 ppm) in thiazolidinones **1** (Table 2, entries 1 and 4) correlate with an increase of the push-pull effect in the former.[19] This is consistent with the reduction-cyclization process **1** $\rightarrow\rightarrow$ **6** (Scheme 3) occurring in the electron-donor portion of reactants **1** (an amide moiety), which creates a more effective donor (i.e. an amine), so fused thiazolidines **6** have larger $\Delta\delta_{C(\beta)C(\alpha)}$ values.

We wish to point out that the choice of solvent for the reduction of thiazolidinones **1a**–**e** was found to be crucial. By replacing EtOH with MeOH no reduced products could be detected in the reaction mixture. Instead, as results reported in entries 8 and 9 of Table 1 indicate, the change of solvent promotes nearly complete transesterification of the acetate group at C(5). From the work of S. Brown and H. Rapoport[14a] it is known that methyl esters of heterocyclic, aromatic or acyclic acids can be reduced by $NaBH_4$ in MeOH. However, if they are resistant to reduction, then, the transesterification especially in MeOH occurs due to the fast generation of the methoxy-substituted complex $NaB(OMe)_4$.[14c]

In conclusion, we have shown that in the case of 5-substituted push-pull thiazolidinones $NaBH_4$ in EtOH is a suitable reagent for the regioslective reduction of the ester functionality. Of particular interest is the synthesis of the condensed 2-alkylidenethiazolidine derivatives by an intramolecular annulation from the selected thiazolidinone precursors.

Acknowledgment

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(10) Palmieri, G.; Cimarelli, C. *Tetrahedron* **1988**, *54*, 915.

(11) **Typical Experimental Procedure:** An appropriate 5-substituted-4-oxothiazolidine **1** (100 mg) dissolved in anhydrous EtOH (10 mL) was added dropwise at r.t. to the tenfold molar excess of $NaBH_4$ in EtOH (ca. 5 mL). When the hydrogen evolution had ceased the reaction mixture was heated under reflux with stirring for a period of time required (2–3 h) to complete the reaction (TLC). The reaction mixture was cooled, neutralized with NH_4Cl and extracted with EtOAc. The combined extracts, washed with brine and dried, were evaporated in vacuo. The residue was purified by column chromatography (SiO_2, toluene–EtOAc, 10:0 $\rightarrow$ 8:2) to afford a pure product **5**.
Spectroscopic data for (*Z*)-[5-(2-Hydroxyethyl)-4-oxothiazolidin-2-ylidene]-1-phenylethanone (**5a**): Colorless solid; mp 158–159 °C. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.71–1.93 (m, 1 H, $CH_AH_BCH_X$), 2.14–2.30 (m, 1 H, $CH_AH_BCH_X$); 3.58 (m, 2 H, CH_2OH), 4.09 (dd, J_1 = 9.5 Hz, J_2 = 4.2 Hz, 1 H, H_x), 4.82 (br s, 1 H, OH; signal disappears upon D_2O addition), 6.72 (s, 1 H, =CH), 7.47–7.62 (m, 3 H, *p*-Ph and *m*-Ph), 7.83 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 1.6 Hz, *o*-Ph), 11.85 (br s, 1 H, NH; signal disappears upon D_2O addition). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 35.7 (CH_AH_B), 44.1 (CH_X), 58.6 (CH_2OH), 94.5 (=CH), 127.2 (*m*-Ph), 129.0 (*o*-Ph), 132.4 (*p*-Ph), 138.5 (C_1-Ph), 161.2 (C=), 177.3 (CO_{ring}), 187.3 (CO_{exo}). IR (KBr): 3453, 3194, 3068, 2924, 1685, 1631, 1577, 1517, 1468, 1364, 1295, 1198 cm^{-1}. MS (EI): *m/z* (rel. intensity%) = 263 (100) [M^+], 232 (86), 178 (8), 146 (20), 105 (80). UV (DMSO): λ_{max} (ε) = 335.0 (18000) nm. Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.03; H, 4.92; N, 5.33; S, 12.24.

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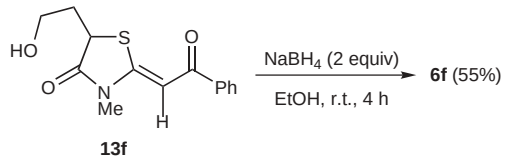
(15) (a) Kikugawa, Y.; Ikegami, S.; Yamada, S. *Chem. Pharm. Bull.* **1969**, *17*, 98. (b) For a reduction of lactams to amines by NaBH4, see: Mandal, S. B.; G iri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, *53*, 4236.
(16) Methylation of (*Z*)-**5a** led to alcohol **13f**, which, in a one-pot sequence, comprising reduction followed by cyclization, was transformed into the identical bicylic thiazolidine **6f** in moderate yield (Scheme 4).



13f

Scheme 4

(17) (*Z*)-(*N*-Methyltetrahydrofuro[2,3-*d*]thiazol-2-ylidene)-1-phenylethanone (**6f**): Colorless solid; mp 121–122 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.12–2.43 (m, 2 H, $CH_AH_BCH_XS$), 3.10 (s, 1 H, NCH_3), 3.77–3.89 (m, 1 H, OCH_YCH_XS), 4.02 (t, 1 H, *J* = 8.0 Hz, OCH_QH_Z), 4.12 (t, 1 H, *J* = 7 Hz, OCH_QH_Z), 5.67 (d, 1 H, J_{XY} = 6.6 Hz, OCH_YCH_XS), 6.08 (s, 1 H, =CH), 7.36–7.47 (m, 3 H, *m*-Ph, *p*-Ph), 7.90–7.95 (m, 2 H, *o*-Ph). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 33.7 (NCH_3), 35.2 (CH_AH_B), 44.6 (CH_X), 65.8 (CH_2O), 87.5 (=CH), 99.1 (CH_Y), 127.2 (*o*-Ph), 128.2 (*m*-Ph), 131.0 (*p*-Ph), 139.7 (C_1Ph), 165.7 (C=), 186.9 (CO). IR (KBr): 3530, 3412, 2974, 2939, 1602, 1571, 1525, 1433, 1355, 1264, 1213, 1028, 973, 727 cm^{-1}. MS (EI, 70 eV): *m*/*z* (rel. intensity) = 261 (57) [M$^+$], 260 (100), 245 (34), 191 (20), 184 (42), 163 (32), 105 (97), 86 (39), 82 (58), 51 (26). UV (DMSO): λ_{max} (ε) = 337.9 (19 700) nm. Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36; S, 12.27. Found: C, 64.24; H, 5.82; N, 5.30; S, 12.59.
(18) In all push-pull thiazolidines **1** and **6** high field ^{13}C chemical shifts (85–96 ppm) for the acceptor-substituted C(α) atoms, and low field shifts (161–169 ppm) for the donor-substituted C(β) atoms are typical.
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