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SYNTHESES AND THERMAL TRANSFORMATIONS OF N-ALKYL THIAZOLIDINE SULFOXIDES

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Abstract: The title compounds are prepared and their novel thermal chemistry studied for the first time. Aldehydes and thiazolidines can be generated thermally from these compounds. Mechanistic possibilities are discussed.

The thiazolidine ring system is an integral part of a variety of compounds that have found diverse application as medicinally active agents, flavor enhancing additives and useful intermediates in synthesis.[1] Polaroid's interest in thiazolidines relates to their argentolytic reactivity[2] which is the basis of an important imaging mechanism in Spectra® instant color film. Thiazolidine sulfoxides gained notoriety two decades ago with the discovery of the *in vitro* ring expansion of penicillin sulfoxides to deacetoxycephalosporins.[3] All previously reported thiazolidine sulfoxides are configured such that the nitrogen in the thiazolidine ring is acylated or sulfonylated. Interestingly, a natural product that incorporates the thiazolidine sulfoxide moiety has been reported and it too possesses an acylated nitrogen.[4] We report here the first syntheses of N-alkyl thiazolidine sulfoxides and some initial findings concerning the novel thermal reactivity these compounds exhibit.

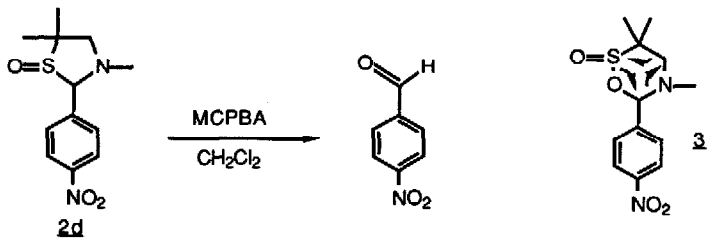
Previous reports describe unsuccessful attempts to synthesize "N-H" thiazolidine sulfoxides[5] and α-aminosulfoxides[6], describing these compounds as intrinsically unstable and prone to complex decomposition reactions. We have found that the N-alkyl thiazolidines 1a-1g can be oxidized (1 equiv. MCPBA, CH_2Cl_2, -15°C-R.T.) in a straightforward manner to the corresponding sulfoxides 2a-2g in 60-95% yields (Table 1).[7] These sulfoxides were purified by chromatography and are quite stable in the crystalline state.

	R_1	R_2	R_3	R_4	R_5	
1a	CH_3	H	$N(CH_3)_2$	H	CH_3	2a
1b	CH_3	S-Ph	$N(CH_3)_2$	H	CH_3	2b
1c	CH_3	S(O)-Ph	$N(CH_3)_2$	H	CH_3	2c
1d	CH_3	H	NO_2	H	CH_3	2d
1e	CH_3	H	$N(CH_3)_2$	CH_3	H	2e
1f	3,5-Dicarboethoxy benzyl	H	$N(CH_3)_2$	CH_3	H	2f
1g	CH_3	H	NO_2	CH_3	H	2g

Table 1

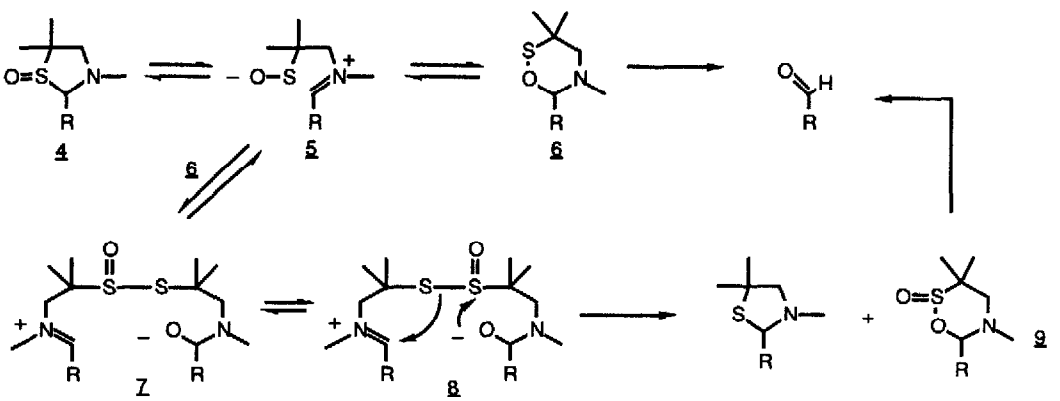
When thiazolidine sulfoxides 2a-2c were refluxed under nitrogen in dry toluene, mixtures of p-dimethylaminobenzaldehyde (DMAB) and thiazolidines 1a-1c were produced in 60-80% yields.[8] The product ratios (aldehyde/thiazolidine) were generally ~1.5/1 for 2a and ~2-3/1 for 2b and 2c.[9] It appears from these compounds and others we have studied that, in general, N-alkyl thiazolidine sulfoxide derivatives of aromatic aldehydes that bear *gem* dimethyl groups at C-5 in the thiazolidine ring produce both aldehyde and thiazolidine products when refluxed in toluene. Interestingly, aldehydes are the sole products produced thermally from thiazolidine sulfoxides bearing *gem* dimethyl groups at C-4. Thus, DMAB is exclusively produced in high yield when 2e or 2f are refluxed in dry toluene.

The nitrobenzaldehyde derivatives 2d and 2g are stable in refluxing toluene suggesting that thiazolidine sulfoxide ring opening to the zwitterions like 5 (Scheme 1) is important for the observed reactivity with DMAB-derived thiazolidine sulfoxides. In contrast to its thermal stability, 2d reacts rapidly with MCPBA under aprotic conditions affording p-nitrobenzaldehyde in high yield. This reaction could involve the spontaneous fragmentation of the unstable sulfone perhaps via the isomeric cyclic sulfinate 3. A similar reaction has been previously reported[10] and the heterocyclic cycloreversion is precedented.[11]



Scheme 1 outlines a possible mechanism for the thermal reaction of thiazolidine sulfoxides such as 2a-2c that give rise to thiazolidines 1a-1c, respectively, and DMAB.

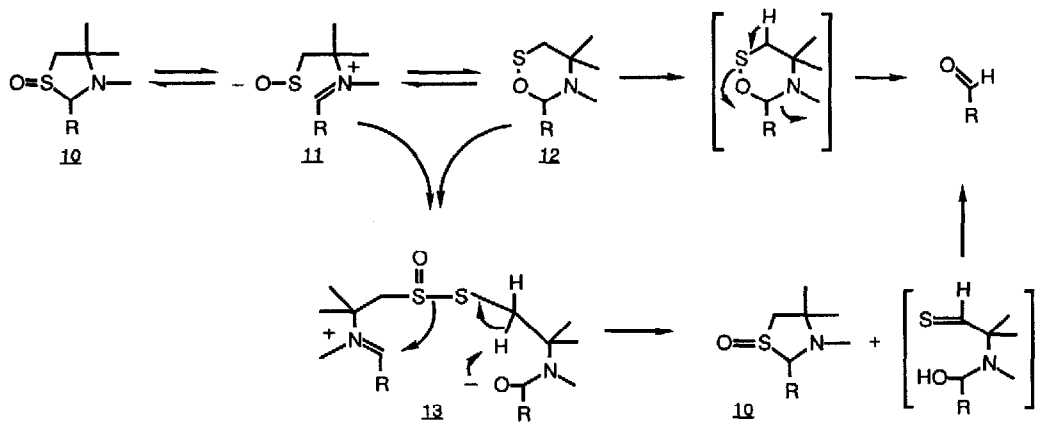
Scheme 1



Sulfenic acid trapping agents did not affect the course of these reactions, indicating that free sulfenic acids are unlikely intermediates. A key step involves the known sulfoxide to sulfenate rearrangement (4 to 6).[6,12] Condensation of 5 and 6 would be expected to generate the thiosulfinate 7.[13] Thiosulfinates have been well studied and are known to undergo isomerizations as shown (7 to 8).[14] Metastable sulfenic anhydrides (R-S-O-S-R') have been suggested as possible intermediates in these isomerizations. Equal amounts of the observed products could arise via fragmentation of thiosulfinate 8, as shown. Note that cyclic sulfinate 9 is analogous to 3 proposed earlier. A product ratio favoring the aldehyde could arise if DMAB is generated directly from 6.

Scheme 2 outlines a similar mechanism for thermal reactions of thiazolidine sulfoxides such as 2e and 2f that produce DMAB as the sole product. With protons adjacent to sulfur, the possiblity for β-eliminations exists for both intermediates 12 and 13. Carbinolamine breakdown to the observed aldehyde products would be expected to follow. Thiosulfinates, such as those proposed (7 , 8 , 13), are capable of disproportionation to disulfides and thiosulfonates.[14,15] Low yields of these were isolated from the aminoethanethiol portion of 2f as minor by-products of the thermolysis (presumably from the adventitious hydrolysis of 13 before breakdown to 10 and carbinolamine) thus supporting the proposition that thiosulfinates might be intermediates. We are continuing to explore these and other aspects of this chemistry.

Scheme 2



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(1) See Meneghini, F.; Luhowy, R. *J. Am. Chem. Soc.* **1979,** *101*, 420 and references therein.

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(7) All newly synthesized compounds were characterized by elemental analysis except for compound 2b which was characterized by HRMS. All compounds exhibited spectral data (PMR, IR, MS) in agreement with their structures.

(8) This range of yields reflects differences in the extent of reaction. The only other materials present along with the DMAB and thiazolidine products were unreacted thiazolidine sulfoxides.

(9) Product ratios were estimated by analysis of PMR integrations on crude product mixtures.

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(13) To test the possibility of 4 reacting with 6 in an oxygen transfer reaction producing 9 directly, a cross-over experiment was conducted in which a 1:1 mixture of 2d and 2a were refluxed together in toluene. Via the oxygen transfer mechanism, one would expect some of 2d to be reduced to the nitro thiazolidine 1d , which in fact did not occur.

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