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Thermal stability investigation of pyridine substituted tosyl oximes

David J. am Ende [a,*], David H. Brown Ripin [a], Neil P. Weston [b]

[a] *Chemical R&D, Pfizer Inc., Groton, CT 06340, USA*
[b] *Astra-Zeneca, Avlon Works, Severn Road, Hallen, Bristol BS 10 7ZE, UK*

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Abstract

A systematic evaluation was performed to evaluate the thermal stability for a series of pyridine substituted oximes and tosyl oximes. This investigation, utilizing DSC and ARC, commenced after finding a surprising result during standard thermal screening of a tosyl oxime indicating high thermal potential energies and low onset temperature. Onset temperatures in the range of 40–50 °C were detected for tosyl oximes as measured by ARC. In addition this class of compounds exhibited some sensitivity to impact and may in fact exhibit explosive properties. As a result of this study a better understanding was obtained for the thermal potential and shock sensitivity properties of these materials. In general, a thorough process safety testing and evaluation should be performed when working with oximes.

Keywords: Oximes; Thermal hazards; Process safety; DSC; ARC; Decomposition

1. Introduction

In the course of preparing to synthesize 2-amino-1-(3-pyridyl)-ethan-1-one (**4**) on a large scale, we evaluated the thermal stability of the intermediates described in the preparation reported by LaMattina and Suleske (Scheme 1) [1]. This testing was focused on tosyl oxime **3** in particular as a standard protocol prior to scaling a reaction above a 5L scale, but also in part due to anecdotal precedent for a structurally very similar tosyl oxime detonating on drying [2].[1] It was found that compound **3** presented a very high thermal hazard with a low onset temperature. As a result of this finding, we synthesized all of the positional isomers of the pyridine substituted tosyl oximes and studied their thermal decompositions [3].

2. Experimental procedures

Differential scanning calorimetry (DSC) was performed on a Mettler-Toledo DSC821^e with a heating rate of 4 °C/min. Typical sample size for DSC testing was 10–16 mg using gold-plated stainless steel sample crucibles employed to prevent escape of liquid or gases upon decomposition. Impact sensitivity testing was performed using 10 kg mass dropped from a height of 60 cm (i.e. 60 J) impacting a 50 mg sample sandwiched between two cylinders. Accelerating rate calorimetry (Columbia Scientific) tests used a heat-wait-search mode with 5 °C heat steps with titanium sample bombs. The ARC was calibrated to track an exotherm with a sensitivity of 0.02 °C/min. ARC samples were approximately 2 g. The thermal inertia for the ARC experiments, where thermal inertia is $(1 + (\text{massCp})_{\text{bomb}}/(\text{massCp})_{\text{sample}})$, were 2.2 for oxime **3** and 2.1 for oxime **3**-HCl salt shown in Fig. 4. ARC onsets were corrected in the typical way by extrapolating the self-heat rate data to the temperature where exotherm sensitivity (0.02 °C/min) is normalized by thermal inertia.[2]

3. Results and discussion

Results obtained from this investigation are compiled in Table 1 where multiple entries refer to additional experiments obtained from different sample lots. Differential

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* Corresponding author. Tel.: +1-860-4416504; fax: +1-860-7159057.
E-mail address: david_j_amende@groton.pfizer.com (D.J. am Ende).

[1] Tosyl (Ts) refers to *para*-toluenesulfonyl functionality (i.e. CH_3–C_6H_4–SO_2–).

[2] The effect of thermal inertia is to slow the reaction. So in Fig. 4 the onset is determined by an extrapolation of the self-heat rate data down to 0.01 °C/min. For further theory on ARC analysis, see Ref. [4].

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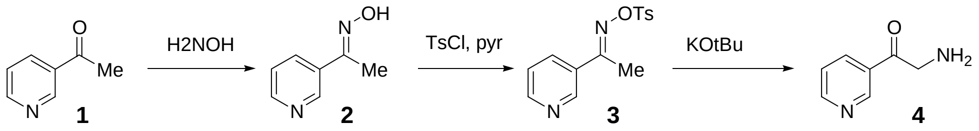


Scheme 1.

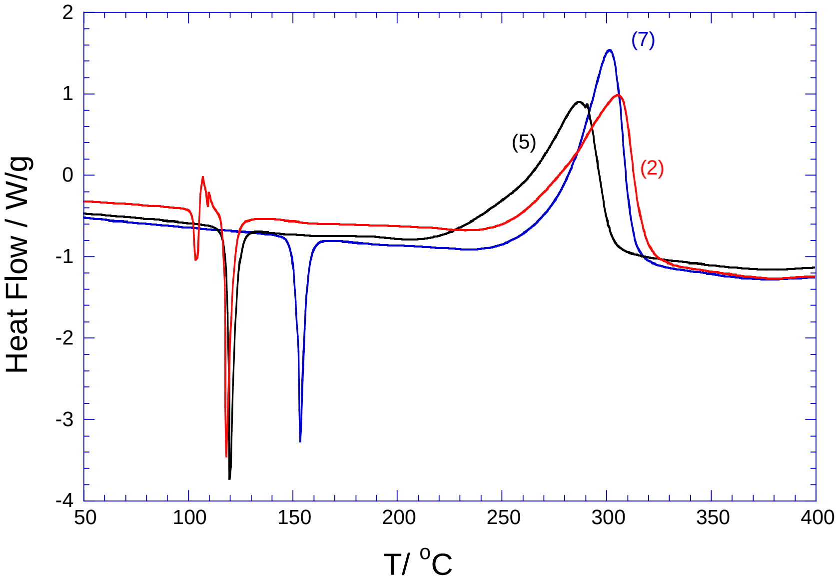


Fig. 1. DSC scans of pyridine isomers (**2**, **5**, **7**). Exotherm is upward. Samples were heated from ambient to 400 °C/min at 4 °C/min.

scanning calorimetry is one of the primary screening tools used by the Process Safety and Reaction Engineering Laboratory. Besides melting point, the DSC trace affords two other key pieces of information: onset temperature for thermal decomposition and the energy of decomposition.

Within one class of pyridine oxime isomers studied (**2**, **5**, **7**) the melting points (m.p.'s) ranged from 104 to 155 °C as shown in Fig. 1. It should be noted that on these traces the exotherms are upward and endotherms are downward. Interestingly the melting points of the tosyl oxime isomers (**3**, **6**, **8**) were essentially identical (i.e. all 80 °C) shown in Fig. 2 and significantly lower than the pyridine oxime precursors (**2**, **5**, **7**). Note the melting points were taken at the peak of the endotherm. For example, comparing the

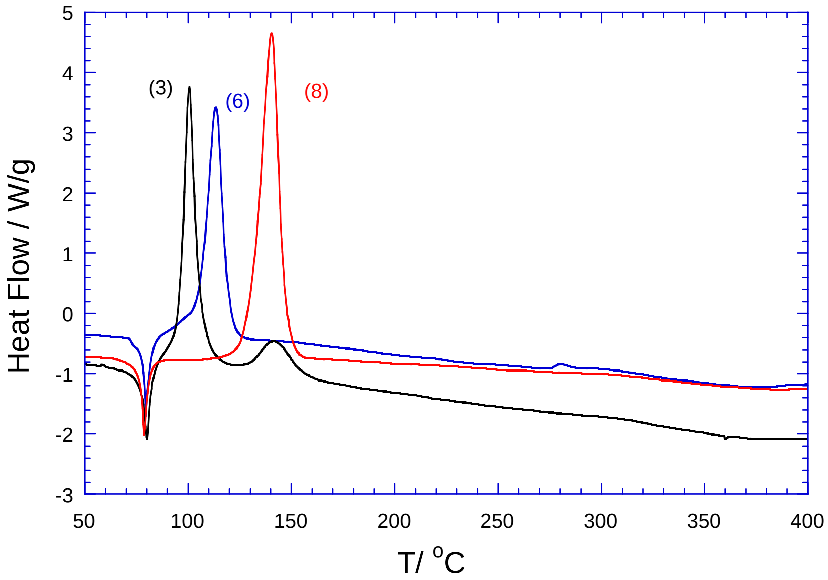
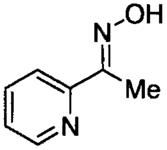
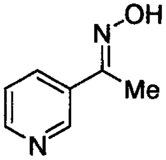
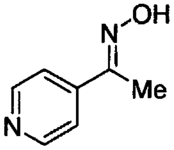
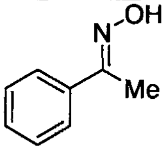
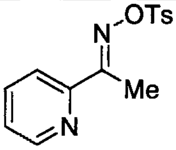
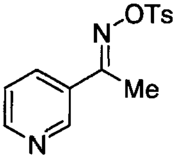
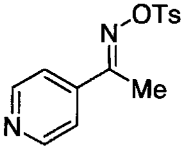
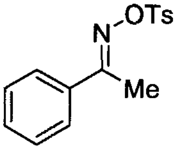


Fig. 2. DSC scans of the tosyl oxime positional isomers (**3**, **6**, **8**). Exotherm is upward. Samples were heated from ambient to 400 °C/min at 4 °C/min.

Table 1
Thermal analysis and impact results for the series of oximes tested

Material		DSC Results			Impact Sensitive
		Melting Point (°C)	Onset Temp (°C)	Energy Released (J/g)	
	**5**	120 120	200 208	1169 1072	Y (10-15J)
	**2**	104 118 120	226 207 226	1095 1210 1087	N (>60J)
	**7**	160 155	205 240	1223 1060	N (>60J)
	**9**	55-60	218	917	Not Tested
	**6**	80	85	637	Y (<10J)
	6-HCl Salt	None Detected	88	552	Y (55-60J)
	**3**	80 80 80	84 83 83	830 966 905	Y (<10J)
	3-HCl Salt	None Detected	133 136	465 402	N (>60J)
	**8**	80 80	92 94	994 999	Not Tested
	**10**	None detected Prior to decomp	42	355	Paste Not Tested

difference in m.p. between the substituted pyridine **7** and its tosylate **8**, the tosylate m.p. was 75–80 °C lower.

In general, the decomposition energies of the oximes tested were in the range reported in the literature by Grewer to be −110 to −140 kJ/mol [5]. However, the tosyl oximes in general had significantly higher heat flows during decomposition (i.e. sharper energy peaks on the DSC trace) than the precursors (**2**, **5**, **7**). Contrast to Figs. 1 and 2 the most striking result is the lowering of the onset temperatures for decomposition for the tosyl oxime isomers. For example the pyridine oxime precursors are very stable (decomposing above 200 °C) while tosyl oxime series of isomers all decomposed near 100 °C. In fact, **3** and **6** decomposed immediately following the melt as shown in the DSC trace of Fig. 2.

Based on DSC data, we observed an apparent lowering of the onset temperature of the tosyl oxime series dissolved in pyridine as compared to their isolated crystalline state. Experiments with **6** and **3** separately dissolved in four volumes of pyridine (the solvent used in the synthesis of these compounds) showed onset temperatures in the 50–60 °C range with decomposition energies measured to be approximately proportional to concentration (i.e. energy decreases with dilution). One simple explanation for the apparent lowering of onset has to do with the way onsets were determined from DSC scans. For example in Fig. 2, for the crystalline oxime

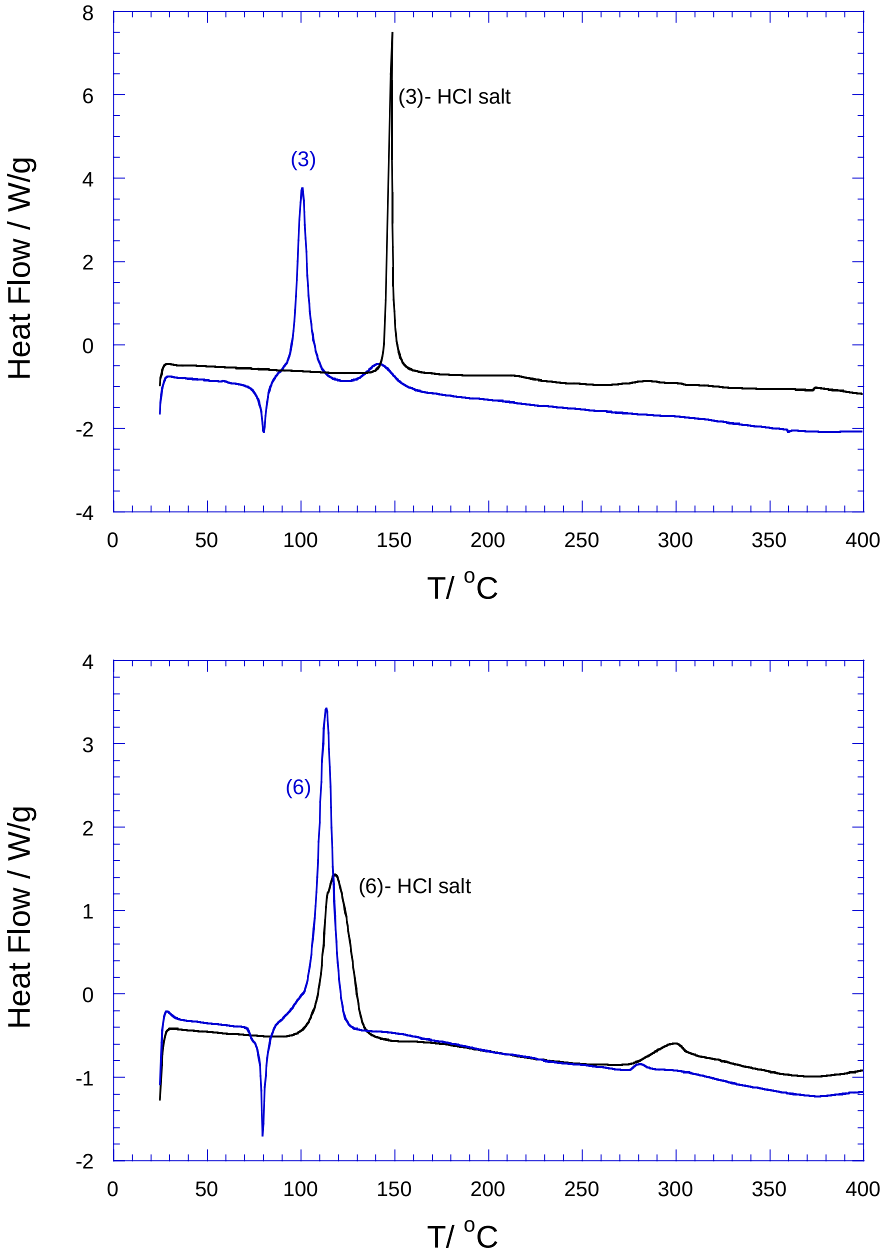


Fig. 3. Top: DSC traces of tosyl oxime free base (**3**) and **3**-HCl salt; bottom: DSC traces of tosyl oxime free base (**6**) and **6**-HCl salt.

3, the onset for decomposition was simply taken as the temperature following the melt but near the hypothetical baseline (i.e. 83 °C). But when the tosyl oximes are dissolved in pyridine there is no melting point and thus the exotherm is detected at a lower temperature. Thus during the DSC scanning experiment at 4 °C/min accurate onset temperatures for decomposition of the tosyl oximes **3** and **6** are obscured by the endothermic melt. Isothermal DSC experiments performed at temperatures slightly below their melting points could potentially indicate whether these materials are autocatalytic but this was not explored here. However, ARC experiments confirmed that tosyl oxime **3** decomposed at 48 °C and thus the onset temperature of the solid state appears to be consistent with measurements made of the pyridine solutions. The results from the present work simply confirm and highlight that exothermic decomposition occurs at relatively low temperatures for these tosyl oximes and should be carefully tested and evaluated prior to use and scale-up of these compounds. Further, it should be emphasized that DSC testing alone on the isolated compounds can lead to an apparently high onset temperature and safety margin and thus confirmation by ARC for process evaluation is critical.

Of the tosyl oximes tested, **10** exhibited the lowest thermal stability having an onset of 42 °C by DSC and coincidentally had the lowest decomposition energy of all the oximes tested. However, with such a low onset temperature, the decomposition energy of **10** reported in Table 1 could be underestimated due to partial decomposition upon standing at room temperature and may explain its lower decomposition energy.

It was found that compound **3** was somewhat stabilized as its hydrochloride salt; the salt decomposed with 465 J/g, 900 J/g of energy at 133 °C as compared to −900 J/g of energy at 83 °C for the free base. However, this was not the case with the HCl salt of **6**, where there is only a slight difference in onset temperature between the salt and free base as evident from Fig. 3 which shows the DSC traces for **3** and **6** and their HCl salts. The total energy of decomposition of the HCl salts tend to be lower. Interestingly, the HCl salt of **3** showed a very sharp decomposition peak yet was not found to be impact sensitive. In addition the HCl salts of **3** and **6** showed no melting point prior to decomposition based on DSC.

The results of the impact sensitivity testing by drop hammer were more variable with the several compounds tested. The Merck process research group [6] has reported similar findings for the 3-substituted pyridine, which demonstrated low level shock sensitivity. In the present work, positive impact results were noted by smoke, explosion, or decomposition. In the case of compounds **3**, **5**, and **6**, high sensitivity to impact was observed with decomposition induced at impact energies below 15 J. The HCl salts of **3** and **6** had much less sensitivity to impact with impact energies above 50 J.

The observations made by drop hammer testing indicate that some of these compounds *may* exhibit explosive properties. However, impact alone does not determine this classification. Specialized tests such as time–pressure and koenen tube tests are needed to determine if a material exhibits explosive properties. Impact testing is used in the UN transportation guidelines to determine whether a material is too sensitive to transport once it has been classified as exhibiting explosive properties.

Compounds **3**, **3**-HCl salt, and **6** were tested by accelerating rate calorimetry (ARC). ARC is an adiabatic technique that is sensitive to self-heating to at least 0.02 °C/min and can be used to design storage or drying conditions of materials. ARC results from **3** and **6** indicate that self-heating begins in the range of 48–52 °C for these compounds. Note that the ARC is a much slower experiment increasing in temperature in 5 °C steps each lasting 30 min and is able to detect exothermic decomposition well below the melting points of the tosyl oxime. This onset is considered low and does not afford an ideal margin of safety for typical handling on scale. The HCl salt of **3** showed an onset of 107 °C by ARC, indicating much higher stability (Fig. 4).

The decomposition of compounds **3** and **6** were studied by GC–MS. Both were injected into a gas chromatograph with the injector temperature at 280 °C. The major decomposition product seen in both cases was the *N*-acetamide (as confirmed by MS and coinjection with a standard). Samples of both compounds were heated in an open dish on a steam bath for 15 min, and the tar was then dissolved and shot onto the GCMS with the same methods. In these experiments, the *N*-acetamide was produced with fewer byproducts than the samples decomposed in the injector port. The decomposition of compound **3** resulted in high amounts of insoluble tar, whereas compound **6** did not. These experiments indi-

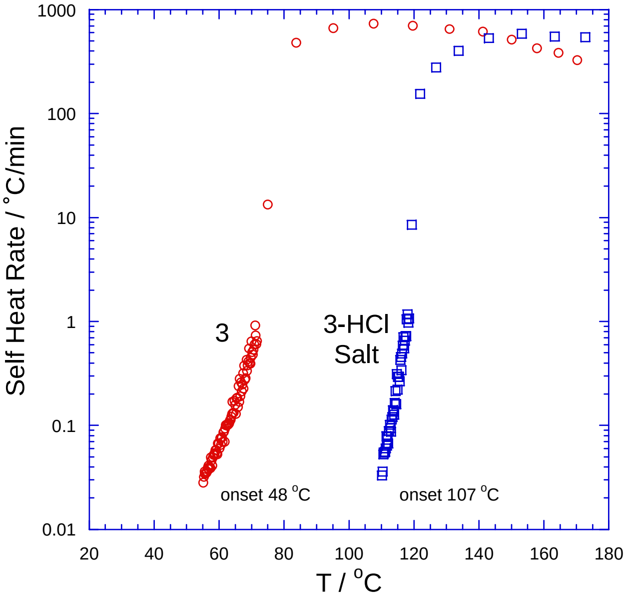


Fig. 4. Accelerating rate calorimetry of **3** and **3**-HCl salt indicating rapid self-heating starting from 48 °C for **3** and 107 °C for **3**-HCl. A significant pressure rise was associated with these decompositions.

cate that the mechanism of decomposition is via Beckmann rearrangement.

4. Conclusions

Caution should be exercised when synthesizing and isolating oximes and in particular tosyl oximes. Onset temperatures for self-heating were in the 40–50 °C range for the tosyl oximes tested by accelerating rate calorimetry. The HCl salt of **3** afforded greater thermal stability exhibiting self-heating above 100 °C. In addition, this class of oximes exhibited some sensitivity to impact and may in fact exhibit explosive properties. As a result of this study a better understanding was obtained for the thermal potential and shock sensitivity properties of these materials.

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