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An Unexpected Incident with 4-Trifluoromethylaniline

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Abstract:

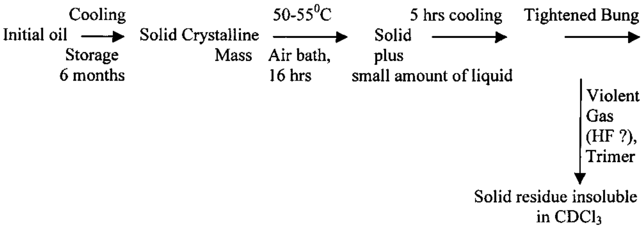
4-Trifluoromethylaniline has been seen to solidify during storage. This manuscript describes an unexpected incident that occurred while attempting to melt the solidified material. Our investigation of the incident suggests a trimer formation with the evolution of HF gas. Autocatalytic decomposition or heat of crystallization maybe potential mechanisms for the trimer formation.

Introduction

4-Trifluoromethylaniline is a commonly used material both in organic synthesis and the manufacture of pharmaceutical compounds. During the course of synthesizing an intermediate, an unexpected phenomenon occurred with the compound 4-trifluoromethylaniline. The CRC handbook[1] reported the melting point to be 38 °C, whereas the initial material was received and used as oil. The material in question was in a poly drum that contained approximately 20 kg of the aniline as an oil. After storing the unused portion of the 4-trifluoromethylaniline for 6 months in a warehouse, the material was brought into the laboratory to be sampled for further pilot work. This particular storage facility did not have temperature control, and no information was received that this material required special storage conditions. Upon examination of the drum contents, the material had formed a solid crystalline mass. As the warehouse storage period had been from autumn to late winter and storage temperatures had recently been close to freezing, it was not surprising to see the material had solidified. In an attempt to melt the solids, the bung of the drum was loosened and the entire drum placed in an air drier at 50−55 °C. The reported boiling point for 4-trifluoromethylaniline is 83°/12 mm. The drum was in the air drier for 16 h; it was then removed, and upon examination it was noted that a small amount of liquid was present but the vast majority of the material remained a solid.

Results and Discussion

With this unexpected result it was decided to examine the contents of the drum by NMR. The entire drum was brought into the laboratory and was placed in a large, empty, stainless steel tub as an added safety precaution. With the bung loose the contents were allowed to equilibrate for 5 h at which point some liquid was removed for analysis, and the bung was tightened. Approximately 15−30 min after sealing the drum it ruptured near the bottom and a white gas exited the drum with tremendous force. This gas quickly filled the entire laboratory, and fortunately the only occupant of the laboratory at the time was able to exit from a rear fire door without being affected. When the gas evolution ceased after 15 min, an investigation of the incident was immediately initiated. The following flowchart describes the entire incident.



First, the contents of the drum were analyzed by NMR; in doing this it was noted that a major change in the physical property of the material had occurred. When first received the aniline was completely soluble in d_3 -chloroform. The solid residue from the ruptured drum was insoluble in d_3 -chloroform, and the small amount of liquid that did dissolve showed a proton NMR consistent with 4-trifluoromethylaniline. At this point the drum contents appeared to be the same as after warming in the air drier: the vast majority as a solid with a small amount of liquid. The solid residue from the drum had to be dissolved in d_6-DMSO and showed a proton spectra that was not consistent with the structure of the aniline and showing extra peaks in the aromatic region. The same inconsistencies were seen for the drum solids in the fluorine and carbon NMR spectra when compared to reference spectra of fresh aniline. A sample of the solid material from the drum was sent for elemental analysis. Because of the unavailability of a pure sample, the possibility of an unknown amount of HF salts being present in the sample, and the unstable nature of the material, the results of the elemental analysis were inconclusive. The isolated solid from the drum was seen to soften at 170 °C and melt at 225−230 °C to a dark amber oil with some bubbling observed.

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(1) *Handbook of Chemistry and Physics*, 76th ed.; CRC Press: Boca Raton, FL, 1995−1996.

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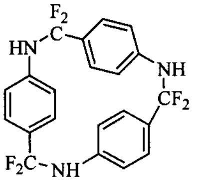
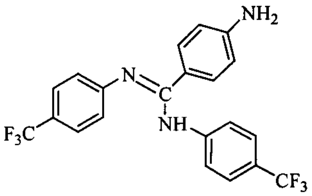
An examination of the literature revealed that a contradiction exists as to the melting point of 4-trifluoromethylaniline, indicating that our first CRC reference may be in error. The literature search showed a 1947 publication[2] reporting a melting point of 8 °C, a 1972 U.S. patent[3] reporting a melting point of 32 °C, and the 2000−2001 Acros Organics/Fisher Scientific Catalog reporting a melting point of 3−8 °C.[4] With the discrepancy of the melting point in the literature it was decided to conduct an experiment to freeze a fresh, pure sample of 4-trifluoromethylaniline. A 5 mL sample of the aniline was magnetically stirred while cooling in an ice bath; thermocouple probes were placed in the liquid aniline and the cooling bath. At 1.5−2 °C the sample rapidly crystallized to a solid mass in seconds, thus favoring the 3−8 °C literature melting point. This experiment was repeated with the same results. During these experiments an interesting observation was made of the heat of crystallization: the temperature of the aniline when it solidified rose in seconds from 1.5 to 7.5 °C. Considering that only 5 mL of aniline was used in the experiment and the sample remained in a 0 °C ice bath throughout the solidification process, this represents a substantial heat of crystallization. After allowing the pilot crystallization to melt back to the liquid state, NMR analysis showed unchanged 4-trifluoromethylaniline. This clearly demonstrated that freezing and thawing (one time in an unsealed flask with ice bath cooling) 4-trifluoromethylaniline did not reproduce the events that had occurred in the large-scale sealed drum while in storage. Analysis of the solid drum residue with differential scanning calorimetry (DSC) showed an exotherm of 296 J/g near 87 °C; subsequent analysis of fresh, clear, 4-trifluoromethylaniline showed an exotherm of 419 J/g near 182 °C. A sample of 4-trifluoromethylaniline that had been stored on a lab shelf for several years and was still liquid but had an amber color was analyzed by DSC and showed an exotherm of 419 J/g near 138 °C.

Clearly from the above observations the solid material in the drum was not the 4-trifluoromethylaniline originally received, and the DSC work also indicated that the material did not need to be totally solidified to show increased risk as the results of the aged liquid sample showed. What needed to be determined was what the solid material in the drum was and what was the gaseous material that exited with such force that it ruptured the sidewall of the container.

For further insight into the structure of the solid residue and the gas generated from the incident an analytical support group conducted mass spectrum analysis. An ion trap mass spectrometer was used to perform flow injection analysis (FIA) and direct infusion experiments which determined the molecular weight of the unknown solid material to be 423 daltons. On the basis of the observation of the release of white fumes (suspected to be HF), mass spectral isotopic distribution, and MS/MS/MS experiments two possible trimeric structures were proposed, a cyclic structure **I** and the open form structure **II**.



Structure I



Structure II

The fragmentation patterns of the unknown seems to indicate that structure **II** is the more likely structure and this also agrees with the proton and carbon NMR data. A search of the literature indicated that compounds such as structure **II** could be produced by the reaction of trifluoromethyl aniline with primary Grignard reagents that involve a series of fluoride eliminations followed by the addition of the nucleophile to the resultant intermediate anion.[5] In this particular incident, it is believed that the heat of crystallization observed in the freezing point experiments or autocatalytic decomposition may be possible initiators for the 4-trifluoromethylaniline to react with itself. If the sealed drum containing ∼18 kg became cold enough to crystallize and the crystallization was rapid, then the potential for a large exotherm seems quite plausible.

Conclusions

4-Trifluoromethylaniline is a liquid at room temperature. This material should be handled carefully and should be stored under controlled conditions. Our experience indicates that the formation of trimer/high-melting solids are potential precursors leading to a hazardous event with violent gas evolution (presumably HF). The trimer could be formed by either autocatalytic decomposition or by the heat of crytallization. However, the mechanism for the trimer formation is not well understood. Both NMR and mass spectral fragmentation pattern results favor structure **II** as the trimer formed in this incident. Further work is necessary to understand fully the mechanism of events leading to this incident.

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(2) *J. Am. Chem. Soc.* **1947**, *69*, 2346.
(3) U.S. Patent 3,632,629, 1972.
(4) *Acros Organics 2000/01 Catalog of Organics and Fine Chemicals*; Catalog Number 20891, p 80.
(5) Lin, S.; Hojjat, M.; Strekowski, L. *Synth. Commun.* **1997**, *27*(*11*), 1975−1980.