Thermal Stability of *N*-Heterocycle-stabilized Iodanes – A Systematic Investigation

Andreas Boelke,‡1 Yulia A. Vlasenko,‡2 Mekhman S. Yusubov,2 Boris J. Nachtsheim*1 and Pavel S. Postnikov*2,3

‡ These authors contributed equally

Address: 1Institute for Organic and Analytical Chemistry, University of Bremen, 28359 Bremen, Germany

2 Research School of Chemistry and Applied Biomedical Sciences, Tomsk Polytechnic University, 634050 Tomsk, Russian Federation

3 Department of Solid State Engineering, University of Chemistry and Technology, 16628 Prague, Czech Republic

*Prof. Dr. Boris J. Nachtsheim, nachtsheim@uni-bremen.de

*Prof. Dr. Pavel S. Postnikov, postnikov@tpu.ru

Abstract

The thermal stability of pseudocyclic and cyclic *N*-heterocycle-stabilized (hydroxy)aryl- and mesityl(aryl)-λ^3-iodanes (NHIs) through thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) is investigated. Peak decomposition temperatures (T_{peak}) were observed within a wide range between 120 and 270 °C. Decomposition enthalpies (ΔH_{dec}) varied from -29.81 to 141.13 kJ/mol. A direct comparison between pseudocyclic and cyclic NHIs revealed high T_{peak} but also higher ΔH_{dec} values for the latter ones. NHIs bearing *N*-heterocycles with a high N/C-ratio such as triazoles show among the lowest T_{peak} and the highest ΔH_{dec} values. A comparison of NHIs with known (pseudo)cyclic benziodoxolones is made and we further correlated their thermal stability with reactivity in a model oxygenation.

Keywords

Hypervalent iodine; *N*-heterocycle; stability; thermogravimetry; differential scanning calorimetry

Introduction

Hypervalent iodine compounds, in particular aryl-λ^3-iodanes, have found wide spread applications as oxidants and electrophilic group transfer reagents in organic synthesis [1–11]. Their reactivity is based on a central 3-center 4-electron bond which connects the central iodine atom, providing two electrons, with two carbon- or heteroatom ligands L^1 and L^2, providing one electron each (Figure 1). These ligands can be arranged along the hypervalent iodine atom through an open-chained, a pseudocyclic or a cyclic structure. One of these ligands, usually L^1, is transferred onto a nucleophilic substrate as an electrophilic or radical coupling partner in a group transfer reaction under reduction of the hypervalent iodine atom into its monovalent state. As an alternative, L^1 is involved in early stages of an iodane-mediated transformation through a ligand exchange with an external nucleophile.

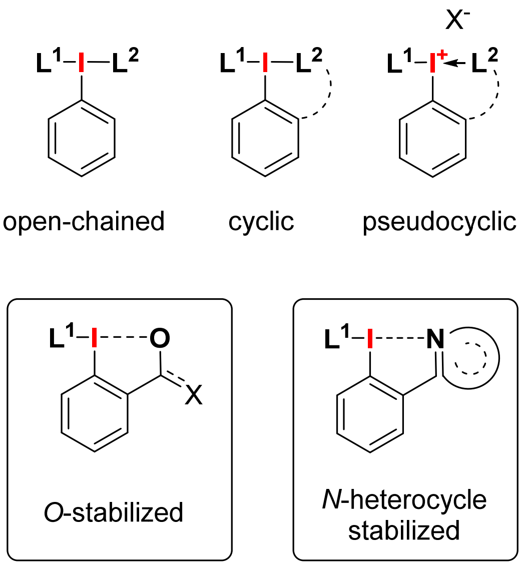


Figure 1: General structure of aryl-λ^3–iodanes.

In contrast, L^2 is usually not transferred or exchanged during the reaction but has a significant stabilizing impact on the iodane and is able to strongly influence its reactivity. In recent years, a plethora of cyclic and pseudocyclic iodanes have been developed with covalently attached ligands L^2 and applied in a variety of group transfer reactions. Prominent examples include ethynyl benziodoxolones (EBX, L^1 = alkyne), the Zhdankin reagent azidobenziodoxole (ABX, $L^1 = N_3$), cyanobenziodoxole (CBX, L^1 = CN) or Togni's reagent ($L^1 = CF_3$) [12]. Even though the transferable ligand L^1 has been varied extensively, the stabilizing ligand L^2 has been treated novercal. In general, carboxylic acid derivatives, ethers or free alcohols are utilized to stabilize the hypervalent iodine center by an oxygen-iodine bond or through dative oxygen-iodine interactions in (pseudo)cyclic iodanes. Even though aryl-λ^3-iodanes are viewed as safe and stable under ambient temperatures, systematic thermal degradation studies of hypervalent iodine reagents are still rare. In 1992 Varvoglis and co-workers investigated the thermal degradation of a variety of aryliodine(III) dicarboxylates into alkyl and aryl radicals through thermogravimetry [13, 14]. In 2013 Kumar and co-workers compared the thermal properties of open-chained aryl-λ^3–iodanes with their polymer bound derivatives and found an endothermic decomposition behavior [15]. In the same year Haller and co-workers investigated the explosive properties of Togni's reagent and very recently, Williams and co-workers analyzed the sensitiveness of common oxidants including 2-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP) [16, 17]. Waser and co-workers examined the thermal stability of the Zhdankin reagent ABX and compared it with the amide-stabilized derivative ABZ (azidobenziodazolone). They found a remarkable higher thermal stability of the latter compound by DSC analysis indicated by a higher onset temperature and a lower heat release during decomposition [18]. ABZ is a rare example of a nitrogen-stabilized iodane, showing promising properties in terms of reactivity and stability. However, iodanes stabilized by nitrogen-based ligands, in particular *N*-heterocycles are still underexplored [19–25]. Recently, our groups investigated systematically cyclic and pseudocyclic *N*-heterocycle-stabilized iodanes (NHIs). We demonstrated that the *N*-heterocycle significantly influences the important I-L^1 bond length and subsequently has a profound impact on the reactivity of the iodane in oxygen transfer reactions [26, 27]. Since the combination of a highly oxidized hypervalent iodine species with *N*-heterocycles with a high N/C-ratio might result in potential hazardous high energy materials, we herein investigated their thermal stability by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

Results and Discussion

We started our experiments with the preparation of appropriate λ^3-iodanes bearing N- and O-centered ligands (Figure 2) according to our reported procedures [26, 27]. The synthesized compounds then have been divided in the following discussion by their principle structural features into pseudocyclic and cyclic hydroxy(phenyl)-λ^3-iodanes and pseudocyclic and cyclic mesityl(phenyl)-λ^3-iodanes.

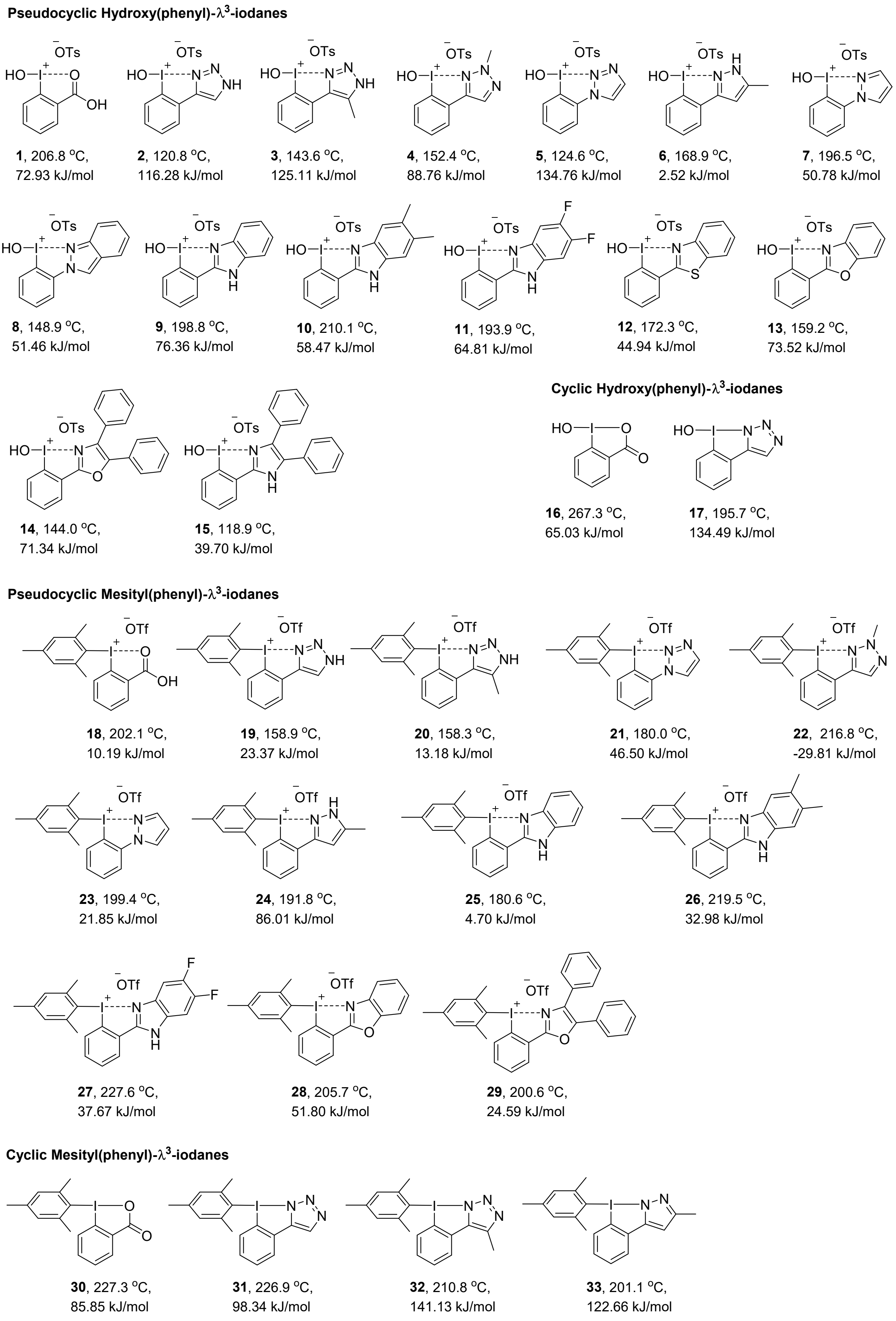


Figure 2: T_{peak} and ΔH_{dec}-values for a range of N- and O-substituted iodanes.

We initially investigated the thermal decomposition of *N*-heterocycle-stabilized pseudocyclic (hydroxy)aryl iodanes **2**-**15** (Figure 2 and Table 1, SI). As the model oxygen-stabilized derivative, we evaluated the thermal decomposition behavior of pseudocyclic iodoso benziodoxolone **1**. The decomposition of **1** has a two-step character and includes initial endothermic melting at 185.1 °C followed by exothermal decomposition at 206.8 °C with an ΔH_{dec} of 72.9 kJ/mol (Figure 3 - a). For the pseudocyclic NHI **2** with a triazole ligand no initial melting process was detected. Instead the solid degraded with a pronounced and narrow (less than 1 °C) exothermal peak at 120.8 °C (Figure 3 - b). Decomposition was associated with a higher ΔH_{dec} of 116.3 kJ/mol.

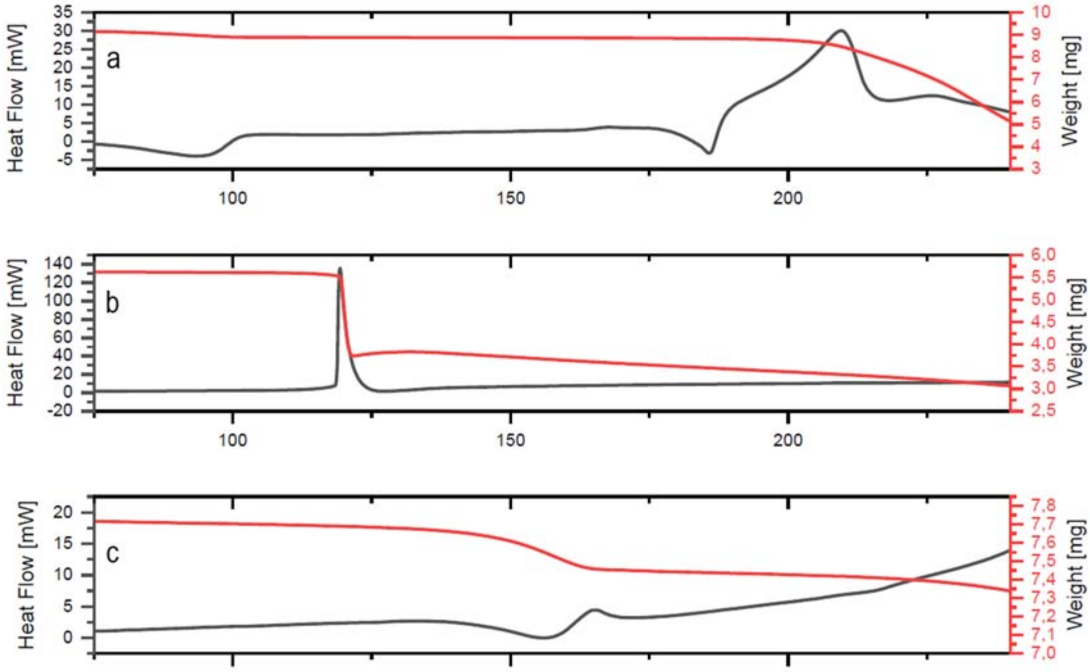


Figure 3: TGA/DSC curves of (a) benziodoxolone **1**, (b) triazole **2** and (c) pyrazole **6**.

A similar decomposition behavior was observed for the other triazole-containing pseudocyclic NHIs **3**-**5**. Introduction of a methyl-substituent at C5 of the triazole (**3**) was accompanied by an increased decomposition enthalpy (ΔH_{dec} = 125.1 kJ/mol). However, thermal stability as indicated by a higher T_{peak}, significantly increased. Methyl substitution at N2 resulted in an even higher T_{peak} of 152.4 °C and a decreased decomposition enthalpy. If the triazole is connected to the iodoarene via N1 as in **5**, T_{peak} decreases and ΔH_{dec} increases. It should be concluded that triazole **4** has the most advantageous decomposition behavior: It is thermally the most stable among the pseudocyclic triazoles with the lowest ΔH_{dec}. However, even the triazoles **2**, **3**, **5** can be considered as safe compounds, but still deserve a common precaution due to the narrow decomposition process.

Pyrazoles **6** and **7** are thermally more stable (T_{peak} = 168.9 and 196.5 °C) with a remarkably lower ΔH_{dec}. NH-pyrazole **6** shows the lowest ΔH_{dec} among all investigated pseudocyclic iodanes (ΔH_{dec} = 2.5 kJ/mol). Interestingly, the exothermal decomposition of **6** is superimposed by an endothermal melting process (Figure 3 - c). In direct comparison, indazole **8** is thermally less stable than **7** with a similar ΔH_{dec}. The throughout higher thermal stability of pyrazoles and indazoles (**6-8**) in direct comparison to triazoles (**2-5**) is very likely connected with the lower C/N ratio.

Benzimidazoles **9**-**11** showed increased ΔH_{dec}-values (58.5-76.4 kJ/mol) in comparison with pyrazoles **6**-**8**. Broad decomposition peaks (up to 14 °C peak width – see SI) were observed at remarkable high T_{peak}-values (193.9 – 210.1 °C). Following these results, it has been intriguing to analyze the influence of the heteroatom in the heterocyclic moiety on the thermal decomposition process. The change of one nitrogen atom to sulfur as in thiazole **12** resulted in a drastic decrease of ΔH_{dec} to 44.9 kJ/mol. In contrast, oxazoles **13** and **14** both had a comparable ΔH_{dec} to **9**, however these NHIs are thermally more labile (T_{peak} = 159.2 and 144.0 °C). Compared to **9**, diphenylimidazole-substituted NHI **15** exhibited a considerably lower ΔH_{dec} (39.7 kJ/mol). Among the 1,3-azoles **15** is thermally the most labile one with a T_{peak} of 118.9 °C. A graphical comparison of the discussed ΔH_{dec}-values is given in Figure 4.

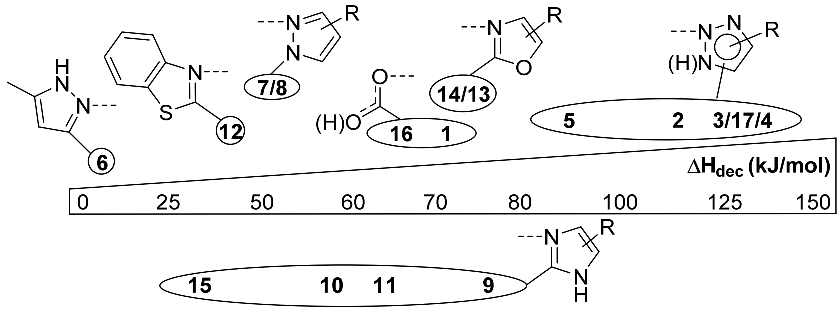


Figure 4: Decomposition enthalpy (ΔH_{dec}) scale for pseudocyclic tosylates **1**-**15** and cyclic iodoso species **16**-**17**.

After obtaining decomposition energies and temperatures for these pseudocyclic NHIs, we were intended to relate these findings with their reactivity. For this purpose, we chose the oxidation of thioanisole at room temperature as the model reaction and used the ascertained reaction times as an estimate for their relative reactivity on a logarithmic scale (Figure 5) [26]. As expected, the thermally least stable triazoles **2**-**5** are also the most reactive iodanes in this model reaction. The reactivity of triazole **3** is comparable to that of benzoxazoles **13**-**14**, pyrazole **7** and indazole **8**. In our view thiazole **12** is the best compromise in this regard since it is thermally even more stable than **7** and **8** with a significant higher reactivity. However, pyrazole **6** still shows a good reactivity in this model reaction with a concurrent outstanding thermal stability. If safety issues are a major concern, for example on a very large-scale synthesis, NHIs **6** or **12** should be the first choices. Except of **15** and **9**, all diazoles are more stable and more reactive than the well-established benziodoxolone **1**. It is also worth mentioning, that even the least stable NHI **4** can be still regarded as “safe” to use [28].

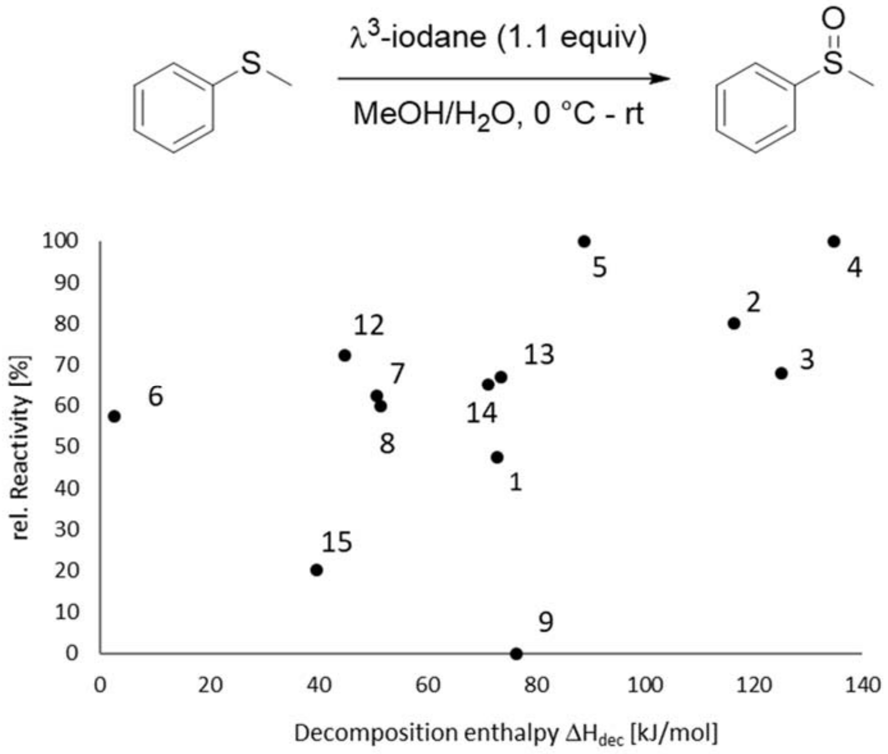


Figure 5: Correlation between the logarithmic relative reactivity for pseudocyclic NHIs based on the oxidation of thioanisole with the corresponding decomposition enthalpy ΔH_{dec}.

Next, we evaluated the decomposition of cyclic hypervalent iodanes. Here, iodosobenzoic acid (IBA, **16**) was chosen as an oxygen-bonded model substrate. In comparison to its pseudocyclic congener **1**, **16** demonstrated a higher T_{peak} (267.3 °C [16]) and a slightly lower ΔH_{dec} (65.0 kJ/mol *vs.* 72.9 kJ/mol). Cyclic triazole **17** has a significantly higher T_{peak} but also a higher ΔH_{dec} compared to the corresponding pseudocycle **2** (134.3 kJ/mol *vs.* 116.5 kJ/mol).

Besides pseudocyclic and cyclic hydroxy(aryl)-λ^3–iodanes, mesityl(phenyl)- λ^3-iodanes **18-33** were systematically investigated by thermogravimetric analysis. Initially, the thermal decomposition of pseudocyclic diaryliodonium salts **18** and **19** was measured. For both salts, initial endothermic melting was followed by exothermal decomposition (SI, Figure 2). Compared to hydroxy(phenyl)-λ^3–iodanes **1** and **2***,* the pseudocyclic diaryliodonium salts **18** and **19** show a significantly decreased ΔH_{dec} from

72.9 kJ/mol to 10.2 kJ/mol for benziodoxolones **1** and **18** and from 116.3 kJ/mol to 23.4 kJ/mol for the triazole derivatives **2** and **19**. The same trend of a higher thermal stability and lower ΔH_{dec} for diaryliodonium salts compared the their hydroxy-substituted congeners can be observed for all other pseudocyclic *N*-heterocycle-substituted derivatives **20-29**. Pyrazole **24** is the only exception. All investigated diaryliodonium salts can be defined as safe due to T_{peak}-values of usually above 180 °C and ΔH_{dec}-values of less than 50 kJ/mol. A graphical comparison of the discussed ΔH_{dec} -values for mesityl(phenyl)- λ^3-iodanes is given in Figure 6.

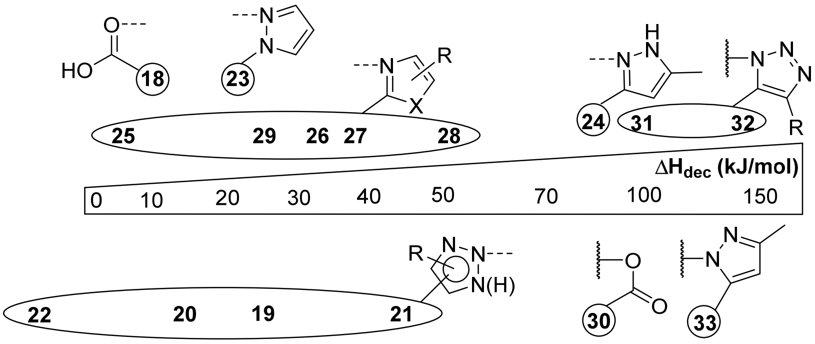


Figure 6: Decomposition enthalpy (ΔH_{dec}) scale for pseudocyclic and cyclic mesitylen(phenyl)- λ^3-iodanes **18-33**.

These overall significant lower decomposition energies are in good agreement with published data in the field of reactivity and stability of hypervalent iodine compounds [29]. As another common key characteristic, the exothermic decomposition of diaryliodonium salts occurs during an endothermic melting process as shown in Figure 7. Only the phenylbenzimidazoles **26-27** do not show this apparent melting-associated endothermic effect. Interestingly, **22** shows a very unusual endothermal decomposition of -29.81 kJ/mol.

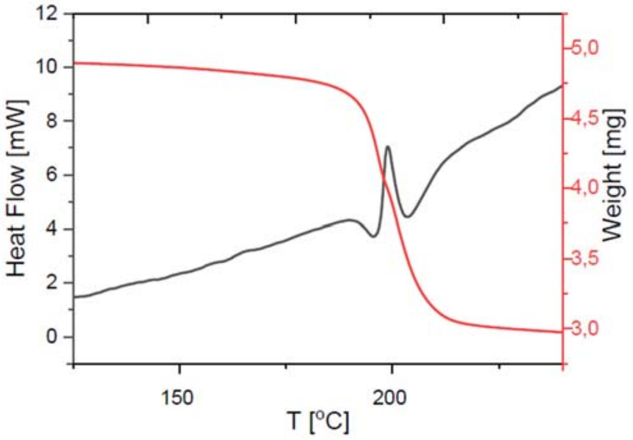


Figure 7: TGA/DSC curves for the benzimidazole based diaryliodonium salt **25**.

Cyclic mesitylene derivatives **30**-**33** have a significantly increased ΔH_{dec}. Their TGA/DSC curves reveal a decomposition behavior similar to the pseudocyclic hydroxy(phenyl)-λ^3-iodanes with an exothermal decomposition without initial melting as exemplarily shown in Figure 8 for compound **32**.

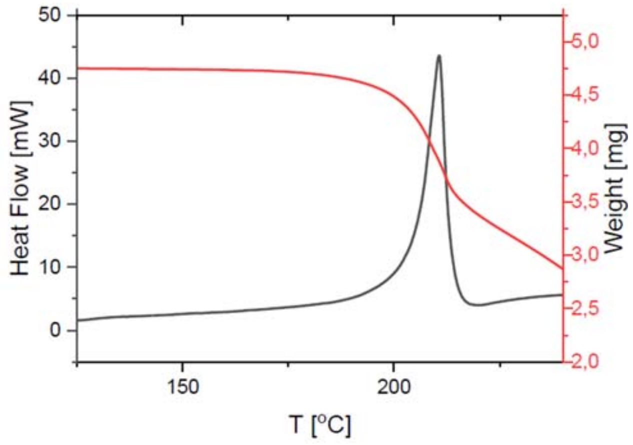
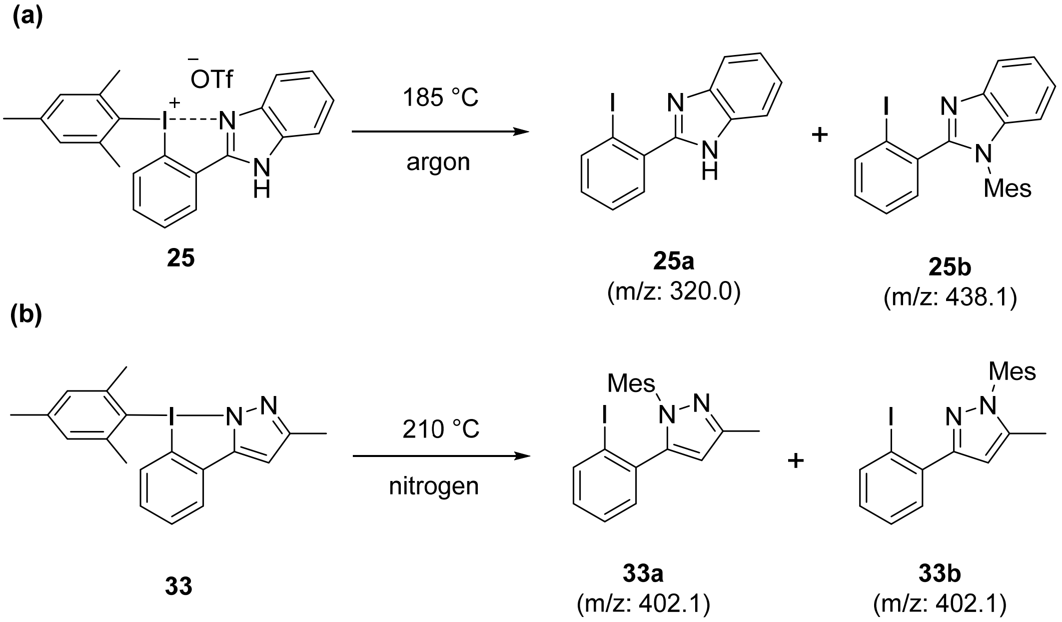


Figure 8: TGA/DSC curves for the cyclic triazole **32**.

We can conclude, that the formation of cyclic iodanes results in an undesired increase of ΔH_{dec} and therefore their pseudocyclic precursors should be used whenever possible.

Finally, we investigated the decomposition products of one pseudocyclic (**25**) and one cyclic (**33**) diaryliodonium salt. Pseudocyclic salt **25** was heated to 185 °C and the resulting oily residue was analyzed by GC/MS (Scheme 1 - a). Besides dearylation to aryl iodide **25a** we observed the formation of an N-arylated product **25b** in significant amounts. In a similar experiment compound **33** was heated to 160 °C and 210 °C according to the two exothermic peaks observed in the TGA/DSC curve (see SI). The resulting product mixture was further analyzed by TLC-MS. While at 160 ˚C no significant decomposition was visible, pronounced decomposition has been observed at 210 ˚C. The MS analysis revealed the formation of the *N*-arylated pyrazoles **33a** and **33b** as the main products (Scheme 1 - b).



Scheme 1. The thermal decomposition of (pseudo)cyclic N-heterocycle-stabilized mesityl(aryl)-λ^3-iodanes **25** and **33**.

Both decomposition studies let us conclude, that intermolecular N-arylation is the major decomposition pathway of (pseudo)cyclic *N*-heterocycle-stabilized mesityl(phenyl)-λ^3-iodanes.

Conclusion

Based on these comprehensive thermoanalytic studies we conclude that (pseudo)cyclic NHIs are throughout safe to use reagents with a sufficient thermal stability. Only the triazole derivatives (**2**, **3**, **5**) deserve common precautions due to the relatively narrow decomposition peak. In particular, benzothiazole- and pyrazole-substituted hydroxy(phenyl)-λ^3-iodanes (**12** and **6-8**) show an excellent relation between thermal stability and reactivity, in particular in direct comparison with well-known benziodoxolones. We can also conclude that the pseudocyclic forms of aryl(phenyl))-λ^3-iodanes should be the reagents of choice as electrophilic aryl group transfer reagents. Thermal decomposition studies indicate that they should be potent electrophilic arene donors.

Supporting Information

Synthetic procedures as well as TGA/DSC curves for all investigated iodanes can be found in the supporting information.

Acknowledgements

Funding by the Fonds der Chemischen Industrie (PhD scholarship to AB), Russian Science Foundation (grant № 17-73-20066) and GACR (19-24603Y) is gratefully acknowledged.

References

1. Wirth, T., Ed. Hypervalent Iodine Chemistry. In *Topics in Current Chemistry*, Vol. 373; Springer International Publishing: Cham, 2016.
2. Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016,** *116*, 3328–3435. doi:10.1021/acs.chemrev.5b00547
3. Boelke, A.; Finkbeiner, P.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2018,** *14*, 1263–1280. doi:10.3762/bjoc.14.108
4. Grelier, G.; Darses, B.; Dauban, P. *Beilstein J. Org. Chem.* **2018,** *14*, 1508–1528. doi:10.3762/bjoc.14.128
5. Yusubov, M. S.; Zhdankin, V. V. *Curr. Org. Synth.* **2012,** *9*, 247–272. doi:10.2174/157017912799829021
6. Zhdankin, V. V. *Arkivoc* **2009,** *i*, 1–62.
7. Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085. doi:10.1039/b821747e
8. Wirth, T. *Angew. Chem. Int. Ed.* **2005,** *44*, 3656–3665. doi:10.1002/anie.200500115
9. Moriarty, R. M. *J. Org. Chem.* **2005,** *70*, 2893–2903. doi:10.1021/jo050117b
10. Wirth, T. *Synthesis* **1999**, 1271–1287. doi:10.1055/s-1999-3540
11. Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996,** *96*, 1123–1178.
12. Hari, D. P.; Caramenti, P.; Waser, J. *Acc. Chem. Res.* **2018,** *51*, 3212–3225. doi:10.1021/acs.accounts.8b00468
13. Katsoulos, G. A.; Lalia-Kantouri, M.; Varvoglis, A. *Thermochimica Acta* **1992,** *197*, 285–294. doi:10.1016/0040-6031(92)85027-S
14. Varvoglis, A. *Chem. Soc. Rev.* **1981,** *10*, 377. doi:10.1039/CS9811000377
15. Verma, V.; Singh, K.; Kumar, A.; Kumar, D. *J. Therm. Anal. Calorim.* **2013,** *114*, 339–344. doi:10.1007/s10973-012-2894-1
16. Fiederling, N.; Haller, J.; Schramm, H. *Org. Process Res. Dev.* **2013,** *17*, 318–319. doi:10.1021/op400035b
17. Dallaston, M. A.; Bettencourt, C. J.; Chow, S.; Gebhardt, J.; Spangler, J.; Johnston, M. R.; Wall, C.; Brusnahan, J. S.; Williams, C. M. *Chem. Eur. J.* **2019. doi:**10.1002/chem.201902036
18. Alazet, S.; Preindl, J.; Simonet-Davin, R.; Nicolai, S.; Nanchen, A.; Meyer, T.; Waser, J. *J. Org. Chem.* **2018,** *83*, 12334–12356. doi:10.1021/acs.joc.8b02068
19. Aertker, K.; Rama, R. J.; Opalach, J.; Muñiz, K. *Adv. Synth. Catal.* **2017,** *359*, 1290–1294. doi:10.1002/adsc.201601178
20. Xie, F.; Zhang, Z.; Yu, X.; Tang, G.; Li, X. *Angew. Chem. Int. Ed.* **2015,** *54*, 7405–7409; *Angew. Chem*. **2015**, *127*, 7513. doi:10.1002/anie.201502278
21. Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009,** *11*, 1221–1223. doi:10.1021/ol8029092
22. Hari, D. P.; Schouwey, L.; Barber, V.; Scopelliti, R.; Fadaei-Tirani, F.; Waser, J. *Chem. Eur. J.* **2019. doi:**10.1002/chem.201900950
23. Zhdankin, V. V.; Koposov, A. Y.; Su, L.; Boyarskikh, V. V.; Netzel, B. C.; Young, V. G. *Org. Lett.* **2003,** *5*, 1583–1586. doi:10.1021/ol0344523
24. Zhdankin, V. V.; Arbit, R. M.; McSherry, M.; Mismash, B.; Young, V. G. *J. Am. Chem. Soc.* **1997,** *119*, 7408–7409. doi:10.1021/ja971606z
25. T. M. Balthazor, D. E. Godar, and B. Ray Stults. *J. Org. Chem.* **1979,** *44*, 1447–1449.
26. Boelke, A.; Lork, E.; Nachtsheim, B. J. *Chem. Eur. J.* **2018,** *24*, 18653–18657. doi:10.1002/chem.201804957

27. Vlasenko, Y. A.; Postnikov, P. S.; Trusova, M. E.; Shafir, A.; Zhdankin, V. V.; Yoshimura, A.; Yusubov, M. S. *J. Org. Chem.* **2018,** *83*, 12056–12070. doi:10.1021/acs.joc.8b01995
28. UN/SCETDG/53/INF.17(https://www.unece.org/fileadmin/DAM/trans/doc/2018/dgac10c3/UN-SCETDG-53-INF17e.pdf)
29. Zhdankin, V. V. Hypervalent Iodine Chemistry; John Wiley & Sons Ltd.: Chichester, U.K., **2013**.