Stabilization of Ethynyl-Substituted Aryl-λ₃-iodanes by Tethered N-Heterocycles

Thomas J. Kuczmera[a], Andreas Boelke[a] and Boris J. Nachtsheim*[a]

Address:
[a]Institute for Organic and Analytical Chemistry, University of Bremen, 28359 Bremen, Germany

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

A systematic investigation of ethynyl \( N \)-heterocycle-substituted-\( \lambda^3 \)-iodanes (ENHIs) is presented. In a straightforward one-pot synthesis these novel reagents can be obtained in high yields bearing a variety of \( N \)-heterocycles. Their reactivity as electrophilic alkyne group transfer reagents was benchmarked in well-established as well as novel inter- and intramolecular group transfer reactions and compared to literature-known ethynyl benziodoxolones.

Keywords

Hypervalent iodine, \( N \)-heterocycles, group transfer reactions, iodonium salts, one-pot synthesis

Introduction

In recent years, the chemistry of hypervalent iodine compounds experienced an immersive grow resulting in a plethora of applications in organic synthesis\[^1,2\] including the oxidation of alcohols\[^3,4\] CH-oxidations\[^4\] and phenol dearromatizations.\[^5\] Besides their remarkable reactivity as dehydrogenative oxidants, in particular aryl-\( \lambda^3 \)-iodanes turned out to be potent electrophilic group transfer reagents.\[^6\] The most prominent representatives are diaryliodonium salts as electrophilic arylating reagents,\[^7\] alkenyl(aryl)iodonium salts as electrophilic vinyl motives\[^8\] and alkynyl(aryl)iodonium salts for electrophilic alkyne transfer reactions.\[^9\] In the latter, thermal stability is a latent problem.\[^10\] Here, intermolecular stabilization by oxygen-based donors in the form of ethynyl-benziodoxol(on)es (EBX) revealed a significantly increased thermal stability and hence an improved synthetic utilization of alkynyl-substituted iodanes (Figure 1).\[^11\]

Figure 1: Pseudocyclic and cyclic TIPS-ethynyl \( N \)-heterocycle-substituted-\( \lambda^3 \)-iodanes (TIPS-ENHIs) as a further development based on ethynyl benziodoxol(on)es (EBX) and ethynyl benziodazol(on)es (EBZ) reagents.

Benziodoxol(on)es (BX) motifs also allow the stabilization of a large range of other transferable substituents at the hypervalent iodine atom such as halides,\[^12\] esters,\[^13\] cyanides,\[^14\] \( CF_3 \)-groups\[^15\] or azides.\[^16\] Intrinsically, BX-based iodanes allow only a limited chemical variation to modify and fine-tune the reactivity of these substituents in umpolung reactions. However, the oxygen atom itself can be substituted by other heteroatoms, in particular nitrogen.\[^17\]
These contemporary benziodazol(on)e (BZ) reagents tolerate a wider range of functional substituents, even the highly delicate SCF$_3$ group.[18] Recently, Waser and coworkers presented the corresponding ethynyl benziodazol(on)es (EBZ), benziodazolimines (EBZI) and benziodosulfoximines (EBS).[19] Their reactivity in electrophilic alkynyl transfer reactions strongly depends on the electron density distribution along the I-N-bond and the resulting trans-effect on the $\sigma$-hole.

Our group is interested in the chemistry of N-heterocycle-stabilized iodonium salts (NHIs), in which regard we systematically investigated pseudocyclic hydroxy(aryl)-NHIs as potent oxidizing reagents.[20] Based on these initial findings, we were intended to systematically describe the chemistry of these potentially useful reagents and herein present a variety of novel (pseudo)cyclic ethynyl N-heterocycle-substituted-$\lambda^3$-iodanes (ENHIs) and demonstrate their application in inter- and intramolecular group transfer reactions and in the synthesis of novel heteroaromatic compounds.

**Results and Discussion**

Initially, we were focused on the synthesis of pseudocyclic TIPS-ENHIs. Starting from our previous results for the synthesis of cyclic diaryliodonium salts using one-pot procedures,[21,22] we were intended to directly develop a convenient oxidation/alkynylation reaction. One-pot procedures for unsubstituted TIPS-ethynyl iodonium salts and EBX reagents have already been described, using meta-chloroperbenzoic acid (mCPBA) as the terminal oxidant in the presence of strong acids such as TfOH or TsOH and the subsequent addition of an alkyne to the in situ formed hydroxy(aryl)iodonium salt.[23] Based on these procedures the reaction conditions were optimized for TIPS-ENHIs (Table 1). First, the equivalents of TfOH were varied using 2,2,2-trifluoroethanol (TFE) as a solvent.

| Entry | Solvent | TfOH (equiv.) | Yield[a] |
|-------|---------|---------------|----------|
| 1     | TFE     | 4.5           | 50%      |
| 2     | TFE     | 3.5           | 53%      |
| 3     | TFE     | 2.5           | 61%      |
| 4     | DCM/TFE | 2.5           | 71%      |
| 5     | DCM     | 2.5           | (55%)[b] |
| 6     | CHCl$_3$| 2.5           | (24%)[b] |
| 7     | MeCN    | 2.5           | 76%      |
| 8     | MeCN    | 1.6           | (11%)[b] |
| 9[c]  | MeCN    | 2.5           | 69%      |
| 10[c] | MeCN    | 3.0           | 71%      |

*Table 1: Optimization of the reaction conditions for the one-pot synthesis of TIPS-ethynyl NHIs.*

Reaction conditions: 3a (0.20 mmol, 1.0 equiv.) was dissolved in the indicated solvent (1 mL) and mCPBA (0.24 mmol, 1.2 equiv.) and TfOH were added. The mixture was stirred at rt for 0.5 h, then TIPS-TMS-acetylene (0.28 mmol, 1.4 equiv.) was added and stirring was continued at rt for 24 h. [a] Isolated yield. [b] Incomplete conversion of the oxidized intermediate. [c] 1.00 mmol scale, oxidation time 1 h.
The best yield of 61% was achieved using 2.5 equiv. of TfOH (entry 1-3). Next, the influence of the solvent was investigated. A 1:1 mixture of DCM and TFE gave an increased yield of 71% (entry 4), while in pure DCM or chloroform only incomplete conversion of the oxidized intermediate was observed (entries 5-6). Finally, MeCN was found to be the best solvent for this transformation, giving 1a in 76% yield (entry 7). Even in this solvent the amount of added TfOH could not be decreased (entry 8). On a 1 mmol scale, 3 equiv. of TfOH were slightly superior (entries 9-10).

Under these optimized conditions different N-heterocycle-substituted iodoarenes 3 were synthesized (Scheme 1 - a). The unsubstituted triazole 1b was isolated in 53% yield, whereas the N-bound triazole 1c could only be obtained in 13% yield. The benzimidazole 1d was smoothly synthesized in 60% yield, while the benzoazole 1e gave a moderate yield of 21%. The absence of an NH-function leads to a better solubility of the salts 1c and 1e and caused problems in the purification process, which rationalizes the observed low yields.
The synthesis of the benzothiazole 1f and the N-bound pyrazole 1h failed despite a successful oxidation. With diphenylimidazole 3g as a substrate, TfOH was not tolerated due to decomposition. Furthermore, the successful synthesis of the C-bound pyrazole 1i in a good yield of 44% was a great success, as the competing ring closure to the cyclic iodolopyrazolium salt under similar conditions had recently been described. It is worth mentioning, that a two-step protocol was also tested with those substrates. These results can be found in the ESI.

After the successful synthesis of ENHIs with different N-heterocycles, the tolerance of various functional groups at the iodoarene was investigated, using the methylated C-bound triazole as a model substrate (Scheme 1 - b). Most electron withdrawing halogen- and CF₃-substituted iodoarenes 3j-3l yielded the desired products 1j-l in good yields of 51-55%. The NO₂-derivative yielded 1m in diminished yields. The low yield of 18% for the chlorinated salt 1n can be explained by steric effects between the substituent and the alkyne. A similar tendency was observed for the methylated derivatives 1o-p. Here, para-methylation gave a yield twice as high as the ortho-substituted salt (31% vs. 65%). The biphenyl 1q was also obtained in a good yield of 52%, so that an overall high functional group tolerance of the pseudocyclic salts could be demonstrated.

Finally, other alkynylation reagents were investigated (Scheme 1 – c and d), giving to the Ph-acetylene salt 1r in 60% yield. For the 1-hexyne derivative the one-pot procedure was not successful, so that the oxidized intermediate was isolated and used for the alkynylation. Here, only the vinyl species 1s could be isolated due to the addition of TfOH to the alkyne. This behavior has previously been described for other unsubstituted as well as stabilized iodonium salts. For salts containing a free NH-function in the N-heterocycle, the corresponding cyclic ENHIs were synthesized through addition of aqueous NaHCO₃-solution to the reaction mixture after the alkynylation step (Scheme 2).

Scheme 2: One-pot synthesis of cyclic ENHIs. [a] 2-Iodoarene 3 (1.0 equiv.), mCPBA (1.1 equiv.) and TfOH (2.5 equiv.) were stirred in MeCN (0.20 M) at room temperature for 1 h, then TIPS-TMS-acetylene (1.4 equiv.) was added and stirred for 42 h. Afterwards aq. NaHCO₃-solution (4.0-5.0 equiv.) was added and stirred for 1-3 h at room temperature.
Accordingly cyclic triazole 2a was isolated in a good yield of 71%. The non-methyl derivative 2b was obtained in only 22%, again due to a better solubility of this derivative and the related difficulties during work-up. In contrast, the insoluble cyclic benzimidazole 2d was isolated in 62% yield. Pyrazole 2i could not be obtained due to cleavage of the TIPS-acetylene moiety. The cyclization of the substituted iodanes revealed yields between 29-50% for the iodanes 2j-l and 2p, while the cyclization of the NO₂-salt 2m failed due to a cleavage of the alkyne as observed for 2i.

Single crystal structure analysis of the two ENHIs 1l and 2a (Figure 2) revealed the expected T-shape structure of the hypervalent iodine center[1] (N-I-O angles of 165.78° for 1l and 164.77° for 2a) and an expected longer N-I distance in the pseudocyclic salt (2.517 Å) compared to the cyclic iodane (2.431 Å). While the alkyne group of the pseudocyclic salt 1l is nearly in plane with the aromatic system, 2a is significantly twisted with a C1-I1-N1-C10 dihedral angle of 17.26°. This twist was previously observed for other bis-N-heterocyclic substituted-λ3-iodanes.[26] Additionally, in 2a 1/6 equiv. of NaOTf is included in the crystal structure (see ESI). Significant intermolecular interactions in ENHI 1l between Br1-N2 (3.149 Å, sum of VdW-radii 3.38 Å) and I1-O2 (2.828 Å, sum of VdW-radii 3.50 Å) indicates substantial halogen bonding between those atoms.

After the successful synthesis of a range of new (pseudo)cyclic ENHIs, their potential in electrophilic alkyne transfer reactions was investigated. First, a relative performance test of all ENHIs was accomplished on the alkyenylation of β-ketoester 4a via the in situ formed free alkyne-NHI (Table 2). This reaction has been previously investigated by Waser and co-workers using TIPS-EBX and TIPS-EBZ reagents,[19,27] Starting with the triazole 1a, quantitative formation of the desired product 5a could be observed after 1 h (entry 1). The cyclic derivative 2a gave 5a in 79% yield, which could be significantly increased to 94% after a prolonged reaction time of 18 h (entries 2-3). The non-methylated triazole salt 1b gave an
improved yield of 5a after 1 h reaction time (70%, entry 4). Similar to the Me-triazoles, the cyclic iodane 2b gave a lower yield of 60% in direct comparison with the corresponding pseudocyclic salt 1b (entry 5). The same tendency was observed with the benzimidazoles (entries 6-7). This reactivity can be derived from the crystal structures. The shorter C-I-distance of the pseudocyclic derivative 1l (2.035 Å) compared with the cyclic iodane 2a (2.071 Å) indicates a stronger trans-effect of the pseudocyclic salts and therefore a higher reactivity in group transfer reactions.[19] With the salts 1c, 1e and 1i a quantitative formation of the alkynyl product 5a was observed (entries 8-10) and showed a similar reactivity to TIPS-EBX (6) (entry 11). It is worth mentioning that in many reactions the iodoarenes 3 could be recovered in moderate to high yields. The Ph-alkynyl salt 1r was not reactive in this type of transfer reaction (entry 12). Using the methyl ester 4b with the triazole leads to a slightly lower yield of 5b (71%), while TIPS-EBX (6) again gave quantitative product formation (entries 13-14).

Table 2: Alkynylation of 1,3-dicarboxyle 4a,b by in situ formation of the free ethynyl-NHIs.

| entry | R | ENHI | Yield 5 [%] | Yield iodoarene 3 [%] |
|-------|---|------|-------------|----------------------|
| 1     | Et | 1a   | quant.      | 88                   |
| 2     | Et | 2a   | 79          | 69                   |
| 3     | Et | 2a   | 94[a]       | 86                   |
| 4     | Et | 1b   | 87          | 70                   |
| 5     | Et | 2b   | 60          | 93                   |
| 6     | Et | 1d   | 76          | (57)[b]              |
| 7     | Et | 2d   | 48          | 85                   |
| 8     | Et | 1c   | quant.      | (> 100)[b]           |
| 9     | Et | 1e   | quant.      | 43                   |
| 10    | Et | 1i   | quant.      | 61                   |
| 11    | Et | 6    | quant.      | -                    |
| 12    | Et | 1r   | 0[c]        | -                    |
| 13    | Me | 1a   | 71%         | -                    |
| 14    | Me | 6    | quant.      | -                    |

[a] reaction time 18 h. [b] not clean after column chromatography. [c] without TBAF.

After these promising results, we were eager to test the ENHIs in other group transfer reactions (Scheme 3). Reaction of ethyl 2-cyano-3-phenylpropanoate[27] 7 (Scheme 3 - a) with the N-bound triazole 1c gave the alkynylated product 8 in a good yield of 71% which is a comparative reactivity to TIPS-EBX (6). The alkynylation of thiophenole 9[28] with 1,5,7-triazabicyclo(4.4.0)dec-5-ene (TBD) to 10 gave only a low product formation of 26% and therefore a significant lower reactivity than TIPS-EBX (Scheme 3 - b).[29] Waser and co-workers also observed a low reactivity of their N-heterocyclic iodanes in this reaction. Calculated MEP-maps of those iodanes reveal a lower electron density of the N-I-bond and assumes a decreased σ-hole compared to TIPS-EBX as a putative reason.[19] Finally, the alkynylation of amines was tested using N-tosylaniline (11).[30] Instead of an aniline alkynylation, N-alkynylation of the ENHI 1a,b was observed, giving N-alkynylated triazoles 12a and 12b in 47% and 41% (Scheme 3 - c). MS/MS experiments of 12a strongly indicated a
selective alkynylation of the triazoles N2 (see ESI). Interestingly the absence of N-tosylaniline leads to only a low intramolecular conversion. Based on this observation, the direct thermolysis as another intramolecular transformation pathway was investigated. While using the pseudocyclic salts 1a and 1d the emerging TfOH leads to no product formation, the cyclic NHIs 2a and 2d gave the TIPS-acetylene triazole 14 in 49% (Scheme 3-d) and benzimidazole 16 in 35% yield (Scheme 3-f).

Scheme 3: Intra- and intermolecular group transfer reactions of the ENHIs.
Those $N$-alkynyl heteroaromatic iodoarenes reveal the possibility for further functionalization, either through the iodine or alkyne. The latter was demonstrated in a click-reaction of the triazole 14 with TMS-N$_3$,[31] yielding the bi-triazole 15 in 61% yield (Scheme 3 - e). To the best of our knowledge this is the first direct C-N connection of two triazoles described so far.

Conclusion

In this work, we demonstrated the systematic synthesis of pseudocyclic and cyclic TIPS-ethynyl NHIs via a one-pot procedure, which revealed a wide range of different heterocycles and substituents to be suitable. The reactivity of those ENHIs was investigated in inter- and intramolecular group transfer reactions, which showed a comparable reactivity to TIPS-EBX. It further enables access to novel $N$-substituted heteroaromatic compounds and bi-triazole motives. Other promising applications of $N$-heteroaromatic substituted-$\lambda^3$-iodanes are under current work in our laboratory.

Acknowledgement

Marian Olaru from the Institute for Inorganic Chemistry and Crystallography, University of Bremen is gratefully acknowledged for crystal structures measurements.

References

[1] A. Yoshimura, V. V. Zhdankin, Chem. Rev. 2016, 116, 3328.
[2] a) T. Wirth, Hypervalent Iodine Chemistry, Springer International Publishing, Cham, 2016; b) V. V. Zhdankin, Hypervalent Iodine Chemistry, Wiley, Chichester, UK, 2013.
[3] T. Dohi, N. Takenaga, A. Goto, H. Fujioka, Y. Kita, J. Org. Chem. 2008, 73, 7365.
[4] M. Ochiai, Chem. Rec. 2007, 7, 12.
[5] a) M. Ochiai, K. Miyamoto, M. Shiro, T. Ozawa, K. Yamaguchi, J. Am. Chem. Soc. 2003, 125, 13006; b) L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus, A. Pelter, J. Chem. Soc., Perkin Trans. 1 1999, 379.
[6] a) V. Gold, Pure Appl. Chem. 1983, 55, 1281; b) T. Okuyama, Acc. Chem. Res. 2002, 35, 12; c) R. Robidas, C. Y. Legault, Helv. Chim. Acta 2021, n/a, e2100111.
[7] a) D. Del Mazza, M. G. Reinecke, W. B. Smith, Org. Magn. Reson. 1980, 14, 540; b) E. A. Merritt, B. Olofsson, Angew. Chem. Int. Ed. 2009, 48, 9052; c) S.-K. Kang, H.-W. Lee, S.-B. Jang, T.-H. Kim, S.-J. Pyun, J. Org. Chem. 1996, 61, 2604.
[8] a) M. Ochiai, J. Organomet. Chem. 2000, 611, 494; b) N. Declas, G. Pisella, J. Waser, Helv. Chim. Acta 2020, 103.
[9] J. P. Brand, J. Waser, Chem. Soc. Rev. 2012, 41, 4165.
[10] Y. A. Vlasenko, M. S. Yusubov, A. Shafir, P. S. Postnikov, Chem. Heterocycl. Compd. 2020, 56, 854.
[11] a) F. Le Vaillant, J. Waser, Chem. sci. 2019, 10, 8909; b) Y. Li, D. P. Hari, M. V. Vita, J. Waser, Angew. Chem. Int. Ed. 2016, 55, 4436.
[12] a) V. Matoušek, J. Václavík, P. Hájek, J. Charpentier, Z. E. Blastik, E. Pietrašiak, A. Budinská, A. Togni, P. Beier, Chem. Eur. J. 2016, 22, 417; b) V. Matoušek, E. Pietrašiak, R. Schwenc, A. Togni, J. Org. Chem. 2013, 78, 6763.
[13] D. B. Dess, J. C. Martin, J. Org. Chem. 1983, 48, 4155.
[14] F. Le Vaillant, J. Waser, CHIMIA Int. J. Chem. 2017, 71, 226.
[15] V. Matoušek, E. Pietrašiak, R. Schwenc, A. Togni, J. Org. Chem. 2013, 78, 6763.
[16] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, M. S. Formaneck, J. T. Bolz, *Tetrahedron lett.* 1994, 35, 9677.

[17] a) D. P. Hari, L. Schouwey, V. Barber, R. Scopelliti, F. Fadaei-Tirani, J. Waser, *Chem. Eur. J.* 2019, 25, 9522; b) H. J. Barber, M. A. Henderson, *J. Chem. Soc. C: Org.* 1970, 862; c) B. Muriel, J. Waser, *Angew. Chem. Int. Ed.* 2021, 60, 4075; d) V. V. Zhdankin, A. Y. Koposov, L. Su, V. V. Boyarskikh, B. C. Netzel, V. G. Young, *Org. Lett.* 2003, 5, 1583.

[18] X.-G. Yang, K. Zheng, C. Zhang, *Org. Lett.* 2020, 22, 2026.

[19] E. Le Du, T. Duhail, M. D. Wodrich, R. Scopelliti, F. Fadaei-Tirani, E. Anselmi, E. Magnier, J. Waser, *Chem. Eur. J.* 2021, 27, 10979.

[20] A. Boelke, E. Lork, B. J. Nachtsheim, *Chem. Eur. J.* 2018, 24, 18653.

[21] A. Boelke, T. J. Kuczmera, L. D. Caspers, E. Lork, B. J. Nachtsheim, *Org. Lett.* 2020, 22, 7261.

[22] L. D. Caspers, J. Spils, M. Damrath, E. Lork, B. J. Nachtsheim, *J. Org. Chem.* 2020, 85, 9161.

[23] a) M. J. Bouma, B. Olofsson, *Chem. Eur. J.* 2012, 18, 14242; b) E. A. Merritt, B. Olofsson, *Eur. J. Org. Chem.* 2011, 2011, 3690; c) D. J. Hamnett, W. J. Moran, *Org. Biomol. Chem.* 2014, 12, 4156.

[24] T. M. Kasumov, N. S. Pirguliyev, V. K. Brel, Y. K. Grishin, N. S. Zefirov, P. J. Stang, *Tetrahedron* 1997, 53, 13139.

[25] A. Yoshimura, K. C. Nguyen, S. C. Klasen, A. Saito, V. N. Nemykin, V. V. Zhdankin, *Chem. Commun.* 2015, 51, 7835.

[26] A. Boelke, S. Sadat, E. Lork, B. Nachtsheim, *Chem. Commun.* 2021, 57, 7434-7437.

[27] D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* 2010, 16, 9457.

[28] S. Racine, B. Hegedüs, R. Scopelliti, J. Waser, *Chem. Eur. J.* 2016, 22, 11997.

[29] D. Fernández González, J. P. Brand, R. Mondière, J. Waser, *Adv. Synth. Catal.* 2013, 355, 1631.

[30] B. Waldecker, F. Kraft, C. Golz, M. Alcarazo, *Angew. Chem. Int. Ed.* 2018, 57, 12538.

[31] S. Stotani, V. Gatta, F. Medda, M. Padmanaban, A. Karawajczyk, P. Tammela, F. Giordanetto, D. Tzalis, S. Collina, *Molecules* 2018, 23, 2545.