Stabilization of Ethynyl-Substituted Aryl-λ³-Iodanes by Tethered *N*-Heterocylces
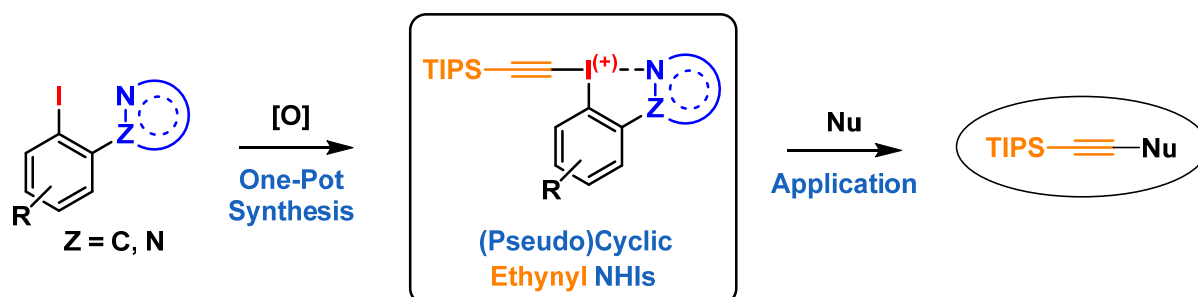
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Abstract

A systematic investigation of ethynyl *N*-heterocycle-substituted-λ³-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 dearomatizations.[5] Besides their remarkable reactivity as dehydrogenative oxidants, in particular aryl-λ³-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]
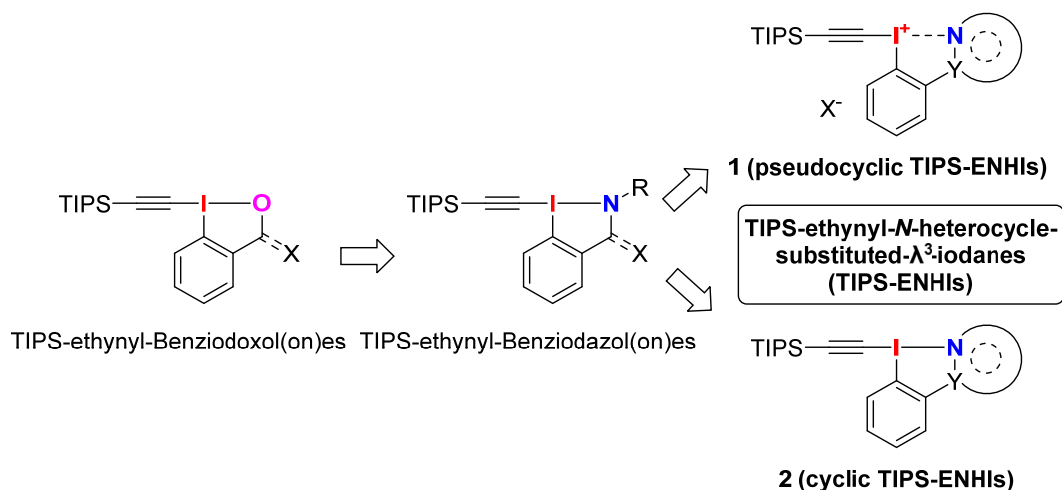

Figure 1: Pseudocyclic and cyclic TIPS-ethynyl N-heterocycle-substituted-λ³-iodanes (TIPS-ENHIs) as a further development based on ethynyl benziodoxol(on)e (EBX) and ethynyl benziodazol(on)e (EBZ) reagents.

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] CF₃-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 σ-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-λ^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 (*m*CPBA) 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-trifluoroethanole (TFE) as a solvent.

*Table 1: Optimization of the reaction conditions for the one-pot synthesis of TIPS-ethynyl NHIs.*
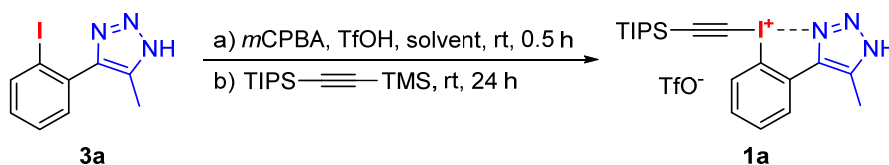
Entry	Solvent	TfOH (equiv.)	Yield[a]
1	TFE	4.5	50%
2	TFE	3.5	53%
3	TFE	2.5	61%
4	DCM/TFE	2.5	71%
5	DCM	2.5	(55%)[b]
6	CHCl$_3$	2.5	(24%)[b]
7	**MeCN**	**2.5**	**76%**
8	MeCN	1.6	(11%)[b]
9[c]	MeCN	2.5	69%
10[c]	**MeCN**	**3.0**	**71%**

Reaction conditions: **3a** (0.20 mmol, 1.0 equiv.) was dissolved in the indicated solvent (1 mL) and *m*CPBA (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 benzoxazole **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.
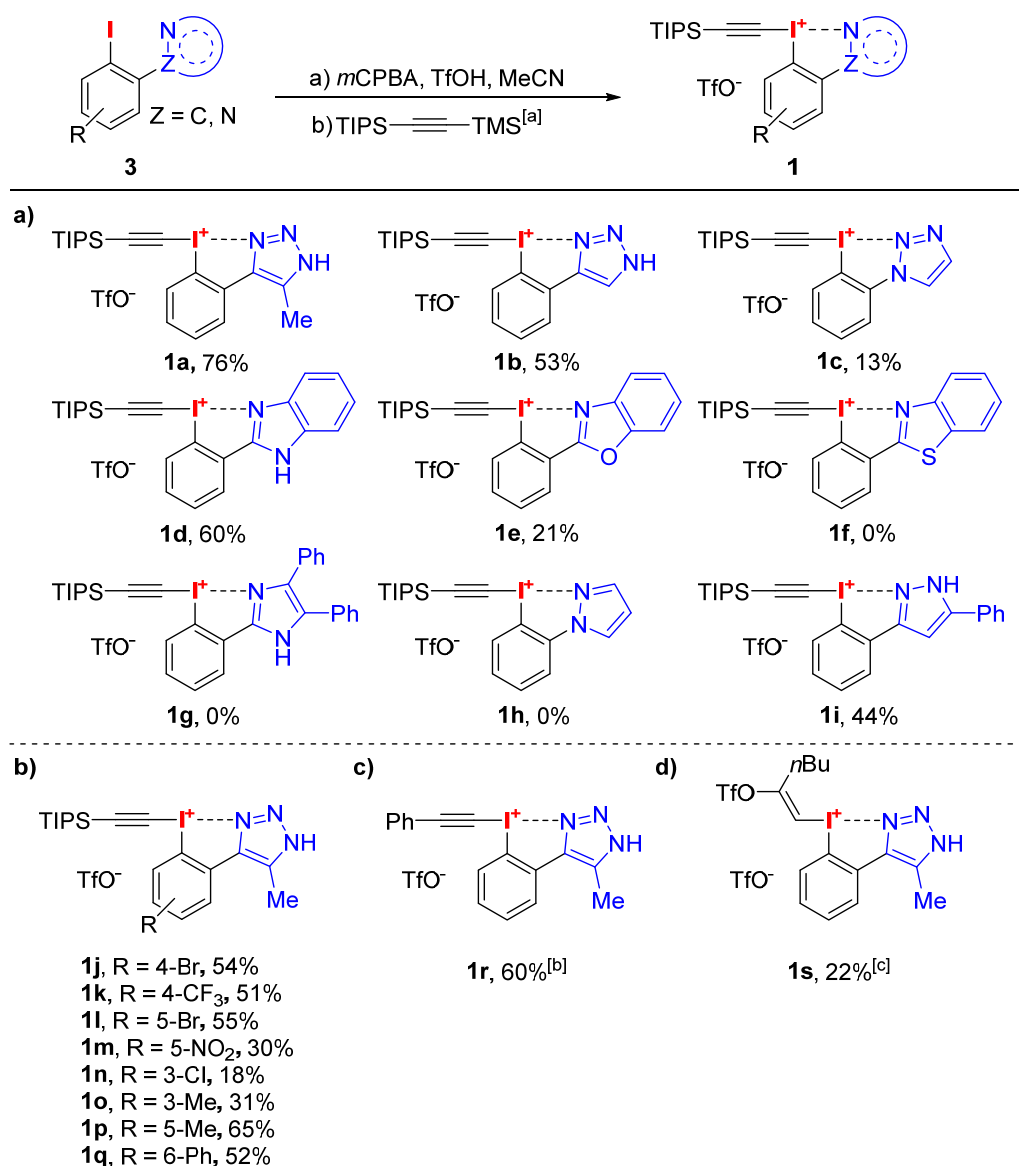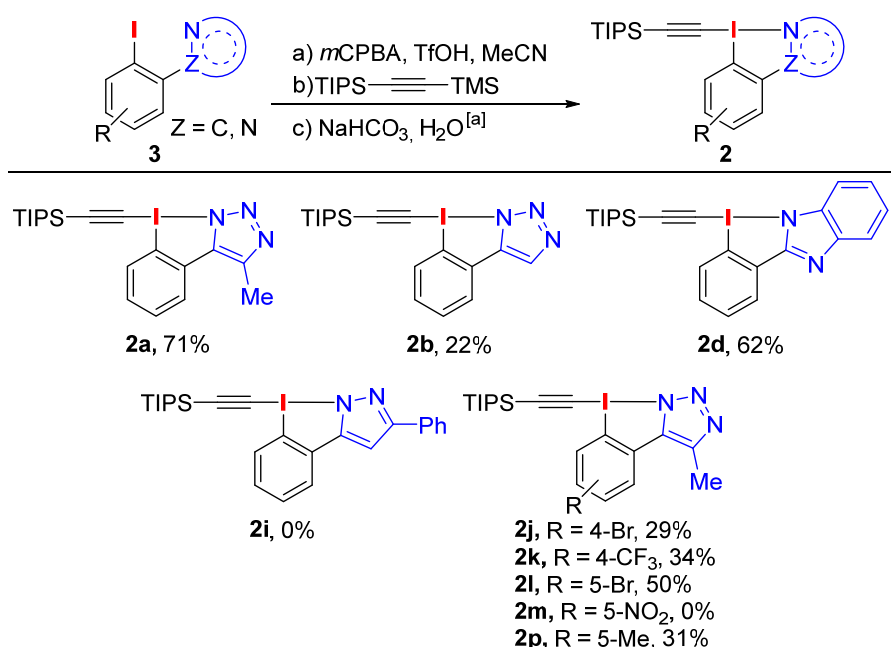

Scheme 1: [a] Conditions: 2-Iodoarene **3** (1.0 equiv.), mCPBA (1.1 equiv.) and TfOH (2.5 equiv.) were stirred in MeCN (0.20 M) at room temperature for 1 h, then TIPS-TMS-acetylene (1.4 equiv.) was added and stirred for 42 h. [c] Ph-TMS-acetylene (1.4 equiv.), [d] 1s was synthesized via a two-step procedure due to a failed one-pot synthesis. nBu-TMS-acetylene (1.4 equiv.) was added as alkynylation reagent.

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.[21] 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[24] as well as stabilized[25] 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 NO$_2$-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.
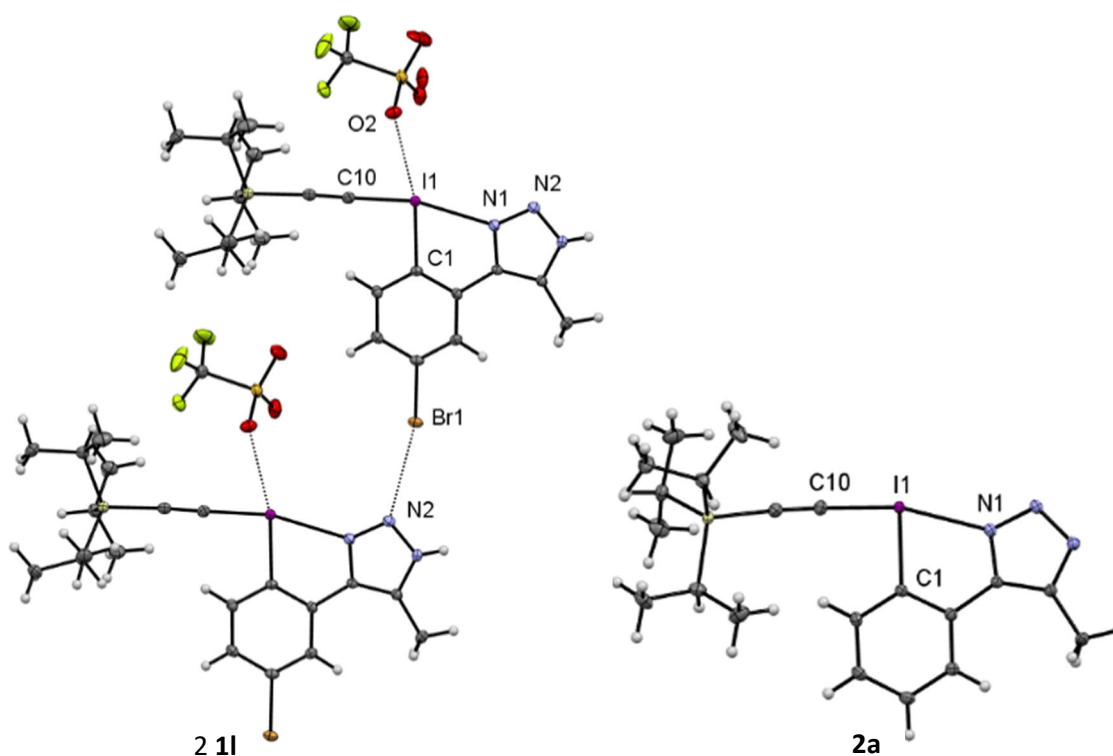

Figure 2: Crystal structures (ORTEP drawing) of 1l (CCDC 2120075) and 2a (CCDC 2120074). Thermal elipsoids with 50% probability. For 1l: C1-I1: 2.183 Å, I1-C10: 2.035 Å, I1-N1: 2.517 Å, C1-I1-C10: 92.40°, C1-I1-N1: 73.38°, N1-I1-C10: 165.78°, C1-I1-N1-C10: 0.27°. For 2a: C1-I1: 2.143 Å, I1-C10: 2.071 Å, I1-N1: 2.431 Å, C1-I1-C10: 90.04°, C1-I1-N1: 74.38°, N1-I1-C10: 164.77°, C1-I1-N1-C10: 17.26°.

After the successful synthesis of a range of new (pseudo)cyclic ENHIs, their potential in electrophilic alkynyl transfer reactions was investigated. First, a relative performance test of all ENHIs was accomplished on the alkynylation of *β*-ketoester **4a** via the *in situ* formed free alkynyl-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-dicarbonyle **4a,b** by in situ formation of the free ethynyl-NHIs.*

4a, R = Et
4b, R = Me

5a, R = Et
5b, R = Me
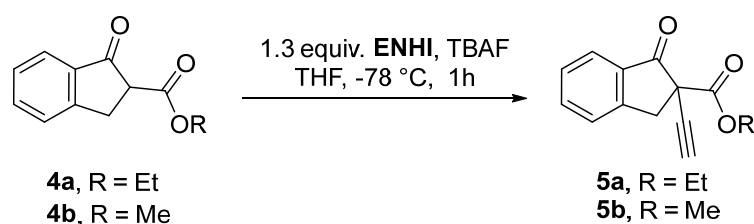
entry	R	ENHI	Yield 5 [%]	Yield iodoarene 3 [%]
1	Et	**1a**	quant.	88
2	Et	**2a**	79	69
3	Et	**2a**	94[a]	86
4	Et	**1b**	87	70
5	Et	**2b**	60	93
6	Et	**1d**	76	(57)[b]
7	Et	**2d**	48	85
8	Et	**1c**	quant.	(> 100)[b]
9	Et	**1e**	quant.	43
10	Et	**1i**	quant.	61
11	Et	**6**	quant.	-
12	Et	**1r**	0[c]	-
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).
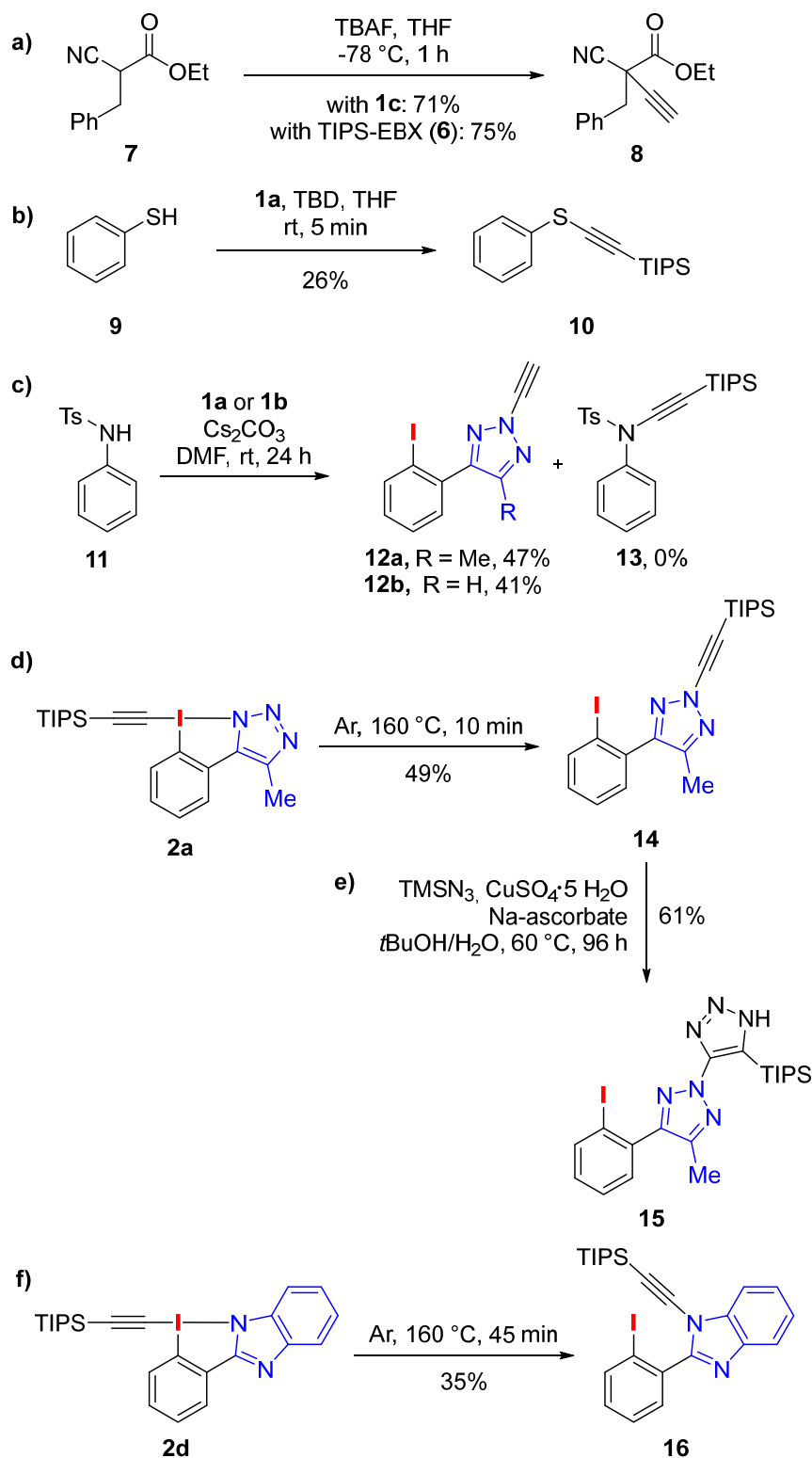
Scheme 3: Intra- and intermolecular group transfer reactions of the ENHIs.

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-λ^3-iodanes are under current work in our laboratory.

Acknowledgement

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