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Letter

Direct Iodination of Electron-Deficient Benzothiazoles: Rapid Access to Two-Photon Absorbing Fluorophores with Quadrupolar D-π-A-π-D Architecture and Tunable Heteroaromatic Core

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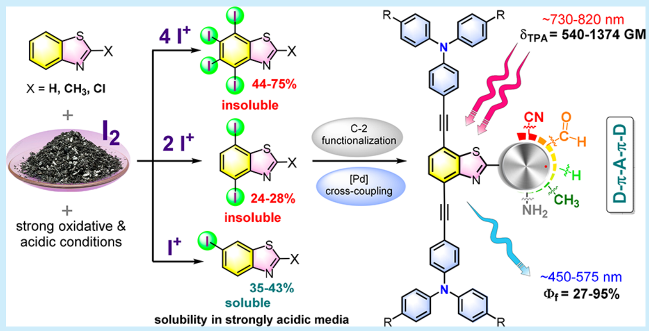
ABSTRACT: Direct iodination of benzothiazoles under strong oxidative/acidic conditions leads to a mixture of iodinated heteroarenes with 1−2 major components, which are easily separable and which structures depend on the I_2 equivalents used. Among the unexpected but dominant products were identified 4,7-diiodobenzothiazoles with a rare substitution pattern for S_EAr reactions of this scaffold. These were employed in the synthesis of 4,7-bis(triarylamine-ethynyl)benzothiazoles — a new class of highly efficient quasi-quadrupolar fluorophores displaying large two-photon absorption cross sections (540−1374 GM) in the near-infrared region.

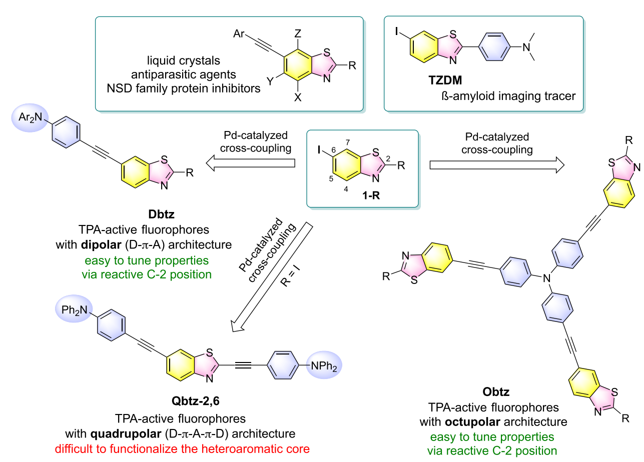


Halogenated, and especially iodinated, heteroaromatics serve as key precursors to π-extended systems, including heteroatom-doped nanographenes[1] or heteroarene acetylenes, emerging as active components in organic light-emitting diodes (OLED),[2] organic field-effect transistors (OFET),[3] as sensitizers in photodynamic therapy[4] or fluorescence probes in two-photon laser scanning microscopy (bioimaging).[5] In addition, iodo-substituted heteroarenes are common products in the pharmaceutical industry and allow rapid access to diversified compound libraries.[6] The great demand for (hetero)aryl iodides stems particularly from their frequently higher reactivity in Pd-catalyzed cross-coupling reactions in comparison with lighter (hetero)aryl-halogenated analogues (bromides, chlorides), allowing for facile carbon−carbon bond formation and extension of π-conjugation.[7]

In this regard, 6-iodobenzothiazoles (**1-R**; Scheme 1)[8] were found as very useful intermediates, since they pave the way to highly efficient two-photon absorbing (TPA) fluorophores,[9] comprising the benzazole unit at periphery of dipolar (D-π-A, **Dbtz**) or octupolar (triphenylamine-cored, **Obtz**) *push*−*pull* structures[10] or in the center of quadrupolar (D-π-A-π-D) architecture (**Qbtz**)[11] with potential applications in bioimaging due to their high TPA cross sections and emission quantum yields.

The structural motif of 6-iodobenzothiazoles is also a part of ^{125}I-labeled β-amyloid imaging tracer TZDM (Scheme 1)—a neutral thioflavin T analogue used for the detection of early signatures of Alzheimer's disease by positron emission tomography (PET)[12]—and can be used in the synthesis of 6-(arylethynyl)benzothiazoles as promising liquid crystal compounds,[13] antiparasitic agents[14] or protein inhibitors.[15]

Scheme 1. 6-Iodobenzothiazoles and Products Thereof with Useful Applications



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The hitherto described synthesis of iodinated benzothiazoles consists of several steps (usually nitration, reduction of the NO_2 group, diazotization, and subsequent Sandmeyer reaction) providing **1-R** in 14−46% yields with respect to the starting 2-R-benzothiazoles (**btz-R**; R = H[10] or R = Me[16]). **1-Me** can be alternatively prepared by 4-step synthesis involving Jacobson's cyclization of *N*-(4-iodophenyl)-thioacetamide, affording **1-Me** in 38% yield when referenced to the starting aniline.[10] Both synthetic routes are, however, disadvantaged by the sensitivity of key steps (diazotization and oxidative cyclization) to small temperature changes, the rate of addition, and the concentration of reagents, providing lower yields when going to a larger scale, and require extensive purification due to side products.

While the introduction of iodine to the reactive C-2 position of benzothiazole proceeds smoothly via reaction of C-2 metalated benzazoles with I_2[17] or *N*-iodosuccinimide (NIS) (see SI), aromatic Finkelstein-type nucleophilic substitution of benzothiazole-2-chlorides with NaI[11] and Sandmeyer-type reactions of 2-aminobenzothiazoles[18] (all with yields exceeding 50%), direct electrophilic iodinations[19] at the benzene ring of benzazoles are challenging to achieve owing to their π-deficient nature.[20]

Our initial attempts to introduce iodine to the benzene ring of 2-methylbenzothiazole (**btz-Me**) in one-step using equimolar amounts or 2-fold excess of reactive iodinating agents,[21] such as I_2/AgOTf, I_2/$SbCl_5$ and ICl in various solvents, failed due to none or a very poor conversion of the starting heteroarene or because of curious aliphatic chlorination (ICl/DMF) instead of iodination, leading to the isolation of 2-(chloromethyl)benzothiazole in 85% yield.

Therefore, we turned to more powerful I^+ sources[21] such as I_2/$KMnO_4$, I_2/H_5IO_6, or NIS in concentrated sulfuric acid,[22] whose action on readily accessible but electron-deficient benzothiazoles **btz-R** (R = Me, H, Cl) leads to complex mixtures with the composition depending on the equivalents of the iodine source. When using 0.5−1.5 mmol of I^+ per 1 mmol of **btz-Me**, the main components were identified as 6-iodo-2-methylbenzothiazole (**1-Me**) and 4,7-diiodo-2-methylbenzothiazole (**2-Me**, featuring a rare substitution pattern for S_EAr reaction of this heteroaromatic scaffold),[23] accompanied by other mono-, di-, and triiodinated isomers as minor byproducts (Scheme 2).

We found that these complex mixtures can be, however, easily separated by pouring the reaction mixture comprising concd. H_2SO_4 into an optimal amount of ice: the precipitate formed from a strongly acidic solution contains a mixture of diiodo- and triiodo-substituted derivatives, whereas monoiodinated products (with dominant 6-iodinated regioisomer, **1-R**) remain in the yet acidic filtrate and can be precipitated by further dilution of supernatant with ice water (R = Cl) or neutralization (R = Me, H) with aqueous NaOH.[24] On the contrary, highly regioselective C-6 iodination with only traces of diiodinated byproducts was observed for benzothiazol-2(3*H*)-one (**btz-OH**),[25] affording **1-OH** in 85% yield when using NIS in H_2SO_4.

The number and positions of iodine atoms on the benzothiazole moiety in major and minor products were unambiguously determined by ^1H, ^{13}C NMR spectroscopies and comparison of experimental and DFT computed ^{13}C NMR shifts (see Tables S5−S6 in SI for the library of NMR shifts for various iodinated benzothiazoles). These were found to be very sensitive/different for various regioisomers, also due to the large spin−orbit induced heavy-atom on light-atom (HALA)[26] shieldings (σ^{SO} = 30−36 ppm) typical for iodine compounds. The structure of **2-Me** was also confirmed by X-ray diffraction, which revealed notably short halogen−halogen contacts, $d(I\cdots I)_{avg}$ = 3.816 Å, shorter than the sum of the van der Waals radii (3.96 Å), hinting at noncovalent σ-hole interactions[27] in the solid-state, as evident from the electrostatic potential map (Figure 1).

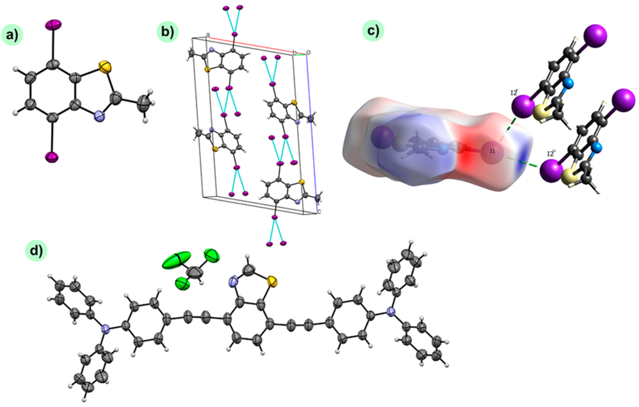
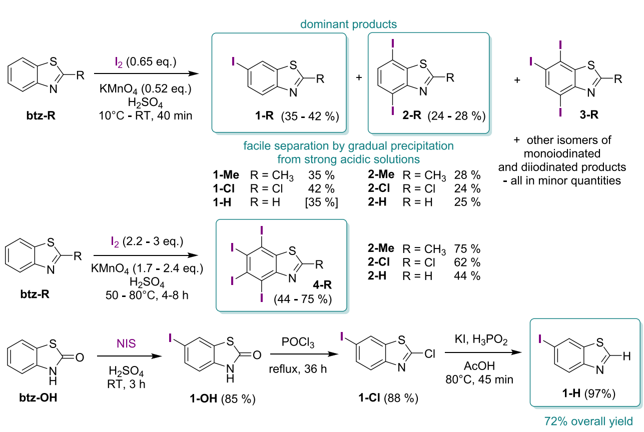


Figure 1. (a) Molecular structure and (b) intermolecular I···I interactions in the unit cell of **2-Me** (each iodine atom forms a bifurcated halogen bond). (c) A view of the I···I interaction. Red and blue regions indicate negative and positive electrostatic potentials, respectively. (d) Molecular structure of **Qbtz-H** (see SI for details).

Scheme 2. Iodinations of Readily Accessible Benzothiazoles



Observing 4,7-diiodobenzothiazoles (**2-R**) among the major products for R = Me, H, Cl, we were curious whether these rare substrates can be isolated in higher yields and purity—with special emphasis on the very low content of triiodinated byproduct (**3-R**), which is difficult to remove from **2-R** due to its limited solubility and similar R_f values. The optimal balance between the yield and purity of **2-Me** was achieved using 0.65 mmol of I_2 and 0.52 mmol of $KMnO_4$ per 1 mmol of **btz-Me**.[28] Employing this iodination protocol and the two-stage workup mentioned above, we isolated **2-Me** as a precipitate from the acidic solution in 28% yield, while **1-Me** was obtained by facile purification of the neutralized fraction in 35% yield. **1-Me** can be prepared in a higher yield (43%) using NIS in H_2SO_4, but this reagent is not suitable for the preparation of **2-Me**.[28]

Application of the I_2/$KMnO_4$ procedure optimized for mono- and diiodinated products to **btz-Cl** afforded **2-Cl** as a

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precipitate from the strongly acidic solution in 24% yield, while **1-Cl** was isolated in 42% yield by substantial dilution of the filtrate (supernatant after isolation of **2-Cl**) with ice water and subsequent crystallization of the obtained precipitate from cyclohexane.

Similarly, we prepared rare **2-H** (25% yield) upon direct iodination of **btz-H** with $I_2/KMnO_4/H_2SO_4$ and subsequent workup of the reaction mixture with the exact amount of ice. Although 6-iodobenzothiazole (**1-H**) was identified as the major product of the reaction, its isolation in pure form turns out to be problematic due to the higher content of other monoiodinated regioisomers. Therefore, we developed an alternative route, where **1-H** is prepared by a reductive hydrodehalogenation of **1-Cl** with KI/H_3PO_2 (97% yield), while **1-Cl** can be obtained easily by direct iodination of **btz-Cl** or by chlorination of 6-iodobenzothiazol-2(3*H*)-one (**1-OH**) with $POCl_3$ (Scheme 2). This procedure affords **1-H** from **btz-OH** in the overall 72% yield.

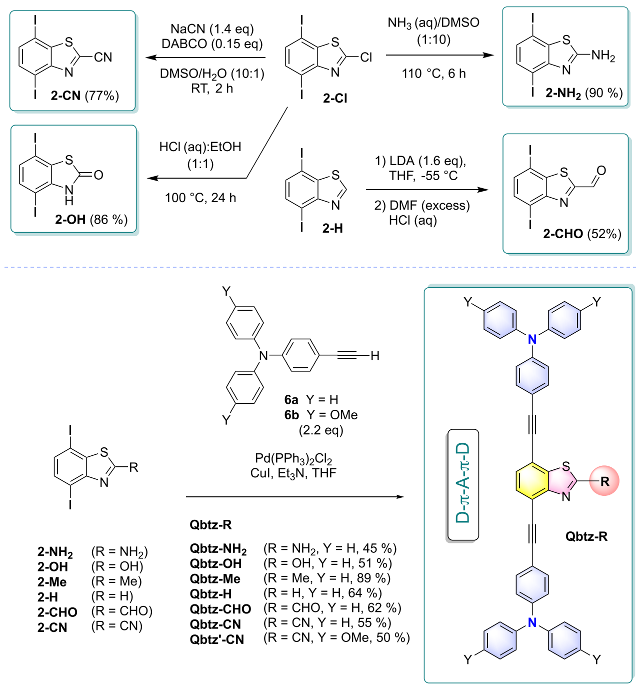
Furthermore, iodination experiments in H_2SO_4 can be easily adjusted to provide 4,5,6,7-tetraiodobenzothiazoles (**4-R**, R = Me, H, Cl), as potential building blocks for S,N-doped nanographenes, with $I_2/KMnO_4$ system providing the highest yields (75% for **4-Me**).

4,7-Diiodobenzothiazoles, **2-R** (easily separable from concomitant **1-R**) represent an expedient and more reactive alternative to 4,7-dibromo-2-methylbenzothiazole,[29] which serves as an intermediate in the synthesis of dyes with potential application in dye-sensitized solar cells[30] and metal-ion sensing,[31] but its preparation requires a 5-step synthetic route. Having a rapid and facile one-step access to valuable **2-R** in reasonable yields, we wondered whether these substrates can be employed in the construction of a new class of D-π-A-π-D benzothiazole-cored TPA fluorophores with reactive C-2 position available for modulation of linear and nonlinear optical properties (Scheme 3). This was not possible in the previously characterized quadrupolar dyes with the C-2 position occupied by one of the two electron-donating branches (cf. **Qbtz-2,6** in Scheme 1).

Computer-aided study of 4,7-bis(triphenylamine-ethynyl)-2-R-benzothiazoles (**Qbtz-R**) by means of the quadratic response time-dependent DFT method[32] at the CAM-B3LYP/6-311++G** level revealed large TPA cross sections (400−1800 GM) for this series, which are comparable or higher than that of **Qbtz-2,6** with C-2/C-6 disubstitution (685 GM), but with a possibility to achieve TPA enhancement and red-shift of absorption/emission peaks upon introduction of auxiliary electron-withdrawing substituents to the C-2 position and electron-donating substituents to the periphery of triphenylamine units (Scheme 3 and Table S8 in SI). On the contrary, derivatives with three or four triarylamine arms linked to the benzothiazole core (products of coupling reactions with **3-R** and **4-R**) are computed to display smaller TPA activities than **Qbtz-R** due to lower transition dipole moments between the excited states (cf. Table S8 in SI).

Encouraged by this finding, we prepared a set of 4,7-bis(triphenylamine-ethynyl)benzothiazoles with D-π-A-π-D setup by Sonogashira-type cross-coupling of **2-R** with 4-(*N,N*-diphenylamino)phenylacetylene (**6a**) and its congener end-capped with two methoxy groups (**6b**). Since the C-2 position in **2-Cl** is prone to nucleophilic substitutions, we employed this derivative in the synthesis of **2-NH$_2$**, **2-OH** and **2-CN**, while **2-CHO** was prepared by formylation of the heteroaryllithium salt derived from **2-H** (Scheme 3).

Scheme 3. Transformations of 2-R Derivatives and Synthesis of Target Qbtz-R Fluorophores



Structures of all target chromophores **Qbtz-R** were confirmed spectroscopically, while **Qbtz-H** was also characterized by single crystal X-ray diffraction (Figure 1d).

Qbtz-R dyes were subjected to measurements of UV−vis absorption and emission spectra, as well as to TPA cross sections, δ_{TPA}, via a two-photon excited fluorescence (TPEF) method with femtosecond laser excitation at wavelengths of 730−850 nm (Figure 2). One-photon and two-photon spectral characteristics are summarized in Table 1.

Following the trends computed by quantum-chemical calculations (Tables S8, S9 and Figure S18 in SI), the absorption spectra of **Qbtz-R** dyes feature an intense intramolecular charge-transfer (ICT) band in the visible region with maxima λ_{abs} in the range of 388−458 nm, which are generally red-shifted for derivatives with stronger electron acceptors. The fluorescence is observed in the blue spectral region for derivatives with electron-donating (R = NH_2, OH, Me) and neutral (R = H) substituents, while electron-withdrawing groups (EWGs) cause a substantial bathochromic shift of emission into green (**Qbtz-CN**), yellow (**Qbtz′-CN**), and orange (**Qbtz-CHO**) region.

Most importantly, **Qbtz-R** chromophores exhibit high TPA cross sections (540−1374 GM)—roughly an order of magnitude higher than most of the conventional one-photon fluorophores, with TPEF maxima λ_{TPA} positioned at 740−820 nm. These positions are less than twice that of the single-photon absorption λ_{abs} ($S_0 \rightarrow S_1$), implying a deeper ($S_0 \rightarrow S_2$ or $S_0 \rightarrow S_3$) transition as expected for quadrupolar dyes due to parity selection rules (Table S8 and Figure S6 in SI). While already **Qbtz-H** exhibits somewhat higher activity than regioisomeric **Qbtz-2,6**, the introduction of small EWG substituents to the C-2 position of **Qbtz-R** leads to further TPA enhancement and red-shift of TPA maxima beyond 800 nm, both effects being reinforced upon introduction of pendant alkoxy groups to triphenylamine moieties. These changes, together with only a moderate drop of emission

Table 1. Photophysical Properties of Quasi-Quadrupolar 4,7-Bis(Triarylamine-Ethynyl)Benzothiazoles in Toluene

dye	λ_{abs} [nm]	ε_{abs} [M^{-1} cm^{-1}]	λ_f [nm]	Φ_f	λ_{TPA} [nm]	δ_{TPA} Φ_f [GM]	δ_{TPA} [GM]
Qbtz-2,6	405	61 500	450	0.83	740	542	653
Qbtz-NH$_2$	388	68 300	428	0.76	730	415	547
Qbtz-OH	399	52 400	437	0.95	740	513	540
Qbtz-Me	399	62 500	439	0.88	740	563	641
Qbtz-H	401	60 100	444	0.89	740	702	788
Qbtz-CHO	444	32 900	575	0.27	820	229	848
Qbtz-CN	442	41 300	516	0.68	800	632	930
Qbtz′-CN	458	44 500	552	0.47	820	646	1374

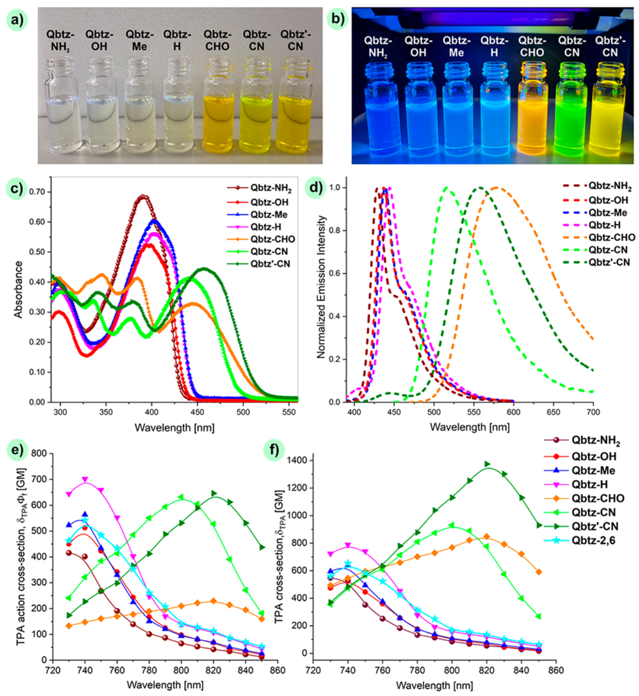


Figure 2. (a,c) UV−vis absorption (c = 1 × 10^{-5} M) and (b,d) emission of **Qbtz-R** dyes in toluene. (e) TPA action cross sections $\delta_{TPA}{\cdot}\Phi_f$ and f) TPA cross sections δ_{TPA} of **Qbtz-R** dyes in toluene.

quantum yield upon ICT enhancement, are beneficial for bioimaging applications, making **Qbtz-CN** platform particularly attractive for further functionalizations and preparation of diagnostic agents for TPEF microscopy.

To conclude, we developed simple synthetic procedures allowing rapid access to known (**1-R**) as well as to hitherto unknown (**2-R**, **4-R**) valuable iodo-substituted benzothiazoles as key precursors for a variety of functional materials and active pharmaceutical ingredients. The one-pot iodinations using inexpensive and readily available reagents are also applicable to multigram-scale synthesis and do not suffer from the drawbacks appearing at diazotization of benzothiazolamines or oxidative cyclization of iodinated *N*-arylthioacetamides. Readily accessible 4,7-diiodobenzothiazoles (**2-R**) were employed in the synthesis of a new class of highly emissive quadrupolar benzothiazole-derived fluorophores **Qbtz-R** with tunable heteroaromatic core and exceptionally large TPA cross sections (930−1374 GM) in the near-IR region (800−820 nm) for **Qbtz-CN** derivatives. **Qbtz-R** dyes with weak EWG substituents in the C-2 position provide thus a low-cost and more efficient alternative to regioisomeric quadrupolar dyes with donor branches attached to C-2 and C-6 positions of the benzothiazole scaffold. In addition, **Qbtz-R** represents a useful platform, of which the modular structure and reactivity of the C-2 position allow further study of the influence of various bioorthogonal functional groups on linear/nonlinear optical properties in an endeavor to construct highly efficient TPA dyes for in vivo bioimaging.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00893.

Experimental and computational details, synthetic procedures, compounds characterization, crystal structure data for **2-Me** and **Qbtz-H**, NMR shift library for iodinated benzothiazoles, computed TPA cross sections, quantum-chemical analysis (PDF)

FAIR data, including the primary NMR FID files, for compounds **1-R**, **2-R**, their regioisomers, **3-R**, **4-R**, and **Qbtz-R** (ZIP)

Accession Codes

CCDC 1901710 and 2043178 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(8) 6-Bromobenzothiazoles are less reactive in Sonogashira-type couplings, and in some cases they do not react at all with donor-substituted phenylacetylenes. See, e.g., ref 11.

(9) A simultaneous absorption of two photons by a single molecule enables activation of chemical/photophysical processes by low-energy IR light (beneficial in deep light penetration through materials) with excitations occurring only in the focal volume. This along with high emission quantum yields make TPA dyes attractive for 3D fluorescence bioimaging. Since most of fluorophores developed for one-photon microscopy display small to moderate TPA cross-sections (20−150 GM), a quest for more efficient dyes is still a hot topic in material science. See, for example: (a) Torres-Moya, I.; Benitez-Martin, C.; Donoso, B.; Tardío, C.; Martín, R.; Carrillo, J. R.; Díaz-Ortiz, Á.; Najera, F.; Prieto, P.; Perez-Inestrosa, E. Extended Alkenyl and Alkynyl Benzotriazoles with enhanced Two-Photon Absorption properties as a promising alternative to Benzothiadiazoles. *Chem. - Eur. J.* **2019**, *25*, 15572−15579. (b) Klausen, M.; Dubois, V.; Clermont, G.; Tonnelé, C.; Castet, F.; Blanchard-Desce, M. Dual-wavelength efficient two-photon photorelease of glycine by π-extended dipolar coumarins. *Chem. Sci.* **2019**, *10*, 4209−4219. (c) Grzybowski, M.; Hugues, V.; Blanchard-Desce, M.; Gryko, D. T. Two-Photon-Induced Fluorescence in New π-Expanded Diketopyrrolopyrroles. *Chem. - Eur. J.* **2014**, *20*, 12493−12501. (d) Hrobarik, P.; Hrobarikova, V.; Semak, V.; Kasak, P.; Rakovsky, E.; Polyzos, I.; Fakis, M.; Persephonis, P. Quadrupolar Benzobisthiazole-Cored Arylamines as Highly Efficient Two-Photon Absorbing Fluorophores. *Org. Lett.* **2014**, *16*, 6358−6361 and references cited therein.

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(24) The principle of this separation can be rationalized by much lower basicity of **2-R**, **3-R** and **4-R** derivatives as compared to **1-R** or **btz-R**. According to DFT calculations (Table S7 in SI), pK_a values of protonated benzothiazoles **2-R**, **3-R**, **4-R** are lower by more than 2 units due to -I effect of iodine atoms, withdrawing electron-density from azole nitrogen.

(25) Benzothiazoles with R = OH feature benzothiazol-2(3*H*)-one skeleton. For the sake of simplicity, we use this general notation, and the keto form is specified when reporting compounds individually.

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(28) Using NIS or I_2/H_5IO_6 instead of $I_2/KMnO_4$ led to lower regioselectivity of diiodination: the crude product obtained by using $I_2/KMnO_4$ reagents contains less than 5% of 6,7-diiodo-2-methylbenzothiazole with respect to **2-Me**, compared to 30−40% when using I_2/H_5IO_6 or 50−60% when using NIS. Substoichiometric amount of I_2 must be used to suppress the formation of **3-Me**. Although according to the reaction stoichiometry only 0.26 mmol of $KMnO_4$ is needed to oxidize 0.65 mmol of I_2 to I^+, the highest yield of **2-R** derivatives was obtained using 2-fold excess of the oxidant. The yields of **2-R** are calculated considering I_2 as a stoichiometry limiting reactant.

(29) Yields of **2-R** obtained here are comparable with the overall 30% yield of analogous 4,7-dibromo-2-methylbenzothiazole prepared by 5-step route from 1,4-dibromobenzene (ref 30). The 5-step synthesis is, however, time and resource demanding and it cannot be applied to the synthesis of **2-Me** due to the decomposition of 1,4-iodobenzene in the initial nitration step.

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