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5,6,7,8-Tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine

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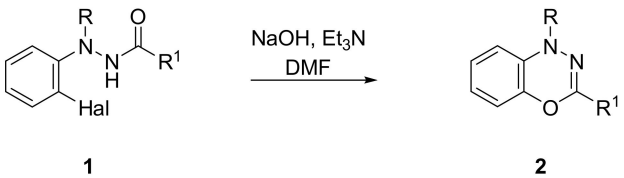
Abstract: Treating 1-fluoro-2-nitrobenzene (**6**) with *N*′-pentafluorophenylbenzohydrazide (**7**) and K_2CO_3 (1.1 equiv) in EtOH at ca. 110 °C (sealed tube) for 24 h affords 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[e][1,3,4]oxadiazine (**5**) (36%) and *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**) (37%). The X-ray crystallography of 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[e][1,3,4]oxadiazine (**5**) is provided. Microwave irradiation (100 W) of perfluorophenylbenzohydrazide **3** with K_2CO_3 (1.1 equiv) in THF at ca. 120 °C (sealed tube, 80 PSI) for 3 h gives oxadiazine **5** (85%), while reduction of the nitro group using Sn (4 equiv) in glacial acetic acid at ca. 20 °C for 30 min, followed by cyclodehydration at ca. 118 °C for 20 min and treatment with 2 M NaOH for 24 h resulted in 1-(perfluorophenyl)-3-phenyl-1,2,4-benzotriazin-4-yl (**4**) with 93% yield.

Keywords: cyclisation; nucleophilic aromatic substitution; oxadiazine; halonitrobenzene; hydrazide; benzotriazine; organic radical

1. Introduction

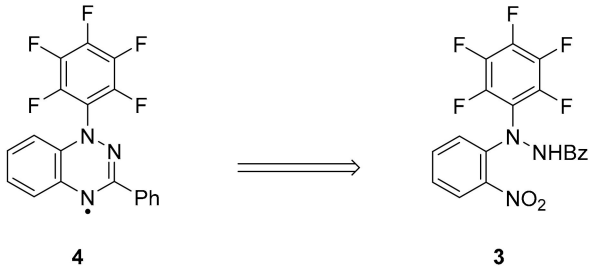
1,3,4-Oxadiazines exhibit a broad array of biological activities such as cardiovascular, antitumor, antibacterial, antimicrobial, acricidal, insecticidal, plant-growth regulating, chitin biosynthesis inhibitors and monoamine oxidase inhibition [1]. The synthesis, chemistry and applications have been extensively reviewed up to 2008 [2]. Recently, isoquinoline-fused analogues displayed antibacterial activity [3,4], quinoline-fused analogues showed antitumour behavior [5], while quinoxalino- and pyrimido-fused analogues showed anti-cancer behavior [6,7].

A classical route to benzo-fused 1,3,4-oxadiazines involves the intramolecular cyclisation of *N*′-(2-halophenyl)benzohydrazides first reported by Elliot and Gibson (Scheme 1) [8,9].



Scheme 1. Route to benzo-fused 1,3,4-oxadiazines **2** via the intramolecular cyclisation of *N*′-(2-halophenyl)benzohydrazides **1** first reported by Elliot and Gibson [8,9].

During our work on the chemistry of 1,2,4-benzotriazinyl radicals [10–20], we needed to prepare *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**) for the synthesis of 1-(perfluorophenyl)-3-phenyl-1,2,4-benzotriazin-4-yl (**4**) (Scheme 2).



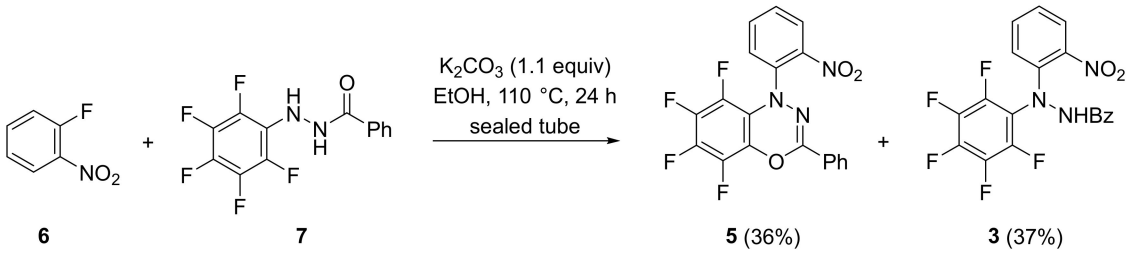
4 **3**

Scheme 2. Structure of 1-(perfluorophenyl)-3-phenyl-1,2,4-benzotriazin-4-yl (**4**) and its precursor *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**).

Herein, we describe our preparation of *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzo-hydrazide (**3**) which 'unexpectedly' led to a new fluoro-substituted 4*H*-1,3,4-benzoxadiazine: 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**).

2. Results and Discussion

Treating 1-fluoro-2-nitrobenzene (**6**) with *N*′-(perfluorophenyl)benzohydrazide (**7**) and potassium carbonate (1.1 equiv) in EtOH heated to 110 °C (sealed tube) for 24 h gave 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**) [R_f 0.72 (*n*-hexane/DCM, 50:50)] and *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**) [R_f 0.57 (*n*-hexane/*t*-BuOMe, 50:50)], in 36 and 37% yields, respectively (Scheme 3).



6 **7** **5** (36%) **3** (37%)

Scheme 3. Reaction of 1-fluoro-2-nitrobenzene (**6**) with *N*′-(perfluorophenyl)benzohydrazide (**7**): Preparation of 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**) and *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**).

Spectroscopic data on compound **5** revealed no ν(N-H) or ν(C=O) stretches in the IR spectra and only nine aromatic H resonances and no NH signal in the ^{1}H NMR spectra (DMSO-d_6). Furthermore, ^{13}C NMR spectra revealed a fluorine splitting pattern consistent with a 1,2-disubstituted tetrafluorobenzene and the absence of an amide C=O signal. MALDI-TOF data (*m*/*z* 403) and elemental analysis supported the formula of $C_{19}H_9F_4N_3O_3$. The data supported the proposed structure of 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**) which was also supported by single crystal XRD studies (Figure 1).

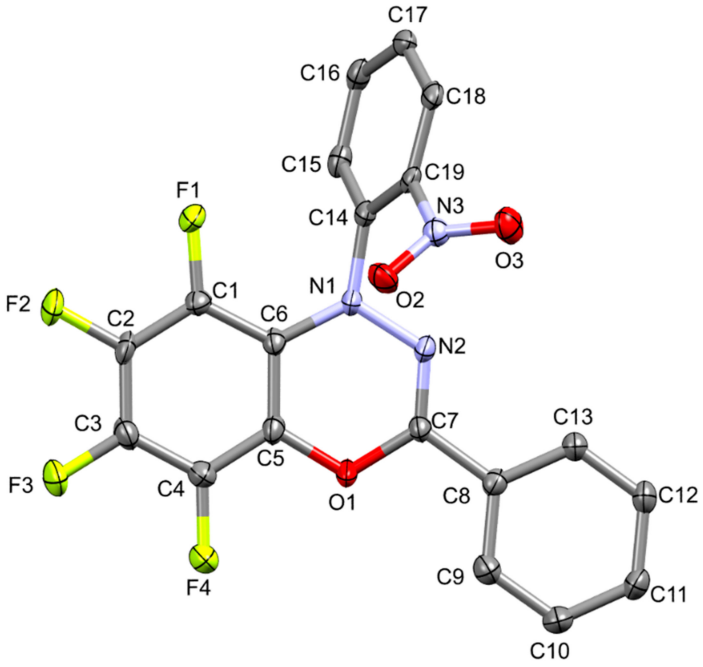


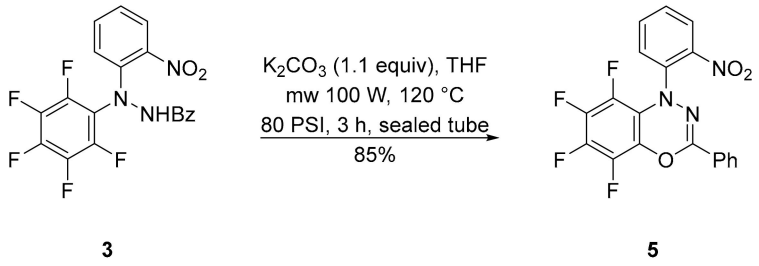
Figure 1. ORTEP view of 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**) (CCDC-1842283). 50% Probability ellipsoids. Hydrogens omitted for clarity. Crystallographic numbering shown.

5,6,7,8-Tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**) crystallized in the centrosymmetric *P*-1 triclinic space group. The 1,3,4-oxadiazine moiety was in a shallow boat geometry, where N1 and O1 (crystallographic numbering) deviated from the plane by 18.4° and 16.4°, respectively. The *N*-(2-nitrophenyl) substituent twisted out of the benzoxadiazine plane by 70.3°, while the phenyl at C7 (crystallographic numbering) remained in the benzoxadiazine plane.

The desired *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**) was isolated as pale yellow needles and was more polar [R_f 0.57 (*n*-hexane/*t*-BuOMe, 50:50)] than the analogous non-fluorinated *N*′-(2-nitrophenyl)-*N*′-phenylbenzohydrazide [R_f 0.27 (*n*-hexane/DCM, 50:50)] [10]. IR spectroscopy, indicated a weak amine stretch at ν(N-H) 3185 cm^{-1} and a medium intensity carbonyl stretch at ν(C=O) 1672 cm^{-1}, while in the NMR spectra the carboxamide group appeared at δ_H 11.83 (CON*H*) and δ_C 165.5 (*C*ONH).

When the above reaction was run for longer reaction times (48 h), the reaction mixture became more complex (by TLC). Lower temperatures (ca. 20–50 °C) yielded only traces of the benzohydrazide **3** (~5–10% by TLC) and mainly unreacted starting materials, even after 72 h. At temperatures above 60 °C, both products appeared (by TLC) and the reaction was complete after 24 h, but the yields remained similar. Combinations of other solvents (MeCN, DMF) and/or bases (Et_3N, Hünig's base) did not afford either products **3** or **5**. The use of microwave conditions (100 W, 120 °C, 80 PSI) also did not improve the yields.

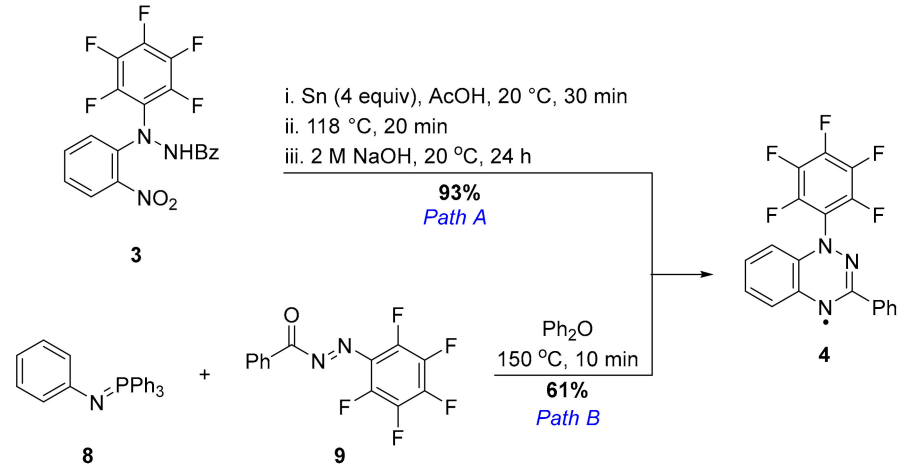
The above formation of the oxadiazine **5** was attributed to an in-situ cyclisation of perfluoro-phenylbenzohydrazide **3** but attempts to verify this by treating benzohydrazide **3** with K_2CO_3 (1.1 equiv) in EtOH at ca. 110 °C (sealed tube) for 24 h yielded only traces of the oxadiazine **5** and a complex reaction mixture. Interestingly, the use of microwave irradiation (100 W) to heat the reaction mixture to ca. 120 °C at 80 PSI gave a similarly complex reaction mixture (by TLC) but in a shorter reaction time of only 1 h. Fortunately, under these conditions (MW 100 W, 120 °C, 80 PSI), replacing EtOH by anhydrous tetrahydrofuran (THF) afforded after 3 h the oxadiazine **5** with 85% yield (Scheme 4).



3 **5**

Scheme 4. Conversion of *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**) into 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**).

Reduction of the nitro group of the benzohydrazide **3**, using Sn (4 equiv) in glacial acetic acid at ca. 20 °C for 30 min, followed by cyclodehydration at ca. 118 °C for 20 min and subsequent treatment with 2 M NaOH solution for 24 h resulted in the anticipated radical **4** with 93% yield (34% overall yield from hydrazide **7**) (Scheme 5, Path A). The latter was prepared more effectively with 61% yield (45% overall yield from hydrazide **7**) via an alternative aza-Wittig protocol involving the phosphoranimine **8** and the azoketone **9** (Scheme 5, Path B) [11].



3 **4**

8 **9**

Scheme 5. Synthesis of radical **4**: (**a**) Path A: via Reduction of *N*′-(2-nitrophenyl)-*N*′-(perfluorophenyl)benzohydrazide (**3**); and (**b**) via Path B: Aza-Wittig protocol.

3. Materials and Methods

3.1. General Methods

All chemicals were commercially available except those whose synthesis is described. Tetrahydrofuran (THF) was dried over Na/benzophenone. Reactions were protected from moisture with $CaCl_2$ drying tubes. All volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by thin-layer chromatography (TLC) using commercial glass-backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}, Darmstadt, Germany). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography [21] was used throughout for all prep-scale chromatographic separations and employed Merck Silica Gel 60 (less than 0.063 mm). Melting and decomposition points were determined using a PolyTherm-A, Wagner & Munz, Kofler hot-stage microscope apparatus (Wagner and Munz, Munich, Germany). The solvents used for recrystallisation are indicated after the respective melting points. UV/vis spectra were obtained using a Perkin-Elmer Lambda-25 UV/vis spectrophotometer (Perkin-Elmer, Waltham, MA, USA), and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with a Pike Miracle

Ge ATR accessory (Pike Miracle, Madison, WI, USA) and strong, medium and weak peaks are represented by s, m and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine (at 500 and 125 MHz, respectively) (Bruker, Billerica, MA, USA). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. APT (Advance Proton Test) NMR studies identified carbon multiplicities, which are indicated by (s), (d), (t) and (q) notations. MALDI-TOF (Matrix Assisted Laser Desorption/Ionization-Time of Flight) mass spectra (+ve mode) were conducted on a Bruker Autoflex III Smartbeam instrument (Bruker). Elemental analyses were run by the London Metropolitan University Elemental Analysis Service. *N*′-Pentafluorophenylbenzohydrazide (**7**) was prepared according to a literature procedure [22]. X-Ray crystallographic data were collected on an Oxford-Diffraction Supernova diffractometer (Rigaku Corporation, Tokyo, Japan), equipped with a CCD area detector utilizing Mo-Kα radiation (λ = 0.71073 Å). A suitable crystal was attached to glass fibers using paratone-N oil and transferred to a goniostat where they were cooled for data collection. Unit cell dimensions were determined and refined by using 3817 ($3.35^\circ \leq \theta \leq 29.52^\circ$) reflections. Empirical absorption corrections (multi-scan based on symmetry-related measurements) were applied using CrysAlis RED software [23]. The structures were solved by direct method and refined on F^2 using full-matrix least squares using SHELXL2014 [24]. Software packages used: CrysAlis CCD [23] for data collection, CrysAlis RED [23] for cell refinement and data reduction, WINGX [25] for geometric calculations and DIAMOND [26] for molecular graphics. The non-H atoms were treated anisotropically. The hydrogen atoms were placed in calculated, ideal positions and refined as riding on their respective carbon atoms.

X-Ray crystal refinement data (**5**) (CCDC-1842283): $C_{19}H_9F_4N_3O_3$, M = 403.29, triclinic, space group P-1, a = 6.7377(7) Å, b = 7.1634(8) Å, c = 17.7391(11) Å, α = 94.898(7)°, β = 93.481(7)°, γ = 108.268(9)°, V = 806.58(14) Å^3, Z = 2, T = 100(2) K, ρ_{calcd} = 1.661 g cm^{-3}, $2\theta_{max}$ = 29.5. Refinement of 262 parameters on 2441 independent reflections out of 3817 measured reflections (R_{int} = 0.0616) led to R_1 = 0.0679 [I > 2σ(I)], wR_2 = 0.1407 (all data) and S = 1.063 with the largest difference peak and hole of 0.313 and −0.289 e^{-3}, respectively. Crystallographic data for **5** have been deposited with the Cambridge Crystallographic Data Centre with the deposit number CCDC-1842283. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).

*3.2. 5,6,7,8-Tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1H-benzo[e][1,3,4]oxadiazine (**5**)*

A stirred mixture of 1-fluoro-2-nitrobenzene (**6**) (0.527 mL, 5.0 mmol), *N*′-(perfluorophenyl)-benzohydrazide (**7**) (1.662 g, 5.5 mmol) and powdered K_2CO_3 (0.760 g, 5.5 mmol) in EtOH (4 mL), sealed in a thick walled glass pressure tube was heated at ca. 110 °C for 24 h. The mixture was then allowed to cool to ca. 20 °C, diluted with DCM (10 mL), filtered through Celite, rinsed with additional DCM and the volatiles were removed in vacuo. The residue was chromatographed (*n*-hexane/DCM, 50:50) to yield the *title compound* **5** (722.2 mg, 36%) as orange cubes; m.p. (hot-stage) 175.0-176.0 °C (EtOH); m.p. (DSC) onset: 179.9 °C, peak max: 180.7 °C (EtOH); R_f 0.72 (*n*-hexane/DCM, 50:50); found: C, 56.54; H, 2.17; N, 10.33. $C_{19}H_9F_4N_3O_3$ requires C, 56.59; H, 2.25; N, 10.42%; λ_{max}(DCM)/nm 243 (log ϵ 4.66), 360 (3.82); ν_{max}/cm^{-1} 1603w, 1518s, 1510s, 1493s, 1451m, 1364m, 1327s, 1298w, 1279w, 1258m, 1155m, 1130m, 1096m, 1067s, 1042m, 1026m, 961m, 891s, 878w, 858m, 814m, 776m, 772s, 743m, 706m; δ_H (500 MHz, DMSO-d_6) 8.07 (1H, dd, J = 8.3, 1.2 Hz), 7.86 (1H, d, J = 8.0 Hz), 7.82 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.75–7.73 (2H, m), 7.61–7.57 (2H, m), 7.54–7.51 (2H, m); δ_C (125 MHz, DMSO-d_6) one *C*F resonance missing, 145.1 (s), 144.3 (s), 138.2 (dm, $^{1}J_{CF}$ = 242.5 Hz), 136.4 (dm, $^{1}J_{CF}$ = 218.8 Hz), 136.3 (s), 134.6 (dm, $^{1}J_{CF}$ = 227.5 Hz), 133.9 (d), 131.9 (d), 128.9 (d), 128.1 (d), 127.6 (d, $^{2}J_{CF}$ = 13.8 Hz), 126.9 (s), 126.8 (d), 125.8 (d), 125.0 (d), 118.2 (d, $^{2}J_{CF}$ = 10.0 Hz); m/z (MALDI-TOF) 404 (MH$^+$, 74%), 403 (M$^+$, 100), 253 (39), 104 (22). Further elution (*n*-hexane/*t*-BuOMe, 50:50) gave *N*′-(2-nitrophenyl)-*N*′-(perfluoro-phenyl)benzohydrazide (**3**) (782.9 mg, 37%) as light yellow needles; m.p. (hot-stage) 220.3-222.1 °C (EtOH); m.p. (DSC) onset:

223.0 °C, peak max: 223.1 °C (EtOH); R_f 0.57 (*n*-hexane/*t*-BuOMe, 50:50); found: C, 53.74; H, 2.30; N, 9.76. $C_{19}H_{10}F_5N_3O_3$ requires C, 53.91; H, 2.38; N, 9.93%; λ_{max}(DCM)/nm 256 (log ε 4.40), 280 inf (4.09), 360 (3.44); ν_{max}/cm^{-1} 3185w (N-H), 1672m, 1667m, 1605w, 1518s, 1514s, 1483m, 1346m, 1335m, 1279m, 1221w, 1094w, 1069m, 1013m, 1005m, 986m, 928m, 916m, 824m, 806m, 776m, 756w; δ_H (500 MHz, DMSO-d_6) 11.83 (1H, s, N*H*), 7.90–7.86 (3H, m), 7.68 (1H, ddd, *J* = 8.0, 8.0, 1.2 Hz), 7.61 (1H, ddd, *J* = 7.2, 2.3, 2.3 Hz), 7.55-7.50 (2H, m), 7.43 (1H, dd, *J* = 8.4, 0.9 Hz), 7.28 (1H, ddd, *J* = 7.8, 1.0 Hz); δ_C (125 MHz, DMSO-d_6) 165.5 (s, *C*=O), 142.6 (dm, $^1J_{CF}$ = 249.8 Hz), 139.4 (s), 138.5 (dm, $^1J_{CF}$ = 249.8 Hz), 138.4 (s), 137.2 (dm, $^1J_{CF}$ = 249.8 Hz), 134.2 (d), 132.5 (d), 131.1 (s), 128.6 (d), 127.6 (d), 125.5 (d), 123.6 (d), 120.2 (d), 119.6–119.4 (m, *C*-CF); *m/z* (MALDI-TOF) 424 (MH^+, 54%), 405 (27), 403 (100).

*3.3. Conversion of N′-(2-Nitrophenyl)-N′-(perfluorophenyl)benzohydrazide (**3**) into 5,6,7,8-Tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1H-benzo[e][1,3,4]oxadiazine (**5**)*

A stirred suspension of *N′*-(2-nitrophenyl)-*N′*-(perfluorophenyl)benzohydrazide (**3**) (15.0 mg, 0.035 mmol) and K_2CO_3 (5.30 mg, 1.1 mmol) in anhydrous tetrahydrofuran (1.5 mL) in a sealed vial was inserted in a CEM Discovery microwave reactor and irradiated (100 W) to ca. 120 °C for 3 h at 80 PSI (551.58 kPa). Upon completion, the reaction vessel was air cooled to ca. 20 °C and the residue was chromatographed (*n*-hexane/DCM, 50:50) to yield 5,6,7,8-tetrafluoro-1-(2-nitrophenyl)-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine (**5**) (12.0 mg, 85%) as orange cubes; m.p. (hot-stage) 175.0-176.0 °C (EtOH); R_f 0.72 (*n*-hexane/DCM, 50:50); λ_{max}(DCM)/nm 243 (log ϵ 4.66), 360 (3.82); δ_H (500 MHz, DMSO-d_6) 8.07 (1H, dd, *J* = 8.3, 1.2 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.82 (1H, ddd, *J* = 7.5, 7.5, 1.5 Hz), 7.75–7.73 (2H, m), 7.61–7.57 (2H, m), 7.54–7.51 (2H, m); identical to that described above.

*3.4. 1-(Perfluorophenyl)-3-phenyl-1,2,4-benzotriazin-4-yl (**4**)*

To a vigorously stirred suspension of *N′*-(2-nitrophenyl)-*N′*-(perfluorophenyl)benzohydrazide (**3**) (0.4233 g, 1.0 mmol) in acetic acid (5 mL) at ca. 20 °C, Sn powder (0.475 g, 4.0 mmol) was added in one portion and the reaction mixture was stirred for 30 min and subsequently heated at ca. 118 °C for 20 min. The mixture was then allowed to cool to ca. 20 °C, diluted with DCM (50 mL) and washed with 2 M NaOH (50 mL). To the organic phase, 2 M NaOH (50 mL) was added and the biphasic mixture was left to stir at ca. 20 °C for 24 h. The organic phase was again separated, washed with H_2O (2 × 50 mL), dried ($MgSO_4$) and the volatiles were removed in vacuo. Recrystallization of the residue (c-hexane) yielded the title compound **4** as black cubes; m.p. (hot-stage) 192.4-193.0 °C (lit. [11] 188.6-190.1 °C); λ_{max}(CH_2Cl_2)/nm 268 (log ε 4.61), 322 (3.66), 375 (3.76), 423 inf (3.40), 455 inf (3.17), 486 (3.10), 565 inf (2.78); ν_{max}/cm^{-1} 1514s, 1491w, 1391s, 1244w, 1198w, 1177w, 1146w, 1121w, 1076m, 1069w, 1028m, 989s, 928m, 783m, 760s, 735m; *m/z* (MALDI-TOF) 375 (MH^+, 25%), 374 (M^+, 100); identical to an authentic sample.

Supplementary Materials: The following are available online at http://www.mdpi.com/1422-8599/2018/2/M997/s1, cif file for compound **5**, ^{1}H and ^{13}C-NMR spectra for new compounds **3** and **5** (PDF).

Author Contributions: G.A.Z. carried out the synthetic studies; A.K. collected the X-ray data; G.A.Z and P.A.K. conceptually designed the study, wrote and edited the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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