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4b,5,6,9-Tetrahydro-7*H*-dibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepin-7-one

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Abstract: A simple approach to synthesize 4b,5,6,9-tetrahydro-7*H*-dibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepin-7-one has been developed, based on a three-step transformation of 2-(2-bromophenyl)cyclopropane-1,1-diester. The key stage in this method is an intramolecular cross-coupling of 1-(2-bromobenzyl)-5-(2-bromophenyl)pyrrolidin-2-one under continuous flow conditions in an H-Cube-Pro using commercially available supported Pd catalysts.

Keywords: donor-acceptor cyclopropanes; tetrahydrodibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepines; cross-coupling reactions; flow chemistry

1. Introduction

Dibenz[*c*,*e*]azepine derivatives attract the attention of synthetic and medicinal chemists due to their potential use in human and veterinary medicine. This scaffold is present in the vasodilator azapetine [1], as well as in a broad variety of compounds exhibiting anticancer [2–8], anti-inflammatory [9], hypolipidemic [10,11], and other types of biological activities [6,12–18]. In addition, dibenz[*c*,*e*]azepines have been used as chiral organocatalysts in enantioselective synthesis [19,20]. Owing to these applications, the development of new efficient methodologies for the preparation of dibenz[*c*,*e*]azepines is of great interest [21]. One of the methods for the synthesis of this scaffold is based on a palladium-catalyzed intramolecular cross-coupling reaction between two aromatic rings in *N*,*N*-dibenzylamine derivatives [22–29].

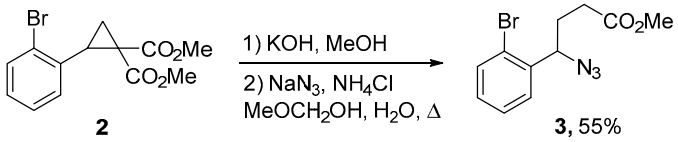
As a part of our efforts towards the synthesis of *N*-containing heterocycles of potential pharmacological value based on the donor-acceptor cyclopropane transformations [30–35], we have recently described a convenient synthesis of polyoxygenated tetrahydrodibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepines [35]. This protocol included: (1) Cyclopropane ring opening with an azide ion, followed by in situ Krapcho dealkoxycarbonylation; (2) the phosphine-mediated reaction of the obtained 4-aryl-4-azidobutyrate with aromatic aldehydes and subsequent in situ reductive cyclization of the formed imine, yielding 5-aryl-1-benzylpyrrolidin-2-ones; (3) their oxidative cyclization to dibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepine derivatives. The last step, however, can be carried out only for substrates containing two electron-rich aromatic rings, and, therefore, has limited application.

We envisioned that the related dibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepines without electron-donating groups in the aryl moieties could be synthesized by an intramolecular cross-coupling reaction of

pyrrolidones bearing halogen(s) in *ortho*-position(s) of the aromatic groups. Herein, we report the synthesis of 4b,5,6,9-tetrahydro-7*H*-dibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepin-7-one (**1**) from donor-acceptor cyclopropane in only three steps, the key one is an intramolecular cross-coupling under continuous flow conditions.

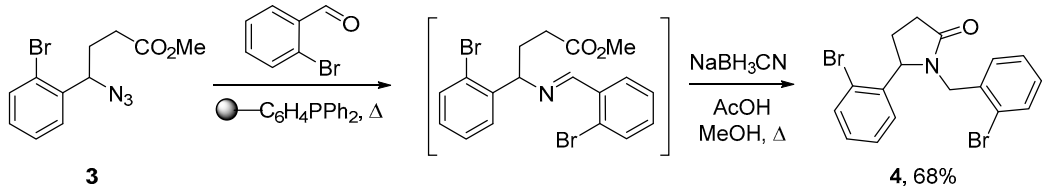
2. Results and Discussion

Title compound **1** was synthesized from readily available dimethyl 2-(2-bromophenyl)-cyclopropane-1,1-dicarboxylate **2**. At the first step, cyclopropane **2** was converted into azide **3** by the Kerr's procedure [36], including partial hydrolysis of **2** followed by cyclopropane ring opening with sodium azide, accompanied by decarboxylation (Scheme 1).



Scheme 1. Synthesis of azide **3**.

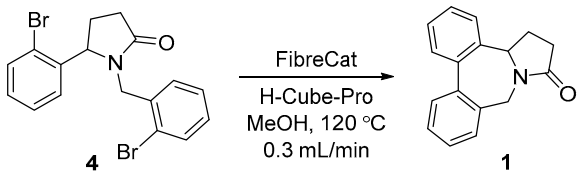
Afterward, we transformed 4-aryl-4-azidobutyrate **3** into pyrrolidone **4** using a simple synthetic methodology developed earlier [30]. Namely, azide **3** reacted with 2-bromobenzaldehyde in the presence of triphenylphosphine producing the corresponding imine via a sequence of the Staudinger and *aza*-Wittig reaction. The treatment of the obtained imine in a one-pot manner with sodium cyanoborohydride induced its reductive cyclization to 5-aryl-1-benzylpyrrolidin-2-one **4**. We found that the use of polymer-bound triphenylphosphine instead of the conventional reagent both increased the yield and saved the trouble of imine separation from triphenylphosphine. These advantages outweigh the increase of the reaction time required for the full conversion of azide **3**. The formed imine was treated with methanolic $NaBH_3CN$ in the presence of acetic acid using a "telescoped" procedure [37]. The resulting amine underwent immediate cyclization affording the desired pyrrolidin-2-one **4** in a reasonable yield (Scheme 2).



Scheme 2. Synthesis of pyrrolidin-2-one **4**.

The synthesis of tricyclic compound **1** was accomplished by the palladium-catalyzed coupling of two aryl halide functionalities in compound **4**. This cross-coupling proceeds with low-to-moderate yield under continuous flow conditions [38] using commercial cartridges, with Pd catalysts FibreCat 1001, FibreCat 1007, FibreCat 1031, FibreCat 1032 (Scheme 3). The best results were achieved with cartridge FibreCat 1007, containing a complex of palladium(II) acetate with polymer-supported phenyldicyclohexylphosphine as a catalyst.

In summary, the facile three-step sequence, including a cyclopropane ring opening with an azide ion, accompanied by decarboxylation, a Staudinger/*aza*-Wittig domino reaction combined with the reductive cyclization, and an intramolecular cross-coupling reaction of 1-(2-bromobenzyl)-5-(2-bromophenyl)pyrrolidin-2-one, provides a concise route to 4b,5,6,9-tetrahydro-7*H*-dibenzo[*c*, *e*]pyrrolo[1,2-*a*]azepin-7-one.



Scheme 3. Synthesis of tetrahydrodibenzo[*c*,*e*]pyrrolo[1,2-*a*]azepine **1**.

3. Materials and Methods

NMR spectra were acquired on Bruker Avance 500 spectrometer at room temperature; the chemical shifts δ were measured in ppm with respect to the solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.0). The splitting patterns are designated as s, singlet; d, doublet; m, multiplet; dd, double doublet; br., broad. The coupling constants (*J*) were in Hertz. The ^{1}H-NMR, ^{13}C-NMR for the synthesized compounds, as well as 2D (HSQC and HMBC) NMR spectra for the selected compounds, are available in the Supplementary Materials. Infrared spectra were recorded on the Infralum FT-801 spectrometer. High resolution and accurate mass measurements were carried out using a micrOTOF-Q^{TM} ESI-TOF (Electro Spray Ionization/Time of Flight, Bruker, Billerica, MA, USA) and LTQ Orbitrap mass spectrometer (Thermo Fischer Scientific, Waltham, MA, USA). Elemental analyses were performed with an EA-1108 CHNS elemental analyzer instrument (Fisons, Ipswich, UK). The microwave reaction was performed in a Monowave 300–Anton Paar microwave reactor (Anton Paar Gmbh, Graz, Austria) in sealed reaction vessels. The temperature was monitored with the installed IR detector. The melting points (m.p.) were determined using a 9100 capillary melting point apparatus (Electrothermal, Stone, UK). Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F_{254}, supported on aluminum); the revelation was done by UV lamp (365 nm). Column chromatography was performed on silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany). All reactions were carried out using freshly distilled and dry solvents. Dimethyl 2-(2-bromophenyl)cyclopropane-1,1-dicarboxylate **2** was synthesized by the published procedure [30]. Commercial reagents employed in the synthesis were analytical grade, obtained from Aldrich (St. Louis, MI, USA) or Alfa Aesar (Ward Hill, MO, USA). The flow reactions were carried out in a ThalesNano H-Cube Pro featuring an HPLC pump to deliver the substrates at flow rates of 0.3 mL/min, the reactor box for CatCarts (FibreCat 1001, FibreCat 1007, FibreCat 1032) employed in this study were purchased in ABCR Gmbh (Karlruhe, Germany).

*3.1. Methyl 4-Azido-4-(2-bromophenyl)butanoate (**3**)*

A solution of cyclopropane **2** (225 mg, 0.72 mmol) and KOH (60 mg, 1.07 mmol) in a mixture of methanol (2.9 mL) and water (3.6 mL) was refluxed for 6.5 h. Then, the reaction mixture was quenched with water (2.9 mL) and concentrated to half volume under reduced pressure. The residue was extracted with ethyl acetate (10 mL); aqueous HCl was added to the aqueous layer until pH 1. The obtained suspension was extracted with diethyl ether (3 × 10 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated, affording 165 mg (76%) of a crude cyclopropane hemimalonate as a colorless oil. This oil was dissolved in the mixture of 2-methoxyethanol (5 mL) and water (0.5 mL), NaN_3 (43 mg, 0.66 mmol) and NH_4OAc (42 mg, 0.54 mmol) were added. The reaction mixture was heated under reflux for 2 h, quenched with water and extracted with diethyl ether (3 × 10 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated. Purification by flash chromatography gave 117 mg (72%) of the desired product **3** as a colorless oil, R_f = 0.54 (ethyl acetate:petroleum ether, 1:10).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 2.03–2.16 (m, 2H, CH_2), 2.43–2.49 (m, 2H, CH_2), 3.69 (s, 3H, CH_3O), 5.10 (dd, ^3J = 8.4 Hz, ^3J = 5.4 Hz, 1H, CH), 7.20 (ddd, ^3J = 8.0 Hz, ^3J = 7.5 Hz, ^4J = 1.7 Hz, 1H,

Ar), 7.38 (ddd, ^3J = 7.8 Hz, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.45 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, Ar), 7.60 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, Ar). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ = 30.5 (CH_2), 30.7 (CH_2), 51.8 (CH_3O), 63.9 (CH), 123.3 (C, Ar), 128.0 (CH, Ar), 128.2 (CH, Ar), 129.8 (CH, Ar), 133.3 (CH, Ar), 138.6 (C, Ar), 173.1 (CO). IR (cm^{-1}) 2995, 2952, 2101, 1739, 1590, 1568, 1469, 1437, 1328, 1251, 1198, 1169, 1120, 1024. HRMS ESI/Q-TOF: *m*/*z* = 320.0003 $[M + H]^+$ (320.0005 calculated for $C_{11}H_{12}BrN_3NaO_2$). Anal. calculated for $C_{11}H_{12}BrN_3O_2$: C, 44.32; H, 4.06; N, 14.09. Found: C, 44.31; H, 3.89; N, 14.08.

*3.2. 1-(2-Bromobenzyl)-5-(2-bromophenyl)pyrrolidin-2-one (**4**)*

A suspension of azide **3** (1.18 g., 3.96 mmol) and polymer-bound triphenylphosphine (Sigma-Aldrich 93093; 1.34 g, ca. 3 mmol/g, 4.02 mmol) in 1,2-dichloroethane (8 mL) was stirred at room temperature for 45 min. After that, 2-bromobenzaldehyde (2.22 g, 12 mmol) was added, the resulting mixture was heated in a microwave reactor at 90 °C for 15 h. The resin was filtered off and washed with dichloroethane; the combined filtrates were concentrated in vacuo. The residue was dissolved in methanol (9.7 mL) and treated with sodium cyanoborohydride (1.51 g, 24 mmol) and glacial acetic acid (2.5 mL, 43.7 mmol). The reaction mixture was refluxed for 4 h, quenched with concentrated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on a silica gel to afford the desired product. The yield was 1.10 g (68%) as a yellowish solid; mp 112–113 °C; R_f = 0.50 (ethyl acetate:petroleum ether, 1:1). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 1.81–1.86 (m, 1H, C(4)H_2), 2.44–2.65 (m, 3H, C(4)H_2, C(3)H_2), 3.93 (d, ^2J = 15.2 Hz, 1H, CH_2N), 4.91 (br. s, 1H, C(5)H), 5.13 (d, ^2J = 15.2 Hz, 1H, CH_2N), 7.11–7.36 (m, 6H, Ar), 7.51 (d, ^3J = 8.1 Hz, 1H, Ar), 7.56 (d, ^3J = 8.1 Hz, 1H, Ar). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ = 26.8 (CH_2), 29.2 (CH_2), 44.9 (CH_2N), 60.4 (CH), 123.0 (C, Ar), 123.9 (CH, Ar), 126.3 (C, Ar), 127.6 (CH, Ar), 127.8 (CH, Ar), 129.1 (CH, Ar), 129.2 (CH, Ar), 130.4 (CH, Ar), 132.9 (CH, Ar), 133.4 (C, Ar), 135.1 (CH, Ar), 139.4 (C, Ar), 175.8 (C=O). IR (cm^{-1}) 3361, 3086, 3057, 2989, 2969, 2934, 2899, 2852, 2695, 1647, 1587, 1567, 1463, 1447, 1436, 1426, 1410, 1358, 1349, 1323, 1292, 1265, 1239, 1216, 1207, 1115, 1099, 1066, 1045, 1038, 1025. HRMS ESI/Q-TOF: *m*/*z* = 386.1605 $[M + H]^+$ (385.1598 calculated for $C_{17}H_{15}Br_2NO$).

Continuous Flow Procedure

In a typical experiment for the reductive coupling, a solution containing pyrrolidin-2-one **4** (1 equivalent) and K_2CO_3 (3 equivalents) in ultra-pure methanol (0.001 M) was pumped through a catalyst cartridge (FibreCat 1001, FibreCat 1007, FibreCat 1032) heated up to 120 °C at a flow rate of 0.3 mL/min (optimized flow conditions) in the H-Cube Pro A. The solvent was removed under reduced pressure, the product was purified by silica gel flash column chromatography (eluent–petroleum ether:ethylacetate, 10:1 to 1:1).

4b,5,6,9-Tetrahydro-7H-dibenzo[c,e]pyrrolo[1,2-a]azepin-7-one (**1**). This compund was obtained in a 41% yield (102 mg) using the FiberCat 1007, as a yellow thick oil; R_f = 0.54 (ethyl acetate:petroleum ether; 1:3). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 2.23–2.29 (m, 1H, CH_2), 2.51–2.61 (m, 3H, CH_2), 3.67 (d, ^2J = 13.3 Hz, 1H, CH_2N), 4.41 (dd, ^3J = 7.6 Hz, ^3J = 5.7 Hz, 1H, CH), 4.90 (d, ^2J = 13.3 Hz, 1H, CH_2N), 7.39–7.54 (m, 8H, Ar). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ = 21.9 (CH_2), 31.7 (CH_2), 44.2 (CH_2N), 57.5 (CH), 124.4 (CH, Ar), 128.3 (CH, Ar), 128.5 (CH, Ar), 128.6 (CH, Ar), 128.7 (CH, Ar), 129.0 (CH, Ar), 129.3 (CH, Ar), 129.5 (CH, Ar), 133.1 (C, Ar), 134.1 (C, Ar), 140.5 (C, Ar), 140.6 (C, Ar), 172.4 (C=O). HRMS ESI-TOF: *m*/*z* = 250.1226 $[M + H]^+$ (250.1229 calculated for $C_{17}H_{16}NO$).

Supplementary Materials: The following are available online, Figure S1: ^{1}H-NMR spectrum of **3**; Figure S2: ^{13}C-NMR spectrum of **3**; Figure S3: HSQC ^{1}H-^{13}C spectrum of **3**; Figure S4: HMBC ^{1}H-^{13}C spectrum of **3**; Figure S5: ^{1}H-NMR spectrum of **4**; Figure S6: ^{13}C-NMR spectrum of **4**; Figure S7: COSY ^{1}H-^{1}H spectrum of **4**; Figure S8: HSQC ^{1}H-^{13}C spectrum of **4**; Figure S9: HMBC ^{1}H-^{13}C spectrum of **4**; Figure S10: ^{1}H-NMR spectrum of **1**; Figure S11: ^{13}C-NMR spectrum of **1**; Figure S12–S15: GC/MS data of mass spectrometry.

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O.A.I., A.O.C. and I.Y.B.; data curation, O.A.I. and I.V.T.; writing—original draft preparation, O.A.I. and I.V.T.; writing—review and editing, O.A.I. and I.V.T.; supervision, O.A.I. and I.V.T.; project administration, A.O.C.; funding acquisition, A.O.C.

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