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Azide Tripodal Dendrons from Behera's Amine and Their Clicked Dendrimers

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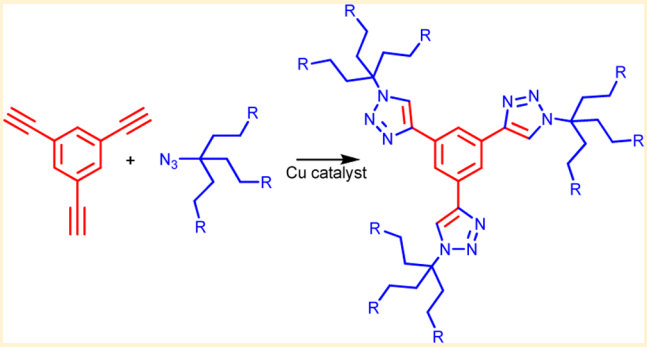
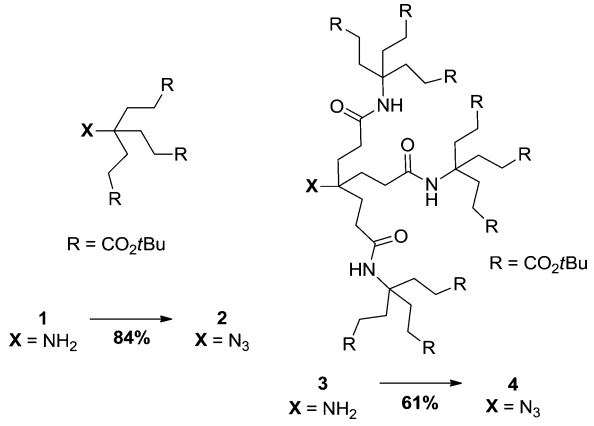
Supporting Information

ABSTRACT: Diazo transfer reactions on Behera's amine and its next-generation analogue formed G0 and G1 azide dendrons bearing three and nine *tert*-butyl-protected esters, respectively. The utility of the new dendrons was demonstrated by copper-catalyzed azide−alkyne cycloaddition, with 1,3,5-triethynylbenzene, forming two novel dendrimers in a convergent manner. Acid-mediated dendrimer deprotection was successful, and the resulting carboxy-terminated dendrimers were analyzed by NMR and DOSY experiments.



Dendrimers find ever-increasing applications in sensing, catalysis, molecular electronics, photonics, and nanomedicine.[1] Dendrimers are attractive sources of nanomaterials with predictable size, shape, and function because they can be synthesized in a controlled fashion. Generally, dendrimers are made via either a convergent or divergent approach that builds up the dendrimer from smaller components. The convergent method allows for addition of presynthesized dendrons to a core resulting in a well-defined, symmetric dendrimer after a relatively straightforward purification. Behera's amine[2] (**1**, Scheme 1) is a unique source of further branching that can be used during dendrimer synthesis and is commercially available with the three carboxylic acids protected by *tert*-butyl esters. Removal of the *tert*-butyl groups is facile and allows for further coupling to various types of branching and/or peripheral groups. Coupling Behera's amine to relatively simple benzenecarboxylic acid cores gives a series of efficiently synthesized dendrimers.[3]

Scheme 1. Behera's Amine (1) and Synthesis of the Azide-Bearing G0 and G1 Dendrons 2 and 4



Copper-catalyzed azide alkyne cycloaddition (CuAAC) is a robust coupling reaction that forms a 1,2,3-triazole linker used in various areas of research.[4] The triazole linker is comparable to a peptide bond electronically.[5] CuAAC reactions are a relatively facile method to couple dendrimer components to reach high-yielding product.[6,7] The mild reactions conditions and tolerance of different functionalities and lack of byproducts make CuAAC an attractive synthetic method to build dendrimers and dendritic polymaterials.[8] Combining the branching capability of Behera's amine with CuAAC could lead to more efficient and controlled synthesis of dendrimers. There are examples of azide-bearing dendrons[6,9] as well as alkyne-bearing dendrons[10] for clicking to an alkyne or azide core, respectively. Behera's amine can be coupled by an amide group to an alkyne-bearing linker allowing CuAAC coupling to the resulting azide-bearing core or branch,[11] but to our surprise, until this report we have neither seen reports of the simplest azide analogs of Behera's amine (**2**, **4**, Scheme 1), nor subsequent CuAAC for synthesis of dendrimers such as **5** or **6**, Scheme 2. Subsequent to starting our work, a patent[12] reported acylating Behera's amine with 5-azidopentanoic acid to enable CuAAC chemistry, but we wanted to avoid the added atoms and flexibility of a pentanoic linker and study **2**, **4**, **5**, and

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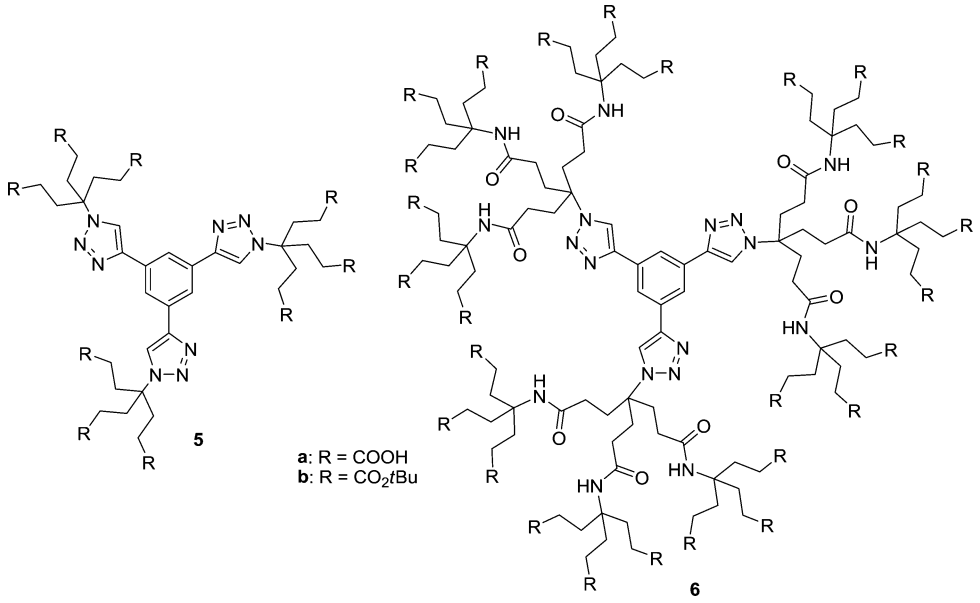
Scheme 2. G0 (5a) and G1 (6a) Dendrimers and Their *tert*-Butyl-Protected Precursors 5b and 6b



6. Here, we report the synthesis of two dendrimers **5** and **6** (Scheme 2) using click chemistry to couple azide-bearing dendrons to an alkyne core. The dendrimers were characterized by NMR and diffusion-ordered NMR spectroscopy (DOSY) to verify expected sizes.

In this work, the focal point of our dendrons is the azide functional group which is made from an amine−azide conversion. Generally, an azide group is introduced by a nucleophilic displacement of a leaving group with an azide anion, but we wanted to place an azide on tertiary carbons and S_N2 displacement would not be possible. Therefore, Cu^{II}-catalyzed conversion of a primary amine to an azide using a diazo-transfer reagent was attempted. Because of the explosive nature of TfN_3, in 2007, Goddard-Borger et al.[13] developed a one-pot synthesis of a cheaper, safer, more robust diazo-transfer reagent, imidazolyl-1-sulfuryl azide hydrochloride. The reported reagent was less expensive and more stable than TfN_3 and gave good yields with high purity without the need of chromatography.[14] We followed the literature procedure to make imidazolyl-1-sulfuryl azide hydrochloride, which was used to convert amine dendrons **1** and **3** to their azide analogues **2** and **4**.

The conditions used for the diazo-transfer reaction were 5 mol % of $CuSO_4{\cdot}5H_2O$ as the copper catalyst and K_2CO_3 as the base. The reaction was monitored by TLC, but the product spot could neither be visualized with UV light nor iodine stain. Hanessian stain was used to visualize the azide product giving a blue-colored spot on developed silica TLC plates. The G0-amine (Behera's amine) **1** was converted to the corresponding G0-azide **2** as colorless oil in 84% yield at room temperature in 45 min. A similar method was used for conversion of G1-amine to G1-azide. The catalyst amounts used were similar, but for the formation of the G1-azide dendron, the reaction time was increased to 4 h. Purification by chromatography gave **4** in 61% yield as a white solid. In the IR spectrum, a strong absorption at 2100 and 2102 cm^{-1} was observed corresponding to the N_3 stretch vibration for G0-azide **2** and G1-azide **4**, respectively. The syntheses of the dendrimers were carried out using click chemistry between 1,3,5-triethynylbenzene and 3 mol of the azide-bearing dendrons, a convergent methodology which results in the inward growth of the dendrimer in a stepwise fashion. The core alkyne unit, 1,3,5-triethynylbenzene, was synthesized following literature protocols.[15]

A model reaction was performed to evaluate the efficiency of the click reaction between the azide functionalized dendron **2** and core triyne **7** using $CuSO_4{\cdot}5H_2O$ (15 mol %) as the copper source and sodium ascorbate (30 mol %) as the reducing agent. Several reaction conditions were carried out on small scale with different catalyst loadings, temperatures, solvents (THF, DCM, cyclohexane, cyclooctane, dioxane), and duration to find the optimal reaction conditions. Room temperature even after 3 days was insufficient, whereas heating at 70 °C for 3 days was effective. Among the solvents used, cyclohexane was chosen on the basis of the solubility of the starting material and qualitative yield given by NMR. The differences in yields and rates were modest considering the wide range of solvent polarities used (alkane vs alcohol−water). Similar insensitivity of click reaction rates has been by others.[16]

The ester-protected G0-dendrimer **5b** was obtained pure after SiO_2 column chromatography in 56% yield and the structure determined by ^1H, ^{13}C, and 2D $^1H-^{13}C$ correlation spectroscopy. The triazole C−H proton appears at δ 8.33 ppm. The nine carboxylic acid groups on the periphery were obtained by acid-catalyzed deprotection of the *tert*-butyl groups on the G0-dendrimer giving compound **5a**. The reaction was performed with formic acid, and the conversion was monitored by ^1H NMR spectroscopy looking for disappearance of the *tert*-butyl protons in the low-frequency region. The successful acid-mediated deprotection is significant since the triazole rings are basic enough that some protonation by formic acid could be expected. This could have resulted in isolation of product as a formate salt as well as in unwanted dendrimer fragmentation by S_N1 or E1 reactions at the tertiary branching carbons. However, no evidence for these unwanted reactions was seen. After the conditions for making the G0 dendrimer were optimized, similar conditions were applied to the synthesis of the G1 dendrimer **6b**. The solvent used here was cyclooctane, and the reaction was monitored by ^1H NMR spectroscopy looking for the triazole C−H proton of the final product which appears at δ 8.32 ppm. White solid product **6b** was isolated in 67% yield

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after column chromatography. Deprotection using formic acid gave **6a** in 100% yield with 27 carboxylic acid groups on the periphery. The disappearance of the *tert*-butyl protons in the low-frequency region confirmed the formation of the G1-dendrimer **6a**.

The DOSY experiments were carried out to calculate[17] the hydrodynamic radii of **5a** and **6a** in D_2O solvent, giving values of 0.98 ± 0.02 and 1.64 ± 0.12 nm, respectively. Significantly, the DOSY data were consistent with the radii calculated for the two dendrimers (0.9 nm for **5a** and 1.5 nm for **6a**) based on MMFF94 minimization calculations and van der Waals radii in ChemBio3D Ultra.

In summary, we report (a) the synthesis of the two novel azide-bearing dendrons (G0-azide and G1-azide) which were made in good yield and high purity using the diazotransfer reagent imidazolyl-1-sulfonyl azide hydrochloride, (b) the synthesis of both *tert*-butyl ester protected and free carboxylic acid forms of the corresponding G0-dendrimer and G1 dendrimer, and (c) determination of dendrimer radii experimentally and computationally, with good agreement. The new azide analogues of Behera's amine are expected to be useful for adding further uniform branching in making other dendrimers.

EXPERIMENTAL SECTION

All reactions were performed using commercially available reagents and solvents from the manufacturer without further purification. Unless otherwise stated, all reactions were performed in air. Column chromatography and TLC were performed on silica gel using UV light and/or indicated stains to visualize the products.. ^1H and ^{13}C NMR spectra were measured in the indicated deuterated solvent at 30 °C on a 600 MHz spectrometer. Chemical shifts are reported in ppm downfield and upfield from tetramethylsilane and referenced to solvent resonances (^1H NMR: δ 7.27 for $CDCl_3$, δ 2.50 for $(CD_3)(CHD_2)SO$, and ^{13}C NMR: δ 77.02 for $CDCl_3$, δ 39.51 for $(CD_3)_2SO$. ^1H NMR signals are given followed by multiplicity, coupling constants J in hertz, integration in parentheses. IR spectra were obtained at ambient temperature.

Synthesis of Compound 2. A 100 mL round-bottom flask was charged with Behera's amine **1** (3.013 g, 7.250 mmol), K_2CO_3 (1.700 g, 12.300 mmol), and $CuSO_4{\cdot}5H_2O$ (106.7 mg, 0.427 mmol), methanol (40 mL) was added, and the resulting mixture was stirred. To the resulting blue mixture was added imidazole-1-sulfonyl azide hydrochloride (1.813 g, 8.733 mmol) and the mixture stirred at room temperature for 45 min, by which time it had turned green. Reaction progress was monitored by TLC (**1** R_f value = 0.4, **2** R_f value = 0.6, solvent system = 30% ethyl acetate/hexanes, Hanessian stain used to develop the azide spot). The resulting green mixture was concentrated to remove methanol, diluted with H_2O (50 mL), acidified with concentrated NaH_2PO_4 solution until pH = 4, and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over magnesium sulfate and filtered, and the filtrate was concentrated in vacuo. The crude product thus obtained was purified by column chromatography (silica gel, 30−45% ethyl acetate/hexane) to obtain the product (2.676 g, 6.060 mmol, 84%) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.25−2.32 (m, 6 H), 1.78−1.84 (m, 6 H), 1.45 (s, 27 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.9, 80.7, 64.5, 31.1, 29.9, 28.0. IR (KBr): 2978, 2934, 2100, 1731, 1456, 1421, 1392, 1367, 1315, 1256, 1153, 1081, 849 cm^{-1}. Anal. Calcd for $C_{22}H_{39}N_3O_6$ (441.56): C, 59.84; H, 8.90; N, 9.52. Found: C, 59.84; H, 8.60; N, 9.78.

Synthesis of Compound 4. A 250 mL round-bottom flask was charged with G1-amine **3** (1.038 g, 0.720 mmol, 1.0 equiv), K_2CO_3 (182.0 mg, 1.316 mmol, 1.82 equiv), and $CuSO_4{\cdot}5H_2O$ (18.3 mg, 0.073 mmol, 0.1 equiv), methanol (25.0 mL) was added, and the mixture was stirred. To the resulting blue mixture was added imidazole-1-sulfonyl azide hydrochloride (182.1 mg, 1.307 mmol, 1.20 equiv), and the mixture stirred at room temperature for 4 h, by which time it had turned green. Reaction progress was monitored by TLC (**3** R_f value = 0.3, **4** R_f value = 0.6, solvent system = 5% methanol/dichloromethane, iodine stain used to develop the azide spot). The resulting green mixture was concentrated to remove methanol, diluted with H_2O (100 mL), acidified with concentrated NaH_2PO_4 solution until pH = 4, and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over magnesium sulfate and filtered and the filtrate concentrated in vacuo. The crude product thus obtained was purified by column chromatography (silica gel, 0−2% methanol/dichloromethane) to obtain the product (0.640 g, 0.436 mmol, 61%) as a fluffy white solid. Mp: 179−181 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 6.14 (s, 3 H), 2.12−2.28 (m, 24 H), 1.90−2.00 (m, 18 H), 1.77−1.86 (m, 6 H), 1.42 (s, 81 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.8, 171.5, 80.6, 64.8, 57.6, 31.9, 31.4, 29.9, 29.8, 28.1. IR (KBr): 3354, 2979, 2102, 1734, 1652, 1393, 1367, 1257, 1156, 1101, 957, 849, 758 cm^{-1}. MS (MALDI-TOF, m/z): calcd for $C_{76}H_{132}N_6O_{21}$ $[M + H]^+$ 1466, $[M + Na]^+$ 1488, found 1467 $[M + H]^+$, 1489 $[M + Na]^+$. Anal. Calcd for $C_{76}H_{132}N_6O_{21}$ (1465.89): C, 62.27; H, 9.08; N, 5.73. Found: C, 62.04; H, 8.88; N, 5.85.

Synthesis of Compound 5b. To a vial were added 1,3,5-triethynylbenzene (11.9 mg, 0.070 mmol), G0-azide **2** (93.3 mg, 0.211 mmol, 3.0 equiv), sodium ascorbate (42.6 mg, 0.215 mmol, 300 mol %), $Cu(OAc)_2{\cdot}H_2O$ (8.00 mg, 0.040 mmol, 60 mol %), and cyclohexane (0.2 mL), and the mixture was heated at 70 °C for 24 h. The reaction progress was monitored by TLC (R_f value = 0.5, solvent system = 30% ethyl acetate/hexane). The reaction mixture was diluted with dichloromethane and concentrated, resulting in a crude dark yellow solid. The crude product thus obtained was purified by column chromatography (silica gel, 30% ethyl acetate/hexane) to obtain the product (66.0 mg, 0.044 mmol, 56%) as a white solid. Mp: 73−75 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.33 (s, 3 H), 8.04 (s, 3 H), 2.33−2.36 (m, 18 H), 2.15−2.17 (m, 18 H), 1.43 (s, 81 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.5, 146.7, 131.8, 122.3, 118.5, 80.6, 65.8, 31.8, 29.4, 28.0. MS (MALDI-TOF, m/z): calcd for $C_{78}H_{123}N_9O_{18}$ $[M + H]^+$ 1475, $[M + Na]^+$ 1497, found 1476 $[M + H]^+$, 1498 $[M + Na]^+$. Anal. Calcd for $C_{78}H_{123}N_9O_{18}$ (1474.86): C, 63.52; H, 8.41; N, 8.55. Found: C, 63.56; H, 8.56; N, 8.90.

Synthesis of Compound 6b. To a microwave vial were added 1,3,5-triethynylbenzene (10.4 mg, 0.069 mmol), G1-azide **4** (292.5 mg, 0.199 mmol, 2.89 equiv), sodium ascorbate (41.7 mg, 0.210 mmol, 305 mol %), $Cu(OAc)_2{\cdot}H_2O$ (8.9 mg, 0.044 mmol, 65 mol %), and cyclohexane (0.4 mL), and the mixture was heated at 70 °C for 24 h. The reaction progress was monitored by ^1H NMR spectroscopy and TLC (solvent system = 3% methanol/dichloromethane). The diclicked and the triclicked product spots are observed on TLC (R_f value of the diclicked intermediate = 0.5, R_f value of the triclicked product **6b** = 0.3). To the reaction mixture was added cyclohexane (0.4 mL), and heating was continued at 70 °C for 6 days until the reaction was complete as monitored by ^1H NMR spectroscopy (triazole *CH* peak at 8.20 ppm) and TLC. The color of the reaction mixture was dark yellow. The reaction mixture was diluted with dichloromethane and concentrated, resulting in crude dark yellow solid. The crude product thus obtained was purified by column chromatography (silica gel, 0−3% methanol/dichloromethane) to obtain the product (213 mg, 0.046 mmol, 67%) as a white solid. Mp: 59−61 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.32 (s, 3 H), 8.13 (s, 3 H), 6.13 (s, 9 H), 2.32−2.42 (m, 18 H), 2.14−2.24 (m, 54 H), 2.04−2.12 (m, 18 H), 1.90−2.00 (m, 54 H), 1.41 (s, 243 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.6, 171.2, 146.9, 131.8, 122.5, 118.4, 80.49, 66.37, 57.6, 32.8, 31.1, 29.9, 29.8, 28.1. MS (MALDI-TOF, m/z): calcd for $C_{240}H_{402}N_{18}O_{63}$ $[M + H]^+$ 4532, found 4532 $[M + H]^+$. Anal. Calcd for $C_{240}H_{402}N_{18}O_{63}$ (4547.84): C, 63.38; H, 8.91; N, 5.54. Found: C, 62.90; H, 8.77; N, 5.46.

Synthesis of Compound 5a. In a scintillation vial, **5b** (32 mg, 0.021 mmol) was dissolved in dichloromethane (0.3 mL) to which was added formic acid (1 mL). The reaction mixture was stirred overnight. An aliquot was removed from the reaction mixture to check for completion by ^1H NMR spectroscopy. The reaction mixture was kept under reduced pressure to remove excess formic acid. To the oily

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white solid thus obtained was added diethyl ether (1 mL), and the solvent was evaporated in vacuo. This procedure was done three times, pentane was added (2 mL), and the residue was kept under high vacuum overnight. White solid **5a** was obtained (21 mg, 0.021 mmol, 100%). Mp: 220−222 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.90 (s, 3 H), 8.39 (s, 3 H), 2.22−2.40 (m, 18 H), 2.05−2.18 (m, 18 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 173.7, 145.9, 132.0, 121.5, 120.6, 65.8, 31.1, 27.9. HRMS (ESI-TOF, m/z): calcd for $C_{42}H_{51}N_9O_{18}$ $[M + H]^+$ 970.3425, found 970.3426 $[M + H]^+$. Anal. Calcd for $C_{42}H_{51}N_9O_{18}$ (969.90): C, 52.01; H, 5.30; N, 13.00. Found: C, 53.04; H, 6.42; N, 12.81.

Synthesis of Compound 6a. In a scintillation vial, **6b** (118 mg, 0.021 mmol) was dissolved in dichloromethane (0.3 mL) to which was added formic acid (1 mL). The reaction mixture was stirred overnight. An aliquot was removed from the reaction mixture to check for completion by ^{1}H NMR spectroscopy. The reaction mixture was kept under reduced pressure to remove excess formic acid. To the oily white solid obtained was added diethyl ether (1 mL), and the solvent was evaporated in vacuo. This procedure was done three times, pentane was added (2 mL), and the residue was kept under high vacuum overnight to remove the solvent resulting in a white solid (79 mg, 0.026 mmol, 100%). Mp: 178−180 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.82 (s, 3 H), 8.42 (s, 3 H), 7.26 (s, 9 H), 2.16−2.26 (m, 18 H), 2.05−2.15 (m, 54 H), 1.94−2.03 (m, 18 H), 1.74−1.90 (m, 54 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 174.4, 171.1, 145.9, 132.1, 121.4, 120.2, 66.1, 56.5, 32.4, 29.7, 29.1, 28.2. MS (MALDI-TOF, m/z): calcd for $C_{132}H_{186}N_{18}O_{63}$ $[M + H]^+$ 3032, $[M + Na]^+$ 3054, found 3034 $[M + H]^+$, 3056 $[M + Na]^+$. HRMS (ESI-TOF) m/z: calcd for $C_{132}H_{186}N_{18}O_{63}$ $[M + 2H]^{2+}$ 1516.6025, found 1516.6017. Anal. Calcd for $C_{132}H_{186}N_{18}O_{63}$ (3032.97): C, 52.27; H, 6.18; N, 8.31. Found: C, 51.37; H, 7.04; N, 7.70.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00859.

^{1}H and ^{13}C NMR and HRMS spectra, and DOSY calculations (PDF)

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Notes

The authors declare no competing financial interest.

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