JOC The Journal of Organic Chemistry

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Potassium *tert*-Butoxide-Catalyzed Synthesis of Benzofuroazepines via Cyclization of (2-Alkynylbenzyl)oxy Nitriles

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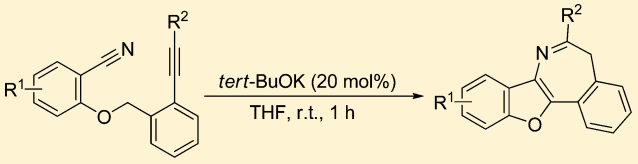
Supporting Information

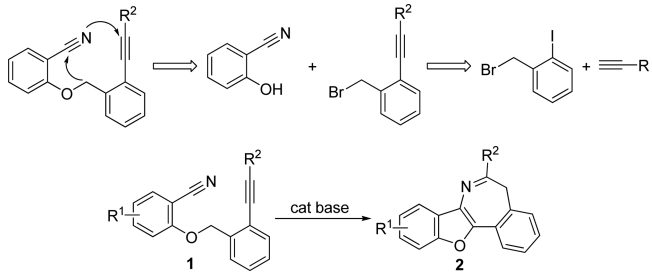
ABSTRACT: Herein, we report that potassium *tert*-butoxide-catalyzed intramolecular anionic cyclization of (2-alkynylbenzyl)-oxy nitriles has been developed for the preparation of substituted benzofuroazepines. The effects of solvent, base, temperature, reaction time, and amount of base on the efficiency of cyclization reaction was investigated. The results led us to conclude that the reactions can be carried out simply by the addition of a catalytic amount of potassium *tert*-butoxide (20 mol %) to a solution of (2-alkynylbenzyl)oxy nitriles in tetrahydrofuran at room temperature in a short reaction time. The reaction proceeded selectively through a sequential intramolecular 5-*exo*-*dig* mode followed by a 7-*endo*-*dig* mode to give the benzofuroazepines via formation of two new carbon−carbon bonds in a one-pot procedure.



INTRODUCTION

The benzodiazepine skeleton, consisting of benzene fused to a seven-membered diazepine ring, is an important class of *N*-heterocyclic compounds that possess important biological properties, such as anxiolytic, amnesic, hypnotic, and anticonvulsant and can function as a skeletal muscle relaxant and sedative.[1] Their actions are mediated by binding to γ-aminobutyric acid (GABA) receptors, increasing GABA affinity and its effects.[2] Their great pharmacological application is exemplified by the commercial success of drugs, such as diazepam, flurazepam, clorazepate, triazolam, midazolam, oxazepam, chlordiazepoxide, alprazolam, temazepam, lorazepam, bromazepam, estazolam, clonazepam, and others. However, the benzodiazepines can produce several types of adverse reactions including drowsiness, sedation, dizziness, loss of balance, confusion, disorientation, amnesia, breathing difficulties, depression, and hypersensitivity.[3] Since their discovery by Sternbach in 1955,[4] the synthesis of benzodiazepines has attracted a great deal of attention, and several protocols have been developed to access these seven-membered heterocycles with high activity and fewer adverse effects. Thus, a number of very efficient methods including condensation, palladium-mediated carbonylation reactions, reduction/lactamization sequence, electrophilic aromatic substitution, palladium-catalyzed carbon−nitrogen bond formation, and amination of aryl halides have been developed for the synthesis of benzodiazepines.[5] Inter- or intramolecular sequential reactions have recently attracted much attention owing to their facile access to polysubstituted heterocycles.[6] Even though intramolecular sequential reactions have been reported as an attractive possibility for the preparation of benzodiazepine derivatives,[7] there is still a demand for developing base-catalyzed intramolecular cyclization that allows for their construction. In this study, we expected that the generation of a carbanion at an appropriate distance to the nitrile and alkyne groups might provide the benzofuroazepine through a base-promoted double-annulation sequence (Scheme 1). Base-promoted anionic annulations of unsaturated substrates have been developed previously, becoming a powerful synthetic route for the construction of carbo- and heterocycles.[8] Some general methods include the intramolecular cyclization of 2-alkynylphenyl benzoylmethyl ethers as well as 2-allylphenyl benzoylmethyl ethers or 2,3-oxopropenyl propargyl ethers.[9] Other approaches involve the cyclization of unsymmetrical bispropargyl ethers, using benzyltrimethylammonium hydroxide (120 mol %) in DMSO, to give naphthofurans via an anionic intramolecular Diels−Alder process.[10] In addition, efficient procedures for the cyclization of bispropargyl ethers involving stoichiometric amounts of *t*-BuOK were also described.[11] Herein, we report the synthesis of benzofuroazepines **2** from (2-alkynylbenzyl)oxy nitriles **1** via a base-catalyzed intramolecular cyclization reaction (Scheme 1).

Scheme 1



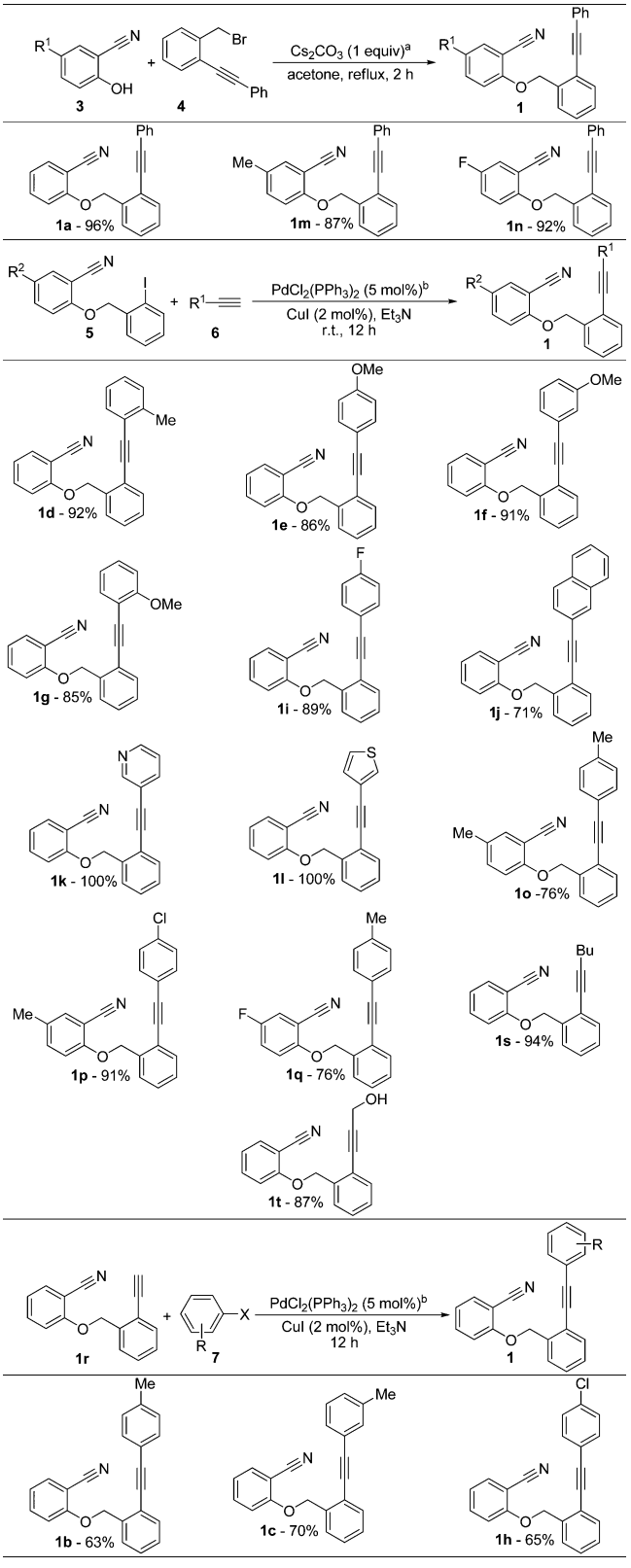
RESULTS AND DISCUSSION

Our studies began with the preparation of the (2-alkynylbenzyl)-oxy nitriles **1** following the routes shown in Table 1. For the

Received: August 13, 2015
Published: September 23, 2015

DOI: 10.1021/acs.joc.5b01884
J. Org. Chem. 2015, 80, 10278−10287

Table 1. Synthesis of (2-Alkynylbenzyl)oxy Nitriles 1

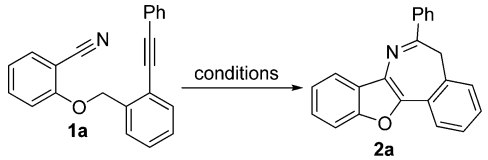


[a]The reaction was performed by the addition of benzyl bromide (1.1 equiv), at room temperature, to a solution of 2-hydroxybenzonitrile (2 mmol), Cs_2CO_3 (1.0 equiv) in acetone (10 mL). [b]The reaction was performed by addition of aryl iodide (2 mmol) and terminal alkyne (2.5 equiv) to a solution containing $PdCl_2(PPh_3)_2$ (5 mol %) and Et_3N (10 mL). After 5 min, the CuI (2 mol %) was added, and the reaction mixture was allowed to stir at room temperature for 12 h.

(2-alkynylbenzyl)oxy nitriles **1a,m,n**, the reaction of phenol derivatives **3** with propargyl bromides **4** in the presence of Cs_2CO_3 in acetone at reflux for 2 h[12] was the most efficient route (Table 1, entries 1−3). The Sonogashira reaction of the corresponding benzyloxy nitriles **5** with terminal alkynes **6** in the presence of a catalytic amount of palladium salt in triethylamine at room temperature for 12 h proceeded to give (2-alkynylbenzyl)oxy nitriles **1d−g,i−l,o−q,s,t** in 71−100% yields (Table 1, entries 4−16). For preparation of required (2-alkynylbenzyl)oxy nitriles **1b,c,h**, we chose the Sonogashira reaction of benzyloxy nitrile **1e** with aryl halides **7** (Table 1, entries 17−19). As shown in Table 1, the formation of (2-alkynylbenzyl)oxy nitriles **1** was efficient in all cases, giving the products in high yields.

We started our investigation by studying the variable parameters such as solvent, the choice of base, amount of base, temperature, and reaction time that could affect the cyclization of (2-alkynylbenzyl)oxy nitrile **1a**. On the reaction of **1a** (0.25 mmol) with *t*-BuOK (2.0 equiv) in DMSO (4.0 mL) at room temperature for 1 h, benzofuroazepine **2a** was obtained in 68% yield (Table 2, entry 1). Under the same conditions, the reaction carried out in THF, CH_3CN, dioxane, and DMF also afforded **2a** in good yields (Table 2, entries 2−5). By comparison,

Table 2. Effect of Different Reaction Parameters on the Preparation of Benzofuroazepine 2a[a]



entry	base (equiv)	solvent	time (h)	yield (%)
1	*t*-BuOK (2.0)	DMSO	1	68
2	*t*-BuOK (2.0)	THF	1	74
3	*t*-BuOK (2.0)	CH_3CN	1	68
4	*t*-BuOK (2.0)	dioxane	1	74
5	*t*-BuOK (2.0)	DMF	1	65
6	*t*-BuOK (2.0)	toluene	48	19
7	*t*-BuOK (2.0)	hexane	24	*b*
8	*t*-BuOK (2.0)	CH_2Cl_2	24	*b*
9	*t*-BuOK (2.0)	Et_2O	24	*b*
10	KOH (2.0)	THF	24	*b*
11	NaH (2.0)	THF	24	*b*
12	Cs_2CO_3 (2.0)	THF	24	*b*
13	K_2CO_3 (2.0)	THF	24	*b*
14	DBU (2.0)	THF	24	*b*
15	*t*-BuOK (2.0)	THF	3	76[c]
16	*t*-BuOK (2.0)	THF	1	78[d]
17	*t*-BuOK (2.5)	THF	1	74
18	*t*-BuOK (1.5)	THF	1	70
19	*t*-BuOK (1.0)	THF	1	72
20	*t*-BuOK (0.5)	THF	1	71
21	*t*-BuOK (0.2)	THF	1	81[e]
22	*t*-BuOK (0.2)	THF	1	82[e,f]
23	*t*-BuOK (0.2)	THF	1	77[e,g]

[a]The reaction was performed in the presence of **1a** (0.25 mmol) and base in solvent (2 mL) under an argon atmosphere at room temperature for the time indicated. [b]Product **2a** was not formed. [c]The reaction was performed at 0 °C. [d]The reaction was performed at 65 °C. [e]The reaction was performed with **1a** (0.5 mmol). [f]The reaction was performed with THF (2 mL). [g]The reaction was performed with THF (1 mL).

DOI: 10.1021/acs.joc.5b01884
J. Org. Chem. 2015, 80, 10278−10287

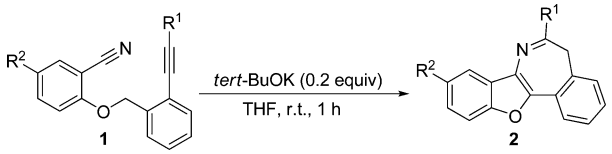
toluene gave **2a** in lower yield, and hexane, CH_2Cl_2, and Et_2O were not suitable solvents for this cyclization reaction (Table 2, entries 6−9). Although good results were observed by using different solvents, owing to some benefits, such as ease of workup and removal, THF was adopted for further studies. When other bases, such as KOH, NaH,Cs_2CO_3, K_2CO_3, and DBU were used, under identical reaction conditions, the starting material **1a** was recovered exclusively (Table 2, entries 10−14). No significant improvement in the yields was observed by either lowering the reaction temperature to 0 °C or increasing to 65 °C (Table 2, entries 15 and 16). On further screening, the base loading was investigated. The increase in the amount of *t*-BuOK to 2.5 equiv did not have a major effect, while the reduction of *t*-BuOK to a catalytic amount (20 mol %) improved the yield of **3a** (Table 2, entries 17−21). In terms of solvent employed, we observed that good yields were still achieved by using 1.0 and 2.0 mL of THF (Table 2, entries 22 and 23). Thus, we concluded that the optimum reaction conditions for this cyclization were the addition of *t*-BuOK (20 mol %) to a solution of (2-alkynylbenzyl)oxy nitrile **1a** (0.5 mmol) in THF (2.0 mL) at room temperature for 1 h.

After having established the optimal reaction conditions for the cyclization of (2-alkynylbenzyl)oxy nitrile **1a**, we investigated the effect of different substituents on the (alkynylbenzyl)oxy nitriles **1a−t** with respect to reactivity under the optimized reaction conditions, and the results are shown in Table 3. First, the substituents on the alkyne terminus were evaluated (Table 3, entries 1−12). A series of (alkynylbenzyl)oxy nitriles (**1a−d**) having an *o*-, *m*-, and *p*-tolyl or anisoyl group showed that reactivity did not significantly depend on the electronic effects of these substituents; however, the yields decreased with the steric bulk of the methyl and methoxyl groups at the *ortho* position (Table 3, entries 1−7). We also found that the presence of electron-deficient aromatic rings directly bonded to alkyne affected the reaction yields. For example, aryl group with a chlorine atom gave superior yields than aryl group with a fluorine atom (Table 3, entries 8 and 9). It could be explained by partial polarization of the acetylene moiety, influenced by the aryl substitution. Inductively, Cl is mildly electron-withdrawing, but when in conjugation, it can participate in the resonance and hence exerts some electron density to the π-system that leads to favorable polarization of the acetylene moiety (Scheme 2). We observed that even with a sterically hindered naphthyl substituent at alkyne, the (2-alkynylbenzyl)oxy nitrile **1j** cyclized under the optimized conditions to afford benzofuroazepine **2j** in good yield (Table 3, entry 10). The introduction of a 3-pyridyl group on the alkyne terminus resulted in a decrease in the yield of the product; however, the presence of a 3-thienyl group at the same position gave the product in 74% yield (Table 3, entries 11 and 12). Thus, pyridine as well as the fluorine atom polarize the acetylene moiety in the opposite direction. Hence, the yield with pyridine (the poorest aromatic system among the substrates used) was modest (for the simplicity, the cyclization arrows from the N-centered anion were omitted) (Scheme 2). Thiophene, an electron-rich heterocycle, also polarizes the acetyle moiety favorably by resonance, whereas the more electronegative fluorine atom inductively pulls out electron density away from the aryl ring and normally does not participate in the resonance (Scheme 2). We next investigated the influence of substituent directly bonded to the aromatic ring containing the nitrile group (Table 3, entries 13−17). In all cases examined, the cyclized products were obtained in similar good yields, indicating that the cyclization was not influenced by the electronic effect of the methyl and fluorine substituents at the aromatic ring. When (2-alkynylbenzyl)oxy nitriles **1r** and **1s** were treated with *t*-BuOK, under optimized reaction conditions, the starting materials were fully consumed; however, the products **2r** and **2s** were not obtained (Table 3, entries 18 and 19). This limitation is probably due to the absence of π bonds next to the alkyne that could hamper the nucleophilic attack at the carbon−carbon triple bond. An additional limitation of the protocol was observed by using substrate **1t**, having a propargyl alcohol attached to the alkyne bond, which did not provide the cyclized product **2t** even under various conditions (Table 3, entry 20).

To further gain additional information about the reaction mechanism, the following experimental data have been obtained in this study. A deuterium-labeling experiment showed that the reaction of **1a** under optimized reaction conditions, and subsequent quenching of the reaction mixture with D_2O, give the benzofuroazepine **2a** in the complete absence of product with the incorporation of deuterium at the C-5 position. This result indicates that the equilibrium *t*-BuOK/*t*-BuOH can play a crucial role in the formation and stabilization of the anionic intermediates through multiple acid−base reactions. This explains why D_2O experiments did not incorporate deuterium in the product (see the mechanism proposal; Scheme 3). Additional evidence for the anionic pathway was obtained from the use of a radical inhibitor as additive. Treatment of (alkynylbenzyl)oxy nitrile **1a** with *t*-BuOK under the optimized reaction conditions in the presence of TEMPO (1.0 equiv) gave the benzofuroazepine **2a** in a yield similar to that in the absence of TEMPO. This result suggests that the radical pathway, via an unstable iminyl radical,[13] could be ruled out. On the basis of these experiments, the mechanism of this reaction is proposed as shown in Scheme 3. Accordingly, the pathway could involve (a) the formation of benzyl anion **I** via abstraction of benzylic hydrogen from **1** by *t*-BuOK; (b) the intramolecular anionic addition to nitrile to give the iminyl anion **II**, via a 5-*exo dig* mode;[14] and (c) nucleophilic attack of the nitrogen atom at the carbon−carbon bonds of alkyne to produce the vinyl anion **III**, via 7-*endo-dig* mode (the *endo*-selectivity is due to the strain effects that generally favor the formation of *endo*-products if the cycle is annealed to a structure where a five-membered ring is already present);[15] and (d) obtention of a proton by the intermediate carbanion **III** either from *t*-BuOH or from **IV** (via intermolecular reaction). Then **IV** upon further deprotonation gives **VI**. The intermediate **VI** would be unstable due to the antiaromatic 8π-electron system and would spontaneously pick up a proton from *t*-BuOH to give product **2**. Alternatively, intermediate **IV** could undergo sigmatropic [1,5] hydride shift to give **2**. This is more likely as anions **V** and **VI** are antiaromatic 8π-electron systems. In the second cyclization step, the 6-*exo-dig* mode competes with the 7-*endo-dig* mode; therefore, a mixture of isoquinolines **11** and benzofuroazepines **2** would be produced (Scheme 3). For stereoelectronic reasons,[16] the nucleophilic attack of nitrogen atom at the carbon−carbon bonds of alkyne produces the vinyl anion **VII**. The protonation/deprotonation sequence gives the cyclized isoquinoline **11** products. In our methodology, except for the reaction of (2-alkynylbenzyl)oxy nitriles **1d** and **1g**, each of which gave traces of isoquinoline derivative, only the product resulting from 7-*endo-dig* cyclization was obtained. According to the Baldwin rules, the influence of steric and electronic effects as well as the stability of the ions could control the high selectivity.[17] The presence of a unique isomer was confirmed by spectral ^{13}C NMR data fromthe crude reaction mixture to avoid error in the detection isomer peaks by

DOI: 10.1021/acs.joc.5b01884
J. Org. Chem. 2015, 80, 10278−10287

Table 3. Synthesis of Benzofuroazepines 2[a]



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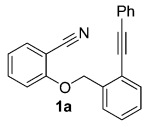
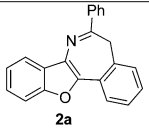
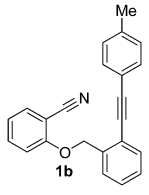
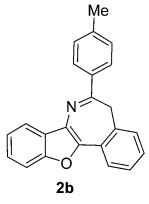
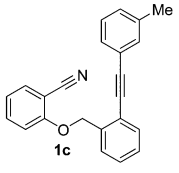
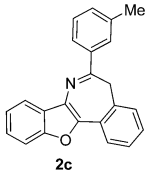
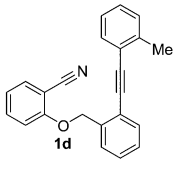
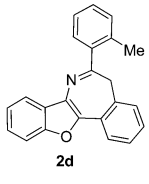
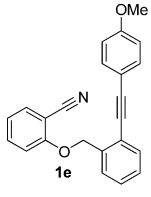
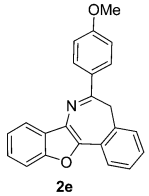
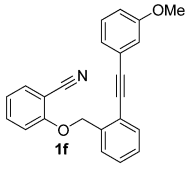
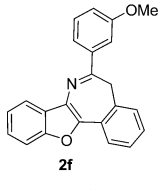
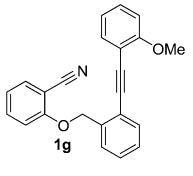
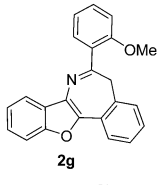
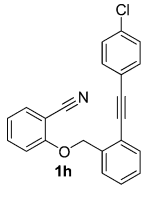
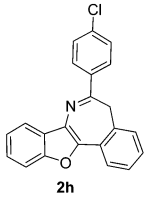
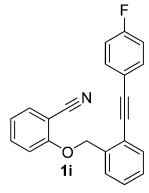
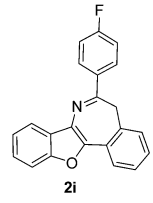
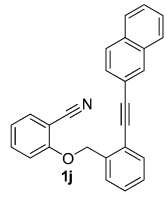
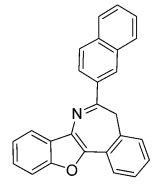
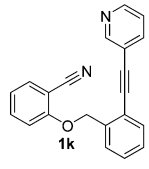
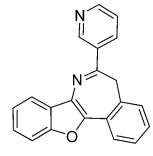
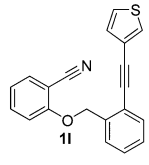
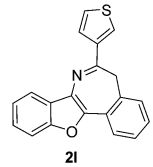
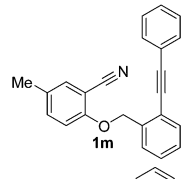
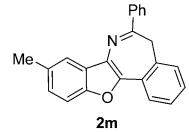
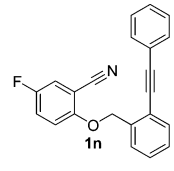
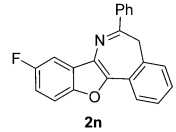
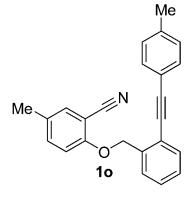
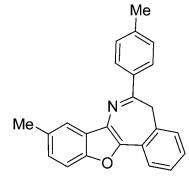
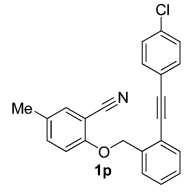
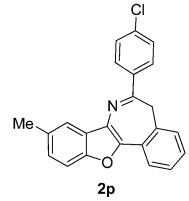
1	 1a	 2a	82
2	 1b	 2b	82
3	 1c	 2c	77
4	 1d	 2d	65[c]
5	 1e	 2e	80
6	 1f	 2f	72
7	 1g	 2g	63[c]
8	 1h	 2h	82
9	 1i	 2i	66
10	 1j	 2j	70
11	 1k	 2k	51
12	 1l	 2l	74
13	 1m	 2m	78
14	 1n	 2n	75
15	 1o	 2o	79
16	 1p	 2p	71

DOI: 10.1021/acs.joc.5b01884
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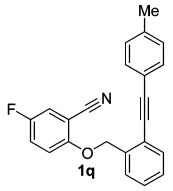
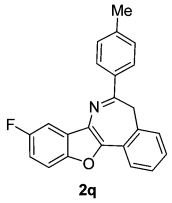
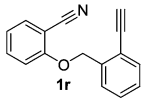
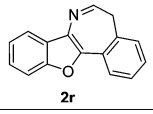
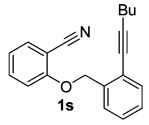
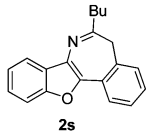
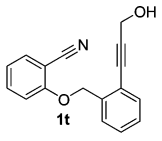
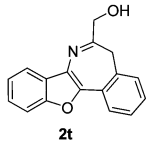
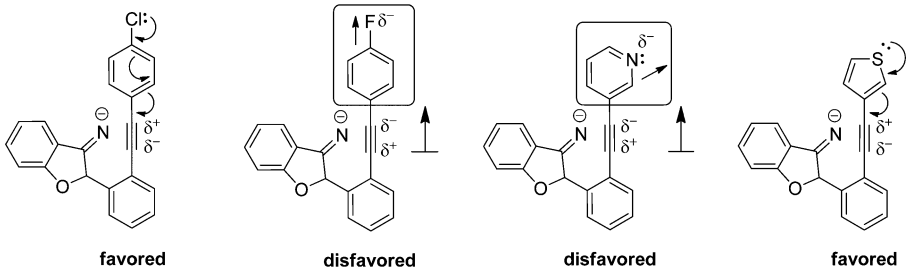
Table 3. continued

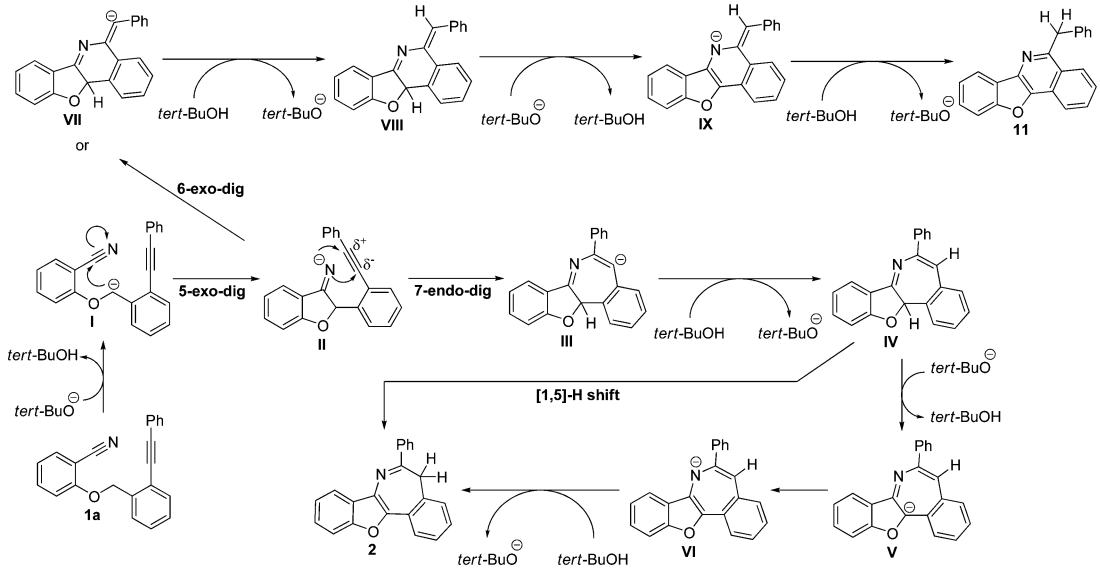
entry	(2-alkynylbenzyl)oxy nitriles 1	benzofuroazepines 2	yield (%)[b]
17	 1q	 2q	72
18	 1r	 2r	-[d]
19	 1s	 2s	-[d]
20	 1t	 2t	-[d]

[a]The reaction was performed in the presence of **1** (0.5 mmol) and *t*-BuOK (20 mol %) in THF (2.0 mL) under an argon atmosphere at room temperature for 1 h. [b]Yields of purified products. [c]Traces of isoquinoline **11** were obtained. [d]The benzofuroazepines **2** were not formed.

Scheme 2



Scheme 3



^{1}H NMR. All compounds were characterized by ^{1}H and ^{13}C NMR, GC/MS, and HR-mass spectra (see the Supporting Information). In addition, the structure of benzofuroazepine **2a** was confirmed by X-ray diffraction analysis (Figure S1, Supporting Information, CCDC 1413101).

CONCLUSION

Starting from a suitable building block, various (2-alkynylbenzyl)-oxy nitriles have been prepared and subjected to intramolecular anionic cyclization catalyzed by *t*-BuOK. This methodology leads to the preparation of substituted benzofuroazepines via two new carbon−carbon bonds formation in an one-pot procedure. The reaction is regioselective, providing the desired benzofuroazepines as a unique regioisomer via a sequential intramolecular 5-*exo-dig* mode followed by a 7-*endo-dig* mode. The simple and easy preparation of (2-alkynylbenzyl)oxy nitriles, the chemo- and regioselectivity of cyclizations, the use of a catalytic amount of *t*-BuOK, and the generality of the reaction sequences make this transformation a powerful tool for constructing various benzofuroazepine derivatives.

DOI: 10.1021/acs.joc.5b01884
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EXPERIMENTAL SECTION

General Procedure for the Preparation of (2-Alkynylbenzyl)-oxy Nitriles Derivatives 1a,m,n. To a two-necked round-bottomed flask equipped with a reflux condenser, under argon atmosphere, containing the appropriate 2-hydroxybenzonitrile (2 mmol), Cs_2CO_3 (1.0 equiv), and acetone (10 mL), was added benzyl bromide (1.1 equiv). The reaction mixture was allowed to stir under reflux for 2 h. After this time, the solution was cooled to room temperature, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel.

*2-[[2-(Phenylethynyl)benzyl]oxy]benzonitrile (**1a**).* Compound **1a** was isolated by column chromatography (eluent 5% EtOAc in hexane) as a white solid. Yield: 0.593 g (96%). Mp: 104−107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64−7.62 (m, 1H), 7.58−7.52 (m, 2H), 7.51−7.43 (m, 3H), 7.39−7.25 (m, 5H), 7.04 (d, J = 8.5 Hz, 1H), 6.98 (td, J = 7.6 Hz, J = 1.0 Hz, 1H), 5.44 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 137.2, 134.3, 133.8, 132.0, 131.5, 128.9, 128.6, 128.4, 127.8, 126.9, 122.8, 121.2, 121.0, 116.3, 112.9, 102.4, 94.9, 86.2, 68.8. MS (EI, 70 eV; m/z (relative intensity): 309 (9), 280 (5), 232 (7), 191 (100), 176 (3), 165 (30), 152 (4). HRMS (ESI-TOF): m/z calcd for $C_{22}H_{16}NO$ $[M + H]^+$ 310.1232, found 310.1236.

*5-Methyl-2-[[2-(phenylethynyl)benzyl]oxy]benzonitrile (**1m**).* Compound **1m** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.562 g (87%). Mp: 103−106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66−7.60 (m, 1H), 7.57−7.53 (m, 1H), 7.52−7.46 (m, 2H), 7.41 (d, J = 7.5 Hz, 1H), 7.39−7.26 (m, 5H), 6.86 (s, 1H), 6.81−6.76 (m, 1H), 5.41 (s, 2H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 145.6, 137.3, 133.4, 132.0, 131.4, 128.8, 128.5, 128.4, 127.8, 127.0, 122.8, 122.0, 121.2, 116.7, 113.6, 99.3, 94.8, 86.3, 68.6, 22.2. MS (EI, 70 eV; m/z (relative intensity): 324 ([M + 1], 1), 323 (8), 294 (6), 246 (8), 191 (100), 165 (39), 115 (4). Anal. Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.68; H, 5.34; N, 4.38.

*5-Fluoro-2-[[2-(phenylethynyl)benzyl]oxy]benzonitrile (**1n**).* Compound **1n** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.601 g (92%). Mp: 96−99 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62−7.47 (m, 5H), 7.41−7.30 (m, 5H), 6.79 (dd, J = 10.4 Hz, J = 2.3 Hz, 1H), 6.71 (ddd, J = 8.5 Hz, J = 7.8 Hz, J = 2.3 Hz, 1H), 5.42 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 166.1 (d, J = 256.0 Hz), 162.1 (d, J = 11.0 Hz), 136.4, 135.3 (d, J = 11.0 Hz), 132.2, 131.5, 128.9, 128.7, 128.4, 128.1, 127.1, 122.6, 121.4, 115.6, 108.6 (d, J = 23.0 Hz), 101.5 (d, J = 27.0 Hz), 98.6 (d, J = 3.0 Hz), 95.1, 86.0, 69.2. MS (EI, 70 eV; m/z (relative intensity): 328 ([M + 1], 2), 327 (8), 298 (3), 250 (5), 191 (100), 165 (34), 115 (4). Anal. Calcd for $C_{22}H_{14}FNO$: C, 80.72; H, 4.31; N, 4.28. Found: C, 80.81; H, 4.38; N, 4.33.

General Procedure for the Preparation of (2-Alkynylbenzyl)-oxy Nitrile Derivatives 1b−l,o−q,s,t. To a two-necked round bottomed flask under argon atmosphere, containing $PdCl_2(PPh_3)_2$ (5 mol %) and Et_3N (10 mL), were added the appropriate aryl iodide (2 mmol) and terminal alkyne (2.5 equiv). The resulting solution was stirred for 5 min at room temperature. After this time, the CuI (2 mol %) was added, and the reaction mixture was allowed to stir at room temperature for 12 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated solution of NH_4Cl (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography on silica gel.

*2-[[2-(p-Tolylethynyl)benzyl]oxy]benzonitrile (**1b**).* Compound **1b** was isolated by column chromatography (eluent 3% EtOAc in hexane) as a white solid. Yield: 0.407 g (63%). Mp: 107−110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62−7.60 (m, 1H), 7.54−7.50 (m, 2H), 7.45 (ddd, J = 8.5 Hz, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.40−7.23 (m, 4H), 7.12 (d, J = 7.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.97 (td, J = 7.5 Hz, J = 1.0 Hz, 1H), 5.42 (s, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 138.8, 137.1, 134.2, 133.7, 131.9, 131.3, 129.1, 128.6, 127.8, 126.8, 121.4, 121.0, 119.7, 116.3, 112.9, 102.4, 95.2, 85.6, 68.8, 21.4. MS (EI, 70 eV; m/z (relative intensity): 323 (13), 205 (100), 190 (35), 178 (5), 165 (13), 90 (6). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1388, found 324.1391.

*2-[[2-(m-Tolylethynyl)benzyl]oxy]benzonitrile (**1c**).* Compound **1c** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.452 g (70%). Mp: 80−83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62−7.60 (m, 1H), 7.56−7.49 (m, 2H), 7.48−7.44 (m, 1H), 7.40−7.09 (m, 6H), 7.04 (d, J = 8.5 Hz, 1H), 6.98 (td, J = 7.5 Hz, J = 1.0 Hz, 1H), 5.44 (s, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.3, 138.1, 137.2, 134.2, 133.8, 132.0 (2C), 129.5, 128.8, 128.6, 128.3, 127.8, 126.9, 122.6, 121.4, 121.0, 116.3, 112.9, 102.5, 95.2, 85.9, 68.9, 21.1. MS (EI, 70 eV; m/z (relative intensity): 323 (13), 294 (7), 232 (11), 205 (100), 190 (64), 178 (16), 165 (20). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1388, found 324.1390.

*2-[[2-(o-Tolylethynyl)benzyl]oxy]benzonitrile (**1d**).* Compound **1d** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a light brown solid. Yield: 0.594 g (92%). Mp: 70−72 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67−7.63 (m, 1H), 7.59−7.53 (m, 2H), 7.50−7.43 (m, 2H), 7.37 (td, J = 7.5 Hz, J = 1.3 Hz, 1H), 7.34−7.13 (m, 4H), 7.04−6.95 (m, 2H), 5.46 (s, 2H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 139.9, 137.0, 134.3, 133.8, 132.1, 131.9, 129.5, 128.8, 128.6, 127.8, 126.8, 125.7, 122.6, 121.4, 121.0, 116.3, 112.7, 102.4, 93.9, 90.1, 68.8, 20.9. MS (EI, 70 eV; m/z (relative intensity): 324 ([M + 1], 4), 323 (19), 294 (4), 232 (3), 205 (100), 190 (44), 178 (31), 165 (20). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1388, found 324.1391.

*2-[[2-[(4-Methoxyphenyl)ethynyl]benzyl]oxy]benzonitrile (**1e**).* Compound **1e** was isolated by column chromatography (eluent 4% EtOAc in hexane) as a beige solid. Yield: 0.583 g (86%). Mp: 104−106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, J = 7.5 Hz, 1H), 7.57−7.20 (m, 7H), 7.06−6.94 (m, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.43 (s, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 159.8, 136.9, 134.3, 133.7, 132.9, 131.8, 128.5, 127.7, 126.8, 121.4, 121.0, 116.4, 114.8, 114.0, 112.8, 102.2, 95.0, 84.9, 68.7, 55.2. MS (EI, 70 eV; m/z (relative intensity): 341 ([M + 2], 4), 340 ([M + 1], 4), 339 (19), 267 (3), 221 (100), 206 (45), 189 (12), 178 (97), 165 (12), 152 (35). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}NO_2$ $[M + H]^+$: 340.1338, found 340.1341.

*2-[[2-[(3-Methoxyphenyl)ethynyl]benzyl]oxy]benzonitrile (**1f**).* Compound **1f** was isolated by column chromatography (eluent 3% EtOAc in hexane) as a light brown solid. Yield: 0.617 g (91%). Mp: 81−83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65−7.61 (m, 1H), 7.57−7.54 (m, 2H), 7.48 (ddd, J = 8.5 Hz, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.37 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.33−7.22 (m, 2H), 7.10−7.06 (m, 1H), 7.05−7.01 (m, 2H), 6.99 (td, J = 7.5 Hz, J = 0.9 Hz, 1H), 6.92−6.88 (m, 1H), 5.44 (s, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 159.4, 137.3, 134.3, 133.8, 132.1, 129.5, 128.9, 127.8, 126.9, 124.0, 123.8, 121.1, 121.0, 116.4, 116.3, 115.0, 112.8, 102.3, 94.8, 86.0, 68.8, 55.3. MS (EI, 70 eV; m/z (relative intensity): 340 ([M + 1], 3), 339 (14), 310 (6), 232 (9), 221 (68), 206 (31), 189 (28), 178 (100), 152 (30). Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.52; H, 5.09; N, 4.16.

*2-[[2-[(2-Methoxyphenyl)ethynyl]benzyl]oxy]benzonitrile (**1g**).* Compound **1g** was isolated by column chromatography (eluent 3% EtOAc in hexane) as a white solid. Yield: 0.576 g (85%). Mp: 85−87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, J = 7.5 Hz, 1H), 7.60−7.52 (m, 2H), 7.48−7.42 (m, 2H), 7.40−7.25 (m, 3H), 7.11 (d, J = 8.5 Hz, 1H), 7.01−6.87 (m, 3H), 5.53 (s, 2H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 160.0, 137.4, 134.2, 133.7, 133.0, 131.6, 130.0, 128.7, 127.6, 126.6, 121.4, 120.9, 120.5, 116.4, 112.9, 112.1, 110.7, 102.3, 91.5, 90.4, 68.6, 55.7. MS (EI, 70 eV; m/z (relative intensity): 340 ([M + 1], 6), 339 (26), 310 (3), 221 (34), 206 (100), 193 (21), 178 (80), 165 (23), 115 (41). Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.58; H, 5.07; N, 4.19.

*2-[[2-[(4-Chlorophenyl)ethynyl]benzyl]oxy]benzonitrile (**1h**).* Compound **1h** was isolated by column chromatography (eluent 3% EtOAc in hexane) as a white solid. Yield: 0.446 g (65%). Mp: 117−120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64−7.61 (m, 1H), 7.58−7.54 (m, 2H), 7.49 (ddd, J = 8.5 Hz, J = 7.5 Hz, J = 1.7 Hz, 1H),

DOI: 10.1021/acs.joc.5b01884
J. Org. Chem. 2015, 80, 10278−10287

7.41−7.37 (m, 3H), 7.34−7.30 (m, 3H), 7.04−6.98 (m, 2H), 5.44 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.3, 137.3, 134.7, 134.3, 133.9, 132.7, 132.2, 129.1, 128.8, 128.0, 127.2, 121.4, 121.2, 121.1, 116.3, 112.9, 102.6, 93.7, 87.3, 69.0. MS (EI, 70 eV; m/z (relative intensity): 345 ([M + 2], 3), 344 ([M + 1], 4), 343 (11), 314 (5), 225 (100), 189 (92), 163 (13), 139 (3). HRMS (ESI-TOF) m/z calcd for $C_{22}H_{15}ClNO$ $[M + H]^+$: 344.0842, found 344.0847.

*2-[[2-[(4-Fluorophenyl)ethynyl]benzyl]oxy]benzonitrile (**1i**).* Compound **1i** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a light brown solid. Yield: 0.582 g (89%). Mp: 110−112 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, J = 7.5 Hz, 1H), 7.57−7.42 (m, 5H), 7.40−7.22 (m, 2H), 7.10−6.95 (m, 4H), 5.42 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 162.6 (d, J = 250.0 Hz), 160.2, 137.1, 134.3, 133.8, 133.3 (d, J = 8.0 Hz), 132.0, 128.9, 127.9, 127.0, 121.0 (2C), 118.8 (d, J = 4.0 Hz), 116.3, 115.7 (d, J = 22.0 Hz), 112.7, 102.3, 93.8, 85.9 (d, J = 1.0 Hz), 68.8. MS (EI, 70 eV; m/z (relative intensity): 327 (9), 298 (7), 232 (6), 209 (100), 183 (43), 163 (6). HRMS (ESI-TOF) m/z calcd for $C_{22}H_{15}FNO$ $[M + H]^+$: 328.1138, found 328.1140.

*2-[[2-(Naphthalen-2-ylethynyl)benzyl]oxy]benzonitrile (**1j**).* Compound **1j** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.509 g (71%). Mp: 119−122 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (s, 1H), 7.84−7.72 (m, 3H), 7.67−7.26 (m, 9H), 7.05 (d, J = 8.6 Hz, 1H), 7.00−6.94 (m, 1H), 5.47 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.2, 137.3, 134.2, 133.8, 132.9, 132.8, 132.1, 131.4, 128.9, 128.1, 127.9, 127.7, 127.0, 126.8, 126.6, 121.2, 121.0, 120.0, 116.3, 112.9, 102.4, 95.3, 86.6, 68.9. MS (EI, 70 eV; m/z (relative intensity): 360 ([M + 1], 1), 359 (13), 281 (3), 241 (100), 226 (13), 189 (2), 163 (3), 119 (21). HRMS (ESI-TOF) m/z calcd for $C_{26}H_{18}NO$ $[M + H]^+$: 360.1388, found 360.1390.

*2-[[2-(Pyridin-3-ylethynyl)benzyl]oxy]benzonitrile (**1k**).* Compound **1k** was isolated by column chromatography (eluent 30% EtOAc in hexane) as a beige solid. Yield: 0.620 g (100%). Mp: 93−96 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.70−8.67 (m, 1H), 8.54 (dd, J = 4.9 Hz, J = 1.7 Hz, 1H), 7.75 (ddd, J = 8.0 Hz, J = 2.2 Hz, J = 1.7 Hz, 1H), 7.66−7.62 (m, 1H), 7.59−7.53 (m, 2H), 7.50 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.40 (td, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.36−7.30 (m, 1H), 7.26 (ddd, J = 8.0 Hz, J = 4.9 Hz, J = 1.0 Hz, 1H), 7.07−7.03 (m, 1H), 7.00 (td, J = 7.5 Hz, J = 1.0 Hz, 1H), 5.41 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.1, 151.9, 148.7, 138.2, 137.3, 134.2, 133.7, 132.2, 129.3, 128.0, 127.2, 123.0, 121.1, 120.6, 119.9, 116.2, 112.7, 102.4, 91.2, 89.5, 68.8. MS (EI, 70 eV; m/z (relative intensity): 311 ([M + 1], 1), 310 (4), 281 (8), 232 (11), 192 (100), 165 (64), 139 (15), 115 (8). HRMS (ESI-TOF) m/z calcd for $C_{21}H_{15}N_2O$ $[M + H]^+$: 311.1184, found 311.1190.

*2-[[2-(Thiophene-3-ylethynyl)benzyl]oxy]benzonitrile (**1l**).* Compound **1l** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a light brown solid. Yield: 0.630 g (100%). Mp: 74−77 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63−7.58 (m, 1H), 7.57−7.50 (m, 2H), 7.49−7.43 (m, 2H), 7.35 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.31−7.26 (m, 2H), 7.14 (dd, J = 4.9 Hz, J = 1.0 Hz, 1H), 7.04−7.00 (m, 1H), 6.98 (td, J = 7.5 Hz, J = 1.0 Hz, 1H), 5.41 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.2, 137.2, 134.2, 133.7, 132.0, 129.6, 128.8, 128.7, 127.8, 127.0, 125.5, 121.8, 121.2, 121.0, 116.3, 112.9, 102.4, 90.0, 85.8, 68.8. MS (EI, 70 eV; m/z (relative intensity): 316 ([M + 1], 1), 315 (6), 286 (7), 197 (100), 165 (32), 152 (32), 139 (6), 115 (2). HRMS (ESI-TOF) m/z calcd for $C_{20}H_{14}NOS$ $[M + H]^+$: 316.0796, found 316.0801.

*5-Methyl-2-[[2-(p-tolylethynyl)benzyl]oxy]benzonitrile (**1o**).* Compound **1o** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.512 g (76%). Mp: 106−107 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66−7.61 (m, 1H), 7.57−7.53 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.36 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.33−7.27 (m, 1H), 7.18−7.13 (m, 2H), 6.88−6.85 (m, 1H), 6.83−6.78 (m, 1H), 5.43 (s, 2H), 2.37 (s, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.3, 145.6, 138.8, 137.3, 133.4, 132.0, 131.4, 129.2, 128.7, 127.8, 127.0, 122.0, 121.4, 119.8, 116.7, 113.6, 99.4, 95.0, 85.7, 68.7, 22.2, 21.5. MS (EI, 70 eV; m/z (relative intensity): 338 ([M + 1], 4), 337 (16), 308 (7), 246 (7), 205 (100), 190 (47), 178 (11), 165 (14). HRMS (ESI-TOF) m/z calcd for $C_{24}H_{20}NO$ $[M + H]^+$: 338.1545, found 338.1549.

*2-[[2-[(4-Chlorophenyl)ethynyl]benzyl]oxy]-5-methylbenzonitrile (**1p**).* Compound **1p** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.649 g (91%). Mp: 119−121 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65−7.60 (m, 1H), 7.58−7.53 (m, 1H), 7.46−7.36 (m, 4H), 7.35−7.29 (m, 3H), 6.86 (s, 1H), 6.83−6.79 (m, 1H), 5.40 (s, 2H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.3, 145.6, 137.4, 134.6, 133.5, 132.7, 132.2, 129.1, 128.8, 128.0, 127.3, 122.1, 121.3, 121.0, 116.7, 113.6, 99.5, 93.6, 87.3, 68.7, 22.3. MS (EI, 70 eV; m/z (relative intensity): 359 ([M + 2], 4), 358 ([M + 1], 8), 357 (13), 328 (10), 246 (11), 225 (100), 189 (95), 163 (9). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{17}ClNO$ $[M + H]^+$: 358.0999, found 358.1002.

*5-Fluoro-2-[[2-(p-tolylethynyl)benzyl]oxy]benzonitrile (**1q**).* Compound **1q** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.518 g (76%). Mp: 127−130 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63−7.52 (m, 3H), 7.43−7.29 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 6.80 (dd, J = 10.4 Hz, J = 2.3 Hz, 1H), 6.72 (ddd, J = 8.6 Hz, J = 8.0 Hz, J = 2.3 Hz, 1H), 5.43 (s, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.2 (d, J = 256.0 Hz), 162.1 (d, J = 11.0 Hz), 139.0, 136.3, 135.3 (d, J = 11.0 Hz), 132.1, 131.4, 129.2, 128.8, 128.1, 127.0, 121.6, 119.6, 115.7 (d, J = 1.0 Hz), 108.6 (d, J = 23.0 Hz), 101.5 (d, J = 26.0 Hz), 98.6 (d, J = 3.0 Hz), 95.4, 85.4, 69.2, 21.5. MS (EI, 70 eV; m/z (relative intensity): 342 ([M + 1], 4), 341 (15), 312 (3), 205 (100), 190 (40), 178 (10), 165 (13), 115 (2). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{17}FNO$ $[M + H]^+$: 342.1294, found 342.1295.

*2-[[2-(Hex-1-ynyl)benzyl]oxy]benzonitrile (**1s**).* Compound **1s** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a light yellow oil. Yield: 0.543 g (94%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59−7.53 (m, 2H), 7.51−7.44 (m, 1H), 7.42 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.30 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.26−7.20 (m, 1H), 7.02−6.95 (m, 2H), 5.36 (s, 2H), 2.46 (t, J = 7.2 Hz, 2H), 1.65−1.42 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.3, 137.0, 134.2, 133.7, 132.0, 128.0, 127.6, 126.7, 122.0, 120.9, 116.4, 112.8, 102.3, 96.3, 77.7, 68.8, 30.8, 22.0, 19.2, 13.5. MS (EI, 70 eV; m/z (relative intensity): 289 (2), 260 (4), 246 (5), 171 (34), 143 (15), 129 (100), 115 (25). HRMS (ESI-TOF) m/z calcd for $C_{20}H_{20}NO$ $[M + H]^+$: 290.1545, found 290.1549.

*2-[[2-(3-Hydroxyprop-1-ynyl)benzyl]oxy]benzonitrile (**1t**).* Compound **1t** was isolated by column chromatography (eluent 20% EtOAc in hexane) as a white solid. Yield: 0.455 g (87%). Mp: 84−86 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59−7.51 (m, 2H), 7.50−7.42 (m, 2H), 7.34 (td, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.28−7.22 (m, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.00−6.94 (m, 1H), 5.33 (s, 2H), 4.52 (s, 2H), 2.50 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.1, 137.3, 134.3, 133.7, 132.4, 128.9, 127.9, 127.2, 121.1, 120.9, 116.6, 113.1, 102.2, 93.1, 82.5, 68.9, 51.4. MS (EI, 70 eV; m/z (relative intensity): 262 (2), 246 (1), 232 (1), 145 (46), 127 (6), 115 (100), 91 (25). HRMS (ESI-TOF) m/z calcd for $C_{17}H_{14}NO_2$ $[M + H]^+$: 264.1025, found 264.1030.

General Procedure for Preparation of (2-Alkynylbenzyl)oxy Nitriles 1r. To a two-necked round-bottomed flask equipped with a reflux condenser containing the 2-[[2-(3-hydroxy-3-methylbut-1-ynyl)-benzyl]oxy]benzonitrile (3 mmol) and toluene (10 mL) was added NaOH (3.0 equiv). The resulting solution was stirred under reflux for 5 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with a saturated solution of NH_4Cl (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography on silica gel. Compound **1r** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a white solid. Yield: 0.489 g (70%). Mp: 91−93 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63−7.61 (m, 1H), 7.55 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.52−7.45 (m, 2H), 7.37 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.28−7.24 (m, 1H), 7.02−6.97 (m, 2H), 5.36 (s, 2H), 3.37 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.1, 138.0, 134.2, 133.7, 132.7, 129.3, 127.7, 126.9, 121.1, 120.0, 116.2, 113.0, 102.5, 82.7, 80.6, 68.6. MS (EI, 70 eV; m/z (relative intensity): 233 (2), 205 (3), 115 (100), 102 (1), 89 (14). HRMS (ESI-TOF) m/z calcd for $C_{16}H_{12}NO$ $[M + H]^+$: 234.0919, found 234.0923.

DOI: 10.1021/acs.joc.5b01884
J. Org. Chem. 2015, 80, 10278−10287

General Procedure for the Preparation of Benzofuroazepine Derivatives 2a–q. To a Schlenk tube under argon atmosphere, containing the substrate 1 (0.5 mmol) and THF (2 mL), was added *t*-BuOK (0.2 equiv) at room temperature. The reaction mixture was allowed to stir at this temperature for 1 h. After this time, the reaction was diluted with ethyl acetate (20 mL) and washed with a saturated solution of NH_4Cl (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography on silica gel.

*6-Phenyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2a**).* Compound **2a** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.126 g (82%). Mp: 140–143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18–8.07 (m, 2H), 7.99–7.86 (m, 2H), 7.57–7.50 (m, 1H), 7.45–7.30 (m, 8H), 3.73 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 154.8, 154.0, 144.5, 138.5, 130.3, 130.0, 129.9, 129.7, 128.7, 128.5, 128.2, 128.1, 127.4, 126.9, 125.6, 124.4, 123.0, 119.9, 111.4, 37.7. MS (EI, 70 eV; *m*/*z* (relative intensity): 310 ([M + 1], 21), 309 (100), 280 (16), 205 (13), 176 (27), 151 (12), 139 (6). HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{16}NO$ $[M + H]^+$: 310.1232, found 310.1233.

*6-p-Tolyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2b**).* Compound **2b** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.132 g (82%). Mp: 135–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.96–7.91 (m, 2H), 7.57–7.54 (m, 1H), 7.48–7.32 (m, 5H), 7.26–7.21 (m, 2H), 3.77 (s, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 154.8, 153.9, 144.4, 140.3, 135.8, 130.2, 130.1, 129.8, 129.3, 128.7, 128.2, 128.1, 127.4, 126.9, 125.5, 124.4, 123.0, 119.9, 111.3, 37.7, 21.3. MS (EI, 70 eV; *m*/*z* (relative intensity): 324 ([M + 1], 21), 323 (100), 307 (11), 294 (9), 207 (8), 176 (15), 151 (7), 117 (11). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1388, found 324.1393.

*6-m-Tolyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2c**).* Compound **2c** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow viscous oil. Yield: 0.124 g (77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01–7.87 (m, 4H), 7.58–7.51 (m, 1H), 7.48–7.27 (m, 6H), 7.23–7.16 (m, 1H), 3.75 (s, 2H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 155.2, 154.0, 144.5, 138.6, 138.2, 130.9, 130.3, 130.1, 129.9, 128.9, 128.8, 128.4, 128.2, 127.5, 127.0, 125.6, 125.4, 124.5, 123.0, 119.9, 111.4, 37.9, 21.5. MS (EI, 70 eV; *m*/*z* (relative intensity): 325 ([M + 2], 4), 324 ([M + 1], 24), 323 (100), 307 (23), 294 (14), 278 (5), 254 (4), 205 (17), 176 (29), 151 (13). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1388, found 324.1391.

*6-o-Tolyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2d**).* Compound **2d** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow viscous oil. Yield: 0.105 g (65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00–7.96 (m, 1H), 7.89 (ddd, *J* = 7.6 Hz, *J* = 1.5 Hz, *J* = 0.7 Hz, 1H), 7.57 (ddd, *J* = 8.0 Hz, *J* = 1.0 Hz, *J* = 0.7 Hz, 1H), 7.52–7.18 (m, 9H), 3.70 (s, 2H), 2.48 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.8, 153.9, 144.3, 140.8, 136.6, 131.1, 130.3, 129.9, 129.6, 128.7, 128.6 (2C), 128.5, 127.4, 127.1, 125.7, 125.6, 124.5, 123.1, 119.9, 111.3, 42.3, 20.9. MS (EI, 70 eV; *m*/*z* (relative intensity): 325 ([M + 2], 3), 324 ([M + 1], 25), 323 (100), 306 (6), 231 (15), 219 (5), 206 (30), 176 (25), 151 (12). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1388, found 324.1390.

*6-(4-Methoxyphenyl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2e**).* Compound **2e** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.135 g (80%). Mp: 112–115 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.97–7.88 (m, 2H), 7.57–7.51 (m, 1H), 7.48–7.28 (m, 5H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.4, 154.4, 154.0, 144.3, 131.3, 130.2, 130.1, 130.0, 129.9, 128.9, 128.2, 127.6, 127.0, 125.5, 124.5, 123.0, 119.9, 114.0, 111.4, 55.4, 37.6. MS (EI, 70 eV; *m*/*z* (relative intensity): 341 ([M + 2], 14), 340 ([M + 1], 22), 339 (100), 324 (12), 294 (10), 265 (17), 206 (21), 176 (27), 165 (13). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{18}NO_2$ $[M + H]^+$: 340.1338, found 340.1341.

*6-(3-Methoxyphenyl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2f**).* Compound **2f** was isolated by column chromatography (eluent 2% EtOAc in hexane) as a yellow solid. Yield: 0.122 g (72%). Mp: 90–93 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97–7.88 (m, 2H), 7.74–7.72 (m, 1H), 7.71–7.67 (m, 1H), 7.56–7.51 (m, 1H), 7.45–7.28 (m, 6H), 6.92 (ddd, *J* = 8.2 Hz, *J* = 2.7 Hz, *J* = 1.0 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 159.8, 154.5, 153.9, 144.6, 139.9, 130.4, 129.9, 129.7, 129.4, 128.6, 128.1, 127.3, 127.0, 125.6, 124.4, 123.0, 120.6, 119.9, 116.0, 113.5, 111.3, 55.2, 37.8. MS (EI, 70 eV; *m*/*z* (relative intensity): 341 ([M + 2], 4), 340 ([M + 1], 24), 339 (100), 323 (11), 294 (15), 265 (7), 207 (26), 176 (27), 151 (11). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{18}NO_2$ $[M + H]^+$: 340.1338, found 340.1350.

*6-(2-Methoxyphenyl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2g**).* Compound **2g** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow viscous oil. Yield: 0.107 g (63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98–7.90 (m, 2H), 7.69 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.58–7.52 (m, 1H), 7.49–7.28 (m, 6H), 6.98 (td, *J* = 7.6 Hz, *J* = 0.6 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.6, 157.3, 153.8, 144.8, 131.5, 131.0, 130.9, 130.2, 129.9, 129.5, 129.4, 128.8, 127.5, 126.8, 125.4, 124.2, 122.9, 120.8, 119.8, 111.3, 111.1, 55.2, 41.4. MS (EI, 70 eV; *m*/*z* (relative intensity): 341 ([M + 2], 4), 340 ([M + 1], 21), 339 (100), 321 (16), 282 (14), 246 (25), 207 (25), 176 (47), 165 (29), 151 (20). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{18}NO_2$ $[M + H]^+$: 340.1338, found 340.1346.

*6-(4-Chlorophenyl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2h**).* Compound **2h** was isolated by column chromatography (eluent 1% EtOAc in hexane) as yellow solid. Yield: 0.140 g (82%). Mp: 131–134 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05–8.00 (m, 2H), 7.94–7.86 (m, 2H), 7.56–7.50 (m, 1H), 7.46–7.29 (m, 7H), 3.66 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 154.0, 153.2, 144.6, 136.9, 136.1, 130.5, 129.9, 129.5, 129.4, 128.7, 128.6, 128.0, 127.2, 127.1, 125.7, 124.5, 123.1, 119.8, 111.4, 37.5. MS (EI, 70 eV; *m*/*z* (relative intensity): 345 ([M + 2], 35), 344 ([M + 1], 40). 343 (100), 314 (17), 307 (40), 278 (9), 205 (16), 176 (30), 151 (14). HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{15}ClNO$ $[M + H]^+$: 344.0842, found 344.0845.

*6-(4-Fluorophenyl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2i**).* Compound **2i** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.108 g (66%). Mp: 123–126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17–8.09 (m, 2H), 7.96–7.88 (m, 2H), 7.56–7.51 (m, 1H), 7.48–7.30 (m, 5H), 7.13–7.06 (m, 2H), 3.72 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 164.0 (d, *J* = 251.0 Hz), 154.1, 153.5, 144.6, 134.8 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 6.0 Hz), 130.3, 130.0, 129.6, 128.8, 128.1, 127.4, 127.1, 125.7, 124.6, 123.1, 119.9, 115.5 (d, *J* = 22.0 Hz), 111.4, 37.8. MS (EI, 70 eV; *m*/*z* (relative intensity): 328 ([M + 1], 23), 327 (100), 298 (22), 205 (15), 176 (30), 151 (12), 139 (4). HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{15}FNO$ $[M + H]^+$: 328.1138, found 328.1140.

*6-(Naphthalen-2-yl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2j**).* Compound **2j** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.125 g (70%). Mp: 174–177 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54–8.51 (m, 1H), 8.36 (dd, *J* = 8.6 Hz, *J* = 1.8 Hz, 1H), 8.01–7.91 (m, 3H), 7.88–7.78 (m, 2H), 7.59–7.54 (m, 1H), 7.51–7.32 (m, 7H), 3.89 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 154.7, 154.0, 144.6, 135.9, 134.1, 133.1, 130.4, 130.2, 129.8, 128.9, 128.8, 128.3 (2C), 128.2, 127.6, 127.4, 127.2, 127.0, 126.4, 125.6, 125.5, 124.5, 123.1, 120.0, 111.4, 37.7. MS (EI, 70 eV; *m*/*z* (relative intensity): 361 ([M + 2], 2), 360 ([M + 1], 27), 359 (100), 330 (19), 281 (6), 253 (4), 231 (5), 206 (22), 176 (32), 151 (20). HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{18}NO$ $[M + H]^+$: 360.1388, found 360.1392.

*6-(Pyridin-3-yl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2k**).* Compound **2k** was isolated by column chromatography (eluent 7% EtOAc in hexane) as a yellow solid. Yield: 0.085 g (51%). Mp: 170–173 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.36 (d, *J* = 1.7 Hz, 1H), 8.62 (dd, *J* = 4.6 Hz, *J* = 1.5 Hz, 1H), 8.43 (ddd, *J* = 8.0 Hz, *J* = 2.3 Hz, *J* = 1.7 Hz, 1H), 7.98–7.87 (m, 2H), 7.58–7.28 (m, 7H), 3.77 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 154.0, 151.9, 150.5, 149.3, 144.8, 135.6, 134.1, 130.7, 129.9, 129.2, 128.6, 128.1, 127.3, 127.1, 125.8, 124.7, 123.4, 123.2, 119.8, 111.4, 37.5. MS (EI, 70 eV; *m*/*z* (relative intensity): 312 ([M + 2], 3), 311 ([M + 1], 22), 310 (100), 281 (17), 254 (4), 232 (2), 206 (11), 176 (19), 151 (10). HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{15}N_2O$ $[M + H]^+$: 311.1184, found 311.1186.

DOI: 10.1021/acs.joc.5b01884
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*6-(Thiophene-3-yl)-5H-benzo[d]benzofuro[3,2-b]azepine (**2l**).* Compound **2l** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.116 g (74%). Mp: 155−157 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (dd, J = 2.9 Hz, J = 1.2 Hz, 1H), 7.94−7.87 (m, 2H), 7.81 (dd, J = 5.1 Hz, J = 1.2 Hz, 1H), 7.56−7.53 (m, 1H), 7.47−7.28 (m, 6H), 3.73 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 154.0, 150.5, 144.5, 142.4, 130.4, 130.0, 129.7, 128.7, 128.2, 127.8, 127.4, 127.2, 127.1, 126.2, 125.6, 124.6, 123.0, 119.9, 111.4, 39.0. MS (EI, 70 eV; m/z (relative intensity): 317 ([M + 2], 7), 316 ([M + 1], 24), 315 (100), 286 (26), 270 (17), 205 (15), 176 (32), 151 (16). HRMS (ESI-TOF) m/z calcd for $C_{20}H_{14}NOS$ [M + H]$^+$: 316.0796, found 316.0798.

*9-Methyl-6-phenyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2m**).* Compound **2m** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.126 g (78%). Mp: 138−141 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21−8.12 (m, 2H), 7.96−7.91 (m, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.52−7.34 (m, 7H), 7.17 (ddd, J = 7.8 Hz, J = 1.3 Hz, J = 0.6 Hz, 1H), 3.79 (s, 2H), 2.53 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 154.6, 154.5, 144.2, 138.7, 136.0, 130.2, 130.1, 130.0, 129.6, 129.0, 128.6, 128.3, 128.2, 127.0, 125.0, 124.5, 124.4, 119.5, 111.6, 37.9, 21.8. MS (EI, 70 eV; m/z (relative intensity): 325 ([M + 3] 4), 324 ([M + 1], 24), 323 (100), 294 (12), 280 (7), 246 (3), 219 (10), 189 (11), 165 (4). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}NO$ [M + H]$^+$: 324.1388, found 324.1396.

*9-Fluoro-6-phenyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2n**).* Compound **2n** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.122 g (75%). Mp: 177−180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.10 (m, 2H), 7.92−7.87 (m, 1H), 7.83 (dd, J = 8.6 Hz, J = 5.5 Hz, 1H), 7.51−7.37 (m, 6H), 7.27 (dd, J = 8.6 Hz, J = 2.1 Hz, 1H), 7.09 (ddd, J = 9.5 Hz, J = 8.6 Hz, J = 2.1 Hz, 1H), 3.77 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8 (d, J = 244.0 Hz), 155.2, 154.0 (d, J = 13.0 Hz), 145.2 (d, J = 4.0 Hz), 138.4, 130.5, 130.2, 129.7, 129.4, 128.6, 128.5, 128.3, 128.2, 127.1, 124.3, 123.8 (d, J = 1.0 Hz), 120.4 (d, J = 10.0 Hz), 111.3 (d, J = 24.0 Hz), 99.2 (d, J = 27.0 Hz), 37.9. MS (EI, 70 eV; m/z (relative intensity): 329 ([M + 2], 3), 328 ([M + 1], 25), 327 (100), 298 (16), 250 (4), 223 (17), 194 (18), 175 (15), 148 (6). HRMS (ESI-TOF) m/z calcd for $C_{22}H_{15}FNO$ [M + H]$^+$: 328.1138, found 328.1139.

*9-Methyl-6-p-tolyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2o**).* Compound **2o** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.133 g (79%). Mp: 151−154 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d. J = 8.2 Hz, 2H), 7.93−7.88 (m, 1H), 7.83−7.78 (m, 1H), 7.47−7.34 (m, 4H), 7.26−7.21 (m, 2H), 7.18−7.13 (m, 1H), 3.75 (s, 2H), 2.51 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 154.6, 154.4, 144.0, 140.3, 136.0, 135.9, 130.2, 130.0, 129.6, 129.3, 128.9, 128.2, 128.1, 126.9, 125.0, 124.4, 124.3, 119.4, 111.6, 37.8, 21.9, 21.4. MS (EI, 70 eV; m/z (relative intensity): 339 ([M + 2], 3), 338 ([M + 1], 25), 337 (100), 321 (20), 294 (8), 269 (3), 220 (13), 207 (6), 189 (21), 165 (10). HRMS (ESI-TOF) m/z calcd for $C_{24}H_{20}NO$ [M + H]$^+$: 338.1545, found 338.1548.

*6-(4-Chlorophenyl)-9-methyl-5H-benzo[d]benzofuro[3,2-b]-azepine (**2p**).* Compound **2p** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.126 g (71%). Mp: 137−140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, J = 8.8 Hz, 2H), 7.95−7.89 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.53−7.33 (m, 6H), 7.20−7.14 (m, 1H), 3.73 (s, 2H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 154.4, 153.0, 144.2, 137.0, 136.2, 136.1, 130.3, 130.0, 129.5, 129.2, 128.8, 128.7, 128.0, 127.1, 124.8, 124.5, 124.4, 119.4, 111.7, 37.7, 21.9. MS (EI, 70 eV; m/z (relative intensity): 359 ([M + 2], 33), 358 ([M + 1], 38), 357 (100), 328 (13), 321 (29), 278 (4), 219 (13), 189 (23), 165 (11). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{17}ClNO$ [M + H]$^+$: 358.0999, found 358.1001.

*9-Fluoro-6-p-tolyl-5H-benzo[d]benzofuro[3,2-b]azepine (**2q**).* Compound **2q** was isolated by column chromatography (eluent 1% EtOAc in hexane) as a yellow solid. Yield: 0.122 g (72%). Mp: 145−148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 8.2 Hz, 2H), 7.91−7.87 (m, 1H), 7.83 (ddd, J = 8.6 Hz, J = 5.5 Hz, J = 0.5 Hz, 1H), 7.49−7.37 (m, 3H), 7.29−7.21 (m, 3H), 7.09 (ddd, J = 9.5 Hz, J = 8.6 Hz, J = 2.3 Hz, 1H), 3.75 (s, 2H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8 (d, J = 243.0 Hz), 155.2, 154.0 (d, J = 13.0 Hz), 145.1 (d, J = 4.0 Hz), 140.6, 135.6, 130.3, 129.8, 129.4, 129.3, 128.6, 128.3, 128.2, 127.0, 124.3, 123.8 (d, J = 1.0 Hz), 120.4 (d, J = 10.0 Hz), 111.3 (d, J = 24.0 Hz), 99.2 (d, J = 27.0 Hz), 37.7, 21.4. MS (EI, 70 eV; m/z (relative intensity): 343 ([M + 2], 4), 342 ([M + 1], 25), 341 (100), 325 (24), 312 (15), 296 (3), 250 (4), 223 (13), 194 (13), 175 (11). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{17}FNO$ [M + H]$^+$: 342.1294, found 342.1297.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01884.

X-ray data for compound **2a** (CIF)

Experimental and spectroscopic data for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to FAPERGS, CAPES and CNPq for financial support. CNPq is also acknowledged for the fellowships (R.G., D.F.B., and G.Z.).

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