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Synthesis and Characterization of a Two Stage, Nonlinear Photobase Generator

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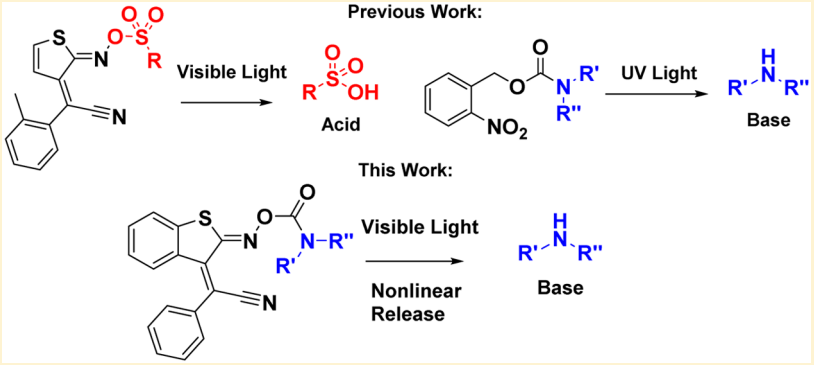
Supporting Information



ABSTRACT: Amine photobase generators (PBGs) are uncommon yet useful compounds. Rarer still are examples of PBGs that are active at visible wavelengths. We report the synthesis and characterization of new photolabile amine protecting groups that are active under visible light. The new chromophore, benzothiophene imino-phenylacetonitrile (BTIPA), was synthesized in four steps without use of chromatography and found to release any one of several amines upon exposure to 405 nm light. The chromophore was also demonstrated to be useful as a Merrifield synthesis protecting group. Experimental evidence suggests a sequential, two stage photolysis mechanism which leads to a nonlinear response to dose.

INTRODUCTION

Photobase generators (PBGs) are "neutral" compounds that generate basic species upon irradiation. Unlike their photoacid generator counterparts, which have immense commercial value in photoresists, PBGs have received relatively little attention.[1] However, PBGs have found many niches such as curing epoxies and poly(amic acid),[2−6] utility in the realm of pitch division lithography,[7] interface chemistry,[8] and as photolabile protecting groups.[9] However, most PBGs and photoacids are only useful in UV wavelengths. Ortho-nitro benzyl carbamates are a notable class of such compounds. Attempts to red shift the photoactivity of many PBGs result in decreased quantum efficiency and reduced thermal stability.[10,11] An unusual thiophene based chromophore (Igracure 103 from BASF) is a notable exception to this rule. Igracure 103, a photoacid generator, has good sensitivity at 436 nm.[12] However, the thiophene chromophore that is the basis of Igracure 103 has only been employed in photoacid generation. We have adopted this chromophore to serve as an amine protecting group. The photolysis of the chromophore has been investigated, revealing efficient deprotection upon exposure to 405 nm light. A sequential, two stage photolysis mechanism has been proposed.

RESULTS AND DISCUSSION

Synthesis. PBGs **6a**, **7a**, and **8a** were synthesized in 5 steps from benzothiophene **1** (Scheme 1). Benzothiophene was first brominated, then nitrated,[13] and debrominated with copper in molten benzoic acid. This three step sequence was found to be much cleaner than direct nitration of **1**.[14−16] 2-Nitrobenzothiophene **4** was then reacted with benzyl cyanide using KOH in MeOH to yield benzothiophene imino-phenylacetonitrile (BTIPA) **5a**,[17−19] which produced the (Z,Z) isomer as the major product confirmed by X-ray crystallography (see Supporting Information). The oxime **5** was reacted with carbamoyl chlorides to yield PBGs of general structure **6**. It should be noted that column chromatography is not required to purify any of the intermediates. All can be purified by recrystallization.

Investigation of Photolysis. A UV−vis photobleaching experiment was performed, and it was found that compound **6a** bleaches upon exposure to visible light (405 nm). A number of isosbestic points were observed, indicating clean photochemistry.

An NMR study was performed to investigate the pathway to generation of amine. Compound **6a** was exposed to increasing doses of 405 nm light in a deuterated acetonitrile solution (Scheme 2). The disappearance of **6a** and formation of dipentylamine, as well as a resonance at 3.2 ppm assigned to be

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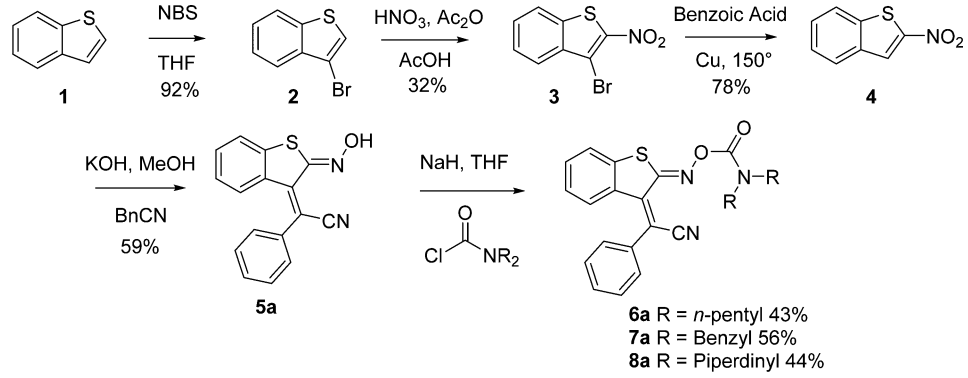
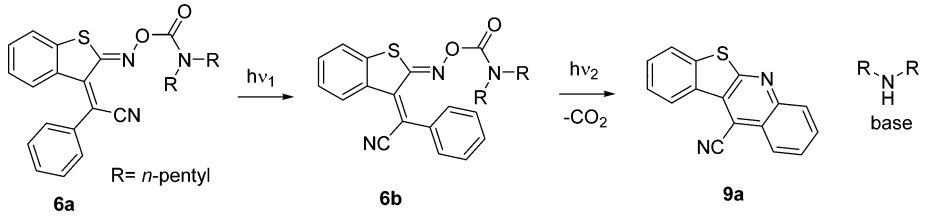
Scheme 1. Synthesis of Photobase Generator



Scheme 2. Proposed Chromophore Mechanism and Photoproduct



the (*E*,*Z*) isomer **6b** (which disappears upon extended exposure), are documented in the Supporting Information.

To further investigate the reaction mechanism, an LC/MS study was performed using the dibenzyl carbamate **7a**, also in acetonitrile solution (Figure 1). Several product peaks from the

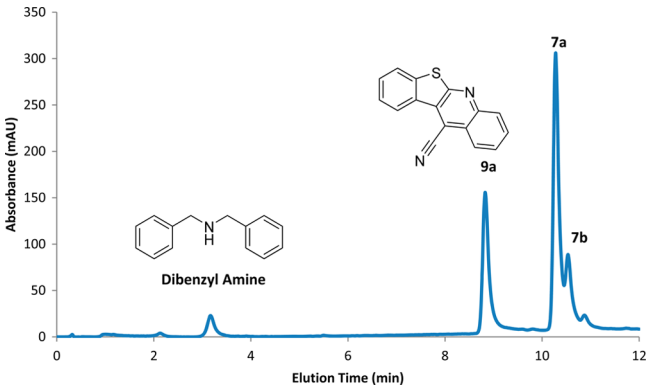


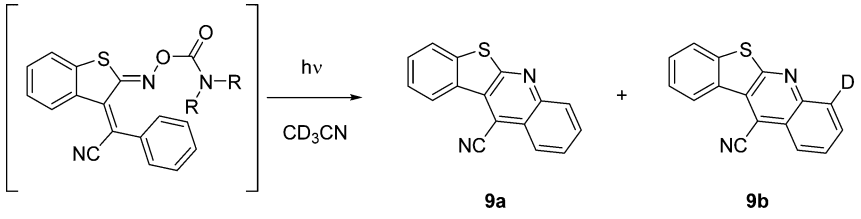
Figure 1. LC/MS trace of photolysis of **7a**.

photoreaction were identified, including a peak that has the same *m*/*z* (524, M + Na) as the isolated **7a**, which is consistent with the proposal that the first photochemical event is the isomerization from the (*Z*,*Z*) to the (*E*,*Z*) carbamate. The other peaks observed correlate with expected products. There is an unknown ultimate photoproduct formed with an *m*/*z* of 261. While many alkene isomerizations can also be identified via thin layer chromatography (TLC),[20] it was not possible to resolve **7a** and its isomer via TLC.

Characterization of Photoproducts. The carbamates readily generated amine on exposure to visible light, but another photoproduct was generated simultaneously. This product was isolated from photolysis experiments and subjected to a series of 2D NMR experiments to confirm structure. The resulting photoproduct was identified as benzo[4,5]thieno[2,3-*b*]quinoline-11-carbonitrile **9a** (Scheme 3), an interesting and unusual heterocycle.[21−23] The isolation of this product suggests a sequential, two step photolysis mechanism, in which the first photon isomerizes the phenylnitrile based double bond, and the second photon induces homolysis of the N−O bond of the oxamic acid ester, followed by decarboxylation and radical addition into the adjacent aryl ring. Interestingly, when the reaction was run in deuterated acetonitrile, the product **9a** was isolated along with deuterated photoproduct **9b** in a 1:1 mixture.[24]

Photochemistry of Oxime Skeleton. In order to better understand the photochemistry of the chromophore, the photochemistry of the oxime skeleton **5a** was investigated (Scheme 4). Under the same reaction conditions, oxime **5a** also underwent a two step photolysis process. The reaction was tracked by LC/MS, and production of the same photoproduct **9a** was observed Figure 2. The LC/MS trace of the reaction

Scheme 3. Photoproducts from Chromophore



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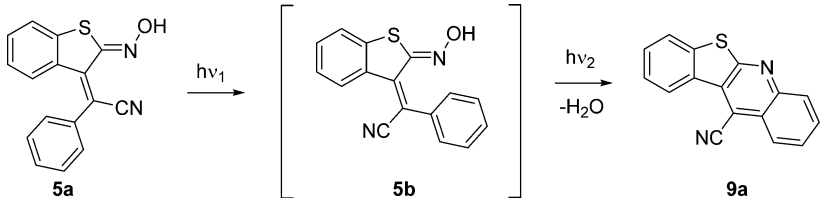
Scheme 4. Photochemistry of BTIPA Chromophore



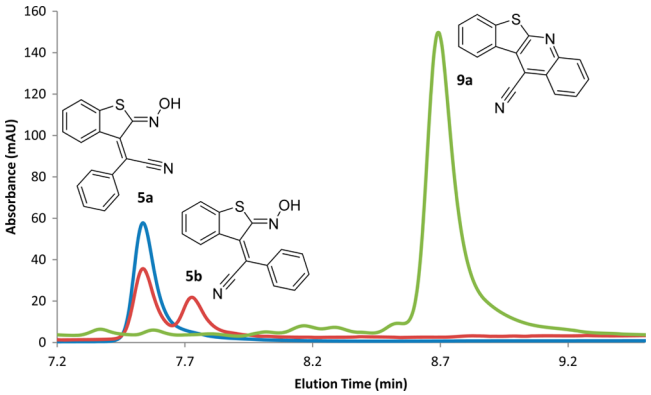


Figure 2. LC/MS traces of photolysis of **5a**.

reveals a new peak with identical m/z, which was assigned to the isomer **5b**, and as the reaction was allowed to proceed to completion, a peak with m/z of 261, corresponding to the photoproduct of the carbamates **9a**, appeared. These data suggest that the BTIPA chromophore undergoes the same photochemistry as the carbamates. The data are consistent with an initial isomerization around the double bond, formation of the ketamine radical, and subsequent radical addition on proximate phenyl C−H bond to form the quinolone heterocycle.

Application as a Merrifield Protecting Group. A classical application of amine protecting groups is amino acid protection for peptide synthesis. The Merrifield synthesis is the standard for peptide synthesis, and in light of the success of *o*-nitrobenzyloxycarbonyl carbamate protecting groups,[25−28] as well as other work in the field of polymer-bound photochemistry,[29−34] BTIPA was investigated as a Merrifield protecting group. Merrifield beads were prepared and reacted with Boc-protected proline, deprotected, then reacted with triphosgene and the oxime **5a** to give protected beads **10** (Scheme 5). The protected beads were then kept in the dark and subjected to a DCC coupling with tryptophan as a control. Another set of protected beads was exposed to 405 nm light for 30 min and then reacted with DCC and tryptophan. A third set of proline-tryptophan beads was prepared conventionally. All beads were hydrolyzed and then analyzed for amino acid composition. The resulting thin layer chromatography plate showed that the BTIPA protected beads successfully blocked the DCC coupling and hydrolysis produced only proline (see Supporting Information). Hydrolysis of the photodeprotected BTIPA beads produced tryptophan as well as proline, documenting a successful deprotection and subsequent amino acid coupling.

CONCLUSION

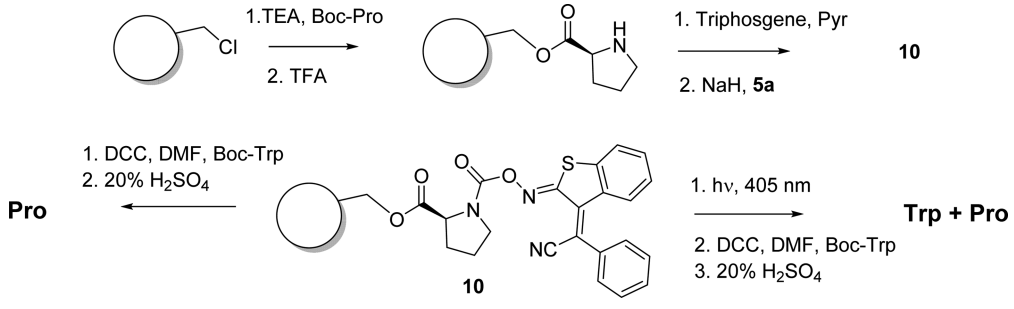
The chromophore **5a** was synthesized in four steps from benzothiophene by a process requiring no chromatography. Carbamates were synthesized from corresponding carbamoyl chlorides, and the resulting compounds were found to successfully and cleanly generate amine upon exposure to visible light (405 nm). This is likely a sequential two photon process, as evidenced by LC/MS and NMR studies. The BTIPA chromophore has demonstrated potential viability as a PBG and as a Merrifield amine protecting group; further studies will explore the scope of amine protection and quantify the efficiency of the reaction.

EXPERIMENTAL SECTION

General Methods and Materials. All solvents and reagents were obtained from commercial sources and were used without further purification except where noted. TEA was distilled from CaH_2 while THF was distilled from sodium/benzophenone. Reactions were run in flame-dried glassware and under an atmosphere of nitrogen unless otherwise noted. Photosensitive reactions were protected from ambient light by wrapping reaction flasks with aluminum foil. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz instrument. Chemical shifts are reported in ppm downfield from TMS using residual protonated solvent as an internal standard (DMSO-d_6, ^{1}H 2.49 ppm and ^{13}C 39.5 ppm, or $CDCl_3$, ^{1}H 7.26 ppm and ^{13}C 77.0 ppm). Coupling constants are expressed in Hz. IR data was recorded on an FT-IR using either a KBr pellet or thin film on a NaCl disk. Melting points were recorded using a glass pipet and heating source and are uncorrected.

*Synthesis of 3-Bromobenzo[b]thiophene (**2**).* Benzo[*b*]thiophene (5.051 g, 37.64 mmol) was dissolved in 120 mL of THF and added to

Scheme 5. Investigation of Chromophore 5a as a Merrifield Protecting Group



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a 250 mL round-bottom flask. The solution was cooled to 0 °C, and NBS (10.147 g, 57.01 mmol) was added portionwise. The mixture was stirred for 30 min at 0 °C, then warmed to room temperature, and stirred for an additional 48 h. The reaction was quenched with aqueous $Na_2S_2O_3$ and extracted with ether. The extracts were combined and washed, dried with $MgSO_4$, filtered, and concentrated to obtain approximately 10 g of crude material. This was purified by column chromatography (hexanes), yielding a clear oil (7.373 g, 92%). Data matched literature precedent.[35] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.79 (m, 2H), 7.56−7.35 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.4, 137.3, 125.1, 124.9, 123.4, 122.9, 122.6, 107.6. HRMS (ESI-TOF) m/z $[M]^+$ calcd for C_8H_5BrS = 211.9295, found = 211.9294. FTIR: ν = 3104, 3058, 1492, 1453, 1429, 1316, 1253, 1145, 1060, 1017, 929, 820 cm^{-1}.

*Synthesis of 3-Bromo-2-nitrobenzo[b]thiophene (**3**).* To a 500 mL round-bottom flask was added 3-bromobenzo[b]thiophene (12.795 g, 60.045 mmol) and 200 mL of acetic anhydride. The solution was cooled to 0 °C, and a mixture of 25 mL of nitric acid and 20 mL of acetic acid was added dropwise with vigorous stirring. A yellow precipitate began to form after several minutes. Once the addition was complete, the ice bath was removed and the reaction mixture stirred for 2 h at room temperature. The mixture was then poured into ice water and the resulting precipitate collected by filtration. The solid was washed with water and crystallized from ethanol, yielding a fluffy golden solid (4.926 g, 32%). Only the first crop of material contains the desired product. Data matched literature precedent.[36] Mp: 160−162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H), 7.73 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.99 (ddd, J = 8.2, 1.2, 0.7 Hz, 1H), 8.16 (ddd, J = 8.2, 1.4, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 111.9, 123.8, 126.3, 127.3, 130.7, 136.5, 136.6, 145.9. HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_8H_5BrNO_2S$ = 257.9224, found = 257.9220. FTIR: ν = 3074, 1591, 1552, 1520, 1484, 1334, 1303, 1243, 917, 867, 803, 761, 740, 727, 710 cm^{-1}.

*Synthesis of 2-Nitrobenzo[b]thiophene (**4**).* 3-Bromo-2-nitrobenzo[b]thiophene (4.313 g, 16.71 mmol) and benzoic acid (7.555 g, 61.87 mmol) were added to a 3-neck 100 mL round-bottom flask. The solids were mixed thoroughly with a magnetic stir bar, and the reaction was purged 3 times before heating to 150 °C. Under a cone of nitrogen, copper powder (5.159 g, 81.19 mmol) was then added to the melt. The reaction was stirred for an additional 30 min at 150 °C and then slowly cooled to room temperature. The resulting solid was suspended in dichloromethane, and the residual copper was removed by gravity filtration. The DCM solution was washed three times with saturated $NaHCO_3$, once with water, and once with brine. This was then dried over $MgSO_4$, filtered, and concentrated to obtain a golden power (2.326 g, 78%). Data matched literature precedent.[37−39] Mp: 109−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 3.3 Hz, 1H), 7.93 (dd, J = 8.0, 2.5 Hz, 1H), 7.83 (dd, J = 8.2, 2.9 Hz, 1H), 7.61−7.53 (m, 1H), 7.49 (td, J = 7.6, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3, 140.3, 136.1, 129.1, 127.0, 126.1, 125.6, 122.9. HRMS (ESI-TOF) $[M]^+$ calcd for $C_8H_5NO_2S$ = 179.0041, found = 179.0044. FTIR: ν = 3098, 1594, 1558, 1516, 1496, 1451, 1424, 1346, 1315, 1250, 1190, 1160, 1126, 1081, 1052, 872, 849, 802, 757 cm^{-1}.

*Synthesis of (Z)-2-((Z)-2-(Hydroxyimino)benzo[b]thiophen-3(2H)-ylidene)-2-phenylacetonitrile (**5a**).* Potassium hydroxide (0.530 g, 9.44 mmol) was dissolved in 10 mL of methanol and added to a 50 mL round-bottom flask. The solution was then cooled to 0 °C and benzyl cyanide (0.276 g, 2.36 mmol) was added dropwise. 2-Nitrobenzo[b]-thiophene (0.422 g, 2.36 mmol) was dissolved in 25 mL of methanol and added dropwise to the reaction vessel. The solution immediately became brilliant yellow and gradually darkened to a vibrant orange color. The reaction was then protected from light by covering the flask with aluminum foil and stirred overnight at room temperature. Upon completion as determined by TLC, the reaction was poured into 200 mL of water and then acidified with 50% acetic acid/water. The resulting suspension was extracted 3 times with ethyl acetate. The extracts were combined, washed with water and brine, dried with $MgSO_4$, filtered, and concentrated to obtain 0.62 g of crude material. Purification by column chromatography (20% ethyl acetate in hexanes) yielded oxime as a yellow powder (0.389 g, 59%). Mp: 184−185 °C (dec; sample darkened at 175 °C without melting). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 7.70−7.48 (m, 6H), 7.39−7.30 (m, 1H), 6.89 (ddd, J = 8.4, 7.4, 1.2 Hz, 1H), 6.38 (dd, J = 8.2, 0.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 150.9, 142.2, 139.1, 134.4, 132.3, 131.8, 130.1, 128.8, 128.7, 126.6, 125.3, 123.8, 119.4, 106.6. HRMS $[M + H]^+$ calcd for $C_{16}H_{11}N_2OS$ = 279.0592, found = 279.0590. FTIR: ν = 3325, 3061, 2201, 1583, 1546, 1487, 1445, 1363, 1308, 1286, 1261, 1211, 1166, 988, 892, 766 cm^{-1}.

*Synthesis of (Z)-2-((Z)-2-(Dipentylcarbamoyloxyimino)benzo[b]-thiophen-3(2H)-ylidene)-2-phenylacetonitrile (**6a**).* To a 5 mL round-bottom flask were added (Z)-2-((Z)-2-(hydroxyimino)benzo-[b]thiophen-3(2H)-ylidene)-2-phenylacetonitrile (0.109 g, 0.392 mmol), dry THF (3 mL), and dipentylcarbamyl chloride (0.315 g, 1.43 mmol). This solution was cooled to −78 °C, and NaH (0.037 g, 60% mineral oil dispersion—0.925 mmol) was added in one portion. The reaction was then shielded from light and warmed to room temperature. Stirring was continued for 3 h, at which point all starting material was consumed, as determined by TLC. The reaction was then quenched with water and diluted with ethyl acetate (50 mL). This was washed three times with water and once with brine, dried over $MgSO_4$, filtered, and concentrated to obtain 0.286 g of crude material. Crystallization from hexanes yielded carbamate as a yellow solid (0.077 g, 43%). Mp: 106−108 °C (dec; pronounced outgassing from the melt was observed, suggesting carbamate thermolysis). ^{1}H NMR (400 MHz, CD_3CN): δ 7.66−7.46 (m, 5H), 7.42 (d, J = 7.9 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 6.88 (dd, J = 8.2, 7.3 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 3.33 (t, J = 7.1 Hz, 4H), 1.65 (d, J = 27.1 Hz, 4H), 1.38 (s, 8H), 0.94 (s, 6H). ^{13}C NMR (101 MHz, CD_3CN): δ 159.5, 153.2, 142.8, 139.2, 135.5, 133.4, 132.7, 131.3, 131.1, 129.4, 128.1, 126.8, 124.3, 119.5, 111.9, 49.1, 48.6, 29.8, 29.6, 29.3, 28.3, 23.2, 14.4. HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{27}H_{31}N_3O_2SNa$ = 484.2029, found = 484.2039. FTIR: ν = 2956, 2927, 2858, 2199, 1739, 1584, 1538, 1489, 1460, 1440, 1414, 1312, 1272, 1232, 1204, 1139, 1010, 972, 859, 757 cm^{-1}.

*Formation of Photoproduct Benzo[4,5]thieno[2,3-b]quinoline-11-carbonitrile (**9a**).* To a quartz cuvette was added (Z)-2-((Z)-2-(dipentylcarbamoyloxyimino)benzo[b]thiophen-3(2H)-ylidene)-2-phenylacetonitrile (22.6 mg, 0.056 mmol) in acetonitrile (8 mL, 7 mM), and the mixture was exposed for 30 min through a 405 nm bandpass filter. Upon completion, a solid had precipitated in solution, which was filtered and washed with hexanes to give a pale yellow solid, identified as benzo[4,5]thieno[2,3-b]quinoline-11-carbonitrile (11.7 mg, 92%). Mp: 208−213 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (ddd, J = 7.9, 1.3, 0.6 Hz, 1H), 8.44 (ddd, J = 8.4, 1.4, 0.6 Hz, 1H), 8.25 (ddd, J = 8.5, 1.2, 0.6 Hz, 1H), 7.96−7.90 (m, 2H), 7.81 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.69 (td, J = 7.6, 1.3 Hz, 1H), 7.64 (ddd, J = 7.9, 7.3, 1.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.8, 146.6, 139.8, 130.8, 130.4, 130.3, 129.2, 128.9, 128.1, 125.8, 125.14, 125.08, 124.1, 123.3, 115.3, 109.8. HRMS (ESI-TOF) (M^+) calcd for $C_{16}H_8N_2S$ = 260.0408, found = 260.0408. FT-IR (neat): 2923, 2360 (strong), 1736, 1599, 1454, 1367, 1216, 1115, 844, 754 cm^{-1}.

*Synthesis of (Z)-2-((Z)-2-(((Dibenzylcarbamoyl)oxy)imino)benzo-[b]thiophen-3(2H)-ylidene)-2-phenylacetonitrile (**7a**).* To a 25 mL round-bottom flask were added (Z)-2-((Z)-2-(hydroxyimino)benzo-[b]thiophen-3(2H)-ylidene)-2-phenylacetonitrile (0.370 g, 1.329 mmol), dry THF (13 mL), and dibenzylcarbamyl chloride (1.208 g, 4.652 mmol). This solution was cooled to −78 °C, and NaH (0.080 g, 60% mineral oil dispersion—3.3 mmol) was added in one portion. The reaction was then shielded from light and warmed to room temperature. Stirring was continued for 3 h, at which point all starting material was consumed, as determined by TLC. The reaction was then quenched with water and diluted with ethyl acetate (50 mL). This was washed three times with water and once with brine, dried over $MgSO_4$, filtered, and concentrated to obtain 0.880 g of crude material. Crystallization from hexanes yielded carbamate as a yellow solid (0.373 g, 56%). Mp: 172−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.17 (m, 17H), 6.83 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 4.49−4.62 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 153.2, 141.6, 138.3, 136.5, 133.9, 132.1, 131.7, 130.3, 129.9, 128.8, 128.7, 127.8, 127.7, 127.3, 125.7, 123.0, 118.4, 112.0, 50.2, 49.3.

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HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{31}H_{24}N_3O_2S$ = 502.1584, found = 502.1585. FTIR: ν = 3268, 3142, 2422, 1727, 1373, 1219, 1056 cm^{-1}.

*Synthesis of (Z)-2-Phenyl-2-((Z)-2-(((piperidine-1-carbonyl)oxy)-imino)benzo[b]thiophen-3(2H)-ylidene)acetonitrile (**8a**).* To a 25 mL round-bottom flask were added (*Z*)-2-((*Z*)-2-(hydroxyimino)-benzo[*b*]thiophen-3(2*H*)-ylidene)-2-phenylacetonitrile (0.213 g, 0.765 mmol), dry THF (11 mL), and dibenzylcarbamyl chloride (0.335 mL, 2.678 mmol). This solution was cooled to −78 °C, and NaH (0.076 g, 60% mineral oil dispersion—1.9 mmol) was added in one portion. The reaction was then shielded from light and warmed to room temperature. Stirring was continued for 3 h, at which point all starting material was consumed, as determined by TLC. The reaction was then quenched with water and diluted with ethyl acetate (50 mL). This was washed three times with water and once with brine, dried over $MgSO_4$, filtered, and concentrated to obtain 0.411 g of crude material. Crystallization from hexanes yielded carbamate as a yellow solid (0.131 g, 44%). Mp: 163−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.38 (m, 5H), 7.26 (dd, *J* = 8.0, 4.5 Hz, 2H), 6.89−6.78 (m, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 3.52−3.60 (m, 4H), 1.65 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.8, 151.6, 141.7, 138.5, 134.0, 132.0, 131.8, 130.2, 129.8, 128.7, 127.2, 125.6, 123.0, 118.4, 111.8, 45.5, 24.2. HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{22}H_{19}N_3O_2SNa$ = 412.1095, found = 412.1090. FTIR: ν = 3388, 3259, 3208, 1925, 1575, 1364, 1278, 1168, 1138 cm^{-1}.

Synthesis of Boc-Protected Proline-Functionalized Merrifield Resin. To a 50 mL round-bottom flask was added 0.25 g of Merrifield resin (loading capacity: 1.3 mmol of Cl/g). In a separate flask, *N*-Boc-L-proline (0.35 g, 1.6 mmol) and triethylamine (0.16 g, 1.6 mmol) were dissolved in 20 mL of ethyl acetate. This solution was then added to the initial flask. The mixture was heated to reflux and stirred for 48 h. It was then allowed to cool to room temperature and filtered. The resin was washed sequentially with ethyl acetate, ethanol, water, and methanol. It was then dried under vacuum. Boc-protected proline-functionalized Merrifield resin was obtained (0.17 g).

Deprotection of Boc-Protected Proline-Functionalized Merrifield Resin. The resin was washed in neat trifluoroacetic acid for 2 min. It was then washed 2× with 10% *N*,*N*-diisopropylethylamine in DMF, then 5× with DMF.

Synthesis of Proline Carbamoyl Chloride-Functionalized Merrifield Resin. Immediately after deprotection, the proline-functionalized beads (0.17 g) and CH_2Cl_2 (5 mL) were added to a 50 mL round-bottom flask. Pyridine (0.12 g, 2.0 mmol) and triphosgene (0.10 g, 0.34 mmol) in CH_2Cl_2 (5 mL) were then added. The reaction was stirred under N_2 at room temperature for 24 h. The reaction was quenched with saturated NH_4Cl solution, then filtered, and washed sequentially with ethyl acetate, ethanol, water, and methanol. 0.041 g of proline carbamoyl chloride-functionalized Merrifield resin was recovered.

Synthesis of Photobase Generator-Protected Proline-Functionalized Merrifield Resin. A 50 mL round-bottom flask was taken and cooled in a dry ice/acetone bath. The proline carbamoyl chloride-functionalized Merrifield resin (0.040 g) was added. The flask was purged with N_2 for 10 min. Next, THF (10 mL), photobase generator oxime (0.022 g, 0.078 mmol), and NaH (0.0062 g, 0.156 mmol) were added sequentially. The flask was then stirred under N_2 at room temperature for 16 h. The reaction was then filtered and washed sequentially with ethyl acetate, ethanol, water, and methanol. Photobase generator-protected proline-functionalized Merrifield resin was recovered (62 mg).

Test for Blocking Behavior. Photobase generator-protected proline-functionalized Merrifield resin (0.029 g) in 1.45 g acetonitrile was exposed to 66.9 mW/cm^2 of light through a 405 nm band-pass filter for 30 min. This deprotected the resin, making it able to react with further amino acids under a standard Merrifield procedure. The beads were then washed with acetonitrile and added to a microtube. 0.03 g of unexposed resin was added to another microtube as a control. *N*-Boc-L-tryptophan (0.03 g, 0.2 mmol) in DMF (0.5 mL) was added to each tube. Then, dicyclohexylcarbodiimide (0.04 g, 0.2 mmol) in DMF (0.5 mL) was added to each tube. The tubes were shaken at room temperature for 24 h. Each sample was then filtered and washed sequentially with DMF, ethanol, and acetic acid. Each sample was then transferred to new microtubes and hydrolyzed in 20% sulfuric acid for 48 h. Solutions of *N*-Boc-L-proline and *N*-Boc-L-tryptophan were also exposed to 20% sulfuric acid for 48 h. Each sample was then separated by TLC using 4:1:1 butanol:acetic acid:water eluent and analyzed with ninhydrin stain.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **5a**, **6a**, **7a**, **8a**, and **9a**, COSY, HSQC, and HMBC NMR spectra for compound **9a**, crystallographic information, and Merrifield resin data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01078.

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Notes

The authors declare no competing financial interest.

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