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Tandem Reactions via Barton Esters with Intermolecular Addition and Vinyl Radical Substitution onto Indole

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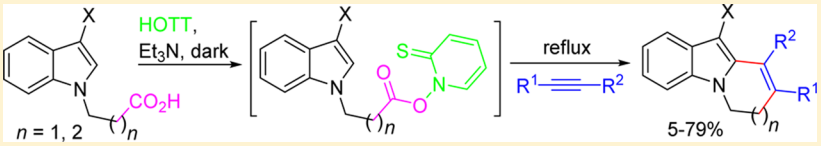
Supporting Information



ABSTRACT: A one-pot initiator-free Barton ester decomposition with tandem radical addition onto alkyl propiolates or phenylacetylene with aromatic substitution of the resultant vinyl radical allows convenient access to new 9-substituted 6,7-dihydropyrido[1,2-*a*]indoles. Propyl radical cyclizations compete when forming the expanded 7,8-dihydro-6*H*-azepino[1,2-*a*]indole system. 2-Thiopyridinyl *S*-radical is incorporated into aromatic adducts when using unsubstituted indole-1-alkanoic acid precursors. X-ray crystallography on substitution products allows selectivity of the radical addition onto less reactive internal alkynes to be determined.

Stork and Baine first demonstrated the synthetic utility of vinyl radicals by carrying out reductive cyclizations to form five- and six-membered rings.[1] Bu_3SnH and azobis(isobutyronitrile) (AIBN) were used to carry out vinyl radical cyclizations onto indoles, yielding mainly reduced adducts.[2] Later, vinyl radical cyclization with aromatic substitution was achieved using a tin-free chain reaction, where displacement of an indole-2-sulfonyl substitutent occurs.[3] Effective five- and six-membered intramolecular aromatic substitutions of vinyl radicals using Bu_3SnH and AIBN were reported by Padwa et al.,[4] although, usually, the use of the "reductant" Bu_3SnH is not conducive with efficient aromatic substitution, where net loss of $H^{\bullet}$ or "oxidation" occurs.[5,6] Where, prior to the substitution, the vinyl radical is generated via an intermolecular addition onto alkynes,[7] yields of aromatic product are traditionally modest.[8] The first synthetically viable tandem process containing an intermolecular addition onto alkynes was reported by Santi et al. using Mn(III)-mediated oxidation of benzylmalonates with the subsequent vinyl radical aromatic substitution giving naphthalene derivatives in moderate to good yields.[9] Most recently, Zhou and co-workers used a photoredox catalytic system to synthesize 2-trifluoromethyl quinolines with imidoyl radical addition onto an alkyne, followed by aromatic substitution,[10] and Li and co-workers reported benzothiophenes under oxidative catalytic conditions with an initial sulfanyl radical addition onto but-2-ynedioates.[11]

The decomposition of Barton esters {*O*-acyl thiohydroxamate ester or pyridine-2-thione-*N*-oxycarbonyl (PTOC)}[12] provides a means of achieving aromatic substitution under mild initiator-free conditions,[13−15] as demonstrated by Barton et al. for intermolecular substitution of nucleophilic alkyl radicals onto heteroaromatic salts.[13] Most recently, we used Barton esters in radical cyclizations, resulting in some high yielding five- to seven-membered alkyl and cyclopropyl annulations of indoles and benzimidazoles.[14,15] In the present article, we report a new use of Barton esters, as precursors for one-pot initiator-free cascade/tandem reactions (Scheme 1). The tandem reaction involves intermolecular addition of alkyl radicals onto alkyl propiolates or phenylacetylene, followed by intramolecular substitution of vinyl radicals onto indoles. Investigations into the use of disubstituted (internal) alkynes with two different substituents are also presented with substitution products demonstrating the selectivity of the radical addition onto the alkyne.

The two-step one-pot protocol involves initial transformation of indole carboxylic acids (e.g., **1a** and **1b**) into Barton esters using Garner's HOTT (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyl thiouronium hexafluorophosphate)[16] in the absence of light (Scheme 1). HOTT is a useful coupling reagent for forming labile Barton esters from hindered or difficult carboxylic acids. The alkyne is present in excess (8 equiv) in order to favor the intermolecular addition with reactions using terminal alkynes only proceeding efficiently by carrying out the radical generation and tandem reactions step under acidic conditions {4 equiv of camphorsulfonic acid (CSA)}. CSA neutralizes the remaining triethylamine from the Barton ester formation step, which would otherwise cause inadvertent dimerization of the alkyne. The one-pot reaction sequence begins with Barton ester thermal dissociation to give a nucleophilic ethyl radical that undergoes addition onto the unsubstituted carbon of the terminal alkyne, resulting in a vinyl radical for aromatic substitution. The yields for reactions with indole-3-carbonitrile **1a** and indole-3-carbaldehyde **1b** with methyl and ethyl propiolate to give 6,7-dihydropyrido[1,2-*a*]indoles **2a**, **2b**, and **2d** are 72−79%, with a smaller isolated

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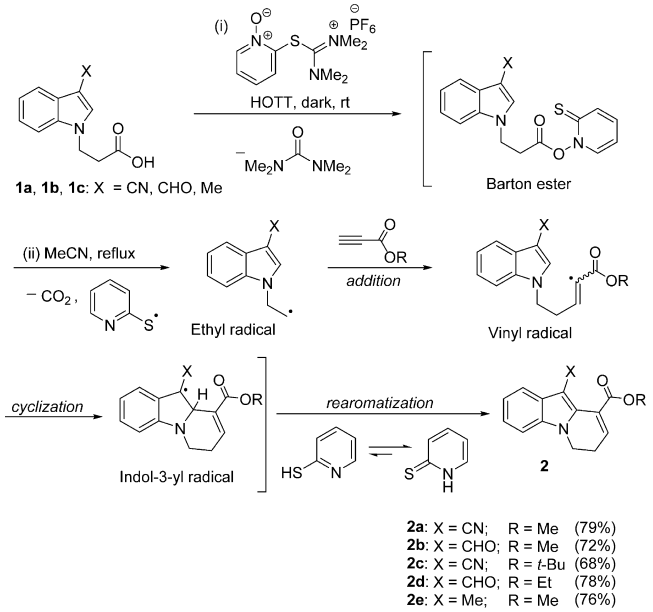
Scheme 1. One-Pot Initiator-Free Tandem Reactions with 3-Substituted Indoles[a]

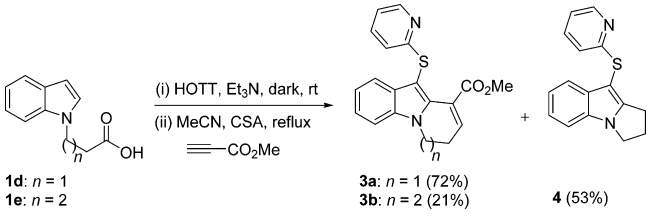


[a]Conditions: (i) Barton ester formation; HOTT (1.5 equiv), Et_3N (3 equiv), THF−MeCN, rt, dark, 40 min; (ii) radical generation and tandem reactions; alkyl propiolate (8 equiv), CSA (4 equiv), MeCN, reflux, 6 h.

yield obtained of adduct **2c** (68%) from the reaction of **1a** with *tert*-butyl propiolate. The tandem protocol is insensitive to substituents at the indole-3-position with 3-methylindole-1-propanoic acid (**1c**), giving 10-methyl-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate **2e** in 76% yield inferring a nonpolar cyclizing radical. An efficient chain for vinyl radical aromatic substitution is indicated since no other indole adducts were observed.

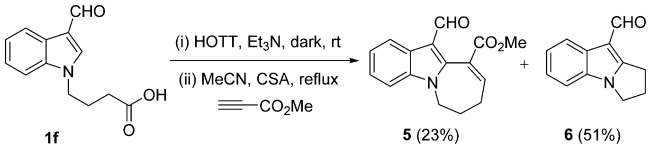
Though ESR data have suggested that α-carboxy and α-phenyl vinylic radicals adopt close to linear π-type resonance stabilized structures,[17,18] a bent σ-type structure has been reported.[19] The conjugation of the vinyl radical with the adjacent substituent gives an electrophilic radical, while a nucleophilic or neutral radical would be expected if the σ-type structure is adopted. The isolation of only aromatic substitution product **3a** in 72% yield from the reaction of 3-unsubstituted 1-indolepropanoic acid **1d** with methyl propiolate (Scheme 2) confirmed that the intermediate vinyl radical is not influenced by polar effects. In agreement with the Barton et al. chain proposal,[13] it can be inferred that the 2-thiopyridinyl *S*-radical traps the intermediate cyclized radical (the indol-3-yl radical in Scheme 1) prior to elimination of 2-pyridinethiol on rearomatization. In contrast to 3-substituted indoles, aromatic *S*-radical adduct **3a** is formed by oxidation during the reaction (presumably by the presence of adventitious oxygen), as confirmed by analysis of the reaction mixture. A mechanism similar to that proposed by Curran and Keller may be involved where hydrogen atom transfer to oxygen would give $HO_2^{\bullet}$,[20] which is used to explain the formation of "oxidized" aromatic substitution products from metal hydride-mediated reactions.[20,21]

Scheme 2. One-Pot Initiator-Free Tandem Reactions with 3-Unsubstituted Indole



A seven-membered vinyl radical cyclization would allow access to the 7,8-dihydro-6*H*-azepino[1,2-*a*]indole system. Use of 3-formylindole-1-butanoic acid **1f** and methyl propiolate allowed isolation of seven-membered adduct 7,8-dihydro-6*H*-azepino[1,2-*a*]indole-10-carboxylate **5**, albeit in 23% yield, with 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **6** predominating in 51% yield (Scheme 3). The higher yield for the propyl radical adduct

Scheme 3. 7,8-Dihydro-6*H*-azepino[1-2-*a*]indole via One-Pot Initiator-Free Tandem Reactions



6 is in accordance with a more favorable five-membered cyclization, where there is also compatible polar effects between the nucleophilic radical and the activated 2-position of indole-3-carbaldehyde. We previously reported a five-membered alkyl radical cyclization occurring in 78% yield via the decomposition of the Barton ester of 3-cyanoindole-1-butanoic acid.[14] Thus, it seemed that the tandem reaction via a cyclizing seven-membered vinyl radical would be more favorable using nonactivated indole **1e** (Scheme 2); however, unexpectedly, this gave 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **4** as the major product in 53% yield with the desired 7,8-dihydro-6*H*-azepino[1,2-*a*]indole-10-carboxylate **3b** isolated in 21% yield. Therefore, it seems that cyclizations of alkyl radicals like vinyl radicals onto indoles are not significantly influenced by polar effects.

The addition of nucleophilic radicals (t-Bu$^{\bullet}$) onto electron-deficient alkyl propiolates is reported to be about 10 times faster than onto phenylacetylene ($\sim k = 2 \times 10^5$ M^{-1} s^{-1} for alkyl propiolates in 1,2-epoxypropane in comparison to $k = 2.1 \times 10^4$ M^{-1} s^{-1} for phenylacetylene in isopropanol at 300 K),[7,17] which may explain the higher yield for reaction of indole-3-carbaldehyde **1b** with alkyl propiolates (Scheme 1) in comparison with phenylacetylene to give the phenyl analogue **7a** in 61% yield with 14% isolated of 2-thiopyridine **8a** (Scheme 4). Nevertheless, this convenient tandem radical approach represents the first synthesis of 9-substituted 6,7-dihydropyrido[1,2-*a*]indoles.

Yields of 8,9-disubstituted 6,7-dihydropyrido[1,2-*a*]indoles **7b** and **7c** (5−23% in Scheme 4) were low from reactions of 3-cyanoindole-1-propanoic acid (**1a**) with internal alkynes under analogous Barton ester conditions to those used for terminal alkynes. The major product was 1-[2-(pyridin-2-ylthio)ethyl]-1*H*-indole-3-carbonitrile (**8b**) (in 59−81% yield), indicative of a less competitive chain for the aromatic substitution. The addition of the intermediate ethyl radical onto disubstituted alkynes is expected to be slow, as indicated by the literature radical addition rates of nucleophilic radicals (t-Bu$^{\bullet}$) onto ethyl 3-phenylprop-2-ynoate and methyl but-2-ynoate, which are k =

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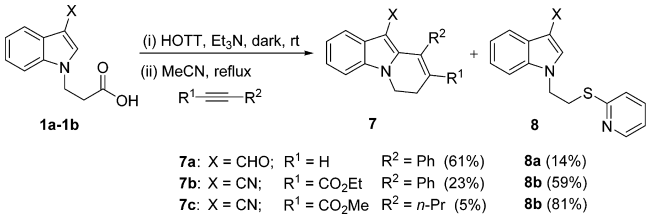
Scheme 4. One-Pot Initiator-Free Tandem Reactions with Less Reactive Alkynes



4.2×10^4 M^{-1} s^{-1} and $k = 5.2 \times 10^2$ M^{-1} s^{-1}, respectively, in 1,2-epoxypropane at 300 K,[7,17] factors of 10−1000 times slower than onto alkyl propiolates. The selectivity of the ethyl radical addition onto ethyl 3-phenylprop-2-ynoate to give an α-styryl vinylic radical and onto methyl hex-2-ynoate to give an α-propyl vinylic radical, respectively, was confirmed by the X-ray crystal structures of the substitution products (Figures S1 and S2, Supporting Information), ethyl 10-cyano-9-phenyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**7b**) and methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**7c**). The addition is thus dictated by steric factors in agreement with the ESR observation of α-phenyl vinyl radical formation from the addition of $Me_3C^{\bullet}$ onto alkyl 3-phenylprop-2-ynoates.[17] The lowest yielding tandem reaction to give adduct **7c** emphasizes the steric congestion about methyl hex-2-ynoate. The formation of sulfides **8a** and **8b** is only observed where the alkyne is less reactive and can occur by alternative ethyl radical reactions such as combination with the 2-thiopyridinyl *S*-radical or from addition onto the Barton ester[13,22] to establish a chain.

In summary, a radical initiator-free (and metal catalyst-free) tandem approach has allowed access to novel alicyclic [1,2-*a*] ring-fused indoles from commercially available reactants. The aromatic substitutions revealed that the vinyl radical is nonpolar as well as allowed the assessment of alkyl radical reactivity toward alkynes.

EXPERIMENTAL SECTION

Materials. Carboxylic acids **1b**−**1f** used are commercially available, although **1a** and **1e** were readily prepared on a gram scale from indole-3-carbonitrile[14] and indole,[23] respectively, by basic alkylation and hydrolysis of methyl esters. HOTT, though commercially available, was accessed using the literature procedure,[16] which, in our hands, yielded almost 10 g of HOTT in 65% yield. Solvents were distilled over appropriate drying agents prior to use, and all reactions were carried out under a nitrogen atmosphere. Et_3N was distilled over CaH_2 before use. Monitoring of reactions by thin layer chromatography (TLC) was carried out on aluminum-backed plates coated with silica gel (60 F_{254}). Column chromatography was carried out using silica gel 60 (particle size 0.040−0.063 mm).

Measurements. IR spectra were obtained using an FT-IR spectrophotometer with an ATR accessory. NMR spectra were recorded using a 400 MHz instrument. Chemical shifts are reported relative to Me_4Si as internal standard, and NMR assignments were supported by DEPT and $^1H-^{13}C$ and $^1H-^1H$ NMR correlation 2D spectra. High-resolution mass spectra (HRMS) were measured using an ESI time-of-flight mass spectrometer (TOFMS) in positive mode. The precision of all accurate mass measurements is better than 5 ppm.

General Procedure for One-Pot Barton Ester Formation and Tandem Radical Reactions. Et_3N (0.32 mL, 2.30 mmol) in THF (5.7 mL) was added to a mixture of carboxylic acid **1a**−**1f** (0.76 mmol) and HOTT (0.424 g, 1.14 mmol) in MeCN (1.9 mL). The solution was stirred at room temperature in the absence of light for 40 min. Alkyne (6.08 mmol) in MeCN (40 mL) and containing CSA (0.711 g, 3.06 mmol) for alkyl propiolates and phenylacetylene was added and heated under reflux for 6 h. The solution was evaporated, dissolved in CH_2Cl_2 (10 mL), and washed with H_2O (2 × 10 mL). The organic extract was evaporated and purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and Et_2O or CH_2Cl_2.

*Methyl 10-Cyano-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (**2a**).* (0.151 g, 79%) off-white solid; mp 125−126 °C; R_f 0.62 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2952, 2215 (CN), 1724 (C═O), 1623, 1473, 1457, 1439, 1337, 1276, 1198, 1082, 1017; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* 8.2 Hz, 1H, 1-H), 7.32−7.25 (m, 4H), 4.17 (t, *J* 7.1 Hz, 2H, 6-CH_2), 3.98 (s, 3H, OCH_3), 2.83−2.77 (m, 2H, 7-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (C═O), 138.7 (8-CH), 135.2, 128.9, 125.7 (all C), 124.8, 122.4 (2,3-CH), 120.2 (1-CH), 115.8 (C), 109.6 (4-CH), 85.1 (CN), 52.2 (OCH_3), 39.0 (6-CH_2), 24.3 (7-CH_2); HRMS (ESI) *m*/*z* (M + H)$^+$ Calcd for $C_{15}H_{13}N_2O_2$ 253.0977; Found 253.0973.

*Methyl 10-Formyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (**2b**).* (0.140 g, 72%) yellow solid; mp 119−120 °C; R_f 0.32 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2952, 1724 (C═O), 1623 (C═O), 1473, 1457, 1439, 1337, 1276, 1198, 1082, 1017; ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H, CHO), 8.36 (d, *J* 7.7 Hz, 1H, 1-H), 7.33−7.24 (m, 4H), 4.14 (t, *J* 7.0 Hz, 2H, 6-CH_2), 3.88 (s, 3H, OCH_3), 2.76 (q, *J* 7.0 Hz, 2H, 7-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0 (CHO), 166.3, (COOMe), 138.6 (8-CH), 136.7, 136.0, 127.1, 126.2 (all C), 124.5, 123.2 (2,3-CH), 122.5 (1-CH), 113.5 (C), 109.2 (4-CH), 52.8 (OCH_3), 38.6 (6-CH_2), 24.2 (7-CH_2); HRMS (ESI) *m*/*z* (M + H)$^+$ Calcd for $C_{15}H_{14}NO_3$ 256.0974; Found 256.0971.

*tert-Butyl 10-Cyano-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (**2c**).* (0.152 g, 68%) yellow oil; R_f 0.76 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2978, 2217 (CN), 1715 (C═O), 1533, 1457, 1428, 1393, 1368, 1287, 1254, 1163, 1080, 1016; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* 7.8 Hz, 1H, 1-H), 7.34−7.24 (m, 3H), 7.17 (t, *J* 4.8 Hz, 1H, 8-H), 4.16 (t, *J* 7.1 Hz, 2H, 6-CH_2), 2.78−2.73 (m, 2H, 7-CH_2), 1.65 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (C═O), 137.3 (8-CH), 135.7, 135.0, 128.7, 127.5 (all C), 124.5, 122.1 (2,3-CH), 120.1 (1-CH), 115.9 (C), 109.5 (4-CH), 83.4 (CN), 38.8 (6-CH_2), 28.0 ((*C*H_3)C), 24.1 (7-CH_2); HRMS (ESI) *m*/*z* (M + H)$^+$ Calcd for $C_{18}H_{19}N_2O_2$ 295.1447; Found 295.1439.

*Ethyl 10-Formyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (**2d**).* (0.160 g, 78%) brown solid; mp 105−107 °C; R_f 0.49 (Et_2O); IR ν_{max} (neat, cm^{-1}) 1719 (C═O), 1649 (C═O), 1456, 1436, 1400, 1333, 1271, 1185, 1130, 1085; ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, CHO), 8.39−8.36 (m, 1H, 1-H), 7.33−7.22 (m, 4H), 4.36 (q, *J* 7.1 Hz, 2H), 4.14 (t, *J* 7.1 Hz, 2H, 6-CH_2), 2.78−2.73 (m, 2H, 7-CH_2), 1.35 (t, *J* 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1 (CHO), 165.9 (COOEt), 138.4 (8-CH), 136.9, 136.0, 127.4, 126.2 (all C), 124.5, 123.2 (2,3-CH), 122.6 (1-CH), 113.5 (C), 109.2 (4-CH), 62.0 (OCH_2), 38.6 (6-CH_2), 24.2 (7-CH_2), 14.2 (CH_3); HRMS (ESI) *m*/*z* (M + H)$^+$ $C_{16}H_{16}NO_3$ Calcd 270.1130; Found 270.1132.

*Methyl 10-Methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (**2e**).* (0.139 g, 76%) yellow oil; R_f 0.43 (CH_2Cl_2); IR ν_{max} (neat, cm^{-1}) 2949, 1726 (C═O), 1464, 1438, 1385, 1334, 1271, 1195, 1179, 1077, 1016; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* 7.8 Hz, 1H, 1-H), 7.22−7.21 (m, 2H), 7.10−7.05 (m, 1H), 6.79 (t, *J* 5.0 Hz, 1H, 8-H), 4.07 (t, *J* 6.6 Hz, 2H, 6-CH_2), 3.90 (s, 3H, OCH_3), 2.68−2.63 (m, 2H, 7-CH_2), 2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C═O), 135.8 (C), 131.8 (8-CH), 129.0, 127.9, 127.2 (all C), 122.7 (CH), 119.3 (1-CH), 119.0 (CH), 109.1 (C), 108.4 (4-CH), 52.1 (OCH_3), 38.7 (6-CH_2), 24.8 (7-CH_2), 10.0 (CH_3); HRMS (ESI) *m*/*z* (M + H)$^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1181; Found 242.1178.

*Methyl 10-(Pyridine-2-ylthio)-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (**3a**).* (0.183 g, 72%) yellow oil; R_f 0.45 (Et_2O); IR ν_{max} (neat, cm^{-1}) 3052, 2947,2983, 1726 (C═O), 1574, 1559, 1448, 1435, 1417, 1341, 1272, 1194, 1170, 1127, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41−8.39 (m, 1H, pyr-6-H), 7.56 (d, *J* 8.0 Hz, 1H, 1-H), 7.37−7.28 (m, 3H), 7.15−7.11 (m, 1H), 6.95−6.92 (m, 1H, pyr-5-H), 6.79 (t, *J* 4.9 Hz, 1H, 8-H), 6.75 (d, *J* 8.0 Hz, 1H, pyr-3-H), 4.22 (t, *J* 6.8 Hz, 2H, 6-CH_2), 3.50 (s, 3H, OCH_3), 2.77−2.72 (m, 2H, 7-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, (C═O), 162.6 (pyr-2-C), 149.2 (pyr-6-CH), 136.5 (pyr-4-CH), 135.1 (C), 133.1 (8-CH), 130.0,

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128.0 (both C), 123.9, 121.1 (both CH), 120.2 (×2 CH), 119.2 (pyr-5-CH), 109.2 (4-CH), 98.3 (C), 52.1 (OCH_3), 39.3 (6-CH_2), 24.4 (7-CH_2); HRMS (ESI) m/z $(M + H)^+$ $C_{19}H_{17}N_2O_2S$ Calcd 337.1011; Found 337.1003.

*Methyl 11-(Pyridin-2-ylthio)-7,8-dihydro-6H-azepino[1,2-a]indole-10-carboxylate (**3b**).* (56 mg, 21%) yellow oil; R_f 0.55 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2949, 1719 (C═O), 1577, 1559, 1449, 1417, 1265, 1126, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39–8.37 (m, 1H, pyr-6-H), 7.57 (d, J 8.0 Hz, 1H, 1-H), 7.41 (d, J 8.5 Hz, 1H, 4-H), 7.36 (t, J 7.0 Hz, 1H, 9-H) 7.33–7.28 (m, 2H), 7.17–7.12 (m, 1H) 6.92–6.89 (m, 1H, pyr-5-H), 6.69 (d, J 8.3 Hz, 1H, pyr-3-H), 4.28 (t, J 6.3 Hz, 2H, 6-CH_2), 3.43 (s, 3H, OCH_3), 2.35–2.29 (m, 2H), 2.28–2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C═O), 162.3 (pyr-2-C), 149.1 (pyr-6-CH), 144.0 (9-CH), 139.3, 136.6 (both C), 136.3 (pyr-4-CH), 129.1, 128.4 (both C), 123.1, 120.9 (both CH), 119.9 (×2 CH), 119.0 (pyr-5-CH), 109.3 (4-CH), 99.9 (C), 52.0 (OCH_3), 41.9 (6-CH_2), 29.7, 25.3 (both CH_2); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{20}H_{19}N_2O_2S$ 351.1167; Found 351.1180.

*9-(Pyridin-2-ylthio)-2,3-dihydro-1H-pyrrolo[1,2-a]indole (**4**).* (107 mg, 53%) off-white solid; mp 147–148 °C; R_f 0.68 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2953, 1574, 1558, 1449, 1417, 1339, 1298, 1229, 1125, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41–8.39 (m, 1H, pyr-6-H), 7.55 (d, J 8.0 Hz, 1H, 8-H), 7.33–7.28 (m, 2H), 7.22–7.18 (m, 1H), 7.15–7.11 (m, 1H), 6.92–6.89 (m, 1H, pyr-5-H), 6.70 (d, J 8.3 Hz, 1H, pyr-3-H), 4.19 (t, J 7.1 Hz, 2H, 3-CH_2), 3.08 (t, J 7.6 Hz, 2H, 1-CH_2) 2.70–2.62 (m, 2H, 2-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (pyr-2-C), 151.0 (C), 149.3 (pyr-6-CH), 136.4 (pyr-4-CH), 134.1, 133.3 (both C), 121.5, 120.4, 119.2, 119.1 (all CH), 118.9 (pyr-5-CH), 109.9 (5-CH), 90.3 (C), 44.8 (3-CH_2), 27.0 (2-CH_2), 24.0 (1-CH_2); HRMS (ESI) m/z $(M + H)^+$ $C_{16}H_{15}N_2S$ Calcd 267.0956; Found 267.0963.

*Methyl 11-Formyl-7,8-dihydro-6H-azepino[1,2-a]indole-10-carboxylate (**5**).* (47 mg, 23%) yellow oil; R_f 0.33 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2952, 1720 (C═O), 1653 (C═O), 1575, 1518, 1458, 1438, 1393, 1376, 1267, 1246, 1210, 1128, 1072, 1051; ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H, CHO), 8.34–8.31 (m, 1H, 1-H), 7.69 (t, J 7.3 Hz, 1H, 9-H), 7.40–7.30 (m, 3H), 4.24 (t, J 6.4 Hz, 2H, 6-CH_2), 3.82 (s, 3H, OCH_3), 2.33–2.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8 (CHO), 165.5 (COOMe), 147.0 (9-CH), 142.1, 136.2, 127.8, 125.8 (all C), 123.9, 123.0 (2,3-CH), 121.7 (1-CH), 114.9 (C), 109.2 (4-CH), 52.6 (OCH_3), 41.5 (6-CH_2), 30.4, 24.7 (both CH_2); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{16}H_{16}NO_3$ 270.1130; Found 270.1136.

*2,3-Dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (**6**).* (72 mg, 51%) off-white solid; mp 134–135 °C (mp[24] 136 °C).

*9-Phenyl-6,7-dihydropyrido[1,2-a]indole-10-carbaldehyde (**7a**).* (0.127 g, 61%) yellow solid; 123–124 °C; R_f 0.65 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2978, 1643 (C═O), 1576, 1469, 1456, 1428, 1394, 1368, 1331, 1300, 1175, 1127, 1067; ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H, CHO), 8.41 (d, J 7.8 Hz, 1H, 1-H), 7.45–7.30 (m, 7H), 7.29–7.26 (m, 1H), 6.33 (t, J 5.0 Hz, 1H, 8-H), 4.22 (t, J 7.1 Hz, 2H, 6-CH_2), 2.80–2.74 (m 2H, 7-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, (CHO), 142.2, 139.9, 136.2, 134.5 (all C), 129.0 (8-CH, Ph-CH), 128.6, 128.3 (Ph-CH), 126.2 (C), 124.4, 123.2, 123.1 (1,2,3-CH), 113.8 (C), 109.0 (4-CH), 39.4 (6-CH_2), 24.0 (7-CH_2); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{19}H_{16}NO$ 274.1232; Found 274.1229.

*1-[2-(Pyridin-2-ylthio)ethyl]-1H-indole-3-carbaldehyde (**8a**).* (30 mg, 14%) pale yellow oil; R_f 0.35 (Et_2O); IR ν_{max}(neat, cm^{-1}) 3046, 2809, 1655 (C═O), 1558, 1577, 1531, 1467, 1454, 1415, 1400, 1388, 1164, 1151, 1125, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H, CHO), 8.43–8.41 (m, 1H, pyr-6-H), 8.28 (d, J 7.8 Hz, 1H, 4-H), 7.72 (s, 1H, 2-H), 7.56 (d, J 8.3 Hz, 1H, 7-H), 7.48–7.43 (m, 1H, pyr-4-H), 7.36–7.27 (m, 2H, 5,6-H), 7.14 (d, J 8.2 Hz, 1H, pyr-3-H), 7.02–6.98 (m, 1H, pyr-5-H), 4.48 (t, J 7.1 Hz, 2H, NCH_2), 3.55 (t, J 7.1 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7 (CHO), 156.9 (pyr-2-C), 149.6 (pyr-6-CH) 139.0 (2-CH), 137.2 (C), 136.3 (pyr-4-CH), 125.5 (C), 124.1, (pyr-3-CH), 123.0, 122.7 (5,6-CH) 122.2 (4-CH), 120.1 (pyr-5-CH), 118.3 (C), 110.4 (7-CH), 47.1 (NCH_2), 29.3 (CH_2); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{16}H_{15}N_2OS$ 283.0905; Found 283.0911.

*Ethyl 10-Cyano-9-phenyl-6,7-dihydropyrido[1,2-a]indole-8-carboxylate (**7b**).* (60 mg, 23%) off-white solid; mp 119–120 °C; R_f 0.31 (CH_2Cl_2); IR ν_{max}(neat, cm^{-1}) 2980, 2213 (CN), 1696 (C═O), 1475, 1426, 1378, 1296, 1247, 1216, 1130, 1110, 1017; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J 8.0 Hz, 1H, 1-H), 7.53–7.43 (m, 3H), 7.40–7.35 (m, 2H), 7.30–7.21 (m, 3H), 4.31 (t, J 7.2 Hz, 2H, 6-CH_2), 3.98 (q, J 7.2 Hz, 2H, OCH_2), 3.11 (t, J 7.2 Hz, 2H, 7-CH_2), 0.90 (t, J 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C═O), 140.1, 137.5, 135.9, 135.8, 129.2 (all C), 129.1, 129.0, 128.5 (Ph-CH), 126.6 (C), 125.5, 122.5 (2,3-CH), 120.3 (1-CH), 113.6 (CN), 109.9 (4-CH), 88.3 (C), 61.0 (OCH_2), 40.0 (6-CH_2), 25.7 (7-CH_2), 13.6 (CH_3); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{22}H_{19}N_2O_2$ 343.1447; Found 343.1444.

*1-[2-(Pyridin-2-ylthio)ethyl]-1H-indole-3-carbonitrile (**8b**).* (0.125 g, 59%) yellow oil; R_f 0.28 (CH_2Cl_2); IR ν_{max} (neat, cm^{-1}) 2927, 2217 (CN), 1578, 1558, 1533, 1467, 1455, 1415, 1392, 1349, 1283, 1250, 1167, 1125, 1015; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J 5.0 Hz, 1H, pyr-6-H), 7.73 (d, J 8.3 Hz, 1H, pyr-4-H), 7.64 (s, 1H, 2-H), 7.61 (d, J 8.2 Hz, 1H, 4-H), 7.52–7.46 (m, 1H, 7-H), 7.37–7.26 (m, 2H, 5,6-H), 7.15 (d, J 7.8 Hz, 1H, pyr-3-H), 7.04–7.00 (m, 1H, pyr-5-H), 4.50 (t, J 7.1 Hz, 2H, NCH_2), 3.55 (t, J 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (pyr-2-C), 149.6 (pyr-6-CH), 136.4 (pyr-4-CH), 135.4 (C), 135.3 (2-CH), 128.0 (C), 124.0 (pyr-3-CH) 122.8, 122.3 (5,6-CH), 120.1 (pyr-5-CH), 120.0 (4-CH), 116.0 (CN), 110.9 (7-CH), 85.9 (C), 47.1 (NCH_2), 29.4 (CH_2); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{16}H_{14}N_3S$ 280.0908; Found 280.0905.

*Methyl 10-Cyano-9-propyl-6,7-dihydropyrido[1,2-a]indole-8-carboxylate (**7c**).* (11 mg, 5%) pale yellow solid; mp 120–122 °C; R_f 0.63 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2925, 2215 (CN), 1715 (C═O), 1596, 1457, 1423, 1292, 1272, 1245, 1213, 1086; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J 8.0 Hz, 1H, 1-H), 7.39–7.33 (m, 2H), 7.29–7.25 (m, 1H), 4.15 (t, J 7.1 Hz, 2H, 6-CH_2), 3.85 (s, 3H, OCH_3), 3.18 (t, J 8.0 Hz, 2H), 2.93 (t, J 7.1 Hz, 2H, 7-CH_2), 1.76–1.66 (m, 2H), 1.08 (t, J 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C═O), 149.9, 139.9, 135.4, 128.9 (all C), 125.3, 122.6 (2,3-CH), 122.3 (C), 120.1 (1-CH), 116.3 (CN), 109.9 (4-CH), 85.4 (C), 52.1 (OCH_3), 39.9 (6-CH_2), 31.2 (CH_2), 25.6 (7-CH_2), 23.8 (CH_2), 13.9 (CH_3); HRMS (ESI) m/z $(M + H)^+$ Calcd for $C_{18}H_{19}N_2O_2$ 295.1447; Found 295.1445.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystal structures of **7b** and **7c** (with CIF files) and ^1H NMR and ^{13}C NMR of all products. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-996100 for (**7b**) and CCDC-996099 for (**7c**).

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Notes

The authors declare no competing financial interest.

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