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Two-Step Route to Indoles and Analogues from Haloarenes: A Variation on the Fischer Indole Synthesis

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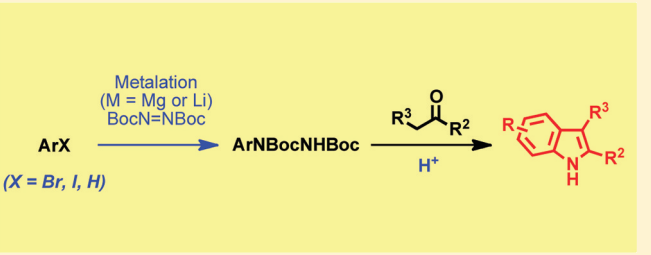
Supporting Information

ABSTRACT: In a new variation on the Fischer indole synthesis, readily available haloarenes are converted into a wide range of indoles in just two steps by halogen−magnesium exchange and quenching with di-*tert*-butyl azodicarboxylate, followed by reaction with aldehydes or ketones under acidic conditions. The protocol, which is readily extended to the preparation of indole isosteres, 4- and 6-azaindoles and thienopyrroles, obviates the need to prepare potentially toxic aryl hydrazines, simultaneously avoiding undesirable anilines such as naphthylamines.



INTRODUCTION

Indoles exhibit potent and wide-ranging biological activity, and complex and unusual architectures are found among their naturally occurring derivatives. As a result, this important ring system continues to hold a fascination for chemists worldwide,[1−6] and therefore, useful methodologies for the synthesis of this venerable, but nonetheless ever relevant, heteroaromatic ring continue to be developed. Unfortunately, even modern methods, often transition-metal catalyzed, frequently start from *ortho*-substituted anilines,[7−9] thereby greatly restricting the availability of starting materials. A more general approach would start from a monofunctionalized arene such as an aniline, followed by cyclization with C−C bond formation to an unactivated C−H bond, and several classical and modern approaches both fall into this category.

The Bischler reaction, discovered 100 years ago,[10,11] involves the reaction of anilines with α-halo ketones followed by acid-catalyzed cyclization of the resulting α-(*N*-arylamino) ketones (Scheme 1A). Subsequent modifications by Nordlander and by Sundberg replaced α-halo ketones with the corresponding acetals,[12,13] while work from our own laboratory employed rhodium(II)- or copper(II)-mediated carbene N−H insertion reactions to form the α-(*N*-arylamino) ketones.[14−16] Other routes which also start from anilines are the Gassman method (Scheme 1B),[17] the Sugasawa method (Scheme 1C),[18] and the reaction of *N*-tosylanilines with propynyl iodonium triflates.[19]

Other notable advances in the synthesis of indoles from anilines have been reported in the past decade, and these include the ruthenium-catalyzed routes from ethanolamines (Scheme 2A),[20] or 1,2-diols (Scheme 2B).[21] In the same vein, Glorius and colleagues described the palladium(II)-catalyzed oxidative cyclization of *N*-arylenamines derived from anilines and 1,3-dicarbonyl compounds,[22,23] with related copper(I)-, iron(III)-, iodine(III)-, and iodine-mediated oxidative cyclizations being subsequently reported (Scheme 2C,D),[24−27] while the Fagnou group conceived a complementary approach involving rhodium-catalyzed coupling of acetanilides with alkynes (Scheme 2E).[28] Finally in a recent development, Knochel and co-workers found that reaction of aryldiazonium salts with organozinc reagents followed by microwave heating delivered a range of indoles (Scheme 2F).[29,30] Notwithstanding the efficiency of some of these contemporary approaches, the toxicity associated with many anilines makes them less than ideal starting materials.

However, despite modern advances, we should also recognize that some of the historically most important indole syntheses also start from a monofunctionalized arene followed by cyclization with C−C bond formation to an unactivated C−H bond. Pre-eminent among these is the most famous of all indole syntheses, the Fischer reaction,[5,31,32] that involves functionalization of an unactivated aromatic C−H position by way of a [3,3]-sigmatropic shift. Although maybe passé, this celebrated reaction meets all the requirements of a modern indole synthesis in its convenience and simplicity—coupling a monofunctionalized arene with a readily available aldehyde or ketone, the only disadvantage being the relatively small range of aryl hydrazines that are readily available. Mindful of this limitation, we now report the full details of a new variation on the Fischer reaction that starts from much more readily available haloarenes and -heteroaromatics, rather than the more toxic anilines, and delivers a wide range of indoles and heterocyclic-fused pyrroles and in just two steps.[33]

RESULTS AND DISCUSSION

In planning a straightforward route from haloarenes to aryl hydrazines, and hence indoles, we were attracted by the use of di-*tert*-butyl azodicarboxylate as a source of the hydrazine unit,

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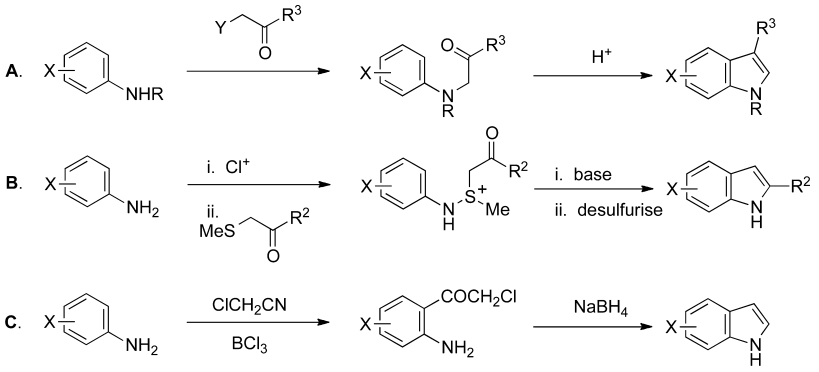
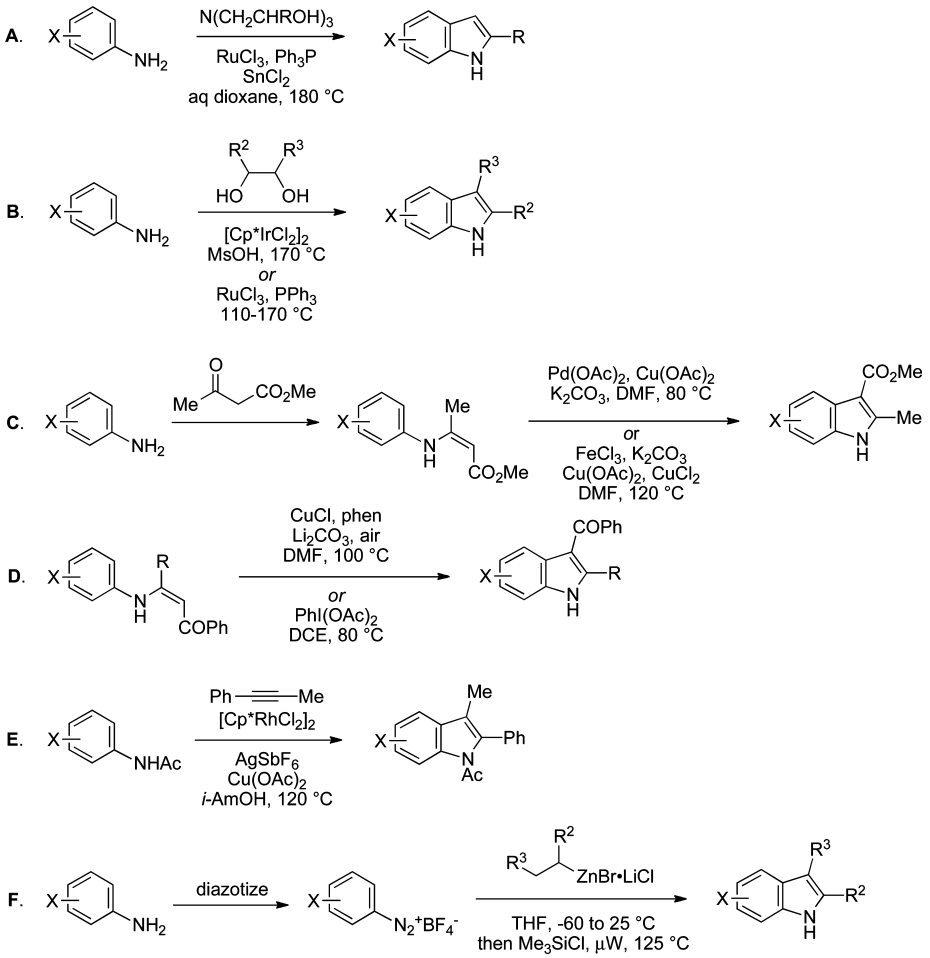
Scheme 1. Some Routes from Anilines to Indoles



Scheme 2. Further Routes from Anilines to Indoles



since the ensuing Boc-protecting groups would undergo concomitant cleavage under the Brønsted or Lewis acidic conditions of the Fischer cyclization. Such a method would complement and extend other routes from haloarenes to aryl hydrazine derivatives that have been developed recently, starting a decade ago with Hartwig's palladium-catalyzed coupling of bromobenzenes with benzophenone hydrazone.[34] Almost simultaneously, Buchwald and co-workers reported a similar Pd-coupling to benzophenone hydrazone,[35,36] followed by concomitant removal of benzophenone and indolization under acidic conditions (Scheme 3A), and in a useful recent development the reaction has been extended to the Pd-catalyzed coupling of chlorobenzenes with hydrazine itself.[37]

Related indolization strategies involving copper(I)-catalyzed coupling of iodobenzenes with *tert*-butyl or benzyl carbazates have also been reported (Scheme 3B).[38−40] An alternative entry into the Fischer reaction manifold comes from the addition of aryllithiums to α-diazoesters (Scheme 3C), a reaction that proceeds by nucleophilic attack of the organometallic reagent onto the terminal nitrogen of the diazo group to give the corresponding hydrazone after tautomerization of the intermediate azo compound.[41,42] The recently published method involving organozinc addition to aryldiazonium species (Scheme 2F) presumably proceeds by the same mechanism.

The low-lying LUMOs of azodicarboxylates render them reactive dienophiles, enophiles,[43] and electrophiles, and as such

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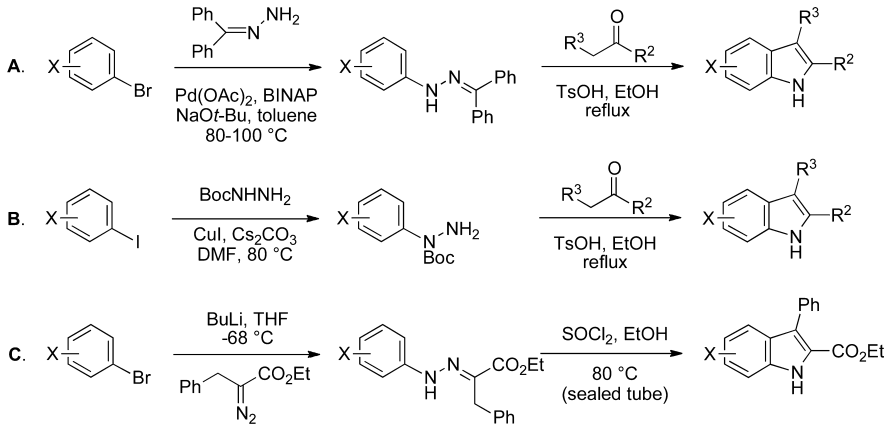
Scheme 3. Routes from Halobenzenes to Indoles



they readily participate in Diels–Alder cycloadditions and the well-known Mitsunobu reaction. However, they have also found use as electrophiles in reactions with electron-rich aromatic rings,[44,45] organolithiums and Grignard reagents,[46,47] organozincs,[48] or boronic acids under copper[49,50] or palladium catalysis.[51] In order to access aryl hydrazines from azodicarboxylates, we elected to employ the underutilized Grignard-based procedure because of the advantages of functional group compatibility using modern methods of halogen–magnesium exchange.[52] Thus, aryl halides underwent halogen–magnesium exchange upon treatment with isopropylmagnesium chloride in THF,[52] or phenylmagnesium chloride in the case of nitro containing aromatics,[53] followed by reaction with di-*tert*-butyl azodicarboxylate to give the di-Boc-protected aryl hydrazines **2a–i** in 71–98% yield (Table 1). The reaction is tolerant of a wide range of functional groups including fluoride, chloride, sulfonyloxy, nitro, and carboxylate ester. As expected, aryl bromides underwent slower halogen–magnesium exchange than the iodides,[54] allowing for selective magnesiation of 2-bromoiodobenzene (entry 1). Nevertheless the di-Boc-protected aryl hydrazines **2c,f–h,j** were readily obtained from the corresponding bromides in good yields (entries 4, 8, 10, 12, and 17), although the more reactive isopropylmagnesium chloride–lithium chloride reagent[52] had to be used to effect efficient magnesiation in two cases. For the synthesis of more electron-rich aryl hydrazides such as **2g**, where bromine–magnesium exchange is slow,[54] more traditional Grignard formation using magnesium metal proved the best method. In the case of 2,4,6-tribromophenyl mesylate, selective mono-metalation gave the hydrazine **2j** when the magnesiation was carried out at −40 °C. The procedure is not limited to halogen-metal exchange, and aryllithiums obtained by directed *ortho*-metalation[55] also react readily with di-*tert*-butyl azodicarboxylate, as illustrated by the synthesis of hydrazine derivatives **2k** and **2l** (entries 18 and 19).

With a range of di-Boc-protected aryl hydrazines **2** available, their conversion into indoles was investigated. Reaction of hydrazines **2** with an array of ketones under acidic conditions resulted in cleavage of the protecting groups, hydrazone formation, and Fischer indolization in a single pot to give a variety of indoles **3** in good to excellent yield (Table 1), the only exceptions being the tetrahydrocarbazoles **3n** and **3o**. A variety of acidic conditions were investigated (Table 1), but the most generally applicable were the use of concentrated hydrochloric acid in ethanol at 70 °C, although in some cases the use of acetic acid as solvent, or the use of neat TFA, was found to be superior (Table 1). Indoles bearing a broad range of substituents were readily obtained by this method, the *meta*-chloro-substituted hydrazide **2f** giving, as expected,[56] only the 6-chloroindole **3f**. Likewise, the hydrazone derived from hydrazide **2g** gave a single indole product **3g**. Aldehydes can also be used as the carbonyl component as illustrated by the synthesis of the 2-unsubstituted indole **3m** (entry 15).

This new variation of the classical Fischer indole synthesis is operationally straightforward, and the use of haloarenes as starting materials obviates the need to prepare aryl hydrazines from anilines by the oft problematic diazotization-reduction sequence, simultaneously avoiding undesirable anilines such as naphthylamines. Given the success of this practical, modern variation on the Fischer indole synthesis, we next extended it to the synthesis of azaindoles, compounds of current interest as isosteres of bioactive indoles. Although azaindoles are accessible by a range of methods,[57−59] the Fischer cyclization has been rarely used.[60] After some experimentation, 2-methoxy-5-bromopyridine **4** was metalated with *n*-butyllithium and converted into the Boc-protected pyridyl hydrazine **5** (80%). Likewise, the 2-methoxy-3-bromo isomer **7** was converted into hydrazine **8** in good yield. Metalation employing isopropylmagnesium chloride–lithium chloride or the use of the corresponding chloropyridines were unsatisfactory. Reaction of the hydrazine **5** with ketones and aldehydes under acidic conditions (4% aqueous sulfuric acid[60]) resulted in cleavage of the protecting groups, hydrazone formation, and Fischer indolization in a single pot to give a variety of 4-azaindoles **6** in modest to good yield (Table 2). In agreement with recent findings,[60] the indolization of the unsymmetrical hydrazine derivative **5** gave exclusively 4-azaindoles, with no evidence for the formation of 6-azaindoles, the alternative cyclization products. 6-Azaindoles **9** were, however, readily prepared in modest yield from reaction of the pyridyl hydrazine derivative **8** with aldehydes and ketones (Table 2). In general, yields of azaindoles were somewhat lower than their indole counterparts, possibly a reflection of the effect of the electron withdrawing pyridine ring on the [3,3]-sigmatropic rearrangement. Owing to their reported unreactivity,[60] no attempts were made to extend the method to pyridylhydrazines lacking the electron-donating methoxy group.

Finally, we extended the methodology to the synthesis of thieno[2,3-*b*]pyrroles, another isosteric replacement for indoles that is attracting attention among medicinal chemists.[61,62] Starting from methyl 5-bromothiophene-2-carboxylate **10**, magnesiation and reaction with of di-*tert*-butyl azodicarboxylate

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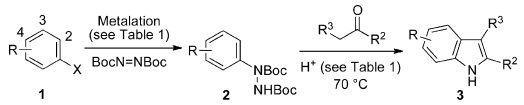
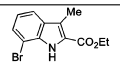
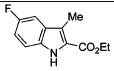
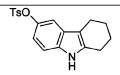
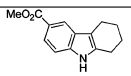
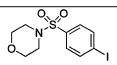
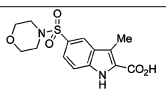
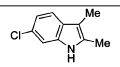
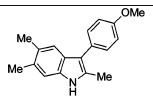
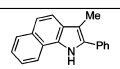
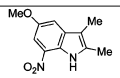
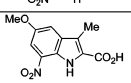
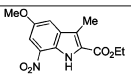
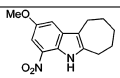
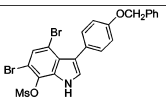
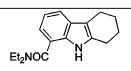
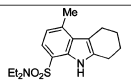
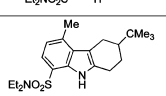
Table 1. Two-Step Synthesis of Indoles from Halobenzenes



Entry	ArX	2	Metalation Conditions[a]	Yield /%	R^2	R^3	Fischer Conditions[b]	Indole	3	Yield /%
1		**2a**	A	72	CO_2H	Me	A		**3a**[c]	70
2		**2b**	A	93	CO_2H	Me	A		**3b**[c]	66
3		**2c**	A	87	$(CH_2)_4$		A		**3c**	90
4		**2c**	B	76	-	-	-	-	-	-
5		**2d**	A	71	$(CH_2)_4$		B		**3d**	89
6		**2e**	A	74	CO_2H	Me	C		**3e**	83
7		**2f**	A	81	Me	Me	A		**3f**	76
8		**2f**	B	77	-	-	-	-		
9		**2g**	A	76	Me	4-$MeOC_6H_4$	A		**3g**	68
10		**2g**	C	79	-	-	-	-		
11		**2h**	A	98	Ph	Me	A		**3h**	92
12		**2h**	B	66	-	-	-	-	-	-
13		**2i**	D	80	Me	Me	C		**3i**	96
14		**2i**			CO_2H	Me	C		**3j**	100
15		**2i**			CO_2Et	Me	B		**3k**	97
16		**2i**			$(CH_2)_5$		C		**3l**	75
17		**2j**	E	80	H	4-$BnOC_6H_4$	D		**3m**	65
18		**2k**	F	61	$(CH_2)_4$		D		**3n**	26
19		**2l**	G	75	$(CH_2)_4$		A		**3o**	38
20		**2l**			$(CH_2)_2CCMe_3(CH_2)$		A		**3p**	70

[a]Metalation conditions: (A) *i*-PrMgCl, −20 to 0 °C, THF; (B) *i*-PrMgCl·LiCl, rt, THF; (C) Mg (activated with I_2), THF, rt; (D) PhMgCl, −40 °C, THF; (E) *i*-PrMgBr, THF, −40 °C; (F) *s*-BuLi, TMEDA, −78 °C, THF; (G) n-BuLi, −78 °C, THF. [b]Fischer conditions: (A) aq HCl (35%), 70 °C, EtOH; (B) TFA, 70 °C; (C) aq HCl (35%), 70 °C, AcOH; (D) PTSA, EtOH, reflux. [c]Esterification occurs during reaction.

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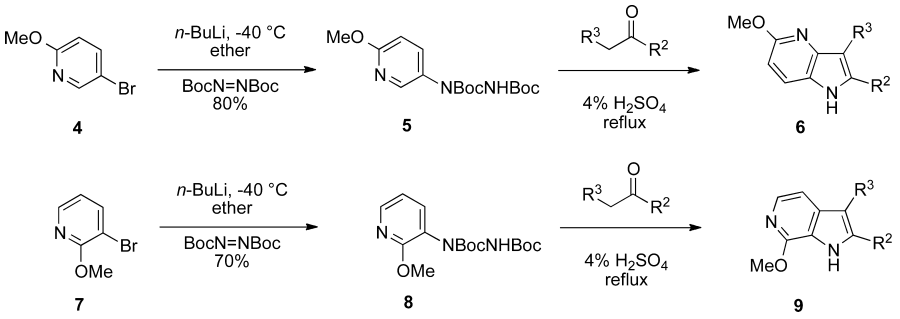
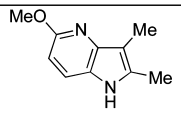
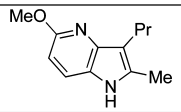
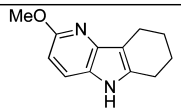
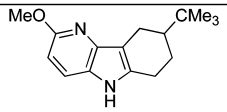
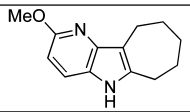
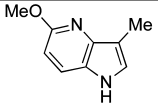
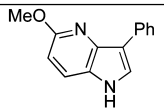
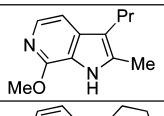
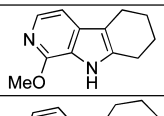
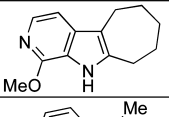
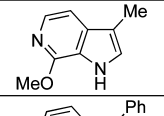
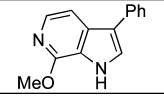
Table 2. Two-Step Synthesis of 4- and 6-Azaindoles from Bromopyridines



Entry	Hydrazide	R^2	R^3	Azaindole	6/9	Yield /%
1	**5**	Me	Me		**6a**	57
2	**5**	Me	Pr		**6b**	41
3	**5**	$(CH_2)_4$			**6c**	82
4	**5**	$(CH_2)_2CCMe_3(CH_2)$			**6d**	53
5	**5**	$(CH_2)_5$			**6e**	62
6	**5**	H[a]	Me		**6f**	72
7	**5**	H[a]	Ph		**6g**	56
8	**8**	Me	Pr		**9a**	33
9	**8**	$(CH_2)_4$			**9b**	49
10	**8**	$(CH_2)_5$			**9c**	46
11	**8**	H	Me		**9d**	41
12	**8**	H	Ph		**9e**	40

[a]When aldehydes used (R^2 = H) as their diethyl or dimethyl acetals.

gave the thiophene hydrazine derivative **11** in excellent yield. Reaction of the di-Boc-protected hydrazine **11** with a range of ketones in ethanol in the presence of *p*-toluenesulfonic acid (PTSA) gave the corresponding thienopyrroles **12** in good to excellent yield (Table 3). Attempts to extend the protocol to the corresponding furo[2,3-*b*]pyrroles or thiophenes lacking

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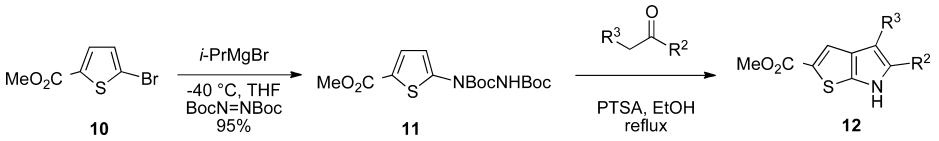
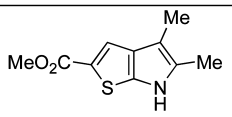
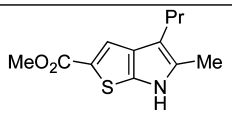
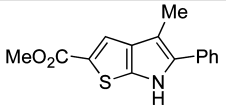
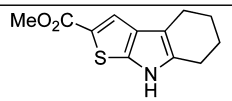
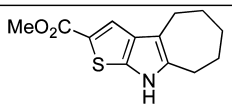
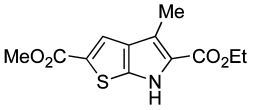
Table 3. Two-Step Synthesis of Thieno[2,3-*b*]pyrrole-2-carboxylates



Entry	R^2	R^3	Thieno[2,3-*b*]pyrrole	**12**	Yield /%
1	Me	Me		**12a**	62
2	Me	Pr		**12b**	86
3	Ph	Me		**12c**	61
4	$(CH_2)_4$			**12d**	71
5	$(CH_2)_5$			**12e**	59
6	CO_2Et	Me		**12f**	62

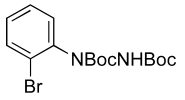
the electron-withdrawing ester group were unsuccessful owing to the instability of the heterocyclic ring under the acidic Fischer indolization conditions.

The advantages of this new variation of the classical Fischer indole synthesis, incorporating the previously little used reaction of Grignard reagents with azodicarboxylate electrophiles as a key step, lie in its simplicity and versatility. Haloarenes are appealing starting materials that are more readily available and less toxic than aryl hydrazines or anilines. The method can be extended to halopyridines and -thiophenes, and hence azaindoles and thienopyrroles. These features combine to make this an attractive and highly practical alternative modern protocol for the synthesis of the fundamentally important indole ring system and its isosteres.

■ EXPERIMENTAL SECTION

General Experimental Details. Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere. Light petroleum refers to the fraction with bp 40−60 °C. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin-layer chromatography was carried out on aluminum backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm and/or potassium permanganate or ethanolic vanillin dip. Chromatography was carried out on silica gel. Fully characterized compounds were chromatographically homogeneous. Infrared spectra were recorded on an FT-IR spectrometer in the range 4000−600 cm^{-1} as solutions in chloroform. NMR spectra were recorded on a 400 MHz (^1H frequency) spectrometer. Chemical shifts are quoted in ppm and *J* values in Hz. Chemical shift values are referenced against residual proton in the deuterated solvents. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 are assigned from DEPT-90 and −135 spectra; all others are quaternary C. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI).

General Procedures. *Synthesis of Aryl Hydrazides from Aryl Iodides.* An oven-dried flask was cooled to room temperature under argon, charged with a solution of aryl iodide (1.0 mol equiv) in THF (4−20 mL/mmol), and then cooled to −20 °C. A solution of isopropylmagnesium chloride in THF (2.0 M; 1.1 mol equiv) was added dropwise over 5 min, and the resulting mixture was stirred at −20 °C for 1 h then 0 °C for 1 h (note that phenylmagnesium chloride was used for halides containing a nitro group). A solution of di-*tert*-butyl azodicarboxylate (1.3 mol equiv) in THF (4 mL/mmol) was added dropwise over 5 min at 0 °C, and the resulting mixture was stirred at 0 °C to room temperature for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL/10 mmol), diluted with water (50 mL/10 mmol), and extracted with ethyl acetate (3 × 40 mL/10 mmol). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Column chromatography of the residue gave the product.



*Di-tert-butyl 1-(2-Bromophenyl)hydrazine-1,2-dicarboxylate (**2a**).* Prepared by the general procedure from 2-bromoiodobenzene (2.83 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum

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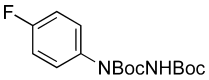
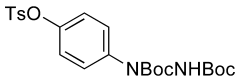
and ethyl acetate (11:1) as a mixture of rotamers, as a colorless solid (2.771 g, 72%): mp 94−96 °C; found M + Na^+, 409.0737, $C_{16}H_{23}{}^{79}BrNaN_2O_4$ requires 409.0739); ν_{max} ($CHCl_3$)/cm^{-1} 3401, 2983, 1716, 1480, 1370, 1244, 1155; δ_H (400 MHz; $CDCl_3$) 7.71 (1H, br s), 7.58 (1H, d, *J* 7.9), 7.35−7.33 (1H, m), 7.18 (1H, td, *J* 7.5, 1.5), 6.97 (1H, br s), 1.49 (18H, s); δ_C (100 MHz; $CDCl_3$) mixture of rotamers 155.3, 154.8, 153.7, 141.2, 140.6, 132.8 (CH), 132.6 (CH), 131.2 (CH), 129.5 (CH), 129.4 (CH), 128.3 (CH), 128.1 (CH), 122.7 (CH), 122.6 (CH), 82.3, 81.6, 81.5, 28.2 (Me), 28.1 (Me), 28.0 (Me); *m*/*z* (ESI) 409 (M + Na^+, 99), 411 (M + Na^+, 100).

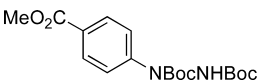


Di-tert-butyl 1-(4-Fluorophenyl)hydrazine-1,2-dicarboxylate (**2b**). Prepared by the general procedure from 4-fluoroiodobenzene (2.22 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (9:1) as a colorless solid (3.03 g, 93%): mp 128−130 °C; found M + Na^+, 349.1541, $C_{16}H_{23}FNaN_2O_4$ requires 349.1534; ν_{max} ($CHCl_3$)/cm^{-1} 3402, 2983, 1746, 1716, 1510, 1370, 1152; δ_H (400 MHz; $CDCl_3$) 7.39 (2H, br s), 7.02 (2H, dd, *J* 8.8, 8.6), 6.77 (1H, br s), 1.51 (18H, s); δ_C (100 MHz; $CDCl_3$) 160.5 (d, *J* 246, CF), 155.4, 153.7, 138.3, 125.9 (CH), 115.2 (d, *J* 23, CH), 85.5, 81.7, 28.2 (Me), 28.1 (Me); *m*/*z* (ESI) 349 (M + Na^+, 100).

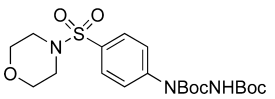


Di-tert-butyl 1-(4-(Tosyloxy)phenyl)hydrazine-1,2-dicarboxylate **2c**. *(a) From the Iodide.* Prepared by the general procedure from 4-iodophenyl 4-toluenesulfonate (3.74 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (6:1) as a colorless solid (4.16 g, 87%): mp 110−112 °C; found M + Na^+, 501.1679, $C_{23}H_{30}NaN_2O_7S$ requires 501.1671; ν_{max} ($CHCl_3$)/cm^{-1} 3403, 2934, 1720, 1371; δ_H (400 MHz; $CDCl_3$) 7.71 (2H, d, *J* 8.0), 7.36 (2H, d, *J* 8.6), 7.31 (2H, d, *J* 8.0), 6.93 (2H, d, *J* 8.6), 2.46 (3H, s), 1.49 (18H, s); δ_C (100 MHz; $CDCl_3$) 155.3, 153.2, 146.6, 145.3, 140.9, 132.3, 129.8 (CH), 128.6 (CH), 124.2 (CH), 122.3 (CH), 82.7, 81.9, 28.2 (Me), 28.1 (Me), 21.7 (Me); *m*/*z* (ESI) 979 (2M + Na^+, 90), 580 (100), 501 (M + Na^+, 45). Anal. Calcd for $C_{23}H_{30}N_2O_7S$: C, 57.7; H, 6.3; N, 5.9. Found: C, 57.6; H, 6.3; N, 5.8.

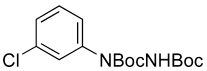
(b) From the Bromide. An oven-dried flask was cooled under argon to room temperature, and charged with a solution of 4-bromophenyl 4-toluenesulfonate (3.27 g, 10 mmol) in THF (20 mL). A solution of isopropylmagnesium chloride lithium chloride complex (1.3 M in THF; 8.46 mL, 11 mmol) was added over 5 min, and the resulting mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 °C, and a solution of di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) in THF (20 mL) was added over 5 min. The mixture was stirred at room temperature for 1.5 h,and worked up as in the general procedure. The title compound was obtained in 76% yield.



Di-tert-butyl 1-(4-(Methoxycarbonyl)phenyl)hydrazine-1,2-dicarboxylate (**2d**). Prepared by the general procedure from methyl 4-iodobenzoate (2.62 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (7:1) as a colorless solid (2.609 g, 71%): mp 104−106 °C; found M + Na^+, 389.1693, $C_{18}H_{26}NaN_2O_6$ requires 389.1683; ν_{max} ($CHCl_3$)/cm^{-1} 3402, 3011, 2983, 1747, 1719, 1283; δ_H (400 MHz; $CDCl_3$) 8.00 (2H, d, *J* 7.6), 7.55 (2H, d, *J* 7.6), 6.76 (1H, br s), 3.92 (3H, s), 1.54 (18H, s); δ_C (100 MHz; $CDCl_3$) 166.7, 155.3, 152.9, 146.1, 130.0 (CH), 126.2, 121.6 (CH), 83.1, 82.0, 52.0 (Me), 28.2 (Me), 28.1 (Me); *m*/*z* (ESI) 755 (2M + Na^+, 100), 389 (M + Na^+, 11).

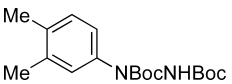


Di-tert-butyl 1-(4-(Morpholinosulfonyl)phenyl)hydrazine-1,2-dicarboxylate (**2e**). Prepared by the general procedure from *N*-(4-iodobenzenesulfonyl)morpholine (2.118 g, 6 mmol) and di-*tert*-butyl azodicarboxylate (1.794 g, 7.8 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (3:1) as a colorless solid (2.031 g, 74%): mp 179−181 °C; found M + Na^+, 480.1763, $C_{20}H_{31}NaN_3O_7S$ requires 480.1775); ν_{max} ($CHCl_3$)/cm^{-1} 3401, 2930, 1747, 1726, 1320, 1163; δ_H (400 MHz; $CDCl_3$) 7.71−7.69 (4H, m), 6.74 (1H, br s), 3.75 (4H, t, *J* 4.6), 3.02 (4H, t, *J* 4.6), 1.54 (18H, s); δ_C (100 MHz; $CDCl_3$) 155.2, 152.7, 146.3, 130.5, 128.4 (CH), 121.8 (CH), 83.6, 82.4, 66.1 (CH_2), 46.0 (CH_2), 28.2 (Me), 28.1 (Me); *m*/*z* (ESI) 480 (M + Na^+, 100).



Di-tert-butyl 1-(3-Chlorophenyl)hydrazine-1,2-dicarboxylate (**2f**). *From the Iodide.* Prepared by the general procedure from 3-chloroiodobenzene (2.38 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (9:1) as a colorless solid (2.76 g, 81%): mp 95−97 °C; found M + Na^+, 365.1241, $C_{16}H_{23}{}^{35}ClNaN_2O_4$ requires 365.1239); ν_{max} ($CHCl_3$)/cm^{-1} 3403, 2971, 1721; δ_H (400 MHz; $CDCl_3$) 7.49 (1H, br s), 7.33 (1H, br s), 7.25 (t, *J* 8.0), 7.14 (1H, d, *J* 8.0), 6.74 (1H, br s), 1.53 (18H, s); δ_C (100 MHz; $CDCl_3$) 155.3, 153.2, 143.2, 133.9, 129.3 (CH), 125.4 (CH), 123.3 (CH), 121.2 (CH), 82.9, 82.0, 28.2 (Me), 28.1 (Me); *m*/*z* (ESI) 707 (2M + Na^+, 100), 365 (M + Na^+, 63).

From the Bromide. An oven-dried flask was cooled under argon to room temperature and charged with a solution of 1-bromo-3-chlorobenzene (1.90 g, 10 mmol) in THF (20 mL). A solution of isopropylmagnesium chloride lithium chloride complex (1.3 M in THF; 8.46 mL, 11 mmol) was added over 5 min, and the resulting mixture was stirred at room temperature for 3 h. The mixture was cooled to 0 °C, and a solution of di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) in THF (20 mL) was added over 5 min. The mixture was stirred at room temperature for 1.5 h, and worked up as in the general procedure. The title compound was obtained in 77% yield.



Di-tert-butyl 1-(3,4-Dimethylphenyl)hydrazine-1,2-dicarboxylate (**2g**). *From the Iodide.* Prepared by the general procedure from 4-iodo-*o*-xylene (2.32 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (9:1) as a colorless solid (2.551 g, 76%): mp 94−96 °C; found M + Na^+, 359.1947, $C_{18}H_{28}NaN_2O_4$ requires 359.1947); ν_{max} ($CHCl_3$)/cm^{-1} 3404, 3011, 2982, 1934, 1715, 1370; δ_H (400 MHz; $CDCl_3$) 7.21 (1H, br s), 7.13 (1H, br s), 7.08 (1H, d, *J* 8.1), 6.85 (1H, br s); 2.25 (3H, s), 2.23 (3H, s), 1.49 (18H, s); δ_C (100 MHz; $CDCl_3$) 155.7, 155.4, 139.9, 136.6, 134.1, 129.5 (CH), 125.3 (CH), 121.5 (CH), 81.9, 81.3, 28.3 (Me), 28.2 (Me), 19.9 (Me), 19.2 (Me); *m*/*z* (ESI) 695 (100), 359 (M + Na^+, 10).

From the Bromide. Iodine (0.127 g, 0.5 mmol) was added to a stirred suspension of magnesium turnings (0.288 g, 12 mmol) in THF (1 mL), and the resulting mixture was stirred under argon at room temperature for 30 min until the iodine was consumed. A solution of 4-bromo-*o*-xylene (1.85 g, 10 mmol) in THF (2.5 mL) was added dropwise over 5 min, and the resulting mixture was stirred at room temperature for 3 h. The stirring was stopped, and the clear solution was transferred *via* cannula to a dry flask under argon, and the excess magnesium was washed with THF (2 × 1 mL). The solution was cooled to 0 °C, and a solution of di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) in THF (7.5 mL) was added dropwise over 5 min. The resulting mixture was stirred at room temperature for 1.5 h and

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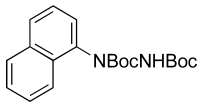
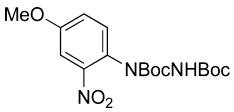
worked up as in the general procedure. The title compound was obtained in 79% yield.

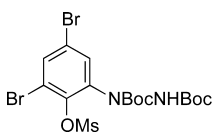


*Di-tert-butyl 1-(Naphthalen-1-yl)hydrazine-1,2-dicarboxylate (**2h**). From the Iodide.* Prepared by the general procedure from 1-iodonaphthalene (2.54 g, 10 mmol) and di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) and isolated by chromatography eluting with light petroleum and ethyl acetate (11:1) as a colorless solid (3.52 g, 98%): mp 144−146 °C; found M + Na^+, 381.1793. $C_{20}H_{26}NaN_2O_4$ requires 381.1785); ν_{max} ($CHCl_3$)/cm^{-1} 3401, 2983, 1745, 1714, 1370, 1153; δ_H (400 MHz; $CDCl_3$) 7.98 (1H, br s), 7.88 (1H, d, *J* 8.0), 7.83 (1H, d, *J* 8.4), 7.70 (1H, br s), 7.57−7.47 (3H, m); 7.01 (1H, br s); 1.57 (18H, s); δ_C (100 MHz; $CDCl_3$) 155.6, 155.0, 138.8, 134.3, 130.2, 128.3 (CH), 126.5 (CH), 126.0 (CH), 125.6 (CH), 122.9 (CH), 82.0, 81.4, 28.3 (Me), 28.1 (Me); two CH overlapped; *m*/*z* (ESI) 739 (2M + Na^+, 66), 734 (49), 418 (100), 381 (M + Na^+, 86).

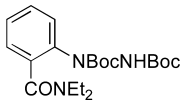
From the Bromide. An oven-dried flask was cooled under argon to room temperature and charged with a solution of 1-bromonaphthalene (2.07 g, 10 mmol) in THF (20 mL). A solution of isopropylmagnesium chloride lithium chloride complex (1.3 M in THF; 8.46 mL, 11 mmol) was added over 5 min, and the resulting mixture was stirred at room temperature for 9 h. The mixture was cooled to 0 °C, and a solution of di-*tert*-butyl azodicarboxylate (2.99 g, 13 mmol) in THF (20 mL) was added over 5 min. The mixture was stirred at room temperature for 14 h and worked up as in the general procedure. The title compound was obtained in 66% yield.



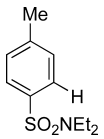
*Di-tert-butyl 1-(4-Methoxy-2-nitrophenyl)hydrazine-1,2-dicarboxylate (**2i**).* Phenylmagnesium chloride (2 M solution in THF; 13.75 mL, 27.5 mmol) was added dropwise over 10 min to a stirred solution of 4-iodo-3-nitroanisole (6.975 g, 25 mmol) in THF (100 mL) at −40 °C under argon. The resulting mixture was stirred at that temperature for 25 min, and then di-*tert*-butyl azodicarboxylate (7.475 g, 32.5 mmol) in THF (25 mL) was added dropwise over 15 min. The resulting mixture was stirred at −40 °C for 30 min and then at room temperature for 4 h and then quenched with saturated aqueous ammonium chloride solution (20 mL), diluted with H_2O (100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue eluting with light petroleum and ethyl acetate (7:1) gave the *title compound* as mixture of rotamers as a viscous pale orange oil (7.62 g, 80%): found M + Na^+, 406.1599, $C_{17}H_{25}NaN_3O_7$ requires 406.1590; ν_{max} ($CHCl_3$)/cm^{-1} 3394, 2935, 1725, 1536, 1370; δ_H (400 MHz; $CDCl_3$) 7.73 (1H, d, *J* 8.1), 7.54 (0.5H, br s), 7.48 (0.5H, d, *J* 2.9), 7.19−7.15 (1H, m), 7.01 (1H, br s), 3.90 (1.5H, s), 3.88 (1.5H, s), 1.54 (13.5H, s), 1.34 (4.5H, s); δ_C (100 MHz; $CDCl_3$) 159.0, 158.9, 155.5, 155.0, 153.9, 153.1, 145.5, 145.3, 132.2 (CH), 131.9 (CH), 128.9, 128.4, 120.1 (CH), 119.8 (CH), 109.8 (CH), 109.5 (CH), 82.8, 82.7, 81.5, 81.4, 56.0 (Me), 59.9 (Me), 28.2 (Me), 28.1 (Me), 28.0 (Me), 27.7 (Me); *m*/*z* (ESI) 789 (2M + Na^+, 92), 406 (M + Na^+, 100).



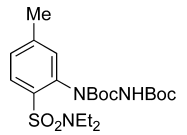
*Di-tert-butyl 1-(2-Methanesulfonyloxy-3,5-dibromophenyl)-hydrazine-1,2-dicarboxylate (**2j**).* A solution of isopropylmagnesium bromide in 4-methyltetrahydrofuran (2.9 M; 0.31 mL, 0.89 mmol) was added dropwise at −40 °C to a stirred solution of 2,4,6-tribromophenyl mesylate (0.30 g, 0.73 mmol) in tetrahydrofuran (5 mL) under an argon atmosphere. The reaction mixture was stirred at −40 °C for 2 h, and then a solution of di-*tert*-butyl azodicarboxylate (0.18 g, 0.80 mmol) in tetrahydrofuran (5 mL) was added dropwise. The solution was allowed to warm to room temperature over 2 h, quenched with a saturated aqueous ammonium chloride solution (10 mL), extracted with dichloromethane (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (1:1.5) gave the *title compound* as a colorless solid (0.33 g, 80%): mp 79−80 °C; found M + Na^+, 580.9560, $C_{17}H_{24}{}^{79}Br_2N_2O_7S$ + Na^+ requires 580.9563; ν_{max} ($CHCl_3$)/cm^{-1} 3396, 3009, 2983, 1728, 1580, 1559, 1477, 1161; δ_H (400 MHz; DMSO-d_6) 9.78 (1H, br s), 8.0 (1H, d, *J* 2.4), 7.58 (1H, d, *J* 2.4), 3.53 (3H, s), 1.45 (9H, s), 1.41 (9H, s); δ_C (100 MHz; DMSO-d_6) 156.1 (2 × C), 138.6, 134.7 (CH), 130.3 (CH), 120.0 (2 × C), 119.0, 82.8, 81.2, 40.5 (Me), 28.4 (Me), 28.0 (Me); *m*/*z* (ESI) 580/582/584 (M + Na^+, 48, 100, 53%).



*Di-tert-butyl 2-(N,N-Diethylbenzamide)hydrazine-1,2-dicarboxylate (**2k**).* A mixture of *N,N,N′,N′*-tetramethylethylenediamine (0.19 mL, 1.24 mmol) and *sec*-butyllithium (1.3 M in tetrahydrofuran, 0.96 mL, 1.24 mmol) in tetrahydrofuran (10 mL) was treated dropwise at −78 °C with a solution of *N,N*-diethylbenzamide (0.20 g, 1.13 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred at −78 °C for 1 h, and then a solution of di-*tert*-butyl azodicarboxylate (0.31 g, 1.36 mmol) in tetrahydrofuran (10 mL) was added dropwise. The solution was stirred at −78 °C for 2 h, quenched with a saturated aqueous ammonium chloride solution (10 mL), extracted with ethyl acetate (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:4) gave the *title compound* as a colorless gummy oil (0.28 g, 61%): found M + Na^+, 430.2316, $C_{21}H_{33}N_3O_5$ + Na^+ requires 430.2312); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2982, 2936, 1709, 1619, 1475, 1368, 1293, 1242, 1154; δ_H (400 MHz; DMSO-d_6) 9.12 (1H, br s), 7.44−7.23 (4H, m), 3.42 (2H, s), 3.08 (2H, s), 1.43 (9H, s), 1.40 (9H, s), 1.13 (3H, t, *J* 7.0), 1.03 (3H, t, *J* 5.7); δ_C (100 MHz; DMSO-d_6) 168.3 (2 × C), 155.9, 153.7, 139.5, 129.7 (2 × CH), 127.0 (2 × CH), 80.3 (2 × C), 42.9 (CH_2), 38.5 (CH_2), 28.5 (Me), 28.2 (Me), 14.0 (Me), 13.0 (Me); *m*/*z* (ESI) 430 (M + Na^+, 100%).

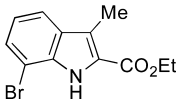


N,N-Diethyl-4-methylbenzenesulfonamide. Diethylamine (2.20 mL, 20.98 mmol) was added at 0 °C over 10 min to a stirred solution of *p*-tosyl chloride (2.0 g, 10.49 mmol) and triethylamine (2.9 mL, 20.98 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with hydrochloric acid (2 M; 26 mL) and saturated acqueous sodium hydrogen bicarbonate solution (26 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the *title compound* as a colorless solid (2.30 g, 96%): mp 58−59 °C (lit.[63] mp 48−49 °C); found M + Na^+, 250.0868, $C_{11}H_{17}NO_2S$ + Na^+ requires 250.0872); ν_{max} ($CHCl_3$)/cm^{-1} 2980, 2939, 2876, 1599, 1494, 1467, 1384, 1333, 1305, 1153, 1091, 1021; δ_H (400 MHz; DMSO-d_6) 7.68 (2H, d, *J* 7.9), 7.41 (2H, d, *J* 7.9), 3.15 (4H, q, *J* 7.1), 2.39 (3H, s), 1.04 (6H, *J* 7.1); δ_C (100 MHz; DMSO-d_6) 143.3, 137.4, 130.3 (CH), 127.2 (CH), 42.2 (CH_2), 21.4 (Me), 14.1 (Me); *m*/*z* (ESI) 250 (M + Na^+, 100).

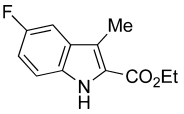


*Di-tert-butyl 2-(N,N-Diethyl-4-methylbenzenesulfonamide)-hydrazine-1,2-dicarboxylate (**2l**).* A solution of *n*-butyllithium in hexane (1.6 M; 2.60 mL, 4.20 mmol) was added dropwise at −78 °C

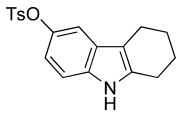
to a solution of *N*,*N*-diethyl-4-methylbenzenesulfonamide (0.800 g, 3.50 mmol) in tetrahydrofuran (10 mL) under argon atmosphere. The reaction mixture was stirred for 1 h at −78 °C, and then a solution of di-*tert*-butyl azodicarboxylate (0.97 g, 4.20 mmol) in tetrahydrofuran (10 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h and then at 0 °C for 1 h. Water (10 mL) was added followed by ethyl acetate (10 mL). The phases were separated, and the organic layer was dried with $MgSO_4$, filtered, and evaporated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:19) gave the *title compound* as a colorless solid (1.20 g, 75%): mp 139−140 °C; found M + Na^+, 480.2133, $C_{21}H_{35}N_3O_6S$ + Na^+ requires 480.2139; ν_{max} ($CHCl_3$)/cm^{-1} 3015, 2982, 2936, 1731, 1716, 1601, 1477, 1369, 1325, 1241, 1154; δ_H (400 MHz; $CDCl_3$) 7.82 (1H, d, *J* 8.0), 7.63 (1H, s), 7.58 (1H, br s), 7.25 (1H, d, *J* 8.0), 3.38 (2H, q, *J* 7.1), 3.14 (2H, q, *J* 7.1), 2.42 (3H, s), 1.52 (9H, s), 1.46 (9H, s), 1.11 (6H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 154.5, 154.2, 145.0, 139.2, 134.7, 133.1 (CH), 130.3 (CH), 129.4 (CH), 82.0, 81.0, 41.6 (CH_2), 28.2 (Me), 28.1 (Me), 21.3 (Me), 14.2 (Me); *m*/*z* (ESI) 480 (M + Na^+, 100). Anal. Calcd for $C_{21}H_{35}N_3O_6S$: C, 55.12; H, 7.71; H, 9.18. Found: C, 55.05; H, 7.71; N, 9.13.



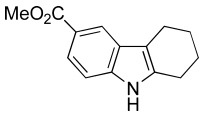
Synthesis of Indoles. *Ethyl 7-Bromo-3-methylindole-2-carboxylate (**3a**).* Hydrochloric acid (35%; 5 mL) was added to a suspension of di-*tert*-butyl 1-(2-bromophenyl)hydrazine-1,2-dicarboxylate (**2a**) (0.386 g, 1.0 mmol), 2-ketobutyric acid (0.102 g, 1.0 mmol), and ethanol (5 mL), and the mixture was stirred at 70 °C for 16 h, cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:50) gave the *title compound* as a colorless solid (0.196 g, 70%): mp 81−83 °C; found M + Na^+, 303.9965, $C_{12}H_{12}{}^{79}BrNaNO_2$ requires 303.9949; ν_{max} ($CHCl_3$)/cm^{-1} 3452, 2985, 2938, 1700, 1311, 1242; δ_H (400 MHz; $CDCl_3$) 8.78 (1H, br s), 7.62 (1H, dd, *J* 8.0, 0.7), 7.49 (1H, dd, *J* 7.5, 0.7), 7.04 (1H, dd, *J* 8.0, 7.5), 4.47 (2H, q, *J* 7.2), 2.62 (3H, s), 1.47 (3H, t, *J* 7.2); δ_C (100 MHz; $CDCl_3$) 162.2, 134.6, 129.6, 127.7 (CH), 124.1, 121.0, 120.9 (CH), 120.0 (CH), 105.0, 61.0 (CH_2), 14.5 (Me), 10.2 (Me); *m*/*z* (ESI) 304 (M + Na^+, 100%), 305 (M + Na^+, 98).



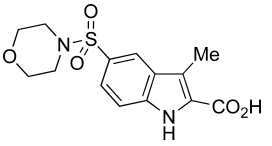
*Ethyl 5-Fluoro-3-methylindole-2-carboxylate (**3b**).* Hydrochloric acid (35%; 5 mL) was added to a suspension of di-*tert*-butyl 1-(4-fluorophenyl)hydrazine-1,2-dicarboxylate (**2b**) (0.386 g, 1.0 mmol), 2-ketobutyric acid (0.102 g, 1.0 mmol), and ethanol (5 mL), and the mixture was stirred at 70 °C for 16 h, cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:14) gave the *title compound* as a colorless solid (0.146 g, 66%): mp 121−123 °C; found M + Na^+, 244.0745, $C_{12}H_{12}FNaNO_2$ requires 244.0750; ν_{max} ($CHCl_3$)/cm^{-1} 3463, 2985, 2938, 1695, 1456, 1242; δ_H (400 MHz; DMSO-d_6) 7.43−7.39 (2H, m), 7.12 (1H, ddd, *J* 9.4, 8.9, 2.4), 4.34 (2H, q, *J* 7.2), 2.51 (3H, s), 1.34 (3H, t, *J* 7.2); δ_C (100 MHz; DMSO-d_6) 162.2, 127.3 (d, *J* 233, CF), 133.4, 128.2 (d, *J* 9.6, C), 125.3, 118.7 (d, *J* 5.8, C), 114.2 (d, *J* 24, CH), 114.1 (d, *J* 12, CH), 105.0 (d, *J* 23, CH), 60.7 (CH_2), 14.7 (Me), 10.2 (Me); *m*/*z* (ESI) 244 (M + Na^+, 100%).



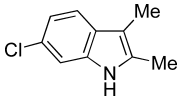
*6-(4-Toluenesulfonyloxy)-1,2,3,4-tetrahydrocarbazole (**3c**).* Hydrochloric acid (35%; 2 mL) was added to a suspension of di-*tert*-butyl 1-(4-(tosyloxy)phenyl)hydrazine-1,2-dicarboxylate (**2c**) (0.239 g, 0.5 mmol), cyclohexanone (0.098 g, 1.0 mmol), and ethanol (2 mL), and the mixture was stirred at 70 °C for 2 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:6) gave the *title compound* as a pale yellow solid (0.154 g, 90%): mp 112−114 °C; found M + H^+, 342.1166, $C_{19}H_{20}NO_3S$ requires 342.1164; ν_{max} ($CHCl_3$)/cm^{-1} 3605, 3011, 2941, 1600, 1477, 1369; δ_H (400 MHz; $CDCl_3$) 7.80 (1H, br s), 7.72 (2H, d, *J* 7.8), 7.29 (2H, d, *J* 7.8), 7.10−7.08 (2H, m), 6.65 (1H, dd, *J* 8.8, 2.4), 2.71 (2H, t, *J* 6.0), 2.60 (2H, t, *J* 5.8), 2.07 (3H, s), 1.92−1.84 (4H, m); δ_C (100 MHz; $CDCl_3$) 144.9, 143.1, 136.3, 134.0, 132.7, 129.6 (CH), 128.6 (CH), 128.0, 115.2 (CH), 111.3 (CH), 110.7 (CH), 110.6, 23.2 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 21.7 (Me), 20.7 (CH_2); *m*/*z* (ESI) 364 (M + Na^+, 100%), 342 (M + H^+, 63).



*Methyl 5,6,7,8-Tetrahydrocarbazole-3-carboxylate (**3d**).* A suspension of di-*tert*-butyl 1-(4-(methoxycarbonyl)phenyl)hydrazine-1,2-dicarboxylate (**2d**) (0.183 g, 0.5 mmol), cyclohexanone (0.098 g, 1.0 mmol), and trifluoroacetic acid (2 mL) was stirred at 70 °C for 4 h, cooled to room temperature, diluted with saturated sodium hydrogen solution (30 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:7) gave the *title compound* as a colorless solid (0.102 g, 89%): mp 153−155 °C (lit.[64] mp 155−157 °C); found M + H^+, 230.1174. $C_{14}H_{16}NO_2$ requires 230.1181; ν_{max} ($CHCl_3$)/cm^{-1} 3468, 3011, 2946, 2846, 1703, 1312, 1243; δ_H (400 MHz; $CDCl_3$) 8.26 (1H, s), 8.03 (1H, br s), 7.86 (1H, dd, *J* 8.6, 1.6), 7.29 (1H, d, *J* 8.6), 3.96 (3H, s), 2.77−2.75 (4H, m), 1.97−1.67 (4H, m); δ_C (100 MHz; $CDCl_3$) 168.5, 138.4, 135.6, 127.5, 122.6 (CH), 121.0, 120.7 (CH), 111.5, 110.0 (CH), 51.8 (Me), 23.2 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 20.8 (CH_2); *m*/*z* (ESI) 481 (2M + Na^+, 100), 252 (M + Na^+, 33), 230 (M + H^+, 25).

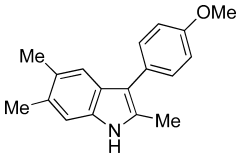


*3-Methyl-5-(morpholinosulfonyl)indole-2-carboxylic Acid (**3e**).* Hydrochloric acid (35%; 2 mL) was added to a suspension of di-*tert*-butyl 1-(4-(morpholinosulfonyl)phenyl)hydrazine-1,2-dicarboxylate **2e** (0.229 g, 0.5 mmol), 2-ketobutyric acid (0.051 g, 0.5 mmol), and acetic acid (2 mL), and the mixture was stirred at 70 °C for 3 h, cooled to room temperature and diluted with water (25 mL). The resulting precipitate was collected by filtration and dried in vacuo to give the *title compound* as a gray solid (0.134 g, 83%): mp >250 °C; found M + H^+, 325.0862, $C_{14}H_{17}N_2O_5S$ requires 325.0858; ν_{max} ($CHCl_3$)/cm^{-1} 3320, 2987, 2845, 1683, 1363; δ_H (400 MHz; $CDCl_3$) 8.05 (1H, s), 7.61−7.55 (2H, m), 3.62 (4H, t, *J* 4.6), 2.85 (4H, t, *J* 4.6), 2.59 (3H, s); δ_C (100 MHz; $CDCl_3$) 163.5, 138.2, 127.7, 127.0, 125.5, 123.6 (CH), 122.1 (CH), 119.7, 113.5 (CH), 65.8 (CH_2), 46.5 (CH_2), 10.1 (Me); *m*/*z* (ESI) 347 (M + Na^+, 100), 325 (56).

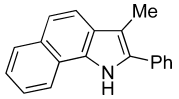


*6-Chloro-2,3-dimethylindole (**3f**).* Hydrochloric acid (35%; 4 mL) was added to a suspension of di-*tert*-butyl 1-(3-chlorophenyl)-hydrazine-1,2-dicarboxylate **2f** (0.342 g, 1.0 mmol), butan-2-one (0.144 g, 2.0 mmol), and ethanol (4 mL), and the mixture was stirred

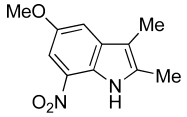
at reflux for 4 h, cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:19) gave the *title compound* as a pale yellow solid (0.137 g, 76%): mp 151−153 °C (lit.[56] mp 166−167 °C); found M + H^+, 180.0577, $C_{10}H_{11}{}^{35}ClN$ requires 180.0580; ν_{max} ($CHCl_3$)/cm^{-1} 3472, 3011, 2920, 1624, 1464; δ_H (400 MHz; $CDCl_3$) 7.61 (1H, br s), 7.38 (1H, d, *J* 8.3), 7.25 (1H, d, *J* 1.7), 7.07 (1H, dd, *J* 8.3, 1.7), 2.37 (3H, s), 2.23 (3H, s); δ_C (100 MHz; $CDCl_3$) 135.5, 131.4, 128.1, 126.7, 119.6 (CH), 118.7 (CH), 110.0 (CH), 107.3, 11.6 (Me), 8.4 (Me); *m*/*z* (ESI) 396 (100), 180 (27).



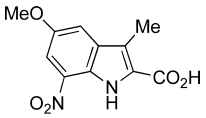
3-(4-Methoxyphenyl)-2,5,6-trimethylindole (**3g**). Hydrochloric acid (35%; 2 mL) was added to a suspension of di-*tert*-butyl 1-(3,4-dimethylphenyl)hydrazine-1,2-dicarboxylate (**2g**) (0.336 g, 1.0 mmol), 4-methoxyphenylacetone (0.164 g, 1.0 mmol), and ethanol (2 mL), and the mixture was stirred at reflux for 4 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:49) gave the *title compound* as a colorless solid (0.180 g, 68%): mp 119−121 °C; found M + Na^+, 288.1355, $C_{18}H_{19}NaNO$ requires 288.1359; ν_{max} ($CHCl_3$)/cm^{-1} 3471, 3009, 1512, 1243; δ_H (400 MHz; $CDCl_3$) 7.73 (1H, br s), 7.43 (2H, d, *J* 8.6), 7.42 (1H, s), 7.12 (1H, s), 7.06 (2H, d, *J* 8.6), 3.91 (3H, s), 2.48 (3H, s), 2.40 (3H, s), 2.37 (3H, s); δ_C (100 MHz; $CDCl_3$) 157.7, 134.1, 130.4 (CH), 130.1, 128.3, 118.9 (CH), 114.0 (CH), 113.1, 113.0, 110.8 (CH), 55.3 (Me), 20.4 (Me), 20.1 (Me), 12.4 (Me); two C unobserved; *m*/*z* (ESI) 288 (M + Na^+, 100), 266 (M + H^+, 70).



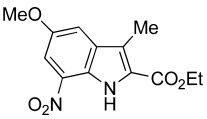
3-Methyl-2-phenylbenz[g]indole (**3h**). Hydrochloric acid (35%; 2 mL) was added to a suspension of di-*tert*-butyl 1-(naphthalen-1-yl)hydrazine-1,2-dicarboxylate (**2h**) (0.179 g, 0.5 mmol), propiophenone (0.134 g, 1.0 mmol), and ethanol (2 mL), and the mixture was stirred at 70 °C for 2 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:49) gave the *title compound* as a pale yellow solid (0.114 g, 92%): mp 115−117 °C (lit.[65] mp 117 °C); found M + H^+, 258.1274, $C_{19}H_{16}N$ requires 258.1277; ν_{max} ($CHCl_3$)/cm^{-1} 3466, 3058, 3011, 2974, 1387; δ_H (400 MHz; $CDCl_3$) 8.75 (1H, br s), 8.06 (1H, d, *J* 8.4), 7.96 (1H, d, *J* 8.4), 7.73 (1H, d, *J* 8.4), 7.68−7.52 (6H, m), 7.45 (1H, t, *J* 7.6), 7.39 (1H, dd, *J* 7.6, 7.2), 2.57 (3H, s); δ_C (100 MHz; $CDCl_3$) 133.5, 132.6, 130.7, 130.4, 129.0 (CH), 128.9 (CH), 127.7 (CH), 127.1 (CH), 125.7, 125.5 (CH), 123.9 (CH), 121.5, 120.5 (CH), 119.5 (CH), 119.1 (CH), 110.5, 9.9 (Me); *m*/*z* (ESI) 258 (M + H^+, 100).



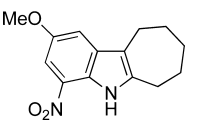
5-Methoxy-2,3-dimethyl-7-nitroindole (**3i**). A mixture of di-*tert*-butyl 1-(4-methoxy-2-nitrophenyl)hydrazine-1,2-dicarboxylate (**2i**) (1.915 g, 5 mmol), butan-2-one (0.70 g, 10 mmol), hydrochloric acid (35%; 25 mL) and acetic acid (25 mL) was stirred at 70 °C for 4 h, cooled to room temperature, neutralized with saturated aqueous sodium hydrogen carbonate solution (400 mL), and extracted with ethyl acetate (4 × 150 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the product as a brown solid (1.06 g, 96%): mp 146−148 °C; found M + Na^+, 243.0735, $C_{11}H_{12}NaN_2O_3$ requires 243.0746; ν_{max} ($CHCl_3$)/cm^{-1} 3467, 2922, 1518, 1289; δ_H (400 MHz; $CDCl_3$) 9.30 (1H, br s), 7.66 (1H, d, *J* 2.4), 7.35 (1H, d, *J* 2.4), 3.93 (3H, s), 2.44 (3H, s), 2.24 (3H, s); δ_C (100 MHz; $CDCl_3$) 152.7, 134.8, 133.9, 131.3, 124.9, 111.9 (CH), 108.0, 103.9 (CH), 56.5 (Me), 11.7 (Me), 3.4 (Me); *m*/*z* (ESI) 243 (M + Na^+, 100). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 59.8; H, 5.5; N, 12.6.



5-Methoxy-3-methyl-7-nitroindole-2-carboxylic Acid (**3j**). A suspension of di-*tert*-butyl 1-(4-methoxy-2-nitrophenyl)hydrazine-1,2-dicarboxylate **2i** (0.038 g, 0.1 mmol), 2-ketobutyric acid (0.020 g, 0.2 mmol), hydrochloric acid (35%; 0.5 mL), and acetic acid (0.5 mL) was stirred at 70 °C for 5 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (2:1 then 1:0) gave the *title compound* as a bright yellow solid (0.025 g, 100%): mp 236−238 °C; found M − H^-, 249.0507, $C_{11}H_9N_2O_5$ requires 249.0511); ν_{max} ($CHCl_3$)/cm^{-1} 3476, 2937, 1920, 1662, 1562; δ_H (400 MHz; DMSO-d_6) 10.4 (1H, br s), 7.80 (1H, s), 7.76 (1H, s), 3.90 (3H, s), 2.54 (3H, s); δ_C (100 MHz; $CDCl_3$) 163.1, 152.8, 132.9, 132.8, 128.6, 124.0, 118.7, 113.0 (CH), 110.3 (CH), 56.8 (Me), 10.0 (Me); *m*/*z* (ESI) 249 (M − H^-, 100), 205 (M − CO_2H^-, 60).

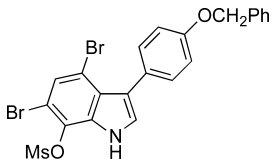


Ethyl 5-Methoxy-3-methyl-7-nitroindole-2-carboxylate (**3k**). A suspension of di-*tert*-butyl 1-(4-methoxy-2-nitrophenyl)hydrazine-1,2-dicarboxylate (**2i**) (0.038 g, 0.1 mmol), ethyl 2-ketobutyrate (0.026 g, 0.2 mmol), and trifluoroacetic acid (0.5 mL) was stirred at 70 °C for 16 h and concentrated in vacuo. Column chromatography eluting with ethyl acetate and light petroleum (1:11) gave the *title compound* as a bright yellow solid (0.027 g, 97%): mp 123−125 °C; found M + Na^+, 301.0827, $C_{13}H_{14}NaN_2O_5$ requires 301.0819; ν_{max} ($CHCl_3$)/cm^{-1} 3465, 2985, 1704, 1568, 1523; δ_H (400 MHz; $CDCl_3$) 9.95 (1H, br s), 7.95 (1H, d, *J* 2.0), 7.51 (1H, d, *J* 2.0), 4.47 (2H, q, *J* 7.1), 3.96 (3H, s), 2.63 (3H, s), 1.47 (3H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 161.5, 153.0, 132.8, 132.6, 126.6, 124.6, 120.0, 112.6 (CH), 110.7 (CH), 61.2 (CH_2), 56.5 (Me), 14.4 (Me), 9.8 (Me); *m*/*z* (ESI) 301 (M + Na^+, 100%). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.1; H, 5.1; N, 10.1. Found: C, 55.8; H, 5.0; N, 9.9.

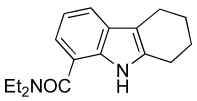


2-Methoxy-4-nitro-5,6,7,8,9,10-hexahydrocyclohept[b]indole (**3l**). Hydrochloric acid (35%; 12 mL) was added to a suspension of di-*tert*-butyl 1-(4-methoxy-2-nitrophenyl)hydrazine-1,2-dicarboxylate (**2i**) (1.532 g, 4.0 mmol), cycloheptanone (0.448 g, 4.0 mmol), and acetic acid (12 mL), and the mixture was stirred at 70 °C for 6 h, cooled to room temperature, diluted with water (150 mL), and extracted with dichloromethane (3 × 80 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:24) gave the *title compound* as an orange solid (0.781 g, 75%): mp 134−136 °C; found M + Na^+, 283.1059, $C_{14}H_{16}NaN_2O_3$ requires 283.1053; ν_{max} ($CHCl_3$)/cm^{-1} 3465, 2928, 2851, 1514, 1316; δ_H (400 MHz; $CDCl_3$) 9.28 (1H, br s), 7.66 (1H, d, *J* 2.4), 7.36 (1H, d, *J* 2.4), 3.92 (3H, s), 2.91 (2H, t, *J* 5.7), 2.79 (2H, t, *J* 5.7), 1.94−1.91 (2H, m), 1.85−1.78 (4H, m); δ_C (100 MHz; $CDCl_3$) 152.7, 141.5, 133.6, 131.5,

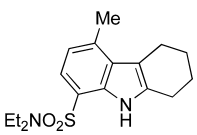
123.9, 114.5, 111.6 (CH), 104.0 (CH), 56.5 (Me), 31.5 (CH_2), 29.4 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 24.6 (CH_2); *m*/*z* (ESI) 283 (M + Na^+, 100). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8. Found: C, 64.4; H, 6.2; N, 10.6.



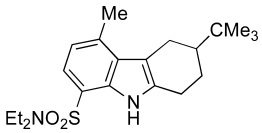
3-(4-Benzyloxyphenyl)-4,6-dibromo-7-methanesulfonyloxyindole (***3m***). A mixture of di-*tert*-butyl 1-(2-methanesulfonyloxy-3,5-dibromophenyl)hydrazine-1,2-dicarboxylate (**2j**) (1.1 g, 1.96 mmol), (4-benzyloxyphenyl)acetaldehyde (0.44 g, 1.96 mmol), and *p*-toluenesulfonic acid (1.86 g, 9.8 mmol) in ethanol (30 mL) was heated under reflux for 1 h. After the reaction mixture was allowed to cool to room temperature and ethanol was removed in vacuo, the residue was diluted with ethyl acetate (30 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (1:2.3) gave the *title compound* as a colorless solid (0.70 g, 65%): mp 110−111 °C; found M + Na^+, 571.9133, $C_{22}H_{17}{}^{79}Br_2NO_4S$ + Na^+ requires 571.9137; ν_{max} ($CHCl_3$)/cm^{-1} 3009, 3011, 1618, 1587, 1502 1469, 1363, 1240, 1176; δ_H (400 MHz; DMSO-d_6) 11.87 (1H, br s), 7.52−7.34 (9H, m), 7.05 (1H, s), 7.03 (1H, s), 5.15 (2H, s), 3.67 (3H, s); δ_C (100 MHz; DMSO-d_6) 158.0, 137.6, 132.8 (CH), 132.5, 131.1, 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.0 (CH), 126.8, 126.3, 118.8, 114.2 (CH), 112.4, 109.0, 69.7 (CH_2), 31.2 (Me); *m*/*z* (ESI) 572 (M + Na^+, 100).



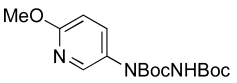
5,6,7,8-Tetrahydrocarbazole-1-carboxylic Acid Diethylamide (***3n***). A mixture of di-*tert*-butyl 2-(*N*,*N*-diethylbenzamide)hydrazine-1,2-dicarboxylate (**2k**) (0.17 g, 0.42 mmol), cyclohexanone (0.09 mL, 0.84 mmol), and *p*-toluenesulfonic acid (0.48 g, 2.52 mmol) in ethanol (5 mL) was heated under reflux for 1 h. After the reaction mixture was allowed to cool to room temperature and ethanol was removed in vacuo, the residue was diluted with ethyl acetate (10 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:19) gave the *title compound* as a colorless solid (0.03 g, 26%); mp 109−110 °C; found M + Na^+, 293.1628, $C_{17}H_{22}N_2O$ + Na^+ requires 293.1624; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 3011, 2938, 2847, 1609, 1582, 1491, 1461, 1434, 1303, 1290; δ_H (400 MHz; $CDCl_3$) 8.67 (1H, br s), 7.37 (1H, d, *J* 7.6), 7.15 (1H, d, *J* 7.6), 7.05 (1H, t, *J* 7.6), 3.57 (4H, q, *J* 6.9), 2.72−2.71 (4H, m), 1.90−1.89 (4H, m), 1.28 (6H, t, *J* 6.9); δ_C (100 MHz; $CDCl_3$) 170.4, 135.4, 134.6, 129.0, 119.5 (CH), 118.9 (CH), 117.7 (CH), 117.6, 110.0, 23.3 (CH_2), 23.1 (CH_2), 20.9 (CH_2), 13.8 (Me); *m*/*z* (ESI) 293 (M + Na^+, 100).



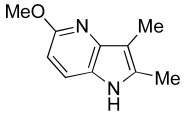
4-Methyl-5,6,7,8-tetrahydrocarbazole-1-sulfonic Acid Diethylamide (***3o***). Hydrochloric acid (35%; 1.3 mL) was added to a suspension of di-*tert*-butyl 2-(*N*,*N*-diethyl-4-methylbenzenesulfonamide)hydrazine-1,2-dicarboxylate (**2l**) (0.15 g, 0.33 mmol), cyclohexanone (0.07 mL, 0.66 mmol) in ethanol (6 mL), and the reaction mixture was stirred at reflux for 1 h. The mixture was cooled at room temperature, diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (1:1) gave the *title compound* as a colorless solid (0.04 g, 38%): mp 151 °C; found M + Na^+, 343.1444, $C_{17}H_{24}N_2O_2S$ + Na^+ requires 343.1451; ν_{max} ($CHCl_3$)/cm^{-1} 3019, 2979, 2939, 2859, 1609, 1568, 1500, 1462, 1444, 1394, 1313; δ_H (400 MHz; DMSO-d_6) 10.49 (1H, br s), 7.24 (1H, d, *J* 7.7), 6.81 (1H, d, *J* 7.7), 3.21 (4H, q, *J* 7.1), 2.07 (2H, s), 2.76 (2H, s), 2.62 (3H, s), 1.78 (4H, s), 0.98 (6H, t, *J* 7.1); δ_C (100 MHz; DMSO-d_6) 137.0, 135.3, 131.0, 128.7, 120.8 (CH), 119.7 (CH), 119.6, 109.8, 41.7 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 22.6 (CH_2), 20.3 (Me), 14.3 (Me); *m*/*z* (ESI) 343 (M + Na^+, 100).



6-tert-Butyl-4-methyl-5,6,7,8-tetrahydrocarbazole-1-sulfonic Acid Diethylamide (***3p***). Hydrochloric acid (35%; 2 mL) was added to a stirred suspension of di-*tert*-butyl 2-(N,N-diethyl-4-methylbenzenesulfonamide)hydrazine-1,2-dicarboxylate (**2l**) (0.229 g, 0.5 mmol) and 4-*tert*-butylcyclohexanone (0.077 g, 0.5 mmol) in ethanol (2 mL), and the resulting mixture was stirred at 70 °C for 2 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:24) gave the *title compound* as a colorless solid (0.131 g, 70%): mp 217−219 °C; found 399.2064, $C_{21}H_{32}N_2O_2SNa$ requires 399.2077; ν_{max} ($CHCl_3$)/cm^{-1} 3443, 3011, 2964, 1613, 1463, 1312; δ_H (400 MHz; $CDCl_3$) 9.17 (1H, br s), 7.32 (1H, d, *J* 7.7), 6.85 (1H, d, *J* 7.7), 3.28 (4H, q, *J* 7.2), 3.15 (1H, dd, *J* 15.2, 4.6), 2.87−2.62 (3H, m), 2.72 (3H, s), 2.14−2.10 (1H, m), 1.60−1.44 (2H, m), 1.13 (6H, t, *J* 7.2), 1.03 (9H, s); δ_C (75 MHz; $CDCl_3$) 135.7, 135.6, 132.4, 128.7, 120.5 (CH), 120.2 (CH), 119.1, 111.1, 45.6 (Me), 41.9 (CH_2), 32.6, 27.6 (Me), 27.8 (CH_2), 24.2 (CH_2), 24.0 (CH_2), 20.1 (CH), 14.1 (Me); *m*/*z* (ESI) 1152 (3M + Na^+, 100), 775 (2M + Na^+, 44), 399 (M + Na^+, 57).



Di-tert-butyl 1-(6-Methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (***5***). A solution of *n*-butyllithium in hexane (1.6 M; 1.80 mL, 2.92 mmol) was added dropwise at −40 °C to a solution of 5-bromo-2-methoxypyridine (0.50 g, 2.66 mmol) in ether (4 mL) under an argon atmosphere. The reaction mixture was stirred at −40 °C for 20 min and then a solution of di-*tert*-butyl azodicarboxylate (0.67 g, 2.92 mmol) in tetrahydrofuran (4 mL) was added dropwise. The reaction mixture was stirred at −40 °C for 30 min and allowed to warm to room temperature over 30 min. Water (15 mL) was added followed by dichloromethane (15 mL). The phases were separated and organic layer dried ($MgSO_4$), filtered and evaporated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:19) gave the *title compound* as a colorless solid (0.72 g, 80%): mp 113.7 °C; found M + Na^+, 362.1677, $C_{16}H_{25}N_3O_5$ + Na^+ requires 362.1686; ν_{max} ($CHCl_3$)/cm^{-1} 3403, 2983, 1717, 1608, 1495, 1394, 1370, 1151; δ_H (400 MHz; DMSO-d_6) 9.66 (1H, br s), 8.09 (1H, s), 7.63 (1H, d, *J* 8.9), 6.82 (1H, d, *J* 8.9), 3.84 (3H, s), 1.43 (9H, s), 1.41 (9H, s); δ_C (100 MHz; DMSO-d_6) 161.5, 155.6 (2 × C), 134.0, 110.5 (CH), 110.4 (2 × CH), 81.6, 80.4, 52.3 (Me), 28.5 (Me), 28.2 (Me); *m*/*z* (ESI) 362 (M + Na^+, 100). Anal. Calcd for $C_{16}H_{25}N_3O_5$: C, 56.62; H, 7.42; N, 12.38. Found: C, 56.42; H, 7.41; N, 12.43.



Synthesis of 4- and 6-Azaindoles. *5-Methoxy-2,3-dimethyl-1H-pyrrolo[3,2-b]pyridine* (***6a***). 2-Butanone (0.10 mL, 1.20 mmol)

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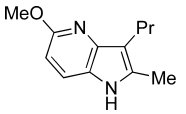
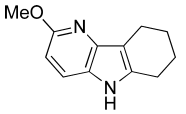
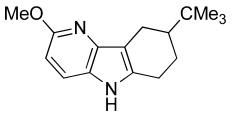
was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.20 g, 0.60 mmol) in an aqueous solution of sulfuric acid (4%; 1.25 mL). The reaction mixture was heated under reflux for 2 h, quenched with a saturated aqueous solution of sodium carbonate (4 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane gave the *title compound* as a colorless solid (0.06 g, 57%): mp 134−135 °C; found M + Na^+, 199.0850, $C_{10}H_{12}N_2O$ + Na^+ requires 199.0842; ν_{max} ($CHCl_3$)/cm^{-1} 3050, 2925, 2857, 1602, 1586, 1439, 1404, 1282, 1241; δ_H (400 MHz; $CDCl_3$) 7.70 (1H, br s), 7.43 (1H, d, *J* 8.6), 6.51 (1H, d, *J* 8.6), 4.03 (3H, s), 2.39 (3H, s), 2.27 (3H, s); δ_C (100 MHz; $CDCl_3$) 159.7, 143.6, 134.0, 123.7, 120.2 (CH), 107.9, 103.3 (CH), 53.2 (Me), 12.2 (Me), 7.4 (Me); *m*/*z* (ESI) 177 (M + H^+, 100).



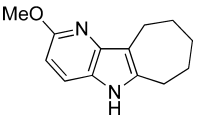
5-Methoxy-2-methyl-3-propyl-1H-pyrrolo[3,2-b]pyridine (**6b**). 2-Hexanone (0.08 mL, 0.66 mmol) was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.20 g, 0.60 mmol) in an aqueous solution of sulfuric acid (4%; 1.25 mL). The reaction mixture was heated under reflux for 2 h, quenched with a saturated aqueous solution of sodium carbonate (4 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane gave the *title compound* as a colorless oil (0.05 g, 41%): found M + Na^+, 227.1162, $C_{12}H_{16}N_2O$ + Na^+ requires 227.1155; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2960, 2870, 1582, 1439, 1404, 1284, 1246; δ_H (400 MHz; $CDCl_3$) 7.77 (1H, br s), 7.41 (1H, d, *J* 8.6), 6.52 (1H, d, *J* 8.6), 4.03 (3H, s), 2.73 (2H, t, *J* 7.4), 2.39 (3H, s), 1.81−1.72 (2H, m), 0.98 (3H, t, *J* 7.4); δ_C (100 MHz; $CDCl_3$) 159.4, 143.4, 134.0, 123.8, 120.2 (CH), 112.8, 103.0 (CH), 53.3 (Me), 25.2 (CH_2), 23.4 (CH_2), 14.1 (Me), 12.3 (Me); *m*/*z* (ESI) 205 (M + H^+, 100).



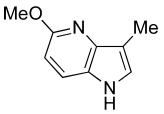
2-Methoxy-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indole (**6c**). Cyclohexanone (0.03 mL, 0.33 mmol) was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.10 g, 0.30 mmol) in an aqueous solution of sulfuric acid (4%; 0.69 mL). The reaction mixture was heated under reflux for 2 h, quenched with a saturated aqueous solution of sodium carbonate (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:49) gave the *title compound* as a colorless solid (0.05 g, 82%): mp 133−134 °C (lit.[60] mp 134 °C); found M + Na^+, 225.1001, $C_{12}H_{14}N_2O$ + Na^+ requires 225.0998; ν_{max} ($CHCl_3$)/cm^{-1} 2932, 1602, 1404; δ_H (400 MHz; $CDCl_3$) 7.65 (1H, br s), 7.46 (1H, d, *J* 8.6), 6.53 (1H, d, *J* 8.6), 4.02 (3H, s), 2.82−2.75 (4H, m), 1.97−1.88 (4H, m); δ_C (100 MHz; $CDCl_3$) 159.8, 142.3, 137.4, 124.2, 120.5 (CH), 110.7, 103.3 (CH) 53.3 (Me), 23.7 (CH_2), 23.2 (CH_2), 23.1 (CH_2), 20.1 (CH_2); *m*/*z* (ESI) 203 (M + H^+, 100).



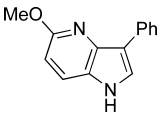
8-tert-Butyl-2-methoxy-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]-indole (**6d**). 4-*tert*-Butylcyclohexanone (0.07 g, 0.48 mmol) was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)-hydrazine-1,2-dicarboxylate (**5**) (0.15 g, 0.44 mmol) in an aqueous solution of sulfuric acid (4%; 0.92 mL). The reaction mixture was heated under reflux for 1 h, quenched with a saturated aqueous solution of sodium carbonate (2 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane gave the *title compound* as a colorless solid (0.06 g, 53%): mp 169−170 °C; found M + Na^+, 281.1631, $C_{16}H_{22}N_2O$ + Na^+ requires 281.1624; ν_{max} ($CHCl_3$)/cm^{-1} 2961, 1585, 1404; δ_H (400 MHz; $CDCl_3$) 7.73 (1H, br s), 7.46 (1H, d, *J* 8.6), 6.53 (1H, d, *J* 8.6), 4.03 (3H, s), 3.01−2.79 (3H, m), 2.47−2.12 (2H, m), 1.56−1.51 (2H, m), 1.04 (9H, s); δ_C (100 MHz; $CDCl_3$) 159.8, 142.5, 137.6, 124.7, 120.6 (CH), 111.0, 103.2 (CH) 53.4 (Me), 45.4 (CH), 32.7, 27.6 (Me), 24.7 (CH_2), 24.6 (CH_2), 21.5 (CH_2); *m*/*z* (ESI) 259 (M + H^+, 100).



2-Methoxy-5,6,7,8,9,10-hexahydro-4,10-diazabenzo[a]azulene (**6e**). Cycloheptanone (0.08 mL, 0.66 mmol) was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.20 g, 0.60 mmol) in an aqueous solution of sulfuric acid (4%; 1.25 mL). The reaction mixture was heated under reflux for 2 h, quenched with a saturated aqueous solution of sodium carbonate (4 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane gave the *title compound* as a colorless solid (0.08 g, 62%): mp 125−126 °C; found M + Na^+, 239.1154, $C_{13}H_{16}N_2O$ + Na^+ requires 239.1155; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2926, 2851, 1602, 1580, 1439, 1404; δ_H (400 MHz; $CDCl_3$) 7.61 (1H, br s), 7.45 (1H, d, *J* 8.5), 6.51 (1H, d, *J* 8.5), 4.03 (3H, s), 2.96 (2H, t, *J* 5.6), 2.87 (2H, t, *J* 5.5), 1.94−1.79 (6H, m); δ_C (100 MHz; $CDCl_3$) 159.7, 143.1, 140.8, 122.8, 120.25 (CH), 114.5, 103.2 (CH), 53.2 (Me), 32.1 (CH_2), 30.4 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 23.3 (CH_2); *m*/*z* (ESI) 217 (M + H^+, 100).

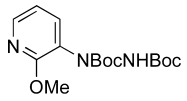


5-Methoxy-3-methyl-1H-pyrrolo[3,2-b]pyridine (**6f**). Propionaldehyde diethyl acetal (0.10 mL, 0.66 mmol) was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.20 g, 0.60 mmol) in an aqueous solution of sulfuric acid (4%; 3 mL). The reaction mixture was heated under reflux for 1 h, quenched with a saturated aqueous solution of sodium carbonate (8 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:99) gave the *title compound* as a colorless solid (0.07 g, 72%): mp 88−89 °C (lit.[60] mp 88 °C); found M + Na^+, 185.0693, $C_9H_{10}N_2O$ + Na^+ requires 185.0685); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2947, 1580, 1442, 1406, 1287, 1244; δ_H (400 MHz; $CDCl_3$) 8.16 (1H, br s), 7.51 (1H, d, *J* 8.8), 7.12 (1H, q, *J* 1.0), 6.62 (1H, d, *J* 8.8), 4.06 (3H, s), 2.38 (3H, d, *J* 1.0); δ_C (100 MHz; $CDCl_3$) 159.8, 142.3, 124.8, 124.4 (CH), 121.6 (CH), 111.7, 104.9 (CH), 53.3 (Me), 8.6 (Me); *m*/*z* (ESI) 163 (M + H^+, 100).

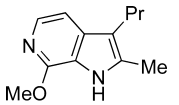


5-Methoxy-3-phenyl-1H-pyrrolo[3,2-b]pyridine (**6g**). Phenylacetaldehyde dimethyl acetal (0.05 mL, 0.44 mmol) was added to a solution of di-*tert*-butyl 1-(6-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.15 g, 0.40 mmol) in an aqueous solution of sulfuric acid (4%; 0.83 mL). The reaction mixture was heated under reflux for 1 h, quenched with a saturated aqueous solution of sodium carbonate (2 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography eluting with dichloromethane and

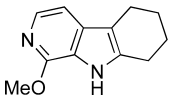
light petroleum (2.3:1) gave the *title compound* as a colorless solid (0.05 mg, 56%): mp 155−156 °C (lit.[60] mp 156 °C); found M + Na^+, 247.0837, $C_{14}H_{12}N_2O$ + Na^+ requires 247.0842); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2947, 1611, 1583, 1406, 1239; δ_H (400 MHz; $CDCl_3$) 8.24 (2H, dd, *J* 1.2, 7.6), 8.18 (1H, br s), 7.66 (1H, d, *J* 3.0), 7.63 (1H, d, *J* 8.8), 7.47 (2H, *J* 7.6), 7.30−7.26 (1H, m), 6.70 (1H, d, *J* 8.8), 4.11 (3H, s); δ_C (100 MHz; $CDCl_3$) 160.1, 140.2, 134.4, 128.5 (CH), 126.3 (CH), 125.8 (CH), 125.3, 123.3 (CH), 121.9 (CH), 116.4, 105.9 (CH), 53.4 (Me); *m*/*z* (ESI) 225 (M + H^+, 100%).



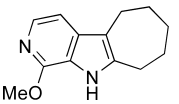
*Di-tert-butyl 1-(2-Methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**8**).* A solution of *n*-butyllithium in hexane (1.6 M; 0.73 mL, 1.16 mmol) was added dropwise at −40 °C to a solution of 3-bromo-2-methoxypyridine (0.20 g, 1.06 mmol) in ether (3 mL) under an argon atmosphere. The reaction mixture was stirred at −40 °C for 20 min, and then a solution of di-*tert*-butyl azodicarboxylate (0.270 g, 1.16 mmol) in tetrahydrofuran (3 mL) was added dropwise. The reaction mixture was stirred at −40 °C for 30 min and allowed to warm to room temperature over 30 min. Water (15 mL) was added followed by dichloromethane (15 mL). The phases were separated, and the organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:9) gave the *title compound* as a colorless solid (0.25 g, 70%): mp 112 °C; found M + Na^+, 362.1687, $C_{16}H_{25}N_3O_5$ + Na^+ requires 362.1686; ν_{max} ($CHCl_3$)/cm^{-1} 3416, 2983, 1721, 1594, 1474; δ_H (400 MHz; DMSO-d_6) 9.60 (1H, br s), 8.08 (1H, dd, *J* 5.1, 1.5), 7.66 (1H, d, *J* 7.4), 7.02 (1H, dd, *J* 7.4, 5.1), 3.89 (3H, s), 1.42 (9H, s), 1.38 (9H, s, *t*Bu); δ_C (100 MHz; DMSO-d_6) 158.7, 156.1, 155.9, 153.6, 145.6 (CH), 117.4 (2 × CH), 81.2, 80.2, 53.7 (Me), 28.5 (Me), 28.2 (Me); *m*/*z* (ESI) 701 (2M + Na^+, 100).



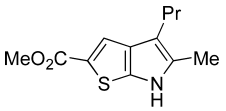
*7-Methoxy-2-methyl-3-propyl-1H-pyrrolo[2,3-c]pyridine (**9a**).* 2-Hexanone (0.08 mL, 0.66 mmol) was added to a solution of di-*tert*-butyl 1-(2-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**8**) (0.20 g, 0.60 mmol) in an aqueous solution of sulfuric acid (4%; 1.25 mL). The reaction mixture was heated under reflux for 1 h, quenched with a saturated aqueous solution of sodium carbonate (4 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:19) gave the *title compound* as a colorless oil (0.04 g, 33%): found M + Na^+, 227.1154, $C_{12}H_{16}N_2O$ + Na^+ requires 227.1155; ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2872, 1629, 1552, 1489, 1471, 1364, 1303; δ_H (400 MHz; $CDCl_3$) 8.56 (1H, br s), 7.74 (1H, d, *J* 5.7, H-5), 7.08 (1H, d, *J* 5.7), 4.13 (3H, s), 2.64 (2H, t, *J* 7.3), 2.41 (3H, s), 1.68−1.59 (2H, m), 0.94 (3H, t, *J* 7.3); δ_C (100 MHz; $CDCl_3$) 150.2, 135.2, 134.4 (CH), 133.9, 119.4, 113.3, 108.4 (CH), 53.6 (Me), 26.2 (CH_2), 23.8 (CH_2), 13.9 (Me), 11.8 (Me); *m*/*z* (ESI) 205 (M + H^+, 100).



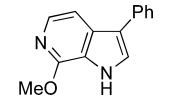
*1-Methoxy-5,6,7,8-tetrahydro-5H-pyrido[3,4-b]indole (**9b**).* Cyclohexanone (0.05 mL, 0.44 mmol) was added to a solution of di-*tert*-butyl 1-(2-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**8**) (0.14 g, 0.40 mmol) in an aqueous solution of sulfuric acid (4%; 0.83 mL). The reaction mixture was heated under reflux for 2 h, quenched with a saturated aqueous solution of sodium carbonate (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:49) gave the *title compound* as a colorless solid (0.04 g, 49%): mp 131 °C (lit.,[60] mp 131 °C); found M + Na^+, 225.1005, $C_{12}H_{14}N_2O$ + Na^+ requires 225.0998; ν_{max} ($CHCl_3$)/cm^{-1} 2944, 1628, 1552, 1487, 1367, 1289, 1111; δ_H (400 MHz; $CDCl_3$) 8.09 (1H, br s), 7.76 (1H, d, *J* 5.6), 7.03 (1H, d, *J* 5.6), 4.10 (3H, s), 2.77 (2H, t, *J* 5.9), 2.70 (2H, t, *J* 5.8), 1.97−1.85 (4H, m); δ_C (100 MHz; $CDCl_3$) 150.6, 136.5, 135.0 (CH), 133.6, 119.9, 110.8, 108.0 (CH) 52.9 (Me), 23.3 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 21.0 (CH_2); *m*/*z* (ESI) 203 (M + H^+, 100).



*1-Methoxy-5,6,7,8,9,10-hexahydro-2,10-diaza-benzo[a]azulene (**9c**).* Cycloheptanone (0.05 mL, 0.44 mmol) was added to a solution of di-*tert*-butyl 1-(2-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.14 g, 0.40 mmol) in an aqueous solution of sulfuric acid (4%; 0.83 mL). The reaction mixture was heated under reflux for 2 h, quenched with a saturated aqueous solution of sodium carbonate (2 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:49) gave the *title compound* as a colorless solid (0.04 g, 46%): mp 124−125 °C; found M + Na^+, 239.1158, $C_{13}H_{16}N_2O$ + Na^+ requires 239.1155); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2927, 2850, 1628, 1549, 1422; δ_H (400 MHz; $CDCl_3$) 8.09 (1H, br s), 7.75 (1H, d, *J* 5.5), 7.04 (1H, d, *J* 5.5), 4.09 (3H, s), 2.86 (2H, t, *J* 5.9), 2.79 (2H, t, *J* 5.7), 1.95−1.89 (2H, m), 1.82−1.73 (4H, m); δ_C (100 MHz; $CDCl_3$) 150.6, 140.2, 135.0, 134.8 (CH), 118.5, 114.6, 107.9 (CH), 52.9 (Me), 31.8 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 27.3 (CH_2), 25.0 (CH_2); *m*/*z* (ESI) 217 (M + H^+, 100).

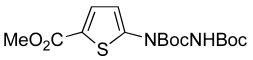


*7-Methoxy-3-methyl-1H-pyrrolo[2,3-c]pyridine (**9d**).* Propionaldehyde diethylacetal (0.11 mL, 0.66 mmol) was added to a solution of di-*tert*-butyl 1-(2-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.20 g, 0.60 mmol) in an aqueous solution of sulfuric acid (4%; 1.25 mL). The reaction mixture was heated under reflux for 1 h, quenched with a saturated aqueous solution of sodium carbonate (4 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and dichloromethane (1:32) gave the *title compound* as a colorless solid (0.04 g, 41%): mp 111−112 °C; found M + H^+, 163.0868, $C_9H_{10}N_2O$ + H^+ requires 163.0866); ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2872, 1629, 1552, 1489, 1471, 1364, 1303; δ_H (400 MHz; $CDCl_3$) 8.29 (1H, br s), 7.79 (1H, d, *J* 5.7), 7.14 (1H, dd, *J* 5.7, 0.7), 7.04−7.05 (1H, m), 4.12 (3H, s), 2.33 (3H, d, *J* 1.0); δ_C (100 MHz; $CDCl_3$) 151.1, 134.8 (CH), 134.1, 123.6 (CH), 121.0, 112.2, 108.6 (CH), 53.0 (Me), 9.7 (Me); *m*/*z* (ESI) 163 (M + H^+, 100). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.39; H, 6.21; N, 17.11.

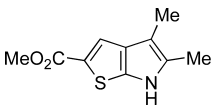


*7-Methoxy-3-phenyl-1H-pyrrolo[2,3-c]pyridine (**9e**).* Phenylacetaldehyde dimethylacetal (0.04 mL, 0.33 mmol) was added to a solution of di-*tert*-butyl 1-(2-methoxypyridin-3-yl)hydrazine-1,2-dicarboxylate (**5**) (0.10 g, 0.30 mmol) in an aqueous solution of sulfuric acid (4%; 0.63 mL). The reaction mixture was heated under reflux for 1 h, quenched with a saturated aqueous solution of sodium carbonate (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane gave the *title compound* as a colorless solid (0.027 mg,

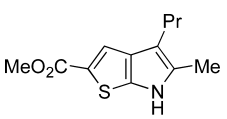
40%): mp 124−125 °C (lit.[60] mp 124 °C); found M + Na^+, 247.0855, $C_{14}H_{12}N_2O$ + Na^+ requires 247.0842); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2983, 1626, 1554, 1490, 1455, 1370, 1090; δ_H (400 MHz; $CDCl_3$) 8.65 (1H, s, br), 7.88 (1H, d, *J* 5.7), 7.67 (2H, dd, *J* 8.1, 1.2), 7.50−7.47 (4H, m, H-2), 7.36−7.32 (1H, m), 4.16 (3H, s); δ_C (100 MHz; $CDCl_3$) 160.1, 51.5, 136.1 (CH), 134.8, 131.6, 128.9 (CH), 127.2 (CH), 126.4 (CH), 123.4 (CH), 121.7 (CH), 118.8, 109.4 (CH), 53.1 (Me); *m*/*z* (ESI) 225 (M + H^+, 100).



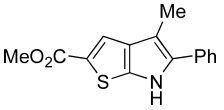
*Di-tert-butyl 1-[5-(Methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**).* A solution of isopropylmagnesium bromide in 4-methyltetrahydrofuran (2.9 M; 0.40 mL, 1.10 mmol) was added dropwise at −40 °C to a stirred solution of methyl 5-bromothiophene-2-carboxylate (0.20 g, 0.90 mmol) in tetrahydrofuran (3 mL) under an argon atmosphere. The reaction mixture was stirred at −40 °C for 30 min, and then a solution of di-*tert*-butyl azodicarboxylate (0.23 g, 0.99 mmol) in tetrahydrofuran (3 mL) was added dropwise. The solution was allowed to warm to room temperature over 3 h, quenched with a saturated aqueous ammonium chloride solution (10 mL), extracted with dichloromethane (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane gave the *title compound* as a colorless solid (0.32 g, 95%): mp 101−102 °C; found M + Na^+, 395.1243, $C_{16}H_{24}N_2O_6S$ + Na^+ requires 395.1247; ν_{max} ($CHCl_3$)/cm^{-1} 3401, 3011, 2984, 1752, 1720, 1461; δ_H (400 MHz; DMSO-d_6) 10.07 (1H, br s), 7.58 (1H, d, *J* 4.2), 6.69 (1H, d, *J* 4.2), 3.78 (3H, s), 1.51 (9H, s), 1.46 (9H, s); δ_C (100 MHz; DMSO-d_6) 162.8, 154.6, 152.2, 151.2, 132.9 (CH), 123.6, 112.1 (CH), 81.3 (2 × C), 52.3 (Me), 28.4 (Me), 28.1 (Me); *m*/*z* (ESI) 395 (M + Na^+, 100).



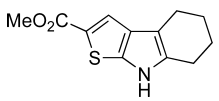
Synthesis of Thieno[2,3-*b*]pyrroles. *Methyl 4,5-Dimethyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (**12a**).* A mixture of di-*tert*-butyl 1-[5-(methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**) (0.20 g, 0.54 mmol), 2-butanone (0.10 mL, 1.08 mmol), and *p*-toluenesulfonic acid (0.62 g, 3.24 mmol) in ethanol (7 mL) was heated under reflux for 1 h. After themixture was cooled to room temperature, the ethanol was removed in vacuo. The residue was diluted with ethyl acetate (10 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (2.3:1) gave the *title compound* as a colorless solid (0.07 g, 62%): mp 162−163 °C; found M + Na^+, 232.0401, $C_{10}H_{11}NO_2S$ + Na^+ requires 232.0403; ν_{max} ($CHCl_3$)/cm^{-1} 3469, 3011, 2360, 2340, 1695, 1599, 1513, 1435, 1410, 1289, 1240, 1075; δ_H (400 MHz; DMSO-d_6) 11.19 (1H, br s), 7.70 (1H, s), 3.78 (3H, s), 2.23 (3H, s), 2.11 (3H, s); δ_C (100 MHz; DMSO-d_6) 163.9, 136.0, 132.9, 132.0, 124.8 (CH), 122.7, 107.6, 52.1 (Me), 11.9 (Me), 9.89 (Me); *m*/*z* (ESI) 232 (M + Na^+, 100%). Anal. Calcd for $C_{10}H_{11}NO_2S$:C, 57.39; H, 5.30; N, 6.69. Found: C, 57.01; H, 5.24; N, 6.49.



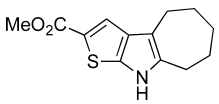
*Methyl 5-Methyl-4-propyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (**12b**).* A mixture of di-*tert*-butyl 1-[5-(methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**) (0.20 g, 0.54 mmol), 2-hexanone (0.13 mL, 1.08 mmol), and *p*-toluenesulfonic acid (0.62 g, 3.24 mmol) in ethanol (7 mL) was heated under reflux for 1 h. After the mixture was cooled to room temperature, the ethanol was removed in vacuo. The residue was diluted with ethyl acetate (10 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (2.3:1) gave the *title compound* as a colorless solid (0.11 g, 86%): mp 150−151 °C; found M + Na^+, 260.0713, $C_{12}H_{15}NO_2S$ + Na^+ requires 260.0716; ν_{max} ($CHCl_3$)/cm^{-1} 3468, 3006, 2957, 2932, 2872, 1693, 1602, 1511, 1435, 1408, 1290, 1256, 1080; δ_H (400 MHz; $CDCl_3$) 8.00 (1H, br s), 7.76 (1H, s), 3.90 (3H, s), 2.57 (2H, t, *J* 7.5), 2.33 (3H, s), 1.72−1.63 (2H, m), 0.96 (3H, t, *J* 7.5); δ_C (100 MHz; $CDCl_3$) 159.7, 131.6, 127.1, 127.0, 120.0 (CH), 119.4, 109.3, 47.1 (Me), 22.5 (CH_2), 19.1 (CH_2), 9.2 (Me), 7.2 (Me); *m*/*z* (ESI) 497 (2M + Na^+, 100).



*Methyl 4-Methyl-5-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (**12c**).* A mixture of di-*tert*-butyl 1-[5-(methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**) (0.20 g, 0.54 mmol), propiophenone (0.20 mL, 1.62 mmol), and *p*-toluenesulfonic acid (0.62 g, 3.24 mmol) in ethanol (7 mL) was heated under reflux for 2 h. After the mixture was cooled to room temperature, the ethanol was removed in vacuo. The residue was diluted with ethyl acetate (10 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:24) gave the *title compound* as a colorless solid (0.09 g, 61%): mp 211−212 °C; found M + Na^+, 294.0561, $C_{15}H_{13}NO_2S$ + Na^+ requires 294.0559); ν_{max} ($CHCl_3$)/cm^{-1} 3461, 3011, 1694, 1603, 1514, 1434, 1410, 1291, 1239, 1078; δ_H (400 MHz; DMSO-d_6) 11.78 (1H, br s), 7.87 (1H, s), 7.56 (2H, dd, *J* 7.6, 1.2), 7.49 (2H, t, *J* 7.6), 7.33 (1H, tt, *J* 7.6, 1.2), 3.82 (3H, s), 2.38 (3H, s); δ_C (100 MHz; DMSO-d_6) 163.7, 138.0, 136.1, 133.2, 133.1, 129.3 (CH), 127.2 (CH), 127.1 (CH), 125.4 (CH), 124.0, 109.4, 52.3 (Me), 11.6 (Me); *m*/*z* (ESI) 565 (2M + Na^+, 100).

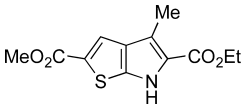


*Methyl 5,6,7,8-Tetrahydro-4H-1-thia-8-aza-cyclopenta[a]indene-2-carboxylate (**12d**).* A mixture of di-*tert*-butyl 1-[5-(methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**) (0.20 g, 0.54 mmol), cyclohexanone (0.10 mL, 1.08 mmol), *p*-toluenesulfonic acid (0.62 g, 3.24 mmol) in ethanol (7 mL) was heated under reflux for 5 h. After the mixture was cooled to room temperature, the ethanol was removed in vacuo. The residue was diluted with ethyl acetate (10 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:24) gave the *title compound* as a colorless solid (0.09 g, 71%): mp 185 °C; found M + Na^+, 258.0552, $C_{12}H_{13}NO_2S$ + Na^+ requires 258.0559; ν_{max} ($CHCl_3$)/cm^{-1} 3468, 3011, 2942, 2847, 1693, 1594, 1515, 1434, 1403, 1288, 1248, 1070; δ_H (400 MHz; DMSO-d_6) 11.20 (1H, br s), 7.67 (1H, s), 3.78 (3H, s), 2.64 (2H, t, *J* 6.0), 2.57 (2H, t, *J* 5.9), 1.79−1.73 (4H, m); δ_C (100 MHz; DMSO-d_6) 163.9, 137.1, 136.1, 130.0, 124.6 (CH), 122.7, 110.5, 52.1 (Me), 23.5 (CH_2), 23.3 (CH_2), 23.1 (CH_2), 22.0 (CH_2); *m*/*z* (ESI) 493 (2M + Na^+, 100).



*Methyl 4,5,6,7,8,9-Hexahydro-1-thia-9-aza-cyclopenta[a]-azulene-2-carboxylate (**12e**).* A mixture of di-*tert*-butyl 1-[5-(methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**) (0.20 g, 0.54 mmol), cycloheptanone (0.13 mL, 1.08 mmol), and *p*-toluenesulfonic acid (0.62 g, 3.24 mmol) in ethanol (7 mL) was heated under reflux for 8 h. After the mixture was cooled to room

temperature, the ethanol was removed in vacuo. The residue was diluted with ethyl acetate (10 mL) and neutralized with sodium saturated aqueous hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:24) gave the *title compound* as a colorless solid (0.08 g, 60 59%): mp 166−167 °C; found M + Na^+, 272.0711, $C_{13}H_{15}NO_2S$ + Na^+ requires 272.0716; ν_{max} ($CHCl_3$)/cm^{-1} 3466, 3011, 2926, 2849, 1691, 1585, 1510, 1434, 1408, 1291, 1254, 1082; δ_H (400 MHz; DMSO-d_6) 11.20 (1H, br s), 7.71 (1H, s), 3.78 (3H, s), 2.74 (2H, t, *J* 5.7), 2.69 (2H, t, *J* 5.5), 1.83−1.77 (2H, m), 1.68−1.62 (4H, m); δ_C (100 MHz; DMSO-d_6) 163.9, 139.7, 134.4, 132.4, 124.8 (CH), 122.8, 114.6, 52.1 (Me), 31.8 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 27.7 (CH_2), 24.6 (CH_2); *m*/*z* (ESI) 521 (2M + Na^+, 100). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.58; H, 6.08; N, 5.69.



*4-Methyl-6H-thieno[2,3-b]pyrrole-2,5-dicarboxylic Acid 5-Ethyl Ester 2-Methyl Ester (**12f**).* A mixture of di-*tert*-butyl 1-[5-(methoxycarbonyl)thien-2-yl]hydrazine-1,2-dicarboxylate (**11**) (0.20 g, 0.54 mmol), 2-oxobutyric acid ethyl ester (0.14 g, 1.08 mmol), and *p*-toluenesulfonic acid (0.62 g, 3.24 mmol) in ethanol (7 mL) was heated under reflux for 3 h. After the mixture was cooled to room temperature, the ethanol was removed in vacuo. The residue was diluted with ethyl acetate (10 mL) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:19) gave the *title compound* as a colorless solid (0.09 g, 62%): mp 191 °C; found M + Na^+, 290.0460, $C_{12}H_{13}NO_4S$ + Na^+ requires 290.0457); ν_{max} ($CHCl_3$)/cm^{-1} 3453, 3045, 2955, 1700, 1510, 1434, 1413, 1292, 1248, 1141, 1084; δ_H (400 MHz; DMSO-d_6) 12.07 (1H, br s), 7.93 (1H, s), 4.30 (2H, q, *J* 7.2), 3.83 (3H, s), 2.49 (3H, s), 1.33 (3H, t, *J* 7.2); δ_C (100 MHz; DMSO-d_6) 163.3, 161.2, 140.3, 132.2, 126.8, 125.9 (CH), 125.8, 121.3, 60.4 (CH_2), 52.6 (Me), 14.8 (Me), 11.7 (Me); *m*/*z* (ESI) 557 (2M + Na^+, 100). Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.95; H, 4.90; N, 5.01.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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