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A Practical Route to Substituted 7-Aminoindoles from Pyrrole-3-carboxaldehydes

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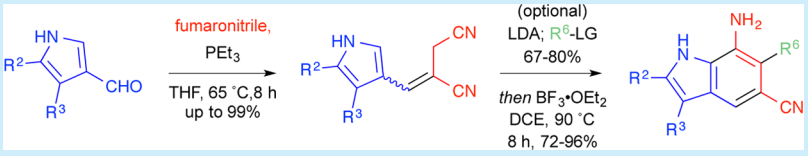
Supporting Information



ABSTRACT: Among privileged structures, indoles occupy a central place in medicinal chemistry and alkaloid research. Here we report a flexible and efficient conversion of pyrrole-3-carboxaldehydes to substituted 7-amino-5-cyanoindoles. Phosphine addition to fumaronitrile proceeds with prototropic rearrangement of the initially formed zwitterion to the thermodynamically favored phosphonium ylide, which is poised for in situ Wittig olefination. The predominantly *E*-alkene product positions the allylic nitrile for facile intramolecular Hoeben–Hoesch reaction in the presence of $BF_3{\cdot}OEt_2$. Syntheses of 2,5- and 3,5-disubstituted 7-aminoindoles are illustrated. Additionally, dianion alkylation of the allylic nitrile is demonstrated to furnish, after cyclization, 5,6-disubstituted 7-aminoindoles to further exemplify this scalable and high-yielding method.

Synthetic routes to indoles have long been prized owing to the prevalence of the aromatic heterocycles in natural products as well as synthetic medicinal agents.[1] Classical indole syntheses, including the work of Fischer,[2] Bartoli,[3] Larock,[4] Reissert,[5] and many others,[6] remain benchmarks in the development of heterocyclic methodology. The majority of these approaches utilize a functionalized benzene ring to annulate the 5-membered pyrrolic portion of the indole. In contrast, few synthetic strategies exist that originate from a substituted pyrrole to build up the benzenoid portion of the indole.[7] The latter strategy can benefit from the unique chemistry of pyrroles, which react with electrophiles preferentially at C-2 but exclusively at C-3 when *N*-protected with the sterically cumbersome triisopropylsilyl group.[8] This tunable reactivity allows for ready introduction of the would be C-2 and C-3 substituents of the indole prior to annulation. Further, the intrinsic reactivity of pyrroles at C-2 introduces a disconnection optimal for the indole-forming cyclization itself. Tactical issues of symmetry and regiochemistry inherent to routes from substituted benzene rings are avoided. This strategy, shown in Figure 1, utilizes a three-component Wittig reaction of pyrrole-3-carboxaldehydes with fumaronitrile and a trialkylphosphine to generate predominantly *E*-alkenes. These allylic nitriles are positioned for intramolecular cyclization under Houben–Hoesch conditions to furnish, after aromatization, substituted 7-aminoindoles. An optional tailoring step to install C-6 substituents prior to ring closure can also be envisioned. This scheme would allow for control of the C-2, C-3, and C-6 indole substituents on the resulting 7-amino-5-cyanoindoles that are not readily accessible using existing methods. The amine (e.g., by diazotization, acylation) and the nitrile (e.g., by hydration, hydrolysis, reduction, etc.) can be differentially modified for rapid structural diversification. Potential targets (Figure 2) include a class of potent β-secretase

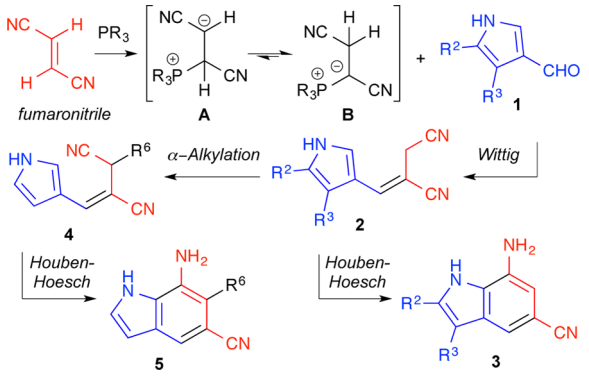


Figure 1. Proposed route to substituted 7-aminoindoles.

1 (BACE1) inhibitors,[9] a class of nicotinic acetylcholine receptor (nAChR) allosteric modulators,[10] and analogues of recently reported inhibitors of glycerol-3-phosphate acyltransferase (GPAT).[11]

Of fundamental importance to the planned synthesis was the acquisition of *E*-alkenes such as **2** (Figure 1). The *E*-selective olefination of aldehydes with esters of fumarate and maleate, maleic anhydride, or maleimide and tributyl- or triphenylphosphine has been previously described.[12] We envisioned a similar 1,4-addition of a phosphine to fumaronitrile proceeded by rapid prototropic rearrangement of the initially formed zwitterion **A** to the thermodynamically favored phosphonium ylide **B**, which is poised for in situ Wittig olefination with pyrrole-3-carboxaldehydes such as **1**. Trimethyl-, triethyl-, tributyl-, and triphenyl-

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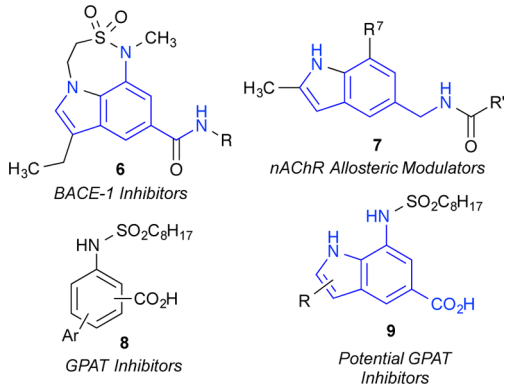
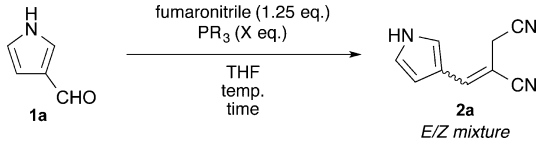


Figure 2. Representative medicinal chemistry targets.

phosphine, as well as trimethyl phosphite, were evaluated for the efficiency of their reactions with fumaronitrile and aldehyde **1a** as shown in Table 1. PPh_3 and $P(OMe)_3$ were unreactive under the

Table 1. Optimization of Wittig Reaction with Aldehyde 1a



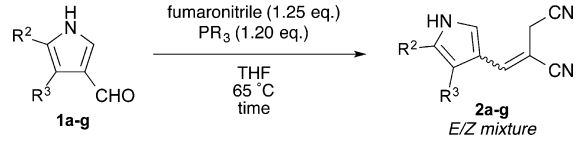
entry	PR_3	X	temp (°C)	time (h)	yield of **2a**[a] (%)	E/Z[b]
1	PMe_3	1.4	23	48	76	4:3
2	PEt_3	1.4	23	48	80	4:3
3	PBu_3	1.4	23	48	72	4:3
4	PPh_3	1.4	23	48	0	
5	$P(OMe)_3$	1.4	23	48	0	
6	PMe_3	1.2	23	48	95	3:1
7	PEt_3	1.2	23	48	99	3:1
8	PBu_3	1.2	23	48	91	3:1
9	PEt_3	1.2	65	8	97	3:1

[a]Isolated yield. [b]E/Z values were calculated from the ratio of the integrals of the allylic methylenes in the ^1H NMR spectra.

reaction conditions. PMe_3, PEt_3, and PBu_3, when used in excess, exhibited understandably similar reactivity, converting aldehyde **1a** to alkene **2a** in moderate yield (72−80%) but with only slight *E*-selectivity (4:3) after extended reaction time (48 h). Concerned that the excess phosphine was adding into the product, itself an α,β-unsaturated nitrile, and causing isomerization of the alkene, we next attempted the reaction with limiting phosphine. At room temperature, these reactions gave the desired alkene **2a** in high yield (91−99%) and good E/Z ratio (3:1), suggesting that the excess phosphine was indeed causing alkene isomerization. To ameliorate the sluggish reaction rate, we heated the reaction with PEt_3 to 65 °C. These improved conditions cut the reaction time 6-fold while maintaining the favorable yield (97%) and E/Z ratio (3:1) of the room temperature reaction. There are distinct advantages to each of the phosphines tested. The volatility of PMe_3 (bp 38 °C) allows for easy removal upon workup but prohibits heating of the reaction without a sealed vessel. PBu_3 (bp 240 °C) requires an additional oxidative workup step but is the most economical choice. Finally, PEt_3 (bp 126 °C) afforded the highest yield and allows for heating to reflux while maintaining the option of low-pressure removal.

To demonstrate scope, the optimized conditions using PEt_3 at 65 °C were applied to various 4- and 5-substituted pyrrole-3-carboxaldehydes **1a−g**. Alkenes **2a−g** were obtained in generally good to excellent yield and moderate diastereoselectivity (Table 2). The reaction conditions were tolerant of a wide range of

Table 2. Scope of Wittig Reaction



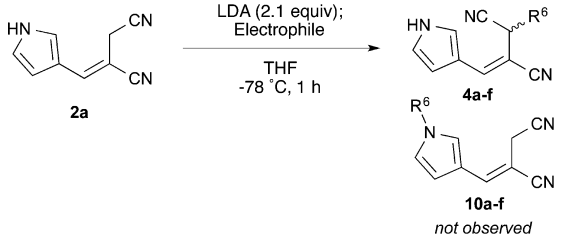
entry	**1**	R^2	R^3	time (h)	product	yield (%)	E/Z[a]
1	**1a**	−H	−H	8	**2a**	97	3:1
2	**1b**	−Br	−H	10	**2b**	97	3:1
3	**1c**	$-CO_2Et$	−H	10	**2c**	96	5:1
4	**1d**	−Ph	−H	8	**2d**	88	3:1
5	**1e**	−H	−Me	8	**2e**	85	4:1
6	**1f**	−H	−Et	8	**2f**	85	4:1
7	**1g**	−H	−Br	8	**2g**	93	5:3

[a]E/Z values were calculated from the ratio of the integrals of the allylic methylenes in the ^1H NMR spectra.

substituents including alkyl, aryl, halogen, and ester moieties. Electron-withdrawing substituents at the pyrrolic α-position led to slower conversion. Additionally, minor substituent effects were observed for the diastereoselectivity of the reactions.

To further diversify the library of *E*-alkenes, we next sought to functionalize the allylic nitrile. To accomplish this task without the use of protecting groups, we elected to exploit the relatively more acidic pyrrole N−H and developed a dianion approach to alkylate the allylic position chemoselectively (Table 3). Addition

Table 3. Alkylation of Allylic Nitrile 2a



entry	electrophile	product	R^6	yield (%)
1	MeI	**4a**	$-CH_3$	77
2	EtI	**4b**	$-CH_2CH_3$	80
3	BnBr	**4c**	$-CH_2Ph$	75
4	allyl-Br	**4d**	$-CH_2CH{=}CH_2$	67
5	propargyl-Br	**4e**	$-CH_2C{\equiv}CH$	72
6	$BrCH_2CO_2Et$	**4f**	$-CH_2CO_2Et$	80

of 2.1 equiv of LDA followed by the addition of various electrophiles effected selective α-alkylation of nitrile **2a** to afford **4a−f** without detection of *N*-alkylated pyrrole side products **10a−f**. Analogous attempts with the electrophiles ethyl chloroformate, methyl acrylate, Br_2, and NBS showed no desired reaction.

With reaction conditions established to *E*-olefinic precursors **2a−g** and **4a−f**, we next sought to optimize indole cyclization conditions as shown in Table 4. Of the Lewis acids tested, only $BF_3{\cdot}OEt_2$ successfully effected cyclization. Initial attempts to use a catalytic amount of $BF_3{\cdot}OEt_2$ gave only stoichiometric yield.

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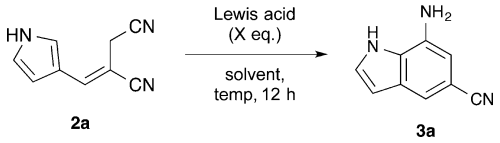
Table 4. Optimization of Cyclization to indole 3a



2a **3a**

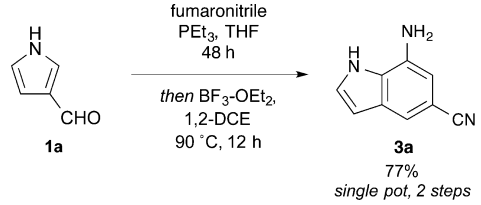
entry	Lewis acid	X	solvent	temp (°C)	yield (%)
1	none		CH_2Cl_2	45	0
2	$AlCl_3$	0.2	CH_2Cl_2	45	0
3	$Sc(OTf)_3$	0.2	CH_2Cl_2	45	0
4	$TiCl_4$	0.2	CH_2Cl_2	45	0
5	$BF_3{\cdot}OEt_2$	0.2	CH_2Cl_2	45	19
6	$BF_3{\cdot}OEt_2$	1.1	THF	70	0
7	$BF_3{\cdot}OEt_2$	1.1	$PhCH_3$	85	61
8	$BF_3{\cdot}OEt_2$	2.5	DCE	90	91

Presumably, this is due to chelation of the Lewis acid by the 7-aminoindole product thereby preventing catalytic turnover. Similarly, using THF as the solvent afforded no reaction, likely owing to association of the Lewis acid with the ethereal solvent. The optimized conditions used 2.5 equiv of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane at 90 °C for 12 h, which gave efficient annulation of alkene **2a** to indole **3a**.

Application of the annulation conditions to the *E*-alkenes **2a–g** and **4a–f** gave indoles **3a–g** and **5a–f** in good to excellent yields (Table 5). The reaction conditions were amenable to a wide scope of substituents. Of particular interest to us, the bromo- and propargyl-substituted indoles can be further functionalized through coupling reactions or click chemistry, respectively, to rapidly generate large libraries of compounds. The more electron-deficient pyrroles (e.g., **2c**, **2g**) demonstrated lower yields, typical of electrophilic aromatic substitution with an electron-deficient arene. The reaction times for the 6-substituted alkenes were slightly shorter than for cyclization of the 2- and 3-substituted examples. This behavior points to a possible Thorpe–Ingold effect, whereby the C-6 substituent increases the population of the reactive rotamer resulting in an increased reaction rate. It is likely that this tactic can also be applied to pyrroles additionally substituted at the 2- and 3-positions.

In addition, a functionally one-pot reaction was run to indole **3a**, shown in Scheme 1, in which pyrrole-3-carboxaldehyde and

Scheme 1. One-Pot Synthesis of indole 3a



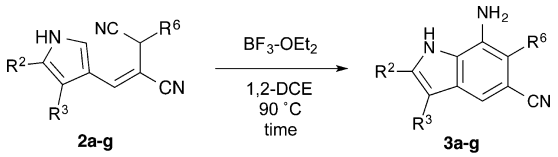
1a **3a**
77%
single pot, 2 steps

fumaronitrile were reacted in dry THF with PMe_3 as before (Table 1). Taking advantage of the relatively low boiling point of PMe_3, the solvent and any unreacted phosphine were removed by rotary evaporation and the residue taken up in 1,2-DCE. Treatment of this mixture as above with $BF_3{\cdot}OEt_2$ gave the desired indole in 77% yield, approximately the theoretical limit from the *E*-isomer, after crystallization of the product from the crude mixture containing unreacted *Z*-isomer.

Encouraged by the success of this approach, we next tested whether the corresponding furan- and thiophene-3-carboxaldehydes could undergo a similar two-step sequence to the corresponding 7-amino-5-cyanobenzofurans and benzothiophenes, respectively (Scheme 2). We hypothesized that, with decreased C-2 nucleophilicity and increased heteroatomic interaction with the $BF_3{\cdot}OEt_2$, the annulation of these heterocycles would be less facile. First, Wittig reaction using the optimized conditions afforded the olefins **12a,b** in excellent yield and better stereoselectivity than for the pyrrolic reactions. Treatment with $BF_3{\cdot}OEt_2$ effected annulation to benzofuran **13a** and benzothiophene **13b** in low to moderate yield. As expected, the reaction rates were much slower with conversion stalling around 24 h. Neither additional equivalents of Lewis acid nor longer reaction times improved the yields. It is possible that use of a less oxophilic Lewis acid could improve the yields for these classes of heterocycles.

Finally, to illustrate practical applications of this method we chose to demonstrate functional group conversions from the 7-

Table 5. Scope of Indole Annulation



2a-g **3a-g**

entry	pyrrole	R^2	R^3	R^6	indole	time (h)	yield (%)
1	**2a**	–H	–H	–H	**3a**	12	91
2	**2b**	–Br	–H	–H	**3b**	12	67
3	**2c**	$-CO_2Et$	–H	–H	**3c**	12	62
4	**2d**	–Ph	–H	–H	**3d**	12	87
5	**2e**	–H	$-CH_3$	–H	**3e**	12	94
6	**2f**	–H	$-CH_2CH_3$	–H	**3f**	12	92
7	**2g**	–H	–Br	–H	**3g**	12	75
8	**4a**	–H	–H	$-CH_3$	**5a**	8	88
9	**4b**	–H	–H	$-CH_2CH_3$	**5b**	8	95
10	**4c**	–H	–H	$-CH_2Ph$	**5c**	8	96
11	**4d**	–H	–H	$-CH_2CH{=}CH_2$	**5d**	8	93
12	**4e**	–H	–H	$-CH_2C{\equiv}CH$	**5e**	8	92
13	**4f**	–H	–H	$-CH_2CO_2Et$	**5f**	8	72

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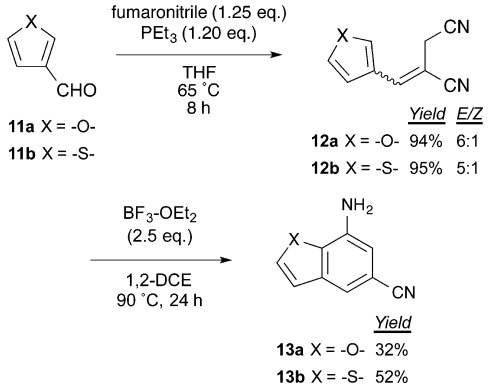
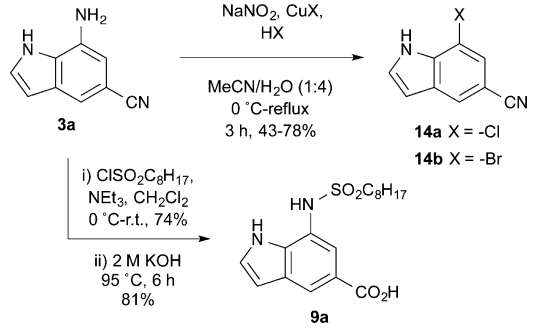
Scheme 2. Application to the Synthesis of Benzofuran and Benzothiophene Derivatives



amino-5-cyanoindole intermediates to readily identifiable precursors of the medicinal chemistry targets noted above (Figure 2). First, we utilized Sandmeyer chemistry to substitute the amino group of indole **3a** with chloro or bromo as shown in Scheme 3. These aryl halides allow access to a variety of C-7

Scheme 3. Functional Group Conversion of 3a to Precursors of Medicinal Chemistry Targets



substituted indoles, such as the nAChR allosteric modulators represented by **7** (Figure 2), through metal-catalyzed coupling reactions. Second, we demonstrated sulfonamide coupling of the aniline with octanesulfonyl chloride, followed by alkaline nitrile hydrolysis to give the GPAT inhibitor analogue **9a**. A similar sulfonamide coupling and hydrolysis sequence can be envisioned to access the diversifiable precursor of the BACE1 inhibitors represented by **6** (Figure 2).

In conclusion, we have developed a flexible and step-efficient method to obtain highly functionalized 7-aminoindoles from pyrrole-3-carboxaldehydes. This method utilizes a three-component Wittig reaction of pyrrole-3-carboxaldehydes with fumaronitrile and PEt_3 to generate predominantly *cis*-allylic nitriles, which can be optionally elaborated further by a chemoselective alkylation at C-6. These *cis*-allylic nitriles undergo cyclization through an intramolecular Houben–Hoesch reaction to afford highly substituted indoles. A one-pot procedure combining the Wittig and Houben–Hoesch reactions was also demonstrated. While the method is substantially linear, the steps are typically high-yielding with chromatographic purification minimized or eliminated, and intermediates and products isolated by crystallization. The reactions are scalable and require no special precautions or protecting groups—in sum, attributes favorable for large-scale applications. Further studies will aim to expand the scope of this method and to demonstrate its potential for the synthesis of bioactive targets of interest.

■ ASSOCIATED CONTENT

Supporting Information

Detailed synthetic procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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