A Practical Synthesis of 2-Aryl-Indole-6-carboxylic Acids

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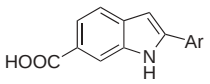
Abstract: A practical synthesis of 2-aryl-indole-6-carboxylic acids was developed via a sequence consisting of S_NAr reaction, reductive cyclization, hydrolysis and decarboxylation. This process is efficient in terms of operational simplicity, cost effectiveness and is amenable to large scale production.

Key words: indole, S_NAr reaction, reductive cyclization

The biological activity displayed by various indole derivatives has made this heterocyclic system one of the most frequent subunit encountered in pharmacologically active compounds.[1] While numerous synthetic methodologies have been reported over the past decades,[2,3] certain specific substitution patterns remain difficult to obtain and elaboration of practical approaches remains desirable. Recently, the use of palladium and copper catalysis [organometallics (Pd, Cu)] emerged to overcome some of those hurdles [1–4] and these methodologies exhibit high compatibilities with a wide range of functional groups. However, they have also shown some limitations for scale-up and may not be practical in terms of raw materials, operational steps, and purification.[4]

Herein we wish to report an alternative strategy that allows for an efficient and practical formation of 2-aryl-indole-6-carboxylic acid derivatives (**1**, Figure 1) from inexpensive material via an aromatic nucleophilic substitution (S_NAr) of aryl chlorides with β-keto esters followed by a reductive cyclization-decarboxylation sequence.



1
1a Ar = 2-pyridyl

Figure 1

The 2-aryl-indole-6-carboxylic acid framework (**1**, Figure 1) is structurally unique and present in a wide range of pharmacophores.[5,6] In particular, we were interested in developing a practical process to produce 2-(2-pyridyl)-indole-6-carboxylic acid (**1a**, Figure 1). The targeted compound **1a** is a challenging disubstituted indole to access via cross-coupling reactions presumably due to the complexation of the metal by the pyridine ring.[4a,d] An attractive strategy, in terms of simplicity and cost-effectiveness, relies on the traditional nucleophilic aromatic substitution with dialkyl malonates[7] leading to indolone.[8] While such S_NAr reaction worked well when malonates were used as nucleophiles, similar attempts using β-keto esters failed to produce the desired S_NAr product as reported by Loudon and Augustine.[9,10] We chose to investigate this approach in further details because of the low cost of the readily available starting materials, and simplicity of operations.

Our synthesis started with commercially available ethyl picolinoylacetate (**3**) and 4-chloro-3-nitrobenzonitrile (**2**, Table 1). Deprotonation of β-keto ester **3** by *t*-BuOK followed by its reaction with aryl chloride **2** were carried out in *N*-methyl pyrrolidinone at 70 °C. Our initial attempts resulted in a complex mixture of products. By extensive 1D and 2D NMR studies, these products were characterized as desired alkylated compound **4**, deacylated and decarboxylated compounds **5** and **6**. The ^1H spectrum of the mixture[11] showed characteristic signals for the methine proton of **4** as a singlet at $\delta = 6.83$ ppm due to the deshielding effect of the keto ester. The methylene protons of deacylated compound **5** appeared as a singlet at $\delta = 4.09$ ppm. The decarboxylated compound **6** was a minor component of the mixture and could not be fully characterized by NMR but was identified by LC-MS. Under a variety of conditions, the yields of **4**, **5**, and **6** were generally high (>95%) while the ratio could vary greatly. These observations indicated that the desired C-C bond formation via S_NAr reaction took place efficiently, but it was followed by decomposition events leading to **5** and **6** through a non-selective decarboxylation/deacylation pathway as reported by Loudon.[10a] The two electron-withdrawing groups on the aromatic ring were the possible cause for the decarboxylation/deacylation and such decomposition most likely occurred during the work-up protocol. After numerous experiments, it was found that careful monitoring of the pH of the work-up medium was critical to avoid such decomposition. These undesired side-reactions could be prevented when the crude reaction mixture was quenched by reverse addition to a HCl solution in dioxane. The desired S_NAr product **4** remained intact as observed in the ^1H NMR spectrum of the crude product (95% yield by NMR with internal standard, Table 1). In contrast, ester **5** could be obtained in 96% yield as a single product when aqueous HCl was added to the reaction mixture.

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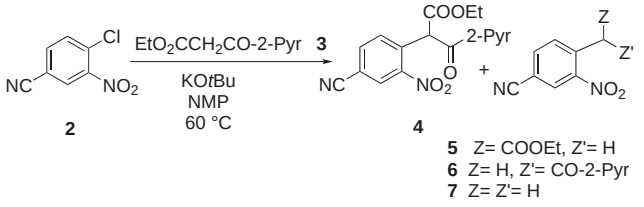
Table Preparation of the S_NAr Product



Entry	Work-up conditions	4	5
1	Aqueous HCl	Not detected	96%
2	HCl in dioxane	95%	Not detected

With a practical synthesis of **4** in place,[12] we attempted to decarboxylate selectively. A variety of conditions failed and led to mixtures of deacylated (**5**), decarboxylated (**6**) and ortho-nitrotoluene [toluidine] (**7**) compounds.[13]

Indole-3-carboxylic acid is reported to undergo easy decarboxylation.[14] We decided to carry out the reductive cyclization first, followed by the decarboxylation in the last step. The reductive cyclization of **4** proceeded well under reported conditions (Fe/HOAc, 85 °C, 4 h)[15] and produced cyclized indole **8a** (Table 2). The crude ester was subjected to decarboxylation under basic conditions. The reaction was monitored by LC-MS and showed rapid hydrolysis of the ester and nitrile. Subsequent regioselective decarboxylation at C-3 position provided the desired 2-(2-pyridyl)-indole-6-carboxylic acid **1a** in 4 hours and an overall 72% isolated yield from aryl chloride **2**. Recrystallization from EtOH could give rise to analytically pure material. On the other hand, the decarboxylation attempted under acidic conditions (aq HCl) resulted in lower rates (4–5 d).

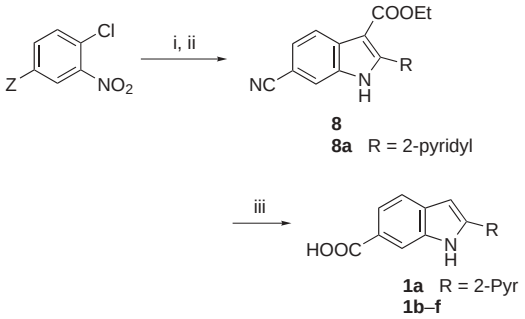
Overall, a sequence consisting of S_NAr reaction, reductive cyclization, hydrolysis and decarboxylation was accomplished without any isolation of intermediates. A multigram quantity of 2-(2-pyridyl)-indole-6-carboxylic acid (**1a**) was generated rapidly in a sequence carried out in a single reaction vessel.

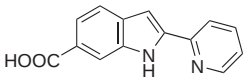
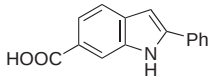
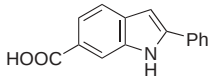
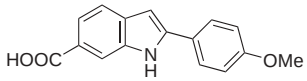
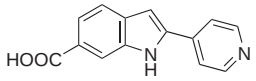
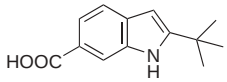
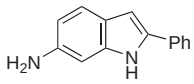
The scope of the method was explored and the results are summarized in Table 2.

The effect of a second activating group was first evaluated. The reaction sequence was repeated with the monoactivated 2-nitro-chlorobenzene and ethyl benzoylacetate. Under the previously described conditions, low conversion was observed during the S_NAr reaction, which rendered the 3 step sequence unpractical. The double activation of the aryl chloride appeared critical for the efficiency of this approach.

When benzoylacetoacetate was reacted with 4-chloro-3-nitrobenzonitrile (entry 2) and ethyl-4-chloro-3-nitrobenzoate (entry 3), the same product was obtained but the more robust nitrile gave significantly higher yield.

Table 2 Synthesis of 2,6-Disubstituted Indoles[a]



Entry	Z	R	Product	Yield (%)[b]
1	CN	2-Pyr	 **1a**	72%
2	COOEt	Ph	 **1b**	45%
3	CN	Ph	 **1b**	79%
4	CN	4-MeOPh	 **1c**	72%
5	CN	4-Pyr	 **1d**	64%
6	CN	*t*-Bu	 **1e**	25%
7	NO_2	Ph	 **1f**	38%

[a] *Reaction conditions*: i) EtO_2CCH_2COR, *t*-BuOK, NMP/dioxane, 70 °C, then HCl dioxane; ii) Fe, HOAc, 85 °C; iii) NaOH, MeOH, reflux.
[b] Yields are based on the overall process and on the aryl chloride.

Other aromatic systems including heterocycles were reacted under similar conditions (entries 1, 3–5) and led to the desired products in yields ranging from 65% to 79% for the sequence.

By contrast, lower yields were observed with aliphatic keto esters. The best results were obtained with *tert*-butyl acetoacetate where the first two steps (S_NAr reaction and reductive cyclization) proceeded almost quantitatively (as observed by quantitative NMR study). However the yield of the final decarboxylation was low (entry 6, 25% overall yield) with numerous side-products observed.

Use of 1-chloro-2,4-dinitrobenzene for this reaction sequence provided an entry into 2-aryl-6-aminoindole (entry 7). Excellent reactivity was observed in the S_NAr reaction and the following reductive cyclization steps (85% yield by NMR). However the subsequent decarboxylation was found to proceed in only ca. 60% yield, the overall isolated yield for the sequence was 38%.

In conclusion, the above protocol discloses the first successful and practical use of β-keto esters in S_NAr reactions. The method allows for a highly efficient access to 2-aryl-indole-6-carboxylic acid systems via a sequence consisting in S_NAr reaction, reductive cyclization, and decarboxylation. Considering its operational simplicity and cost effectiveness, this protocol will be useful in the large scale synthesis of this class of compounds.

General Procedure: 2-(2-Pyridyl)-indole-6-carboxylic Acid (1a)
To a solution of ethyl picolinoylacetate (**3**) (3.86 g, 20 mmol) in *N*-methylpyrrolidinone/dioxane (1:1, 12 mL) at r.t. was added *t*-BuOK portionwise (2.24 g, 20 mmol) over 10 min. The suspension was heated to 70 °C and 4-chloro-3-nitrobenzonitrile (**2**) (1.83 g, 10 mmol) in dioxane (5 mL) was added at such a rate to keep the internal temperature below 80 °C. After the reaction was complete, the mixture was cooled to r.t. and added to a solution of 4 N HCl in dioxane (5 mL, 20 mmol) by cannula. To the resulting mixture was added HOAc (5 mL) and Fe (2.24 g, 40 mmol). The thick slurry was heated to 85 °C and stirred for 3 h. The resulting mixture was filtered hot through a pad of celite, which was washed with EtOAc (20 mL). The organic solvents were removed by distillation under vacuum. The thick oil obtained was suspended in methyl-*tert*-butylmethylether [MTBE] (20 mL) and the slurry was washed with 2 M NaOH solution until pH 8. The organic layer was concentrated and the residue was dissolved in MeOH (50 mL). A 10 M NaOH solution (50 mL) was added and the resulting mixture was heated at reflux for 6 h and cooled to r.t. The reaction mixture was extracted with 10% MeOH in CH_2Cl_2 and acidified with a 6 M HCl solution to pH 1–2. Concentration of the organic layer afforded the desired 2-(2-pyridyl)-indole-6-carboxylic acid (**1a)** (1.72 g, overall 72% yield), which could be further recrystallized from EtOH.

2-(2-Pyridyl)-indole-6-carboxylic Acid (1a): (1.72 g, 72% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.95 (s, 1 H), 8.66 (s, 1 H), 8.11 (s, 1 H), 8.05–8.02 (m, 1 H), 7.89–7.88 (m, 1 H), 7.61–7.60 (m, 1 H), 7.58–7.57 (m, 1 H), 7.35–7.33 (m, 1 H), 7.20 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.2, 149.9, 149.6, 140.2, 137.5, 136.6, 123.1, 120.7, 120.6, 120.3, 114.3, 100.9. HRMS: calcd 238.0742; found: 238.0742.

2-Phenyl-indole-6-carboxylic Acid (1b): (1.71 g, 79% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.88 (s, 1 H), 8.07 (s, 1 H), 7.91–7.88 (m, 2 H), 7.65–7.62 (m, 2 H), 7.51–7.48 (m, 2 H), 7.36–7.34 (m, 1 H), 6.98 (s, 1 H), 3.35 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6,): δ = 168.3, 141.0, 136.4, 132.0, 131.6, 129.0, 128.1, 125.4, 123.6, 120.4, 119.5, 113.2, 99.1. HRMS: calcd 237.0790; found: 237.0788.

2-(4-Methoxyphenyl)-indole-6-carboxylic Acid (1c): (2.11 g, 72% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.46 (br s, 1 H), 11.75 (s, 1 H), 8.00 (s, 1 H), 7.85–7.82 (m, 2 H), 7.61–7.58 (m, 1 H), 7.55–7.53 (m, 1 H), 7.08–7.05 (m, 2 H), 6.87 (s, 1 H), 4.02 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.3, 159.4, 140.5, 135.5, 132.1, 126.8, 124.7, 122.8, 120.4, 119.1, 114.5, 112.9, 97.8, 55.3. HRMS: calcd 267.0895; found: 267.0895.

2-(4-Pyridyl)-indole-6-carboxylic Acid (1d): (1.52 g, 64% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.39 (s, 1 H), 8.88–8.86 (m, 2 H), 8.54–8.52 (m, 2 H), 8.19 (s, 1 H), 7.74–7.71 (m, 1 H), 7.66–7.63 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8, 145.1, 143.4, 138.0, 135.5, 130.9, 126.4, 121.3, 121.2, 120.9, 114.2, 105.9. HRMS: calcd 238.0742; found: 238.0748.

2-(2,2-Dimethylethyl)-indole-6-carboxylic Acid (1e): (0.54 g, 25% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.8, 136.9, 135.3, 128.9, 128.1, 120.7, 120.0, 112.9, 99.0, 30.0, 23.1. HRMS: calcd 217.1103; found: 217.1100.

2-Phenyl-6-aminoindole (1f): (0.79 g, 38% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.35 (s, 1 H), 8.30 (s, 1 H), 7.97–7.90 (m, 2 H), 7.73 (d, m, 1 H), 7.57–7.53 (m, 2 H), 7.46–7.44 (m, 1 H), 7.16 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.9, 141.2, 135.2, 133.6, 130.6, 129.6, 128.9, 125.7, 120.1, 114.8, 107.7, 99.8. HRMS: calcd 208.1000; found: 208.1003.

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(11) The spectral data of compounds **4** and **5** were obtained from the NMR of the mixture. Not all the coupling constants could be calculated due to overlapping signals. Compound **4**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.59 (d, *J* = 1.3 Hz, 1 H), 8.28 (d, *J* = 1.3 Hz, 1 H), 8.06 (d, *J* = 4.5 Hz, 1 H), 7.88 (m, 1 H), 7.86 (m, 1 H), 7.69 (dd, *J* = 1.3, 4.5 Hz, 1 H), 7.67 (dd, *J* = 1.3, 7.8 Hz, 1 H), 6.83 (s, 1 H), 4.27 (q, 2 H), 1.25 (t, 3 H). Compound **5**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50–7.20 (m, 3 H), 4.09 (s, 2 H), 4.17 (q, 2 H), 1.25 (t, 3 H). Compound **6**: MS: calcd 267.24; found: (M + 1) 268.27.
(12) The use of fluoride as a better leaving group for the S_NAr reaction was evaluated but showed little improvement. The less expensive and commercially available aryl chloride was preferred in this study.
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