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Preparation of Indoles from α-Aminonitriles: A Short Synthesis of FGIN-1-27

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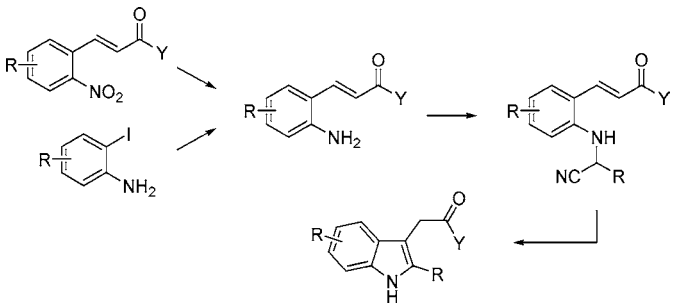
ABSTRACT



α-Aminonitriles derived from 2-aminocinnamic acid esters and amides can be cyclized under basic conditions to furnish substituted indole-3-acetic acid derivatives in quantitative yield. The reaction provides a simple access to a class of biologically active compounds.

The indole ring system is one of the most prevalent structural motifs found in biologically active compounds of both natural and synthetic origin. For example, the neurotransmitter serotonin (5-HT), the semisynthetic hallucinogen lysergic acid diethylamide (LSD), and the alkaloid strychnine, as well as the pharmaceuticals ondansetron (zofran),[1] sumatriptan (imigran),[2] or tadalafil (cialis),[3] are indole derivatives. The first synthesis of substituted indoles was conducted by Fischer and Jourdan as early as 1883, and since then the bicyclic heteroaromatic core has been the target of many synthetic approaches.[4−7] In the past three decades, advances in the field of transition-metal-catalyzed reactions have led to the development of a variety of indole syntheses in which either the formation of the N-C2,[8,9] the C3-C3a,[10,11] or the C2-C3 bond[12] is the key step.[13] Among the methods relying on the transition-metal-free formation of the C2-C3 bond, the Madelung synthesis, which makes use of C2 as an electron acceptor, has an important position.[14,15] Other processes that use the same disconnection involve the cyclization of deprotonated 2-alkylphenyl isonitriles[16] or the generation of radicals at C2.[17,18] Herein, we report on a novel and short synthesis of indoles via the cyclization of α-aminocarbanions derived from 2-aminocinnamic acid derivatives.[19]

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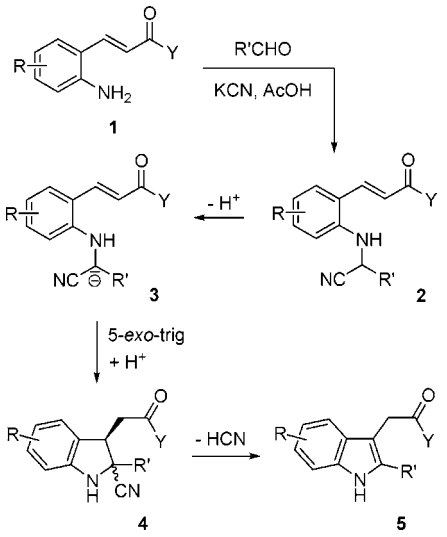
The umpolung of imines by addition of HCN allows the facile generation of stabilized α-aminocarbanions, which can be used, for example, for the preparation of highly substituted pyrrolidines,[20] pyrroles,[21] or vicinal diamines.[22] The Strecker reaction of esters or amides of 2-aminocinnamic acid derivatives **1** with an aromatic or heteroaromatic aldehyde or with cinnamaldehyde furnishes α-aminonitriles **2**. These compounds can undergo a clean cyclization to furnish 2-substituted indole-3-acetic acid derivatives **5** upon treatment with a suitable base. The course of the reaction involves the α-deprotonation of the aminonitrile, 5-*exo*-trig-cyclization by means of an intramolecular Michael addition, elimination of HCN and tautomerization to the 1*H*-indole (Scheme 1).

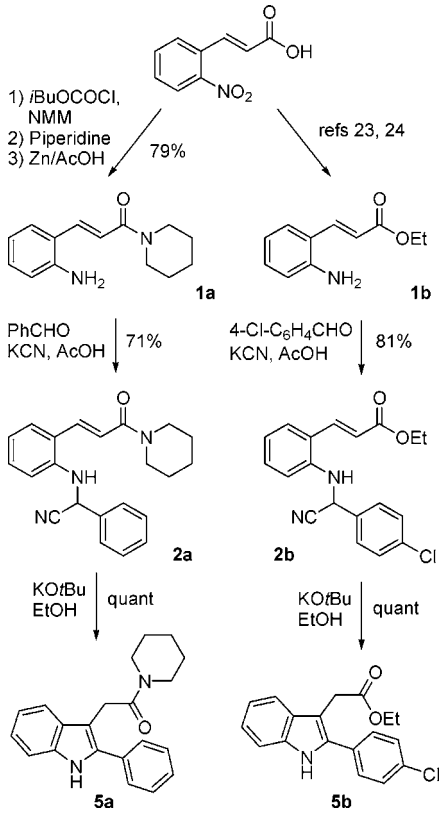
Scheme 1



The retro-Strecker reaction in the last step requires an N-deprotonation by an external base, and the reaction will stop at the stage of the cyclic aminonitrile **4** if conducted under nonequilibrating conditions (e.g., KHMDS, THF, −78 °C). Compounds **4** are, however, unstable and can be converted to indoles **5** by warming in alcoholic solvents in quantitative yield. Whereas DBU in ethanol suffices to effect both cyclization and elimination of HCN at 60 °C, an alcoholic solution of potassium *tert*-butyl alcoholate allows the same transformation to be performed at room temperature (Scheme 2).

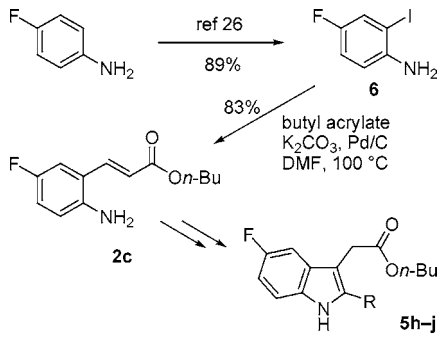
Although the Strecker reaction is normally carried out under acidic conditions, the reaction temperature of 60 °C, chosen to ensure complete conversion of **1** to **2**, already leads to the formation of small amounts of indoles **5**. Therefore, the cyclization of the crude aminonitriles **2** not only simplifies the overall procedure but in some cases even leads to improved yields.

Scheme 2



Presumably as a result of lack of stabilization of the carbanions resulting from deprotonation, no conditions could be found that allowed the cyclization of Strecker products derived from aliphatic aldehydes. Experiments on the cyclization of imines from 2-aminocinnamic acid esters and aromatic aldehydes with catalytic amounts of cyanide, phosphanes, or N-heterocyclic carbenes were also unsuccessful. Esters and amides of 2-aminocinnamic acid can be easily obtained from commercially available 2-nitrocinnamic acid or via Heck reaction from 2-iodoaniline.[23−25] The latter procedure also permits the facile introduction of substituents to positions 4−7 of the indole skeleton. As an example, the 5-fluoro-substituted products **5h**−**j** could be readily prepared from 4-fluoroaniline (Scheme 3).[26]

Scheme 3



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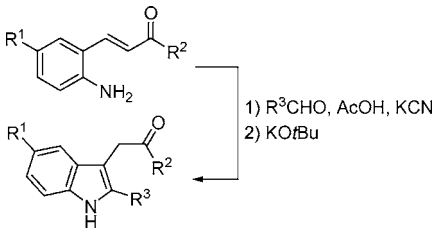
The results of the preparation of various 2-substituted indole-3-acetic acid derivatives are summarized in Table 1.

Table 1. Preparation of Substituted Indoles from 2-Aminocinnamates



indole	R^1	R^2	R^3	yield (%)
5c	H	OEt	2-naph-	73
5d	H	OEt	3,4-$(MeO)_2$-C_6H_3-	56
5e	H	OEt	4-Ph-C_6H_4-	55
5f	H	OEt	3-MeO-C_6H_4-	65
5g	H	OEt	4-Pyr-	37
5h	F	O*n*-Bu	4-Cl-C_6H_4-	64
5i	F	O*n*-Bu	3-Pyr-	69
5j	F	O*n*-Bu	3,4-$(MeO)_2$-C_6H_3-	59
5k	H	$N(CH_2)_5$	(*E*)-styryl-	53
5l	H	$N(CH_2)_5$	2-thienyl-	51
5m	H	$N(CH_2)_5$	3-Pyr-	95
5n	H	N(*n*-Hex)$_2$	4-F-C_6H_4-	73

A number of 2-aryl- and 2-hetaryl-substituted indole-3-acetamides exhibit remarkable affinities to various G-protein coupled receptors or enzymes. For example, FGIN-1-27 (compound **5n**) is a ligand of the mDRC receptor complex (K_i = 4.4 nM),[27] and **7** is an inhibitor of farnesyl transferase (IC_{50} = 31 nM).[28] Tryptamine **8**, which can be obtained by reduction of amide **5a** with lithium aluminum hydride in 99% yield, is a known antagonist of the human 5-HT_{2A} receptor (K_i = 2.7 nM),[29] and 2-aryltryptamines such as **9** that have

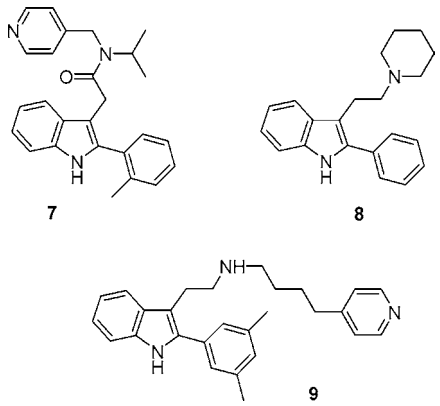


Figure 1. Biologically active 2-arylindole derivatives.

an affinity to the gonadotropin releasing hormone (GnRH) receptor have also been reported (see Figure 1).[30]

In summary, the described synthetic protocol permits the facile preparation of a variety of 2-aryl, 2-hetaryl-, and 2-styryl-substituted indole-3-acetic acid derivatives without the use of expensive or sensitive reagents or catalysts.[31] The products as well as the corresponding tryptamines accessible via reduction of the amide group belong to a class of biologically active compounds.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data as well as ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) **Typical Procedure. Preparation of 5i.** To a solution of butyl (*E*)-2-amino-5-fluorocinnamate **2c** (300 mg, 1.26 mmol) and pyridine-3-carbaldehyde (162.5 mg, 1.52 mmol) in dry *n*-butanol (5 mL) was added acetic acid (87 μL, 1.52 mmol), and the solution was stirred for 1 h at 60 °C under argon. Potassium cyanide (181 mg, 2.78 mmol) and acetic acid (145 μL, 2.53 mmol) were added to the mixture, and stirring at 60 °C was continued for 16 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ solution and dichloromethane, the organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo to yield a yellow oil (588 mg). A portion of the crude Strecker product (558 mg) was dissolved in dry *n*-butanol (3 mL), and after addition of potassium *tert*-butyl alcoholate (142 mg, 1.26 mmol), the solution was stirred for 30 min at room temperature under argon. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ solution and dichloromethane, the organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo to yield a yellow oil (492 mg). A portion of the crude indole (461 mg) was purified by flash chromatography (SiO_2, eluent cyclohexane/ethyl acetate 1:1) to afford butyl [5-fluoro-2-(3-pyridyl)-1*H*-indol-3yl]-acetate **5i** (252 mg, 68.7%) as yellowish crystals, mp 105−107 °C.