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Multicomponent Synthesis of 3-Indolepropionic Acids

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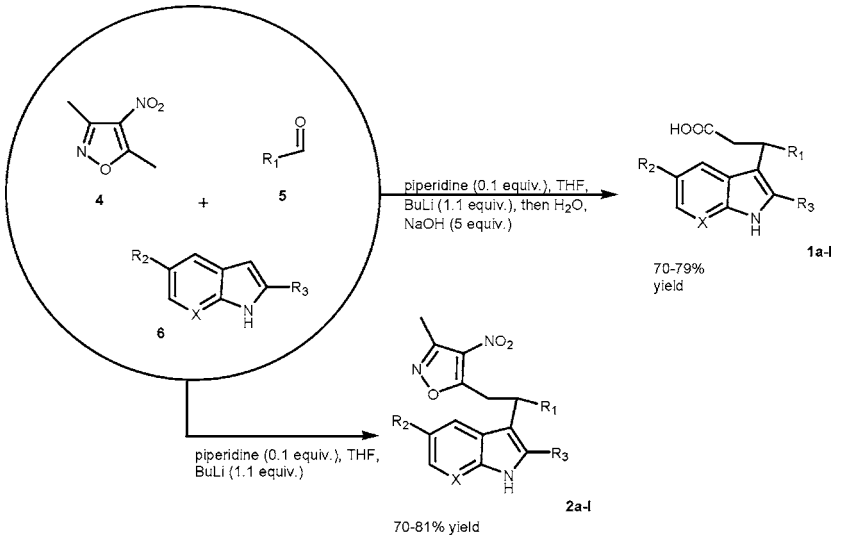
ABSTRACT



A three-component one-pot procedure (3-MC) was developed to assemble 3-indolepropionic acids from commercially available materials. This new methodology affords the title compounds in high yields and without the use of chromatography.

Indole 3-propionic acids (IPAs) **1** (Figure 1) are potent neuroprotective agents.[1] IPA completely protects primary neurons and neuroblastoma cells against oxidative damage and death caused by exposure to amyloid β-protein, by inhibition of superoxide dismutase, or by treatment with hydrogen peroxide. In kinetic competition experiments with free radical-trapping agents, the capacity of IPA to scavenge hydroxyl radicals exceeded that of melatonin, an indoleamine considered to be the most potent naturally occurring scavenger of free radicals.[1] Additionally, acids **1** are structurally related to the NSAID indomethacin and several multistep syntheses have been described in studies aimed at providing the indole acetic acid with preferential COX-2 selectivity.[2]

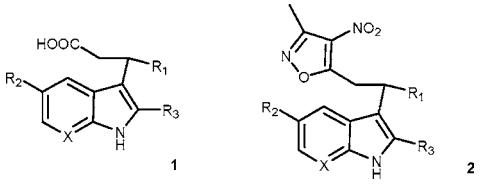


Figure 1. Target compounds: 3-indolepropionic acids **1** and 3-substituted indoles **2**.

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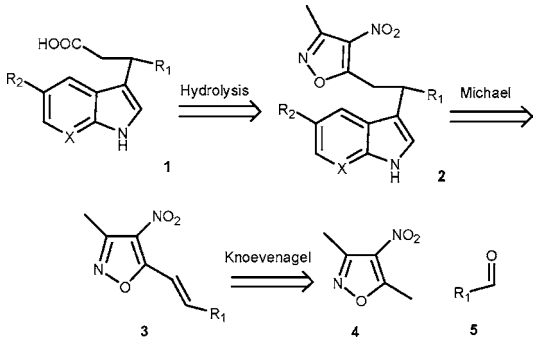
Recently, 3-substituted indoles **2** have been found to possess several biological activities.[3,4] For instance, compounds of structure **2** were found to act as aromatase inhibitors and have been used to treat breast cancer.[3] Other members of this class have been patented as HIV-1 integrase inhibitors.[4] Additionally, the diaryl methine motif in **1** and **2** is present in a number of drugs and natural products.[5] As a part of our ongoing efforts in developing multicomponent one-pot procedures using commercially available materials,[6−9] we envisaged a novel modular synthesis leading to indole 3-propionic acids **1** and 3-substituted indoles **2** (Figure 1). A retrosynthetic analysis of targets **1** and **2** showed that 3,5-dimethyl-4-nitroisoxazole **4** could serve as a starting material for a sequence of anionic driven reactions (Scheme 1).

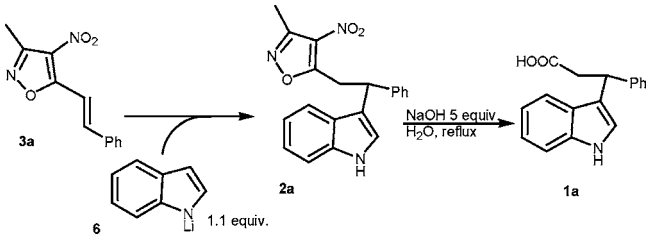
Scheme 1. Retrosynthetic Analysis of Targets **1** and **2**



We have recently reported a one-pot procedure by which the commercially available isoxazole **4** reacted with an aromatic aldehyde **5** and acetylacetone in a tandem Knoevenagel-Michael reaction.[6,8,9] The resulting Michael adducts were then converted to spiroisoxazolines[6] or heteroarylpropionic acids.[9] We reasoned that compounds **2** could be prepared through a Michael reaction of a lithiated indole and 3-methyl-4-nitro-5-styrylisoxazole **3**. This disconnection looked particularly attractive given the large number of substituted indoles available on the market. Finally, we planned to prepare 3-indolepropionic acids **1** by hydrolysis of the 3-methyl-4-nitroisoxazol-5-yl group present in **2**.[9]

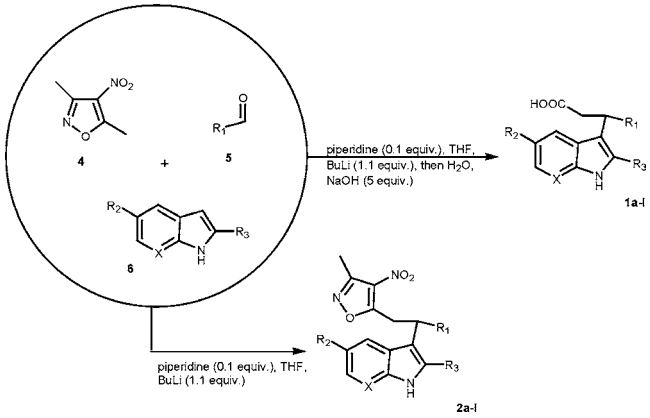
We first carried out a stepwise synthesis of compounds **2a** and **1a** using simple lithiated indole **6** as the nucleophile, to determine an optimal set of reaction conditions (Scheme 2). We were delighted to observe that 1.1 equiv of **6** was

Scheme 2. Synthesis of Compounds **2a** and **1a**



enough to produce **2a** in good yield, and that **2a** was obtained in similar yield by reacting together **4**, **5**, and **6** in a one-pot process (Scheme 3). The procedure involved premixing

Scheme 3. One-Pot Synthesis of 3-Heteroarylpropionic Acids **1a**−***l*** and 4-Nitroisoxazol-5-ethanyl Compounds **2a**−***l***



isoxazole **4** with an aromatic aldehyde **5a**−**f** in the presence of 0.1 equiv of piperidine and subsequent reaction of the styrylisoxazoles so obtained with a solution containing 1.1 equiv of lithiated indole **6**. We then studied the conversion of **2a** to acid **1a**. When compound **2a** was reacted with 5 equiv of NaOH in water/methanol compound **1a** was obtained in 79% yield. We briefly investigated the conversion of **2a** to **1a** reaction in different solvents including water/methanol, water/ethanol, water/dioxane, and water/THF. Interestingly, we identified a mixture of THF/water as an optimal solvent system, which provided an opportunity to extend the one-pot procedure established for the preparation of **2a** to access **1a**. This procedure, which was optimized by adjustment of reaction times, temperature, and concentration of reactants involved reacting isoxazole **4** with an aromatic aldehyde **5a**−**f** in the presence of 0.1 equiv of piperidine and subsequent sequential addition of a solution of 1.1 equiv of lithiated indole **6** followed by a solution of NaOH in water. We were delighted to observe that compound **1a** was obtained in isolated yield comparable to the stepwise preparation. Compounds **1a** and **2a** were obtained pure without the intervention of chromatography. Compound **2a** was purified by crystallization, while compound **1a** was obtained pure by means of base/acid extraction.

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Having determined an appropriate set of reaction conditions, we carried out the synthesis of compounds **1a**−***l*** in a one-pot fashion (Scheme 3, Table 1).

Table 1. One-Pot Synthesis of Compounds **1a**−***l***

entry	compd	R_1	R_2	R_3	X	yield,[a] %
1	**1a**	Ph	H	H	C	79
2	**1b**	*p*-H_3C-Ph	H	H	C	74
3	**1c**	*p*-CH_3O-Ph	H	H	C	74
4	**1d**	*p*-NO_2-Ph	H	H	C	70
5	**1e**	*p*-Cl-Ph	H	H	C	73
6	**1f**	Ph	Cl	H	C	77
7	**1g**	Ph	CH_3	H	C	74
8	**1h**	Ph	OCH_3	H	C	73
9	**1i**	Ph	OCH_3	CH_3	C	75
10	**1k**	Ph	H	H	N	78
11	**1*l***	2-furyl	H	H	C	72

[a] Isolated yields after acid/base extraction.

The results obtained (Table 1 and 2) showed that a great deal of diversity could be introduced without varying the reaction plan. Both electron-withdrawing and electron-donating groups could be included as R_1 or R_2.

As the acid products were isolated by a simple extraction method, the need for chromatography was obviated. Polyheterocyclic compounds **2a**−***l*** were obtained in high yield by omitting the hydrolysis step (aqueous base, Δ) (Scheme 3, Table 2). The ease of purification complements the one-pot procedures making these methodologies facile, practical, and rapid to execute.

In conclusion we reported two 3-MC one-pot procedures to prepare two families of products with potential medicinal properties using inexpensive and commercially available materials. These syntheses are modular and benefit from a simple method of purification, which does not require chromatography. The synthesis of compounds **1** and **2** will be of interest for those involved in two key areas of medicinal chemistry such as Alzheimer's disease and breast cancer chemotherapy. Finally, both families of compounds are highly functionalized and could serve as valuable intermediates for the generation of diverse classes of compounds.

Table 2. One-Pot Synthesis of Compounds **2a**−***l***

entry	compd	R_1	R_2	R_3	X	yield,[a] %
1	**2a**	Ph	H	H	C	79
2	**2b**	*p*-H_3C-Ph	H	H	C	74
3	**2c**	*p*-CH_3O-Ph	H	H	C	74
4	**2d**	*p*-NO_2-Ph	H	H	C	81
5	**2e**	*p*-Cl-Ph	H	H	C	80
6	**2f**	Ph	Cl	H	C	77
7	**2g**	Ph	CH_3	H	C	76
8	**2h**	Ph	OCH_3	H	C	73
9	**2i**	Ph	OCH_3	CH_3	C	79
10	**2k**	Ph	H	H	N	70
11	**2*l***	2-furyl	H	H	C	78

[a] Isolated yields after crystallization.

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Supporting Information Available: General experimental details, general one-pot procedure for the preparation of compounds **1a**−***l*** (Table 1) and **2a**−***l*** (Table 2), spectroscopic data of compounds **1a**−***l*** and **2a**−***l***, and ^{1}H NMR spectra of compounds **1a**−***l*** and **2a**−***l***. This material is available free of charge via the Internet at http://pubs.acs.org.

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