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A New One-Pot Synthesis of Polysubstituted Indoles from Pyrroles and β-Nitroacrylates

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Abstract: The reaction of β-nitroacrylates with pyrroles, under solvent- and catalyst-free conditions, allows the formation of Friedel–Crafts adducts which, after *in situ* treatment with Amberlyst 15 in isopropyl alcohol under reflux, provide polysubstituted indoles, *via* a benzannulation reaction, in a one-pot process.

Keywords: indoles; β-nitroacrylates; one-pot synthesis; pyrroles; solid-supported reagents (SSR)

Indoles are the key subunits of a variety of biologically active molecules and, probably, are the most ubiquitous heterocycles in nature.[1] Substituted indoles are referred to as "privileged structures" in drug discovery because of their capacity to bind to many receptors with high affinity.[2] For many years, the synthesis of indoles has been a major area of focus for organic chemists and numerous methods for their preparation have been developed.[3] In this context, the assembling of the indole core starting from benzene derivatives represents the prevalent procedure. However, these approaches often show important drawbacks, such as the need for hard reaction conditions (very low or high temperature), very strong bases or there are the problems of regioselectivity.

Alternatively, indoles can be prepared by benzannulation of pyrroles but this approach has been less explored and, in this context, just a few elegant preparations have been reported.[3,4] Nevertheless, the latter procedures also evidence relevant drawbacks such as limited generality, modest scalability and the need for toxic solvents or dry conditions. Under these circumstances, the development of new strategies for the synthesis of indoles from pyrroles, *via* benzannulation reactions, remains of great interest.

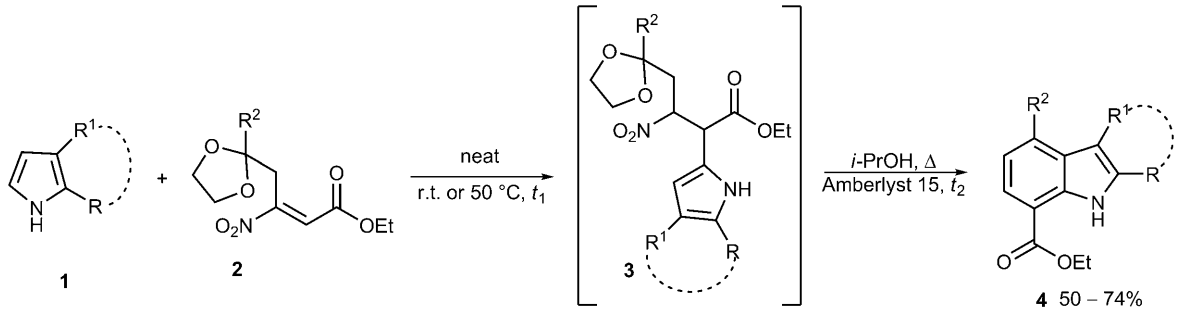
Recently, we have carried out a variety of studies in which benzene derivatives have been prepared starting from aliphatic nitro compounds.[5] In the meantime, β-nitroacrylates have demonstrated a great versatility as key building blocks for the preparation of a variety of molecular structures.[6]

Based on these experiences, herein we present an innovative, mild and efficient method for the one-pot synthesis of polysubstituted indoles starting from pyrroles **1** and ketal-functionalized β-nitroacrylates **2**.[7]

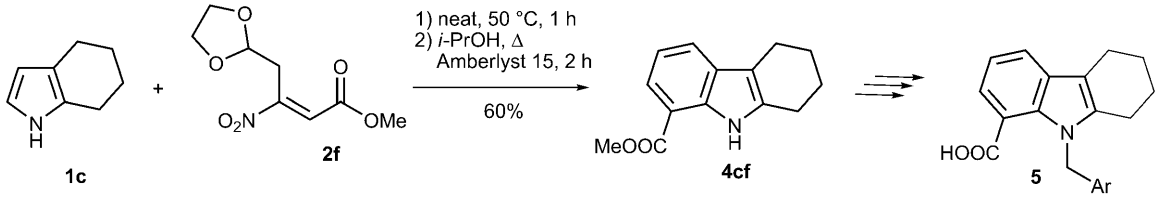
As reported in Scheme 1, the starting compounds **1** and **2** quickly react (with the exception of the reaction between **1d** and **2a**), under solvent- and catalyst-free conditions, giving the intermediate **3** *via* a Friedel–Crafts reaction. Then, *in situ* acidic treatment of the formed adduct **3**, under heterogeneous conditions (Amberlyst 15) in refluxing 2-propanol,[8] favours the aromatization of the former β-nitroacrylate moieties, allowing the one-pot synthesis of indoles **4** in consistent overall yields (50–74%).

The generality of our procedure is demonstrated by the variety of indoles that can be obtained (Table 1) in which, by the appropriate choice of the starting materials, several substituents can be introduced in both the indole and the phenyl rings. As evidenced in Table 1, our methodology works well with 2- and 3-substituted pyrroles, as well as with 2,3-disubstituted ones. Moreover, thanks to the mild reaction conditions a variety of important functionalities, such as ester, cyano and chlorine, can be preserved.

Of particular interest is the product **4cf**, obtained in 60% overall yield (Scheme 2), by the reaction of pyrrole **1c** with methyl β-nitroacrylate **2f**. In fact, **4cf** was



Scheme 1. General pathway to the synthesis of indole derivatives **4**.



Scheme 2. A-FABP inhibitors.

successfully used as key building block for the synthesis of adipocyte fatty-acid binding protein (A-FABP) inhibitors.[9]

A plausible mechanism for the one-pot synthesis of **4**, could be rationalized (Scheme 3) by the initial Friedel–Crafts reaction between the pyrroles **1** and β-nitroacrylates **2**, affording the adduct **3**, *via* the intermediate **A**. Then, *in situ* treatment of **3** with Amberlyst 15 (cationic macromolecular ion-exchange resin) gives the protonated 1,3-dioxolane intermediate **B**, which leads, through the intermediate **C**, to the oxonium cation **D**. Finally, a subsequent Friedel–Crafts reaction **E** generates the bicycle intemediate **F** that, after losing a molecule of both ethylene glycol and nitrous acid, gives the target indoles **4**.

In conclusion, our method represents an innovative, chemoselective procedure for the synthesis of a variety of polysubstituted indoles from pyrroles, since these targets can be easily obtained in a one-pot way and under very mild conditions, affording consistent overall yields of the products and tolerating the presence of important functionalities. Moreover, our approach can be considered of interest from the eco-sustainability point of view because just an eco-friendly solvent[8] is employed and, thanks to the nature of the solid-supported reagents, even the classical aqueous work-up can be avoided, since the crude product **4** can be directly charged on a chromatographic column, after filtration of the Amberlyst 15, for the final purification.

Table 1. One-pot synthesis of indole derivatives **4**.

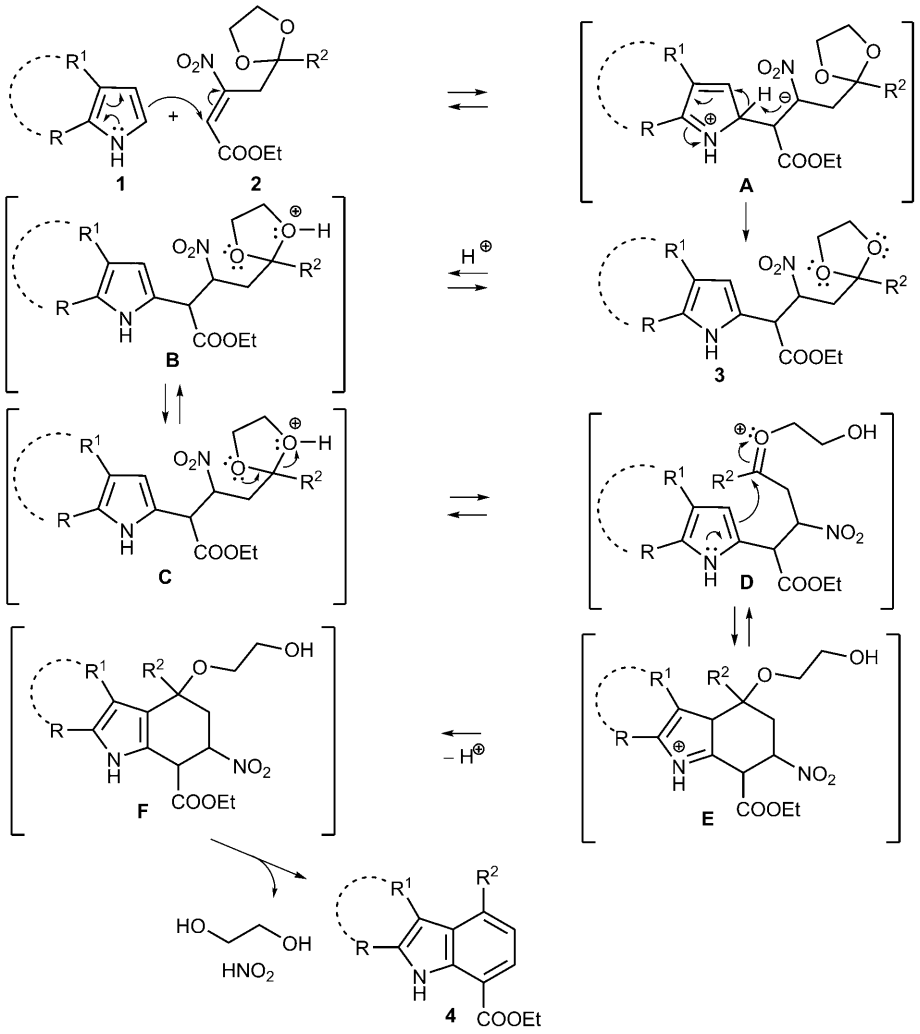
	1[a]			**2**		t_1 [h]	t_2 [h]	Yield [%][c]	
	R	R^1		R^2				of **4**	
1a	Et	H	**2a**	Me		0.5	1	**4aa**	60
1b	H	H	**2a**	Me		2	1.5	**4ba**	70
1a	Et	H	**2b**	Ph		0.5	5	**4ab**	59
1c		$-(CH_2)_4-$	**2c**	Et		0.5[b]	2	**4cc**	61
1c		$-(CH_2)_4-$	**2b**	Ph		1[b]	2	**4cb**	50
1b	H	H	**2c**	Et		2	1.5	**4bc**	61
1b	H	H	**2d**	H		2	1	**4bd**	68
1b	H	H	**2b**	Ph		3	3	**4bb**	57
1b	H	H	**2e**	$Ph(CH_2)_2$		5.5	3.5	**4be**	74
1d	H	p-NCC_6H_4	**2a**	Me		19[b]	3	**4da**	58
1e	H	$Cl(CH_2)_4$	**2a**	Me		3[b]	3	**4ea**	53

[a] 1.2 mmol were used for pyrroles **1a**, **1c**, **1d** and **1e**; while 2 mmol were used for pyrrole **1b**.
[b] The reaction was performed at 50 °C.
[c] Yield of pure, isolated product.

Experimental Section

General Procedure for the Preparation of Indoles 4

A mixture of **2** (1 mmol) and **1** (from 1.2 to 2 mmol, see Table 1), after stirring under solvent-free conditions for the appropriate time (t_1), led to the formation of the intermediate **3**. Then, *in situ* addition of 2-propanol (12 mL) and heating at reflux, followed by addition of Amberlyst 15 (1 g) and stirring for the needed time (t_2), gave the crude compound **4** that can be directly charged on a chromatographic column, after filtration of the Amberlyst 15, for the final purification (cyclohexane:EtOAc = 95:5).



Scheme 3. Proposed reaction mechanism for the formation indole derivatives **4**.

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