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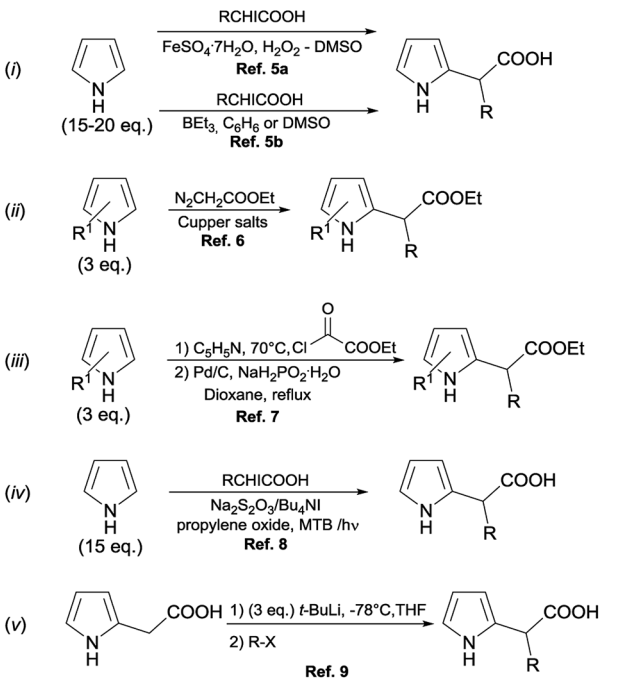
A new fully heterogeneous synthesis of pyrrole-2-acetic acid derivatives†

Serena Gabrielli, Ludovica Ciabattoni, Susanna Sampaolesi, Roberto Ballini* and Alessandro Palmieri*

Herein, we present a new general and efficient protocol to synthesize pyrrole-2-acetic acid derivatives starting from pyrroles and β-nitroacrylates, under fully heterogeneous conditions.

The pyrrole core is a five membered nitrogen-containing heterocycle present in a large variety of biologically active compounds,[1] as well as it is a useful scaffold for the synthesis of highly functionalized materials.[2] Furthermore, molecules containing the pyrrole unit are also used in organic electronic materials.[3] In particular, among the pyrrole subunits, the pyrrole-2-acetic acid derivatives play a relevant role in the synthesis of pharmaceutical interest molecules, such as the anti-inflammatory nonsteroidal *Zomepirac* and *Ketorolac*.[4] Although the importance of these derivatives, only few methodologies for their preparation are reported in the literature, and the most used ones are based on: (i) radical aromatic substitution,[5] (ii) usage of alkyl diazoacetate,[6] (iii) usage of ethoxalyl chloride in a Friedel–Craft-reduction process,[7] (iv) iodine-transfer radical addition of iodoacetic acids to pyrrole,[8] and (v) the alkylation of pyrrole-2-acetic acid by lithiation (Scheme 1).[9] However, all these approaches show some significant limitations, such as large excess of reagents,[5,8] harsh reaction conditions,[7,9] moderate overall yields and a poor functionalization of products.[6,8] In order to overcome these problems, and in the attempt to develop a more general and efficient method to synthesize pyrrole-2-acetic acid derivatives, we exploited the reactivity of β-nitroacrylates with pyrroles.[10] β-Nitroacrylates **1** are conjugated olefins bearing two electron-withdrawing groups in α- and β-positions. This peculiarity makes these structures key precursors of poly-functionalized molecules,[11] and in particular, they are valuable starting materials for the *ex novo* construction and derivatization of the most important heterocyclic systems.[12]

In this regard, our synthetic approach for producing the title targets well reflects this feature. It involves a two-step process based on: (i) an initial one-pot Friedel–Craft-elimination process between the pyrrole unit and the β-nitroacrylate to give **4** *via* **3**, and (ii) a successive heterogeneous catalyzed reduction of **4** to give **5** or **6**, depending on the nature of R (Scheme 2). In order to maximize the process efficiency, both steps were separately investigated. In this context, with the aim to optimized the first step, we firstly studied the Friedel–Craft reaction between **1a** (R = Et; R^1 = Et) and **2a** (R^2 = H). Thanks to



Scheme 1 General method for synthesizing pyrrole-2-acetic acid derivatives.

Green Chemistry Group, School of Science and Technology, Chemistry Division, University of Camerino, via S. Agostino 1, 62032 Camerino, MC, Italy. E-mail: alessandro.palmieri@unicam.it; roberto.ballini@unicam.it; Fax: +39 0737 402297

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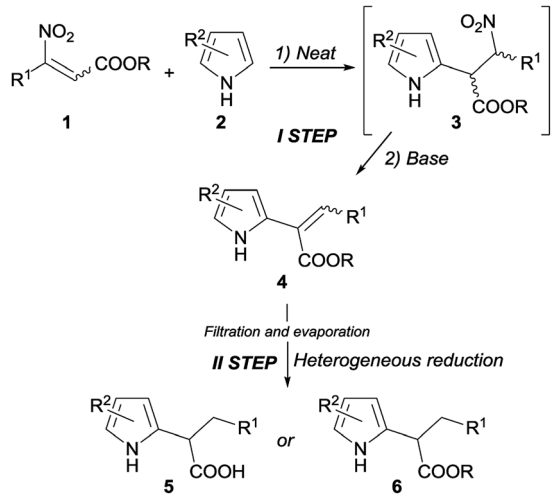
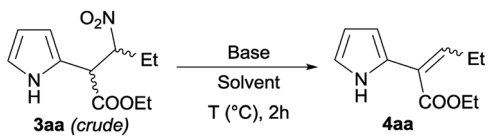


Scheme 2 Synthetic path-way.

the great reactivity of β-nitroacrylates with pyrroles, the adduct **3a** (R = Et; R^1 = Et; R^2 = H) was almost quantitatively obtained, after 3 hours, under promoter-free and solvent-free conditions.

Then, we switched our attention to find the best reaction conditions for promoting the elimination of nitrous acid, thus converting the crude **3aa** into **4aa**. This elimination can be often promoted by basic treatment[13] and, in this sense, after a deep screening in terms of bases, solvents and stoichiometry, the best yield of **4aa** (75%) was obtained, after two hours, using 2 equivalents of TBD on polymer in acetonitrile at 50 °C (Table 1, entry k).[14]

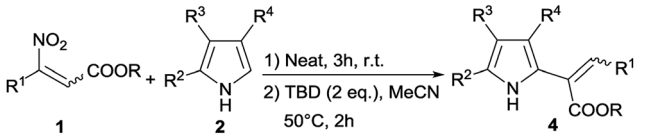
Table 1 Optimization studies



Entry	Base (equiv.)	Solvent	T (°C)	Yield[a] (%)
a[b]	DBU (1.5)	MeCN	25	13
b	DBU (1.5)	MeCN	50	57
c	KF/Al_2O_3	MeCN	50	48
d[c]	TBD on polymer (1.5)	MeCN	50	61
e	Carbonate on polymer (1.5)	MeCN	50	51
f	TBD (1.5)	MeCN	50	60
g[d]	TMG (1.5)	MeCN	50	61
h[e]	BEMP on polymer (1.5)	MeCN	50	59
i	TBD on polymer (1.5)	MeCN	70	62
j	TBD on polymer (1)	MeCN	50	55
k	TBD on polymer (2)	MeCN	50	75
l	TBD on polymer (2.5)	MeCN	50	73
m	TBD on polymer (2)	Toluene	50	69
n	TBD on polymer (2)	THF	50	49
o	TBD on polymer (2)	EtOAc	50	67

[a] Yield of pure isolated product. [b] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). [c] TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene). [d] TMG (1,1,3,3-tetramethylguanidine). [e] BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine).

Table 2 Synthesis of compounds 4[a]



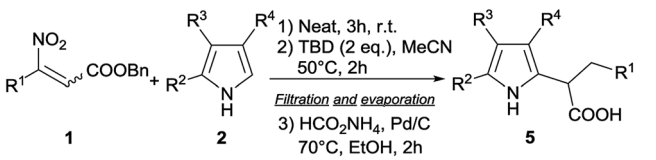
	R	R^1		R^2	R^3	R^4	Yield[b] (%)	
1a	Et	Et	**2a**	H	H	H	**4aa**	75[c]
1a	Et	Et	**2b**	Bu	H	H	**4ab**	87[d]
1a	Et	Et	**2c**	Me	H	Me	**4ac**	85[c]
1a	Et	Et	**2d**	$-(CH_2)_4-$		H	**4ad**	55[e]
1b	Me	Me	**2a**	H	H	H	**4ba**	62[d]
1c	i-Pr	Et	**2a**	H	H	H	**4ca**	53[d]
1d	Et	$CH_3(CH_2)_4$	**2a**	H	H	H	**4da**	54[c]
1e	Bn	$CH_3(CH_2)_6$	**2a**	H	H	H	**4ea**	56[d]
1f	Bn	$Ph(CH_2)_2$	**2a**	H	H	H	**4fa**	68[c]
1g	Et	$NC(CH_2)_4$	**2c**	Me	H	Me	**4gc**	75[e]
1h	Et	$MeO_2C(CH_2)_4$	**2c**	Me	H	Me	**4hc**	69[e]

[a] Reaction conditions: (1) β-nitroacrylates **1** (1 mmol), pyrroles **2** (1 mmol), room temperature, 3 h; (2) MeCN (4 mL), TBD (2 mmol, 667 mg), 50 °C, 2 h. [b] Yield of pure isolated product. [c] Diastereomeric ratio (E/Z) = 80 : 20. [d] Diastereomeric ratio (E/Z) = 70 : 30. [e] Isolated as single *E* diastereomer.

The generality of our approach was demonstrated applying the reaction conditions to a wide range of substrates (Table 2). In all cases, compounds **4** were obtained from moderate to good overall yields (53–87%) and from good to excellent diastereoselectivity.[15] Indeed, compounds **4aa**, **4ac**, **4da** and **4fa** were obtained as diastereomeric ratio of 80 : 20 (E : Z), compounds **4ab**, **4ba**, **4ca** and **4ea** were obtained as diastereomeric ratio of 70 : 30 (E : Z), while compounds **4ad**, **4gc** and **4hc** were isolated as single *E* diastereomer.

Once optimized this step, we completed our synthetic protocol, converting the crude adducts **4**, directly obtainable by

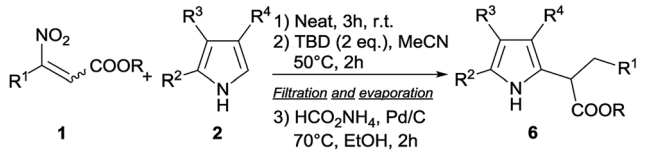
Table 3 Synthesis of compounds 5[a]



	R^1		R^2	R^3	R^4	Yield[b] (%)	
1e	$CH_3(CH_2)_6$	**2a**	H	H	H	**5ea**	52
1f	$Ph(CH_2)_2$	**2a**	H	H	H	**5fa**	51
1i	Et	**2a**	H	H	H	**5ia**	54
1j	$MeO_2C(CH_2)_4$	**2a**	H	H	H	**5ja**	50
1k	Me	**2c**	Me	H	Me	**5kc**	55

[a] Reaction conditions: (1) β-nitroacrylates **1** (1 mmol), pyrroles **2** (1 mmol), room temperature, 3 h; (2) MeCN (4 mL), TBD (2 mmol, 667 mg), 50 °C, 2 h; (3) HCO_2NH_4 (4 mmol, 252 mg), 10% Pd/C (100 mg), EtOH (7 mL), 70 °C, 2 h. [b] Yield of pure isolated product.

Table 4 Synthesis of compounds 6[a]



	R	R^1		R^2	R^3	R^4	Yield[b] (%)	
1a	Et	Et	**2a**	H	H	H	**6aa**	62
1a	Et	Et	**2b**	Bu	H	H	**6ab**	53
1a	Et	Et	**2c**	Me	H	Me	**6ac**	51
1b	Me	Me	**2a**	H	H	H	**6ba**	52
1c	i-Pr	Et	**2d**	$-(CH_2)_4-$		H	**6cd**	64

[a] Reaction conditions: (1) β-nitroacrylates **1** (1 mmol), pyrroles **2** (1 mmol), room temperature, 3 h; (2) MeCN (4 mL), TBD (2 mmol, 667 mg), 50 °C, 2 h; 3) HCO_2NH_4 (4 mmol, 252 mg), 10% Pd/C (100 mg), EtOH (7 mL), 70 °C, 2 h. [b] Yield of pure isolated product.

TBD filtration and solvent evaporation, to the final targets **5** and **6**. In this context, the selection of substrates is crucial to defined the nature of the targets. In fact, β-nitroacrylates bearing the benzylic ester (R = Bn) provides the corresponding acids **5** (Table 3). Alternatively, when R is different to the benzylic group, ester of pyrrole-2-acetic acids **6** are produced (Table 4). In both cases, the best yields were obtained using ammonium formate as hydrogen source, 10% Pd/C as catalyst, at 70 °C in ethanolic solution.

Conclusions

In conclusion, we have found a new efficient and general strategy to synthesize an important class of functionalized pyrrole, such as the 2-acetic acid derivatives. In fact, by our two step approach, the title compounds can be prepared in good overall yields and in short reaction time. In addition, the use of solid supported reagents allows to minimize the use of solvent avoiding any elaborate and wasteful work-up, with evident advantages in terms of sustainable point of view. Moreover, following our synthetic strategy, an interesting class of 2-pyrrolylacrylate derivatives **4** can be easily obtained in a one-pot way, under mild conditions and short reaction times.

Acknowledgements

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