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COMMUNICATION

Fast, mild, eco-friendly synthesis of polyfunctionalized pyrroles from β-nitroacrylates and β-enaminones†

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The reaction of β-nitroacrylates with β-enaminones, at room temperature and under solvent- and promoter-free conditions, affords the one-pot synthesis of polyfunctionalized pyrroles in high yields.

Pyrroles are important *N*-heterocyclic compounds which are present in many natural products.[1] Moreover, they are employed as important skeletons in organic synthesis[2] and are also utilized in other important fields such as material science,[3] medicinal chemistry and pharmacology.[4] In addition, it has been reported that half of the small molecule drugs that received FDA approval in 2005–2007 contain at least one azole or azine ring.[5] Although the most frequently used methods for their preparation are the classic Hantzsch,[6] Knorr,[7] and Paal–Knorr[8] procedures, a variety of alternative syntheses have been developed in the past decade.[9–13] Many of these approaches are based on the transition-metal catalyzed cyclizations[10,11] and multicomponent coupling reactions,[12,13] however, the high catalyst loading in some of the above procedures causes important drawbacks such as higher cost and potential contamination of the products that is particularly significant in the pharmaceutical industry.[14]

In this context, an interesting metal free alternative is represented by the use of conjugated nitroalkenes, excellent Michael acceptors,[15] as key starting reagents in combination with methyl acetoacetate,[16] isocyanoacetates,[17] or, mainly, with enaminoesters.[18] Even the latter procedures have non-negligible drawbacks because they require: (i) the presence of a solvent, (ii) an excess of either starting materials, (iii) the use of a promoter (mainly Lewis or Brønsted acid), (iv) the help of high temperatures (reflux conditions), and (v) long reaction times. Thus, more eco-friendly methodologies are desirable, mainly considering that in the recent years, the employment of solvent-free reactions[19] and the reduction of the energy consumption, by performing the reactions at room temperature,[20] have exhibited great advantages and potential in modern organic synthesis, especially from the eco-sustainable point of view.[21]

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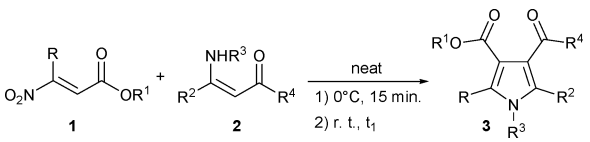
In the last few years, we have demonstrated that β-nitroacrylates are an emerging, more reactive class of functionalized nitroalkenes by which, a variety of important targets can be obtained under easier and more efficient methodologies.[22] On the basis of these experiences, we have now found that the reaction of β-nitroacrylates **1** with β-enaminones **2** gives a highly improved, one-pot synthesis of pyrroles **3** (Scheme 1). In fact, on the contrary to the use of standard nitroalkenes, β-nitroacrylates work well under solvent- and promoter-free conditions, using just stoichiometric amount of the compounds **1** and **2**, avoiding the need of high temperature and under short reaction times.



Scheme 1

As summarized in Table 1, the reaction affords good yields (60–91%) of the title compounds, with a variety of β-nitroacrylates **1** and β-enaminones **2**. It is important to point out that the mildness of our method allows to introduce powerful functionalities, such as tetrahydropyranyl (**3da**), chlorine (**3hb**), C,C double bond (**3gc**), ketones (**3if**, **3lg**) and esters (**3aa–le**), giving access to a class of polyfunctionalized pyrroles that can be easily manipulated for further chemical transformations.

An important class of pyrroles, of pharmaceutical interest, are those reported in Fig. 1 because of their antitumor activity.[23] In this context, our method is particularly suitable for the preparation of these structures, in fact by the appropriate selection of the starting materials, it's possible to introduce both the (i) appropriate substituents (2- and 5-positions) and (ii) ester functionalities (3- and 4-positions) which play a key role to the access, through an easy manipulation, of the corresponding carbamates.

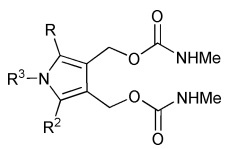


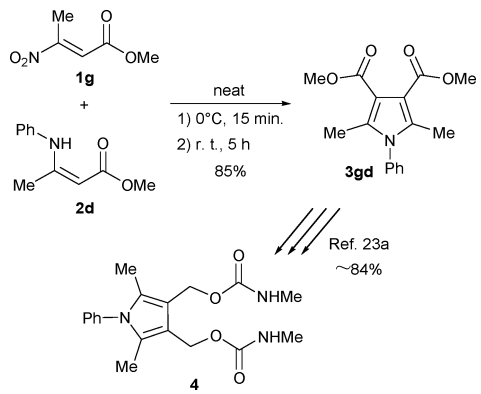
Fig. 1

Table 1 Eco-friendly preparation of polyfunctionalized pyrroles **3**

β-Nitroacrylates **1**			β-Enaminones **2**						
	R	R^1		R^2	R^3	R^4	Yield (%)[a] of **3**		Time (t_1, h)
1a	Et	Et	**2a**	Me	n-C_5H_{11}	OEt	**3aa**	90	3
1b	Et	Me	**2a**	Me	n-C_5H_{11}	OEt	**3ba**	88	2
1c	n-C_5H_{11}	Et	**2a**	Me	n-C_5H_{11}	OEt	**3ca**	84	2
1d	$CH_3(OTHP)CH(CH_2)_2$	Et	**2a**	Me	n-C_5H_{11}	OEt	**3da**	86	4
1e	n-Bu	Et	**2b**	Me	$PhCH_2$	OEt	**3eb**	89	2.5
1f	$Ph(CH_2)_2$	Et	**2b**	Me	$PhCH_2$	OEt	**3fb**	78	2.5
1g	Me	Me	**2b**	Me	$PhCH_2$	OEt	**3gb**	76	2.5
1h	$Cl(CH_2)_3$	Et	**2b**	Me	$PhCH_2$	OEt	**3hb**	70	2.5
1g	Me	Me	**2c**	n-Pr	$CH_2{=}CHCH_2$	OEt	**3gc**	91	2.5
1c	n-C_5H_{11}	Et	**2d**	Me	Ph	OMe	**3cd**	60[b]	6
1i	n-Pr	Bu	**2d**	Me	Ph	OMe	**3id**	65[b]	7
1l	Me	Et	**2e**	Me	Me	OEt	**3le**	70	3
1i	n-Pr	Bu	**2f**	Et	Me	Et	**3if**	66	7
1l	Me	Et	**2g**	Me	Me	Ph	**3lg**	78	3

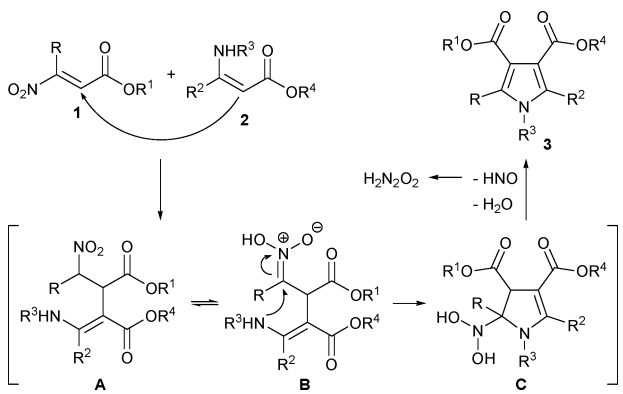
[a] Yield of pure isolated product. [b] The reaction was not cooled at 0 °C, but directly performed at room temperature.

In this sense, as a representative use of our procedure, we synthesized the pyrrole **3gd** (Scheme 2), key intermediate for the preparation of the anti-leukemic compound **4**.[23a]



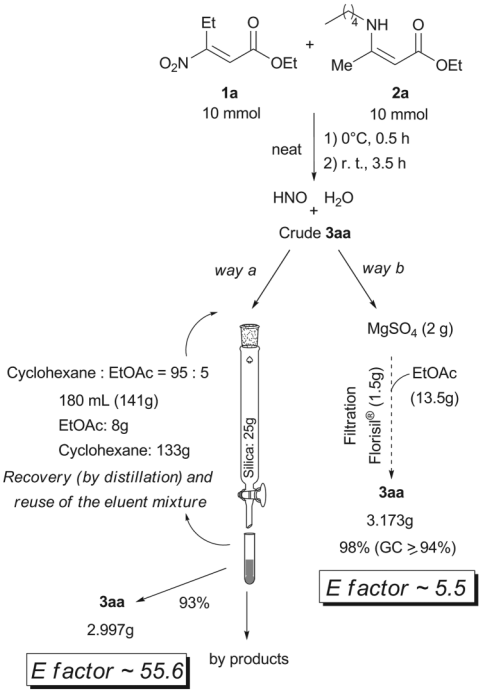
Scheme 2

From a mechanistic point of view, the process can be rationalized as reported by Revial *et al.* (Scheme 3).[18a] In fact, the process starts from the conjugate addition of the β-enaminones **2** to the β-nitroacrylates **1**, giving the Michael adduct **A**. Then, **A** tautomerizes into the reactive species **B** (*aci*-nitro tautomer), which is promptly attacked by the nitrogen atom, with the formation of the five member ring **C**. Finally, the elimination of water and nitroxyl (which probably dimerizes into hyponitrous acid $H_2N_2O_2$) molecules, lead to the formation of the target pyrroles **3**.



Scheme 3

Moreover, in order to test the eco-sustainability of our procedure, we calculate the environmental factor (*E*-factor) process testing the reaction of **1a** with **2a** (10 mmol scale), developing two different protocols (Scheme 4).



Scheme 4

The *way a* can be extended to all products **3**, and consists in a classic flash chromatography column, in which the eluent mixture was recovered by distillation (40 °C/135 torr) and reused. In this context, the closeness of the boiling points of the

selected solvents, permits to maintain, practically unchanged, the polarity of the eluent mixture.

Way b can be applied to the products obtained in high yields, such as **3ba**, **3ca**, **3da**, **3eb**, **3gc** and **3gd**. In these cases, the high purity of products (**3aa** GC ≥ 94%), gives the opportunity to involve, directly, the pyrroles for further reactions.

The *E*-factor for the testing reaction, was calculated considering all the used materials (*way a*: silica and the eluent mixture; *way b*: florisil®, $MgSO_4$ and EtOAc). The amount (grams) of by-products was calculated by the difference between the amount of starting materials (3.720 g for **1a** + **2a**) and amount of the obtained product **3aa** (2.997 g *way a* and 3.173 g *way b*, considered pure). On the basis on these considerations we obtain the following *E*-factors:

$$E\text{-factor}_{way\ a} = 166.723\ \text{g (waste)}/2.997\ \text{g} = 55.63;$$

$$\text{waste} = \text{silica} + \text{eluent mix} + \text{by products (HNO} + H_2O + \text{others)}$$

$$E\text{-factor}_{way\ b} = 17.547\ \text{g (waste)}/3.173\ \text{g} = 5.53;$$

$$\text{waste} = \text{florisil®} + MgSO_4 + \text{EtOAc} + \text{by products (HNO} + H_2O + \text{others)}$$

As reported above, the *E*-factor of the *way a* can be considered acceptable[24] while, much more effective is the *E*-factor obtained by the *way b*.

Conclusions

In conclusion, we have reported a highly improved procedure for the synthesis of polyfunctionalized pyrroles under environmentally benign manner showing acceptable to good *E*-factor. In fact, this method is general, affords good to excellent yields of the products, tolerates the presence of a variety of functionalities and is performed under solvent- and promoter-free conditions, avoiding the need of high temperature and of any excess of the reagents.

Experimental

Compounds **3gb**,[9e] **3gd**,[23a] **3le**,[25] are known, and their spectroscopic data are in agreement with those reported in literature. β-Nitroacrylate **1a–l** were synthesized according to our previously reported procedure,[22a] the β-enaminoester **2a–e** were synthesized by Dong *et al.* methodology[26] and the β-enaminoketones **2f–g** were prepared by Stefani *et al.* procedure.[27]

General procedure for the synthesis of compound 3

The β-nitroacrylate **1** (1 mmol) and β-enaminone **2** (1 mmol) were slowly mixed at 0 °C (ice/water bath). The reaction was stirred for 15 min at the same temperature, after that, the bath was removed, and temperature was left up increase to room temperature, then reaction was stirred for the needed time (monitored by TLC, see Table 1). After the reaction was completed, the crude product **3** was directly purified by flash chromatography column (hexanes : EtOAc = 80 : 20).

Large scale synthesis of compound 3aa

To a stirred β-nitroacrylate **1a** (10 mmol) maintained a 0 °C (ice/water bath), the β-enaminone **2** (10 mmol) was slowly added over 30 min, then the reaction was stirred at room temperature for 3.5 h. After the reaction was completed (TLC), the crude product **3aa** was subjected to the *way a* or the *way b*.

Way a: the product was directly purified by flash chromatography column, using 25 g of silica (60 Å, 40–63 μm) and 180 ml of eluent mixture (cyclohexane : EtOAc = 95 : 5). The eluate was continuously monitored by TLC and, the eluent mixture was recovered by distillation (40 °C/135 torr) and reused. The pure product **3aa** was obtained in 93% yield.

Way b: 3.5 mL (~3 g) of EtOAc and 2 g of dry $MgSO_4$ were added to the crude **3aa**, then the mixture was stirred 15 min and filtered through a pad of florisil® (1.5 g, 100–200mesh) which was washed with fresh EtOAc (12 ml, ~10.5 g). The product **3aa** was obtained in 98% yield (GC purity ≥ 94%).

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