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One-pot synthesis of alkyl pyrrole-2-carboxylates starting from β-nitroacrylates and primary amines†

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Herein, we present a new, efficient, one-pot synthesis of pyrrole-2-carboxylate derivatives starting from ketal-functionalized β-nitroacrylates in combination with primary amines under acidic heterogeneous conditions.

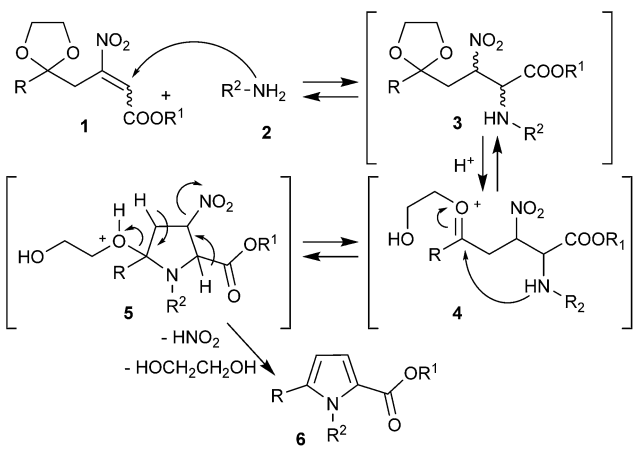
Pyrroles constitute one of the most important classes of nitrogen-containing heterocycles and, due to their importance, several procedures for synthesizing poly-functionalized pyrroles were reported.[1] In this context, pyrrole-2-carboxylate derivatives have been largely investigated for their activities,[2] and exploited as strategic starting materials, or key intermediates, for the preparation of biological active molecules, such as pyrrolnitrin and porphyrins.[3]

Given their great importance, over the years several methodologies have been proposed in the literature for the preparation of these molecules. The first one was the pioneering Kleinspehn's method, which involves the use of diethyl α-oximinomalonate in combination with 1,3-diketones under reductive conditions,[4] then, analogous procedures based on the use of α-oximinomalonate or its amino reduced form were successively proposed.[5] Additional synthetic strategies were developed by Barluenga from azabutadiene,[6] and Gupton from 2-substituted vinamidinium or 3-aryl-3-chloropropeniminium salts.[7] Further useful syntheses were reported by Tashiro, from 1,3-diketones,[8] and Guillard from β-arylacroleins.[9]

Although these methodologies lead to the preparation of pyrrole-2-carboxylates in efficient ways, they present important limitations such as, the need of high temperature (80–140 °C) and inert atmosphere, the use of dangerous reactants (*e.g.* NaH) and unsustainable solvents (*e.g.* DMF, pyridine, AcOH).[10] Furthermore, all the reported procedures involve an articulate work-up, with evident further disadvantages from ecological point of view.

Nowadays, the sustainability of a chemical process is one of the main aspects that must be considered, and the implementation of new green methodologies is of dramatic importance.[11] In this sense, following our on-going research project concerning the development of new low impacting procedures,[12] we focused our attention to ketal-functionalized β-nitroacrylates type **1**, an emerging class of molecules that we have recently used in our laboratory as precursor of the indole system.[13] In fact, the structure **1** seems to be ideal for the ex-novo ring construction and, herein, we report a new application of **1** in combination with primary amines **2** to synthesize the title compounds **6** (Scheme 1).

Scheme 1 Synthesis of trisubstituted pyrroles **6**.



Scheme 2 Plausible mechanism.

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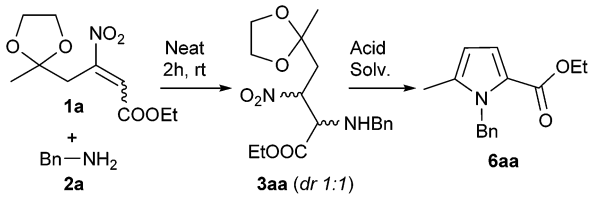
Table 1 Optimization studies



Acid (g mmol^{-1})	Solvent	Temp (°C)	Yield[a] (%) of **6aa** (h)
p-TsOH·H_2O (0.19)	2-MeTHF	40	32 (6)
p-TsOH·H_2O (0.19)	2-MeTHF	60	45 (6)
Amberlyst 15 (0.4)	2-MeTHF	40	39 (6)
Amberlyst 15 (0.4)	2-MeTHF	60	66 (3)
Amberlyst 15 (0.4)	2-MeTHF	75	67 (3)
Amberlyst 15 (0.6)	2-MeTHF	60	62 (3)
Amberlyst 15 (0.2)	2-MeTHF	60	68 (3)
Amberlyst 15 (0.1)	2-MeTHF	60	22 (3)
Amberlyst 15 (0.2)	CPME	60	55 (3)
Amberlyst 15 (0.2)	EtOAc	60	48 (3)
Amberlyst 15 (0.2)	DCM	60	42 (3)
Acidic Al_2O_3 (0.2)	2-MeTHF	60	—
Montm. K10 (0.2)	2-MeTHF	60	—
H_2SO_4/SiO_2 (0.2)	2-MeTHF	60	36 (3)
Zeolite HSZ320 (0.2)	2-MeTHF	60	11 (3)

[a] Yield of pure isolated product.

Our approach consists in a one-pot process (Scheme 2), which involves (i) an initial Michael addition of the primary ammine **2** to β-nitroacrylate **1**,[14] with the formation of the intermediate **3**, (ii) the *in situ* acidic treatment of **3** giving the opening of 1,3-dioxolane ring (**4**), with the successive cyclization-aromatization of the former β-nitroacrylate moiety (**5**) and formation of pyrrole **6**.

In order to find the best reaction conditions, we investigated the reaction between ethyl 4-(2-methyl-1,3-dioxolan-2-yl)-3-nitrobut-2-enoate **1a** (R = Me, R^1 = Et) and benzylamine **2a**.

Thanks to the great reactivity of β-nitroacrylates, the conjugate addition of **2a** to **1a** allows the Michael adduct **3aa** in quantitative yield, over 2 hours, under promoter free and solvent free conditions. On the other hands, with the aim to maximize the reaction efficiency of the cleavage–cyclization–aromatization domino process, a variety of acidic species and solvents were screened (Table 1).

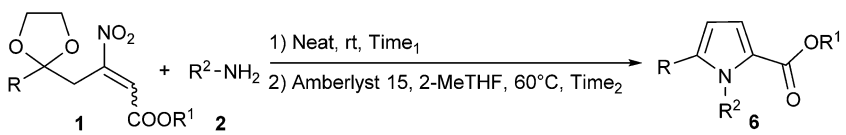
As reported in the Table 1, the best result for pyrrole **6aa** (overall yield = 68%) was obtained over 3 hours, using Amberlyst 15 (200 mg mmol^{-1}) in 2-MeTHF, as green solvent,[15] at 60 °C.

Then, we tested the generality of our protocol to a plethora of β-nitroacrylates **1** and amines **2** (Table 2). In all cases, pyrroles **6** were isolated in good overall yields (53–75%) with both aliphatic and aromatic amines, independently from the nature of substituents present on β-nitroacrylates.

Moreover, by the appropriate selection of the amines **2**, even a variety of protecting groups at *N*-position (benzyl: **6aa** and **6ba**, allyl: **6ce** and PMP: **6cd**), and reactive functionalities such as double (**6ce**) and triple (**6ac** and **6gc**) bonds were introduced. Successively, we applied our method to synthesize pyrrole-benzoxoazinone derivatives **7** (Fig. 1), a valuable class of biologically active molecules,[16] starting from **1** and aminophenols (**2k–l**).

As reported in the Scheme 3, the synthesis was tested studying the reaction of **1g** with **2j**. Applying our reaction conditions the reaction gives the pyrrole **6gj** (57% yield after purification), which in turn, was cyclized into the target compound **7gj**, in quantitative yield, by treatment with *p*-toluensulfonic acid under refluxing toluene. Alternatively, the crude intermediate **6gj** can be directly converted into **7gj** (54%

Table 2 One-pot synthesis of pyrroles **6**



	R	R^1		R^2	$Time_1$ (h)	$Time_2$ (h)	Yield[a] (%) of **6**	
1a	Me	Et	**2a**	Bn	2	3	**6aa**	68
1a	Me	Et	**2b**	$CH_3(CH_2)_4$	2	3	**6ab**	72
1a	Me	Et	**2c**	$CH{\equiv}CCH_2$	2	3	**6ac**	68
1b	$CH_3(CH_2)_7$	Et	**2a**	Bn	2	3	**6ba**	70
1c	*p*-Tol	Et	**2d**	4-$MeOC_6H_4$	3[b]	20	**6cd**	60
1c	*p*-Tol	Et	**2e**	$CH_2 = CHCH_2$	2	3	**6ce**	70
1d	Me	*i*-Pr	**2f**	Ph	3	16	**6df**	75
1e	$CH_3(CH_2)_5$	*i*-Bu	**2g**	*i*-Bu	2	3	**6eg**	73
1f	H	*i*-Bu	**2h**	*i*-Pr	2	15	**6fh**	64
1f	H	*i*-Bu	**2f**	Ph	3	16	**6ff**	63
1g	Me	Me	**2c**	$CH{\equiv}CCH_2$	2	3	**6gc**	53
1g	Me	Me	**2i**	2-$BnOC_6H_4$	7	7	**6gi**	63

[a] Yield of pure isolated product. [b] The first step was performed in presence of 300 μL mmol^{-1} of 2-MeTHF.

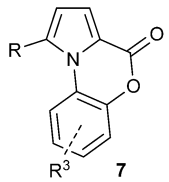
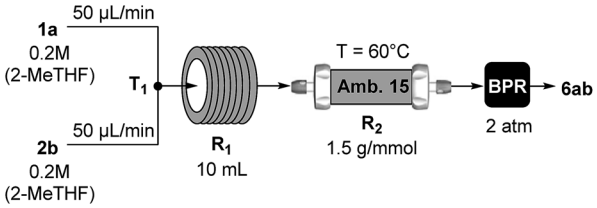


Fig. 1 Pyrrolebenzoxoazinone derivatives 7.



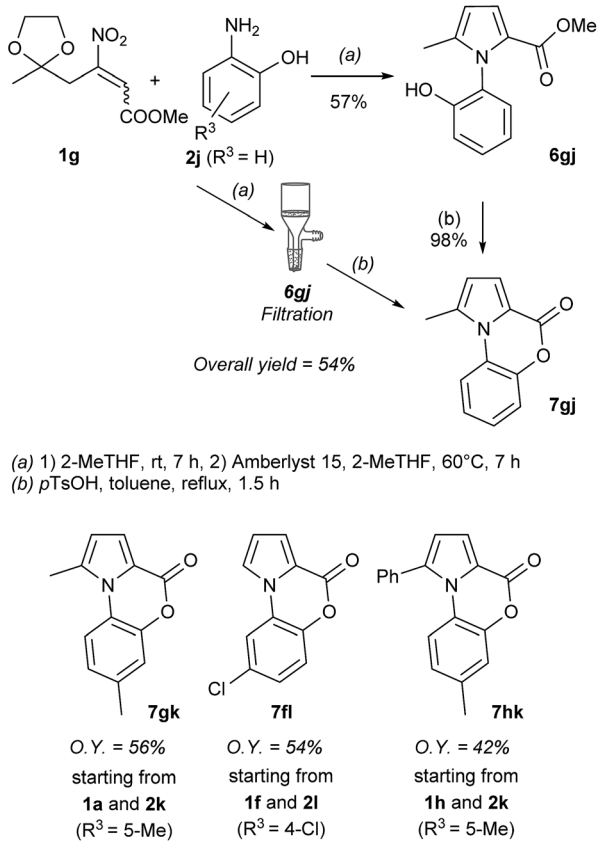
Scheme 4 Flow chemical synthesis of pyrrole **6ab**.

overall yield) avoiding the purification of the intermediate and minimizing the waste production.

The synthetic process was then applied to prepare the additional derivatives 7**gk**, 7**fl**, and 7**hk**.

Finally, in order to automate the process, we explored the reactivity of the starting materials **1a** and **2b** under flow chemical conditions (Scheme 4). A preliminary screening was carried out with the aim to optimize the reaction conditions in terms of concentration, residence time and stoichiometry. The best result was achieved using 0.2 M solution of **1a** and **2b** in 2-MeTHF, a flow rate of 0.05 ml min^{-1} for each pumps, a coil reactor $\mathbf{R_1}$ (PTFE, i.d. = 0.5 mm) having and internal volume of 10 mL (residence time, 100 minutes), an Omnifit column reactor $\mathbf{R_2}$ heated at 60 °C and packed with Amberlyst 15 (1.5 g $mmol^{-1}$), and a back pressure regulator (BPR) set at ~2 atm.

Working under these reaction conditions, the pyrrole **6ab** was synthesized in 70% of yield (*vs.* 72% in batch). The same conditions were extended to substrate **1a** and **2c** for synthesizing **6ac**, which was isolated in 71% of yield (*vs.* 68% in batch). In particular the flow chemical synthesis of **6ac** is of valuable interest, since it could be potentially submitted to further clickable manipulations.[17]



Scheme 3 Synthesis of compounds 7.

Conclusions

In conclusion, by our methodology it has been possible to synthesize several pyrroles introducing a variety of protecting group at *N*-position, as well as an assortment of both aliphatic and aromatics substituents at C-5. Furthermore, we demonstrated the applicability of our synthetic approach preparing benzo[*b*]pyrrolo[1,2-*d*][1,4]oxazin-4-one derivatives, and we extended our methodology to flow chemical conditions demonstrating the easy process-automation.

Finally, by the choices of 2-MeTHF as solvent, and the use of Amberlyst A15 as solid acid, we could avoid any complicate aqueous work-up, saving resources and energy with evident advantages from sustainable point of view.

Acknowledgements

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Notes and references

1 (*a*) R. Martín, C. H. Larsen, A. Cuenca and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 3379; (*b*) N. Azizi, A. Khajeh-Amiri, H. Ghafuri, M. Bolourtchian and M. R. Saidi, *Synlett*, 2009, 2245; (*c*) T. Maehara, R. Kanno, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2012, **14**, 1946; (*d*) B. Gabriele, L. Veltri, R. Mancuso, G. Salerno, S. Maggi and B. M. Aresta, *J. Org. Chem.*, 2012, **77**, 4005; (*e*) R. J. Wakeham, J. E. Taylor, S. D. Bull, J. A. Morris and J. M. J. Williams, *Org. Lett.*, 2013, **15**, 702; (*f*) M. Zahng, X. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384; (*g*) R. Ballini, S. Gabrielli, A. Palmieri and M. Petrini, *RSC Adv.*, 2014, **4**, 43258.

2 (*a*) M. Birouk, S. Harraga, J. Panouse-Perrini, J. F. Robert, M. Damelincourt, F. Theobald, R. Mercier and J. J. Panouse, *Eur. J. Med. Chem.*, 1991, **26**, 91; (*b*) X. Teng, H. Keys, J. Yuan, A. Degterev and G. D. Cuny, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3219; (*c*) F. Micheli, R. Di Fabio,

A. Giacometti, A. Roth, E. Moro, G. Merlo, A. Paio, E. Merlo-Pich, S. Tomelleri, F. Tonelli, P. Zarantonello, L. Zonzini and A. M. Capelli, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7308; (*d*) M. Urbano, M. Guerrero, J. Zhao, S. Velaparthi, M.-T. Schaeffer, S. Brown, H. Rosen and E. Roberts, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5470.

3 (*a*) J. B. Paine III, in *The Porphyrins*, ed. D. Dolphin, Academic Press, New York, 1978, vol. 1, p. 101; (*b*) K. Sakata, K. Aoki, C.-F. Sakurai, S. Tamura and S. Murakoshi, *Agric. Biol. Chem.*, 1978, **42**, 457.

4 G. G. Kleinspehn, *J. Am. Chem. Soc.*, 1955, **15**, 1546.

5 (*a*) J. B. Pain III and D. Dolphin, *J. Org. Chem.*, 1985, **50**, 5598; (*b*) J. B. Pain III, J. R. Brough, K. K. Buller and E. E. Erikson, *J. Org. Chem.*, 1987, **52**, 3986.

6 J. Barluenga, V. Rubio and V. Gotor, *J. Org. Chem.*, 1982, **47**, 1696.

7 (*a*) G. T. Gupton, D. A. Krolikowski, R. H. Yu and S. W. Riesinger, *J. Org. Chem.*, 1990, **55**, 4735; (*b*) G. T. Gupton, D. A. Krolikowski, R. H. Yu and P. Vu, *J. Org. Chem.*, 1992, **57**, 5480.

8 S. Mataka, K. Takahashi, Y. Tsuda and M. Tashiro, *Synthesis*, 1982, 157.

9 J. P. Boukou-Poba, M. Farnier and R. Guilard, *Tetrahedron Lett.*, 1979, **20**, 1717.

10 (*a*) C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927; (*b*) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31; (*c*) P. J. Dunn, *Chem. Soc. Rev.*, 2012, **41**, 1452.

11 (*a*) P. T. Anastas and J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998; (*b*) P. T. Anastas and M. M. Kirchhoff, *Acc. Chem. Res.*, 2002, **35**, 686; (*c*) I. T. Horváth and P. T. Anastas, *Chem. Rev.*, 2007, **107**, 2169; (*d*) P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.

12 (*a*) R. Ballini, D. Fiorini, M. V. Gil and A. Palmieri, *Green Chem.*, 2003, **5**, 475; (*b*) R. Ballini, D. Fiorini, M. V. Gil and A. Palmieri, *Tetrahedron*, 2004, **60**, 2799; (*c*) R. Ballini, G. Bosica, D. Fiorini and A. Palmieri, *Green Chem.*, 2005, **7**, 825; (*d*) R. Ballini, L. Barboni, D. Fiorini, G. Giarlo and A. Palmieri, *Green Chem.*, 2005, **7**, 828; (*e*) R. Ballini, L. Barboni, F. Fringuelli, A. Palmieri, F. Pizzo and L. Vaccaro, *Green Chem.*, 2007, **9**, 823; (*f*) R. Ballini, G. Bosica, A. Palmieri, F. Pizzo and L. Vaccaro, *Green Chem.*, 2008, **10**, 541; (*g*) L. Barboni, S. Gabrielli, A. Palmieri, C. Femoni and R. Ballini, *Chem.–Eur. J.*, 2009, **15**, 7867; (*h*) S. Gabrielli, A. Palmieri, A. Perosa, M. Selva and R. Ballini, *Green Chem.*, 2011, **13**, 2026; (*i*) A. Palmieri, S. Gabrielli, C. Cimarelli and R. Ballini, *Green Chem.*, 2011, **13**, 3333; (*j*) A. Palmieri, S. Gabrielli and R. Ballini, *Green Chem.*, 2013, **15**, 2344.

13 A. Palmieri, S. Gabrielli, D. Lanari, L. Vaccaro and R. Ballini, *Adv. Synth. Catal.*, 2011, **353**, 1425.

14 For example concerning the addition of amines to β-nitroacrylates see: (*a*) R. Ballini, N. A. Bazán, G. Bosica and A. Palmieri, *Tetrahedron Lett.*, 2008, **49**, 3865; (*b*) A. Palmieri, S. Gabrielli, R. Maggi and R. Ballini, *Synlett*, 2014, **25**, 128.

15 V. Pace, P. Hoyos, L. Castoldi, P. Domínguez de María and A. R. Alcántara, *ChemSusChem*, 2012, **5**, 1369.

16 (*a*) G. W. H. Cheeseman, M. Rafiq, P. D. Roy, C. J. Turner and G. V. Boyd, *J. Chem. Soc. C*, 1971, 2018; (*b*) V. A. Vaillard, R. A. Rossi and S. E. Martín, *Org. Biomol. Chem.*, 2011, **9**, 4927; (*c*) T. Sanaeishoar, S. Adibi-Sedeh and S. Karimian, *Comb. Chem. High Throughput Screening*, 2014, **17**, 157; (*d*) R. T. Naganaboina, A. Nayak and R. K. Peddinti, *Org. Biomol. Chem.*, 2014, **12**, 3366; (*e*) L. Moradi, M. Piltan and H. Rostami, *Chin. Chem. Lett.*, 2014, **25**, 123.

17 Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., WO2008/143649 (A2), 2008.