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Fast, Efficient, Mild, and Metal-Free Synthesis of Pyrroles by Domino Reactions in Water

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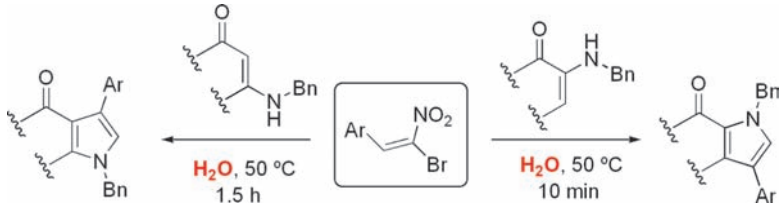
ABSTRACT



(*E*)-*β*-Bromonitrostyrenes react with enaminones in water to afford pyrroles in excellent yields. The domino reaction constitutes a new, mild, and environmentally benign process for the fast and efficient synthesis of diverse pyrroles.

Among the many heteroaromatic compounds, the pyrrole ring has found a wide number of applications and is present in many natural products.[1] It is used as an important skeleton in organic synthesis[2] and is also utilized in other important fields, such as materials science,[3] medicinal chemistry, and pharmacology.[4] Therefore, a large effort has been made to develop more efficient synthetic routes to obtain this valuable heterocycle.[5] The most frequently used methods are the classic Hantzsch,[6] Knorr,[7] and Paal−Knorr[8] procedures. Although these methods have been used during the last century, there are significant drawbacks which have triggered the search for new methodologies, such as multicomponent couplings[9] and transition-metal-catalyzed cyclizations.[10] The success of these newer methods is often limited as in many

(1) (a) Sundburg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264, and references cited here.

(2) (a) *Pyrroles, The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles, Part II*; Jones, R. A., Ed.; Wiley: New York, 1992. (b) Black, D. St. C. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 2, p 39.

(3) For a review, see: (a) Higgins, S. J. *Chem. Soc. Rev.* **1997**, *26*, 247. (b) Groenendaal, L.; Meijer, E.-W.; Vekemans, J. A. J. M. In *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, 1997. (c) Novak, P.; Müller, K.; Santhanam, S. V.; Hass, O. *Chem. Rev.* **1997**, *97*, 207. (d) Gabriel, S.; Cecius, M.; Fleury-Frenette, K.; Cossement, D.; Hecq, M.; Ruth, N.; Jerome, R.; Jerome, C. *Chem. Mater.* **2007**, *19*, 2364.

(4) (a) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Bioorg. Med. Chem.* **2006**, *14*, 8162. (b) Di Santo, R.; Costi, R.; Artico, M.; Miele, G.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Cancio, R.; Maga, G. *ChemMedChem.* **2006**, *1*, 1367. (c) Zeng, L.; Miller, E. W.; Pralle, A.; Isacoff, E. Y.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 10. (d) Clark, B. R.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H. *Org. Lett.* **2006**, *8*, 701. (e) La Regina, G.; Silvestri, R.; Artico, M.; Lavecchia, A.; Novellino, E.; Befani, O.; Turini, P.; Agostinelli, E. *J. Med. Chem.* **2007**, *50*, 922.

(5) Recent references, see: (a) Fu, X.; Chen, J.; Li, G.; Liu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5500. (b) Trofimov, B. A.; Schmidt, E. Y.; Mikhaleva, A. I.; Pozo-Gonzalo, C.; Pomposo, J. A.; Salsamendi, M.; Protzuk, N. I.; Zorina, N. V.; Afonin, A. V.; Vashchenko, A. V.; Levanova, E. P.; Levkovskaya, G. G. *Chem.—Eur. J.* **2009**, *15*, 6435. (c) Fujiwara, M.; Kawatsura, M.; Hayase, S.; Nanjo, M.; Itoh, T. *Adv. Synth. Catal.* **2009**, *351*, 123. (d) Wang, J.-Y.; Liu, S.-P.; Yu, W. *Synlett* **2009**, 2529.

(6) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.

(7) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635.

(8) Pall, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367.

(9) (a) Benedetti, F.; Berti, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Gazz. Chim. Ital.* **1990**, *120*, 25. (b) Shiraishi, H.; Nishitani, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6234. (c) Bian, Y.-J.; Liu, X.-Y.; Ji, K.-G.; Shu, X.-Z.; Guo, L.-N.; Liang, Y.-M. *Tetrahedron* **2009**, *65*, 1424. (d) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques., E. F. *Org. Lett.* **2009**, *11*, 4624. (e) Dou, G.; Shi, C.; Shi, D. *J. Comb. Chem.* **2008**, *10*, 810. (f) Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 129. (g) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2009**, *92*, 2118. (h) Lamande-Langle, S.; Abarbri, M.; Thibonnet, J.; Duchene, A.; Parrain, J.-L. *Chem. Commun.* **2010**, *46*, 5157.

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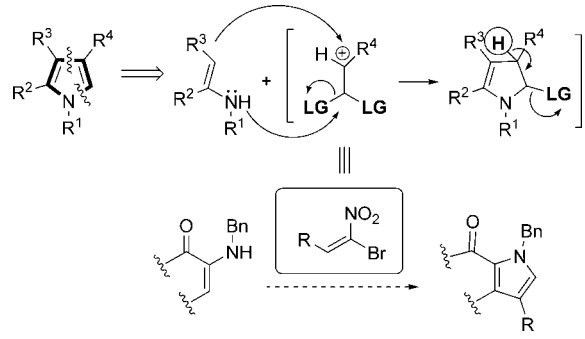
cases the reaction conditions remain harsh. Thus it remains highly desirable to develop methods requiring milder conditions as well as avoiding the need for toxic metal catalysts. Furthermore, to placate environmental and economic demands the use of water as a solvent would be highly advantageous. Therefore, we decided to address this important issue.

A possible retrosynthetic disconnection for the synthesis of pyrroles is given in Scheme 1 and consists of the use of

Scheme 1

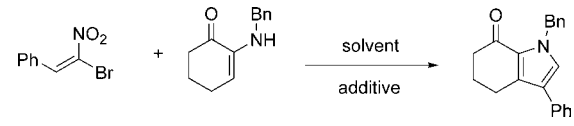


a binucleophilic synthon, the enamine derivative, and the trifunctional synthon, β-bromonitrostyrene[11] (Scheme 1). To validate our hypothesis, we decided to carry out the reaction of β-bromonitrostyrenes and different enaminones to achieve a one-pot synthesis of pyrroles.

In preliminary experiments, we studied the reaction of benzylenaminone **2** with β-bromonitrostyrene **1a**, which can easily be prepared in good yields according to the reported procedure.[12] To our delight, pyrrole **3a** was obtained with full conversion when the reaction was carried out in CH_2Cl_2 at room temperature (Table 1, entry 1). However, increasing the temperature resulted in shorter reaction times (Table 1, entry 2). To find the best reaction conditions, we decided to evaluate different parameters including reaction time, solvent type, and various additives. Selected results are listed in Table 1. Notably, when water was used as a solvent at 50 °C the domino reaction took place extremely rapidly with full conversion occurring in just 10 min (Table 1, entry 4). The use of additives, such as potassium acetate or other bases, resulted only in the formation of complex reaction mixtures (Table 1, entry 5).

With the optimal results in hand, we explored the scope of the reaction by employing various β-bromonitrostyrenes **1a**−**g**. The results are shown in Table 2.

Table 1. Reaction of β-Bromonitrostyrene **1a** and Enaminone **2** under Different Conditions

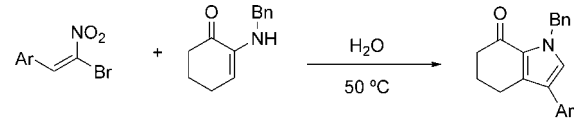


1a **2** **3a**

entry[a]	time	temp	solvent	additive	conversion[b] %
1	30 h	rt	CH_2Cl_2	–	100
2	12 h	50	CH_2Cl_2	–	100
3	12 h	rt	H_2O	–	100
4	10 min	50	H_2O	–	100
5	10 min	50	H_2O	KOAc	–[c]

[a] Reactions were performed with β-bromonitrostyrene **1a** (0.44 mmol) and enaminone **2** (0.44 mmol) in the indicated solvent (1.0 mL). [b] Determined by ^{1}H NMR. [c] A complex product mixture was obtained.

Table 2. Reaction of Different β-Bromonitrostyrenes **1a**−**h** and Enaminone **2**



1a-g **2** **3a-g**

entry[a]	Ar	product	time (min)	yield %[b]
1	C_6H_5-	**3a**	10	90
2	3-Br-C_6H_4-	**3b**	10	80
3	2-MeO-C_6H_4-	**3c**	10	81
4	4-MeO-C_6H_4-	**3d**	30	87
5	2-F-C_6H_4-	**3e**	10	75
6	4-F-C_6H_4-	**3f**	10	85
7	4-Me-C_6H_4-	**3g**	10	79

[a] Reactions were performed with β-bromonitrostyrenes **1a**−**g** (0.44 mmol) and enaminone **2** (0.44 mmol) in H_2O (1.0 mL) at 50 °C for the indicated reaction time. [b] Yield after column chromatography.

In general, β-bromonitrostyrenes with different substitution patterns including electron-withdrawing as well as electron-donating groups could be successfully applied in this reaction providing the pyrroles **3a**−**3g** in good yields. Given the importance of the fluorine atom in pharmacology,[13] we also carried out the synthesis of the pyrroles with fluorine substitution using 2-fluoro- and 4-fluoro-β-bromonitrostyrenes **1e**−**f**. Again we obtained the products in high yields (Table 2, entries 5 and 6). To evaluate the generality and efficiency of the reaction, we became interested in exploring other enaminones. As shown in Table 3, when the enaminone **4a** derived from cyclohexanone was used, pyrrole **5a** was obtained in good yield (Table 3, entry 1). Enaminone **4a**

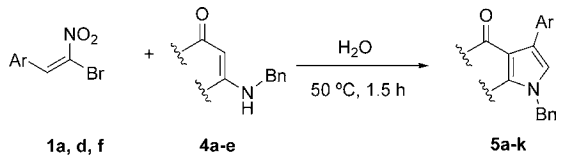
(10) For most recent strategies based on the metal-catalyzed synthesis of pyrroles, see: (a) Sukhendu, M.; Srijit, B.; Umasish, J. *J. Org. Chem.* **2010**, *75*, 1674, and references cited herein. (b) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372. (c) Liu, W.-B.; Jiang, H.-F.; Huang, L.-B. *Org. Lett.* **2010**, *12*, 312. (d) Takahashi, A.; Kawai, S.; Hachiya, I.; Shimizu, M. *Eur. J. Org. Chem.* **2010**, *1*, 191. (f) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.

(11) (a) Campbell, M. M.; Cosford, N.; Li, Z.; Sainsbury, M. *Tetrahedron* **1987**, *43*, 1117. (b) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (c) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494. (d) Muruganantham, R.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2007**, *9*, 1125. (e) Ganesh, M.; Namboothiri, I. N. N. *Tetrahedron* **2007**, *63*, 11973. (f) Itoh, K.; Kishimoto, S.; Sagi, K. *Can. J. Chem.* **2009**, *87*, 760.

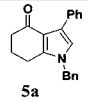
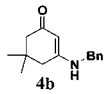
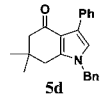
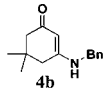
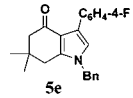
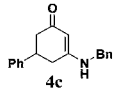
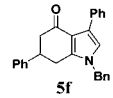
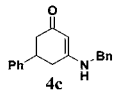
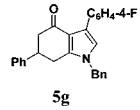
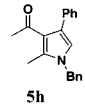
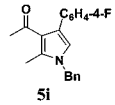
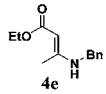
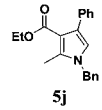
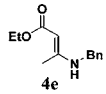
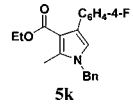
(12) Parham, W. E.; Bleasdale, J. L. *J. Am. Chem. Soc.* **1951**, *73*, 4664.

(13) (a) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15. (b) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 27. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (f) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

Table 3. Reactions with Different Enaminones



1a, d, f **4a-e** **5a-k**

entry[a]	(Ar)	enaminone **4**	product **5**	yield[b] %
1	**1a** (C_6H_5-)	 **4a**	 **5a**	78
2	**1f** (4-F-C_6H_4-)	 **4a**	 **5b**	75
3	**1d** (4-MeO-C_6H_4-)	 **4a**	 **5c**	72
4	**1a** (C_6H_5-)	 **4b**	 **5d**	77
5	**1f** (4-F-C_6H_4-)	 **4b**	 **5e**	82
6	**1a** (C_6H_5-)	 **4c**	 **5f**	75
7	**1f** (4-F-C_6H_4-)	 **4c**	 **5g**	77
8	**1a** (C_6H_5-)	 **4d**	 **5h**	85
9	**1f** (4-F-C_6H_4-)	 **4d**	 **5i**	82
10	**1a** (C_6H_5-)	 **4e**	 **5j**	79
11	**1f** (4-F-C_6H_4-)	 **4e**	 **5k**	78

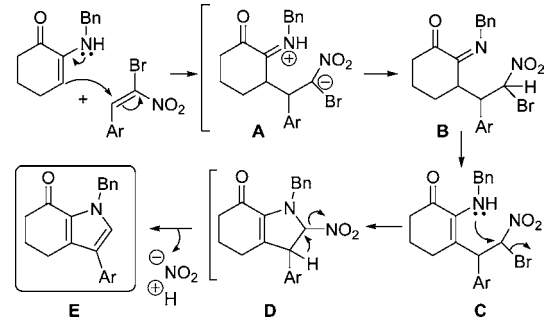
[a] Reactions were performed with β-bromonitrostyrenes **1a**,**d**,**f** (0.44 mmol) and enaminones **4a**−**e** (0.44 mmol) in H_2O (1.0 mL) at 50 °C for 1.5 h. [b] Yield after column chromatography.

also reacted with β-bromonitrostyrenes bearing both an electron-withdrawing (Table 3, entry 2) and an electron-donating group (Table 3, entry 3), and the products were isolated in 75% and 72% yields, respectively.

Furthermore, other cyclic enaminones **4b** and **4c**, as well as acyclic enaminones **4d** and **4e**, could be efficiently applied in the reaction to provide the desired products **5d**−**5k**. Again short reaction times were observed, and the products were obtained in good yields after simple filtration through a silica column avoiding the need for extraction using large amounts of organic solvents.

A plausible mechanistic proposal considering all data obtained is shown in Scheme 2. The first step of the domino

Scheme 2



reaction involves a conjugate addition of the enaminone to a nitrostyrene derivative to give intermediate **A**. The subsequent protonation gives **B**, which tautomerizes to the more stable enaminone **C**. The subsequent intramolecular nucleophilic substitution results in the formation of **D** which upon elimination of the nitro group gives the desired pyrroles **E**.

In summary, we have developed a facile and mild synthesis of trisubstituted pyrroles by reaction of enaminones with β-bromonitrostyrenes. This method constitutes a new approach for the synthesis of diverse pyrroles, in which β-bromonitrostyrenes have been used as a trifunctional synthon. Additionally, the reaction can be carried out in water as a cheap and environmentally benign solvent, and a simple purification step provides the products in good yields after very short reaction times. This method is extremely efficient and can be conducted on a larger scale at low cost making it an ideal alternative to existing methods.

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Supporting Information Available: Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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