

Highly Efficient Synthesis of Polysubstituted Pyrroles via Four-Component Domino Reaction

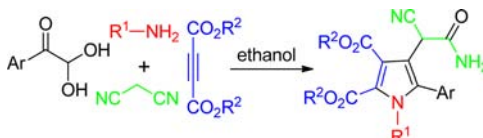
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ABSTRACT



A highly efficient, catalyst-free synthesis of polysubstituted pyrroles by means of a novel four-component domino reaction of an arylglyoxal monohydrate, an aniline, a dialkyl but-2-ynedioate, and malononitrile is reported. This transformation proceeded via a 6,6a-dihydrofuro[2,3-b]-pyrrole as the key intermediate.

Multicomponent reactions, in which multiple reactions are combined into a single synthetic operation, have been extensively used in organic synthesis, as well as in combinatorial and medicinal chemistry. Obviation of the need for isolation and purification of the intermediates results in maximization of yields and reduction of waste, and thus renders the protocols ecofriendly.¹ These features make multicomponent reactions well suited for the construction of complex molecules from readily available starting materials.² In the past decade, many new three- and four-component reactions have been reported, and efforts to develop new multicomponent reactions are continuing.³

Pyrroles are an important class of heterocycles that are widely distributed in various natural products and biologically important molecules such as porphyrins, bile pigments, coenzymes, and alkaloids.⁴ The traditional

methods for the construction of a pyrrole ring include the Knorr reaction,⁵ the Hantzsch reaction,⁶ the Paal–Knorr

(3) (a) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427. (b) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestipolov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423. (c) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147. (d) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309. (e) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. (f) Jiang, B.; Tu, S. J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. (g) Li, M.; Cao, H.; Wang, Y.; Lv, X. L.; Wen, L. R. *Org. Lett.* **2012**, *14*, 3470. (h) Hao, W. J.; Xu, X. P.; Bai, H. W.; Wang, S. Y.; Ji, S. J. *Org. Lett.* **2012**, *14*, 4894. (i) Jiang, B.; Feng, B. M.; Wang, S. L.; Tu, S. J.; Li, G. *Chem.—Eur. J.* **2012**, *18*, 9823. (j) Wen, L. R.; Shi, Y. J.; Liu, G. Y.; Li, M. *J. Org. Chem.* **2012**, *77*, 4252. (k) Jiang, B.; Yi, M. S.; Shi, F.; Tu, S. J.; Pindi, S.; McDowell, P.; Li, G. *Chem. Commun.* **2012**, 48, 808. (l) Jiang, B.; Li, Q. Y.; Zhang, H.; Tu, S. J.; Pindi, S.; Li, G. *Org. Lett.* **2012**, *14*, 700. (m) Chen, Z.; Zhang, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (n) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712. (o) Han, X.; Li, H.; Hughes, R. P.; Wu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10390. (p) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588. (q) Roy, S.; Reiser, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 4722.

(4) (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic: London, 1977; pp 1–5. (b) Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (c) Lehuéde, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, *34*, 991.

(5) (a) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635. (b) Manley, J. M.; Kalman, M. J.; Conway, B. G.; Ball, C. C.; Havens, J. L.; Vaidyanathan, R. *J. Org. Chem.* **2003**, *68*, 6447. (c) Shiner, C. M.; Lash, T. D. *Tetrahedron* **2005**, *61*, 11628.

[†] Soochow University.

[‡] China University of Mining & Technology.

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (c) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (e) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.

(2) (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (b) Davide, B.; Rosario, R.; Rodolfo, L. *Curr. Org. Chem.* **2010**, *14*, 332.

synthesis,⁷ and various cycloaddition methods.⁸ Recently, new approaches based on transition-metal-catalyzed cycloisomerization of alkyne- and allene-containing substrates,⁹ multicomponent reactions,¹⁰ and various other methods¹¹ have been developed. However, some of these new methods have significant limitations, such as tedious work-up procedures, harsh reaction conditions, low yields, long reaction times, and the requirement for an inert atmosphere. Therefore, a simple, efficient method for pyrrole synthesis remains an attractive goal. As a part of our ongoing research on the development of multicomponent approaches to heterocycles,¹² we investigated the rapid construction of a polysubstituted pyrrole ring via a four-component domino reaction of an arylglyoxal monohydrate, an aniline, a dialkyl but-2-ynedioate, and malononitrile under catalyst-free conditions.

We initially evaluated the four-component reaction of a 1:1:1:1 mixture of phenylglyoxal monohydrate (**1a**), 4-methylaniline (**2a**), dimethyl but-2-ynedioate (**3a**), and malononitrile (**4**) under a variety of conditions (Scheme 1, Table 1). When the reaction was carried out in water without any catalyst, the yield of product was low (entry 1). Adding the phase-transfer catalyst TEBAC improved the

Scheme 1. Model Reaction

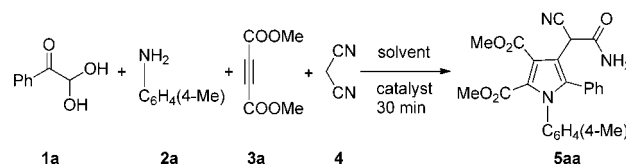


Table 1. Optimization of the Reaction Conditions for the Synthesis of **5aa**

entry	solvent	temp (°C)	catalyst (mol %)	isolated yield (%)
1	water	80	—	39
2	water	80	TEBAC	54
3	DMF	80	—	69
4	acetonitrile	reflux	—	63
5	chloroform	reflux	—	42
6	methanol	reflux	—	55
7	ethanol	reflux	—	81
8	ethanol	rt	—	17
9	ethanol	40	—	43
10	ethanol	60	—	66

(6) (a) Hantzsch, A. *Ber.* **1890**, 23, 1474. (b) Palacios, F.; Aparico, D.; Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, 57, 1961. (c) Trautwein, A. W.; Süssmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, 8, 2381.

(7) (a) Paal, C. *Ber.* **1885**, 18, 367. (b) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, 122, 3801. (c) Bimal, K. B.; Susanta, S.; Indrani, B. *J. Org. Chem.* **2004**, 69, 213. (d) Chen, J.; Wu, H.; Zheng, Z.; Jin, C.; Zhang, X.; Su, W. *Tetrahedron Lett.* **2006**, 47, 5358. (e) Minetto, G.; Raveglia, L. F.; Segal, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277.

(8) (a) Bullington, J. L.; Wolff, R. R.; Jackson, P. F. *J. Org. Chem.* **2002**, 67, 9439. (b) Katritzky, A. R.; Zhang, S.; Wang, M.; Kolb, H. C.; Steel, P. J. *J. Heterocycl. Chem.* **2002**, 39, 759. (c) Washizuka, K. I.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, 55, 969.

(9) (a) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, 6, 2957. (b) Ishikawa, T.; Aikawa, T.; Watanabe, S.; Saito, S. *Org. Lett.* **2006**, 8, 3881. (c) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, 8, 5349. (d) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, 127, 11260. (e) Mihovilovic, M. D.; Stanetty, P. *Angew. Chem., Int. Ed.* **2007**, 46, 3612. (f) Shu, X.; Liu, X.; Xiao, H.; Ji, K.; Guo, L.; Liang, Y. *Adv. Synth. Catal.* **2008**, 350, 313. (g) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, 123, 2074. (h) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, 71, 4525.

(10) (a) Tejedor, D.; Gonzales-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, 126, 8390. (b) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, 127, 10804. (c) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem.—Eur. J.* **2007**, 13, 9973. (d) Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, 129, 12366. (e) Lu, Y.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2008**, 47, 5430. (f) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, 12, 312. (g) Dou, G.; Shi, C.; Shi, D. *J. Comb. Chem.* **2008**, 10, 810. (h) Hong, D.; Zhu, Y.; Li, Y.; Lin, X.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, 13, 4668.

(11) (a) Yan, R. L.; Luo, J.; Wang, C. X.; Ma, C. W.; Huang, G. S.; Liang, Y. M. *J. Org. Chem.* **2010**, 75, 5395. (b) Katritzky, A. R.; Huang, T. B.; Voronkov, M. V.; Wang, M.; Kolb, H. J. *Org. Chem.* **2000**, 65, 8819. (c) Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, 2, 2283. (d) Chiba, S.; Wang, Y. F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, 10, 313. (e) Wang, T.; Chen, X. L.; Chen, L.; Zhan, Z. P. *Org. Lett.* **2011**, 13, 3324. (f) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. *Org. Lett.* **2010**, 12, 4066. (g) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, 10, 2629.

(12) (a) Shi, C.; Wang, J.; Chen, H.; Shi, D. *J. Comb. Chem.* **2010**, 12, 430. (b) Chen, H.; Shi, D. *J. Comb. Chem.* **2010**, 12, 571. (c) Li, Y.; Chen, H.; Shi, C.; Shi, D.; Ji, S. *J. Comb. Chem.* **2010**, 12, 231. (d) Huang, Z.; Hu, Y.; Zhou, Y.; Shi, D. *ACS Comb. Sci.* **2011**, 13, 45. (e) Zou, Y.; Hu, Y.; Liu, H.; Shi, D. *ACS Comb. Sci.* **2012**, 14, 38. (f) Hu, Y.; Zou, Y.; Wu, H.; Shi, D. *Ultrason. Sonochem.* **2012**, 19, 264. (g) Chen, H.; Shi, D. *Tetrahedron* **2011**, 67, 5686.

yield only slightly (entry 2). Ethanol provided higher yields than did other organic solvents (compare entry 7 with entries 3–6), so ethanol was used as the solvent for all further reactions. When the reaction was carried out at room temperature, at 40 °C, at 60 °C, and at reflux temperature, **5aa** was obtained in yields of 17%, 43%, 66%, and 81% (entries 8–10 and 7), respectively. These experiments revealed that refluxing ethanol without any catalyst provided the highest yield.

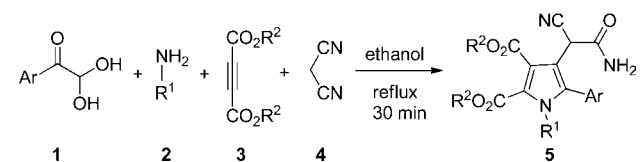
Using the optimal conditions, we investigated the substrate scope of the transformation (Table 2). Methoxy, methyl, chloro, and fluoro substituents on the phenylglyoxal ring and heteroaryl glyoxal ring as well as an *n*-butyl group and phenyl groups bearing either electron-withdrawing or -donating groups on the aniline ring were well tolerated under the reaction conditions and afforded the expected final products in satisfactory yields (up to 93%). However, when the methyl (or ethyl) 2-cyanoacetate was reacted with phenylglyoxal monohydrate, 4-methylaniline, and dimethyl but-2-ynedioate under the standard conditions, the desired products were not obtained.

To expand the scope of the current method, alkyl acetoacetate (**6**) was examined as a replacement for the dialkyl but-2-ynedioate (**3**). The desired polysubstituted pyrroles **7** were obtained with moderate yields (Table 3).

Recently, Alizadeh¹³ and Perumal¹⁴ reported the efficient syntheses of pyrroles and dihydropyridines via a one-pot

(13) Alizadeh, A.; Rezvanian, A.; Zhu, L.-G. *J. Org. Chem.* **2012**, 77, 4385.

(14) Kiruthika, S. E.; Lakshmi, N. V.; Banu, B. R.; Perumal, P. T. *Tetrahedron Lett.* **2011**, 52, 6508.

Table 2. Preparation of Polysubstituted Pyrroles **5**

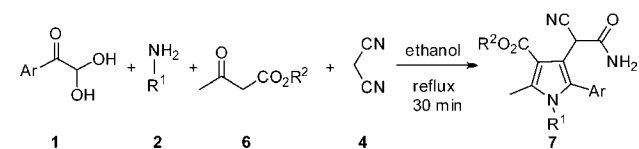
product	Ar	R ¹	R ²	isolated yield (%)
5aa	C ₆ H ₅	4-CH ₃ C ₆ H ₄	CH ₃	81
5ab	C ₆ H ₅	4-CH ₃ OC ₆ H ₄	CH ₃	83
5ac	C ₆ H ₅	4-(CH ₃) ₂ CHC ₆ H ₄	CH ₃	75
5ad	C ₆ H ₅	4-CH ₃ CH ₂ OC ₆ H ₄	CH ₃	88
5ae	C ₆ H ₅	C ₆ H ₅	CH ₃	76
5af	C ₆ H ₅	4-FC ₆ H ₄	CH ₃	84
5ag	C ₆ H ₅	4-ClC ₆ H ₄	CH ₃	73
5ah	C ₆ H ₅	4-BrC ₆ H ₄	CH ₃	81
5ai	C ₆ H ₅	4-NO ₂ C ₆ H ₄	CH ₃	67
5aj	C ₆ H ₅	3-ClC ₆ H ₄	CH ₃	64
5ak	C ₆ H ₅	3-Cl-4-CH ₃ C ₆ H ₃	CH ₃	73
5al	C ₆ H ₅	3,5-(CH ₃) ₂ C ₆ H ₃	CH ₃	75
5am	C ₆ H ₅	3,4-OCH ₂ OC ₆ H ₃	CH ₃	78
5an	C ₆ H ₅	4-CH ₃ CH ₂ OC ₆ H ₄	CH ₃ CH ₂	84
5ao	C ₆ H ₅	4-CH ₃ C ₆ H ₄	CH ₃ CH ₂	93
5ap	C ₆ H ₅	C ₆ H ₅	CH ₃ CH ₂	80
5aq	C ₆ H ₅	4-FC ₆ H ₄	CH ₃ CH ₂	82
5ar	C ₆ H ₅	4-ClC ₆ H ₄	CH ₃ CH ₂	76
5as	C ₆ H ₅	3-Cl-4-CH ₃ C ₆ H ₃	CH ₃ CH ₂	81
5at	C ₆ H ₅	3-CH ₃ C ₆ H ₄	CH ₃ CH ₂	75
5au	C ₆ H ₅	3-HOC ₆ H ₄	CH ₃ CH ₂	76
5av	C ₆ H ₅	4-FC ₆ H ₄ CH ₂	CH ₃ CH ₂	78
5aw	C ₆ H ₅	2,4-(CH ₃) ₂ C ₆ H ₃	CH ₃ CH ₂	74
5ax	C ₆ H ₅	2-CH ₃ CH ₂ C ₆ H ₄	CH ₃ CH ₂	70
5ay	C ₆ H ₅	CH ₃ CH ₂ CH ₂ CH ₂	CH ₃	72
5ba	4-CH ₃ OC ₆ H ₄	3,5-(CH ₃) ₂ C ₆ H ₃	CH ₃	73
5bb	4-CH ₃ OC ₆ H ₄	4-BrC ₆ H ₄	CH ₃	70
5ca	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	CH ₃	81
5cb	4-CH ₃ C ₆ H ₄	4-CH ₃ OC ₆ H ₄	CH ₃ CH ₂	85
5cc	4-CH ₃ C ₆ H ₄	4-FC ₆ H ₄	CH ₃ CH ₂	74
5da	4-FC ₆ H ₄	C ₆ H ₅	CH ₃ CH ₂	77
5db	4-FC ₆ H ₄	4-ClC ₆ H ₄	CH ₃ CH ₂	72
5ea	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	CH ₃	80
5eb	4-ClC ₆ H ₄	4-ClC ₆ H ₄	CH ₃	71
5fa	thiophen-2-yl	4-ClC ₆ H ₄	CH ₃	68

four-component reaction of ninhydrin or mono/di/triketone, malononitrile, primary amines, and dialkyl acetylenedicarboxylates under similar conditions. The divergent outcomes in the obtained products appear to derive from the nature of the 1,2-dicarbonyl substrate, where the first use of an “aldehydic” substrate is likely key toward obtaining the pyrrole products.

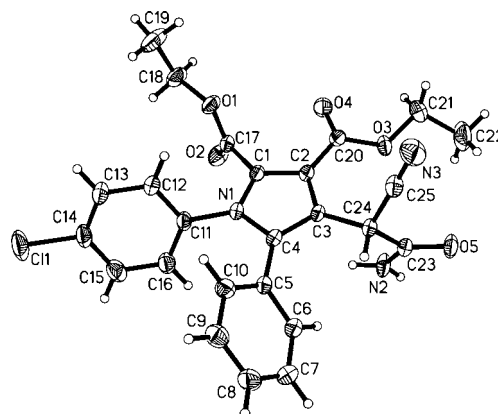
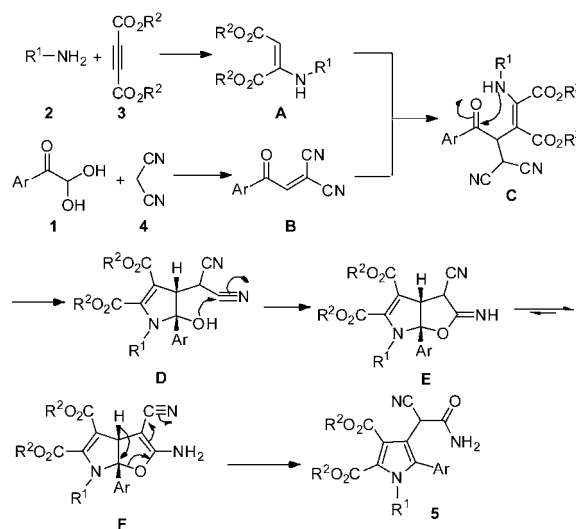
The structures of the products were determined by means of IR, ¹H NMR, ¹³C NMR, and HRMS. The structure of compound **5ar** was confirmed by X-ray analysis (Figure 1).

In accordance with reports from the literature,¹⁵ we propose the following mechanism for the reaction (Scheme 2).

(15) Shu, W. M.; Yang, Y.; Zhang, D. X.; Wu, L. M.; Zhu, Y. P.; Yin, G. D.; Wu, A. X. *Org. Lett.* **2013**, *15*, 456.

Table 3. Preparation of Polysubstituted Pyrroles **7**

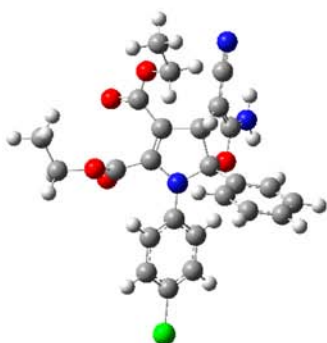
product	Ar	R ¹	R ²	isolated yield (%)
7a	C ₆ H ₅	4-CH ₃ C ₆ H ₄	CH ₃	79
7b	C ₆ H ₅	4-ClC ₆ H ₄	CH ₂ CH ₃	84

**Figure 1.** X-ray structure of compound **5ar**.**Scheme 2.** Proposed Mechanism of the Reaction

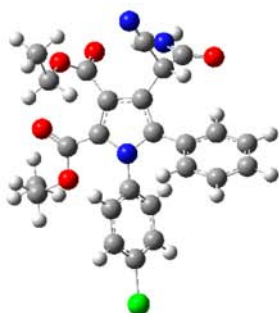
First, intermediate **A** is formed by the addition of the aniline to the dialkyl but-2-ynedioate; simultaneously, intermediate **B** is formed by means of a Knoevenagel condensation between the arylglyoxal monohydrate and



Intermediate **E**: $E = -1965.518871$ hartree



Intermediate **F**: $E = -1965.532094$ hartree



Product **5ar**: $E = -1965.582255$ hartree

Figure 2. Lowest energy minimum of intermediates **E**, **F** and product **5ar**.

malononitrile. Then, Michael addition of β -enamino ester **A** to intermediate **B** gives intermediate **C**, which

subsequently undergoes intramolecular nucleophilic addition to form intermediate **D**. Intramolecular cyclization of intermediate **D** then leads to the formation of intermediate **E**, which tautomerizes to more-stable intermediate **F**. In the last step, polysubstituted pyrrole **5** is formed by a ring-opening reaction of intermediate **F**.

The key reaction is the ring-opening of intermediate **F**, a 6,6a-dihydrofuro[2,3-*b*]pyrrole, to give **5**. A similar ring-opening reaction of a 3a,6a-dihydrofuro[2,3-*b*]furan catalyzed by HCl was reported by Shu et al.¹⁵ To evaluate the likelihood that this transformation occurred in our system, we carried out density functional theory calculations of the possible configurations of **E**, **F** and **5ar** at the B3LYP/6-31G level of theory. First, we optimized the geometries of three possible configurations and then calculated the lowest-energy minima of those configurations (Figure 2). We found that the most stable configuration of **5ar** was 166.41 and 131.69 kJ/mol lower in energy than the most stable configuration of intermediate **E** and **F**, respectively. This result suggests that intermediate **F** could be easily transformed to more stable product **5**.

In conclusion, we have developed a method for the facile, efficient synthesis of polysubstituted pyrroles by means of a novel four-component domino reaction. Using this method, we rapidly constructed a diverse collection of polysubstituted pyrroles in excellent yields simply by refluxing a mixture of an arylglyoxal monohydrate, an aniline, a dialkyl but-2-ynedioate or alkyl acetoacetate, and malononitrile in ethanol under catalyst-free conditions.

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Supporting Information Available. Experimental procedures; characterization, crystallographic data, and CIF file for the products. This materials is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.