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A straightforward one-pot multicomponent synthesis of polysubstituted pyrroles†

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Polysubstituted pyrroles were efficiently synthesized in moderate yields by a one-pot multicomponent reaction starting from primary amines, ethyl glyoxalate and 2-bromoacetophenones in the presence of pyridine in refluxing acetonitrile. This methodology was utilized to synthesize a highly substituted benz[*g*]indole.

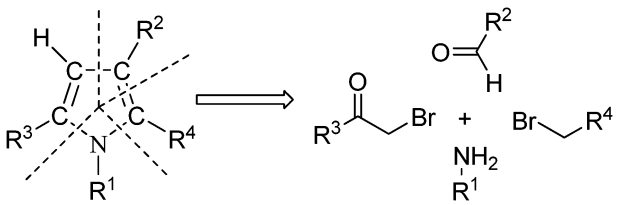
Pyrrole derivatives are an important class of organic compounds. They are structural units of many natural products and important pharmaceuticals and useful building blocks for various biologically active molecules and functional materials.[1] As the world's leading cholesterol-lowering drug, atorvastatin calcium (Lipitor) is a prime example.[2] Consequently, the construction of pyrrole rings bearing diverse substitution patterns has received much attention.[3] Conventional methods for the preparation of polysubstituted pyrroles include the Hantzsch and Paal–Knorr reactions.[4] A variety of transition-metal catalyzed strategies were also developed over the last decade.[5] Although the literature on pyrrole synthesis enjoys a rich history of versatile methodologies, new direct approaches remain highly valuable to the contemporary collection of synthetic strategies due to the continued importance of the pyrrole core in both biological and chemical fields.

Multicomponent reactions (MCRs) have emerged as a powerful strategy in organic, combinatorial, and medicinal chemistry.[6] Various MCRs have been developed not only for their facileness and efficiency, but also for their economy and ecology in organic synthesis.[7] These features make MCRs well-suited for the easy construction of diversified heterocyclic scaffolds.[8] Actually, MCRs have been demonstrated as a straightforward approach to pyrroles,[9] which have been extensively reviewed.[10] More recently, Parrain *et al.* developed the palladium and copper catalyzed synthesis of trisubstituted pyrroles *via* the MCR of 3,4-diiodoalk-2-enoic derivatives, primary amines, and terminal alkynes.[11] Zhu *et al.* reported a MCR/post-functionalization strategy for the synthesis of 2-amino-5-cyanopyrroles.[12] The functionalized pyrroles were also synthesised from 1,3-dicarbonyl compounds, amines, aldehydes, and nitroalkanes *via* an iron-catalyzed MCR.[13]

As part of our current studies on multicomponent synthesis of heterocycles,[14] we were interested in the straightforward construction of a 1,2,3,5-tetrasubstituted pyrrole ring *via* a four-component reaction (Scheme 1), involving the assembling of the pyrrole core from [2 + 1 + 1 + 1] atom fragments and the formation of four new bonds. We herein report the results of this effort.

Exhaustive studies of the reaction conditions for the synthesis of **4a** from *p*-methoxyphenyl amine (**1a**) with ethyl glyoxalate (**2**) and phenacyl bromide (**3a**) in the presence of pyridine were conducted (Table 1). It was found that aceto-nitrile was the most suitable solvent for this transformation among others, such as dichloroethane (DCE), THF and toluene (Table 1, entries 1–4). Then, we moved on to screen the reaction temperatures. Much lower yields were observed when the reaction temperature was decreased below reflux temperature (Table 1, entries 5 and 6). Furthermore, it was found that additives with 4 Å MS, TEA, DBU, DABCO and Na_2CO_3 were ineffective to improve the yield (Table 1, entries 7–11). Thus, the most suitable reaction conditions for the formation of **4a** were established (Table 1, entry 2). It is notable that the reaction proceeded smoothly without exclusion of moisture or air.

With the optimized reaction conditions in hand, we next explored the protocol with a variety of primary amines **1** and 2-bromoacetophenones **3** (Table 2). The primary aromatic amines reacted well, providing the pyrrole products in 42–64% yields (Table 2, entries 1–5). The electron-donating as well as electron-withdrawing groups on aromatic rings were tolerated, although the latter gave slightly reduced yields. In contrast, the reactions of aliphatic primary amines including cyclohexylamine (Table 2, entry 6), benzylamine (Table 2, entry 7) and *n*-butylamine (Table 2, entry 8) afforded the



Scheme 1 Multicomponent approach to pyrroles.

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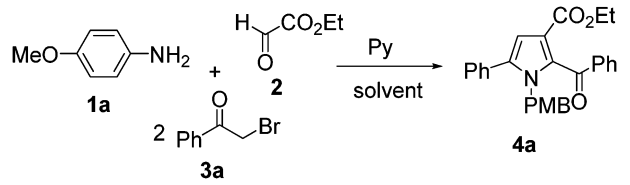
† Electronic supplementary information (ESI) available: Experimental procedure, ^1H and ^{13}C NMR spectra for all compounds. CCDC 798900 and 801307. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11363a.

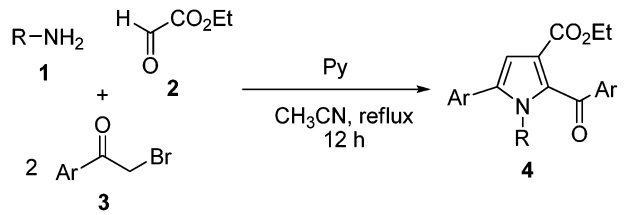
Table 1 Optimization of reaction conditions of the multicomponent reaction[a]



Entry	Solvent	Additive	T/°C	Time/h	Yield[b] (%)
1	DCE	—	Reflux	12	55
2	**CH_3CN**	—	**Reflux**	**12**	**64**
3	THF	—	Reflux	12	Trace
4	Toluene	—	Reflux	12	42
5	CH_3CN	—	50	24	33
6	CH_3CN	—	25	24	28
7[c]	CH_3CN	4 Å MS	Reflux	12	64
8[d]	CH_3CN	TEA	Reflux	12	30
9[d]	CH_3CN	DBU	Reflux	12	35
10[d]	CH_3CN	DABCO	Reflux	12	Trace
11[d]	CH_3CN	Na_2CO_3	Reflux	12	55

[a] All the reactions were carried out using **1a** (1 mmol), **2** (1 mmol), **3a** (2.2 mmol), and pyridine (5 mmol) in 5 mL of solvent. [b] Isolated yields. [c] 0.1 g of 4 Å MS was used. [d] Pyridine (3 mmol) and additive (2 mmol) were used.

Table 2 One-pot multicomponent reactions for the synthesis of pyrroles[a]



Entry	R	Ar	4	Yield[b] (%)
1	4-$MeOC_6H_4$ (**1a**)	Ph (**3a**)	**4a**	64
2	4-MeC_6H_4 (**1b**)	**3a**	**4b**	58
3	Ph (**1c**)	**3a**	**4c**	50
4	4-ClC_6H_4 (**1d**)	**3a**	**4d**	42
5	4-BrC_6H_4 (**1e**)	**3a**	**4e**	45
6	Cyclohexyl (**1f**)	**3a**	**4f**	35
7	Bn (**1g**)	**3a**	**4g**	38
8	*n*-Bu (**1h**)	**3a**	**4h**	28
9	**1a**	4-ClC_6H_4 (**3b**)	**4i**	70
10	**1b**	**3b**	**4j**	61
11	**1c**	**3b**	**4k**	52
12	**1d**	**3b**	**4l**	50
13	**1e**	**3b**	**4m**	48
14	**1g**	**3b**	**4n**	40
15	**1a**	4-MeC_6H_4 (**3c**)	**4o**	52
16	**1c**	**3c**	**4p**	48
17	**1e**	**3c**	**4q**	40
18	**1g**	**3c**	**4r**	32
19	**1a**	4-BrC_6H_4 (**3d**)	**4s**	55
20	**1d**	**3d**	**4t**	41

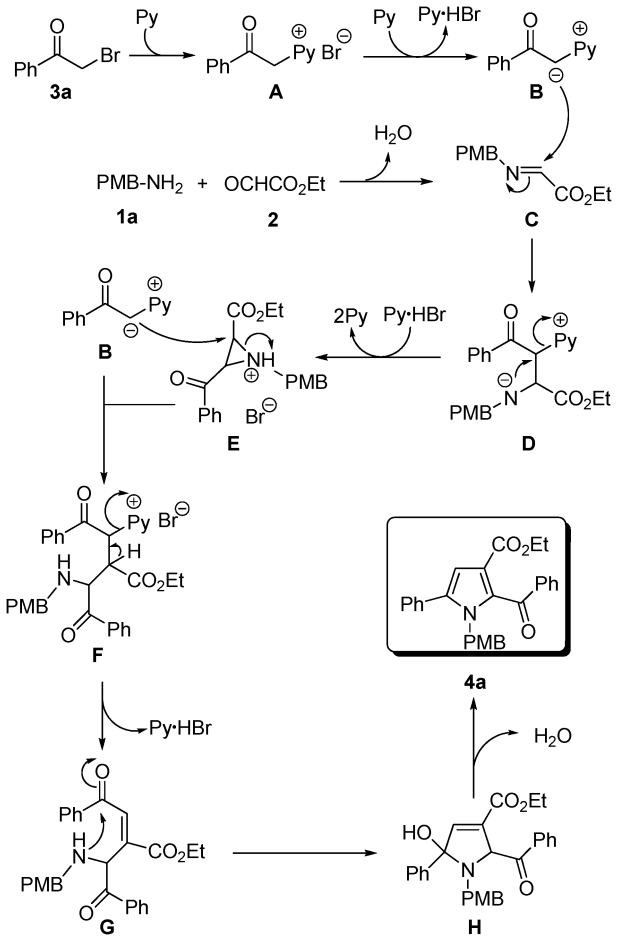
[a] All the reactions were carried out using **1** (1 mmol), **2** (1 mmol), **3** (2.2 mmol), and pyridine (5 mmol) in CH_3CN (5 mL). [b] Isolated yields.

desired products in lower yields (28–38%). On the other hand the 2-bromoacetophenone substrates **3** bearing either an electron-withdrawing group (Table 2, entries 9–14, 19 and 20) or an electron-donating group (Table 2, entries 15–18) on the aryl ring could smoothly afford the desired products in 32–70% yields.

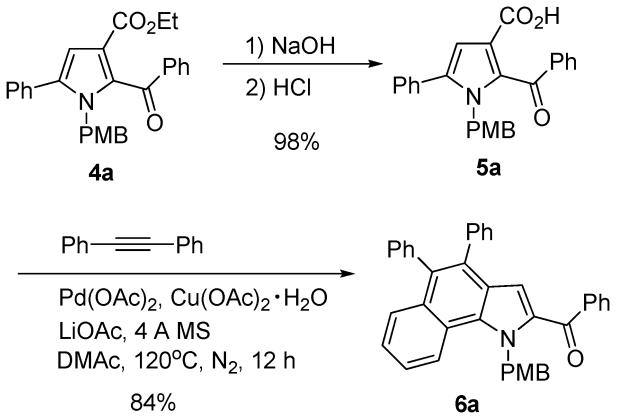
The structures of products **4a–4t** were characterized by ^{1}HNMR, ^{13}CNMR, IR, MS and HRMS spectra. The structure of compound **4a** (Table 2, entry 1) was unambiguously confirmed by single-crystal X-ray analysis.[15] The unusual structure feature for our products **4** is that the aroyl substituent is at the 2-position of the pyrrole ring, which is different from the products of the Hantzsch-type reaction.

A possible mechanism for this tandem reaction is postulated in Scheme 2. Firstly, phenacyl bromide **3a** reacts with pyridine, followed by deprotonation to form pyridinium ylide **B**, while imine **C** is *in situ* generated from amine **1a** and ethyl glyoxylate (**2**). Secondly, **B** nucleophilically attacks **C** *via* a Mannich addition, followed by an intramolecular nucleophilic substitution to form aziridinium bromide **E**. Then, **E** is attacked by **B** to form **F**. The resulting pyridinium salt **F** undergoes an elimination of pyridinium, followed by an intramolecular nucleophilic addition to yield dihydropyrrole **H**. Finally, dehydration of **H** affords pyrrole **4a**.

One interesting application of this methodology is the ready access to a new benz[*g*]indole derivative. A demonstration of the synthetic utility for this method is shown in Scheme 3. Thus, treatment of **5a** (1.0 eq.), which was derived by the hydrolysis of pyrrole **4a**, with 1,2-diphenylethyne (1.2 eq.) in



Scheme 2 Proposed mechanism for the synthesis of pyrrole.



Scheme 3 Concise synthesis of a highly substituted benz[*g*]indole.

the presence of $Pd(OAc)_2$ (0.05 eq.), $Cu(OAc)_2{\cdot}H_2O$ (2.0 eq.), LiOAc (4.0 eq.), and 4 Å molecular sieves in DMAc afforded benz[*g*]indole **6a**[16] in 84% yield. The reaction is proposed to proceed *via* a palladium-catalyzed oxidative decarboxylative coupling reaction of **5a** with 1,2-diphenylethyne.[17] This cascade approach to highly substituted benz[*g*]indoles is concise and efficient, and the product is a potentially useful scaffold for the synthesis of biologically active compounds and photophysical materials.

In conclusion, we have developed a one-pot synthesis of polysubstituted pyrroles *via* the multicomponent reaction of primary amines, ethyl glyoxalate and 2-bromoacetophenones. The reaction involves the assembling of [2 + 1 + 1 + 1] atom fragments and the formation of four new bonds. The starting materials are readily available. By combining with a palladium-catalyzed oxidative decarboxylative coupling reaction, this chemistry provides a rapid access to a highly substituted benz[*g*]indole.

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Notes and references

1 (*a*) R. A. Jones, *Pyrroles, Part II*, Wiley, New York, 1992; (*b*) B. A. Trofimov, L. N. Sobenina, A. P. Demenev and A. I. Mikhaleva, *Chem. Rev.*, 2004, **104**, 2481; (*c*) F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213.

2 R. B. Thompson, *FASEB J.*, 2001, **15**, 1671.

3 (*a*) D. St. C. Black and G. Maas, *Science of Synthesis*, Georg Thieme Verlag, Stuttgart, New York, 2001, vol. 9, p. 441; (*b*) A. Jones and G. P. Bean, *The Chemistry of Pyrroles*, Academic Press, London, 1977.

4 (*a*) A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474; (*b*) L. Knorr, *Ber.*, 1884, **17**, 1635; (*c*) C. Paal, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367.

5 (*a*) S. Rakshit, F. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9585; (*b*) Y. Wang, X. Bi, D. Li, P. Liao, Y. Wang, J. Yang, Q. Zhang and Q. Liu, *Chem. Commun.*, 2011, **47**, 809; (*c*) Y. C. Wong, K. Parthasarathy and C. Cheng, *J. Am. Chem. Soc.*, 2009, **131**, 18252; (*d*) A. Saito, T. Konishi and Y. Hanzawa, *Org. Lett.*, 2010, **12**, 372; (*e*) S. Aggarwal and H.-J. Knölker, *Org. Biomol. Chem.*, 2004, **2**, 3060; (*f*) R. Dhawan and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2004, **126**, 468; (*g*) A. Mizuno, H. Kusama and N. Iwasawa, *Angew. Chem., Int. Ed.*, 2009, **48**, 8318; (*h*) V. Cadierno, J. Gimeno and N. Nebra, *Chem.–Eur. J.*, 2007, **13**, 9973; (*i*) R. Martin, M. R. Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079; (*j*) X. Liu, L. Huang, F. Zheng and Z. Zhan, *Adv. Synth. Catal.*, 2008, **350**, 2778; (*k*) L. Lu, G. Chen and S. Ma, *Org. Lett.*, 2006, **8**, 835; (*l*) S. Zhang, X. Sun, W.-X. Zhang and Z. Xi, *Chem.–Eur. J.*, 2009, **15**, 12608; (*m*) A. S. Demir, M. Emrullahoglu and G. Ardahan, *Tetrahedron*, 2007, **63**, 461; (*n*) S. Rivera, D. Bandyopadhyay and B. K. Banik, *Tetrahedron Lett.*, 2009, **50**, 5445; (*o*) T. Sasada, T. Sawada, R. Ikeda, N. Sakai and T. Konakahara, *Eur. J. Org. Chem.*, 2010, 4237.

6 (*a*) J. Zhu and H. Bienayme, *Multicomponent Reactions*, Wiley-VCH, Weinheim, Germany, 2005; (*b*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (*c*) D. Tejedor and F. Garcia-Tellado, *Chem. Soc. Rev.*, 2007, **36**, 484; (*d*) D. J. Ramon and Y. Miguel, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602.

7 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471; B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259; (*b*) J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*c*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; A. J. Wangelin, H. Neumann, D. Gordes, S. Klaus, D. Strcubing and M. Beller, *Chem.–Eur. J.*, 2003, **9**, 4286.

8 (*a*) J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133; (*b*) B. Willy and T. J. J. Muller, *Curr. Org. Chem.*, 2009, **13**, 1777; (*c*) B. Davide, R. Rosario and L. Rodolfo, *Curr. Org. Chem.*, 2010, **14**, 332; (*d*) B. Jiang, T. Rajale, W. Wever, S. Tu and G. Li, *Chem.–Asian J.*, 2010, **5**, 2318.

9 (*a*) H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1998, **63**, 6234; (*b*) R. U. Braun, K. Zeitler and T. J. J. Muller, *Org. Lett.*, 2001, **3**, 3297; (*c*) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. D. Milton, M. Hidai and S. Uemura, *Angew. Chem., Int. Ed.*, 2003, **42**, 2681; (*d*) R. Dhawan and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2004, **126**, 468; (*e*) C. V. Galliford and K. A. Scheidt, *J. Org. Chem.*, 2007, **72**, 1811; (*f*) V. Cadierno, J. Gimeno and N. Nebra, *Chem.–Eur. J.*, 2007, **13**, 9973; (*g*) D. K. St. Cyr and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2007, **129**, 12366; (*h*) V. Nair, A. U. Vinod and C. Rajesh, *J. Org. Chem.*, 2001, **66**, 4427; (*i*) M. Morin, D. J. St-Cyr and B. A. Arndtsen, *Org. Lett.*, 2010, **12**, 4916.

10 V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402.

11 S. Lamande-Langle, M. Abarbri, J. Thibonnet, A. Duchene and J. Parrain, *Chem. Commun.*, 2010, **46**, 5157.

12 P. Fontaine, G. Masson and J. Zhu, *Org. Lett.*, 2009, **11**, 1555.

13 S. Maiti, S. Biswas and U. Jana, *J. Org. Chem.*, 2010, **75**, 1674.

14 (*a*) S. L. Cui, X. F. Lin and Y. G. Wang, *Org. Lett.*, 2006, **8**, 4517; (*b*) Y. G. Wang, S. L. Cui and X. F. Lin, *Org. Lett.*, 2006, **8**, 1241; (*c*) S. L. Cui, J. Wang, X. F. Lin and Y. G. Wang, *J. Org. Chem.*, 2007, **72**, 7779; (*d*) S. L. Cui, J. Wang, X. F. Lin and Y. G. Wang, *Org. Lett.*, 2007, **9**, 5023; (*e*) S. L. Cui, J. Wang and Y. G. Wang, *J. Am. Chem. Soc.*, 2008, **130**, 13526; (*f*) W. Lu, W. Song, D. Hong, P. Lu and Y. G. Wang, *Adv. Synth. Catal.*, 2009, **351**, 1768; (*g*) H. Jin, X. Xu, J. Gao, J. Zhong and Y. G. Wang, *Adv. Synth. Catal.*, 2010, **352**, 347.

15 CCDC 798900†.

16 The structure of compound **6a** was unambiguously confirmed by single-crystal X-ray analysis. CCDC 801307†.

17 For a proposed formation mechanism for the synthesis of benz-[*g*]indole **6a** please see the ESI†; (*a*) R. C. Larock and Q. Tian, *J. Org. Chem.*, 2001, **66**, 7372; (*b*) M. Yamashita, H. Horiguchi, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 7481.

