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One-pot metal-free synthesis of highly substituted pyrroles from 2-acetyl-3-methylene-1,4-dicarbonyl compounds and primary amines *via* TBHP and activated carbon oxidative aromatization of dihydropyrrole†

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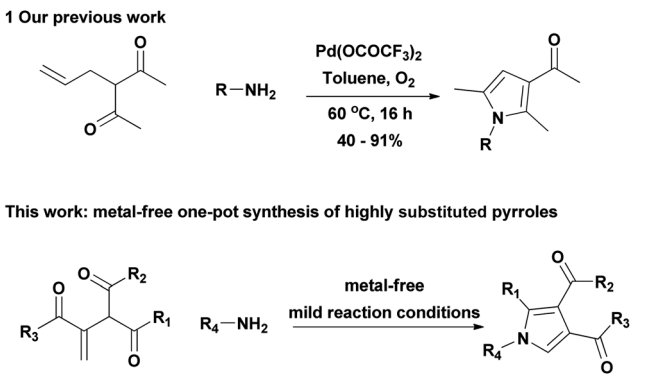
A metal-free one-pot cascade process for the synthesis of 1,2,3,4-tetrasubstituted pyrroles *via* a tandem enamine, aza-Michael addition and TBHP, activated carbon oxidative aromatization is reported. This strategy features the formation of two C–N bonds in moderate to excellent yields and a broad substrate tolerance.

Polysubstituted pyrroles are an important class of nitrogen-containing heterocyclic compounds exhibiting a broad spectrum of biological properties such as antitumor,[1] anti-inflammatory[2] and antibacterial[3] in numerous bioactive natural products[4] and pharmaceuticals.[5] Therefore, considerable efforts have focused on the development of synthetic methods to obtain these valuable compounds. Generally, the classical methods include the Knorr,[6] Paal-knorr[7] and Hantzsch[8] reactions in a multistep process from preformed intermediates. Recently, many novel synthetic approaches catalyzed by transition-metal have been reported.[9] For example, we have reported $Pd(OCOCF_3)_2$ catalyzed-cascade reaction of 2-alkenal-1,3-dicarbonyl compounds with primary amines to synthesize 1,2,3,5-tetrasubstituted pyrroles in moderate to excellent yields (Scheme 1).[9a] Beller's group has disclosed ruthenium catalyzed ketones, amines and vicinal diols into pyrroles in high temperature using borrowing hydrogen method.[9b] However, metal-free mediated approaches may be less explored compared to transition-metal catalyzed systems in recent years.[10] As the majority of transition-metal-catalyzed methods suffered from the employment of precious, toxic transition-metal catalysts, harsh reaction conditions and even in some cases the N-containing components must be preactivated,[9f–h] thus, developing a new synthetic approach obviating employment of transition-metal catalysts from commercially accessible amines under mild conditions is highly attractive. Toward this end, we developed a metal-free and highly efficient strategy to synthesis of 1,2,3,4-tetrasubstituted pyrroles using *tert*-butyl hydroperoxide and activated carbon as oxidative system *via* a tandem enamine, aza-Michael addition and oxidative aromatization at ambient conditions. The protocol provides a potential route for the synthesis of tetrasubstituted pyrroles in moderate to excellent yields.

Initially, 3-acetyl-4-methylenehexane-2,5-dione **1a** and aniline **2a** were selected as the model substrates to explore the optimal reaction conditions for the synthesis of highly substituted pyrrole **3a**. As shown in Table 1, a variety of different solvents were screened for their effect on the production of compound **3a**. We observed that the reaction was stirred in toluene for 18 h at room temperature in the presence of TBHP to afford the targeting product **3a** with 78% yield whereas other solvents such as DMF, $CHCl_3$, THF gave the desired product in 45–62% yields (entries 1–4). Some other oxidants were probed instead of TBHP for further improving the reaction yield. The results showed that only 62% and 35% yields of the desired product **3a** was obtained when $K_2S_2O_8$ and MCPBA were used as oxidants respectively (entries 5 and 6). While, no targeted



Scheme 1 Transition-metal-catalyzed and metal-free mediated synthesis of pyrroles.

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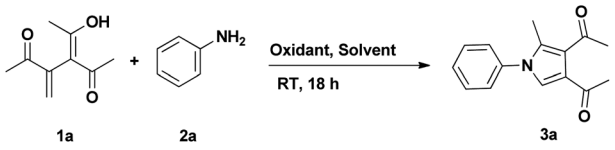
Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

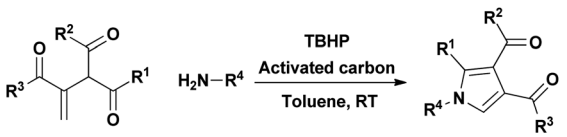
Entry	Solvent	Oxidant	Yield[b] (%)
1	DMF	TBHP	45
2	$CHCl_3$	TBHP	62
3	THF	TBHP	51
4	Toluene	TBHP	78
5	Toluene	$K_2S_2O_8$	62
6	Toluene	MCPBA	35
7	Toluene	$PhI(OAc)_2$	NP[d]
8	Toluene	DDQ	NP[d]
9	Toluene	H_2O_2	NP[d]
10	Toluene	Air	65
11[c]	Toluene	Activated carbon	76
12[c]	Toluene	TBHP + activated carbon	93

[a] A mixture of **1a** (0.25 mmol), **2a** (0.5 mmol) and oxidant (150 μL of 5.5 M TBHP in decane solution or 0.75 mmol for the other ones) in solvent (1 mL) was stirred at room temperature for 18 h. [b] Isolated yield. [c] 36 mg activated carbon was added to the reaction. [d] NP indicated that no desired product **3a** was obtained.

products were obtained by employing $PhI(OAc)_2$, DDQ and H_2O_2 as oxidants respectively (entries 7–9). Treatment of **1a** and **2a** in toluene under air atmosphere as the sole oxidant gave the product **3a** in good yield (65%, entry 10) which facilitated the reaction operation without degas procedure. When activated carbon was involved as the oxidant instead of TBHP, the product **3a** was formed in 76% yield (entry 11) indicating the activated carbon is a highly effective oxidant for this transformation.[11] Therefore, we further explored the combined oxidative system of activated carbon and TBHP, the reaction yield dramatically increased to 93%. In this way, the optimal reaction condition was identified using activated carbon and TBHP as the oxidant system in toluene at room temperature for 18 h.

With the optimal reaction conditions in hand, we then surveyed the scope of this approach to synthesize a wide range of pyrroles derivatives **3** (Table 2). We firstly utilized substrate **1a** to test the reactivity of various amines. The results showed that this protocol was compatible with significant structurally various amines. The substitution pattern of the methyl and ethyl groups on the phenyl ring has a very limited impact (**3b–d**, entries 2–4). With two substituents on the phenyl rings such as 2-naphthalenamine, 3,4-dimethylaniline, 2,4-dimethylaniline, 2-methyl-4-fluoroaniline were suitable for this protocol as illustrated by providing the pyrrole products **3f–i** in good to excellent yields (75–93%, entries 6–9). However, the anilines bearing strong electron-donating groups such as methoxyl, methylenedioxyl on the phenyl rings underwent reaction to afford the targeting product **3e** and **3j** in good yields only when the reaction was performed at −20 °C temperature. The probable reason was attributed to the electronic effect. This explanation was proved

Table 2 The scope of TBHP and activate carbon oxidative aromatization synthesis of pyrroles **3**[a]



1 2 3

Entry	R^1, R^2, R^3, R^4, **3**	Yield[b] (%)
1	CH_3, CH_3, CH_3, Ph, **3a**	93
2	CH_3, CH_3, CH_3, 3-EtPh, **3b**	80
3	CH_3, CH_3, CH_3, 4-MePh, **3c**	80
4	CH_3, CH_3, CH_3, 2-MePh, **3d**	85
5[c]	CH_3, CH_3, CH_3,4-MeOPh, **3e**	80
6	CH_3, CH_3, CH_3, 2-naphthyl, **3f**	78
7	CH_3, CH_3, CH_3, 3,4-Me_2Ph, **3g**	75
8	CH_3, CH_3, CH_3, 2,4-Me_2Ph, **3h**	85
9	CH_3, CH_3, CH_3, 2-Me-4-FPh, **3i**	93
10[c]	CH_3, CH_3, CH_3, 3,4-OCH_2OPh, **3j**	52
11	CH_3, CH_3, CH_3, 4-BrPh, **3k**	80
12	CH_3, CH_3, CH_3, 3-ethynylPh, **3l**	76
13	CH_3, CH_3, CH_3, 3-ClPh, **3m**	80
14	CH_3, CH_3, CH_3, 4-$COOCH_2CH_3$Ph, **3n**	50
15	CH_3, CH_3, CH_3, 4-$NHCOCH_3$Ph, **3o**	70
16	CH_3, CH_3, CH_3, 4-NH_2Ph, **3p**	56
17	CH_3, CH_3, CH_3, 3,4-ClPh, **3q**	62
18	CH_3, CH_3, CH_3, 4-NO_2Ph, **3r**	0
19	CH_3, CH_3, CH_3, isopentyl, **3s**	40
20	CH_3, CH_3, CH_3, Bn, **3t**	46
21	CH_3, CH_3, CH_3, *n*-Bu, **3u**	32
22	CH_3, CH_3, CH_3, allyl, **3v**	35
23	CH_3, CH_3, CH_3, 3-methoxy-propyl, **3w**	25
24	CH_3, CH_3, CH_3, isopropyl, **3x**	18
25	CH_3, CH_3, CH_3, *t*-Bu, **3y**	10
26	Et, Et, CH_3, Ph, **3z**	82
27	CH_3, Ph, CH_3, Ph, **3aa**	80
28	CH_3, OEt, CH_3, Ph, **3 ab**	76
29	CH_3, CH_3, Ph, Ph, **3ac**	80
30	CH_3, CH_3, OEt, Ph, **3ad**	30

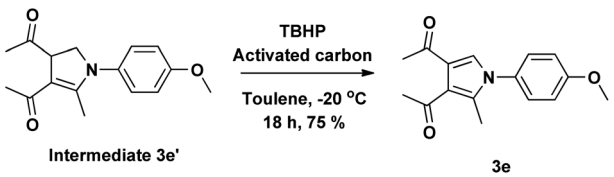
[a] A mixture of **1a** (0.25 mmol), **2a** (0.5 mmol), 150 μL TBHP (5.5 M in decane solution) and 36 mg activated carbon in toluene (1 mL) was stirred at room temperature overnight. [b] Isolated yield. [c] The reaction was conducted at −20 °C.

by the fact that 4-acetamidoaniline **2o** afforded the desired pyrrole in higher yield than the 1,4-diaminobenzene **2p** did under the same reaction conditions. Furthermore, as compared to 2-toluidine **2d**, the substrate **2i** possessing an additional electron-withdrawing group on the phenyl ring supported this explanation for providing the pyrrole **3i** in 93% yield (entry 9). A diverse range of functional groups such as bromo, chloro, ester, ethynyl, acetyl amino, amino on the anilines proceeded smoothly to yield the corresponding pyrrole derivatives **3k–q** in 56% to 80% yields. While, 4-nitroaniline couldn't afford the pyrrole due to the strong electron-withdrawing group reduced the nucelophilicity of the nitrogen of the aniline (**3r**, entry 18). In addition to aromatic amines, the reaction proceeded as expected when aliphatic amines were involved in the reaction (entries 19–25). The isopentyl, Bn, *n*-Bu, allyl, 3-methoxypropyl amines **2s–w**

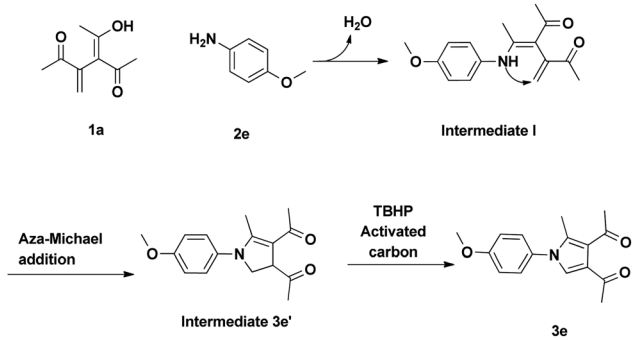
afforded the desired products in moderate yields (entries 19–23). While the more steric isopropyl and *t*-Bu amines gave the poor yields (entries 24–25). Futhermore, by-products were observed when aliphatic amines were involved.

To further expand the scope of the method, we probed several substrate **1** derivatives. The results implied that the more hindered substrate **1z** appeared to be a good candidate for this cascade reaction. Moreover, the variation of R_2 functionalities on **1** such as phenyl and ethoxyl groups could react with aniline **2a** to afford the structurally diverse pyrroles **3aa,ab** (entries 27 and 28). Furthermore, the substrate **1ac** offered the product **3ac** in good yield (80%, entry 29), while switching to substrate **1ad** lead to dramatically decrease in reaction yield under the same conditions. These observed results indicated that the ketone functional group promoted the formation of pyrroles more easily than ester did in this cascade reaction (**3ac** *vs.* **3ad**, entries 29 and 30).

To gain insight into the mechanism, 3-acetyl-4-methyl-enehexane-2,5-dione **1a** and *p*-anisidine **2e** were performed under N_2 atmosphere in the absence of TBHP and activated carbon, giving an intermediate followed by separation. ^{1}H NMR, ^{13}C NMR and HRESI spectrums confirmed the intermediate structure is **3e′**. Then the intermediate **3e′** was added to a mixture of TBHP and activated carbon in toluene under the optimal conditions to afford the desired pyrrole **3e** in 75% yield (Scheme 2). On the basis of the reaction outcomes, a plausible mechanism for synthesis of pyrroles **3** from substrates **1** and **2** is proposed in Scheme 3. Treatment of **1a** and **2e** in toluene at −20 °C generated the enamine intermediate **I** which was followed by intramolecular aza-Michael addition resulting in the formation of intermediate **3e′**. Then, the intermediate **3e′** was subjected to oxidized by TBHP and activated carbon to afford the final pyrrole product **3e**.[10k,l]



Scheme 2 Oxidative aromatization of 2,3-dihydropyrrole intermediate **3e′** to pyrrole **3e**.



Scheme 3 A proposed mechanism for the cascade reaction.

In conclusion, we have successfully developed an efficient metal-free mediated oxidative aromatization cascade approach for the one-pot synthesis of synthetically and biologically meaningful pyrroles. This approach features metal-free, milder reaction conditions, readily available reagents and afford the desired highly substituted pyrroles in cascade fashion in moderate to excellent yields for a diverse range of substrates.

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Notes and references

1 P. Cozzi and N. Mongelli, *Curr. Pharm. Des.*, 1998, **4**, 181.
2 V. Zoete, F. Maglia, M. Rougée and R. V. Bensasson, *Free Radical Biol. Med.*, 2000, **28**, 1638.
3 G. Daidone, B. Maggio and D. Schillari, *Pharmazie*, 1990, **45**, 441.
4 (*a*) I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, **27**, 1801; (*b*) H. Fan, J. G. Peng, M. T. Hamann and J. F. Hu, *Chem. Rev.*, 2008, **108**, 264; (*c*) B. M. Trost and G. B. Dong, *Org. Lett.*, 2007, **9**, 2357; (*d*) C. T. Walsh, S. Garneau-Tsodikova and A. R. Howard-Jones, *Nat. Prod. Rep.*, 2006, **23**, 517; (*e*) A. Grube and M. Koeck, *J. Nat. Prod.*, 2006, **69**, 1212; (*f*) C. Rochais, V. Lisowski, P. Dallemagne and S. Rault, *Bioorg. Med. Chem.*, 2006, **14**, 8162; (*g*) F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213; (*h*) P. Lewer, E. L. Chapin, P. R. Graupner, J. R. Gilbert and C. Peacock, *J. Nat. Prod.*, 2003, **66**, 143.
5 (*a*) Y. Arikawa, H. Nishida, O. Kurasawa, A. Hasuoka, K. Hirase, N. Inatomi, Y. Hori, J. Matsukawa, A. Imanishi, M. Kondo, N. Tarui, T. Hamada, T. Takagi, T. Takeuchi, M. Kajino, *et al.*, *J. Med. Chem.*, 2012, **55**, 4446; (*b*) G. La Regina, R. Silvestri, M. Artico, A. Lavecchia, E. Novellino, O. Befani, P. Turini and E. Agostinelli, *J. Med. Chem.*, 2007, **50**, 922; (*c*) S. Youssef, O. Stuve, S. S. Zamvil, *et al.*, *Nature*, 2002, **420**, 78; (*d*) R. B. Thompson, *FASEB J.*, 2001, **15**, 1671.
6 L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635.
7 C. Pall, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367.
8 A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474.
9 For recent examples of transition-metal-catalyzed pyrrole synthesis, see: (*a*) W. Yang, L. L. Huang, H. Liu, W. Wang and H. Li, *Chem. Commun.*, 2013, **49**, 4667; (*b*) M. Zhang, X. J. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384; (*c*) M. Zhang, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 597; (*d*) L. H. Wang and L. Ackermann, *Org. Lett.*, 2013, **15**, 176; (*e*) W. T. Teo, W. Rao, M. J. Koh and P. W. Chan, *J. Org. Chem.*, 2013, **78**, 7508; (*f*) Z. Z. Shi, M. Suri and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 4892; (*g*) L. K. Meng, K. Wu, C. Liu and A. W. Lei, *Chem. Commun.*, 2013, **49**, 5853; (*h*) Z. Y. Chen, B. L. Lu, Z. H. Ding, K. Gao and N. Yoshikai, *Org. Lett.*, 2013, **15**, 1966; (*i*) S. Y. Peng, L. Wang, J. Y. Huang, S. F. Sun, H. B. Guo and J. Wang, *Adv. Synth. Catal.*, 2013, **355**, 2550; (*j*) T. Miura, K. Hiraga, T. Biyajima, T. Nakamuro and M. Murakami, *Org. Lett.*, 2013, **15**, 3298;

(*k*) S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 140; (*l*) B. V. S. Reddy, M. R. Reddy, Y. G. Rao, J. S. Yadav and B. Sridhar, *Org. Lett.*, 2013, **15**, 464; (*m*) G. Lonzi and L. A. López, *Adv. Synth. Catal.*, 2013, **355**, 1948; (*n*) J. Ke, C. He, H. Y. Liu, M. J. Li and A. W. Lei, *Chem. Commun.*, 2013, **49**, 7549; (*o*) M. Zhao, F. Wang and X. W. Li, *Org. Lett.*, 2012, **14**, 1412; (*p*) Y. J. Jiang, W. C. Chan and C.-M. Park, *J. Am. Chem. Soc.*, 2012, **134**, 4104; (*q*) C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Y. Chen and A. W. Lei, *J. Am. Chem. Soc.*, 2012, **134**, 5766; (*r*) B. M. Trost, J. P. Lumb and J. M. Azzarelli, *J. Am. Chem. Soc.*, 2011, **133**, 740; (*s*) M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, *Angew. Chem., Int. Ed.*, 2011, **50**, 1338; (*t*) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127.

10 For recent examples of metal-free mediated pyrrole synthesis, see: (*a*) F. Tripoteau, L. Eberlin, M. A. Fox, B. Carboni and A. Whiting, *Chem. Commun.*, 2013, **49**, 5414; (*b*) Y. C. Hu, C. X. Wang, D. P. Wang, F. Wu and B. S. Wan, *Org. Lett.*, 2013, **15**, 3146; (*c*) T. Maehara, R. Kanno, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2012, **14**, 1946; (*d*) I. Kumar, N. A. Mir, P. Ramaraju and B. P. Wakhloo, *RSC Adv.*, 2012, **2**, 8922; (*e*) K. Ramesh, S. N. Murthy, K. Karnakar and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 3937; (*f*) B. Das, N. Bhunia and M. Lingaiah, *Synthesis*, 2011, 3471; (*g*) M. Rueping and A. Parra, *Org. Lett.*, 2010, **12**, 5281; (*h*) J. Y. Wang, X. P. Wang, Z. S. Yu and W. Yu, *Adv. Synth. Catal.*, 2009, **351**, 2063; (*i*) Y. Lu and B. A. Arndtsen, *Org. Lett.*, 2009, **11**, 1369; (*j*) D. J. St. Cyr and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2007, **129**, 12366; (*k*) Y. J. Li, H. M. Huang, H. Q. Dong, J. H. Jia, L. Han, Q. Ye and J. R. Gao, *J. Org. Chem.*, 2013, **78**, 9424; (*l*) G. Bharathiraja, S. Sakthivel, M. Sengoden and T. Punniyamurthy, *Org. Lett.*, 2013, **15**, 4996.

11 For selected examples ofactivated carbon oxidative aromatization, see: (*a*) M. Hayashi, K. Okunaga, S. Nishida, K. Kawamura and K. Eda, *Tetrahedron Lett.*, 2010, **51**, 6734; (*b*) Y. Kawashita and M. Hayashi, *Molecules*, 2009, **14**, 3073; (*c*) K.-I. Okunaga, Y. Nomura, K. Kawamura, N. Nakamichi, K. Eda and M. Hayashi, *Heterocycles*, 2008, **76**, 715; (*d*) S. Haneda, A. Okui, C. Ueba and M. Hayashi, *Tetrahedron*, 2007, **63**, 2414; (*e*) Y. Kawashita, N. Nakamichi, H. Kawabata and M. Hayashi, *Org. Lett.*, 2003, **5**, 3713.

