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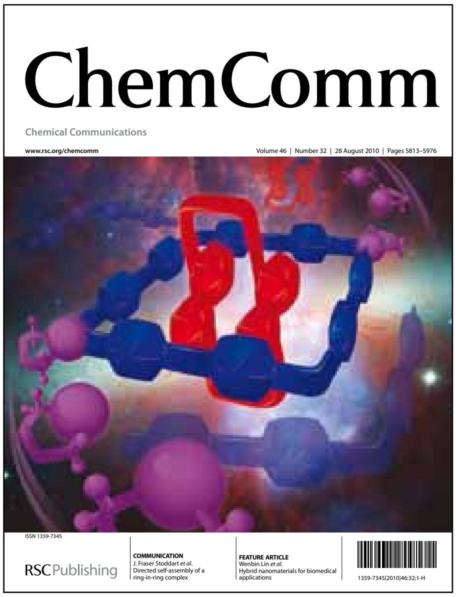

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ARTICLE TYPE

“One pot” regiospecific synthesis of polysubstituted pyrroles from benzylamines and ynones under metal free conditions

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A convenient “one-pot” weak base-promoted synthesis of polysubstituted pyrroles has been developed from benzylamines and ynones. This transformation involves Micheal addition reaction and intramolecular condensation, which features with high regioselectivity, high efficiency, environmental friendliness and metal free. Series of polysubstituted pyrroles were provided in up to 91% yield for 27 examples.

Introduction

Substituted pyrrole is a privileged heretocycle and key skeleton in many natural products, such as hemoglobin, vitamin B_{12}, chlorophylls, lukianols and tetrapentalones. Moreover, they exist widely in pharmaceuticals (e. g. Atorvastatin), agrochemicals (e. g. Fludioxonil) and novel advanced materials (e. g. Polypyrrole) (Figure 1).[1] Thus, great efforts have been devoted to construct such a structure.

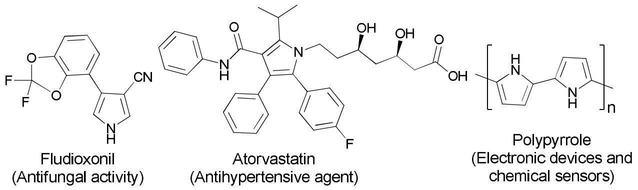
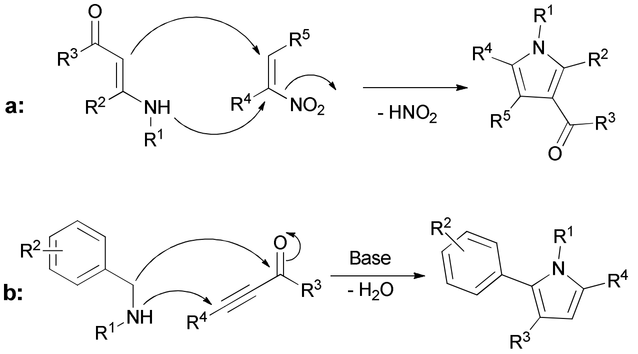


Figure 1. Three examples illustrating the importance of pyrrole skeleton

The Knorr,[2] Paal-Knorr[3] and Hantzch[4] reactions are well-documented as the traditional methods to build pyrrole rings. Recently, transition metal catalyzed cyclizations[5] and multicomponent tandem coupling reactions[6] have become increasingly popular due to their high efficiency. For example, Liang[5c] reported a Cu(I) catalyzed synthesis of polysubstituted pyrroles from oxidative cyclization of enaminones and alkynoates; Glorius[5j] described an aerobic synthesis of pyrroles from imines by Pd(II)-catalyzed intramolecular C-H activation; Milstein[5k] developed a direct protocol to pyrroles by Ru-catalyzed dehydrogenative coupling reaction of β-aminoalcohols with secondary alcohols. However, the less expensive and more available substrates are limited in most cases. And the transition metals are requried, which causes potential contamination of the products, that is particularly significant in the pharmaceutical industry[7].

Recently, some impressive procedures to pyrroles starting from halogenated nitroolefins or nitroolefins and enaminones under metal free conditions have emerged.[8] For instance, Rueping,[8a] Guan[8b] and Palmieri[8c] have independently reported the synthesis of polysubstituted pyrroles from nitroolefins and enaminones without metal catalyst. Nitroolefin acted as a binucleophilic synthon in these reactions and produced HNO_2 as waste (**a**, Scheme 1). In terms of green chemistry, an environmentally friendly route to pyrroles with atom economy becomes highly desired. We envision that a simple and versatile procesure to pyrrole derivatives from benzylamines and α,β- unsaturated ynones could be developed since α,β-unsaturated yones are bielectrophilic[9] and Micheal addition reaction of benzylamines with α,β- unsaturated ynones and base-catalyzed condensation of resultant *N*-benzyl enaminones can be combined in one pot operation. In our continuing effort to develop heterocycle-forming protocols[10], herein, we report a weak base-promoted “one-pot” synthesis of polysubstituted pyrroles from benzylamines and ynones, which avoides transition metal as catalyst under mild reaction conditions. Moreover, high atom economy could be realized since only H_2O was procucted as a byporduct (**b**, Scheme 1).



Scheme 1. Synthesis of pyrroles from nitroolefins (**a**) and ynones (**b**) which serve as a bielectrophilic synthon.

We initially chose (Z)-3-(benzylamino)-1,3-diphenylprop-2-en-1-one **1aa** as a model substate to optimize the reaction parameters. The solution of potassium hydroxide in DMSO was recently reported as a “super base” in some base-promoted

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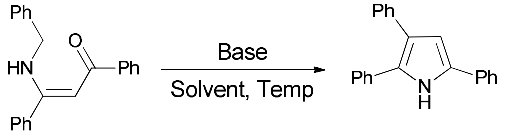
reactions.[11] To our delight, 2,3,5-triphenyl-1*H*-pyrrole **4aa** was obtained in 51% yield in such a "super base" system under air (entry 1). The yield of **4aa** could increase to 67% when the reaction was carried out under N_2 atmosphere (entry 2). Then other DMSO-tailored heterogeneous base systems were tested. Combination of K_3PO_4/DMSO was found to be the most efficient for this transformation at 120 ºC under N_2 atmosphere (entries 3-8). Organic bases were also tested, such as Et_3N and DABCO. No desired products were observed (entries 9-10). The yields were slightly decreased using DMF or NMP as a solvent (entries 11-12). No product was observed in toluene, 1,4-dioxane, H_2O and t-amyl alcohol (entries 13-16). 91% Yield could be achieved when the reaction temperature was increased to 140 ºC (entry 17). Interestingly, considerable yields (78% and 84%) was obtained when 20 mol% K_3PO_4 and 50 mol% K_3PO_4 was loaded (entries 18-19). As (Z)-3-(Benzylamino)-1,3- diphenylprop-2-en-1-one **3** could be easily obtained from benzylamine and 1,3-diphenylprop-2-yn-1-one, we attempted "one pot" tandem reaction starting from benzylamine and 1,3-diphenylprop-2-yn-1-one (see supporting information). Fortunately, the overall yield of the transformation was remarkable (88%, entry 20). In terms of green chemistry and atom economy, "one-pot" operation using benzylamines and ynones as substrates was adopted.

Table 1 Screening reaction parameters for the cyclization [a]



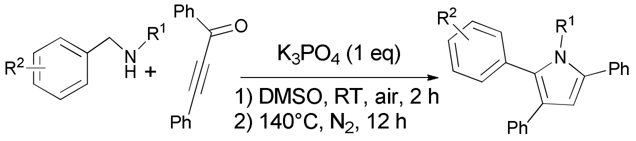
1aa **4aa**

Entry	Base	Solvent	Temperature (ºC)	Yield [b] (%)
1 [c]	KOH	DMSO	120	51
2	KOH	DMSO	120	57
3	NaOH	DMSO	120	54
4	KOtBu	DMSO	120	trace
5	NaOEt	DMSO	120	75
6	Cs_2CO_3	DMSO	120	68
7	K_3PO_4	DMSO	120	84
8	K_2HPO_4	DMSO	120	no reaction
9	Et_3N	DMSO	120	0
10	DABCO	DMSO	120	0
11	K_3PO_4	DMF	120	78
12	K_3PO_4	NMP	120	72
13	K_3PO_4	PhMe	120	no reaction
14	K_3PO_4	Dioxane	120	no reaction
15	K_3PO_4	H_2O	100	no reaction
16	K_3PO_4	t-amyl alcohol	100	no reaction
17	**K_3PO_4**	**DMSO**	**140**	**91**
18 [d]	K_3PO_4	DMSO	140	78
19 [e]	K_3PO_4	DMSO	140	84
20 [f]	**K_3PO_4**	**DMSO**	**140**	**88**

[a] Reaction conditions: **1aa** (0.5 mmol), base (0.5 mmol) and solvent (2.0 mL) under N_2 atmosphere. [b] Isolated yield based on **1aa**. [c] Under air. [d] 0.2 eq K_3PO_4 was used. [e] 0.5 eq K_3PO_4 was used. [f] Benzylamine and 1,3-diphenylprop-2-yn-1-one as substrates.

With the optimized reaction conditions in the hand (1 equiv of K_3PO_4, DMSO as base and solvent, respectively, at 140 ºC), we subsequently investigated the substrate scope of this "one-pot" transformation. The results of the reaction of 1,3-diphenylprop-2-yn-1-one **3a** with various benzylamines **2a-2j** were summarized in Table 2. Benzylamines with both electron-withdrawing and electron-donating groups, such as methyl, methoxy, *tert*-butyl, chloro, trifluoromethyl and 3,4-dimethoxy groups, afforded the corresponding 2,3,5-triarylpyrroles in appreciable yields (75-88 %, Table 2, entries 1-8). This reaction system was also applied to *N*-alkyl benzylamines. The efficiency was effected by the steric hindrance. *N*-Methyl benzylamine gave higher yield (91%) than *N*-*n*butyl benzylamine (55%) (entry 9 *vs* 10). However, *N*-*n*butyl enaminone could give 80% yield under the same reaction conditions. The *N*-aryl benzylamines was limited to this transformation. These results indicated that the large bulk and low electron-density in N atom disfavored the Micheal addition reaction. n-Butylamine, allylamine, propargylamine, 1-aminopropan-2-one and amino acid ester were tested and failed to give the corresponding pyrrole products under the standard reaction conditions.

Table 2 Reaction of 1,3-diphenylprop-2-yn-1-one **3a** with various benzylamines **2a-2j**[a]



2a-2j **3a** **4aa-4ja**

Entry	*2*	*R*[1]	*R*[2]	*4*	*Yield(%)*[b]
1	**2a**	H	H	**4aa**	88
2	**2b**	H	4-Me	**4ba**	82
3	**2c**	H	2-Me	**4ca**	84
4	**2d**	H	4-OMe	**4da**	75
5	**2e**	H	4-tBu	**4ea**	81
6	**2f**	H	4-Cl	**4fa**	85
7	**2g**	H	$4\text{-}CF_3$	**4ga**	79
8	**2h**	H	3,4-OMe	**4ha**	82
9	**2i**	Me	H	**4ia**	91
10	**2j**	nBu	H	**4ja**	55[c]

[a] Reaction condition: Benzylamines **2a-2j** (1 mmol), 1,3-diphenylprop-2-yn-1-one **3a** (1 mmol), K_3PO_4 (1 mmol) and DMSO (2.0 mL) at a 140 ºC under N_2 atmosphere. [b] Isolated yields based on 1,3-diphenylprop-2-yn-1-one **3a**. [c] 80% yield was obtained from corresponding *N*-*n*Butyl enaminone.

The scope of ynones **3** was investigated as well. As shown in Table 3, both of the electron-donating and electron-withdrawing groups on the 1-aryl ring of the 1,3-diarylpropynones were well tolerated and provided the corresponding pyrroles in desirable yields (64-89%, entries 1-6). Moreover, steric hindrance did not influence the transformation obviously (entry 1 *vs* 2). When R^3 was 2-thiophen, cyclohexyl and isopropyl, the reaction could proceed smoothly and gave the corresponding polysubstituted pyrroles in 87%, 91% and 40% yields, respectively (enties 7-9). For 3-aryl ring of the 1,3-diarylpropynones, steric hindrance had a significant impact on the yield. *Ortho* methyl substituted substrate gave lower yield than corresponding substrates with *para*- and *meta*- methyl (entry 12 *vs* 10, 11). A number of electron-donating and electron-withdrawing groups, including methoxy-, chloro- and fluoro- in the 3-aryl ring of the 1,3-diarylpropynones were tolerant and furnished in good yields (entries 13–15). In addition, good yields was obtained when R^4 was aliphatic groups (entries 16-17).

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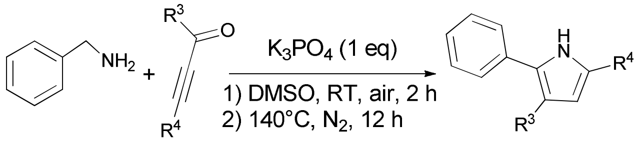
Table 3 Reactions of benzylamine **2a** with various ynones **3a-3h**[a]

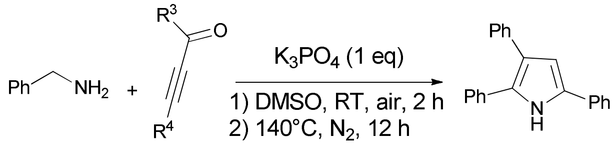


2a **3b-3p** **4ab-4ap**

Entry	*3*	*R^3*	*R^4*	*4*	*Yield (%)*[b]
1	**3b**	2-MeC$_6$H$_4$-	Ph	**4ab**	89
2	**3c**	4-Me C$_6$H$_4$-	Ph	**4ac**	86
3	**3d**	3-MeOC$_6$H$_4$-	Ph	**4ad**	82
4	**3e**	4-tBuC$_6$H$_4$-	Ph	**4ae**	81
5	**3f**	4-ClC$_6$H$_4$-	Ph	**4af**	64
6	**3g**	4-FC$_6$H$_4$-	Ph	**4ag**	85
7	**3h**	Thiophen-2-	Ph	**4ah**	87
8	**3i**	Cyclohexyl-	Ph	**4ai**	91
9	**3j**	isopropyl-	Ph	**4aj**	40
10	**3k**	Ph	4-MeC$_6$H$_4$-	**4ak**	88
11	**3l**	Ph	3-MeC$_6$H$_4$-	**4al**	81
12	**3m**	Ph	2-MeC$_6$H$_4$-	**4am**	49
13	**3n**	Ph	4-MeOC$_6$H$_4$-	**4an**	83
14	**3o**	Ph	4-ClC$_6$H$_4$-	**4ao**	70
15	**3p**	Ph	4-FC$_6$H$_4$-	**4ap**	82
16	**3q**	Ph	*n*Bu	**4aq**	74
17	**3r**	Ph	*t*Bu	**4ar**	70

[a] Reaction condition: Benzylamine **2a** (1 mmol), ynone **3** (1 mmol), K$_3$PO$_4$ (1 mmol), DMSO (2.0 mL) at 140 ℃ under N$_2$ atmosphere. [b] Isolated yields based on ynone **3**.

To prove the practicality of this "one-pot" reaction system, a gram-scale synthesis of the 2,3,5-triphenyl-1*H*-pyrrole **4aa** was performed. The result was shown in Scheme 2. When 1.03g 1,3-diphenylprop-2-yn-1-one **3a** and 0.54g benzylamine **2a** were loaded, 1.27g pyrrole **4aa** was obtained (86% yield). Metal-free and high effciency make this reaction possess extensive synthesis application, especially in the pharmaceutical industry.



2a, 0.54 g **3a**, 1.03 g **4aa**, 1.27g (86 % yield)

Scheme 2. Gram-scale synthesis of 2, 3, 5-triphenyl-1*H*-pyrrole **4aa**

In conclusion, we have developed an efficient, facile and practical one-pot procedure for the polysubstituted pyrroles. This transformation features with easy accessibility of starting materials, good functional group tolerance and transition metal free. A wide variety of poly-substituted pyrroles were obtained in good to excellent yields in an environmentally benign manner.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. (a) A. Gossauer, *Die Chemie der Pyrrole*, Springer Verlag, Berlin, 1974; (b) A. F. Pozharskii, A. T. Soldatenkov and A. R. Katritzky, *Heterocycles in life and society. An introduction to heterocyclic chemistry and biochemistry and the role of heterocycles in science, technology, medicine and agriculture*, John Wiley & Sons, 1997; (c) B. A. Trofimov, L. N. Sobenina, A. P. Demenev and A. b. I. Mikhaleva, *Chem. Rev.*, 2004, **104**, 2481; (d) F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213; (e) C. T. Walsh, S. Garneau-Tsodikova and A. R. Howard-Jones, *Nat. Prod. Rep.*, 2006, **23**, 517; (f) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.
2. L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635.
3. C. Paal, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367.
4. A. Hantzsch, Ber. *Dtsch. Chem. Ges.*, 1890, **23**, 1474.
5. For recent reports, see: (a) K. Hiroya, S. Matsumoto, M. Ashikawa, K. Ogiwara and T. Sakamoto, *Org. Lett.*, 2006, **8**, 5349; (b) S. Rakshit, F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9585; (c) R. L. Yan, J. Luo, C. X. Wang, C. W. Ma, G. S. Huang and Y. M. Liang, *J. Org. Chem.*, 2010, **75**, 5395; (d) F. Chen, T. Shen, Y. Cui and N. Jiao, *Org. Lett.*, 2012, **14**, 4926; (e) B. Li, N. Wang, Y. Liang, S. Xu and B. Wang, *Org. Lett.*, 2012, **14**, 136; (f) Y. Q. Zhang, D. Y. Zhu, B. S. Li, Y. Q. Tu, J. X. Liu, Y. Lu and S. H. Wang, *J. Org. Chem*, 2012, **77**, 4167; (g) R. J. Billedeau, K. R. Klein, D. Kaplan and Y. Lou, *Org. Lett.*, 2013, **15**, 1421; (h) Z. Chen, B. Lu, Z. Ding, K. Gao and N. Yoshikai, *Org. Lett.*, 2013, **15**, 1966; (i) S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 140; (j) Z. Shi, M. Suri and F. Glorius, *Angew. Chem. Int. Ed.*, 2013, **125**, 4992; (k) D. Srimani, Y. Ben - David and D. Milstein, *Angew. Chem., Int. Ed.*, 2013, **52**, 3.
6. (a) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402; (b) S. Zhang, J. Zhao, W.-X. Zhang and Z. Xi, *Org. Lett.*, 2011, **13**, 1626; (c) W. J. Humenny, P. Kyriacou, K. Sapeta, A. Karadeolian and M. A. Kerr, *Angew. Chem.*, 2012, **124**, 11250; (d) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, in press; (e) M. N. Zhao, H. Liang, Z. H. Ren and Z. H. Guan, *Adv. Synth. Catal.*, 2013, **355**, 221.
7. (a) F.-X. Felpin, T. Ayad and S. Mitra, Eur. *J. Org. Chem.*, 2006, 2679; (b) J. Mao, Q. Hua, G. Xie, J. Guo, Z. Yao, D. ShiandS. Jia, *Adv. Synth. Catal.*, 2009, 351 , 635; (c) C.-L. Sun, H. Li, D.-G. Yu, M.Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.*, 2010, 2, 1044; (d)W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132** , 16737.
8. (a) M. Rueping and A. Parra, *Org. Lett.*, 2010, **12**, 5281; (b) Z.-H. Guan, L. Li, Z.-H. Ren, J. Li and M.-N. Zhao, *Green Chem.*, 2011, **13**, 1664; (c) A. Palmieri, S. Gabrielli, C. Cimarelli and R. Ballini, *Green Chem.*, 2011, **13**, 3333.
9. (a) A. S. Karpov, F. Rominger and T. J. Müller, *Org. Bio. Chem.*, 2005, **3**, 4382; (b). C. Boersch, E. Merkul and T. J. Müller, *Angew. Chem., Int. Ed.*, 2011, **50**, 10448; (c). S. Santra, K. Dhara, P. Ranjan, P. Bera, J. Dash and S. K. Mandal, *Green Chem.*, 2011, **13**, 3238.
10. G. Cheng and X. Cui, *Org. Lett.*, 2013, **15**, 1480.
11. (a) C. Yi and R. Hua, *, J. Org. Chem.*, 2006, **71**, 2535; (b) T. Kawabata, K. Moriyama, S. Kawakami and K. Tsubaki, *J. Am. Chem. Soc.*, 2008, **130**, 4153; (c) C. L. Øpstad, T.-B. Melø, H.-R. Sliwka and V. Partali, *Tetrahedron*, 2009, **65**, 7616; (d) B. A. Trofimov, E. Y. Schmidt, I. A. Ushakov, N. V. Zorina, E. V. Skital'tseva, N. I. Protsuk and A. b. I. Mikhaleva, *Chem-Eur. J.,* 2010, **16**, 8516; (e) B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova and I. A. Ushakov, *J. Org. Chem.*, 2012, **77**, 6880.