RSC Advances

RSC Advances

www.rsc.org/advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances

COMMUNICATION

Practical Access to 1,3,5-Triarylbenzenes from Chalcones and DMSO†

Fuyuan Wang, Jinhai Shen, Guolin Cheng and Xiuling Cui*

An unprecedented practical access to 1,3,5-triarylbenzenes has been developed from chalcones with DMSO as a reaction partner and solvent. This procedure involved a base-promoted addition of dimethyl sulfoxide anion to chalcones, followed by an aldol-type cyclization. The results of the isotopic labeling experiments indicated that one C of the central benzene ring was derived from DMSO. In comparison to the reported methods of preparing triarylbenzenes, this protocol could simultaneously provide C_3-symmetric and C_3-unsymmetric triarylbenzenes under obviously milder reaction conditions (60 °C, 5 h). The diverse functionalized triarylbenzenes were obtained in up to 82% yields for 24 examples.

1,3,5-Triarylbenzene is an important motif in advanced functional materials,[1] including electrode devices,[2] optical materials,[3] and conducting polymers.[4] They are also applied as special ligands for synthesizing macromolecules.[5] Therefore, numerous methods have been developed for building such a structure. Transition-metal catalyzed [2+2+2] cyclotrimerizations of phenylacetylene have been widely investigated (Scheme 1, eq 1),[6] in which 1,2,4-triarylbenzenes as side products is unavoidable. Condensation of aryl acetones mediated by Lewis acids provides an alternative pathway (Scheme 1, eq 2).[7] These methodologies only provide C_3-symmetrical 1,3,5-triarylbenzenes. Transition-metal-catalyzed cross-coupling of 1,3,5-trihalobenzenes with boronates or organometallic reagents have been proven to be a powerful tool to build C_3-unsymmetric triarylbenzenes (Scheme 1, eq 3).[8] However, there are some limitations with this strategy, such as problematic substrates, producing excessive wastes from halides and boronates or organometallic reagents, requirement of transition-metal as well as complicate ligands. Therefore, developing an efficient, clean pathway to construct C_3-unsymmetric or C_3-symmetric triarylbenzenes is still in demand. Herein, we disclosed an operationally simple

methodology to simultaneously synthesize both C_3-symmetric and C_3-unsymmetric 1,3,5-triarylbenzene from easily available chalcones and DMSO (Scheme 1, eq 4). DMSO was served as a precursor methine unit (=CH—) to build the benzene ring. In the literature, DMSO was served as a precursor methine unit to form formaldehyde group.[9] Establishing a benzene ring from DMSO have no report.
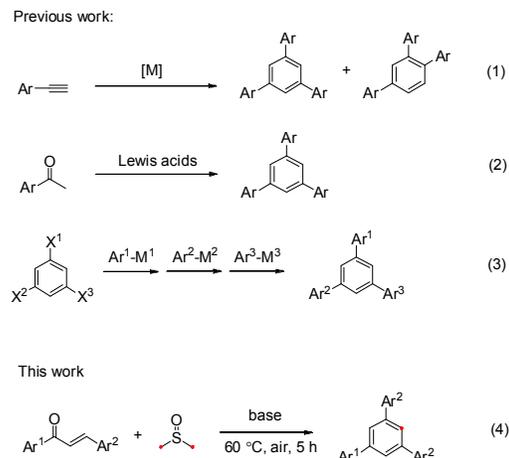
Scheme 1 Syntheses of C_3-Symmetric and C_3-Unsymmetric 1,3,5-Triarylbenzenes

The reaction of 1,3-diphenyl-2-propen-1-one (**1a**) was initially conducted at 80 °C in the presence of NaOtBu as a base in DMSO under air. 1,3,5-Triphenylbenzene (**2a**) was obtained in 33% yield (Table 1, entry 1). No desired product was observed in other solvents, such as toluene, THF, NMP and HMPA (entries 2–6). Further studies were focused on screening of the bases. NaOH, KOH and KOtBu provided poor yields (entries 7–9). Other base resulted in no reaction (entries 10–14). The yield was improved obviously, when the loading of NaOtBu was increased to 4 equivalents (54%, entry 15). Further exploration on loading of base indicated that 6 equivalents of NaOtBu could bring the highest yield of 77% (entries 16-17). Moreover, the reaction could proceed smoothly at 60 °C. The yields were decreased with increasing

Engineering Research Center of Molecular Medicine, Ministry of Education, Key Laboratory of Xiamen Marine and Gene Drugs, Institutes of Molecular Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, 361021. E-mail: cuixl@hqu.edu.cn

or decreasing the reaction temperature (entries 18-21). When the reaction was carried out under the nitrogen and oxygen atmospheres, or in the presence of 4 Å MS, the yield was not improved significantly (entries 22-24). Additionally, trace amounts of product was found using 3 equivalents DMSO as reactant when DMF was used as solvent (entry 25). Finally, the optimal reaction conditions were identified as follows: NaOtBu (6 eq) as a base and DMSO as the solvent at 60 °C for 5 h under air.

Table 1 Optimization of reaction conditions to synthesize 1,3,5-triphenylbenzene[a]
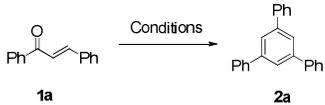
Entry	Base (equiv)	Solvent	T (^{o}C)	Yield (%)[b]
1	NaOtBu (3)	DMSO	80	33
2	NaOtBu (3)	Toluene	80	none
3	NaOtBu (3)	THF	80	none
4	NaOtBu (3)	DMF	80	none
5	NaOtBu (3)	NMP	80	none
6	NaOtBu (3)	HMPA	80	none
7	NaOH (3)	DMSO	80	11
8	KOH (3)	DMSO	80	12
9	KOtBu (3)	DMSO	80	15
10	Li(OH) (3)	DMSO	80	none
11	NaOEt (3)	DMSO	80	none
12	K$_3$PO$_4$ (3)	DMSO	80	none
13	NEt$_3$ (3)	DMSO	80	none
14	DBU (3)	DMSO	80	none
15	NaOtBu (4)	DMSO	80	54
16	NaOtBu (5)	DMSO	80	59
17	NaOtBu (6)	DMSO	80	77
18	NaOtBu (6)	DMSO	20	34
19	NaOtBu (6)	DMSO	40	75
20	**NaOtBu (6)**	**DMSO**	**60**	**78**
21	NaOtBu (6)	DMSO	100	49
22[c]	NaOtBu (6)	DMSO	60	75
23[d]	NaOtBu (6)	DMSO	60	77
24[e]	NaOtBu (6)	DMSO	60	74
25[f]	NaOtBu (6)	DMF	60	trace

[a] Reaction conditions: **1a** (0.25 mmol), solvent (2 ml), under air atmosphere for 5h. [b] Isolated yield based on **1a**. [c] In the presence of 4 Å MS. [d] Under nitrogen atmosphere. [e] Under oxygen atmosphere. [f] DMSO (3 eq) was added.

With the optimized reaction conditions in hand, the generality and scope of the substrates were investigated as illustrated in Table 2. As for Ar[1], the *para*-methoxy and *para*-tert-butyl substituted substrates afforded the desired products in 63% and 49% yields, respectively (Table 2, **2b**, **2c**). When Ar[1] were *para*-fluoro and chloro phenyl groups, the yields decreased with their declining electronegativity (**2d**, **2e**). The slight influence of the steric hindrance on this reaction was observed. For instance, 4'-methoxychalcone, 3'-methoxychalcone, and 2'-methoxychalcone afforded the corresponding products in 63%, 73%, and 47% yields (**2b**, **2f**, **2i**); 4'-fluorochalcone, 3'-fluorochalcone, and 2'-fluorochalcone provided the desired products in 70%, 61%, and 40% yields (**2d**,

2g, **2j**). When Ar[1] were 2-naphenyl, 2-pyridinyl and 3-pyridinyl, the reaction could proceed well and gave the corresponding triarylbenzenes in 74%, 82%, and 45%, respectively (**2k–m**). Compared to **2m**, **2l** was afforded in higher yield, perhaps due to lower electron density at C-2 of pyridine ring.

Table 2 Substrate scope: variation of chalcones at Ar[1] [a]
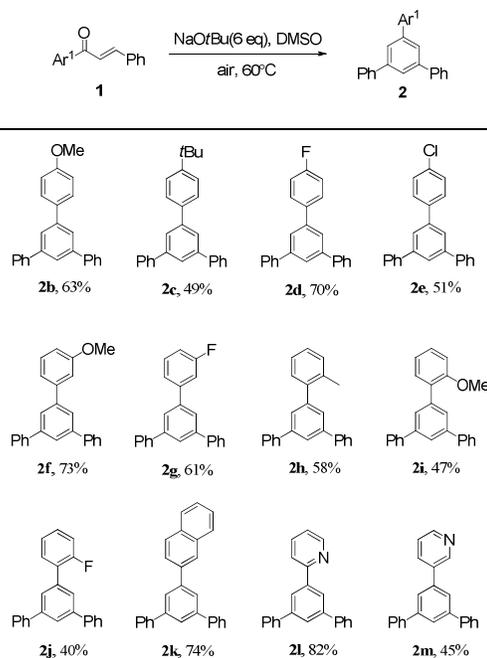
[a] Under the optimized conditions, isolated yield.

Next, we explored the scope of Ar[2] (Table 3). When Ar[2] were electron-donating groups, such as *para*-methoxy, *para*-tert-butyl, and *para*-methylthio phenyl, could give moderate yields (**2n–p**). 4-Fluorochalcone gave a higher yield than 4-chlorochalcone (**2q**, **2r**). Steric effects were still significant, 3-methoxychalcone reacted better than 2-methoxychalcone (**2t**, **2u**). When Ar[2] were 2-thienyl and ferrocenyl, the desired products were afforded in 58% and 57% yields (**2v**, **2w**). In addition, C$_3$-symmetric triarylbenzenes were also obtained in good yields (**2x**, **2y**). While, no product was observed for the substrates substituted by hydroxyl or carboxyl group at para- or ortho- position.

To clarify the reaction mechanism, some controlled experiments were carried out. ^{13}C-labeled dimethyl sulfoxide was used as solvent instead of DMSO for the reaction of 1-(2-thienyl)-3-pheny-2-propen-1-one (**1v**) under the standard reaction conditions. 4-^{13}C-labeled 1-pheny-3,5-di(2-thienyl)benzene (**2v'**) was obtained and identified by ^{13}C NMR spectra (Scheme 2, eq 5). The peak at 122.5 ppm became an extremely strong signal. This result indicated that one single carbon atom (instead of two symmetric carbon atoms) on the benzene ring came from dimethyl sulfoxide. β-Methyl chalcone could not give the desired product under the optimal reaction condition (Scheme 2, eq 6). Therefore, the C-C bond between β-carbon of chalcone and methyl of dimethyl sulfoxide was

suggested to be formed by the Michael addition. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to this reaction system, the reaction was significantly unaffected (Scheme 2, eq 7), suggesting radical processes excluded in this procedure.

Table 3 Substrate scope: variation of chalcones at Ar[2] [a]
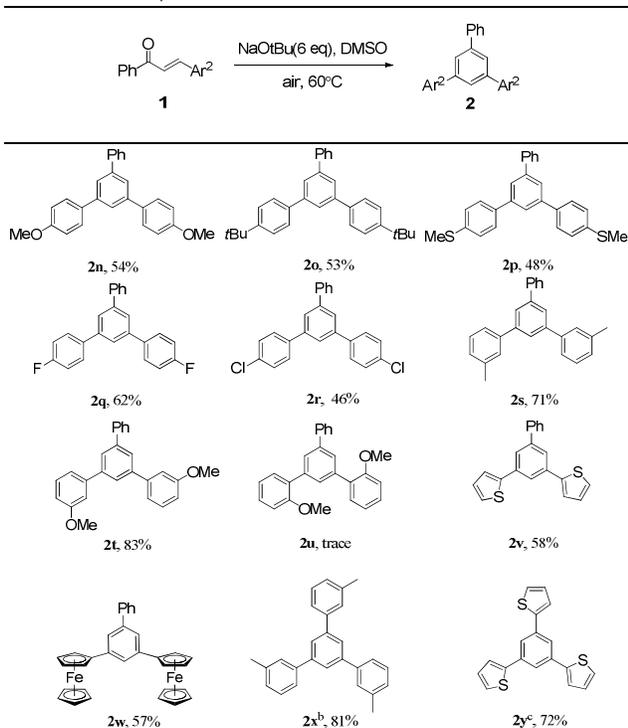
[a] Reaction conditions: **1** (0.25 mmol), NaO*t*Bu (6 eq), DMSO (2 mL), 60 °C, 5 h under air, isolated yield; [b] substrate was 1,3-di-3-methylphenyl-2-propen-1-one; [c] substrate was 1,3-di-2-thienyl-2-propen-1-one.

Scheme 2 Controlled experiments.

A plausible reaction mechanism for the formation of triarylbenzenes from chalcones and DMSO was proposed and depicted in Scheme 3. Initially, chalcones and DMSO went through Michael addition via NaO*t*Bu-mediated deprotonation of dimethyl sulfoxide[10] to form the intermediates **A**. Then **A** proceeded the second Michael addition to form the intermediates **B**. Next, a ring closure via demethylsulfinylation and intramolecular [2+2] cycloaddition[7a] formed **C**, which was

converted to arylformate and 1,3,5-triarylbenzenes via a subsequent retro-[2+2] cycloaddition.[7a]
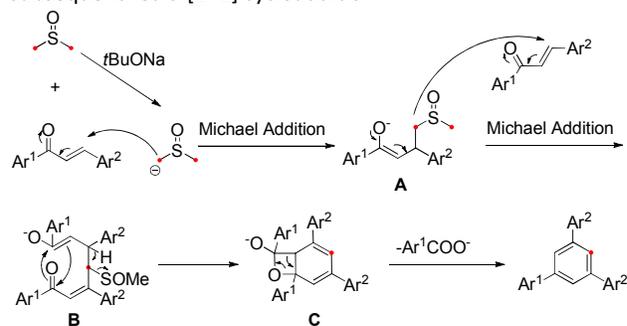
Scheme 3 Plausible reaction mechanism.

Conclusions

In summary, we have developed an unprecedented protocol to synthesize 1,3,5-triarylbenzenes under metal-free and air-tolerant conditions. This substrates-available and operationally simple method gives a rapid access to a variety of complicated multiarylated benzenes. Further mechanism exploration and utilization of this method is ongoing in this laboratory.

Acknowledgments

Notes and references

1   (a) T. R. Cook, Y.-R. Zheng and P. J. Stang, *Chem. Rev.*, 2013, **113**, 734; (b) Y. Shirota, *J. Mater. Chem.*, 2005, **15**, 75.
2   (a) M. J. Plater, M. McKay and T. Jackson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2695; (b) S. V. Lindeman, Y. T. Struchkov, V. N. Michailov, A. L. Rusanov, *Izv. Akad. Nauk. Ser. Khim.*, 1994, 1986; *Chem. Abstr.* 1995, **123**, 32717p; (c) M. Aslam, D. A. Aguilar, *WO 9314065,* 1993; *Chem. Abstr.* 1993, **119**, 270793x.
3   (a) Q. Q. He, H. M. Huang, J. L. Yang, H. Z. Lin and F. L. Bai, *J. Mater. Chem.*, 2003, **13**, 1085; (b) J. Pang, E. J. P. Marcotte, C. Seward, R. S. Brown and S. N. Wang, *Angew. Chem., Int. Ed.*, 2001, **40**, 4042; (c) M. J. Plater, M. McKay and T. Jackson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2695; (d) T. Weil, E. Reuther and K. Mullen, *Angew. Chem., Int. Ed.*, 2002, **41**, 1900; (e) L. H. Yu and J. S. Lindsey, *J. Org. Chem.*, 2001, **66**, 7402.
4   (a) C. Y. Bao, R. Lu, M. Jin, P. C. Xue, C. H. Tan, T. H. Xu, G. F. Liu and Y. Y. Zhao, *Chem.–Eur. J.*, 2006, **12**, 3287; (b) C. Gu, N. Huang, J. Gao, F. Xu, Y. Xu and D. Jiang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4850; (c) L.-R. Tsai, C.-W. Li and Y. Chen, *J. Polym. Sci. Pol. Chem.*, 2008, **46**, 5945.
5   (a) A. Jimenez, R. A. Bilbeisi, T. K. Ronson, S. Zarra, C. Woodhead and J. R. Nitschke, *Angew. Chem., Int. Ed.*, 2014, **53**, 4556; (b) J. S. Kanady, T. Rosalie, J. A. Stull, L. Lu, T. A. Stich, M. W. Day, J. Yano, R. D. Britt and T. Agapie, *Chem. Sci*, 2013, **4**, 3986; (c) C. Morchutt, J. Bjoerk, S. Krotzky, R.

Gutzler and K. Kern, *Chem. Commun.*, 2015, **51**, 2440; (d) M. Taddei, F. Costantino, R. Vivani, S. Sabatini, S.-H. Lim and S. M. Cohen, *Chem. Commun.*, 2014, **50**, 5737; (e) E. Y. Tsui, M. W. Day and T. Agapie, *Angew. Chem., Int. Ed.*, 2011, **50**, 1668; (f) X. Y. Cao, X. H. Liu, X. H. Zhou, Y. Zhang, Y. Jiang, Y. Cao, Y. X. Cui and J. Pei, *J. Org. Chem.*, 2004, **69**, 6050; (g) J. S. Moore and M. L. Kraft, *Science*, 2008, **320**, 620; (h) M. Numata, T. Kozawa, R. Nogami, K. Tanaka, Y. Sanada and K. Sakurai, *B. Chem. Soc. JPN.*, 2015, **88**, 471; (i) M. J. Plater and M. Praveen, *Tetrahedron Lett.*, 1997, **38**, 1081; (j) Q. Wang, C. Zhang, B. C. Noll, H. Long, Y. Jin and W. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 10663; (k) L. Zang, Y. Che and J. S. Moore, *Accounts Chem. Res.*, 2008, **41**, 1596; (l) E. Weber, M. Hecker, E. Koepp and W. Orlia, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1251.

6   (a) X. Bu, Z. Zhang and X. Zhou, *Organometallics*, 2010, **29**, 3530; (b) G. Hilt, T. Vogler, W. Hess and F. Galbiati, *Chem. Commun.*, 2005, 1474; (c) A. Joosten, M. Soueidan, C. Denhez, D. Harakat, F. Helion, J.-L. Namy, J.-L. Vasse and J. Szymoniak, *Organometallics*, 2008, **27**, 4152; (d) Y.-L. Xu, Y.-M. Pan, Q. Wu, H.-S. Wang and P.-Z. Liu, *J. Org. Chem.*, 2011, **76**, 8472.

7   (a) K. Deng, Q.-Y. Huai, Z.-L. Shen, H.-J. Li, C. Liu and Y.-C. Wu, *Org. letters*, 2015, **17**, 1473; (b) X. B. Jing, F. Xu, Q. H. Zhu, X. F. Ren, C. G. Yan, L. Wang and J. R. Wang, *Synthetic Commun.*, 2005, **35**, 3167; (c) A. Kumar, M. Dixit, S. P. Singh, R. Raghunandan, P. R. Maulik and A. Goel, *Tetrahedron Lett.*, 2009, **50**, 4335; (d) F. Ono, Y. Ishikura, Y. Tada, M. Endo and T. Sato, *Synlett*, 2008, 2365; (e) K. Phatangare, V. Padalkar, D. Mhatre, K. Patil and A. Chaskar, *Synthetic Commun.*, 2009, **39**, 4117; (f) G. P. Zhang, R. H. Qiu, X. H. Xu, H. H. Zhou, Y. F. Kuang and S. H. Chen, *Synthetic Commun.*, 2012, **42**, 858; (g) S. Zhao, L. Kang, H. Ge, F. Yang, C. Wang, C. Li, Q. Wang and M. Zhao, *Synthetic Commun.*, 2012, **42**, 3569; (h) Y. Zhao, J. Li, C. Li, K. Yin, D. Ye and X. Jia, *Green Chem.*, 2010, **12**, 1370.

8   (a) Z. G. Hu, J. Liu, G. G. Li, Z. B. Dong and W. Li, *J. Chin. Chem. Soc.*, 2004, **51**, 581; (b) L. Liu, Y. Dong, B. Pang and J. Ma, *J. Org. Chem.*, 2014, **79**, 7193; (c) S. Paul and J. H. Clark, *Green Chem.*, 2003, **5**, 635; (d) M. A. Pena, I. Perez, J. P. Sestelo and L. A. Sarandeses, *Chem. Commun.*, 2002, 2246; (e) D.-G. Yu, M. Yu, B.-T. Guan, B.-J. Li, Y. Zheng, Z.-H. Wu and Z.-J. Shi, *Org. Letters*, 2009, **11**, 3374; (f) F. Zhao, Y.-F. Zhang, J. Wen, D.-G. Yu, J.-B. Wei, Z. Xi and Z.-J. Shi, *Org. Letters*, 2013, **15**, 3230.

9   (a) H. Fei, J. Yu, Y. Jiang, H. Guo and J. Cheng, *Org. Biomol. Chem.*, 2013, **11**, 7092; (b) Z. Zhang, Q. Tian, J. Qian, Q. liu, T. Liu, L. Shi and G. Zhang, *J. Org. Chem.*, 2014, **79**, 8182; (c) H. Cao, S. Lei, N. Li, L. Chen, J. Liu, H. Cai, S. Qiu and J. Tan, *Chem. Commun.*, 2015, **51**, 1823.

10 (a) M. Y. Chang, C. K. Chan, S. Y. Lin and M. H. Wu, *Tetrahedron*, 2013, **69**, 9616; (b) A. A. Fokin, A. O. Kushko, A. V. Kirij, A. G. Yurchenko and P. V. Schleyer, *J. Org. Chem.*, 2000, **65**, 2984; (c) M. Mondal, *Synlett*, 2005, 2697.
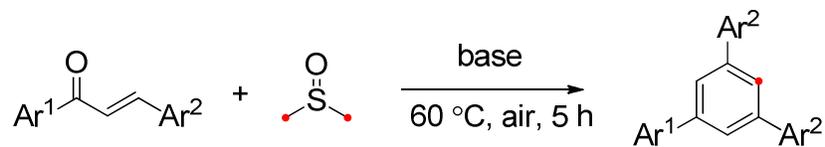
- metal free and mild conditions
- compatible to acid-sensitive heterocycles
- tolerance of air and moisture

We presents a practical access to 1,3,5-triarylbenzenes from simple chalcones and DMSO, which serves as solvent and precursor methine unit. This protocol could simultaneously provide a variety of C_3-symmetric and C_3-unsymmetric 1,3,5-triarylbenzenes under metal-free and mild reaction conditions.