Synthesis of Substituted Phenols via 1,1-Dichloro-2-Nitroethene Promoted Condensation of Carbonyl compounds with DMF

Fukai Wang, Wei Wu, Xiaoyong Xu, Xusheng Shao, Zhong Li

PII: S0040-4039(18)30562-8
DOI: https://doi.org/10.1016/j.tetlet.2018.04.076
Reference: TETL 49939

To appear in: *Tetrahedron Letters*

Received Date: 25 January 2018
Revised Date: 25 April 2018
Accepted Date: 28 April 2018

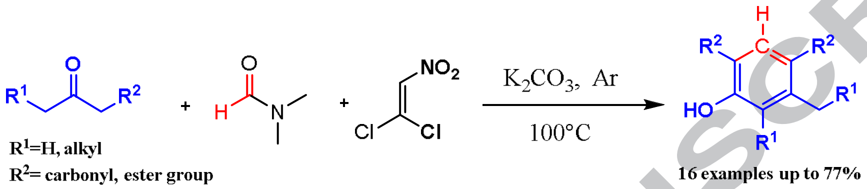
Please cite this article as: Wang, F., Wu, W., Xu, X., Shao, X., Li, Z., Synthesis of Substituted Phenols via 1,1-Dichloro-2-Nitroethene Promoted Condensation of Carbonyl compounds with DMF, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.04.076

Graphical Abstract

.

Synthesis of Substituted Phenols via 1,1-Dichloro-2-Nitroethene Promoted Condensation of Carbonyl compounds with DMF

Fukai Wang, Wei Wu, Xiaoyong Xu, Xusheng Shao, Zhong Li



R^1=H, alkyl

R^2= carbonyl, ester group

16 examples up to 77%

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of Substituted Phenols via 1,1-Dichloro-2-Nitroethene Promoted Condensation of Carbonyl compounds with DMF

Fukai Wang[a] , Wei Wu[a] , Xiaoyong Xu[a], Xusheng Shao[a], Zhong Li[a, b,]*

[a] *Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China.*
[b] *Shanghai Collaborative Innovation Center for Biomanufacturing Technology, 130 Meilong Road, Shanghai 200237, China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1,1-dichloro-2-nitroethene
β-dicarbonyl
N,N-dimethylformamide
phenolic
cyclization

ABSTRACT

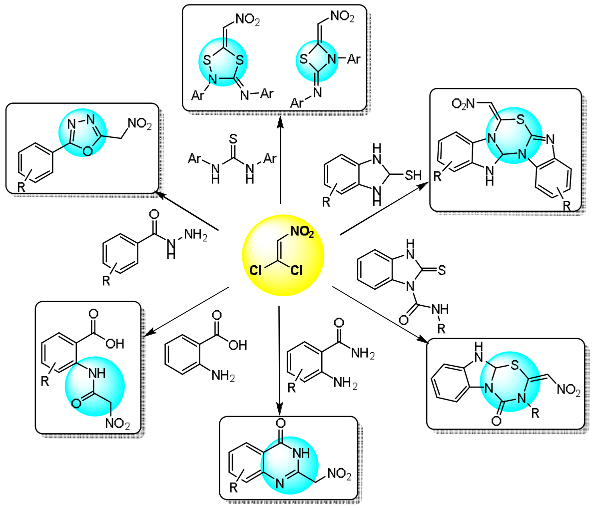
A novel and efficient metal-free synthesis of phenolic compounds was developed via coupling cyclization of DMF as a carbon source with active methylene compounds such as 1,3-dicarbonyl compounds with the assistance of 1,1-dichloro-2-nitroethene. The method we used was different from other traditional phenol functionalization methods. In the reaction, the 1,1-dichloro-2-nitroethene as a promoter which unlike our previous research on 1,1-dichloro-2-nitroethene. The method allows the convenient construction of phenolic compounds under mild reaction conditions and moderate yields.

Introduction

Phenol is originally found in many natural products in the form of monomers or polymers and is a class of compounds in which one or more aromatic rings are bonded to hydroxyl groups.[1-3] The hydroxyl groups on the benzene ring are liable to lose hydrogen electrons.[4-6] Therefore, the phenolic compounds act as good electron donors and can be used as fundamental raw materials in Ullman coupling, Suzuki coupling, and other organic reactions for the synthesis of various functional molecules.[7-13] Phenol and its derivatives are plentiful in pharmaceutical properties such as anti-infective, antiviral, anti-bacterial, anti-allergy, anti-bleeding and enhanced immunity.[14-19] Catalytic hydroxylation of benzene is the most commonly strategy for the synthesis of phenol. These strategies included oxidative decomposition of cumene and catalysis of toluene with benzoic acid etc.[20-22] Although these progresses, directly building a phenol structure from alkanes is still a huge challenge.

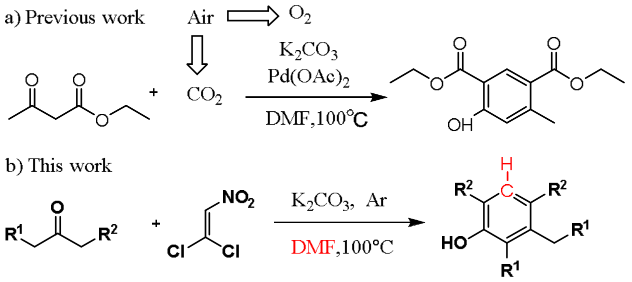
1,1-dichloro-2-nitroethene (DCNE) as an important cyclizing molecule has become a research hot spot within the chemical community in the past few years due to its much higher reactivity in organic and pesticide chemistry.[23-27] In the preliminary study of our group, DCNE was proved that it reacted with thiourea analogues,[28] benzohydrazide analogues,[29] 2-aminobenzoic acid analogues[30] and 2-aminobenzamide[31] respectively to construct corresponding heterocyclic compounds (Scheme 1). DMF, a cheap and popular polar solvent, has been widely used in organic synthesis. Moreover, DMF can be used as a useful precursor to afford Me, CHO synthons.[32,33] In previous reports, Yingming Pan found a protocol for the synthesis of phenolic compounds by palladium-catalyzed reaction of carbonyl compounds with CO_2 and guessed carbon dioxide may be a carbon source (Scheme 2, a).[34] We tried to achieve a one-pot synthesis of phenolic compounds via DCNE promoted condensation of 1,3-dicarbonyl compounds with DMF (Scheme 2, b). The reaction could be smoothly performed to afford the target products in good to excellent yields without any metal catalyst.

Scheme 1. Our recent exploration on 1,1-dichloro-2-nitroethene chemistry.



---

* Corresponding author. Tel.: +86 21 64253540; fax: +86 21 64252603; e-mail: lizhong@ecust.edu.cn

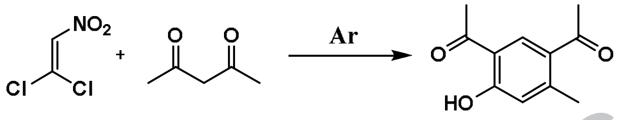


Scheme 2. Carbonyl compounds are cyclized into phenols.

Results and discussion

We began our investigation by using the cyclization of acetylacetone (2a) with DCNE (1) as the model reaction to optimize the reaction conditions. Initially, different metal catalysts were tested (Table 1, entries 1-6). It was found that $Pd(OAc)_2$ exhibited the best result. For further investigation, we luckily found the reaction could proceed satisfied without any metal catalysts. A series of bases were screened, and K_2CO_3 showed good yield and the reaction could also proceed without bases (Table 1, entries 7-12). Further examination of the reaction temperature indicated that the temperature at 100°C was the best choice for this reaction (Table 1, entries 13-16). The effect of different solvents such as dimethyl sulfoxide, dimethyl acetamide, water, and acetonitrile was proved to be inferior to dimethyl formamide (Table 1, entries 17- 20).

Table 1. Optimization of the Reaction Conditions [a]



1 **2a** **3a**

Entry	Catalyst	Base	Solvent	Temp(°C)	Yield(%)[b]
1	$Pd(OAc)_2$	K_2CO_3	DMF	100	81
2	$PdCl_2$	K_2CO_3	DMF	100	Trace
3	$Pd(PPh_3)_4$	K_2CO_3	DMF	100	Trace
4	$Fe(OAc)_2$	K_2CO_3	DMF	100	0
5	$Cu(OAc)_2$	K_2CO_3	DMF	100	0
6	AgOAc	K_2CO_3	DMF	100	0
7[c]	-	K_2CO_3	DMF	100	77
8	-	Na_2CO_3	DMF	100	12
9	-	Cs_2CO_3	DMF	100	53
10	-	KOH	DMF	100	0
11	-	CH_3ONa	DMF	100	0
12[d]	-	-	DMF	100	52
13	-	K_2CO_3	DMF	80	Trace
14	-	K_2CO_3	DMF	90	70
15	-	K_2CO_3	DMF	110	76
16	-	K_2CO_3	DMF	120	67
17	-	K_2CO_3	DMSO	100	64
18	-	K_2CO_3	DMA	100	34
19	-	K_2CO_3	H_2O	100	0
20	-	K_2CO_3	CH_3CN	100	0

[a] Reaction conditions: 2a (2mmol), 1 (1.2mmol), base (0.5 equiv.), solvent (4 mL), 100°C, 10 h. [b] Yield determined by GC analysis and based on 2a. [c] In the absence of catalyst. [d] In the absence of base.

Under the optimized conditions, the scope of carbonyl compounds (**2a**) was explored (table 2). Acetylacetone, 2,4-hexanedione, benzoylacetone and 1-p-toylbutane-1,3-dione reacted smoothly affording the target products (**3a**,**3b**,**3l**,**3m**). The DMF successfully coupled with acetoacetates featuring a range of different substituents(**3c-3k**). To our delight, methyl 3-oxopentanoate and ethyl 3-oxohexanoate could be readily introduced into the reaction, providing the corresponding phenolic compounds **3n**, **3o** and **3p**, but the yields were lower. The structure of the phenolic product **3a** was comfirmed by X-ray crystallographic analysis (Figure 1).

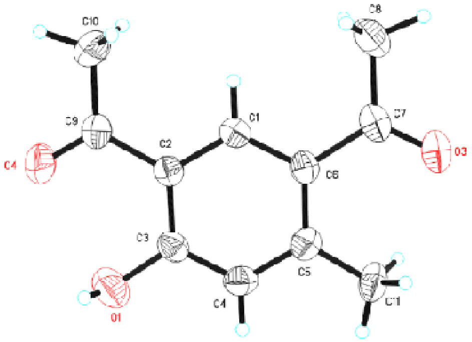
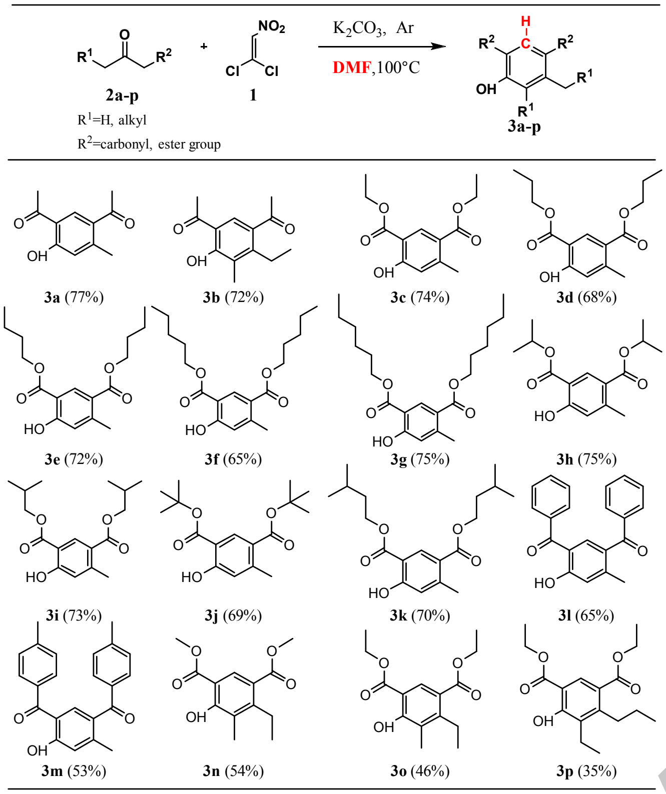
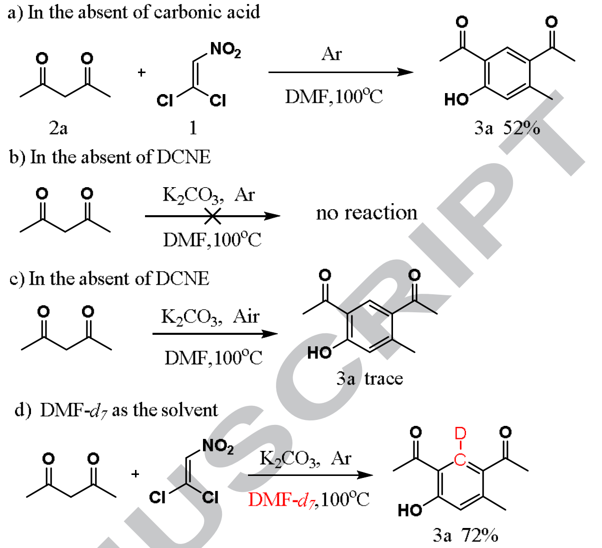


Figure 1. X-ray crystal structure of 3a.

Table 2. Substrate-scope exploration for the formation of phenolic products.



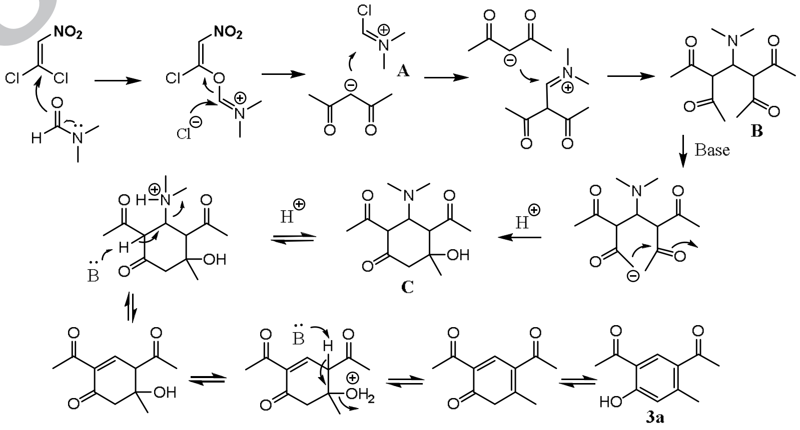
A few experiments have been performed to gain insight into the mechanism of this transformation (scheme 4). First, treatment of the acetylacetone with DCNE in the absent of potassium carbonate by heating at 100°C in DMF afforded the 3a in 52% yield (scheme 4. a). This indicated that the carbon source was not derived from potassium carbonate. The desired product was not observed when the reaction was processed under the Ar without DCNE (scheme 4. b). Third, the reaction in the air only detected trace amounts of the target product in the absence of DCNE (scheme 4. c), supporting the importance of the DCNE in the cyclization process. When DMF was the solvent, the reaction works best, we suspected that DMF promoted and participated in the reaction. So, we chose DMF-d_7 as solvent for the reaction verification. The **3a** was obtained in 72% yield when DMF-d_7 was used as the solvent under the standard conditions (Scheme 4. d). This means that C2 in the benzene ring besides the target product comes from the DMF. This assumption was confirmed by ^{1}H NMR (Figure 1), ^{1}H NMR of **3a** obtained with DMF-d_7 as solvent show in Figure 1-a, ^{1}H NMR of **3a** obtained with DMF as solvent show in Figure 1-b.



Scheme 4. Studies toward the Mechanism of the Reaction.

On the basis of the above experimental observations, plausible reaction mechanism has been depicted in Scheme 5. First, DCNE reacted with DMF to result in intermediate **A**, then which reacted with two molecules of 1,3-dicarbonyl carbanion to form intermediate **B**. **B** underwent cyclization under the action of a base to give intermediate **C**. Then the aromatize of **C** occurred giving the final product **3a**.

In summary, we developed an efficient, metal-free catalysts method to prepare phenol derivatives by the cyclization reaction under mild conditions. Various 1,3-dicarbonyl compounds were able to perform the cascade reaction smoothly to give the desired products in satisfactory yields. It is noteworthy that DMF serves not only as an efficient solvent, but also as a source of one-carbon synthon to benzene ring under the cascade catalysis of 1,1-dichloro-2-nitroethene. The present protocol provides a concise and environmentally benign route to afford highly functionalized phenol derivatives and has potential to be used for the synthesis of natural products and biologically active molecules.



Scheme 5. Plausible Catalytic Mechanism

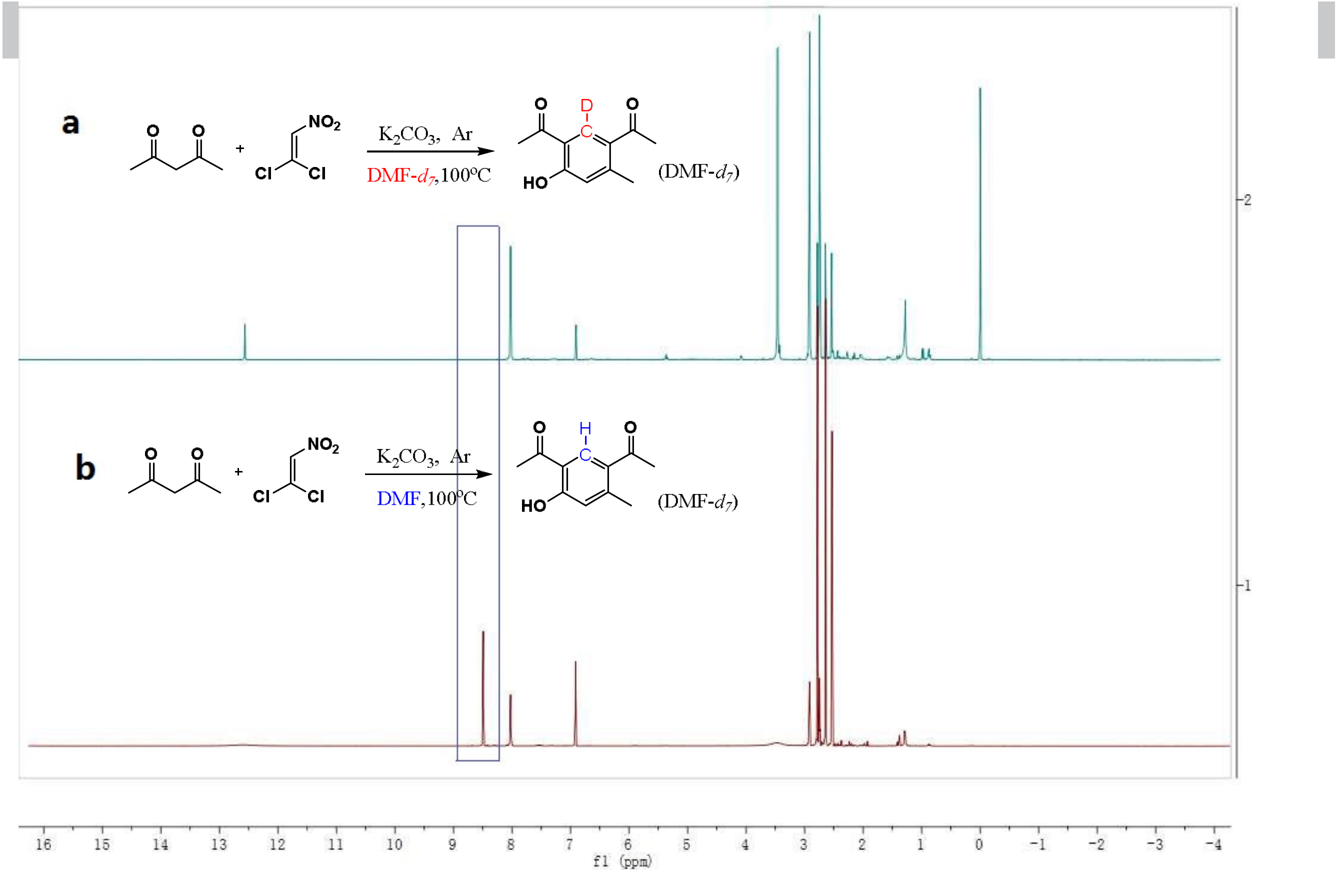


Fig 1. Comparison of ^{1}H NMR of **3a** in different solvents.

Acknowledgments

This work was financial supported by National Key Research and Development Program of China (2017YFD0200505), National Natural Science Foundation of China (Nos. 21472046, 21372079), Science and Technology Commission of Shanghai Municipality (No. 16391902300) and the Fundamental Research Funds for the Central Universities (222201718004).

References and notes

1. Tyman, J. H. P. Volume 52. *Synthetic and Natural Phenols.* 1996.
2. Abdel, A.; Sayed, M.; Rabalski, I. *Open Agriculture Journal*, 2008. 208(1): 7-14(8)
3. Dykes. *Cereal Foods World*, 2007.
4. Fardet, A.; Rock, E.; Rémésy, C. *Journal of Cereal Science*, 2008, 48(2): 258-276.
5. Weber, M.; Kleine-Boymann, M. Phenol[M] Ullmann's Encyclopedia of Industrial Chemistry. *Wiley - VCH Verlag GmbH & Co. KGaA*, 2004:324-326.
6. Liu, R. H. *Journal of Cereal Science*, 2007, 46(3): 207-219.
7. Correa, A.; Martin, R. *Journal of the American Chemical Society*, 2014, 136(20): 7253-7256.
8. Zhu, R.; Wei, J. B.; Shi Z. J. *Cheminform*, 2014, 45(4): 3706-3711.
9. Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. *Angewandte Chemie*, 2014, 53(26): 6791-6794.
10. Yu, Z. Z.; Ma, B.; Chen, M. J.; Zhang, J. L. *Journal of the American Chemical Society*, 2014, 45(48): 6904-6907.
11. Hao, X.Q.; Chen, L.J.; Ren, B. *Organic Letters*, 2014, 16(4): 1104-1107.
12. Alizadeh, A.; Ghanbaripour, R. *Research on Chemical Intermediates*, 2015, 41(11): 8785-8796.
13. Song, W.; Ackermann, L. *Angewandte Chemie*, 2012, 51(33): 8251-8254.
14. Perez-Jimenez, J.; Torres, J. L. *J Agric Food Chem*, 2011, 59(24): 12713-12724.
15. Okarter, N.; Liu, R. H. *Critical Reviews in Food Science and Nutrition*, 2010, **50**(3): 193-208.
16. Amphawan, A.; Vanittanakom, N.; Buddhasu, D. *Journal of Ethnopharmacology* 1995, 49, 163-169.
17. Wang, B. G.; Zhang, W. W.; Duan, X. J.; Li, X. M. *Food Chemistry*, 2009, 113(4): 1101-1105.
18. Bratt, K.; Sunnerheim, K. *Journal of Agricultural and Food Chemistry* 2003, 51 (3): 594-600
19. Prats, E.; Galindo, J. C.; Bazzalo, M. E.; Leon, A. *J Chem Ecol*, 2007, 33(12): 2245-53.
20. Padmasri, A. H.; Kumari, V. D.; Rao, P. K. *Studies in Surface Science & Catalysis*, 1998, 113: 563-571.
21. Karakhanov, E. A.; Narin, S. Y.; Dedov, A.G. *Applied Organometallic Chemistry*, 1991, 5(6): 445–461.
22. Molinari, R.; Poerio, T.; Argurio, P. *Catalysis Today*, 2006, 118(1):52-56.
23. Rudchenko, V. V.; Buevich, V. A.; Grineva, V. S.; Perekalin, V. V. *Chemistry of Heterocyclic Compounds*. 1975, 11(11): 1431-1436.
24. Grimmett, M. R. Product Class 4: Benzimidazoles. *Cheminform*. 2003, 34(45): 49-53.
25. Buevich, V. A.; Rudchenko, V. V.; Perekalin, V. V. *Chemischer Informationsdienst*. 1976, 7(32): 35-39.
26. Grimmett, M. R. Product class 4: benzimidazoles. *Science of Synthesis*. 2002, 12: 529-612.
27. Buevich, V. A.; Nakova, N. Z.; Perekalin, V. V. *Chemischer Informationsdienst*. 1979, 10(48): 621-630.
28. Feng, Y. *Journal of Organic Chemistry*, 2016. 81(21).
29. Zhu, F. J.; Zou, M. M.; Shao, X. S.; Li, Z. *RSC Adv.*, 2015, 5(76): 61752-61758.
30. Zhu, F. J.; Tian, X.; Shao, X. S.; Li, Z. *Tetrahedron Letters*, 2015, 56(43): 5945-5949.
31. Shao, X. S.; Zhu, F. J.; Song, R. J.; Li, S. *Synlett*, 2016, 27(14): 2167-2170.
32. Jones, G.; Stanforth, S. P. *John Wiley & Sons, Inc.* 2004:65–68.
33. Ding, S.; Jiao, N. *Angewandte Chemie*, 2012, 51(37): 9226-9237.
34. Gao, Q.; Tan, X.C.; Pan, Y. M.; Wang, H. S. *Chem Commun (Camb)*, 2012, 48(99): 12080-12081.

- A new synthetic method of polysubstituted phenols is developed.
- The reaction is produced in eco-friendly free-metal catalytic system.
- The synthetic method is simple and efficient.