Tetrahedron Letters 52 (2011) 5220–5223

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nano ceria catalyzed Ullmann type coupling reactions

Sandeep M. Agawane, Jayashree M. Nagarkar *

Department of Chemistry, Institute of Chemical Technology, Nathala Parekh Marg, Matunga, Mumbai 400 019, Maharashtra, India

ARTICLE INFO

Article history:
Received 2 July 2011
Revised 24 July 2011
Accepted 26 July 2011
Available online 2 August 2011

Keywords:
Nano ceria
Synthesis and characterization
Ullmann type coupling
Copper and ligand free
Heterogeneous catalysis

ABSTRACT

Ullmann type intermolecular coupling of aryl halide with hetero-aromatic compounds, such as phenols, amines, and thiophenols are key reactions for the formation of carbon–heteroatom bond in organic synthesis. We report a robust and novel method that provides an efficient and economic route for the synthesis of O, N, and S-arylation via Ullman coupling by using nano cerium oxide (ceria, CeO_2). CeO_2 is a cheaper catalyst compared to related copper based catalysts. This method provides a wide range of substrate applicability in the case of phenols and amines. Less reactive chlorobenzene substituted with strong electron withdrawing groups such as 4-nitrochlorobenzene and 4-cyanochlorobenzene favor the reaction. This protocol avoids the use of ligand and gives arylated product in satisfactory yields.

Diaryl ethers are important biologically active compounds. K13 and perrottetin are the naturally occurring compounds which contain ether linkage.[1a] Halituline having N-substituted pyrrole and **VX-745** being an aryl sulfide possesses biological activity.[1b,c] Aryl ethers and N-arylated compounds are widely used in organic synthesis, pharmaceutical, and biological applications.[2] Polyaromatics own exclusive characteristics that make them useful as organic conductors or semiconductors. Various reactions have been reported for the synthesis of aryl ethers and N-arylated compounds. Such compounds are obtained by employing intermolecular reaction between aryl halide and phenol or amine using Cu or Pd as a catalyst.[3] Many copper catalyzed C–O,[4] C–N,[3a,b] and C–S[1c,5] bond formation reactions have been carried out with or without ligand to form carbon–heteroatom bond and their applications seem to be important.[6] Various ligands have been used to carry out Ullmann reaction, such as phosphazene,[7a] ethylene glycol,[7b] neocuproine,[6d] *N*-methyl glycine,[7c] oxime-phosphine oxide ligand,[7d] tripod ligand,[7e] benzotriazole,[7f] 1,2-diaminocyclohexane,[7g] β-ketoester,[7h] and L-proline.[7i]

The practical applications of nanocrystalline metal oxides as catalysts in organic synthesis have been increased due to their high catalytic activity because of high surface area. The recyclability of the catalyst is the added advantage in the case of these catalysts. Since the reported catalysts are economically less affordable, there is a need to develop cheaper catalyst systems. Furthermore, simpler and more efficient methods for cross-coupling reaction are also needed. A few reactions are reported in which the catalyst is reusable and has the ability to make use of aryl chlorides. Recently, nano CuO,[8a] nano CuI,[3a,b] Cu_2O,[4] and Cu nanoparticle[8b] have been used for Ullmann type coupling.

The catalytic activity of ceria is well known for CO_2 fixation and transalkylation.[9] In continuation of our interest in exploring the catalytic activity of CeO_2 for organic reactions,[10a] herein we report its application in O, N, and S-arylation of phenols, amines, and thiols, respectively. CeO_2 is found to be an efficient, recyclable, and high yielding catalyst for such reactions. The catalyst was found to be highly active and afforded good to excellent yield with high selectivity. The C–O, C–N, and C–S coupling reactions were made attractive with the use of CeO_2, which is cheaper and an alternative to copper and palladium based catalysts without employing the ligand.

The CeO_2 nano particles are prepared by ultrasonically modified CTAB assisted method.[10,11] Figure 1 shows XRD, TEM, SEM, and EDAX spectra of prepared CeO_2. TEM analysis shows particle size 4–5 nm. The calculated surface area was found to be 214 m^2/g.

4-Nitrochlorobenzene was chosen as an alkylating agent for O-alkylation of phenol and this reaction was selected as a model reaction to test the catalytic activity of the different metal oxides (Scheme 1).[12] Table 1 gives the details about the surface area, particle size, and catalytic activity of SiO_2, ZnO, Al_2O_3, TiO_2, MnO_2, La_2O_3, CeO_2, and nano CeO_2. The nano CeO_2 shows better catalytic activity than bulk CeO_2 because of the smaller particle size and high surface area.

This reaction was optimized for various parameters, such as temperature, base, solvent, and catalyst concentration. The results are given in Table 2. Initially 20 mol % of nano ceria was used for optimizing the temperature using DMF as a solvent. It was found that 87% of the product was formed at 110 °C in 3 h. The

---

* Corresponding author. Tel.: +91 22 33611111/2222; fax: +91 22 33611020.
E-mail addresses: smagawane@gmail.com (S.M. Agawane), jayashreenagarkar@yahoo.co.in, jm.nagarkar@ictmumbai.edu.in (J.M. Nagarkar).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.117

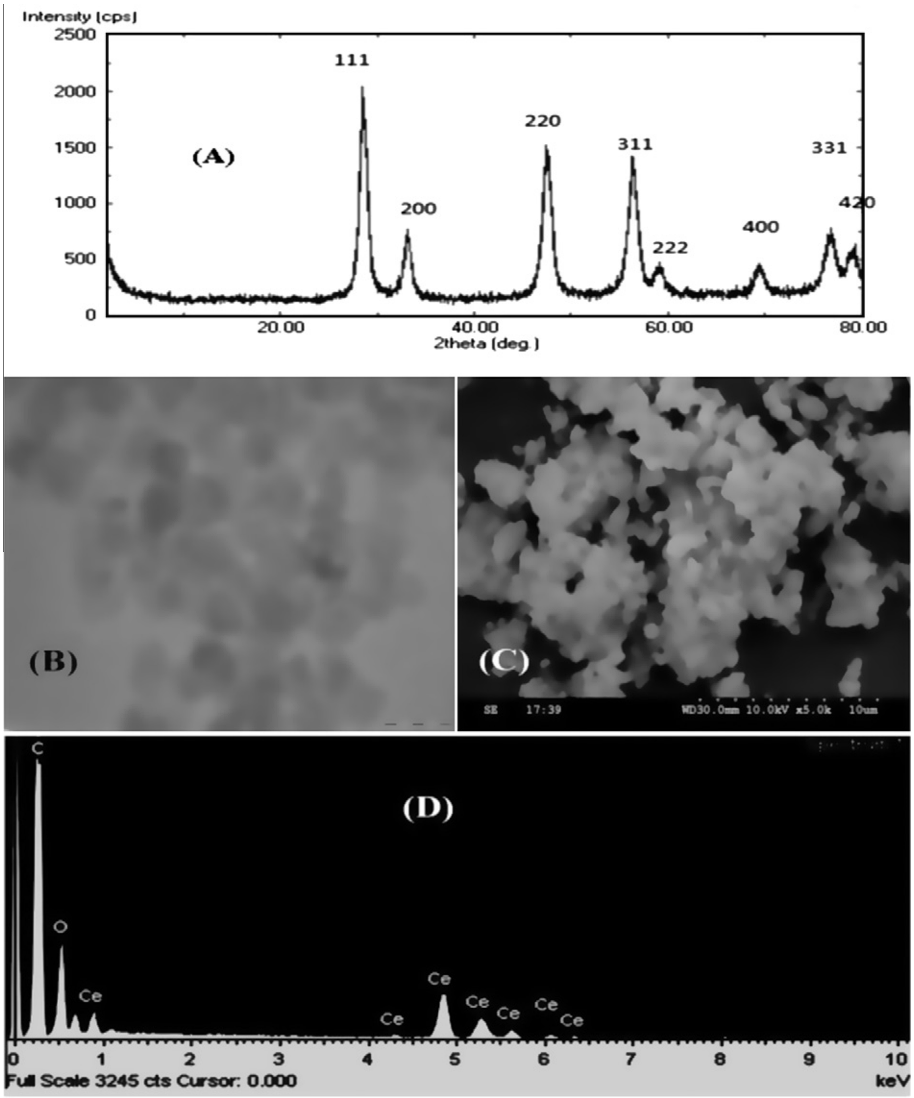
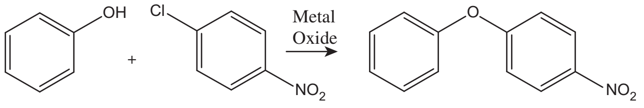


Figure 1. (A) XRD, (B)TEM, (C) SEM, and (D) EDAX spectra of nano CeO_2 powder.



Scheme 1. O-arylation of phenol with 4-nitrochlorobenzene catalyzed by various metal oxides.

Table 1
Influence of the various metal oxides on the O-arylation of phenol[a]

Sr. no.	Metal oxides	Surface area	Size	Yield [b] (%)
1	SiO_2		60–120 mesh	48
2	ZnO	12.16 m^2/g	—	45
3	Al_2O_3	—	150–300 mesh	51
4	TiO_2	14.68 m^2/g	—	47
5	MnO_2	—	22 µm	28
6	La_2O_3	—	14 µm	23
7	CeO_2	11 m^2/g	—	78
8	CeO_2 (nano)	214 m^2/g[c]	4–5 nm	87

[a] Reaction conditions: phenol (1.2 mmol), 4 nitro chlorobenzene (1 mmol), potassium carbonate (1.2 mmol), 1 mL DMF, and 20 mol % catalyst for 3 h at 110 °C.
[b] Isolated yield.
[c] Calculated by formula.

Table 2
Influence of the reaction conditions on the O-arylation of phenol[a]

Sr. no.	Catalyst (mol %)	Solvent	Base	Temp	Yield[b] (%)
1	20	DMF	K_2CO_3	RT	–
2	20	DMF	K_2CO_3	60	21
3	20	DMF	K_2CO_3	80	80
4	20	DMF	K_2CO_3	110	87
5	20	Dioxane	K_2CO_3	110	22
6	20	Toluene	K_2CO_3	110	20
7	20	Ethanol	K_2CO_3	110	—
8	20	DMSO	K_2CO_3	110	93
9	20	DMSO	K_2CO_3	60	55
10	20	DMSO	K_2CO_3	80	53
11	20	DMSO	KOH	110	96
12	20	DMSO	K_3PO_4	110	95
13	20	DMSO	$NaHCO_3$	110	12
14	20	DMSO	$N(Et)_3$	110	—
15	15	DMSO	KOH	110	94
16	10	DMSO	KOH	110	95
17	5	DMSO	KOH	110	96
18	**2.5**	**DMSO**	**KOH**	**110**	**96**

[a] Reaction conditions: phenol (1.2 mmol), 4 nitro chlorobenzene (1 mmol), base (1.2 mmol), and 1 mL solvent for 3 h.
[b] Isolated yield.

temperature below 110 °C lowers the yield. DMSO was found to be the best solvent after screening various solvents. KOH as base gave maximum yield in comparison with bases, such as K_3PO_4, $N(Et)_3$, $NaHCO_3$, and K_2CO_3. The 2.5 mol % catalyst concentration was sufficient to give maximum yield of the required product.

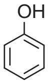
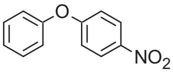
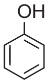
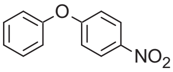
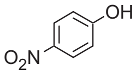
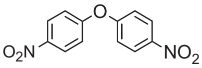
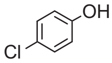
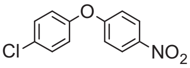
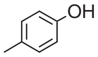
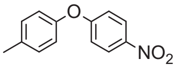
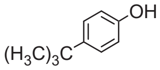
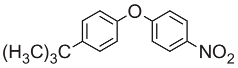
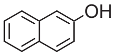
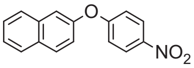
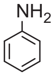
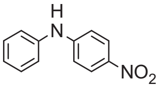
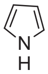
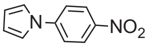
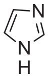
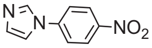
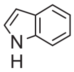
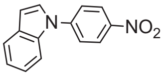
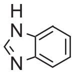
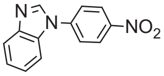
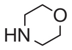
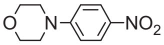
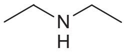
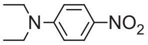
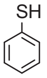
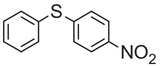
We have also explored different aryl chlorides for the same reaction under the optimized conditions. The results are shown in Table 3. It was observed that chlorobenzene with electron withdrawing groups gives the respective product. The reactivity of chloro compound decreased in the order of 4-NO_2, 4-CN, and 4-CHO groups. 2-Nitrochlorobenzene also gave excellent yield of the product which ruled out the steric effect. The results also show that chlorobenzene, iodobenzene, and bromobenzene were ineffective for the reaction. Hence it was concluded that the cerium

Table 3
O-arylation of phenol with different chlorobenzene[a]

Sr. No	Chlorobenzene	Time (h)	Yield [b] (%)
1	Chlorobenzene	10	—
2	Bromobenzene	10	—
3	Iodobenzene	10	—
4	4-Nitrochlorobenzene	3	96
5	2-Nitrochlorobenzene	3	92
6	4-Cyanochlorobenzene	4	65
7	4-Chlorobenzaldehyde	5	$\leqslant$10
8	4-Chlorotoluene	10	—
9	4-Dichlorobenzene	10	—

[a] Reaction conditions: phenol (1.2 mmol), chlorobenzene (1 mmol), KOH (1.2 mmol), 1 mL DMSO and 2.5 mol % catalyst at 110 °C in air.
[b] Isolated yield.

Table 4
O, N and S-arylation with 4-nitrochlorobenzene[a]

Sr.no.	Phenol/amine/thiophenol	Product	Time (h)/Yield[b] (%)
1			3/96
2[c]			45 min/98
3			6/83
4			1.5/84
5			2/72
6			2/84
7			4/75
8			6/46
9			8/80
10			8/90
11			1.5/91
12			2/93
13			10/96
14			9/42
15			2/80

[a] Reaction conditions: phenol/amine/thiophenol (1.2 mmol), 4-nitrochlorobenzene (1 mmol), KOH (1.2 mmol), 1 mL DMSO, and 2.5 mol % catalyst at 110°C in air.
[b] Isolated yield.
[c] Using 4-nitroiodobenzene.

Table 5
Recyclability of nano CeO_2[a]

Run	Fresh	Run 1	Run 2	Run 3
% Yield[b]	96	95	91	90

[a] Reaction conditions: phenol (1.2 mmol), 4-nitrochlorobenzene (1 mmol), KOH (1.2 mmol), 1 mL DMSO, and 2.5 mol % catalyst at 110 °C for 3 h.

[b] Isolated yield.

oxide can only catalyze the coupling reaction in which strong electron withdrawing group is attached to the aryl chloride.

Various substituted phenols, amines, heterocyclic amines, and thiophenols were also successfully coupled with 4-nitrochlorobenzene to obtain respective O, N, and S-arylated products (Table 4). Both the electron donating and electron withdrawing substituents on the phenol afforded the corresponding O-arylated product with good to excellent yield. Thiophenol also reacts with 4-nitrochlorobenzene and gives the product with satisfactory yield.

The reusability of the catalyst was checked for three cycles. The catalyst was separated by centrifugation, washed twice with dichloromethane, dried and then used for subsequent run. It was found that the catalyst activity decreases slightly for the next cycle (Table 5).

In conclusion, we have prepared nano CeO_2 catalyst for Ullmann type coupling between 4-nitrochlorobenzene and variety of phenols, amines, and thiophenols. The given methodology is an efficient, inexpensive, and environmentally benign heterogeneous catalyst system for the efficient carbon–heteroatom coupling under ligand-free conditions. This recyclable catalyst offers advantages like simple work-up and high yields.

Acknowledgment

The authors are thankful to UGC-Green Technology Centre, New Delhi, India for awarding the fellowship.

References and notes

1. (a) Zhang, J.; Zhang, Z.; Wang, Y.; Zheng, X.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 5112–5116; (b) Banwell, M. G.; Goodwin, T. E.; Sarah, Ng.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043–3060; (c) Bagley, M. C.; Dix, M. C.; Fusillo, V. *Tetrahedron Lett.* **2009**, *50*, 3661–3664.
2. (a) Barchechath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **2005**, *48*, 6409–6422; (b) Zhong, C.; He, J.; Xue, C.; Li, Y. *Bioorg. Med. Chem.* **2004**, *12*, 4009–4015; (c) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345–2347.
3. (a) Shen, G.; Lv, X.; Qian, W.; Bao, W. *Tetrahedron Lett.* **2008**, *49*, 4556–4559; (b) Sreedhar, B.; Arundhathi, R.; Reddy, P. L.; Kantam, M. L. *J. Org. Chem.* **2009**, *74*, 7951–7954; (c) Fernandez Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181; (d) FernandezRodriguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem. Eur. J.* **2006**, *12*, 7782–7796.
4. (a) Liu, Z.; Chen, Y. *Tetrahedron Lett.* **2009**, *50*, 3790–3793; (b) Kim, J. Y.; Park, J. C.; Kim, A.; Kim, A. Y.; Lee, H. J.; Song, H.; Park, K. H. *Eur. J. Inorg. Chem.* **2009**, *28*, 4219–4223.
5. Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 1411–1415.
6. (a) Ouali, A.; Laurent, R.; Caminade, A. M.; Majoral, J.-P.; Taillefer, M. *J. Am. Chem. Soc.* **2006**, *128*, 15990–15991; (b) Ouali, A.; Renard, B.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2006**, *20*, 5301–5313; (c) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Eur. J.* **2006**, *12*, 3636–3646; (d) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803–2806.
7. (a) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283–1286; (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517–3520; (c) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, *7*, 1254–1258; (d) Zhu, D.; Xu, L.; Wu, F.; Wan, B. *Tetrahedron Lett.* **2006**, *47*, 5781–5784; (e) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609–5612; (f) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199–7202; (g) SanMartin, M. R.; Dominguez, E.; Tellitu, I. *Chem. Eur. J.* **2007**, *13*, 5100–5105; (h) Lv, X. J.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867; (i) Zhang, H. K.; Cao, W.; Ma, D. *Synth. Commun.* **2007**, *37*, 25–35.
8. (a) Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett.* **2007**, *9*, 3397–3399; (b) Kidwai, M.; Mishra, N.; Bansal, V.; Kumarb, A.; Mozumdar, S. *Tetrahedron Lett.* **2007**, *48*, 8883–8887.
9. (a) Juarez, R.; Concepcion, P.; Corma, A.; Garcıa, H. *Chem. Commun.* **2010**, *46*, 4181–4183; (b) Bhanage, B. M.; Fujita, S.; Ikushima, Y.; Arai, M. *Appl. Catal. A.* **2001**, *219*, 259–266; (c) Juarez, R.; Corma, A.; Garcia, H. *Green Chem.* **2009**, *11*, 949–952.
10. (a) Agawane, S. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, *52*, 3499–3504; (b) Terribile, D.; Trovarelli, A.; Llorca, J.; Leitenburg, C.; Dolcetti, G. *J. Catal.* **1998**, *178*, 299–308.
11. *General procedure for synthesis of nano ceria:* CeO_2 nanoparticles were prepared by adding ammonia solution to an aqueous solution of cerium (III) nitrate in the presence of CTAB. In a typical procedure, added 1 g of $Ce(NO_3)_3$ in a solution of CTAB dissolved in 100 cm^3 of water. Mole ratio of Ce/CTAB was kept at unity. pH of the solution was adjusted between 10–11 by adding 25% ammonia solution under vigorous stirring for 2–3 h. The resulting mixture was ultrasonicated for 10 min and then filtered off. The obtained precipitate was washed with water and subsequently with acetone and dried at 120 °C for 12 h. It was then calcined at 500 °C for 3 h. The prepared CeO_2 was characterized with various techniques, such as X-ray diffractograms (XRD), Fourier Transform Infra-Red Spectroscopy (FT-IR), Transmission Electron Microscope (TEM), Field Emission Gun-Scanning Electron Microscopes (FEG-SEM) coupled with EDAX.
12. *General procedure for the O-alkylation with 4-nitrochlorobenzene:* In a 25 mL round bottomed flask was taken a mixture of phenol/amine/thiophenol (1.2 mmol, 0.112 g), 4-nitrochlorobenzene (1 mmol, 0.157 g), base KOH (1.2 mmol, 0.08 g) and 1 mL DMSO was added. Further 2.5 mol % catalyst (4.5 mg) was added to the reaction mixture. The reaction mixture was heated to 110 °C for appropriate time. Reaction is monitored on TLC. After completion of the reaction the catalyst was separated by centrifugation and subsequently washed with dichloromethane. The reaction mixture was diluted with water and the product was extracted by dichoromethane ($3 \times 10\ cm^3$). The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure to give the product. The product was purified by column chromatography by using pet ether and ethyl acetate solvent system. The purified product was then confirmed by its spectral analysis after analyzing by IR, ^1H NMR, and mass spectra.