Short Communication: Iodine-DMSO Catalyzed aromatization of Polysubstituted Cyclohexanone Derivatives: An Efficient Method for the Synthesis of Polyfunctionized Biaryls Derivatives

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Citation. S.V. Gaikwad, M. V. Gaikwad, P. D. Lokhande, Iodine-DMSO Catalyzed aromatization of Polysubstituted Cyclohexanone Derivatives: An Efficient Method for the Synthesis of Polyfunctionized Biaryls Derivatives. *J. Appl. Organomet. Chem.*, **2021**, *1*(1), 1-8.

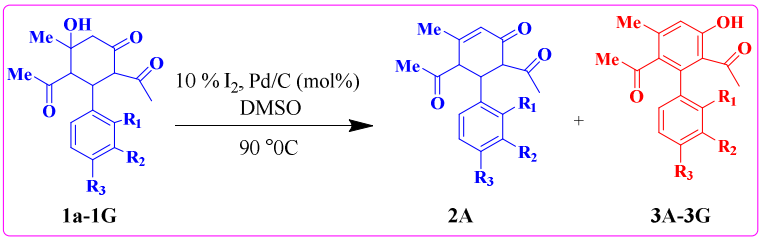
https://doi.org/10.22034/jaoc.2021.128538

Article info:
Received: March 1, 2021
Accepted: March 18, 2021
Available Online: March 25, 2021
Checked for Plagiarism:
Dr. Sami Sajjadifar
Peer Reviewers Approved by:
Dr. Sami Sajjadifar
Editor who Approved Publication:
Professor Dr. Abdelkader Zarrouk

Keywords:
Molecular Iodine, DMSO, Pd/C, Biaryl Phenol, Multi Substituted Cyclohexanone

ABSTRACT

We have developed a simple method for the regioselective aromatization of Polysubstituted Cyclohexanone derivatives in the presence of iodine (25 mol %), Pd/C (10 Mol%) in dimethyl sulfoxide at 90 °C, afforded functionalized biphenyls with at least one phenolic hydroxyl in moderate to very good yields.



Introduction

The polysubstituted aryl group and biphenyls were important scaffolds in synthetic chemistry, natural product chemistry, pharmaceutical chemistry and material sciences. [1] The hydroxy phenolic biaryl derivatives come in a large number of naturally occurring compounds, such asHerbertenediol, Mastigophorene A, and MastigophoreneB (Figure 1) [2]. Therefore, the preparation of polysubstituted aromatics in general and biphenyls, in particular, has been a fascinating area in organic syntheses [3].

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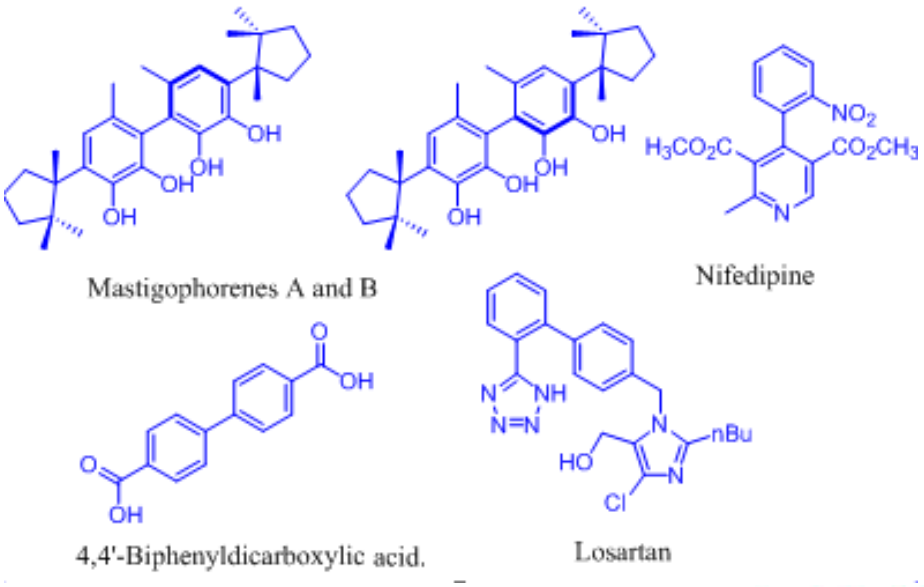


Figure 1.

The traditional approaches are formed on aromatic substitution, which add substituent to the benzene ring. Synthetic processes based on this route have been optimized including transition metals catalyzed coupling reaction [4], nucleophilic [5], and electrophilic substitution reaction [6]. However, these approaches have some drawbacks from the viewpoint of atom economy, temperature [6]. The synthesis of the polysubstituted aromatic backbone from acyclic precursors has received tremendous interest in the researcher for their short synthetic steps and selective nature [7]. The classical synthesis of an alicyclic compound to an aromatic scaffold via aromatization is one of the traditional methods for the synthesis of polysubstituted biaryl derivatives [8]. Considering the above points, we were prompted to synthesize functionalized biphenyls, starting from *β*-keto carbonyl compounds and aromatic aldehydes. It is important to mention here that the reaction of *β*-keto carbonyl compounds and aromatic aldehydes which results in most of these intermediate cyclohexanone derivatives has also been reported earlier and the compounds have been fully characterized by spectroscopic techniques [9]. The *Sharma et al.* used I_2/MeOH reagent previously for the aromatization of multi substituted cyclohexanone derivative to 1diacetyl-bis-phenylethan-1-one [10] with 50-52% yield.

Since the last decade, our research group has explored iodine chemistry in the novel organic transformation, always useful to develop a cost-effective, safe, greener new synthesis approach for organic synthesis [11]. The milder acidic nature of iodine facilitates its usage in organic synthesis. Previously, we have reported the iodine mediated useful chemoselective transformation such as oxidative chemoselective dehydrogenation, aromatization and their synthesis utility for natural product synthesis [12-17]. Considering the difficulties in the aromatization of polysubstituted cyclohexanone derivatives, the development of an efficient and environmentally friendly method is highly desirable. Herein, we wish to report a regioselective aromatization of polysubstituted cyclohexanone iodine, Pd/C in DMSO. To the best of our knowledge, there are no such reports available for the consecutive aromatization using iodine, Pd/C in DMSO.

Experimental Section

General information

General methods of the reagents were commercially available and used without further purification. All reagents were purchased from Sigma Aldrich, Acros, Alfa Aesar and Avra chemical, S.D. Fine chemical Analytical thin-layer chromatography was performed on silica gel using silica gel (100-200 mesh). The solvent was dried including distilled over A4 molecular sieves before use. DMSO was dried over activated A4 molecular sieves before use. ^{1}H NMR, ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) as an internal standard at ambient temperature at Bruker 300, 400, for 1H NMR and 75 &100 MHz for ^{13}C NMR. FT-IR data were collected over a spectrometer. LC-MS was analyzed on a mass spectrometer connected to an AcquityQda detector, 2489 UV/ Vis detector, GC-MS data collected on AOS-20i Autoinjector Shimadzu GC/MS system mass spectrometer.

General procedure for preparation of 1,1'-(1,1'-(4'-fluoro-5-methyl-3-oxo- 1,2,3,4-tetrahydro-[1,1'-biphenyl]-2,6-diyl)bis(ethan-1-one)(2A)

In a dry 10 mL round-bottom flask,1 equiv. of the compound in DMSO was taken and 0.10 mol % of $I_2$was added. The reaction mixture was heated at 90 °C for 8 h, after completion of the reaction, and monitored by TLC. The reaction mixture was cooled at room temp and add chilled saturated sodium thiosulphate solution was added. The solid was filter out dry over vacuum and purified by column chromatography (Ethyl acetate: hexane) to obtain the desired compound.

Semisolid;R*f*: 0.40 (EtOAc/ hexane 3/5), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J*= 3.3 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 6.18 (s, 1H), 2.27 (s, 3H), 1.96 (s, 3H), 1. .89 (d, J = 1.4 Hz, 3H).δ C (101 MHz, $CDCl_3$) 204.72, 191.36,180 .08, 163.13, 160.69, 149.07, 138.06, 128.66, 128.58, 125.18,115.8 115.59, 104.26, 62.95, 41.10, 28.02, 24.55, 22.61.

1,1'-(3',4'-dimethoxy-5-methyl-3-oxo-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2,6- diyl)bis(ethan-1-one) (2D)

White solid, m.p. 57 °C,R*f*: 0.50 (EtOAc/ hexane 2/8), ^{1}H NMR (300 MHz, $cdcl_3$) δ 7.59 (d, *J*=1 .4Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.34 (s, 1H), 5.95(s, 1H), 4.43 4.43 (s, 3H), 4.39 (s, 3H), 4.02 (d, *J* = 15.2 Hz, 1H), 3.66 (d, *J* = 15 .2 Hz, 1H), 2.67 (s, 3H), 2.02 (s, 3H); C (75 MHz, $CDCl_3$) 203.75, 198.44, 191.92, 157.45, 152.52, 148.03, 143.71, 126.21, 129.46, 114.14, 110.52, 70 .72, 57.35, 56.16, 56.73, 29.5, 28.54, 20.2, 19.78.

General procedure for preparation of 1,1'-(4'-fluoro-3-hydroxy-5-methyl-[1,1'-biphenyl]-2,6-diyl)bis(ethan-1-one

In a dry 10 mL round bottamflask, 1 equiv of compound in DMSO was taken and 0.25 equiv of I_2 and Pd/C 10% (20%) was added. The reaction mixture was heated at 90 °C for 3 h, after completion of reaction, monitored by TLC, and cooled at room temperature.Chilled saturated sodium thiosulphate solution was added. The solid was filtered out dry over vacuum and purified by column chromatography (*Ethyl acetate:hexane*)

1,1'-(4'-fluoro-3-hydroxy-5-methyl-[1,1'-biphenyl]-2,6-diyl)bis(ethan-1-one)(3A).

Semisolid, (254 mg, 72%); R*f*: 0.50 (EtOAc/ hexane 2/8^{1}H NMR (400 MHz, $CDCl_3$) δ 16.24 (s,1H), 7.43 – 7.38 (m, 2H), 7.23(t, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 2.50 (s, 3H), 2.19 (s, 3H), 2.12 (d, *J* = 1.4 Hz, 3H).δ C (75 MHz, $dmsod_6$) 205.52, 204.52, 161.16, 144.45, 137.09,130.98, 129.98, 28.66, 124.66, 115.68, 115.21, 109.54, 34.79, 30.41, 29.85, 27.90, 25.12.

1,1'-(3-hydroxy-5-methyl-[1,1'- biphenyl]-2,6-diyl)bis(ethan-1-one).(3B)

Faint yellow solid, m.p. 89-92 °C, R*f*: 0.50 (EtOAc/ hexane 3/), FTIR (cm^{-1}): 3436, 3019, 2363, 1693, 1631; ^{1}H NMR (300MHz, DMSO+d_6), δ 16.47, (s,1H, OH), 7.45–7.42 (m, 3H, 7.30–7.26 (m, 2H), 6.85 (s, 1H), 2.26 (s, 3H), 1.71 and 1.70 (two s, 6H) ^{13}C NMR δ H (75 MHz, dmso) 205.60, 204.19, 139.08, 133.09, 130.94, 129.50, 128.96, 128.9 0, 128.61, 128.20, 124.12, 109.66, 31.74, 30.88, 27.81, 25.32.

1,1'-(3-hydroxy-4'-methoxy-5-methyl-[1,1'-biphenyl]-2,6-diyl)bis(ethan-1-one(3C)

Yellow liquid;^{1}H NMR (300 MHz, $CDCl_3$) δ 16.27 (s, 1H), 7.11(d, *J*= 8.6 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.16 (s, 1H), 3.79 (s, 3H), 2.26 (s, 3H), 1.94 (s, 3H), 1.86 (s, 3H).

1,1'-(3-hydroxy-3',4'-dimethoxy-5-methyl-[1,1'-biphenyl]-2,6-diyl)bis(ethan-1- one(3D)

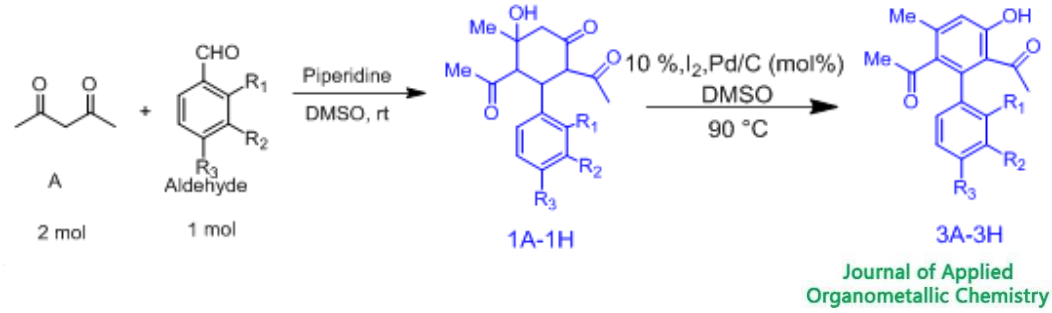
^{1}HNMR (300 MHz, $CDCl_3$) δ 16.15 (s, 1H), 7.53 (d,*J* = 1.4Hz,1 H), 7.29 (dt, *J* = 13.3, 4.9 Hz, 2H), 6.60 (s, 1H), 4.36 (s, 3H),4.33 (s, 3H), 3.13 (s, 3H), 2.60 (s, 3H), 1.96 (s, 3H).

1,1'-(4'-chloro-3-hydroxy-5-methyl-[1,1'-biphenyl]-2,6-diyl)bis(ethan-1-one (3F)

Light yellow solid.R*f*: 0.40 (EtOAc/ hexane 3/8 M.P.142–144 °C. IR (KBr): 3733, 3498, 29 75, 2914, 1699, 1597 ^{1}H NMR (300 MHz, $cdcl_3$) δ 16.25 (s, 1H 7.29 (s, 7H), 7.13 (d, *J*= 8.6 Hz, 4H), 6.16 (d, *J* = 1.5 Hz, 3H), 2.25 (s, 8H), 1.94 (s, 8H), 1.88 (s, 10H); ^{13}CNMR (75 MHz $CHCl_3$), d 206.1, 206.0, 161.7, 141.3, 138.4, 137.8, 136.0, 135.8 131.9, 129.5, 119.8, 109 .9, 32.3, 32.0, 20.4 MS (ESI^{+}): m/z: 303.5 $[M+H]^{+}$ 304.

Result and Discussion

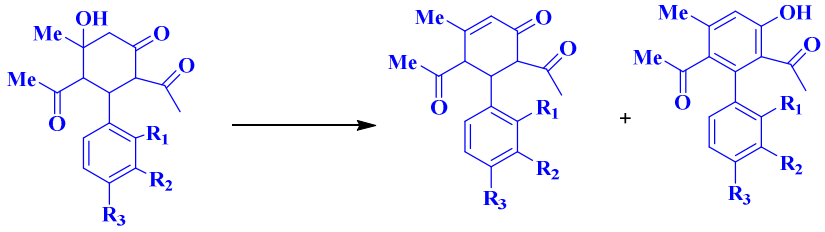
Accordingly, the starting precursor multisubstituted cylohexanone derivatives **1A-1H**were prepared by the reaction of Knoevenagel/Michael/Aldol condensation of aromatic aldehyde and *β*-keto ketones in the presence of piperidine base [9] (Scheme 1, 1A-1H). Initially, we attempted the oxidative aromatization of 2,4-diacetyl-3-(4-flurophenyl)-5-hydroxy-5-methyl cyclohexanone**1A** using iodine (10%) in DMSO at room temperature and no change was observed.



Scheme 1. Synthesis of biphenyl phenol via Knoevenagel/Michael/Aldol condensation of aromatic aldehyde and *β*-keto ketones

When we applied 10 mol % at 60 °C after 3h, TLC confirmed the absence of the reactant and new spots on TLC was developed. The new compound was purified by column chromatography and characterized spectral data such as ^{1}H NMR, ^{13}C NMR and GC-Mass spectra. The ^{1}H NMR of **2A** showed a sharp singlet at 6.18 ppm for 1H and absence of peak for OH proton. Furthermore, in ^{13}C, NMR spectrum revealed a distinct peak at **104.26** ppm for olefin carbon and the absence of one CH_2 carbon peak at the shielded region. The peaks appeared at 204.22, 191.36, and 180.08corresponding to the carbonyl carbon. Based on the spectral data the compound **2A** was confirmed. The detailed study of the spectral analysis showed the formation of compound 65d with 65% yield (**Tabe1, Entry 2**). After that, we had to apply 10% iodine at 90 °C for 8 h to give 64% of product 2A (**Table 1, entry 3**). Increasing the mole% of molecular iodine up to 25mol% at 90 °C produced a mixture of product in 62% of **2A** and 25% of **3A** (**Table1**, **entry 4**).

Table 1. Optimization reaction condition for the conversion of 1A to 2A & 3A

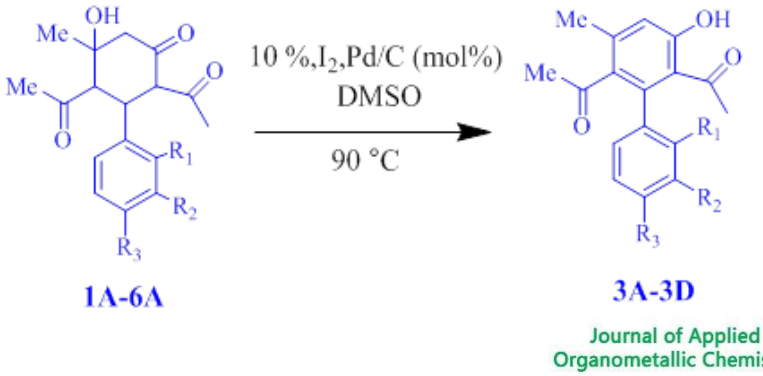


1A 2A 3A

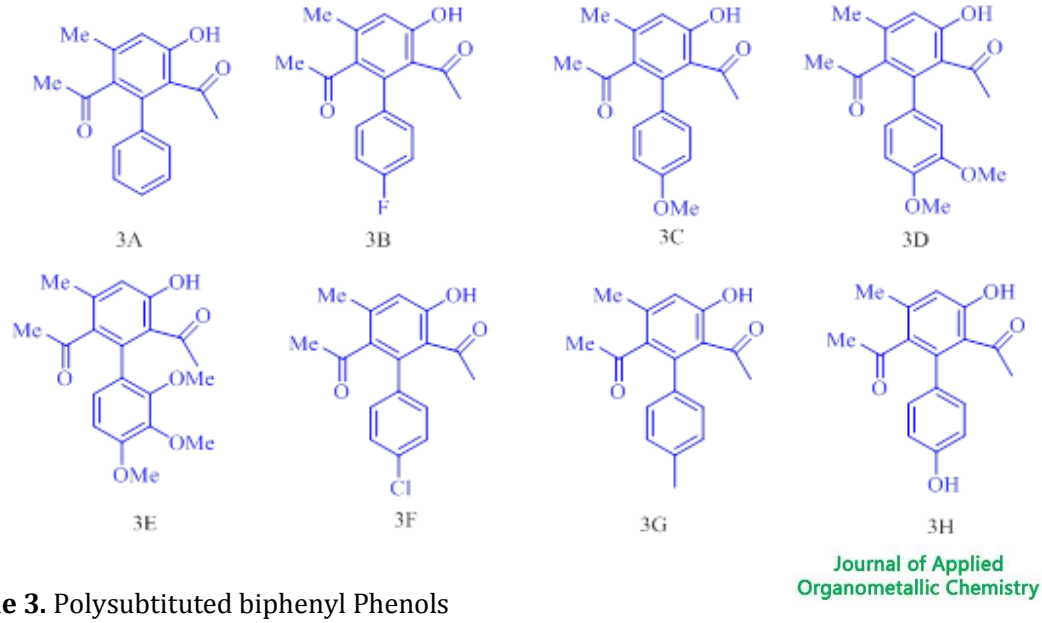
Entry	Iodine (mol%)	Pd/C (mol%)	Temp (°C)	Time (h)	Yield (Product A %)	Yield (Product B %)
1	10	-	rt	12	--	---
2	10	-	60	12	45	-
3	10	-	90	8	64	-
4	25	-	90	8	62	20
5	25	-	100	3	---	Reaction burn
6	25	10%	90	6	10	55
7	25	20	90	3	--	65
8	25	20	100	3	-	62
9	75	20	90	3	-	60
10	100	20	90	3	-	62

Note: Without use of Pd/C reaction burn at 80 to 100 °C; Here we mentioned best-optimized condition

When the 25 mol% iodine was used at 100 °C, the reaction mass was decomposed and turned black tar. After several trials, we obtained a similar result as the reaction mass was burned above 100 °C. We decided to use the I_2/DMSO in combination with 10% P/dC reagent for the aromatization of cyclohexanone derivatives. Surprisingly, when we applied 10% of Iodine with 10%Pd/C at 90 °C afforded compound 2A 10% alone with 3A 55% (**Table 1, entry 6**) with no decomposing (no. burning) of reaction mass. Accordingly, when the use of 20 mol% Pd/C and 25 mol% molecular iodine in DMSO solvent was heated at 90 °C for 3h, the desired product was given. The reaction worked without decomposing giving 65% of **3A** (**Table 1 entry 7**). After this increase in the % of iodine from 25 to 100 %, no improvement in the yield was observed. At 75% and 100% iodine in 20%, Pd/C at 90 °C gave 60 to 65% yield of product **3A**. That is there was no change observed in the percentage yield of product **3A**. Therefore, 25% of iodine with 20% Pd/C is the best-optimizedcondition for the aromatization of multi substituted cyclohexanone tobiphenyl]-2,6-diyl)bis(ethan-1-one) precursor. The products were easily purified by column chromatography; the yields were 65% for **3A** and confirmed by ^{1}H,^{13}C NMR spectroscopy method. The ^{1}HNMR product showed singlet at δ 16.24 (s,1H), for 1H corresponding to the OH group. The peak at 2.50 is singlet for (s, 3H, CH3) and the peak at 2.19 and 2.12 for (two s, 6H, $COCH_3$). In the ^{13}CNMR, the two signals at the downfield region at 205.52, 204.41belong to the carbonyl carbon group. We turned our attention toward testing the scope of the protocol with a variety of multi-substituted cyclohexanone derivatives (Scheme 2).



Scheme 2. Synthesis of Biphenyl Phenolvia aromatization using I_2, Pd/Cin DMSO



Scheme 3. Polysubtituted biphenyl Phenols

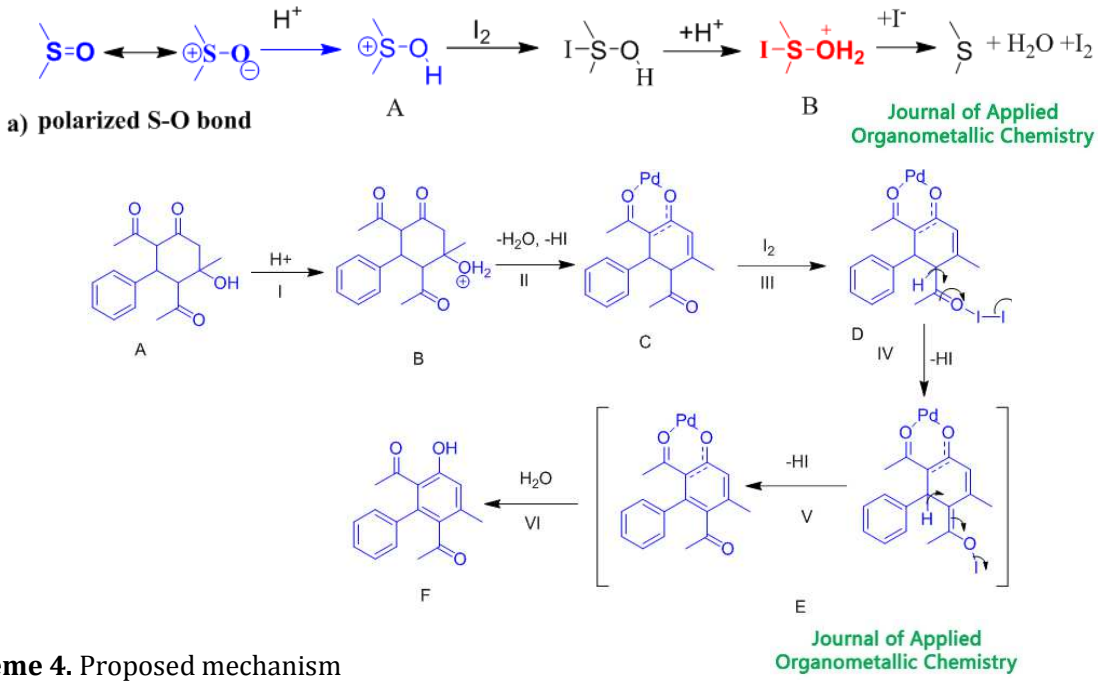
Therefore, 25 mol% iodine and 10 mol% Pd/C in DMSO gave the best result. With the optimized conditions in hand, with this result, we focused on testing the scope of the protocol with a variety of polysubstituted cyclohexanone. The series of polysubstituted cyclohexanone having numerous functional groups,electron-donating and withdrawing group on the phenyl ring was synthesized and treated with the optimized condition for up to 3 h reaction time, giving the desired product with 50-66% yield.

Accordingly, substrates bearing electron-donating substituents offered excellent yields (up to 65%) (Scheme 3). In the case of methoxy substitution, biphenyl was obtained in 60 to 66%% yield (Scheme 3). However, in the case of electron-withdrawing substituent's like -fluoro, -chloro gave yields of the biphenyl phenol 62 to 64%, respectively (Scheme 3).

The methods showed the new approaches for the aromatization of polysubstituted cyclohexanone derivatives. Compared with the previous studies, this method is more superior in terms of yield, temperature, reaction time and efficiency [10]. Future work may include the find out the exact role of Pd/C on this aromatization reaction with molecular iodine. The application of these compounds in the designing of new biologically important molecules is underway.

Mechanism

Dehydration and enolization were facilitated by iodine/DMSO, which generates HI in situ [12-14], acting as a Lewis acid. In situ generated HI protonated the *t*-hydroxyl group and underwent dehydrohalogenation followed by dehydration to afforded compound C. The carbonyl group of acetyl group was polarized by $I_2$and promotes the removal of hydroiodic acid to obtain intermediate (E). Finally, the bond between Pd and carbonyl group broke with the addition of acidic H_2O, giving the desired product F.



Scheme 4. Proposed mechanism

Conclusion

In summary, we have developed a simple method for the preparation of functionalized biphenyls via domino Knoevenagel, Michael and Aldol reactions, followed by the oxidation of the intermediate cyclohexanone with iodine. The compounds were obtained in moderate yields. Our explanation in this work makes it possible to prepare biphenyl phenol products in a high yield compared with those of the reported method.

Acknowledgments

SVG is thankful to UGC-BSR. (UGC file No F.4-3/2006(BSR) dated Dec 2011], UGC-New Delhi.

Supporting Information Summary

Synthesis details of all the novel derivatives and their characterization along with spectrums of novel derivatives available in the Supporting file.
Link:
http://jaoc.samipubco.com/article_128538.html

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