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An efficient regioselective synthesis of functionalized biphenyls *via* sequential reactions of aromatic aldehydes and β-keto esters or ketones

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Abstract: Knoevenagel/ Michael/ Aldol reactions of aromatic aldehydes and β-keto esters/ketones in a sequential manner yielded the intermediate cyclohexanones in good yields. The latter on oxidative aromatization with iodine afforded the functionalized biphenyls with at least one phenolic hydroxyl in moderate to good yields.

Keywords: *Polysubstituted benzenes, Aldol reactions, Michael additions, Knoevenagel reaction, Regioselective, Hydroxylated biphenyls*

Phenyl group and polysubstituted benzenes are key structures of great utility in synthetic and natural product chemistry, medicinal chemistry and material sciences. Hydroxylated biphenyl derivatives occur in a large number of naturally occurring compounds, such as vancomycin, biphenomycin and ellagitannins.[1] Therefore, preparation of polysubstituted aromatics in general and biphenyls in particular has been a fascinating area in organic syntheses.[2] Classical approaches are based on aromatic substitution, which introduces a substituent to the benzene ring. Synthetic methodologies based on this route has been developed including electrophilic[3] or nucleophilic substitutions[4], coupling reactions[5] catalyzed by transition metals, and metallation-functionalization reactions.[6] However, these approaches have some drawbacks from the viewpoint of atom economy[7] or environmental concern. The methods that construct the aromatic backbone from acyclic precursors have received growing interest recently due to their short synthetic steps and selective nature.[8] These general features are common in the most useful benzannulation reactions involving different inter- and intramolecular cyclizations, cycloadditions and benzannulation reactions,[9-16] synthesis of acetophenones and methyl benzoates via the reaction of 1,3-dinitroalkanes with 2-ene-1,4- dione or 2-ene-4-oxo ester derivatives,[17] and [4 + 2] annulation strategy from the Baylis-Hillman reaction.[18] Within a short span of time four different approaches were reported for the synthesis of biphenyls starting from Baylis- Hillman adducts.[19] Keeping in view, the above points we were prompted to synthesize functionalized biphenyls, starting from β-keto carbonyl compounds and aromatic aldehydes. These may serve as starting material for the synthesis of antitubercular agents in our ongoing programme. Our method of preparation is simple, economical as no special apparatus or chemical is required and also devoid of any toxic byproduct during reaction.

The reaction of a mixture of benzaldehyde and pentane-2,4-dione in the presence of piperidine (20 mol%) resulted in an intermediate cyclohexanone derivative **1a** in good yield (Scheme 1).

Insert scheme 1

Compound **1a** was a diastereoisomeric mixture as evident from its spectral data (^{1}H and ^{13}C NMR) and used altogether in the next step. In order to screen the suitability of base used for cyclohexanone preparation we have carried out the above reaction with different organic and inorganic bases and results are shown in Table 1.

Insert table 1

Using the above reaction condition (Table 1, entry 1), other compounds of the series *viz.* **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j** and **1k** were similarly prepared from respective aldehydes and β-keto compounds as diastereoisomeric mixtures and used as such for the next step of oxidative aromatization. It is important to mention here that the reaction of β-keto carbonyl compounds and aromatic aldehydes to give most of these intermediate cyclohexanone derivatives has also been reported[21] earlier and compounds were fully characterized by spectroscopic techniques[20].
The cyclohexanone derivative (**1a**), thus obtained was subjected to oxidative aromatization with iodine in methanol to give the biphenyl derivative (**2a**) in moderate yield (55%) (Scheme 2). A number of other reagents were also explored to carry out oxidative aromatization to the respective biphenyl derivative **2a** (Table 2). However, only iodine/methanol and DABCO/DMF gave the desired results. While a combination of I_2 in methanol afforded the maximum yield (55%), DABCO in DMF gave only 50 % yield of the compound either in presence or absence of oxygen. Therefore, only iodine/ methanol combination was used for oxidative aromatization with other substrates.

Insert scheme 2

Insert table 2

To see the scope of this method different aromatic aldehydes and β-keto compounds were successfully used to get the intermediate cyclohexanone derivatives (**1b-k**) as dastereoisomeric mixtures which in turn were oxidized with iodine separately to give the respective biphenyl derivatives (**2b-k**) (Scheme 3). The results are depicted in Table 3.

Insert scheme 3

Insert table 3

Structural elucidation of all the biphenyls, so obtained was carried out by their detailed spectroscopic analysis.[22] The position of different substituents in the biphenyls (**2b-k**) was further confirmed by NOESY experiment with one of such compounds (**2c**, Figure 2) which shows the interaction of C-4 proton of the penta-substituted benzene ring with the adjacent methyl protons of same ring and no interaction with protons of the other aromatic ring, which clearly indicates the closeness of C-4 proton to the methyl group at C-5 of the penta-substituted benzene ring.
A plausible mechanism for the formation of cyclohexanone derivative during reaction of aldehyde and β-keto ester or ketone is already reported by D. Enders etal.[21] It involves a Knoevenagel condensation of an aldehyde with β-keto ester or ketone to give a

Knoevenagel product (**A**), which undergoes Michael addition of active methylene compound *via* its enol form (**B**) to give an intermediate (**C**). The latter undergoes intramolecular aldol condensation in presence of a base *via* enol (**D**) to give an intermediate cyclised aldol product (**E**), which on dehydration results in a cyclohexenone derivative (**F**), which exists as a tautomeric mixture with predominance of enol form (**G**) in the presence of iodine. Dehydration and enolization both are facilitated by iodine as it acts as Lewis acid. Dehydration in such compounds with iodine in methanol or other solvents is well known.[23,24] Finally, removal of hydroiodic acid from intermediate (I) mediated by iodine results in the desired biphenyl derivatives (Figure 1a). The final ste of aromatization is also possible in presence of base, which may abstract a proton from carbon adjacent to the carbonyl carbon in intermediate G followed by rearrangement to more stable biphenyl derivative (Figure 1b).

Insert figure 1a and 1b

In summary, we have developed a simple method for the preparation of functionalized biphenyls *via* domino Knoevenagel, Michael and Aldol reactions, followed by oxidation of the intermediate cyclohexanone with iodine. The compounds are obtained in moderate yields. Application of these compounds in designing of new biologically important molecules is underway.

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(22) *Typical procedure for the synthesis of biphenyls and their physical data:* To a magnetically stirred solution of β ketocompound (6.07ml, 59.0 mmol) and benzaldehyde (3.0ml, 29.5mmol) in ethanol (5.0 mL), piperidine (0.583ml, 5.9mmol) was added and reaction mixture was stirred at ambient temperature. The stirring continued till the disappearance of aldehyde, the reaction mixture was filtered and the solid so obtained was washed with ethanol followed by water and *n*-hexane sequentially to get cyclised product **1a** as colourless powder which was dried under vaccum. The latter (**1a,** 1.0 g, 3.70 mmol) was undergo oxidation with I_2 (1.88 g, 7.40 mmol) in MeOH under refluxing condition. After refluxing at 70^{o}C for the given time, reaction mixture was evaporated under reduced pressure. The residue was extracted with ethylacetate and water followed by washing with saturated sol. of sodium thiosulphate. The ethyl acetate layer was dried over sodium sulphate (Na_2SO_4) and concentrated under reduced pressure. The crude

product was purified by column chromatography over SiO_2 (60-120 mesh) using EtOAc: *n*-hexane (2:8) as eluent to give the desired biphenyl (**2a)** as a light yellow solid. mp 90-91 °C. IR (KBr): υ_{max} = 3436, 3019, 2363, 1693, 1631. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 11.73 (s, 1H, OH), 7.45-7.42 (m, 3H, ArH), 7.30-7.26 (m, 2H, ArH), 6.85 (s, 1H, ArH), 2.26 (s, 3H, CH_3), 1.71 and 1.70 (two s, 6H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 206.5, 206.1 (2CO), 161.6, 141.2, 139.9, 139.5, 135.9 (5ArC), 130.6, 129.3, 129.2 (5ArCH), 119.8 (ArC), 119.4 (ArCH), 32.1 and 31.7 ($2COCH_3$), 20.5 (CH_3). MS (ESMS): *m/z*: 269$[M+H]^+$. Elemental analysis for $C_{17}H_{16}O_3$: Calcd. C, 76.10; H, 6.01. Found: C, 76.08; H, 6.00. **2b:** Light yellow solid. mp 131-132 °C. IR (KBr): υ_{max} = 3779, 3345, 2922, 2143, 1592. ^{1}H NMR (200MHz, $CDCl_3$+CCl_4): δ = 11.72 (s, 1H, OH), 7.61 (d, 2H, *J* = 8.4 Hz, ArH), 7.18 (d, 2H, *J* = 8.4Hz, ArH), 6.87 (s, 1H, ArH), 2.25 (s, 3H, CH_3), 1.78 and 1.75 (two s, 6H, $COCH_3$). ^{13}C NMR (50MHz, $CDCl_3$+CCl_4,): δ = 205.9, 205.8 (2CO), 161.7, 141.2, 138.3, 135.9 (5ArC), 132.5, 132.2 (4ArCH), 123.9 (ArC), 119.8 (ArCH), 119.6 (ArC), 32.3 and 32.0 ($2COCH_3$), 20.4 (CH_3). MS (ESI^+): *m/z*: 348$[M+H]^+$. Elemental analysis for $C_{17}H_{15}BrO_3$: Calcd. C, 58.81; H, 4.35. Found: C, 58.79; H, 4.37. **2c:** Light yellow solid. mp 140-142 °C. IR (KBr): υ_{max}= 3852, 3430, 3020, 2924, 2361, 1685, 1634, 1596^{1}H NMR (200MHz, $CDCl_3$+CCl_4): δ = 11.72 (s, 1H, OH), 7.45 (d, 2H, *J* = 8.4 Hz, ArH), 7.25 (d, 2H, *J* = 8.4Hz, ArH), 6.86 (s, 1H, ArH), 2.25 (s, 3H, CH_3), 1.78 and 1.74 (two s, 6H, $COCH_3$). ^{13}C NMR (50MHz, $CDCl_3$+CCl_4): δ = 206.1, 206.0 (2CO), 161.7, 141.3, 138.4, 137.8, 136.0, 135.8 (6ArC), 131.9, 129.5, 119.8 (5ArCH), 109.9 (ArC), 32.3, 32.0 ($2COCH_3$), 20.4 (CH_3).. MS (ESI^+): *m/z*: 303.5$[M+H]^+$; Elemental analysis for $C_{17}H_{15}ClO_3$: Calcd. C, 67.44; H, 4.99. Found: C, 67.42; H, 5.00. **2d:** White solid. mp 134-136 °C. IR (KBr): υ_{max} = 3427, 3021, 2923, 2363, 1632. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 11.69 (s, 1H, OH), 7.45-7.33 (m, 5H, ArH), 7.20 (d, 2H, *J* = 8.6Hz, ArH,), 7.04 (d, 2H, *J* = 8.6Hz, ArH), 6.83 (s, 1H, ArH), 5.10 (s, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.74 (s, 6H, $2COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 206.7, 206.5 (2CO), 161.6, 159.8, 141.3, 139.8, 136.6, 136.0, 131.7, 120.1 (6ArC), 131.8, 129.0, 128.6, 127.9 (7ArCH), 120.1 (ArC), 119.1, 115.7 (3ArCH), 32.1, 31.8 ($2COCH_3$), 20.5 (CH_3). MS (ESI^+): *m/z*: 375$[M+H]^+$. Elemental analysis for $C_{24}H_{22}O_4$: Calcd. C, 76.99; H, 5.92. Found: C, 76.97; H, 5.93. **2e:** Light yellow solid. mp 135-136 °C. IR (KBr): υ_{max} = 3781, 3697, 3410, 3021, 2929, 2359, 1725, 1666, 1595. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 11.03 (s, 1H, OH), 7.85-7.75 (m, 3H, ArH), 7.60 (s, 1H, ArH), 7.49-7.47 (m, 2H, ArH), 7.46-7.29 (m, 2H, ArH), 6.91(s, 1H, ArH), 3.32 and 3.23 (two s, 3H, OCH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 171.2, 169.1 (2CO), 162.7, 142.4, 142.3, 138.2, 133.1, 132.6, 128.4 (7ArC), 128.3, 127.9, 127.8, 126.9, 126.7, 126.4, 126.3, 118.8 (8ArCH), 110.4 (ArC), 52.0, 51.8 ($2OCH_3$), 20.6 (CH_3). MS (ESI^+): *m/z*: 351$[M+H]^+$. Elemental analysis for $C_{21}H_{18}O_5$: Calcd. C, 71.99; H, 5.18. Found: C, 71.96; H, 5.19. **2f:** Light yellow oil. IR (neat): υ_{max} = 3692, 3389, 3021, 2360, 1724, 1667, 1578. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 10.97 (s, 1H, OH), 7.31-7.26 (m, 3H, ArH), 7.15-7.11 (m, 2H, ArH), 6.86 (s, 1H, ArH), 3.40 and 3.37 (two s, 6H, OCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 171.2, 169.2 (2CO), 162.4, 142.6, 142.2, 140.5 (5ArC), 128.7, 127.6, 127.3, 118.6 (6ArCH), 110.4 (ArC), 52.0, 51.9 ($2OCH_3$), 20.5 (CH_3). MS (ESI^+): *m/z*: 301$[M+H]^+$. Elemental analysis for $C_{17}H_{16}O_5$: Calcd. C, 67.99; H, 5.37. Found: C, 67.97; H, 5.39. **2g:** Light yellow solid. mp 101-102 °C. IR (KBr): υ_{max} = 3782, 3021, 2360, 1723, 1664, 1596. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 11.11 (s, 1H, OH), 7.30-7.27 (m, 3H, ArH), 7.18-7.13 (m, 2H, ArH),

6.86 (s, 1H, ArH), 3.96-3.80 (m, 4H, OCH_2), 2.34 (s, 3H, CH_3), 0.90 and 0.71 (two t, J = 7.2 Hz, 3H, CH_3,). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 170.8, 168.7 (2CO), 162.5, 142.3, 142.0, 140.8 (4ArC), 129.0 (2ArCH), 128.6 (ArC), 127.5, 127.2, 118.6 (4ArCH), 110.5 (ArC), 61.2, 61.0 ($2OCH_2$), 20.5 (CH_3), 14.0, 13.3 ($2CH_3$). MS (ESI^+): *m/z*: 329$[M+H]^+$. Elemental analysis for $C_{19}H_{20}O_5$: Calcd. C, 69.50; H, 6.14. Found: C, 69.47; H, 6.15. **2h:** Light yellow oil. IR (neat): υ_{max} = 3781, 3425, 3020, 2360, 1724, 1607. ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 11.02 (s, 1H, OH), 7.32 (d, 2H, *J* = 10.0 Hz, ArH), 7.11 (d, 2H, *J* = 10.0 Hz, ArH), 6.87 (s, 1H, ArH), 3.45 and 3.42 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 171.0, 168.9 (2CO), 162.6, 142.4, 141.1, 138.9, 133.5 (5ArC), 130.1(2ArCH), 128.5 (ArC), 127.8, 119.0 (3ArCH), 110.2 (ArC), 52.2, 52.0 ($2OCH_3$), 20.5 (CH_3). MS (ESI^+): *m/z*: 335.5$[M+H]^+$. Elemental analysis for $C_{17}H_{15}ClO_5$: Calcd. C, 61.00; H, 4.52. Found: C, 59.98; H, 4.54. **2i:** Light yellow oil. IR (neat): υ_{max} = 3781, 3410, 3021, 2360, 1721, 1663, 1599. ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 11.17 (s, 1H, OH), 7.31 (d, 2H, *J* = 10.0Hz, ArH), 7.14 (d, 2H, *J* = 10.0 Hz, ArH), 6.87 (s, 1H, ArH), 4.00-3.85 (m, 4H, OCH_2), 2.33 (s, 3H, CH_3), 0.94 (t, 3H, *J* = 7.2 Hz, CH_3), 0.76 (t, 3H, *J* = 7.2 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 170.2, 168.1 (2CO), 162.3, 141.9, 140.5, 138.7, 133.1 (6ArC), 130.0 (2ArCH), 128.1(ArC), 127.3, 118.6 (3ArCH), 109.8 (ArC), 61.1, 60.8, ($2OCH_2$), 20.0, 13.7, 12.9, ($3CH_3$). MS (ESMS): *m/z*: 363.5$[M+H]^+$. Elemental analysis for $C_{19}H_{19}ClO_5$: Calcd. C, 62.90; H, 5.28. Found: C, 62.88; H, 5.29. **2j:** Light yellow solid. mp 95-96 °C. IR (KBr): υ_{max} = 3781, 3407, 3021, 2361, 1726 1599. ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ = 10.97 (s, 1H, OH), 7.46 (d, 2H, *J* = 8.4 Hz, ArH), 7.03 (d, 2H, *J* = 8.4 Hz, ArH), 6.85 (s, 1H, ArH), 3.45 and 3.40 (two s, 3H, OCH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 170.9, 168.7 (2CO), 162.7, 142.4, 141.0, 139.5, (4ArC), 130.7, 130.5, (4ArCH), 128.3, 121.5(2ArC), 119.0 (ArCH), 110.1 (ArC), 52.1, 51.9 ($2OCH_3$), 20.5(CH_3). MS (ESI^+): *m/z*: 380 $[M+H]^+$. Elemental analysis for $C_{17}H_{15}BrO_5$: Calcd. C, 53.85; H, 3.99. Found: C, 53.84; H, 4.00. **2k:** Light yellow solid. mp 104-106 °C. IR (KBr): υ_{max}= 3450, 3020, 2924, 2359, 1631, 1523. ^1H NMR (200MHz, $CDCl_3$+CCl_4): δ = 12.50 (s, 1H, OH), 7.46-7.26 (m, 4H, ArH), 6.88 (s, 1H, ArH), 2.25 (s, 3H, CH_3), 1.84 and 1.78 (two s, 6H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ = 205.3, 205.2 (2CO), 162.9, 141.8, 138.3, 136.6, 135.9, 134.6 (6ArC), 133.0, 130.9, 130.4, 127.7, 120.8 (5ArCH), 118.7 (ArC), 31.6, 31.2 ($2COCH_3$), 20.6(CH_3).MS (ESI^+): *m/z*: 303.5$[M+H]^+$; Elemental analysis for $C_{17}H_{15}ClO_3$: Calcd. C, 67.44; H, 4.99. Found: C, 67.42; H, 5.00.

Intermediate G (Figure 1a): Light yellow solid. mp 75-80 °C. IR (KBr): υ_{max}= 3626, 3020, 2925, 2361, 1521, 1425. ^1H NMR (200MHz, $CDCl_3$+CCl_4): δ = 16.2 (s, 1H, OH), 7.42-7.09 (m, 4H, ArH), 6.14 (s, 1H, H-5), 4.76 (s, 1H, H-2), 3.22 (s, 1H, H-1), 2.36 (s, 3H, CH_3), 1.84 and 1.83 (two s, 6H, $COCH_3$). MS (ESI^+): *m/z*: 305 $[M+H]^+$; Elemental analysis for $C_{17}H_{15}ClO_3$: Calcd. C, 67.00; H, 5.62. Found: C, 67.42; H, 5.00.

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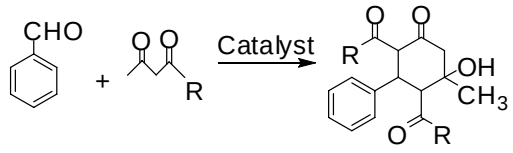
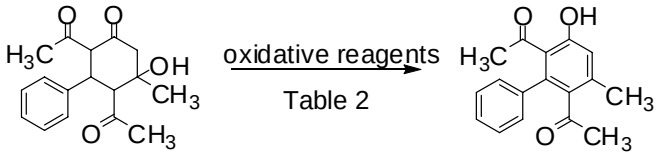


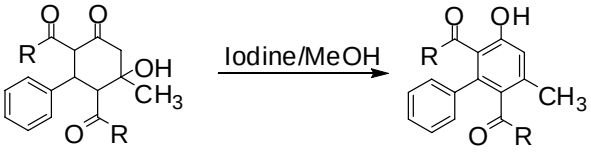
1a-1j

Scheme 1



1a **2a**

Scheme 2



1b-1j **2b-2j**

Scheme 3

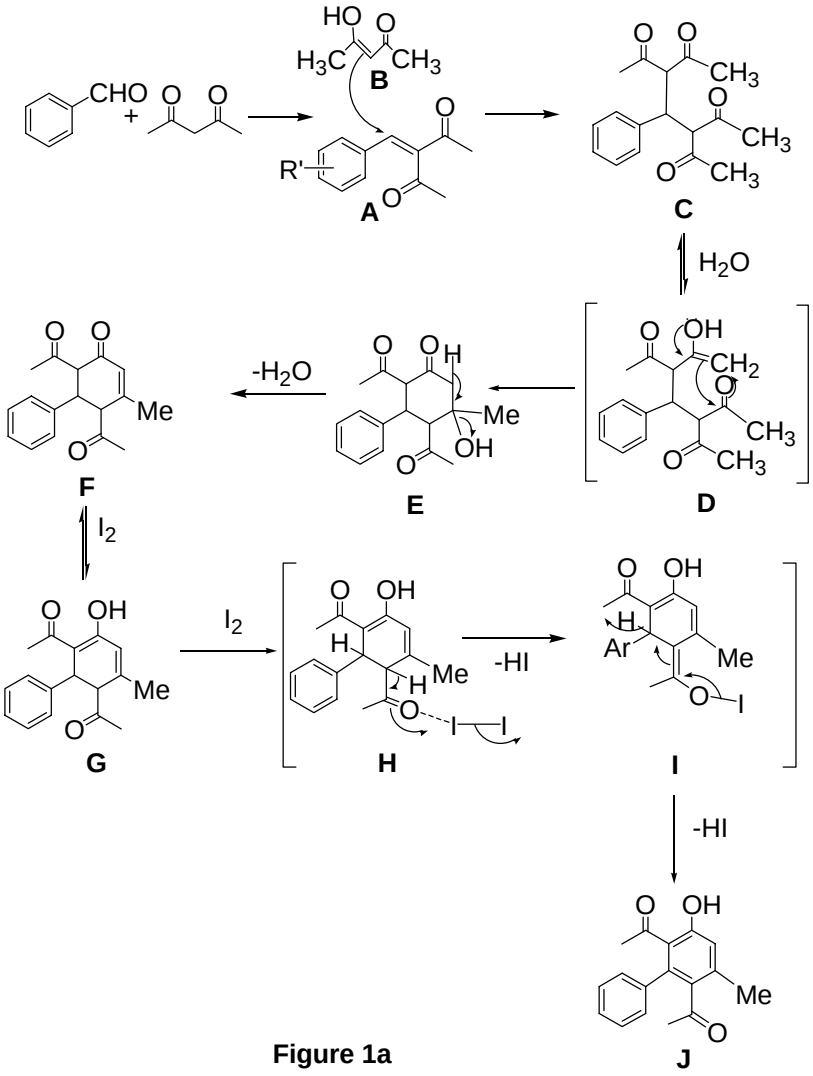


Figure 1a

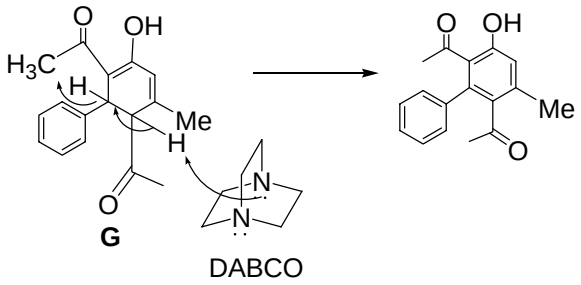


Figure 1b

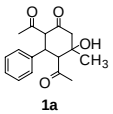
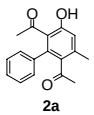
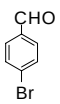
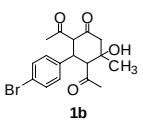
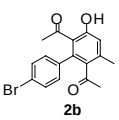
Table 1. Synthesis of intermediate cyclohexanone derivative **1a** under the influence of various catalysts

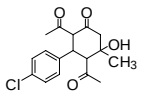
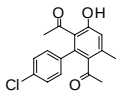
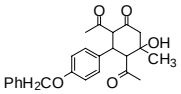
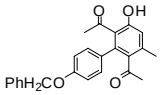
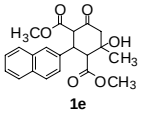
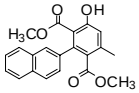
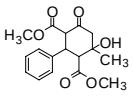
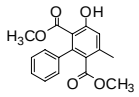
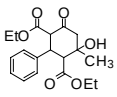
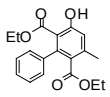
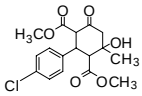
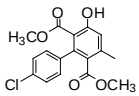
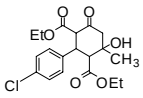
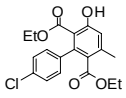
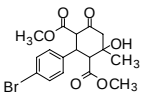
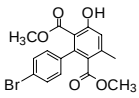
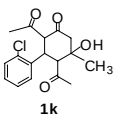
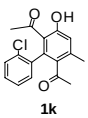
Base	Mol%	Reaction time(hrs)	Yield%
Piperidine	20	10	80
DABCO	20	12	70
DBU	20	12	63
Et_3N	20	15	62
K_2CO_3	20	15	40
Pyrrolidine	20	16	56

Table 2. Optimization of the reaction condition for the conversion of **1a** to **2a**

Entry	Conditions	% yield
1.	DDQ(1.0eq), Benzene, 80-120°C, 24 h	No reaction
2.	DDQ(5.0eq), Toluene, 120-140°C, 24 h	No reaction
3.	DBU(10 mol%), THF, 80-100°C, 72 h	No reaction
4.	DBU(3.0eq), DMF, 120-140°C, 12 h	20%
5.	DABCO(5.0eq), DMF, 120-140°C, 12 h	50%
6.	I_2, Toluene, 120-140°C, 16 h	20%
7.	I_2, Isopropanol, 80-120°C, 16 h	No reaction
8.	I_2, Propanol, 80-120°C, 14 h	30%
9.	I_2, Ethanol, 80-120°C, 14 h	20% and *trans*-esterification product
10.	I_2, methanol, 80-120°C, 12 h	55%

Table 3. Synthesis of biphenyls via sequential reactions of different aromatic aldehydes and β-keto esters or ketones

Entry	Aromatic aldehyde	β-keto compound	cyclohexanone	% yield	Biphenyl derivatives	Reaction Time(h)	% yield
1.			 **1a**	82	 **2a**	12	55
2.			 **1b**	61	 **2b**	12	55

3.			 **1c**	75	 **2c**	11	55
4.			 **1d**	72	 **2d**	12	55
5.			 **1e**	69	 **2e**	14	40
6.			 **1f**	75	 **2f**	14	45
7.			 **1g**	66	 **2g**	14	45
8.			 **1h**	65	 **2h**	14	45
9.			 **1i**	69	 **2i**	14	50
10.			 **1j**	70	 **2j**	14	40
11.			 **1k**	75	 **1k**	12	60