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REGULAR ARTICLE

A novel tandem Betti/Ullmann oxidation reaction as an efficient route for synthesis of new oxazepine derivatives

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Abstract. A novel tandem Betti/Ullmann/oxidation reaction was used for synthesis of new oxazepine derivatives containing kojic acid. This protocol includes a three-component Betti reaction of 2-naphthol, 2-haloanilines and kojic aldehyde followed by copper-mediated intramolecular Ullmann C-O coupling reaction and subsequently aerobic oxidation. This method provides a new and useful strategy for the construction of heterocycles. Also novel Betti bases based on kojic acid derivatives have been synthesized. In this regard, boric acid functionalized silica supported Fe_3O_4 nanoparticle have been designed, synthesized and used as a highly efficient, environmentally benign and recyclable heterogeneous magnetic nanocatalyst for the direct synthesis of desired Betti bases under solvent free conditions.

Keywords. Betti reaction; cross-coupling reaction; oxidation; heterogeneous catalysis.

1. Introduction

Design and modification of multicomponent reactions to provide maximum structural diversity and complexity with a minimum number of synthetic steps is a challenge of modern synthesis.[1] One approach to address this challenge involves the development of tandem reactions.[2]

Due to several significant biological,[3] synthetic[4] and catalytic[5] applications of Betti bases, the synthesis of these compounds has become an important area of synthetic organic chemistry.[6,7] Recently, copper-catalyzed Ullmann *O*-arylation reactions have made great progress,[8] and multicomponent reactions followed by a metal-catalyzed intramolecular cyclization has been introduced as efficient methods in the synthesis of complex molecules.[9]

Kojic acid and its derivatives are an important class of natural and synthetic compounds.[10] Due to its accessibility, potential biological activity and high reactivity, the synthesis of new and more potent kojic acid derivatives is of great importance to organic chemists.[11] Recently, new class of Betti bases via three-component condensation of amine, aldehyde and kojic acid as enolizable part have been developed to enhance their biological activity,[12] but there is no report about the Betti bases based on three-component reaction of amine, 2-naphthol and kojic acid derivatives. On the other hand, oxazepines have attracted widespread interest because of their biological and pharmacological activities.[13] The modification of the oxazepine nucleus and synthesizing the fused oxazepines have been the subject of the most extensive studies,[14] but there is no article describing the synthesis of oxazepine derivatives containing kojic acid. Furthermore, to the best of our knowledge, there is no example for the synthesis of *O*-heterocycles via tandem Betti/Ullmann reaction together with aerobic oxidation. Moreover, boric acid (H_3BO_3) is a very weak acid, stable and relatively benign to human.[15] Therefore, this reagent has been utilized as efficient catalyst in various reactions.[16]

As a part of our ongoing interest in the efficient synthesis of Betti bases[17] and tandem Betti/ Ullmann reaction,[18] herein, we report a practical and efficient strategy for synthesis of oxazepine derivatives containing kojic

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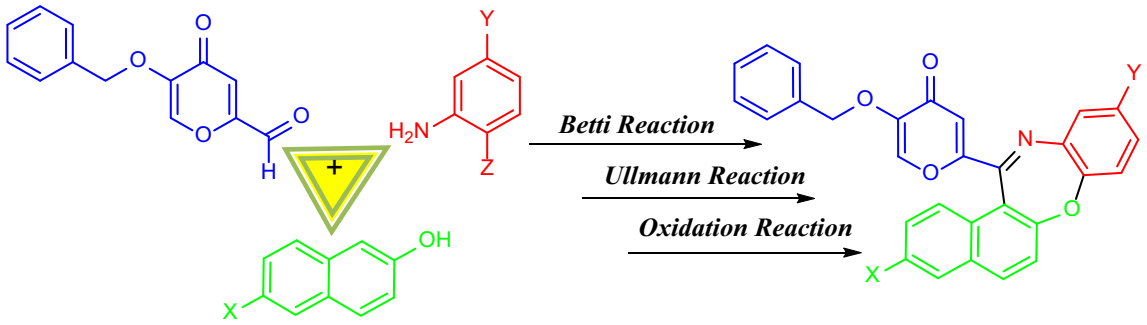


Scheme 1. Tandem Betti/Ullmann/oxidation reaction for the synthesis of oxazepine derivatives containing kojic acid.

acid through tandem Betti/ Ullmann/ oxidation reaction. The Betti reaction of 2-naphthol, 2-haloaniline and kojic aldehyde followed by copper-mediated intramolecular Ullmann C-O coupling reaction and subsequently aerobic oxidation produced novel oxazepine derivatives (Scheme 1). We have also introduced boric acid functionalized silica supported Fe_3O_4 magnetic nano particles as new nanocatalyst and used it for the synthesis of new Betti bases based on kojic acid derivatives.

2. Experimental

2.1 *Materials and Apparatus*

All chemicals were purchased from Merck or Aldrich chemical companies and were used without further purification. Melting points were determined with a MEL-TEMP model 1202D and are uncorrected. FT-IR spectra were recorded on a Bruker Tensor 27 spectrometer as KBr disks. The ^{1}H NMR spectra were recorded with a Bruker Spectrospin Avance 400 spectrometer with DMSO-d_6 as solvent and TMS as internal standard. ^{13}C NMR spectra were determined on the same instrument at 100 MHz. All chemical shifts were reported as δ (ppm) relative to solvent peaks as internal standards and coupling constants (J) are given in Hz. Elementary analyses (C, H, N) were performed on a Vario EL III analyzer. X-ray diffraction patterns of samples were taken on a Siemens D500 X-ray powder diffraction diffractometer (CuK radiation, $\lambda = 1.5406$ Å). FE-SEM images of the products visualized by a TESCAN MIRA3 Field Emission Scanning Electron Microscope.

2.2 *Synthesis of Fe_3O_4@SiO_2-boric acid nanocatalyst*

Magnetic (Fe_3O_4) nanoparticles were prepared by the reported coprecipitation method. $FeCl_3 \cdot 6H_2O$ (11.00 g) and $FeCl_2 \cdot 4H_2O$ (4.00 g) were dissolved in deionized water (250 mL) under nitrogen gas with vigorous mechanical stirring at 85°C for 1 h. The pH value was then adjusted to 9 using the concentrated aqueous ammonia (25 wt %). When the color of the bulk solution turned to black, the magnetic precipitates were separated and washed several times with deionized water until the pH value of the eluent decreased to 7. The obtained Fe_3O_4 nanoparticles were coated by a layer of silica using sol-gel method. The naked Fe_3O_4 nanoparticles were highly dispersed in ethanol (200 mL) by ultrasonic irradiation. The concentrated $NH_3 \cdot H_2O$ (20 mL) and tetraethyl orthosilicate (10 mL) were successively added into the solution. Then the reaction was stirred for 24 h at room temperature. The resulting magnetic nanoparticles were collected by an external permanent magnet and washed three times with ethanol. Finally, the solids were further dried in a vacuum oven at 60°C for 10 h to give the Fe_3O_4@SiO_2 magnetic nanoparticles. The synthesized Fe_3O_4@SiO_2 magnetic nanoparticles (1.00 g) were dispersed in absolute ethanol (50 mL) and boric acid (0.50 g) was added to the suspension. The mixture was stirred at 80°C till the evaporation of the solvent. The solid was repeatedly washed with ethanol to remove any unadsorbed boric acid, filtered off and dried under vacuum at 80 °C for 6 h to furnish catalyst as a white powder.

2.3 *General procedure for the synthesis of Betti bases **4** and **5(a–d)***

To a mixture of 2-naphthol (1 mmol), aniline derivatives (1 mmol) and Kojic aldehyde (1 mmol) was added nano Fe_3O_4@SiO_2-boric acid (15 mg). The mixture was stirred at 40°C under solvent free condition in an oil bath and the completion of reaction was monitored by TLC (EtOAc / n-hexane: 1:4). After completion of the reaction, the mixture was cooled to room temperature, ethanol (2 mL) was added, and the mixture was stirred for 10 min. The catalyst was separated out using an external magnet and the obtained solid was collected by filtration and purified by recrystallization from (EtOH/acetone, 4:1) or was subjected to silica gel preparative layer chromatography (EtOAc/*n*-hexane, 1:5) to give pyran as a pure solid. The recovered catalyst was washed with EtOH, dried and reused for the next run. The catalyst was recovered and reused for five times without any significant changes in the yield and the reaction time.

2.3a *1-[(5-(Benzyloxy)-4-oxo-4H-pyran-2-yl) (phenylamino)methyl]naphthalene 2-ol (**4**)*: Pale yellow solid;

M.p. 123–125°C; FT-IR (KBr) ν 3391, 3324, 3061, 2925, 1637, 1601, 1506, 1209, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.90 (1H, bs, N-H), 5.03 (2H, s, benzylic-H), 6.16 (1H, s, methine-H), 6.48 (1H, s, pyrone-H), 6.74 (2H, d, J = 8.0 Hz, Ar-H), 6.88 (1H, t, J = 7.2 Hz, Ar-H), 7.14–7.18 (3H, m, Ar-H), 7.33–7.38 (6H, m, Ar-H), 7.50 (1H, t, J = 8.0 Hz, Ar-H), 7.58 (1H, s, pyrone-H), 7.72 (1H, d, J = 8.8 Hz, Ar-H), 7.80 (1H, d, J = 8.0 Hz, Ar-H), 7.86 (1H, d, J = 8.8 Hz, Ar-H), 10.24 (1H, bs, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 70.8, 112.9, 114.4, 118.6, 119.8, 120.1, 122.2, 126.5, 126.6, 127.5, 127.8, 128.0, 128.3, 128.5, 130.1, 130.7, 134.4, 136.2, 140.2, 144.7, 146.2, 154.5, 174.1 ppm. Anal. Calcd. For $C_{29}H_{23}NO_4$: C, 77.49; H, 5.16; N, 3.12; Found: C, 77.28; H, 5.20; N, 3.10%.

2.3b *1-[(5-(Benzyloxy)-4-oxo-4H-pyran-2-yl) (2-brobreakmophenylamino)methyl]naphthalen-2-ol (**5a**)*: yellow solid; M.p. 144–146°C; FT-IR (KBr) ν 3372, 3341, 3061, 2964, 2802, 1637, 1579, 1505, 1206cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.03 (2H, 2d, J=12.2 Hz, benzylic-H), 6.16 (1H, d, J = 6.1 Hz, methine-H), 6.33 (1H, d, J = 6.1 Hz, N-H), 6.65 (1H, t, J = 7.8 Hz, Ar-H), 6.69 (1H, d, J = 8.1 Hz, Ar-H), 6.79 (1H, s, pyrone-H), 7.12 (1H, t, J = 7.1 Hz, Ar-H), 7.25–7.41 (8H, m, Ar-H), 7.52 (1H, t, J = 7.3 Hz, Ar-H), 7.59 (1H, s, pyrone-H), 7.62 (1H, d, J = 8.9 Hz, Ar-H), 7.77 (1H, d, J = 8.0 Hz, Ar-H), 8.04 (1H, d, J = 8.6 Hz, Ar-H), 10.23 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.8, 70.9, 110.3, 111.4, 111.6, 112.1, 118.1, 118.6, 120.4, 122.1, 126.3, 126.6, 127.4, 127.5, 127.8, 127.9, 128.2, 129.9, 131.0, 131.7, 134.4, 140.6, 142.3, 145.9, 153.3, 167.1, 174.9 ppm. Anal. Calcd. For $C_{29}H_{22}BrNO_4$: C, 65.92; H, 4.20; N, 2.65; Found: C, 65.67; H, 4.23; N, 2.64%.

2.3c *1-[(5-(Benzyloxy)-4-oxo-4H-pyran-2-yl) (2,5-dibromophenylamino)methyl]naphthalen-2-ol (**5b**)*: Pale yellow solid; M.p. 151–153°C; FT-IR (KBr) ν 3395, 3343, 3066, 2989, 1636, 1581, 1507, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.90 (2H, m, benzylic-H), 6.20 (1H, s, methine-H), 6.62–6.65 (2H, m, N-H, Ar-H), 6.73 (1H, s, pyrone-H), 6.88 (1H, s, Ar-H), 7.08 (1H, d, J = 8.3 Hz, Ar-H), 7.19–7.25 (7H, m, Ar-H), 7.43–7.49 (3H, m, Ar-H, pyrone-H), 7.65 (1H, d, J = 8.0 Hz, Ar-H), 8.01 (1H, d, J = 8.6 Hz, Ar-H), 10.64 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 70.9, 108.4, 110.6, 110.7, 112.8, 112.9, 117.9, 120.3, 120.5, 121.2, 22.1, 126.3, 126.6, 127.5, 127.8, 127.9, 128.2, 129.9, 131.1, 132.7, 140.8, 143.7, 145.9, 152.9, 168.1, 175.4 ppm. Anal. Calcd. For: $C_{29}H_{21}Br_2NO_4$: C, 57.36; H, 3.49; N, 2.31; Found: C, 57.12; H, 3.48; N, 2.30%.

2.3d *1-[(5-(Benzyloxy)-4-oxo-4H-pyran-2-yl) (2, 5-dibromophenylamino)methyl]-6-bromo-naphthalen-2-ol (**5c**)*: Light brown solid; M.p. 184–186°C; FT-IR (KBr) ν 3368, 3302, 3066, 2917, 1638, 1580, 1499, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.05 (2H, 2d, J = 12.2 Hz, benzylic-H), 6.19 (1H, s, methine-H), 6.62 (1H, s, N-H), 6.75–6.77 (2H, m, Ar-H), 6.87 (1H, s, pyrone-H), 7.20 (1H, d, J = 8.8 Hz, Ar-H), 7.33–7.38 (6H, m, Ar-H), 7.51 (1H, d, J = 8.8 Hz, Ar-H), 7.58–7.61 (2H, m, Ar-H, pyrone-H), 7.90 (1H, s, Ar-H), 7.95 (1H, d, J = 9.2 Hz, Ar-H), 10.65 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 71.1, 108.5, 110.7, 110.8, 112.9, 113.1, 115.7, 119.1, 120.8, 121.2, 122.4, 126.4, 126.6, 127.6, 127.8, 129.0, 129.5, 129.6, 130.1, 132.8, 140.9, 143.5, 145.6, 153.1, 168.3, 175.3 ppm. Anal. Calcd. For: $C_{29}H_{20}Br_3NO_4$: C, 50.76; H, 2.94; N, 2.04; Found: C, 50.51; H, 2.95; N, 2.03%.

2.3e *1-[(5-(Benzyloxy)-4-oxo-4H-pyran-2-yl)((5-chloro-2-iodophenyl)amino)methyl]-6-bromo-naphthalen-2-ol (**5d**)*: Brown solid; M.p. 192–194°C; FT-IR (KBr) ν 3389, 3342, 3066, 2925, 2820, 1637, 1576, 1499, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.03 (2H, 2d, J = 12.1 Hz, benzylic-H), 6.18 (1H, d, J = 7.5 Hz, methine-H), 6.49–6.53 (2H, m, Ar-H), 6.61 (1H, d, J = 7.5 Hz, N-H), 6.99 (1H, s, pyrone-H), 7.32–7.38 (6H, m, Ar-H), 7.47–7.51 (2H, m, Ar-H), 7.57–7.61 (2H, m, Ar-H, pyrone-H), 7.89 (1H, d, J = 1.9 Hz, Ar-H), 7.98 (1H, d, J = 9.2 Hz, Ar-H), 11.00 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 71.0, 82.5, 109.4, 110.6, 112.9, 115.6, 118.6, 119.1, 122.5, 126.6, 127.6, 127.8, 128.9, 129.0, 129.4, 129.6, 130.0, 134.1, 134.4, 138.9, 140.8, 145.8, 145.9, 153.1, 167.9, 175.4 ppm. Anal. Calcd. For: $C_{29}H_{20}BrClINO_4$: C, 50.57; H, 2.93; N, 2.03; Found: C, 50.29; H, 2.95; N, 2.01%.

2.4 *General Procedure for the Synthesis of oxazepine derivatives **7(a–d)***

To a solution of Betti bases **(5a–d)** (0.2 mmol) in DMF (3 mL), K_2CO_3 (2 eq), CuI (10 mol %), and L-proline (20 mol %) were added and the reaction mixture was heated at 110 °C for 18 h (monitored by TLC). After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel preparative layer chromatography (EtOAc / *n*-hexane, 1:9) to give the desired products **7(a–d)**.

2.4a *2-(Benzo[b]naphtho[1,2-f][1,4]oxazepin-13-yl)-5-(benzyloxy)-4H-pyran-4-one (**7a**)*: Yellow solid; M.p. 156–158°C; FT-IR (KBr) ν 3064, 2924, 1638, 1605, 1508, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.08 (2H, 2d, J = 12.3 Hz, benzylic-H), 7.10 (1H, s, pyrone-H), 7.21–7.26 (3H, m, Ar-H), 7.31–7.45 (11H, m, Ar-H, pyrone-H), 7.82 (1H, d, J = 7.5 Hz, Ar-H), 7.99 (1H, d, J = 8.9 Hz, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.7, 114.9, 119.1, 119.8, 123.6, 124.6, 125.1, 126.4, 126.7, 126.8, 127.4, 127.6, 127.7, 127.9, 130.0, 130.2, 133.6, 134.3, 139.3, 140.1, 146.9, 151.2, 158.0, 160.5, 161.7, 173.5 ppm. Anal. Calcd. For $C_{29}H_{19}NO_4$: C, 78.19; H, 4.30; N, 3.14; Found: C, 78.01; H, 4.33; N, 3.12%.

2.4b *5-(Benzyloxy)-2-(10-bromobenzo[b]naphtho[1,2-f][1,4]oxazepin-13-yl)-4H-pyran-4-one (**7b**)*: Light brown solid; M.p. 181–183°C; FT-IR (KBr) ν 3067, 2923,

16454, 1591, 1462, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.08 (2H, 2d, J = 12.1 Hz, benzylic-H), 7.06–7.09 (2H, m, pyrone-H, Ar-H), 7.31–7.46 (11H, m, Ar-H, pyrone-H), 7.54 (1H, d, J = 1.8 Hz, Ar-H), 7.83 (1H, d, J = 7.9 Hz, Ar-H), 7.99 (1H, d, J = 8.9 Hz, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.9, 115.1, 116.9, 117.6, 118.9, 121.2, 123.6, 124.8, 126.8, 126.9, 127.5, 127.7, 128.9, 130.0, 130.3, 130.4, 133.9, 134.3, 140.4, 140.5, 147.1, 150.4, 159.2, 160.2, 161.6, 173.5 ppm. Anal. Calcd. For $C_{29}H_{18}BrNO_4$: C, 66.43; H, 3.46; N, 2.67; Found: C, 66.19; H, 3.48; N, 2.65%.

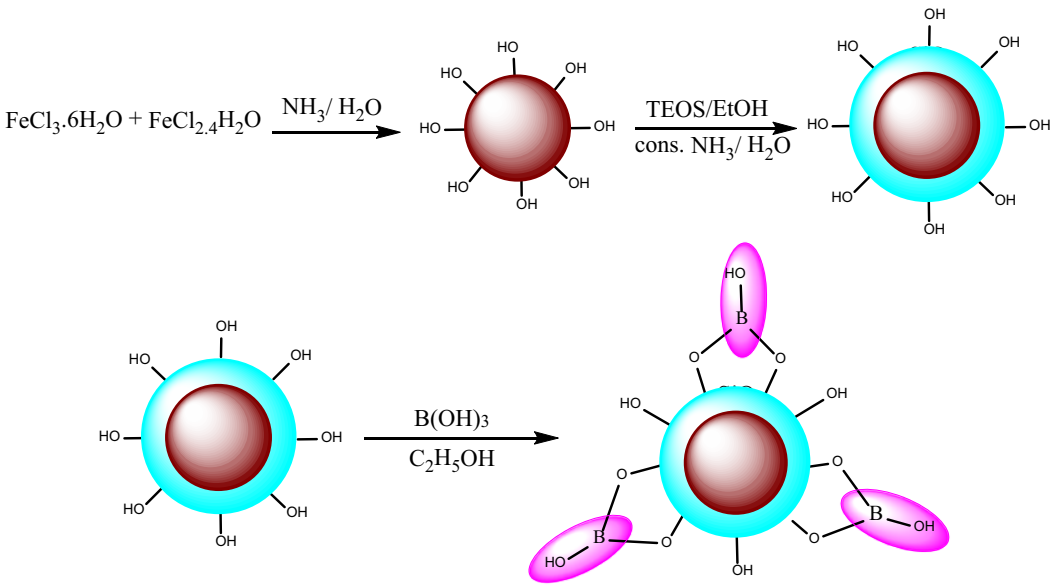
2.4c *5-(Benzyloxy)-2-(3,10-dibromobenzo[b]naphtho[1,2-f][1,4]oxazepin-13-yl)-4H-pyran-4-one* (**7c**): Light brown; M.p. 182–184°C; FT-IR (KBr) ν 3060, 2933, 1639, 1590, 1543, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.09 (2H, 2d, J = 12.2 Hz, benzylic-H), 7.07 (1H, d, J = 8.6 Hz, Ar-H), 7.14 (1H, s, pyrone-H), 7.24–7.26 (2H, m, Ar-H) 7.33–7.45 (8H, m, Ar-H, pyrone-H), 7.54 (1H, d, J = 1.9 Hz, Ar-H), 7.91 (1H, d, J = 8.9 Hz, Ar-H), 8.00 (1H, s, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.9, 114.9, 116.8, 117.6, 119.3, 121.2, 123.3, 125.1, 126.8, 126.9, 127.6, 127.7, 129.1, 129.6, 130.2, 130.7, 132.8, 140.4, 140.7, 147.3, 150.5, 159.3, 160.6, 161.7, 173.4 ppm. Anal. Calcd. For $C_{29}H_{17}Br_2NO_4$: C, 57.74; H, 2.84; N, 2.32; Found: C, 57.46; H, 2.86; N, 2.30%.

2.4d *5-(Benzyloxy)-2-(3-bromo-10-chlorobenzo[b]naphtho[1,2-f][1,4]oxazepin-13-yl)-4H-pyran-4-one* (**7d**): Light brown solid; M.p. 193–195°C; FT-IR (KBr) ν 3063, 2924, 2855, 1594, 1464, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (2H, 2d, J = 12.0 Hz, benzylic-H), 7.14 (1H, s, pyrone-H), 7.20 (1H, dd, J = 8.7 Hz, J = 2.4 Hz, Ar-H), 7.24–7.26 (2H, m, Ar-H) 7.33–7.40 (8H, m, Ar-H, pyrone-H), 7.45 (1H, dd, J = 9.1 Hz, J = 1.9 Hz, Ar-H), 7.91 (1H, d, J = 8.9 Hz, Ar-H), 8.00 (1H, d, J = 1.6 Hz, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.9, 114.9, 118.9, 120.2, 120.8, 125.1, 126.2, 126.9, 127.6, 127.7, 128.6, 129.6, 130.2, 135.0, 131.4, 132.8, 134.3, 140.1, 140.4, 147.7, 149.7, 159.2, 160.0, 161.1, 173.4 ppm. Anal. Calcd. For $C_{29}H_{17}BrClNO_4$: C, 62.33; H, 3.07; N, 2.51; Found: C, 62.07; H, 3.09; N, 2.49%.

3. Results and Discussion

Initially boric acid functionalized silica supported Fe_3O_4 nanoparticle (Fe_3O_4@SiO_2-boric acid) was prepared with a multistep reaction as shown in Scheme 2. Magnetite (Fe_3O_4) nanoparticles were easily prepared via the chemical co-precipitation of Fe^{2+} and Fe^{3+} ions in basic solution[19]. Subsequently Fe_3O_4 nanoparticles were coated with silica (Fe_3O_4@SiO_2) through the well-known Stober method.[20] In the end, Fe_3O_4@SiO_2 magnetic nanoparticles were reacted with boric acid in ethanol to obtain Fe_3O_4@SiO_2-boric acid nanoparticles.

The structure of boric acid functionalized silica supported Fe_3O_4 nanoparticle was characterized using FT-IR analysis. Figure 1 shows the FT-IR spectra of the nanoparticles (a) Fe_3O_4 (b) Fe_3O_4@SiO_2 (c) Fe_3O_4@SiO_2-boric acid. FT-IR spectroscopy of the magnetic Fe_3O_4 nanoparticles presented a characteristic absorption peak of Fe–O bond at about 575 cm^{-1}. The absorption peaks of the silica shell in the Fe_3O_4@SiO_2



Scheme 2. Preparation steps for synthesis of silica supported Fe_3O_4 nanocatalyst.

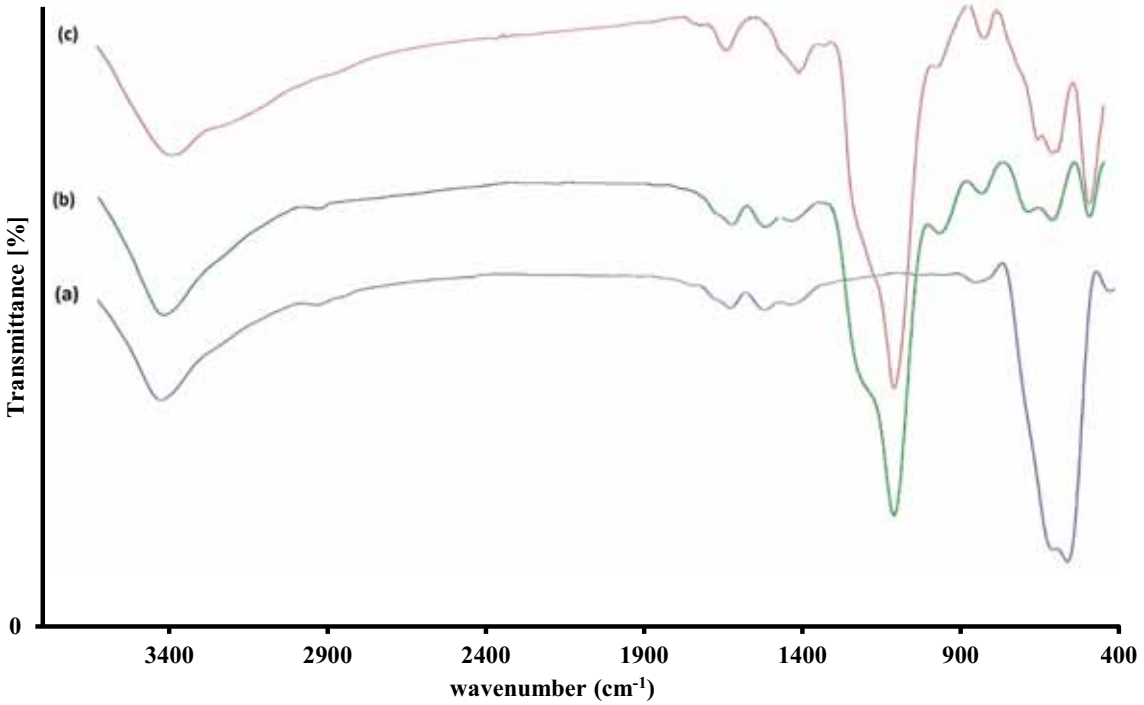


Figure 1. The FT-IR spectra of (a) Fe_3O_4 (b) Fe_3O_4@SiO_2 (c) Fe_3O_4@SiO_2-boric acid nanocatalyst.

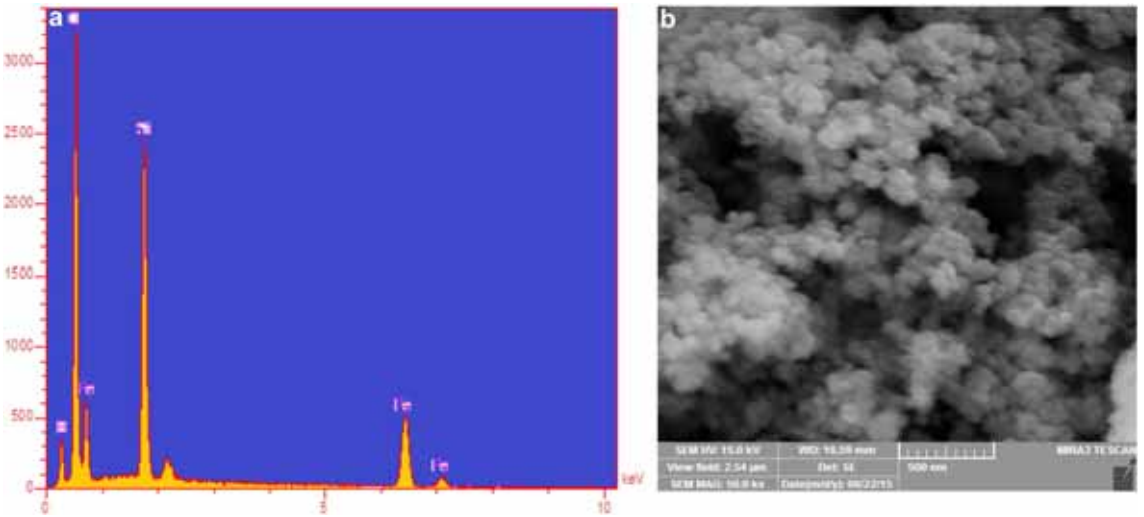


Figure 2. (a) EDX analysis and (b) FE-SEM image of the Fe_3O_4@SiO_2-boric acid nanocatalyst.

core-shell MNPs about 1090 cm^{-1} is linked to the asymmetric stretching vibrations of Si–O–Si bond. The broad band at 3420 $cm^{-1}$is due to the stretching vibration of O-H groups. The characteristic band at about 950 cm^{-1} is assigned to the stretching vibrations of B–O-Si groups and a band located at 1400 cm^{-1} is related to the B–O stretching vibrations. These results indicate the loading of the H_3BO_3 on the nano Fe_3O_4@SiO_2 surface and formation of the Fe_3O_4@SiO_2-boric acid nanocatalyst.

Energy-dispersive X-ray spectroscopy (EDX) of the Fe_3O_4@SiO_2-boric acid catalyst introduced the presence of the expected elements (Fe, Cl, Si, O and B) in the structure of the catalyst and confirmed the formation of desired nanocatalyst (Figure 2a and Table 1). The surface morphology of the Fe_3O_4@SiO_2-boric acid nanoparticle was investigated by Field Emission Scanning Electron Microscopy (FE-SEM) analysis. FE-SEM

Table 1. EDX analysis data for Fe_3O_4@SiO_2-boric acid.

Element	B	O	Si	Fe	Total
Weight (%)	10.86	47.01	14.49	27.64	100.00

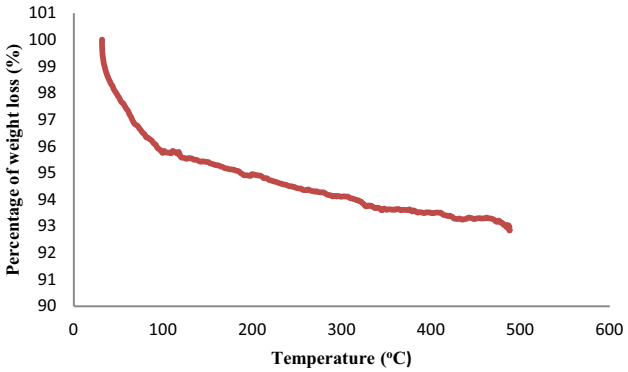


Figure 3. Thermogravimetric analysis of the Fe_3O_4@SiO_2-boric acid nanocatalyst.

Table 2. Recyclability of the Fe_3O_4@SiO_2-boric acid nanocatalyst for the synthesis of **4**.

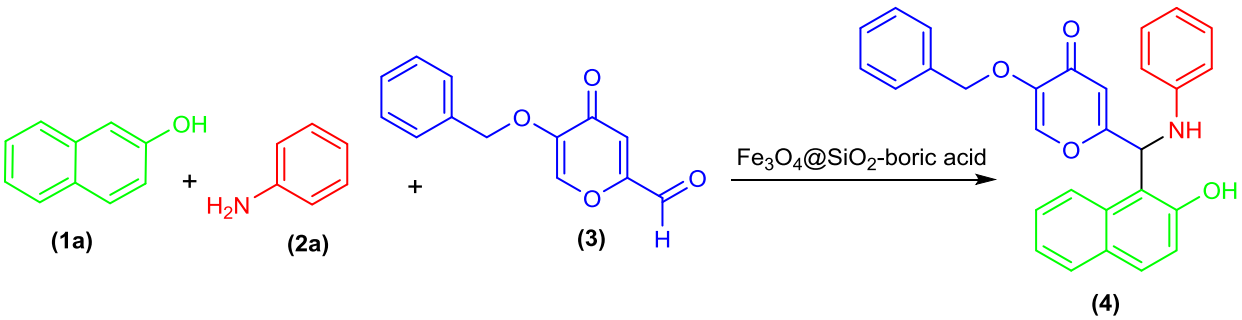
	1	2	3	4	5
Product Yield (%)	85	85	83	80	80
Time (min)	60	60	65	65	70

images show that the particles are nanosized and uniformly distributed (Figure 2b).

The thermal properties of the Fe_3O_4@SiO_2-boric acid nanocatalyst was also investigated by thermogravimetric analysis (TGA). As shown at the thermogravimetric curves in Figure 3, the nanocatalyst demonstrated relatively high thermal stability. The TGA profile of Fe_3O_4@SiO_2-boric acid exhibits two steps of weight loss. The first weight loss occurs below 100°C is attributed to the evaporation of physically adsorbed water. Above 100°C, a small weight loss due to a partial dehydroxylation of the silanol groups on the surface of the catalyst has occurred.

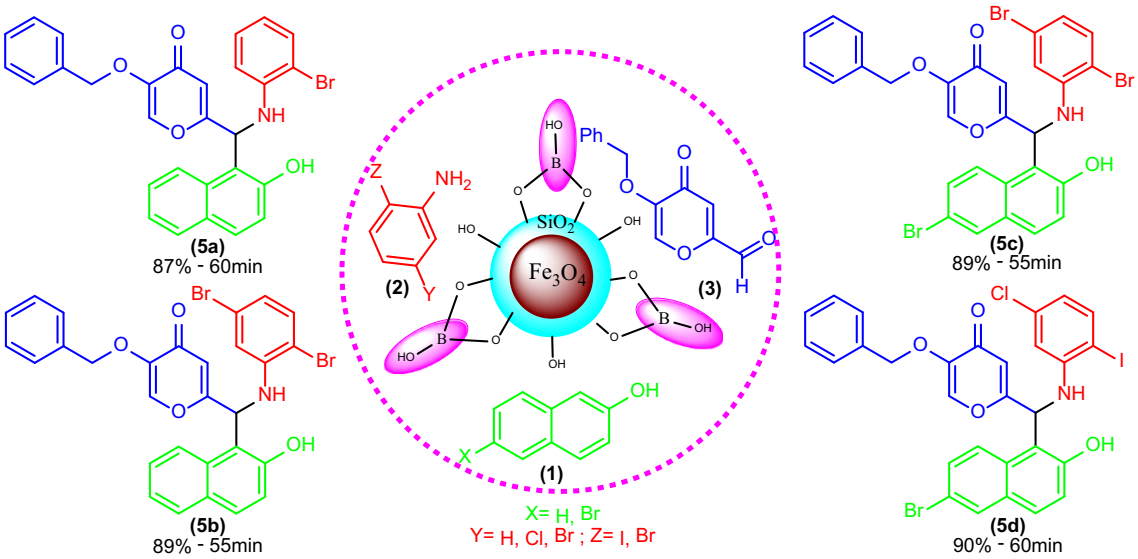
The reusability of the catalyst was investigated with the model reaction at modified conditions and the results are shown in Table 2. After completion of the reaction, the reaction mixture was dissolved in hot ethanol and the catalyst was easily separated from the reaction mixture by placing an external magnetic field. Subsequently the collected nanocatalyst was washed with hot ethanol and acetone for two times and dried in vacuum. The recovered catalyst was reused for 5 runs with only a slight decrease in its weights and activities.

Table 3. Optimization of solvent, temperature, and amount of Fe_3O_4@SiO_2-boric acid nanocatalyst [a].



Entry	Catalyst amount (mg)	Solvent	Temperature (°C)	Time (min)	Yield (%) [b]
1	50	EtOH	rt	90	35
2	50	$CHCl_3$	rt	90	10
3	50	CH_2Cl_2	rt	90	15
4	50	H_2O	rt	90	30
5	50	–	rt	90	55
6	40	–	rt	75	54
7	30	–	rt	75	54
8	20	–	rt	75	54
9	15	–	rt	75	55
10	10	–	rt	75	45
11	5	–	rt	75	30
12	15	–	40	60	85
13	15	–	50	60	85
14	15	–	60	60	75

[a] Reaction conditions: 2-naphthol/aniline/kojicaldehyde = 1:1:1.
[b] Isolated yield.



[a] Reaction conditions: 2-naphthol (**1**)/ aniline derivatives (**2**) / kojicaldehyde (**3**) = 1:1:1 and nano Fe_3O_4@SiO_2-boric acid (15 mg) at 40 °C under solvent free condition

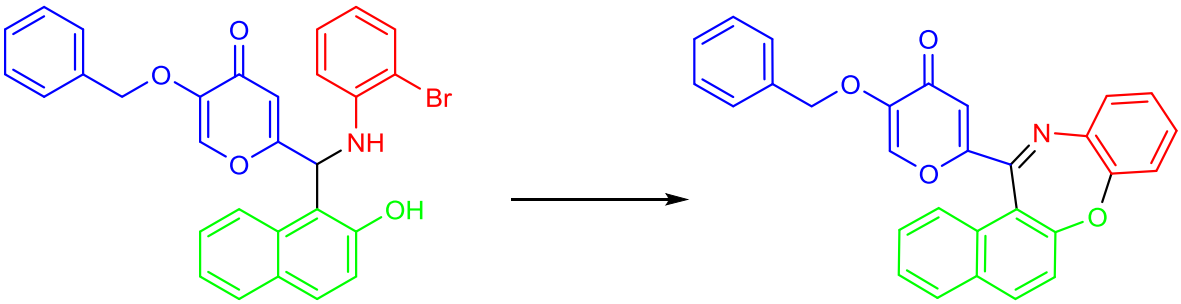
Scheme 3. Synthesis of Betti bases **(5a–d)**[a].

In continuation, we studied the catalytic activity of the synthesized Fe_3O_4@SiO_2-boric acid nanocatalyst for the synthesis of new kojic acid containing Betti bases. In order to optimize the Betti reaction conditions and obtain the best catalytic activity, the reaction of 2-naphthol (**1a**), aniline (**2a**) and kojic aldehyde (**3**) was chosen as a model reaction to optimize the reaction conditions. For this purpose, the efficiency of Fe_3O_4@SiO_2-boric acid nanocatalyst was investigated in a variety of solvents, different temperatures and different amounts of the nanocatalyst to achieve more effective, simple and rapid method for the synthesis of naphthopyran derivatives. As shown in Table 3, a variety of conventional organic solvents such as EtOH, CH_2Cl_2, $CHCl_3$ and H_2O and solvent-free condition were screened for the model reaction at room temperature in the presence of 50 mg of nanocatalyst (Table 3, entries 1–5). Interestingly, the best result was achieved under solvent-free condition and different conventional solvents afforded low to moderate yields at room temperature (Table 3, entries 1–4, 10–35%). In continuation, the model reaction was exposed to different quantities of nanocatalyst (50, 40, 30, 20, 10, 5 and 15 mg) and various temperatures. It was observed that the excellent yield was achieved by using 15 mg of Fe_3O_4@SiO_2-boric acid (Table 3, entry 9) and further decrease or increase in catalyst quantity beyond 15 mg did not increase the yield of the product significantly. As shown in Table 1, the best result (85% yields) was obtained when the reaction was performed using 15 mg of catalyst at 40°C (Table 3, entry 12). Notably, there was no need for creating an inert atmosphere and the reactions were done at ambient conditions.

To demonstrate the scope of the procedure, we designed and synthesized a new class of Betti bases which contain kojic acid part and could be precursors for the subsequent Ullmann reaction. The condensation of 2-naphthols (**1**), aniline derivatives (**2**) and kojic aldehyde (**3**) was examined in the presence of nano Fe_3O_4@SiO_2-boric acid (15 mg) at 40°C under solvent free condition. As shown in Scheme 3, the reactions were carried out efficiently within 55–60 min and the desired products were obtained in good to high yields. All compounds were characterized by mp, FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (C, H, and N).

Then, we focused on the feasibility of the following copper catalyzed intramolecular Ullmann cyclization reaction. 1-[(5-(Benzyloxy)-4-oxo-4*H*-pyran-2-yl) (2-bromophenylamino) methyl]naphthalen-2-ol (**5a**) was used as the model substrate to screen the Ullmann reaction conditions. Surprisingly when the Ullmann reaction conditions were induced, the expected product

Table 4. Optimization of the Ullmann reaction conditions[a].



(5a) **(7a)**

Entry	Solvent	Base	Ligand	Temp. (°C)	Yield (%)
1	Toluene	K_2CO_3	L-proline	80	10
2	1,4-Dioxane	K_2CO_3	L-proline	80	15
3	Acetonitrile	K_2CO_3	L-proline	80	20
4	DMSO	K_2CO_3	L-proline	80	40
5	DMF	K_2CO_3	L-proline	80	45
6	DMF	NaOH	L-proline	80	25
7	DMF	KOH	L-proline	80	20
8	DMF	$CsCO_3$	L-proline	80	40
9	DMF	K_3PO_4	L-proline	80	40
10	DMF	K_2CO_3	picolinic acid	80	35
11	DMF	K_2CO_3	DABCO	80	20
12	DMF	K_2CO_3	DBU	80	25
13	DMF	K_2CO_3	1,2-ethylenediamine	80	20
14	DMF	K_2CO_3	1,10-phenanthroline	80	20
15	DMF	K_2CO_3	L-proline	90	60
16	DMF	K_2CO_3	L-proline	100	72
17	DMF	K_2CO_3	L-proline	110	78
18	DMF	K_2CO_3	L-proline	120	70

[a] Reaction conditions: **5a** (0.2 mmol), CuI (10 mol%), ligand (20 mol%), base (2 eq), solvent (3 mL), 18h.

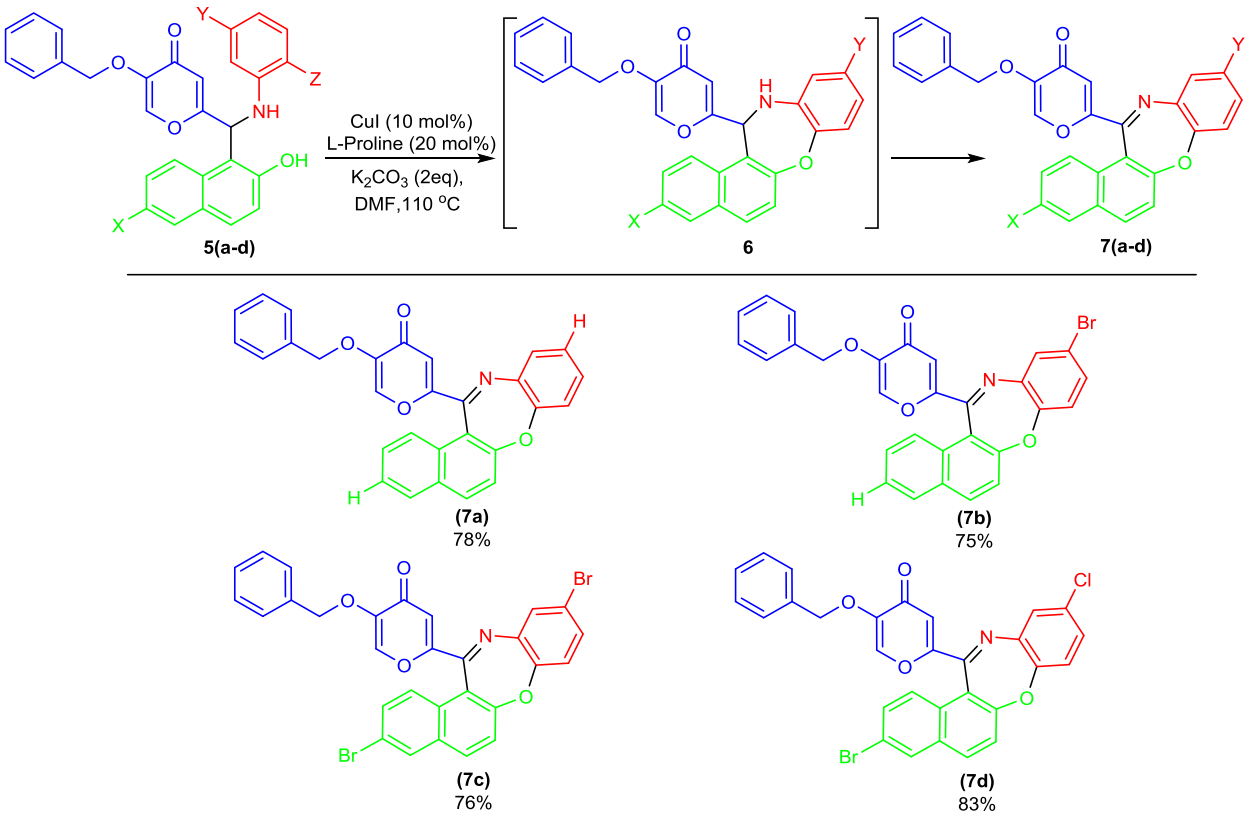
6a was not detected, instead the main isolated product was the oxazepine derivative (**7a**) formed from subsequent oxidation reaction. As shown in Table 4, the coupling reaction was surveyed by variety of solvents, bases and ligands. Among the various solvents and bases screened at 80°C and in the presence of L-proline, the optimal result was obtained when DMF was used as solvent and potassium carbonate was employed as the base (Table 4, entry 5). It was also observed that L-proline was better than other ligands in promoting yield of the reaction. In continuation, the reaction was studied at different temperatures (Table 4, entries 15–18) and 110°C was found to be the optimal temperature (Table 4, entry 17). Thus, a catalyst system consisting of 10 mol% CuI, 20 mol% L-proline, and 2.0 equiv K_2CO_3 in DMF at 110°C was employed and 78% of the desired product **7a** was obtained.

The scope of the methodology was also transferred to the other synthesized Betti bases **5(b–d)**. The intramolecular Ullmann reaction of Betti bases **5(b–d)** in the presence of catalytic amount of CuI, L-proline and K_2CO_3 followed by subsequent oxidation reaction produced oxazepine derivatives **7c–d** in 75–83% yields (Table 5). It provides a novel synthesis of oxazepine derivatives via a tandem Betti/Ullmann/oxidation reactions starting from easily accessible derivatives of 2-naphthol, 2-haloanilines and kojic aldehyde.

4. Conclusion

In summary, we have developed novel tandem Betti/ Ullmann/ oxidation reaction for the synthesis of new oxazepine derivatives. In this protocol three-component reaction of 2-naphthol, 2-haloanilines and kojic aldehyde followed by copper-mediated intramolecular Ullmann C-O coupling reaction and subsequent aerobic oxidation. This method provides a new and useful strategy for the construction of heterocycles. For this purpose, we have designed, synthesized and characterized Fe_3O_4@SiO_2-boric acid for the first time and

Table 5. Synthesis of oxazepine derivatives **7(a–c)** from **5(a–d)** by tandem Ullmann/oxidation reactions.



used it as an environmentally benign and recyclable heterogeneous catalyst for the direct synthesis of Betti bases. A series of new Betti bases containing kojic acid were synthesized via a one-pot three-component reaction of 2-naphthol, haloaniline and kojic aldehyde in the presence of magnetic nanocatalyst under solvent free condition. The operational simplicity of the procedure, short reaction times, easy workup, extremely mild reaction conditions and environmental friendliness make this method more attractive.

Supplementary Information (SI)

Supplementary Information (experimental procedure and characterization data of all compounds and copies of their NMR spectra) is available at www.ias.ac.in/chemsci.

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