CHAPTER 2

EXPERIMENTAL

2.1 Chemicals

Iron(II)sulphate, $FeSO_4 \cdot 7H_2O$, assay 99%, Carlo Erba, Italy

Iron(III)chloride, $FeCl_3 \cdot 6H_2O$, assay 98%, Fluka, witzerland

Silica gel, 70-230 mesh ASTM, Merck, Germany

Ammonium hydroxide, NH_4OH, assay 29.2%, J.T. Beaker, U.S.A.

3-aminopropyltriethoxysilane, $C_9H_{23}NO_3Si$, assay 98%, Aldrich, U.S.A.

Benzyl amine, C_7H_9N, assay 99%, Aldrich, U.S.A.

Benzenesulfonyl chloride, $C_6H_5ClO_2S$, assay 99%, Fluka, Switzerland

Triethylamine, $C_8H_{15}N$, assay 99%, AJAX, Australia

Diisopropylamine, $C_6H_{15}N$, assay 99%, Merck, Germany

N,*N*-Diisopropylethylamine, $C_8H_{19}N$, assay 99%, Merck, Germany

Trifluoroacetic acid, $C_2HF_3O_2$, assay 99%, Fluka, Switzerland

Bromothylmol blue , BDH, England

Sodium hydroxide, NaOH, Merck, Germany

Potassium carbonate, K_2CO_3, MAY&BAKER, Germany

Potassium iodide, KI, Carlo Erba, Italy

Piperidine, $C_5H_{11}N$, assay 99%, Aldrich, U.S.A.

Morpholine, C_4H_9NO, assay 99%, Fluka, Switzerland

Diethylamine, $C_4H_{11}N$, assay 99%, Merck, Germany

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Benzyl bromine, C_7H_7Br, assay 98%, Fluka, Switzerland

Benzoyl chloride, C_7H_5ClO, assay 99%, Fluka, Switzerland

Aniline, C_6H_7N, assay 99%, Aldrich, U.S.A.

N-butylamine, $C_4H_{11}N$, assay 99%, BDH, England

Trifluoroacetic acid, $C_2HF_3O_2$, assay 99%, Fluka, Switzerland

Hydrochloric acid, HCl, assay 37% Carlo Erba, Italy

Bromothylmol blue, BDH, England

Methanol, CH_4O, Fluka, Switzerland

Acetone, C_3H_6O, Fluka, Switzerland

Toluene, C_7H_8, Fluka, Switzerland

Dichloromethane, CH_2Cl_2, Fluka, Switzerland

2.2 Instruments

UV-Vis spectrophotometer (Perkin Elmer, Lambda25), U.S.A.

Scanning Electron Microscope (SEM) (JEOL, 6335F), JAPAN

NMR spectrometer (Bruker, Avance), Germany

Fourier transform infrared (FT-IR) spectrometer (Bruker, TENSOR 27), Germany

Centrifuge (BECKMAN COULTER, Allergra), U.S.A.

Rocking table (Specimen mixer, BCT-33)

Atomic Absorption Spectroscopy (Shimadzu Model AA-680G)

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2.3 Synthesis of magnetic nanoparticles supported DIPA (Fe_3O_4-DIEA, Fe_3O_4-DIPAP) and nonmagnetic silica supported DIPA (Si-DIPA, Si-DIPAP)

2.3.1 Synthesis magnetic nanoparticles silica supported DIPA (Fe_3O_4-DIPA and Fe_3O_4-DIPAP)

2.3.1.1 Synthesis of magnetic nanoparticles (Fe_3O_4)

Magnetic nanoparticles (Fe_3O_4) were synthesized by the chemical co-percipitation method [46]. Typically, the mixture of ferric chloride (16.2 g) and ferrous sulfate (8.5 g) in water (50 ml) were heated until the temperature was at 80 °C then 25% NH_4OH (50 ml) was slowly added. The reaction mixture was maintained for 30 min. The black solid was washed with water and dry at 80 °C overnight to give magnetic Fe_3O_4 nanoparticles as black powder.

2.3.1.2 Synthesis of 3-aminopropyl Fe_3O_4-1

3-Aminopropyltriethoxysilane (3 ml) was dissolved in toluene (10 ml) in a round-bottomed flask. Whilst the solution was stirred vigorously, 3 g of the magnetic nanoparticle (Fe_3O_4) was slowly added. After sonicating for 10 min, the reaction mixture was refluxed for 3 h. The product Fe_3O_4-**1** was washed with toluene, methanol and acetone respectively via external magnetic field decantation, and oven dried at 80 °C for 12 h and kept in desiccators to give 3-aminopropyl Fe_3O_4-**1** [47].

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2.3.1.3 Synthesis of Fe_3O_4-2 and Fe_3O_4-2-1

3-Aminopropyl Fe_3O_4-**1** (2 g) was added as a powder into a 25 ml round-bottomed flask containing triethylamine (1.67 ml, 12 mmol), the reaction mixture were cooled at 0^oC then chloroacetyl chloride (1.9 ml, 24 mmol) in dichloromethane (10 ml) was added. After stirring for 1 h at 0^oC, the reaction mixture was stirred at room temperature for 16 h. After the completion of the reaction as indicated by negative ninhydrin test of the resulting Fe_3O_4-**2**, the solid was separated from the reaction via external magnetic field decantation. After that the resulting Fe_3O_4-**2** was washed with dichloromethane, followed by deionized water, acetone and dichloromethane, respectively. The Fe_3O_4-**2** was oven dried at 80°C for 12 h and kept in desiccator [48]. Fe_3O_4-**2-1** was synthesized under identical synthesis conditions used for synthesis of Fe_3O_4-**2-1** that using acryloyl chloride for acylated with Fe_3O_4-**1** instead of chloroacetyl chloride to give Fe_3O_4-**2-1.**

2.3.1.4 Synthesis of Fe_3O_4-DIPA and Fe_3O_4-DIPAP

The Fe_3O_4-**2** (1 g) was added as a powder into a 50 ml round-bottomed flask containing diisopropylamine (1.59 ml, 11.3 mmol) and K_2CO_3 (780 mg, 5.65 mmol) in toluene 20 ml, the solution was stirred vigorously at room temperature for 16 h. The Fe_3O_4-DIPA was washed with toluene, followed by water, methanol and acetone respectively via external magnetic field decantation. The Fe_3O_4-DIPA was oven dried at 80°C for 12 h and kept in desiccators. The Fe_3O_4-**2-1** (1 g) was added as a powder

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into a 20 ml of dimethylfomamide containing diisopropylamine (1.45 ml, 0.9 mmol) the solution was stirred vigorously at room temperature for 16 h. The Fe_3O_4-DIPAP was washed with dimethylformamide, followed by methanol and acetone respectively via external magnetic field decantation**.**

2.3.2 Synthesis nonmagnetic silica supported DIPA (Si-DIPA and Si-DIPAP)

2.3.2.1 Silica pretreatment

Silica gel (10 g) was added with a mixture of nitric acid and sulfuric acid (1:1, 700 ml), followed by sonicating for 10 min. The mixture was then refluxed for 3 h, and washed with deionized water until pH ~ 7. The pre-purified silica gel was then oven dried at 120°C for 24 h and kept in desiccators [47].

2.3.2.2 Synthesis of 3-aminopropyl silica-1

3-Aminopropyltriethoxysilane (3 ml) was dissolved in 50 ml of toluene in a round-bottomed flask. Whilst the solution was stirred vigorously, 3 g of the silica gel was slowly added. After sonicating for 10 min, the reaction mixture was refluxed for 3 h. The silica gel was then rinsed with toluene, followed by methanol and acetone, respectively to obtain 3-aminopropyl silica-**1** then it was oven dried at 80°C for 12 h and kept in desiccators [47].

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2.3.2.3 Synthesis of silica-2 and silica-2-1

3-Aminopropyl silica-**1** (2 g) was added as a powder into a 100 ml round-bottomed flask containing chloroacetyl chloride (1.2 ml, 16 mmol) in dichloromethane (50 ml), the reaction mixture were cold at 0^{o}C then triethylamine (1.1 ml, 8 mmol) was added. After stirring for 1 h at 0^{o}C, the reaction mixture was stirred at room temperature overnight. After the completion of the reaction as indicated by negative ninhydrin test of the resulting silica, the solid was then filtered and washed with dichloromethane, followed by deionized water, acetone and dichloromethane, respectively. The silica-**2** was oven dried at 80°C for 12 h and kept in desiccator [48]. Silica-**2-1** was synthesized under identical synthesis conditions used for synthesis of silics-**2-1** that using acryloyl chloride for acylated with silics-**1** instead of chloroacetyl chloride to give silics-**2-1.**

2.3.2.4 Synthesis of Si-DIPA and Si-DIPAP

The silica-**2** (1 g) was added as a powder into a 100 ml round-bottomed flask containing diisopropylethylamine (1.05 ml, 7.5 mmol), K_2CO_3 (518 mg, 3.75 mmol) in 30 ml toluene, the solution was stirred vigorously at room temperature for overnight. The silica supported base (Si-DIPA) was then filtered and washed with toluene, followed by methanol, and acetone, respectively. The Si-DIPA was oven dried at 80°C for 12 h and kept in desiccators. The silics-**2-1** (1 g) was added as a powder into a 20 ml of dimethylfomamide containing diisopropylamine (1.45 ml, 0.9

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mmol) the solution was stirred vigorously at room temperature for 16 h. The Si-DIPAP was washed with dimethylformamide, followed by methanol and acetone, respectively and dried at 80°C for 12 h and kept in desiccators.

2.4 Determine loading of amino group on 3-aminopropyl silica-1 and 3-aminopropyl Fe_3O_4-1 by quantitative ninhydrin test

The sample 5.0 mg. was poured into test tube, ninhydrin solution was admixed to start the reaction at 95 °C for 2-5 min. The resulting colored solution was diluted with ethanol to 10 ml then was spectroscopically measured at λ 570 nm using UV spectrometer [49, 50]**.**

2.5 Determine basicity of Fe_3O_4-DIPA, Fe_3O_4-DIPAP, Si-DIPA and Si-DIPAP

The basic character of Fe_3O_4-DIPA and Si-DIPA base were determined by a method adapted from the indicator titration method used to study the surface basicity of solid catalyst particles [51]. This method relies on the color change of Hammett [52] indicators adsorbed to the particle surface to determine the strength of surface basic sites, and subsequent titration to reverse the color change gives a quantitative measure of the amount of surface basicity. Indicator solutions were prepared by adding 30 ml toluene to 0.05 g bromothymol blue. To perform the titrations, 5 mg of sample in 4 ml of toluene and one to three drops of indicator were added then the solution color change into blue. The titrant, 0.01 molar trifluoroacetic acid, was slowly added to the solution being titrated until the indicator changes color into

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yellow, showing that the reaction is completed. The amount of titrant require to reverse the color change could then be used to express the surface basicity in mmol per gram of silica supported base reagents.

2.6 Synthesis of *N*-Benzyl-benzenesulfonamide

To demonstrate the applicability of the obtained Fe_3O_4-DIPA, Fe_3O_4-DIPAP, Si-DIPA and Si-DIPAP, these supported bases were applied as base reagent in the synthesis of *N*-benzyl-benzenesulfonamide. The same reaction using *N*,*N*-diisopropylethylamine (DIPEA) in homogeneous solution was also performed for comparison. 1.2 equiv. of DIPEA was used in the solution phase synthesis, while 1.2 equiv. of all supported bases were applied in the solid supported reagent mediated reaction. Typical aqueous work up and product purification by column chromatography was performed when using DIPEA reagent. When using supported bases, the sulfonamide product was isolated by concentrated the crude reaction mixture after Fe_3O_4-DIPA and Fe_3O_4-DIPAP were separated via external magnetic field, Si-DIPA and Si-DIPAP were filtered off. From general synthesis to give *N*-benzyl-benzenesulfonamide product.

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Specteral data:

***N*-Benzyl-benzenesulfonamide (1a);** *Rf* = 0.68 (10% CH_2Cl_2/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.54 (dt, *J* = 34.3, 7.3 Hz, 3H), 7.23 (dd, *J* = 24.2, 6.4 Hz, 5H), 5.29 (s, 1H) and 4.31 (d, *J* = 4.3 Hz, 2H).

2.7 Stability of 3-aminopropyl (Fe_3O_4-Si-2) and 3-aminopropyl (Fe_3O_4-1)

To demonstrate the stability of the obtained amino bead including Fe_3O_4-Si-**2** and 3-aminopropyl Fe_3O_4-**1**, both of them were test under acid condition to determine the concentration of iron ion (Fe^+) that leach out from these amino beads. The amino beads 50 mg were mixed with various concentration of hydrochloric acid (%v/v) which are 0.0035, 0.0050, 0.0100, 0.0150, 0.0200, 0.0250, 0.0300 and 0.0350, the mixture were incubated for 18 h then the liquid after incubation was collected for analysis by atomic absorption spectrophotometer technique (AAS).

2.8 Synthesis of magnetic silica nanoparticles supported base reagents (Fe_3O_4-Si-base: Fe_3O_4-Si-TEA, Fe_3O_4-Si-DIPA, Fe_3O_4-Si-NMM and Fe_3O_4-Si-NMP)

2.8.1 Preparation of silica coated magnetic nanoparticle (Fe_3O_4-Si-1)

The magnetic nanoparticles were functionalized with triethoxysilane (TEOS) according to a slightly modified reported procedure [53]. Fe_3O_4 nanoparticles (10 g) were dispersed in ethanol and water (6:1, v/v). The suspension was sonicated 30 min at room temperature. TEOS and ammonium solution (29%, v/v) (2:1, v/v) were added, and the mixture was stirred vigorously at room temperature for 16 h. The product Fe_3O_4-Si-**1** was washed with water, methanol and acetone via external magnetic field decantation, and oven dried at 80 °C for 12 h and kept in desiccators.

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2.8.2 Synthesis of 3-aminopropyl Fe_3O_4-Si-2

3-Aminopropyltriethoxysilane (3 ml) was dissolved in 50 ml of toluene in a round-bottomed flask. Whilst the solution was stirred vigorously, 10 g of the Fe_3O_4-Si-**1** was slowly added. After sonicating for 10 min, the reaction mixture was refluxed for 3 h. The product was then rinsed with toluene, followed by methanol and acetone, respectively via external magnetic field decantation to obtain Fe_3O_4-Si-**2**. The Fe_3O_4-Si-**2** was oven dried at 80°C for 12 h and kept in desiccators.

2.8.3 Synthesis of Fe_3O_4-Si-3

3-Aminopropyl Fe_3O_4-Si-**2** (10 g) was added as a powder into a 250 ml round-bottomed flask containing triethylamine (8.16 ml, 58.5 mmol), the reaction mixture were cold at 0^oC then chloroacetyl chloride (5.58 ml, 70.2 mmol) in dichloromethane (100 ml) was added. After stirring for 1 h at 0^oC, the reaction mixture was stirred at room temperature for 16 h. After the completion of the reaction as indicated by negative ninhydrin test of the resulting Fe_3O_4-Si-**3**, the solid was washed with dichloromethane, followed by deionized water, acetone and dichloromethane, respectively via external magnetic field decantation. The Fe_3O_4-Si-**3** was oven dried at 80°C for 12 h and kept in desiccators [48].

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2.8.4 Synthesis of Fe_3O_4-Si-base

To synthesize Fe_3O_4-Si-base, amine solution which are; diethylamine, diisopropylamine, morpholine and piperidine were immobilized onto the surface of

Fe_3O_4-Si-**3**. The Fe_3O_4-Si-**3** (3 g) was added as a powder into a 100 ml round-bottomed flask containing amine solution (5 equiv.), KI (10 mg) in toluene 50 ml, the solution was stirred vigorously at 60 °C for 13h. The Fe_3O_4-Si-base was washed with toluene, followed by water, methanol and acetone, respectively via external magnetic field decantation. The Fe_3O_4-Si-base was oven dried at 80 °C for 12 h. and kept in desiccators. Fe_3O_4-Si-base was characterized with fourier transform infrared (FT-IR) spectrometer (Bruker, TENSOR 27), Germany. The particles size and morphology were studies by SEM using a JEOL scanning electron microscope (SEM). SEM specimens were prepared by diluting the particle dispersions with acetone and placing one drop each on stub. The drops were allowed to dry at room temperature and then sputter coated with gold prior to imaging.

2.9 Synthesis of *N*-benzyl-benzenesulfonamide

To demonstrate the applicability of the obtained Fe_3O_4-Si-base, these base were applied as base reagent in the synthesis of *N*-benzyl-benzenesulfonamide. The same reaction using Fe_3O_4-Si-base were performed for comparison. 1.2 equiv. of supported base was used in the solution phase synthesis. After the reaction was completed, Fe_3O_4-Si-base was removed via magnetic decantation, excess amine were scavenged with Si-DCT [47], the sulfonamide product was isolated by concentrated the crude reaction mixture via evaporated to give *N*-benzyl-benzenesulfonamide as a white solid.

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2.10 Application of Fe_3O_4-Si-DIPA in sulfonation, acylation, and alkylation

All the reactions were carried out in mini tube using Fe_3O_4-Si-DIPA (1.2 equiv.) as base. The starting materials, benzenesulfonyl chloride, benzoyl chloride and benzyl bromide, were used as limiting agents in sulfonation, acylation and alkylation, respectively. Amines (1.2 equiv.) were added to a mixture containing the selected starting material and Fe_3O_4-Si-DIPA (1.2 equiv.) in 3 ml dichloromethane. The reaction mixture was incubated by rocking table (Specimen mixer, BCT-33) at room temperature for 30 minute. After the reaction was completed, Fe_3O_4-Si-DIPA was removed via external magnetic field, excess amine were scavenged with Si-DCT [47]. The crude reaction mixture was evaporated to give the sulfonamide products **1a-e** or amide products **2a-e** or amine products **3a-e**.

Spectra data:

***N*-Phenyl-benzenesulfonamide (1b)**; *Rf* = 0.57 (10% CH_2Cl_2/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 2H), 7.56 – 7.42 (m, 4H), 7.26 – 7.22 (m, 2H) and 7.15 – 7.10 (m, 2H).

***N*-Butyl-benzenesulfonamide (1c)**; *Rf* = 0.65 (10% CH_2Cl_2/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.64 – 7.47 (m, 3H), 4.96 (t, *J* = 5.7 Hz, 1H), 2.94 (q, *J* = 13.4, 6.9 Hz, 2H), 1.51 – 1.37 (m, 2H), 1.34 – 1.21 (m, 2H) and 0.83 (t, *J* = 7.3 Hz, 3H).

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4-Benzenesulfonylmorpholine (1d); *Rf* = 0.77 (10% CH_2Cl_2/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.48 (m, 1H), 3.74 (t, 4H) and 3.00 (t, 4H).

1-Benzenesulfonylpiperidine (1e); *Rf* = 0.32 (10% CH_2Cl_2/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 2H), 7.84 – 7.19 (m, 3H), 2.99 (t, 4H) and 1.71 – 1.35 (m, *J* = 90.7, 11.7, 5.8 Hz, 6H).

***N*-Benzylbenzamide (2a)**; *Rf* = 0.65 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.55 – 7.23 (m, 3H) and 4.65 (d, *J* = 5.7 Hz, 2H).

***N*-Phenylbenzamide (2b)**; *Rf* = 0.8 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.83 (m, 2H), 7.65 (t, *J* = 10.1 Hz, 2H), 7.50 (dt, *J* = 15.0, 7.3 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H) and 7.17 (dd, *J* = 29.2, 21.8 Hz, 2H).

***N*-Butylbenzamide (2c)**; *Rf* = 0.52 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.69 (m, 2H), 7.47 – 7.28 (m, 3H), 3.39 (q, *J* = 13.6, 6.7 Hz, 2H), 1.65 – 1.47 (m, 2H), 1.44 – 1.20 (m, *J* = 15.1, 7.5 Hz, 2H) and 0.90 (t, *J* = 7.4 Hz, 3H).

Morpholin-4-yl-phenylmethanone (2d); *Rf* = 0.28 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.24 (m, *J* = 73.9 Hz, 5H), 3.80 (bs, 4H) and 3.06 (bs, 4H).

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Phenyl-piperidin-1-yl-methanone (2e); *Rf* = 0.4 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.28 (m, 5H), 3.52 (bd, *J* = 155.1 Hz, 4H) and 1.75 – 1.17 (m, 6H).

Dibenzylamine (3a); *Rf* = 0.42 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.21 (m, 5H) and 3.55 (s, 4H).

Benzylphenylamine (3b); *Rf* = 0.38 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 6.61 (m, 10H) and 4.65 (s, 2H).

Benzylbutylamine (3c); *Rf* = 0.35 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 5H), 3.54 (s, 2H), 2.40 (t, 2H), 1.51 – 1.43 (m, *J* = 7.4 Hz, 2H), 1.35 – 1.23 (m, *J* = 15.1, 7.4 Hz, 2H) and 0.82 (t, *J* = 7.4 Hz, 3H).

4-Benzylmorpholine (3d); *Rf* = 0.34 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 5H), 3.70 (t, 4H), 3.49 (s, 2H) and 2.44 (s, 4H).

1-Benzylpiperidine (3e); *Rf* = 0.11 (100% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 5H), 3.46 (s, 2H), 2.37 (bs, 4H) and 1.74 – 1.18 (m, 6H).

2.11 Reusability of Fe_3O_4-Si-DIPA

The reusability of Fe_3O_4-Si-DIPA was studied in repeated synthesis of *N*-benzylbenzenesulfonamide. After each experiment, Fe_3O_4-Si-DIPA was removed via external magnetic decantation. Fe_3O_4-Si-DIPA was washed with dichloromethane, methanol and treated with 15% triethylamine in dichloromethane. The neutralized Fe_3O_4-Si-DIPA was then washed with dichloromethane and dried at room temperature under *vacuum* before using in the subsequent runs.

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