

# **A Convenient Synthesis of dithiolane and benzyloximates derivatives for Ligand studies.**

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## **Abstract**

We report the synthesis of new aromatic derivatives containing the 1,3-dithiolane ether and benzyloximino moiety which are attached by simple alkylation and esterification reaction by treating 1,3-dithiolane-2-methanol and  $\alpha$ -benzyloximino acid chloride respectively with various aromatic halides and alcohols, respectively. The isolated yields of these compounds range from 65 to 85%. 1,3-dithiolane ether and the benzyloxy substituted hydroquinone are white solids or residual oil and stable to air and moisture.

**Keywords:** dithiolane; benzyloximate, ligands; multidentate

## **INTRODUCTION**

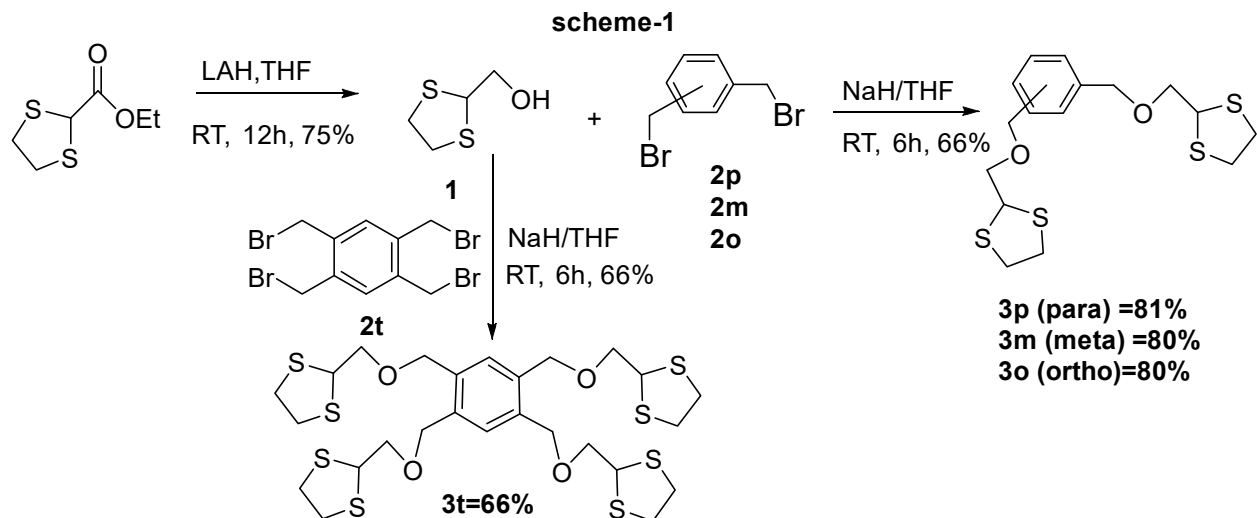
Cyclic thioethers are popular ligands for the construction of discrete transition metal complexes, coordination polymers, and three-dimensional networks<sup>1-2</sup>. The presence and positioning of multiple sulfur atoms in the rings allow for a variety of multidentate binding modes to transition metals. Recent examples of cyclic thioethers used in this manner include 1,3,5-trithiane<sup>3-4</sup>, 1,4-dithiane<sup>5-6</sup>, 1,3-dithiane<sup>7</sup>, 1,4,7-trithiacyclononane<sup>8</sup>, 1,4,8,11-tetrathiacyclododecane<sup>8</sup>, and various macrocyclic thioether-esters<sup>9</sup> and aza-thioethers<sup>10</sup>. Among cyclic thioethers, multidentate heterocycles such as 1,3-dithiane and 1,4-dithiane have been utilized for this

purpose. However, to the best of our knowledge, 1,3-dithiolanes have not been used as ligands in AgI complexes. Moreover it received very little attention as potential ligands for transition metal ions<sup>11</sup>. On other hand, the known donor properties of nitrogen in a variety of ligand structures, little has been reported concerning the potential ligand properties of oxime ethers<sup>12</sup>. Oxime ethers are stable and are relatively simple to synthesize and thus it was of interest to us to explore their ligand properties.

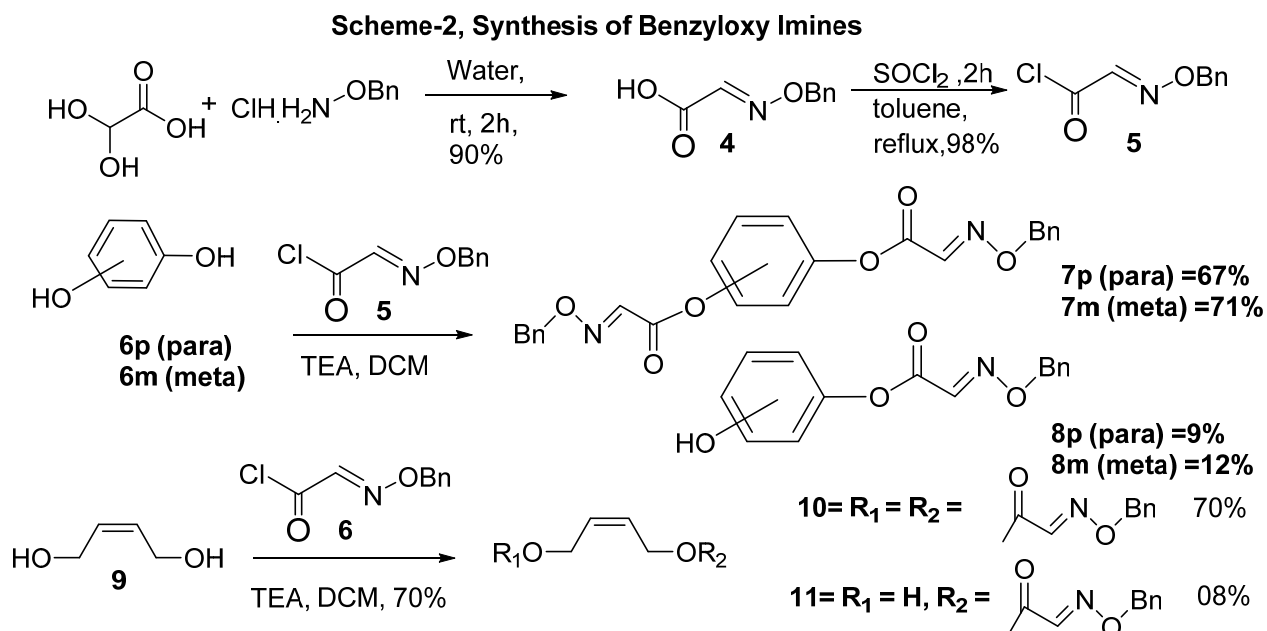
## PRESENT WORK

In a continuation of our research in the design of multidentate heteroaromatic ligands<sup>13-18</sup>, benzyloximino-acetic acid<sup>19</sup>, 1,3-Dithialane-methanol<sup>20</sup> and sulfur ethers<sup>21</sup> are successfully formed topological structure with soft transition metals ion. Encouraged by these results, we synthesize and characterize of new aromatic derivatives containing the 1,3-dithiolane and benzyloximate moiety. Such compounds contain multiple sulfur atoms and oximate nitrogen atoms in differing positions and thus have the potential to form new complex structures or networks from interactions with soft transition metal ions.

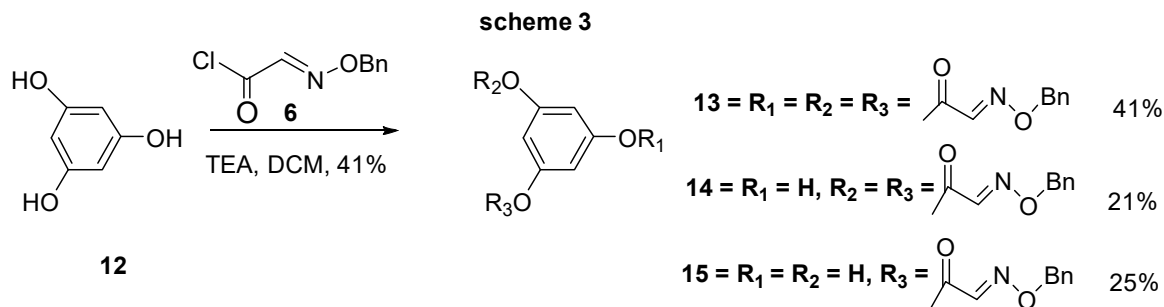
1,3-dithiolane-2-methanol<sup>22</sup>, synthesized in single steps from commercially available ethyl 1,3-dithiolane-2-carboxylate (Scheme 1) by lithium aluminum hydride reduction in 75% yield. We chose this approach because the ready availability of *ortho*-, *meta*-, and *para*-dibromomethylbenzene would provide flexibility in positioning the dithiolane groups around the benzene ring. Based on the success of these reactions, we then attempted a reaction between **1** and 1,2, 4,5- tetrabromo methylbenzene give tetra dithiolane moieties on the benzene ring, was obtained in 66% isolated yield.



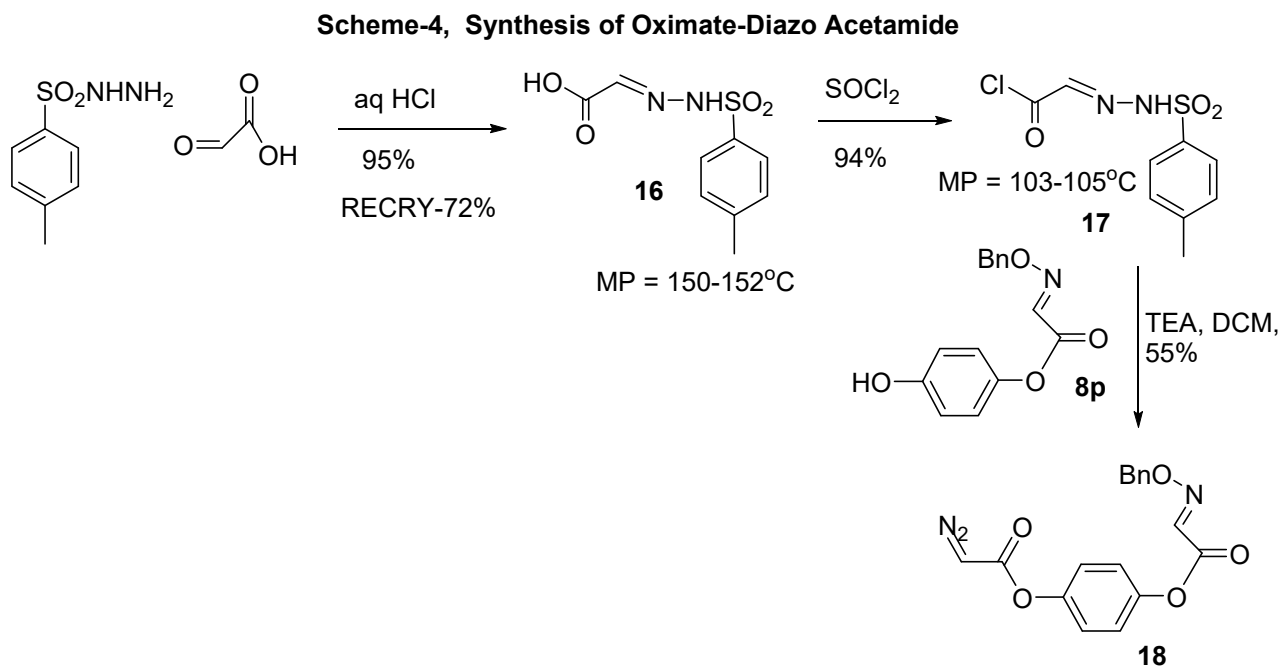
After getting encouraging results from this reaction, we attempted to synthesize the substituted oximate molecules by treating  $\alpha$ -Benzoyloximino acid chloride<sup>23</sup> **5** with commercially available, *ortho*-, *meta*-, and *para*-dihydroxybenzene (**6o**, **6m**, **6p**), and *cis*-2-butene-1,4-diol **9** and 1,3,5-trihydroxybenzene **12**. In case of *meta* and *para* dihydroxybenzene and *cis*-2-butene-1,4-diol **9**, we obtained disubstituted (**7m**, **7p**, **10**) and mono substituted product (**8m**, **8p**, **11**) in good yields.



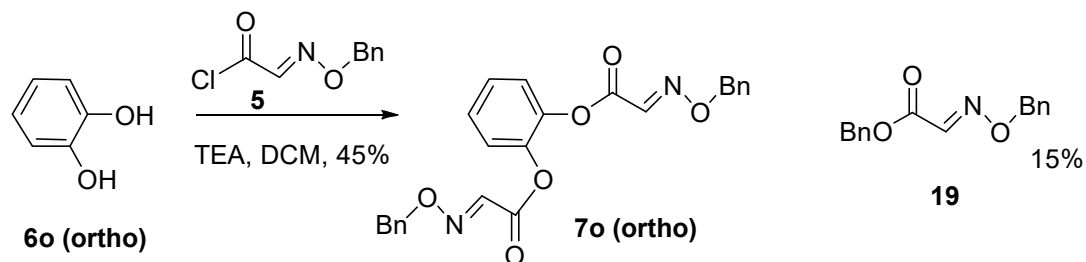
In case of 1,3,5-trihydroxybenzene **12**, we obtained triester **13** along with diester **14** and monoester **15** in 41%, 21% and 25% yields.



The 1,4 -mono substituted benzene Oximate **8p**, we carried one reaction with glyoxylic acid chloride *p*-toluenesulfonyl hydrazones<sup>24-26</sup> **17** to obtained diazo product **18** in 55% yield. (scheme-4)



In case of 1,2 dihydroxy benzene **60**, it gives the dibenzyloxy product **70** in 45% yield, along with complex product, benzyloxyimino-acetic acid benzyl ester **19** in 15% yield. The mechanism is not clear, but it is expected the steric hinderance play a key role in the formation of benzyloxyimino-acetic acid benzyl ester **19**. (scheme-5)



### Solubility and Characterizations:

All new compounds were isolated as air- and moisture-stable solids. All compounds were fully characterized using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and elemental analysis. 1,3-dithiolane ether and the Oximate substituted hydroquinone are white solids or residual oil and stable to air and moisture. The solubilities of all compounds were excellent in common organic solvents, except hexane, benzene and toluene. And as expected insoluble in water, sat,  $\text{NaHCO}_3$ , and dilute  $\text{HCl}$ .

### Crystal Studies:

Preliminary experiments in which these compounds were mixed with various silver salts resulted in the formation of insoluble suspensions that could not be recrystallized for X-ray crystallographic analysis. However, elemental analysis of the isolated suspensions confirms the presence of silver, suggesting that complexation reactions are indeed occurring.

### CONCLUSION

We have prepared a series of new compounds containing one, two, or three dithiolane rings bonded to an aromatic core. The synthetic procedure is straightforward, and the yields are moderate to excellent yield after chromatographic purification. All these compounds possess multiple sulfur atom and Oximate moiety are thus capable of binding in a multidentate fashion to soft transition metal ions. Reactions of these ligands with late transition metal ions is a current focus in our laboratory.

## ACKNOWLEDGMENTS

The authors thank the National Science Foundation and the Welch Foundation for support of this work.

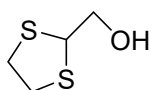
**Declaration of Competing Interest** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Data and materials availability:** Requests for materials should be addressed to Sudershan R Gondi (gondisr@gmail.com)

## EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reagents were obtained from either Aldrich (Milwaukee, WI, USA) or Acros (Morris Plains, NJ, USA) and used without further purification.  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra were recorded using a 400-MHz Bruker AVANCE DRX multinuclear NMR spectrometer. All chemical shifts are reported in parts per million. Infrared spectra were obtained on a Nicolet Magna-IR 560 spectrometer E.S.P. Elemental analyses were obtained with a CE Elantech Thermo-Finnigan Flash 1112 CHN elemental analyzer. Melting points were collected on a TA Instruments DSC 2010 Differential Scanning Calorimeter using a heating rate of 108C/min and nitrogen as a purge gas.

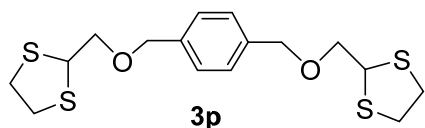
**[1,3]-Dithialane-methanol (1):** Dissolve 5.0 g (28.0 mmol, 1.0 eq) the [1,3]-dithionate ethyl ester in THF (50 mL) and cool to 0°C. Add 2.13 g (56.0 mmol, 2.0 eq) of lithium aluminum hydride portion wise over a period of 10 minutes. Stir at room temperature for 12 h, quench the reaction mass by drop wise addition of water (10 mL). Filter the aluminum precipitate and wash the precipitate with ethylacetate (100 mL X 2) and wash the clear organic (filtrate) layer with water, brine solution, dried over  $\text{MgSO}_4$  and filter. The filtrate was concentrated and the residue chromatographed on silica gel (1:5 EtOAc:hex) to



1

give **1** as a residual oil (2.9 g, 75%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 4.43-4.40 (t, 1H, *J* = 6.3 Hz), 3.42-3.41 (d, 2H, *J* = 5.8 Hz), 3.0 (s, 4H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 66.6, 54.5, 37.5 IR (KBr): 3404, 2924, 2863, 1422, 1275, 1057, 734 cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>4</sub>H<sub>8</sub>OS<sub>2</sub>: C, 35.26; H, 5.92. Found: C, 35.29; H, 5.92.

**1,4-bis(((1,3-dithiolan-2-yl)methoxy)methyl)benzene (3p):** [1,3]-Dithialane-methanol (**1**) (910



mg, 7.6 mmol, 2.0 eq) was dissolved in THF (10 mL) and the

resulting clear solution was cooled in an ice bath. Sodium

hydride (220 mg, 9.1 mmol, 2.4 eq) was added, resulting in

effervescence and the formation of a suspension. The mixture was stirred in the ice bath for 15

minutes, and then 1,4-benzene di methylbromide (**2p**) (1.0g, 3.3 mmol, 1.0 eq) was added

dropwise over a period of 10 minutes. The mixture was stirred at room temperature for 6 h. The

THF was removed using a rotary evaporator, and water (100 mL) was added to the residue. The

solution was extracted with dichloromethane (100 mL), and the organic layer was washed with

water (100 mL), saturated sodium bicarbonate solution (100 mL), water (100 mL), and brine

(100 mL), and then dried over anhydrous magnesium sulfate and filtered. The filtrate was

concentrated and the residue chromatographed on silica gel (1:4 EtOAc:hex) to give **3p** as a

white solid (1.15 g, 81%). Mp 98-100°C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.25 (s, 4H), 4.54 (s,

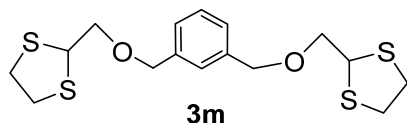
2H), 4.50 (s, 4H), 3.48-3.47 (d, 4H, *J* = 4.0 Hz), 3.11 (s, 8H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ

137.3, 127.6, 75.0, 72.8, 51.6, 37.8 IR (KBr): 2925, 2848, 1468, 1352, 1274, 1119, 1014, 797,

cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>S<sub>4</sub>: C, 51.30; H, 5.92. Found: C, 51.36; H, 6.07.

**1,3-bis(((1,3-dithiolan-2-yl)methoxy)methyl)benzene (3m):** In the manner described above,

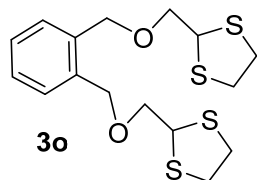
910 mg (7.6 mmol, 2.0 eq) of [1,3]-Dithialane-methanol (**1**)



was treated with 1.0 g (3.7 mmol, 1.0 eq) of 1,3-benzene

dimethylbromide (**2m**) in presence of sodium hydride (220 mg, 9.1 mmol, 2.4 eq) in THF (30 mL) and cool to 0°C under nitrogen atmosphere. Column chromatographic purification (25:75 EtOAc:hex) gave **3m** as residual oil (1.1 g, 78%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.25-7.20 (m, 4H), 4.55-4.54 (t, 2H, *J* = 6.9 Hz), 4.51 (s, 4H), 3.49-3.47 (d, 4H, *J* = 6.9 Hz), 3.10 (s, 8H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 137.9, 128.3, 126.7, 126.7, 75.0, 72.8, 51.5, 37.8. IR (KBr): 2922, 2852, 1445, 1352, 1276, 1103, cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>S<sub>4</sub>: C, 51.300; H, 5.92. Found: C, 51.92; H, 6.03.

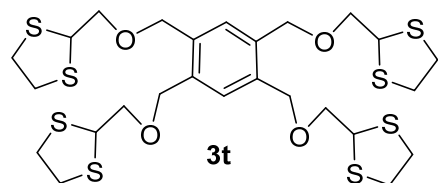
**1,2-bis(((1,3-dithiolan-2-yl)methoxy)methyl)benzene (3o):** In the manner described above,



910 mg (7.6 mmol, 2.0 eq) of [1,3]-Dithialane-methanol (**1**) was treated with 1.0 g (3.7 mmol, 1.0 eq) of 1,2-benzene dimethylbromide (**2o**) in presence of sodium hydride (220 mg, 9.1 mmol, 2.4 eq) in THF (30 mL) and cool to 0°C under nitrogen atmosphere. Column chromatographic

purification (25:75 EtOAc:hex) gave **3o** as residual oil (1.1 g, 78%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.32-7.30 (dd, 2H, *J* = 3.3 & 1.6 Hz), 7.21-7.19 (dd, 2H, *J* = 3.2 & 2.0 Hz), 4.60 (s, 4H), 4.57-4.53 (t, 2H, *J* = 6.9 Hz), 3.50-3.49 (d, 4H, *J* = 6.9 Hz), 3.10 (s, 8H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 135.9, 128.7, 127.7, 75.2, 70.8, 51.5, 37.8. IR (KBr): 3050, 2927, 2853, 1453, 1354, 1265, 1095, 736, cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>S<sub>4</sub>: C, 51.30; H, 5.92. Found: C, 50.90; H, 5.62.

**1,2,4,5-tetrakis(((1,3-dithiolan-2-yl)methoxy)methyl)benzene (3t):** In the manner described

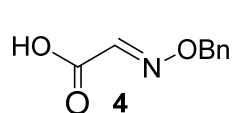


above, 1.067 g, 8.8 mmol) of [1,3]-Dithialane-methanol (**1**) was treated with 1.0 g (2.2 mmol) of 1,2,4,5-benzene tetramethylbromide (**2t**) in presence of sodium hydride (234 mg, 9.7 mmol) in THF (30 mL) and cool to 0°C under



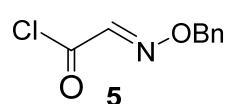
nitrogen atmosphere. Column chromatographic purification (20:80 EtOAc:hex) gave **3t** as residual oil (0.99 g, 66%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.22 (s, 2H), 4.46 (s, 8H), 4.41-4.40 (t, 4H, *J* = 7.3 Hz), 3.36-3.35 (d, 8H, *J* = 6.6 Hz), 2.98 (s, 16H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 135.7, 129.6, 75.3, 70.6, 51.6, 38.0. IR (KBr): 3051, 2927, 2856, 1423, 1352, 1265, 1098, 737 cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>26</sub>H<sub>38</sub>O<sub>4</sub>S<sub>8</sub>: C, 46.53; H, 5.71. Found: C, 46.40; H, 5.59.

**Benzyloxyimino-acetic acid<sup>23</sup> (4):** 50% Glyoxylic acid (3.0 mL, 34.0 mmol, 2.2 eq) was added



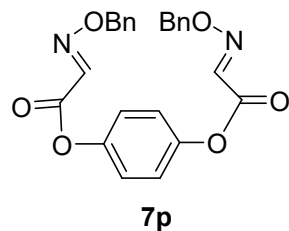
at room temperature to a stirred solution of benzylhydroxylamine hydrochloride (2.5 g, 15.6 mmol) in 100 mL of water. Within a few minutes a crystalline mass. Stirring was continued for 30 minutes, then extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL x 2). The combined organic layer was separated dried over MgSO<sub>4</sub> and filtered. The solvent was evaporated to give pure 2.6 g of product in 92.8% yield. MP = 87.82°C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 11.57 (s, 1H, COOH), 7.41 (s, 1H), 5.35 (s, 2H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 166.4, 140.2, 135.5, 128.6, 128.5, 78.5. IR (KBr): 3034, 1215 (medium), 1715, 1680, 1591, 1263 cm<sup>-1</sup> (strong).

**Benzyloxyimino-acetyl chloride<sup>23</sup> (5):** A solution of SOCl<sub>2</sub> (2.0 mL, 3.0 g, 28 mmol) in 10 mL



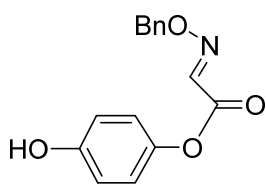
of dry toluene was added at room temperature to a stirred solution of acid (1 g, 5.5 mmol) in 10 mL of dry toluene. Stirring was continued for 2 h at 80°C. After 2 h, 50 mL of toluene was added and evaporated; this was repeated twice to afford the pure acid chlorides 1.0 g in 91% yield. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.68 (s, 1H), 7.48-7.47, (d, 5H, *J* = 4.6 Hz) 5.44-5.43 (d, 2H, *J* = 2.7 Hz).

**Benzyloxyimino-acetic acid 4-(2-benzyloxyimino-acetoxy)-phenyl ester (7p):** Dissolve the



250 mg (2.2 mmol) of 1,4-dihydroquinone (**6p**) in THF (100 mL) and cool to 0°C under nitrogen atmosphere. Add triethylamine (550 mg, 0.8

mL, 5.4 mmol) at same temperature under nitrogen atmosphere. Stir at same temperature for 10 minutes. Add 895 mg (4.5 mmol) of  $\alpha$ -Benzyloximino acid chloride<sup>22</sup> (**4**) portion-wise over a period of 15 minutes at 0°C. Stir at room temperature for 24 h. Remove the THF on rota evaporator and quench the residue by addition of water (100 mL). Extract with ethyl acetate (100 mL), wash the organic layer with water (100 mL), saturated sodium bicarbonate solution (100 mL), water (100 mL), brine solution (100 mL), dried over MgSO<sub>4</sub> (1.0 g). The filtrate was concentrated and the residue chromatographed on silica gel (20:80 EtOAc:hex) to give **7p** as a white solid (655 mg, 67%). Mp 101.34°C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.75 (s, 2H), 7.45-7.40 (m, 10H), 7.25 (s, 4H), 5.40 (s, 4H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  160.0, 147.7, 140.3, 135.7, 128.6, 128.5, 122.3, 78.4. IR (KBr): 3031, 2955, 1760, 1599, 1504, 1325, 1174 cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 66.66; H, 4.66; N, 6.48. Found: C, 66.30; H, 4.60; N, 6.36. and eluted with (30:70 EtOAc:hex) to give Benzyloxyimino-acetic acid 4-



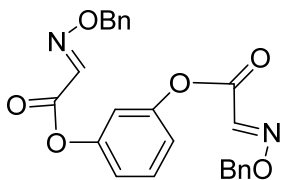
**8p**

hydroxy-phenyl ester (**8p**) as white solid. (61 mg, 9%). Mp 94°C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.77 (s, 1H), 7.43-7.41 (m, 5H), 7.01-6.99 (d, 2H, *J* = 8.6 Hz), 6.81-6.79 (d, 2H, *J* = 8.1 Hz), 5.38 (s, 2H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  161.2, 153.8, 143.1, 140.4, 135.6, 128.6, 128.5, 122.0, 116.0,

78.3. IR (KBr): 3417, 3022, 2949, 1760, 1615, 1460, 1330, 1139 cm<sup>-1</sup>. Elemental Analysis:

Calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>4</sub>: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.44; H, 4.78; N, 5.09.

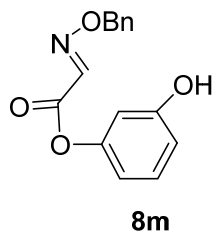
**Benzyloxyimino-acetic acid 3-(2-benzyloxyimino-acetoxy)-phenyl ester (7m):** In the manner



**7m**

described above, 250 mg (2.2 mmol) of 1,3-dihydroquinone (**6m**) was treated with 895 mg (4.5 mmol) of  $\alpha$ -Benzyloximino acid chloride<sup>22</sup> (**5**) in presence of triethylamine (0.8 mL, 550 mg, 5.4 mmol) in THF (30 mL). Column chromatographic purification (20:80 EtOAc:hex) gave

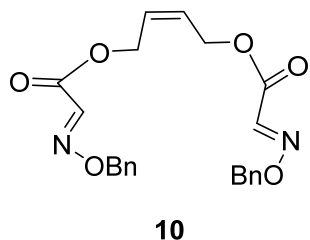
**7m** as residual oil (690 mg, 71%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.74 (s, 2H), 7.44 (s, 11H), 7.15-7.12 (d, 3H, *J* = 2.9 Hz), 5.39 (s, 4H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 159.8, 150.5, 140.2, 135.6, 129.8, 128.6, 128.5, 119.2, 115.1, 78.4. IR (neat): 3034, 2943, 1762, 1592, 1484, 1325, 1163 cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 66.66; H, 4.66; N, 6.48. Found: C, 66.46; H, 4.60; N, 6.42. and eluted with (30:70 EtOAc:hex) gave benzyloxyimino-acetic acid



3-hydroxy-phenyl ester (**8m**) (75 mg, 12%). Mp 116-118°C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.75 (s, 1H), 7.40 (s, 5H), 7.25-7.24 (d, 1H, *J* = 4.8 Hz), 6.73 (s, 2H), 6.66 (s, 1H), 5.36 (s, 2H), 5.24 (br-s, 1H, OH). <sup>1</sup>H-NMR (400 MHz, Dms<sub>o</sub>-d<sub>6</sub>): δ 9.81 (s, 1H, OH), 7.93 (s, 1H), 7.41-7.38 (m, 5H), 7.23-7.19 (t,

1H, *J* = 7.7 Hz), 6.71-6.69 (d, 1H, *J* = 7.5 Hz), 6.62-6.60 (d, 1H, *J* = 7.3 Hz), 5.31 (s, 2H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 160.4, 156.6, 150.8, 140.4, 135.7, 130.1, 128.7, 128.6, 113.6, 113.3, 108.9, 78.4. <sup>13</sup>C-NMR (100.6 MHz, Dms<sub>o</sub>-d<sub>6</sub>): δ 160.7, 159.2, 151.5, 142.4, 137.1, 130.8, 129.3, 129.1, 114.1, 112.7, 109.6, 78.0. IR (KBr): 3422, 3022, 2948, 1716, 1615, 1498, 1278 cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>4</sub>: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.50; H, 4.76; N, 5.14.

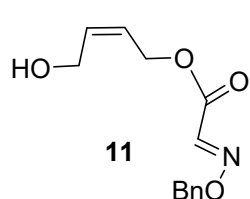
**Benzyloxyimino-acetic acid 4-(2-benzyloxyimino-acetoxy)-but-2-enyl ester (10):** In the



manner described above, 250 mg (2.0 mmol) of 1,4-cis butane-diol (**15**) was treated with 895 mg (4.5 mmol) of α-Benzyloximino acid chloride<sup>22</sup> (**4**) in presence of triethylamine (0.8 mL, 5.4 mmol) in THF (30 mL) and cool to 0°C under nitrogen atmosphere. Column

chromatographic purification (10:90 EtOAc:hex) gave diester **16** as residual oil (810 mg, 70%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.57 (s, 2H), 7.39-7.36 (m, 10H), 5.86-5.84 (m, 2H), 5.32 (s, 4H), 4.92-4.90 (d, 4H, *J* = 4.8 Hz). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 161.5, 140.6, 135.8, 128.5,

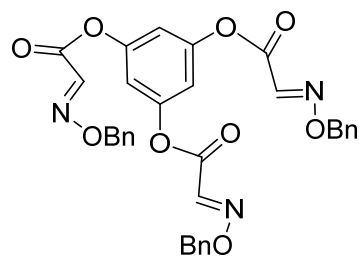
128.4, 127.8, 78.1, 60.9. IR (neat): 2944, 1724, 1598, 1455, 1356, 921  $\text{cm}^{-1}$ . Elemental Analysis: Calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6$ : C, 64.38; H, 5.40; N, 6.83. Found: C, 64.21; H, 5.84; N, 6.94. and eluted with (20:80 EtOAc:hex) gave benzyloxyimino-acetic acid 4-hydroxy-but-2-enyl ester (**17**) as



residual (60 mg, 08%).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.55 (s, 1H), 7.37 (s, 5H), 5.92-5.86 (m, 1H), 5.70-5.64 (m, 1H), 5.29 (s, 2H), 4.85-4.84 (d, 2H,  $J = 6.6\text{Hz}$ ), 4.27-4.25 (d, 2H,  $J = 6.0\text{ Hz}$ ), 2.85 (br-s, 1H, OH).  $^{13}\text{C-NMR}$  (400

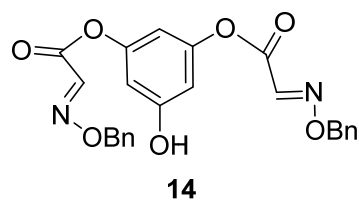
MHz,  $\text{CDCl}_3$ ):  $\delta$  161.7, 140.7, 135.7, 134.1, 128.5, 128.4, 128.3, 124.3, 78.0, 61.0, 58.2. IR (neat): 3377, 2984, 1724, 1618, 1455, 1369, 922  $\text{cm}^{-1}$ . Elemental Analysis: Calcd for  $\text{C}_{13}\text{H}_{15}\text{NO}_4$ : C, 62.64; H, 6.07; N, 5.62. Found: C, 62.50; H, 6.57; N, 5.77.

**Benzyloxyimino-acetic acid 3,5-bis-(2-benzyloxyimino-acetoxy)-phenyl ester (**13**):** In the

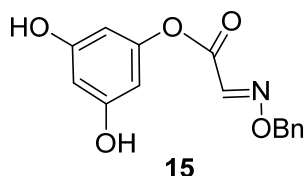


manner described above, 250 mg (2.0 mmol) of 1,3,5-trihydroxy benzene (**11**) was treated with 1.17 g (6.0 mmol) of  $\alpha$ -Benzyloximino acid chloride<sup>22</sup> (**4**) in presence of triethylamine (1.0 mL, 725 mg, 6.6 mmol) in THF (30 mL) and cool to  $0^\circ\text{C}$  under nitrogen atmosphere. Column chromatographic purification (20:80 EtOAc:hex) gave **13** as residual oil (500 mg, 41%).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.59 (s, 3H), 7.31-7.27 (m, 15H), 6.96 (s, 3H), 5.26 (s, 6H).  $^{13}\text{C-NMR}$  (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.4, 150.5, 139.9, 135.6, 128.7, 128.6, 113.0, 78.5. IR (neat): 3033, 2941, 1747, 1618, 1584, 1454  $\text{cm}^{-1}$ . Elemental Analysis: Calcd for  $\text{C}_{33}\text{H}_{27}\text{N}_3\text{O}_9 \cdot 1/2\text{H}_2\text{O}$ :

Calcd: C, 64.07; H, 4.56; N, 6.79. Found: C, 63.93; H, 4.25; N, 6.60. and eluted with (30:70 EtOAc:hex) gave benzyloxyimino-acetic acid 3-(2-benzyloxyimino-acetoxy)-5-hydroxy-phenyl ester (**14**) as residual oil (1.77 g, 21%).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$



7.57 (s, 2H), 7.28-7.24 (m, 10H), 6.49-6.47 (t, 3H,  $J = 1.8$  Hz), 5.23 (s, 4H).  $^{13}\text{C-NMR}$  (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.0, 157.4, 150.8, 140.1, 135.6, 128.6, 128.5, 107.3, 106.7, 78.5. IR (neat): 3033, 2942, 1762, 1592, 1484, 1240, 991  $\text{cm}^{-1}$ . Elemental Analysis: Calcd for  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_7 \cdot 1/2\text{H}_2\text{O}$ : Calcd: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.09; H, 4.55; N, 6.16. and eluted (40:60 EtOAc:hex) gave benzyloxyimino-acetic acid 3,5-dihydroxy-phenyl ester (**15**) as



white solid (139 mg, 25%). Mp 93-95°C.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):

$\delta$  7.61 (s, 1H), 7.32-7.31 (m, 5H), 6.20-6.19 (d, 2H,  $J = 1.8$  Hz), 6.18 (s,

1H), 5.28 (2H), 5.18 (br-s, 2H, OH).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$

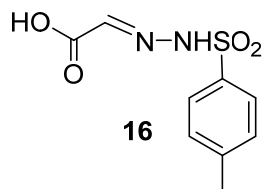
9.60 (s, 2H, OH), 7.89 (s, 1H), 7.40 (s, 5H), 6.14 (s, 1H), 6.02 (2H),

5.30 (s, 2H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  160.5, 159.7, 152.0, 142.5, 137.1, 129.3, 129.1,

101.3, 100.7, 78.0. IR (KBr): 3368, 2947, 1709, 1636, 1460, 1369  $\text{cm}^{-1}$ . Elemental Analysis:

Calcd for  $\text{C}_{15}\text{H}_{13}\text{NO}_5 \cdot \text{H}_2\text{O}$ : Calcd: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.37; H, 5.43; N, 4.78.

**Glyoxylic Acid *p*-Toluenesulfonyl Hydrazone<sup>24-26</sup> (**16**):** Suspend *p*-toluenesulfonyl hydrazide



in 75 mL of 2.5 M Hydrochloric acid and heat at 60°C, clear solution is

formed. Add glyoxylic acid solution, resulted in salt formation. Maintain

at 60°C for 25 minutes then cool to room temperature. Store in Refrizator

for overnight (12 h). Filter and wash the solid with water (250 mL) and

dry in open air for two days to obtained pale white solid (35.5 g). Dissolve in 120 mL of ethyl

acetate at reflux condition for 20 minutes. Filter in hot condition and dilute with carbon

tetrachloride (250 mL) and kept in refrizator for 24 h. Filter and wash the crystals with cooled

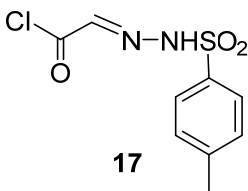
ethyl acetate (50 mL) and cooled  $\text{CCl}_4$  (25 mL) and dry to obtain **8** as white crystal solid (30 g,

91.5%). Mp 173.24°C. (Reported<sup>23</sup> Mp 149.5-152 °C).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  12.30

(s, 1H, COOH), 7.73-7.71 (d, 2H,  $J = 7.8$  Hz), 7.43-7.41 (d, 2H,  $J = 7.8$  Hz), 7.20 (s, 1H), 2.37

(s, 3H).  $^{13}\text{C}$ -NMR (100.6 MHz, DMSO- $d_6$ ):  $\delta$  164.4, 144.9, 138.3, 136.6, 130.7, 127.9, 21.8. IR (KBr): 3551, 1703, 1631, 1588, 1449, 1263  $\text{cm}^{-1}$ .

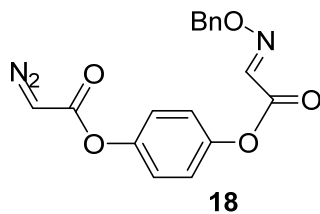
**Glyoxylic acid chloride *p*-toluenesulfonyl hydrazones<sup>24-26</sup> (17):** Glyoxylic Acid *p*-



Toluenesulfonyl Hydrazone (**16**), (1.5 g, 6.1 mmol 1.0 eq) and  $\text{SOCl}_2$  (6.0 mL/7.4 g, 61 mmol, 10.0 eq) was added to single neck round bottom flask

at room temperature and stirring was continued for 1 h at  $80^\circ\text{C}$ . To remove residual  $\text{SOCl}_2$  and liberated  $\text{SO}_2$ , 10 mL of toluene was added and evaporated under reduced pressure at  $40^\circ\text{C}$ ; this was repeated twice. Apply high vacuum to afford **9** (1.51 g, 94%). IR (KBr): 3180, 3066, 1744, 1595, 1369, 1171, 1083, 867  $\text{cm}^{-1}$ .

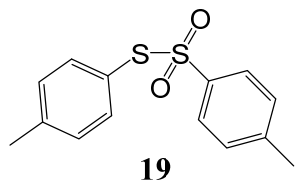
**Benzyloxyimino-acetic acid 4-(2-diazo-acetoxy)-phenyl ester (18):** The (1.15g, 4.4 mol)



glyoxylic acid chloride *p*-toluenesulfonyl hydrazone (**17**) and

Benzyloxyimino-acetic acid 4-hydroxy-phenyl ester (**8p**) (1.0 g, 3.69 mmol) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (25 mL) in an ice bath under an nitrogen atmosphere. Triethylamine (0.895 g, 1.3 mL, 8.8 mmol) was added. The resulting dark orange solution was stirred for 20 min at  $0^\circ\text{C}$  and then 6 h at room temperature. The reaction was dilute with dichloromethane (100 mL) and washed with saturated  $\text{NaHCO}_3$  solution (100 mL), water (100 mL), brine solution (100 mL), dried over  $\text{MgSO}_4$  and filter. Concentrated under reduced pressure (below  $40^\circ\text{C}$ ) on rota evaporator. Column chromatographic purification (20:80 EtOAc:hex) gave **18** as yellow solid. (690 mg, 55%). Mp  $78\text{-}80^\circ\text{C}$   $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.61 (s, 1H), 7.29-7.26 (m, 5H), 7.06 (s, 1H), 6.87-6.85 (d, 2H,  $J = 8.8$  Hz), 6.6-6.64 (d, 2H,  $J = 8.8$  Hz).  $^{13}\text{C}$ -NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.0, 153.9, 143.2, 140.5, 135.6, 128.6, 128.5, 122.5, 122.2, 122.1, 116.0, 78.3. IR (neat): 3059, 2122, 1742, 1601, 1508, 1454  $\text{cm}^{-1}$ .

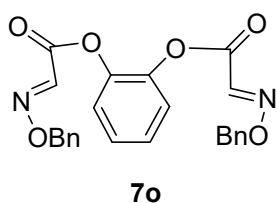
**S-(p-tolyl) 4-methylbenzenesulfonylthioate<sup>27</sup> (19):** 73 mg of impurity obtained. <sup>1</sup>H-NMR (200



MHz, CDCl<sub>3</sub>): δ 7.36-7.34 (d, 2H, *J* = 8.2 Hz), 7.14-7.10 (m, 4H), 7.05-7.03 (d, 2H, *J* = 7.9 Hz), 2.32 (s, 3H), 2.27 (s, 3H). <sup>13</sup>C-NMR (200

MHz, CDCl<sub>3</sub>): δ 144.5, 141.9, 140.3, 136.3, 130.1, 129.2, 127.4, 124.4, 21.5, 21.3. IR (neat): 1590, 1488, 1329, 815 (medium), 1323, 11139, 806, 585 cm<sup>-1</sup> (strong).

**Benzyloxyimino-acetic acid 2-(2-benzyloxyimino-acetoxy)-phenyl ester (7o):** In the manner



described above for esterification, 250 mg (2.2 mmol) of 1,2-dihydroquinone (**6o**) was treated with 895 mg (4.5 mmol) of α-benzyloximino acid chloride<sup>22</sup> (**5**) in presence of triethylamine (0.8 mL, 550 mg, 5.4 mmol) in THF (30 mL) and cool to 0°C under nitrogen

atmosphere. Column chromatographic purification (20:80 EtOAc:hex) gave **7o** as residual oil

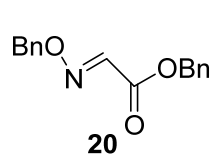
(450 mg, 45%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.56 (s, 2H), 7.29-7.24 (m, 14H), 5.22 (s, 4H).

<sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 159.1, 141.4, 139.8, 135.6, 128.7, 128.6, 127.0, 123.2, 78.5. IR

(neat): 3033, 2943, 1848, 1742, 1593, 1478, 1311 cm<sup>-1</sup>. Elemental Analysis: Calcd for

C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 66.66; H, 4.66; N, 6.48. Found: C, 66.86; H, 4.51; N, 6.45. and eluted with

(10:90 EtOAc:hex) gave benzyloxyimino-acetic acid benzyl ester (**20**) as residual oil (100 mg,



15%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.47 (s, 1H), 7.26 (s, 10H), 5.18 (s, 2H),

5.11 (s, 2H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 161.6, 140.8, 135.8, 135.0,

128.6, 128.5, 128.45, 128.41, 78.0, 67.0, IR (neat): 3033, 1848, 1742, 1720,

1598, 1455, 1330, 1042 cm<sup>-1</sup>. Elemental Analysis: Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub>: C, 71.36; H, 5.61; N,

5.20. Found: C, 71.30; H, 5.67; N, 5.15.

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