Tetrahedron Letters 55 (2014) 6007–6010

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of Lapatinib via direct regioselective arylation of furfural

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ARTICLE INFO

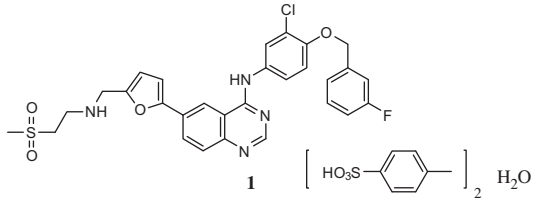
Article history:
Received 1 August 2014
Revised 4 September 2014
Accepted 8 September 2014
Available online 16 September 2014

Keywords:
Lapatinib
Direct arylation
C–H activation
Pivalic acid
Palladium acetate

ABSTRACT

A new synthesis of Lapatinib, an orally active drug for breast cancer, is described. The synthesis involves a palladium catalyzed regioselective arylation of furfural with 6-bromo-*N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)quinazolin-4-amine. This key step replaces an atom inefficient Suzuki cross coupling reaction used in a previously disclosed route and significantly shortens the synthesis.

Lapatinib (Tykerb, **1**), a dual ErbB1/ErbB2 tyrosine kinase inhibitor, is an orally active drug discovered by GlaxoSmithKline for the treatment of patients with advanced or metastatic breast cancer.[1–3]



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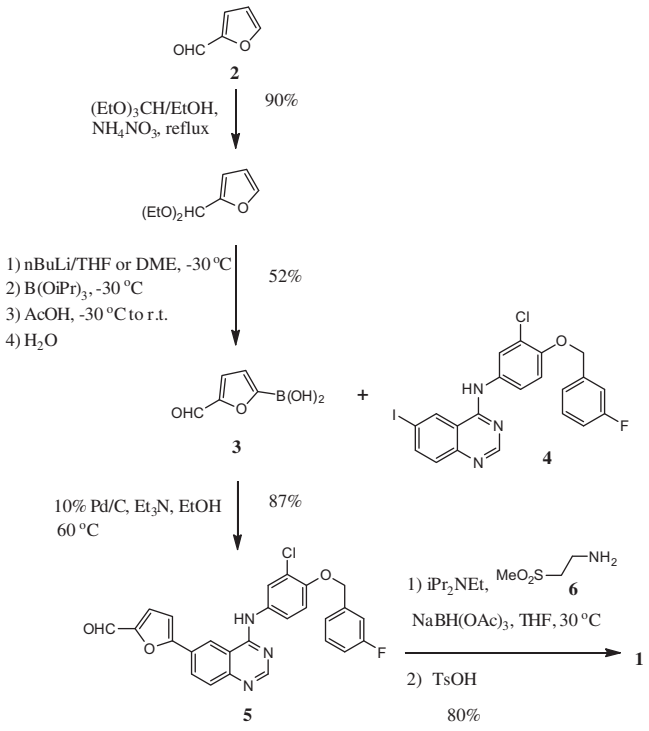
Lapatinib (ditosylate monohydrate)

A previously disclosed route of synthesis is detailed in Scheme 1 and the key step in the synthesis is the Suzuki cross coupling of 5-formyl-2-furanylboronic acid (**3**) and iodoquinazoline (**4**).[4] Although this reaction is very high yielding it is atom inefficient as it produces a significant amount of iodide and boron wastes. Furthermore the synthesis of the boronic acid (**3**) is lengthy and requires low temperature.



Scheme 1. Previous disclosed route of synthesis.

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http://dx.doi.org/10.1016/j.tetlet.2014.09.039
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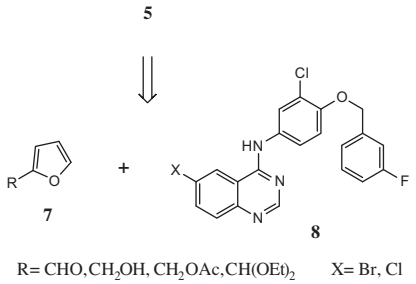


Scheme 2. Retrosynthetic analysis.

We envisioned that the Suzuki coupling could be replaced by a single step direct arylation of a suitably functionalized furan (**7**) and quinazoline (**8**) derivatives as detailed in Scheme 2.

If successful, this direct arylation approach would not only significantly shorten the synthesis of Lapatinib but also eliminate both the undesirable iodide and boron wastes, remove the need of pre-preparing the boronic acid and is therefore more atom-economical and environmentally friendly.

Formation of an aryl–aryl bond through direct C–H activation has been intensively investigated and significant progress in this area has been achieved.[5–10] Direct arylation has also been applied to aromatic heterocycles including furan derivatives.[11] Control of the regioselectivity in arylation of substituted furans remains a challenge due to the presence of several C–H bonds. GlaxoSmithKline previously reported the first palladium catalyzed (5 mol % $PdCl_2$, 10 mol % Cy_3P, and KOAc and Bu_4NBr in DMF at 110 °C) direct arylation at the C-5 position of furfural with aryl iodides or aryl bromides.[12] Doucet described low catalyst loading ligand-free palladium-catalyzed (0.1 mol % $Pd(OAc)_2$, KOAc, DMAc, 150 °C) direct C-5 arylation of furfural with aryl bromides.[13] Fagnou has developed a protocol for aryl–aryl bond formation via C–H activation with palladium catalyst (2 mol % $Pd(OAc)_2$, 4 mol % $Cy_3P{\cdot}BHF_4$ and additive pivalic acid) and applied the protocol to direct C-5 arylation of furfural with aryl bromides.[14] Fagnou has also reported direct C-5 arylation of furfural using aryl bromides and Pearlman's catalyst.[15] Copper-catalyzed direct arylation of furfural at the C-5 position with aryl bromides has also been reported.[16]

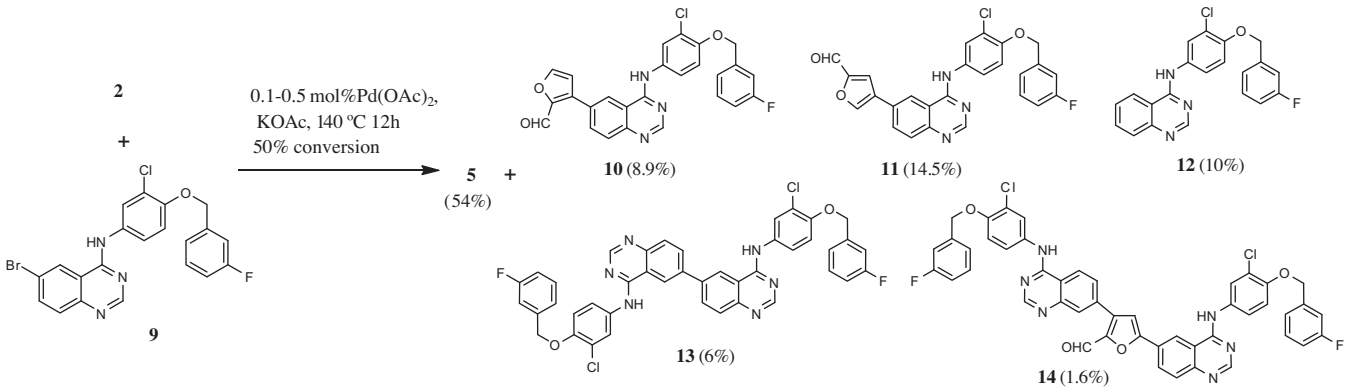
In the first instance it was necessary to determine what was the optimal substitution on both furan (**7**) and quinazoline (**8**) which would best facilitate the directed arylation. Doucet's catalyst conditions were used due to their simplicity and after extensive screening it was found that furfural (**2**) and bromo-quinazoline (**9**) were the optimal substrates albeit significant amounts of C3 and C4-arylated regio-isomers (**10** and **11**) along with desbromo (**12**), homocoupling (**13**), and 3,5-bis-arylated furfural (**14**) side products were formed (Scheme 3). It was also found that the best conversions were achieved when furfural was used in excess. In this case no additional solvent was required. The use of $PdCl_2$/Cy_3P/KOAc in DMF at 110 °C gave similar results to the Doucet catalyst system.

The Fagnou protocol[14] was then investigated. Heating a mixture of **9**, furfural (2–10 equiv), $Pd(OAc)_2$, Cy_3P, PivOH (0.3 equiv), and K_2CO_3 in DMF at 130 °C resulted in poor conversion to **5** along with many side products. The reaction was sluggish and **9** was not completely consumed even after very long reaction time (24 h). None of the other solvents screened (DMAc, diethyl carbonate, Me-THF, cyclopentyl methyl ether, toluene, trifluorotoluene, xylene, and DMSO) gave better results. However, when furfural was used as the solvent, the reaction proceeded very smoothly at 130 °C and **9** was completely consumed in 2–3 h.

We then focused on the optimization of the direct arylation of furfural under various conditions. $Pd(OAc)_2$ gave the best results among the catalysts evaluated, which include $Pd(OAc)_2$, $PdCl_2$, $Pd(OH)_2$/C, $Pd(Cy_3P)_2Cl_2$, and $Pd_2(dba)_3$.

A number of ligands were screened and it was found that the ligands played a key role in reaction rate and regioselectivity (Chart 1). The reaction with Me(*t*-Bu)$_2$P·HBF_4 was the fastest and gave the highest yield among the ligands screened. The reaction with $Cy_3P{\cdot}BHF_4$ was slightly slower than Me(*t*-Bu)$_2$P·HBF_4 but significantly faster and gave much higher yields than other ligands. The reaction proceeded either very slowly or did not proceed with some very bulky ligands such as *t*-Bu_3P and strong electron-donating ligands such as (*o*-MeOPh)$_3$P. Prolonged reactions gave more desbromo side product. More undesired regioisomers were formed with bidentate ligands such as DPPM and BDPP.

The effect of various additives and bases was also studied. Stronger, weaker, and bulkier acids (including diacids) were evaluated. Pivalic acid was found to be the most efficient acid for the arylation, which is consistent with the literature report.[14] Use of pivalic acid is crucial for a successful regioselective arylation. The reaction did not proceed or was extremely slow in the absence of PivOH. The amount of PivOH also has a significant impact on the reaction rate and regioselectivity. The reaction was significantly slower with <0.2 equiv of PivOH while significantly faster with increased amounts of PivOH (>1 equiv). However, reaction with more than 1 equiv of PivOH also generated more undesired regioisomers. The optimal amount was identified as 0.3–0.5 equiv of PivOH.



Scheme 3. Direct arylation of furfural with **9** under ligandless/low catalyst loading conditions.

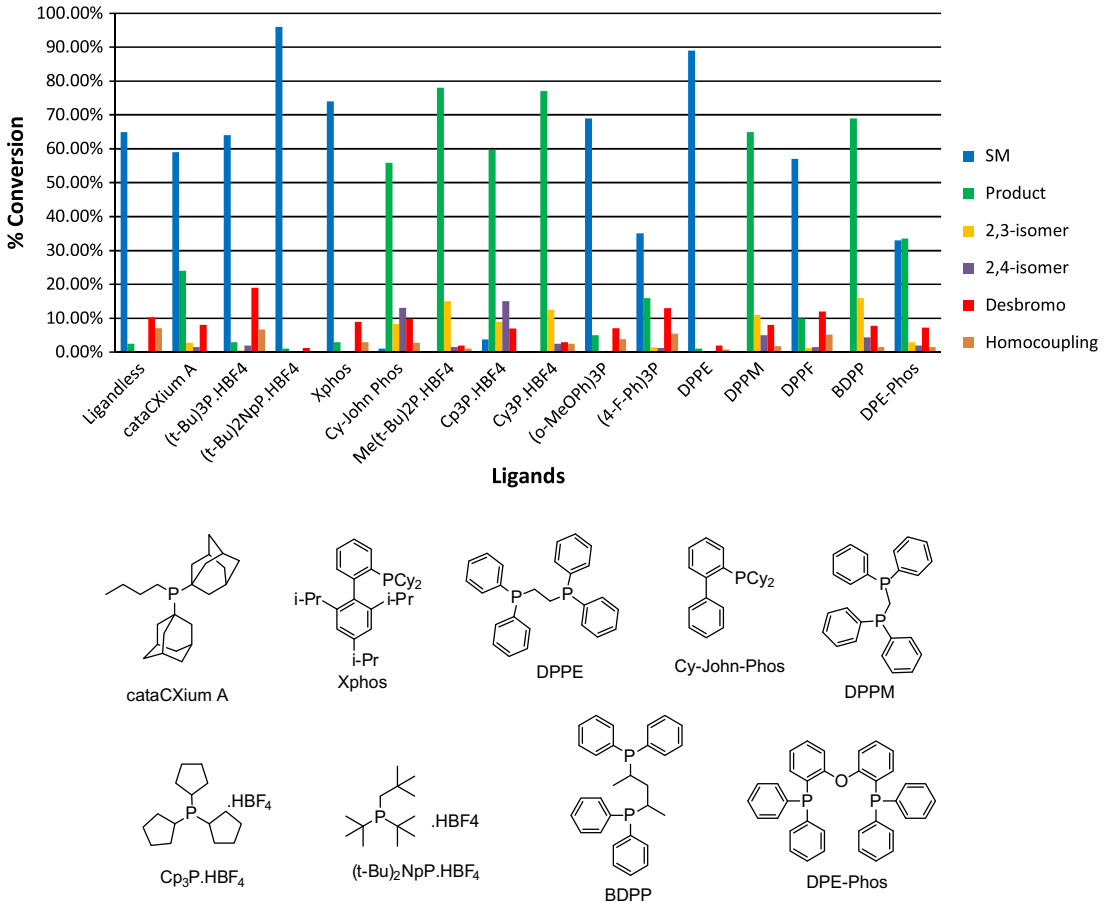
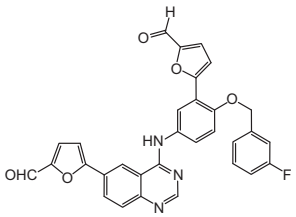


Chart 1. Impact of Ligands on Direct Arylation of furfural with 9. (a) Conditions: **9** (1 equiv), furfural (27.7 equiv), $Pd(OAc)_2$ (0.02 equiv), PivOH (0.5 equiv); ligand (0.04 equiv); 115 °C.

Base also played a key role in the reaction. Significant by-products were observed with organic bases such as Et_3N and Hunig's base and minimal conversion was observed with Li_2CO_3, Na_2CO_3, and $CaCO_3$. The reaction proceeded significantly faster with K_2CO_3 than other bases. However, the chloride in **9** also reacted with furfural once the bromide in **9** had been completely consumed to form a bis-furfural coupling side product (**15**).[17]



15

It was very difficult to control the formation of **15** unless the reaction was closely monitored near the completion and cooled down immediately after the reaction was complete. Similarly, **15** was also formed when $KHCO_3$, Cs_2CO_3, K_3PO_4, K_2HPO_4, and CsOPiv were used. When KOAc or CsOAc was used, the reaction was slower than K_2CO_3 as the base and **15** was not formed even if the reaction mixture was heated overnight after all bromide in **9** had been consumed.

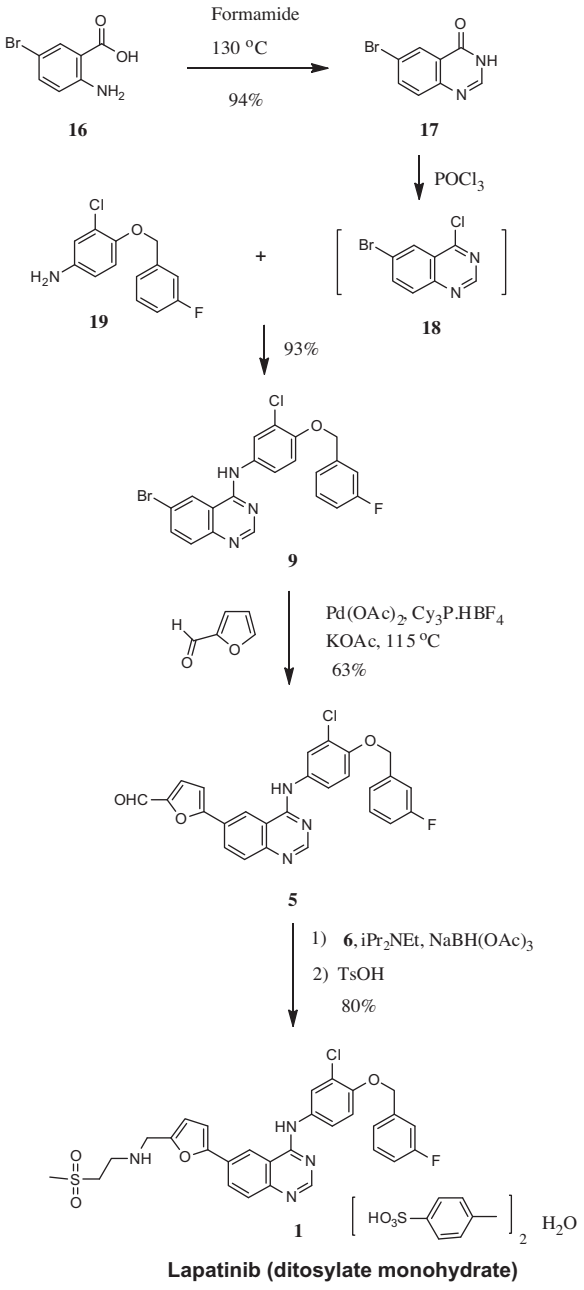
The reaction temperature is also a very important factor for the reaction. Higher temperature (>130 °C) resulted in the formation of higher amounts of **15** (even when KOAc was used as the base) while the reaction did not proceed at lower temperature (<90 °C). The optimal temperature range was identified as 110–120 °C.

Other additives/co-catalysts such as Ag_2CO_3, Ag_2O, CuBr, and $Cu(OAc)_2$ and phase transfer catalysts gave no improvement in either the reaction rate or the regioselectivity.

Although the reaction with $Me(t\text{-}Bu)_2P{\cdot}HBF_4$ gave the highest yield, **15** was also formed as a side product. Finally, the best reaction conditions were identified as 2 mol % $Pd(OAc)_2$, 4 mol % $Cy_3P{\cdot}BHF_4$, 0.5 equiv PivOH, and 2 equiv KOAc in 5 volume of furfural at 110–120 °C for 4–7 h under inert atmosphere. The desired product **5** was formed in around 75–80% reaction yield under the optimized conditions. The work-up and isolation process was straightforward. The reaction mixture was diluted with acetone, cooled to room temperature, and filtered to remove potassium salts. The product was crystallized by adding water to the filtrate to give **5** in 63–65% isolated yield with >98% purity.[18]

The complete synthesis is then illustrated in Scheme 4. Condensation of 2-amino-5-bromobenzoic acid (**16**) with formamide under mild conditions afforded 6-bromo-4(1*H*)-quinazolinone (**17**) in 94% yield. Conversion of **17** to 6-bromo-4-chloroquinazoline (**18**) by treatment with $POCl_3$ followed by in situ displacement with aniline (**19**) gave **9** in 93% yield. Regioselective arylation then subsequent reductive amination with $NaBH(OAc)_3$ followed by formation of a tosylate salt afforded Lapatinib in 44% overall yield.

In summary, we have developed an elegant high yielding new route for the synthesis of Lapatinib. The new route is 5-steps shorter than the previously disclosed route, significantly more atom efficient and eliminates a hazardous waste stream.



Scheme 4. New route for the synthesis of Lapatinib.

Acknowledgments

We thank Ping Xiong, Byron Johnson Daniel Reynolds, and Anna Vogt for analytical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.039.

References and notes

1. Burris, H. A., III *Oncologist* **2004**, *9*, 10–15.
2. Lackey, K. E. *Curr. Top. Med. Chem.* **2006**, *6*, 435–460.
3. Petrov, K. G.; Zhang, Y.-M.; Carter, M.; Cockerill, G. S.; Dickerson, S.; Gauthier, C. A.; Guo, Y.; Mook, R. A., Jr.; Rusnak, D. W.; Walker, A. L.; Wood, E. R.; Lackey, K. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4686–4691.
4. (a) McClure, M. S.; Osterhout, M. H.; Roschangar, F.; Sacchetti, M. J. PCT Int. WO 02/02552.; (b) Parry, P. R.; Bryce, M. R.; Tarbit, B. *Org. Biomol. Chem.* **2003**, *1*, 1447–1449; (c) Thames, S. F.; Odom, H. C. *J. Heterocycl. Chem.* **1966**, 490.
5. Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115.
6. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.
7. Campeau, L. C.; Stuart, D. R.; Fagnou, F. *Aldrichim. Acta* **2007**, *40*, 35–41.
8. McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464.
9. Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826.
10. Verrier, C.; Lassalas, P.; Théveau, L.; Quéguiner, G.; Trécourt, F.; Marsais, F.; Hoarau, C. *Beilstein J. Org. Chem.* **2011**, *7*, 1584–1601.
11. Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.
12. McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680.
13. (a) Dong, J. J.; Roger, J.; Požgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 1832–1846; (b) Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Organometallics* **2007**, *26*, 472–474.
14. (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497; (b) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015–6020; (c) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826–1834; (d) Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23*, 1594–1600; (e) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658–668; (f) Tan, Y.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 3308–3311; (g) Wakioka, M.; Nakamura, Y.; Wang, Q.; Ozawa, F. *Organometallics* **2012**, *31*, 4810–4826; (h) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749–759.
15. Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584.
16. Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296–3300.
17. The structure of **15** was tentatively assigned by LC–MS/MS.
18. Typical procedure for the synthesis of **5** via direct regioselective arylation of furfural. A reaction vessel was charged with **9** (50 g, 109.0 mmol), $Cy_3P{\cdot}HBF_4$ (1.606 g, 4.36 mmol), $Pd(OAc)_2$ (0.489 g, 2.18 mmol), KOAc (21.4 g, 218.0 mmol), and PivOH (5.57 g, 54.5 mmol). The mixture was purged with nitrogen. Furfural (250 ml) was added. The mixture was purged with nitrogen for 10 min, then heated to 110–115 °C and stirred at 110–115 °C until the reaction was complete. The reaction mixture was cooled to 70 °C and treated with acetone (600 ml). The mixture was further cooled to 30 °C and filtered to remove the undesired solids. The filtrate was heated to 55 °C. Water (250 ml) was added at a rate maintaining the temperature above 45 °C. The mixture was then cooled to 40 °C. The resultant slurry was stirred at 40 °C for 2 h and then cooled to 30 °C over 1.5 h. The solids were filtered, washed twice with acetone/water (1:1, 150 ml), and dried at 60 °C in a vacuum oven to give **5** as a yellow crystalline solid (32.5 g, 63% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.26 (s, 2H), 7.18 (m, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.30–7.36 (m, 2H), 7.38 (d, J = 3.8 Hz, 1 H), 7.47 (m, 1H), 7.71 (m, 1H), 7.73 (d, J = 3.8 Hz, 1H), 7.83 (d, J = 8.8, 1H), 7.99 (d, J = 2.5 Hz, 1H), 8.26 (dd, J = 8.8, 1.50 Hz, 1H), 8.58 (s, 1H), 8.93 (s, 1H), 9.67 (s, 1H), 10.06 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 69.4, 109.7, 114.0 (d, J = 21.8 Hz), 114.2, 114.7 (d, J = 20.9 Hz), 115.2, 119.4, 121.1, 122.6, 123.3 (d, J = 2.7 Hz), 124.5, 126.2, 128.7, 129.4, 130.5 (d, J = 8.2 Hz), 132.8, 139.6 (d, J = 7.3 Hz), 149.9, 150.1, 152.0, 155.2, 157.6, 157.7, 162.2 (d, J = 244.3 Hz), 177.7. The analytical data are identical to those of an authentic sample.