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SYNTHESIS OF A STABLE PYRIDYL BORONATE AND ITS REACTION WITH ARYL AND HETEROARYL HALIDES

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Abstract - The synthesis and reaction of a versatile 5-pyridyl boronate is described. This intermediate can be used to synthesize a range of biologically interesting 2-(1*H*)-pyridones.

INTRODUCTION

2-(1*H*)-pyridones provide a good isostere for the *cis*-amino acid functionality and as such have been utilized in many peptidomimetic drugs.[1] In addition, this functionality has been used as a hinge binding motif in kinase inhibitors.[2] We were interested in 2-(1*H*)-pyridone derivatives designed to perform this latter function and to explore pockets accessible from the 5-position of the pyridone ring.

In our efforts to synthesize 5-aryl-2-(1*H*)-pyridones, a stable late stage intermediate was utilized for rapid SAR generation. We envisaged synthesizing a 5-boronate substituted 2-(1*H*)-pyridone whereby a range of functionalized aryl and heteroaryl groups could be introduced.

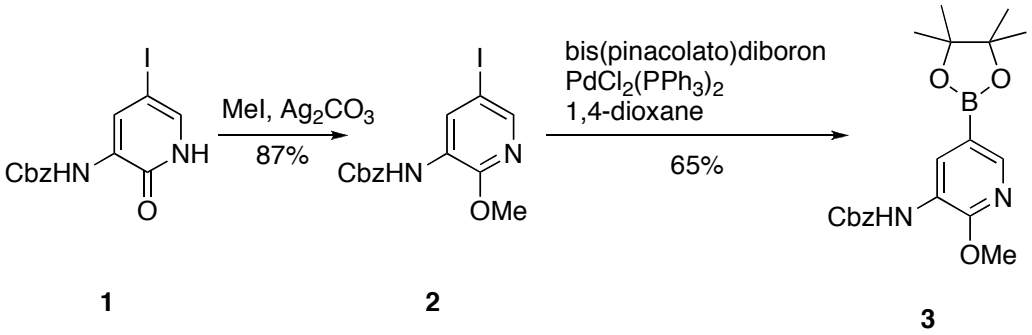
In this note, we wish to disclose the synthesis and utility of [2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridin-3-yl]carbamic acid benzyl ester (**3**) as a useful intermediate for the synthesis of 5-aryl substituted 2-(1*H*)-pyridones.

RESULTS AND DISCUSSION

The required pyridine boronate intermediate (**3**) was prepared as outlined in **Scheme 1**. Protection of the known[1g] (5-iodo-2-oxo-1,2-dihydro-pyridin-3-yl)carbamic acid benzyl ester **(1)** with methyl iodide in the presence of silver carbonate yielded (5-iodo-2-methoxy-pyridin-3-yl)carbamic acid benzyl ester (**2**). Treatment of iodide (**2**) with bis(pinacolato)diboron in the presence of bis(triphenylphosphine)-palladium(II) dichloride and potassium acetate gave 5-pyridyl boronate (**3**) in 65% yield.[3] Boronate (**3**)

This paper is dedicated to Professor Steven M. Weinreb on the occation of his 65th birthday.

was found to be air stable and can be stored at room temperature for a number of months.

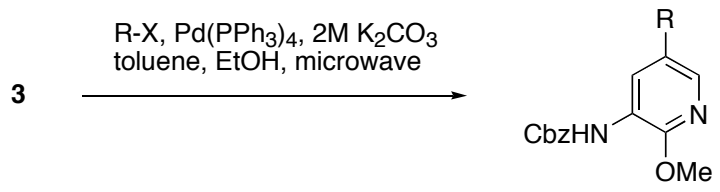


1 **2** **3**

Scheme 1. Synthesis of [2-methoxy-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)pyridin-3-yl]-carbamic acid benzyl ester (**3**)

Reaction of boronate (**3**) with a range of aryl and heteroaryl halides with varying electronic properties was then investigated (**Scheme 2**). Hallberg and Larhed have shown that microwave radiation can both accelerate and increase the yield of palladium cross coupling reactions.[4] We therefore treated boronate (**3**) with an aryl or heteroaryl halide in the presence of tetrakis (triphenylphosphine)palladium and potassium carbonate under microwave conditions and produced the desired aryl and heteroaryl pyridyl compounds (**4a-h**) in good yields and in short reaction times. The entries in **Table 1** illustrate that the reaction conditions are suitable for use with a range of aryl bromides, iodides and activated chlorides.

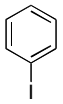
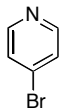
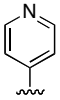
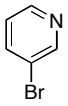
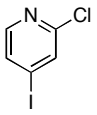
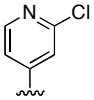
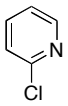
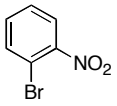
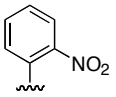
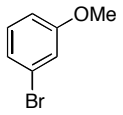
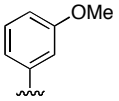
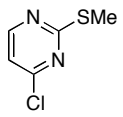
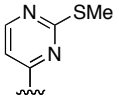
Entries **2**, **3**, **4** and **5** demonstrate the value of the 5-pyridyl boronate (**3**) in the preparation of pyridinyl pyridines. Entries **4** and **5** are of particular interest because one shows that selectivity for the iodine over an activated 2-chloro substituent can be achieved while the other shows that a good yield can be obtained when an activated chloro substituent is the only reacting halide. This latter reaction provides an attractive route for the production of 2-arylpyridines, for although 2-pyridylboronates are known and could provide an alternative approach, the boron-carbon bond in such molecules is too unstable to be of practical utility.[5] The value of this reaction type is further exemplified by entry **8** where a 2-methylthio(4-pyrimidinyl)]-2-methoxypyridine (**4h**) is prepared in high yield from 4-chloro-2-methylthiopyrimidine. Entries **6** and **7** show that the reaction is compatible with both electron withdrawing and electron donating substituents; both reactions proceed in good yield.



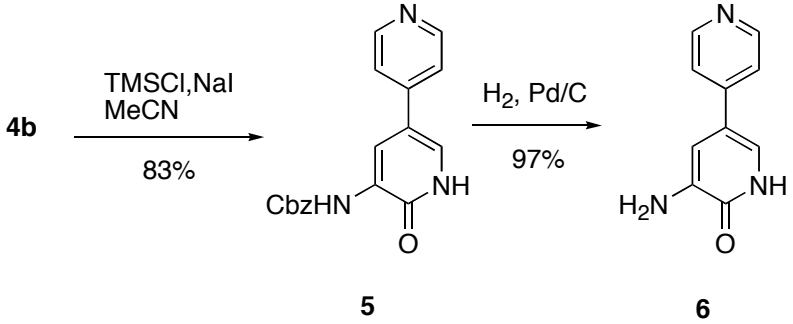
3 **4a-h**

Scheme 2.

Table 1. The structures and yields of the 2-methoxypyridin-3-ylcarbamates (**4**)

Entry	R-X	4	Yield (%)
1		R=  **4a**	**65**
2		R=  **4b**	**66**
3		R=  **4c**	**72**
4		R=  **4d**	**72**
5		R=  **4e**	**62**
6		R=  **4f**	**64**
7		R=  **4g**	**67**
8		R=  **4h**	**71**

Compound (**4b**) was elaborated to Amrinone (**6**), a marketed cardiotonic, by removal of the methyl ether with TMS-I,[6] followed by hydrogenation to remove the benzyloxycarbonyl protecting to give (**6**) in good overall yield (53% from boronate (**3**)) (**Scheme 3**). Amrinone (**6**) prepared according to this sequence was shown to be identical to an authentic sample.[7]



5 **6**

Scheme 3. Deprotection and elaboration to Amrinone (**6**).

In conclusion, we have described the preparation and reaction of a pyridyl boronate as a highly versatile precursor to 5-aryl-2-(1*H*)-pyridones that may find utility as pharmaceutical agents. Use of this functionalized boronate offers several advantages over the existing routes to 5-aryl or heteroaryl pyridones. Many of these routes involve cyclocondensations of a cyanoacetamide with 3-(dimethylamino)-2-propenones. 3-(Dimethylamino)-2-propenones cannot always be obtained in good yields and the subsequent cyclocondensation reaction is known to be capricious.[8] This means that variations in an aryl substituent of 5-aryl-2-(1*H*)-pyridones can be hard to obtain. The functionalized boronate described herein provides a concise method to prepare 5-aryl or heteroaryl pyridones and provides increased flexibility by introduction of the aryl substituent late in the synthetic route. In addition, the route described enables a wider range of functional and protecting groups to be present throughout the synthesis due to the comparatively mild reaction conditions.

EXPERIMENTAL

All commercially available solvents and reagents were used as received. Microwave reactions were carried out using a CEM Discovery microwave. Analytical thin layer chromatography was carried out using glass-backed plates coated with Merck Kieselgel 60 GF_{240}. Plates were visualised using UV light (254 nm or 366 nm) and/or by staining with potassium permanganate followed by heating. Flash chromatography was carried out on an ISCO© Combiflash^R Companion^{TM} system eluting with a 0 to 100% EtOAc/petroleum ether gradient. Samples were applied pre-absorbed on silica. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz using a Bruker DPX 400 instrument. MS samples were analyzed on a MicroMass Quattro Micro mass spectrometer operated in single MS mode with electrospray ionization. Samples were introduced into the mass spectrometer using chromatography. Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet Avatar 360 FT-IR spectrometer and were recorded neat. Elemental analysis was carried out on a Control Equipment Corporation 440 Elemental Analyser. Melting points were measured on a Buchi B-545 electrothermal digital melting point apparatus and are uncorrected.

(5-Iodo-2-methoxypyridin-3-yl)carbamic acid benzyl ester (2)

(5-Iodo-2-oxo-1,2-dihydropyridin-3-yl)carbamic acid benzyl ester (**1**) (131.6 g, 0.36 mol, 1.0 eq.) was charged to a flask followed by $CHCl_3$ (1.45 L). In the dark, silver carbonate (132.5 g, 0.48 mol, 1.35 eq.) and methyl iodide (221 mL, 3.6 mol, 10.0 eq.) were charged to the flask and the reaction was then allowed to stir at ambient temperature for 48 h. The reaction mixture was filtered through celite (100 g) and the filter pad washed with $CHCl_3$ (5 x 200 mL). The combined organic extracts were concentrated *in vacuo* to give an orange oil which was purified by column chromatography using silica gel eluting with

20% EtOAc/hexane to give the (**2**) as a pale pink solid. The material was recrystallised from hexane to give pale pink needles, (112.4 g, 0.29 mol, 82%); mp 72.9-74.4 °C; ^{1}H NMR ($CDCl_3$) 8.64 (1H, s, NH), 8.00 (1H, s, ArH), 7.42-7.37 (5H, m, ArH), 7.15 (1H, s, ArH), 5.24 (2H, s, CH_2), 3.97 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 153.3, 152.6, 145.4, 141.7, 136.0, 132.5, 129.1, 129.0, 128.8, 124.5, 83.1, 67.9, and 54.3; IR: 1688, 1521, 1243, 1053, 755, 688; ES M+H 385.01, M-H 383.18; Anal. Calcd for $C_{14}H_{13}IN_2O_2$: C: 43.77; H: 3.41; N: 7.29. Found: C: 43.85; H: 3.43; N: 7.10.

[2-Methoxy-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)pyridin-3-yl]carbamic acid benzyl ester (3)

A mixture of (5-iodo-2-methoxy-pyridin-3-yl)carbamic acid benzyl ester (**2**) (100 g, 260.5 mmol, 1.0 eq.), bis(pinacolato)diboron (69.4g, 273.3 mmol, 1.05 eq.) and potassium acetate (76.64 g, 780.8 mmol, 3.0 eq.) in anhydrous dioxane (900 mL) was degassed and flushed with nitrogen. $PdCl_2(PPh_3)_2$ (5.48 g, 7.8 mmol, 3 mol%) was added and the reaction heated to reflux overnight. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue dissolved in EtOAc, washed with aqueous brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography eluting with 20% EtOAc/petroleum ether to give, after concentration an orange solid. This was treated with *n*-heptane (500 mL) and heated to reflux. On cooling the resultant precipitate was collected by filtration and washed with hexane to give **(3)** as a golden solid (65.25 g, 169.8 mmol, 65%); mp 105.1-106.2 °C; ^{1}H NMR ($CDCl_3$) 8.65 (1H, s, NH), 8.21 (1H, s, ArH), 7.43-7.40 (5H, m, ArH), 7.20 (1H, s, ArH), 5.24 (2H, s, CH_2), 4.02 (3H, s, OMe), 1.35 (12H, s, 3 x Me); ^{13}C NMR ($CDCl_3$) 155.3, 153.6, 147.1, 136.4, 130.7, 129.0, 128.8, 128.7, 122.5, 84.3, 67.6, 54.2, 27.3, 25.2; IR: 2935, 1719, 1533, 1476, 1438, 1359, 1254, 1216, 1141, 1049, 757, 687; ES M+H 385.20, M-H 383.1840; Anal. Calcd for $C_{20}H_{25}BN_2O_5$: C: 62.52; H: 6.56; N: 7.29. Found: C: 62.60; H: 6.59; N: 6.96.

General procedure for the palladium catalysed Suzuki reaction

A mixture of the aryl halide (1.5 eq.), [2-methoxy-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]carbamic acid benzyl ester (**3**) (1.0 eq.), $Pd(PPh_3)_4$ (0.1 eq.) and potassium carbonate (2M aqueous solution, 2.0 eq.) in toluene (1.6 mL) and EtOH (0.4 mL) was heated under microwave conditions, with cooling, at 100 °C for 15 min. The reaction mixture was cooled, and extracted with EtOAc (5 mL) and water (5 mL). The aqueous layer was extracted further with EtOAc (2 x 5 mL) and the combined organics dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica eluting with EtOAc/petroleum ether.

3-Benzyloxycarbonylamino-5-phenyl-2-methoxypyridine (4a)

Colourless oil, Yield 65%; ^{1}H NMR ($CDCl_3$) 8.65 (1H, s, NH), 8.01 (1H, s, ArH), 7.60 (2H, m, ArH),

7.47-7.28 (8H, m, ArH), 7.20 (1H, s, ArH), 5.32 (2H, s, CH_2), 4.00 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 153.7, 152.6, 145.4, 138.3, 137.7, 136.2, 131.3, 129.3, 128.9, 128.8, 127.8, 127.4, 124.2, 123.1, 67.7 and 54.3; IR (thin film): 3681, 3422, 2950, 1733, 1522, 1468, 1400, 1213, 1064, 1047, 1033, 1018, 764, 696; ES M+H 335.41, M-H 333.67.

3-Benzyloxycarbonylamino-5-(4-pyridyl)-2-methoxypyridine (4b)

White crystalline solid; Yield 66 %; mp 159.8-160.8 °C (cyclohexane); ^1H NMR ($CDCl_3$) 8.67 (3H, m, 2 x ArH and 1 x NH), 8.14 (1H, s, ArH), 7.51-7.38 (7H, m, ArH), 7.28 (1H, s, ArH), 5.26 (2H, s, CH_2), 4.01 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 153.7, 150.7, 145.7, 138.0, 136.0, 129.1, 129.0, 128.0, 128.2, 123.6, 123.4, 121.6, 67.9 and 54.4; IR (solid): 3190, 3031, 1728, 1600, 1551, 1466, 1215, 1067, 1048, 1034, 1028, 833, 694; ES M+H 336.13, M-H 334.31; Anal. Calcd for $C_{19}H_{17}N_3O_3$: C: 68.05; H: 5.11; N: 12.53. Found: C: 67.78; H: 5.15; N: 12.20.

3-Benzyloxycarbonylamino-5-(3-pyridyl)-2-methoxypyridine (4c)

White Solid; yield 72 %; mp 122.9-123.6 °C (cyclohexane); ^1H NMR ($CDCl_3$) 8.85 (1H, s, NH), 8.62 (2H, d, J = 10.0 Hz, ArH), 8.06 (1H, s, ArH), 7.86 (1H, d, J = 7.6 Hz, ArH), 7.46-7.36 (6H, m, ArH), 7.28 (1H, s, ArH), 5.23 (2H, s, CH_2), 4.06 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 153.7, 153.1, 149.1, 148.4, 137.7, 136.1, 134.6, 134.0, 129.1, 128.9, 128.8, 128.1, 124.0, 123.8, 123.5, 67.8 and 54.4; IR (solid): 3355, 2950, 1702, 1470, 1230 and 1052; ES M+H 336.2, M-H 334.3; Anal. Calcd for $C_{19}H_{17}N_3O_3$: C: 68.05; H: 5.11; N; 12.53. Found: C: 67.63; H: 5.09; N: 12.27.

3-Benzyloxycarbonylamino-5-[(2-chloro)4-pyridyl]-2-methoxypyridine (4d)

Orange solid; Yield 72%; mp 90.0-91.3 °C (cyclohexane); ^1H NMR ($CDCl_3$) 8.65 (1H, s, NH), 8.44 (1H, d, J = 5.2 Hz, ArH), 8.11 (1H, d, J = 2.4 Hz, ArH), 7.60-7.28 (8H, m, ArH), 5.27 (2H, s, CH_2), 4.10 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 154.0, 153.7, 152.8, 150.5, 148.9, 138.1, 136.0, 129.1, 129.0, 128.8, 127.0, 123.7, 123.2, 121.9, 120.4, 67.9 and 54.6; IR (solid): 3721, 2945, 1695, 1539, 1456, 1394, 1055, 1033, 688; ES M+H 370.41, M-H 368.62.

3-Benzyloxycarbonylamino-5-(2-pyridyl)-2-methoxypyridine (4e)

White solid; Yield 62 %; mp 105.6-107.4 °C (cyclohexane); ^1H NMR ($CDCl_3$) 8.97 (1H, s, NH), 8.70 (1H, d, J = 4.8 Hz, ArH), 8.49 (1H, d, J = 2 Hz, ArH), 7.76 (2H, m, ArH), 7.47-7.37 (4H, m, ArH), 7.28–7.23 (3H, s, ArH), 5.27 (2H, s, CH_2), 4.07 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 155.6, 153.7, 153.6, 150.2, 138.6, 137.1, 136.3, 129.8, 129.1, 128.9, 128.8, 123.8, 123.0, 122.4, 120.6, 67.7 and 54.4; IR (solid); 3684, 1700, 1536, 1258, 1233, 1056, 1033, 688; ES M+H 335.41, M-H 333.67.

3-Benzyloxycarbonylamino-5-(2-nitrophenyl)-2-methoxypyridine (4f)

Yellow needles; Yield 59%; mp 95.3-97.2 °C (EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) 8.45 (1H, s, NH), 7.95 (1H, dd, *J* = 0.8 and 8.0 Hz, ArH), 7.78 (1H, d, *J* = 2.4 Hz, ArH), 7.64 (1H, m, ArH), 7.53 (1H, m, ArH), 7.47-7.27 (6H, m, ArH), 7.26 (1H, s, ArH), 5.23 (2H, s, CH_2), 4.05 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 153.5, 153.0, 149.6, 138.2, 136.2, 133.5, 132.8, 132.7, 129.1, 128.94, 128.89, 128.8. 127.7, 124.9, 124.7, 123.0, 67.8 and 54.3; IR (solid); 3681, 2936, 1723, 1521, 1468, 1400, 1361, 1258, 1216, 1065, 1053, 1033, 738; ES M+H 380.16, M-H 378.33.

3-Benzyloxycarbonylamino-5-(3-methoxyphenyl)-2-methoxypyridine (4g)

White needles; Yield 67%; mp 88.1-89.3 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) 8.62 (1H, s, NH), 8.06 (1H, d, *J* = 2.0 Hz, ArH), 7.47-7.35 (6H, m, ArH), 7.25 (1H, s, ArH), 7.18-7.16 (1H, m, ArH), 7.12 (1H, s, ArH), 6.93-6.91 (1H, m, ArH), 5.26 (2H, s, CH_2), 4.05 (3H, s, OMe), 3.89 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) 160.4, 153.7, 152.7, 139.8, 137.8, 136.2, 131.3, 130.3, 129.1, 128.9, 128.8, 124.2, 123.1, 119.9, 113.3, 113.1, 67.7, 55.7 and 54.2; IR (solid): 3323, 2956, 1697, 1527, 1473, 1267, 1237, 1207, 1056, 1023, 691; ES M+H 365.17, M-H 363.28; Anal. Calcd for $C_{21}H_{20}N_2O_4$: C: 69.22; H: 5.53; N: 7.69. Found: C: 69.01; H: 5.51; N: 7.66.

3-Benzyloxycarbonylamino-5-[2-methylthio(4-pyrimidinyl)]-2-methoxypyridine (4h)

White needles; Yield 71%; mp 125.0-126.2 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) 9.10 (1H, s, NH), 8.66 (1H, d, *J* = 2.4 Hz, ArH), 8.54 (1H, d, *J* = 4.0 Hz, ArH), 7.47-7.27 (7H, m, ArH), 5.27 (2H, s, CH_2), 4.08 (3H, s, OMe), 2.66 (3H, s, SMe); ^{13}C NMR ($CDCl_3$) 173.2, 162.2, 158.0, 154.9, 153.6, 139.6, 136.1, 129.1, 129.0, 128.8, 126.7, 123.3, 123.2, 111.8, 67.9 and 14.7; IR (solid): 3409, 2590, 1736, 1522, 1391, 1202, 1046, 697; ES M+H 383.20, M-H 381.36; Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C: 59.67; H: 4.74; N: 14.65. Found C: 59.53; H: 4.77; N: 14.18.

3-Amino-5-(pyridin-4-yl)pyridin-2(1*H*)-one (Amrinone (6))

TMS-Cl (189 μL, 1.49 mmol, 5 eq.) was added dropwise to a stirred mixture of benzyl 2-methoxy-5-(pyridin-4-yl)pyridin-3-ylcarbamate (**4b**) (100 mg, 0.3 mmol, 1 eq.) and sodium iodide (223 mg, 1.49 mmol, 5 eq.) in MeCN (5 mL) at rt. The resulting suspension was stirred for 1.5 h at rt and the precipitate was collected by filtration. The resulting solid was then dissolved in a mixture of MeCN (1 mL) and water (1 mL) and added to a solution of saturated aqueous sodium hydrogen carbonate (10 mL). The suspension was then stirred for 30 min and benzyl 1,2-dihydro-2-oxo-5-(pyridin-4-yl)pyridin-3-ylcarbamate (**5**) was collected by filtration as a cream solid, which was used directly in the next step without further purification (80 mg, 83%). Benzyl 1,2-dihydro-2-oxo-5-(pyridin-4-yl)pyridin-3-ylcarbamate (**5**) (50 mg, 0.16 mmol, 1 eq.) was suspended in MeOH (5 mL) and treated with $Pd(OH)_2$/C (5 mg) and placed under an atmosphere of hydrogen. The reaction was stirred overnight at rt. The

palladium was then removed by filtration and the filtrate *concentrated in vacuo* to give (**6**) as yellow solid (29 mg, 97%); ^{1}H NMR ($CDCl_3$) 11.75 (1H, s, NH), 8.52 (2H, dd, J = 4.8 and 1.6 Hz, ArH), 7.50 (2H, dd, J = 4.4 and 1.2 Hz, ArH), 7.20 (1H, s, ArH), 6.89 (1H, dd, J = 2.4 Hz, ArH) and 5.26 (1H, s, CH_2); ^{13}C NMR ($CDCl_3$) 157.8, 150.4, 144.9, 139.4, 119.8, 119.6, 116.3 and 108.3; ES M+H 188.17, M-H 186.31

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