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Double Suzuki cross-coupling reaction of pyrimidine boronic acid: synthesis of new versatile dielectrophile

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The double Suzuki cross-coupling reaction has successfully been applied for the synthesis of 5,5′-(5-butoxy-1,3-phenylene)bis (2-chloropyrimidine) with two reactive chloro groups and an alkoxy side chain starting from 2-chloropyrimidin-5-ylboronic acid and 1,3-dibromo-5-butoxybenzene. The reactivity of this dielectrophile was tested by reaction with aniline and phenol, a nitrogen and oxygen nucleophile, respectively. The new dielectrophile would further provide an ideal platform for the construction of large hetero-atom bridged macrocycles for desired properties and functions in supramolecular and material chemistry. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: pyrimidine boronic acid; double coupling reaction; dielectrophile; substitution

Introduction

Dielectrophiles are important building blocks for the construction of various macrocycles used in host–guest chemistry.[1,2] For example, dielectrophiles and dinucleophiles react together to form hetero-atom bridged calixarenes,[3–10] whereas dielectrophiles and trinucleophiles react to produce molecular cages.[11–15] The size of these electrophiles and nucleophiles determines the cavity size of the macrocycles and the cavity size in turn is very important for their applications. Recently, extensive utilization of giant macrocycles in the field of supramolecular[16–20] and material chemistry[21–25] has opened up a need for the synthesis of large, rigid and reactive dielectrophilic fragments.

In the past two decades, the palladium-catalyzed Suzuki cross-coupling reaction has evolved into one of the most widely employed, powerful and versatile tools for carbon–carbon bond-forming processes.[26–35] This cross-coupling reaction has gained importance due to the growing availability of the boronic acids, their stability to moisture and air, and their excellent compatibility with a large variety of functional groups. Its impact on organic synthesis is largely recognized due to the fact that it provides a general, convenient and applicable method for the formation of biaryls, which are found in many biologically active compounds,[36–38] polymers,[39] ligands,[40] and other useful materials.[41]

In spite of the enormous progress, limitations of this method include its inability to maintain the efficiency displayed in simple aryl–aryl bond formation when nitrogen heterocycles are employed as one or both of the coupling partners.[42,43] Nitrogen-based heterocycles are an important component of most of the biologically active compounds, but usually insertion of these heterocyclic motifs are detrimental to catalytic activity of palladium-catalyzed reactions.[36–38] Although there are few reports available in the literature where heteroarylboronic acids are used as one of the coupling partner,[44–48] to best of our knowledge no one has reported double Suzuki cross-coupling of heteroarylboronic acids. Herein we report the double Suzuki cross-coupling reaction of 2-chloropyrimidin-5-ylboronic acid and 1,3-dibromo-5-butoxybenzene to obtain a unique and versatile dielectrophile which was further reacted with nitrogen and oxygen nucleophiles to certify its reactivity for its further utility in the field of supramolecular, material and medicinal chemistry.

Results and Discussion

We initiated our study with the synthesis of 1,3-phenylenebisboronic acid (**1**),[49,50] from 1,3-dibromo-5-butoxybenzene, which was then treated with 5-bromo-2-chloropyrimidine (**2**) to obtain our desired dielectrophile (**3**). Two different Suzuki cross-coupling reaction conditions were used for this purpose (Scheme 1).[51,52] Thin-layer chromatographic analysis gave a clear indication of some product formation in both cases. However, we were unable to take that product from the flask in pure form, which led us to think about the solubility of the product. Fortunately, a small amount of the pure product was obtained when the reaction scale was enlarged. As we were thinking, the solubility of the compound **3** was very poor in almost all of the solvents and the pure product was indeed difficult to isolate from the reaction mixture. Nevertheless, we were able to identify the structure of compound **3** by ^{1}H NMR spectroscopy and electrospray ionization (ESI) mass spectrometry.

Aiming to obtain dielectrophile with reasonable solubility for its further applications, 1,3-dibromo-5-butoxybenzene[53,54] (**5**) was prepared by reacting 1,3,5-tribromobenzene with sodium *n*-butoxide. When the same strategy as for the synthesis of 1,3-phenylenebisboronic acid (**1**) from 1,3-dibromobenzene was

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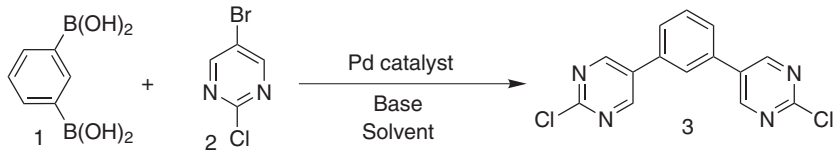
Applied Organometallic Chemistry



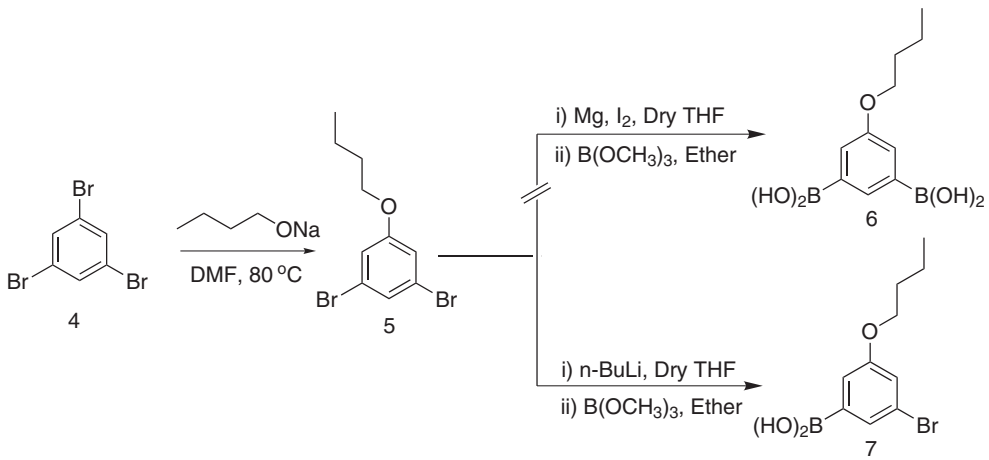
Scheme 1. Synthesis of dielectrophile from 1,3-phenylenebisboronic acid and 5-bromo-2- chloropyrimidine: (a) $Pd(PPh_3)_4$, Na_2CO_3, H_2O, dioxane, reflux, 20 h; (b) $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dioxane, reflux, 25 h

applied to 1,3-dibromo-5-butoxybenzene (**5**) for the synthesis of 5-butoxy-1,3-phenylenebisboronic acid (**6**) (Scheme 2), it unfortunately failed and no boronic acid product was isolated. Interestingly, almost all the starting material was recovered, suggesting the poor reactivity of 1,3-dibromo-5-butoxybenzene (**5**) towards magnesium metal for the formation of Grignard reagent. Lithiation reaction of compound **5** was then attempted. Surprisingly, all our attempts again failed to obtain bisboronic (**6**) acid of compound **5**. However, a small quantity of monoboronic acid (**7**) was isolated and identified in almost all cases (Scheme 2).

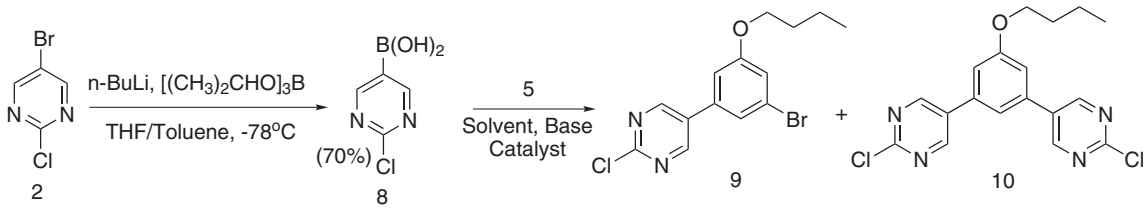
After failing to obtain bisboronic acid of compound **5**, an alternative route for approaching the target dielecrophile was designed (Scheme 3). Lithium–halogen exchange of compound **2** with *n*-BuLi in THF/toluene mixture in the presence of triisopropylborate, followed by an aqueous acid workup, gave pure compound **8** in 70% yield (Scheme 3). Sequential addition of triisopropyl borate after the lithiation gave compound **8** in only 7% yield. It is an established fact that successful preparation of certain heteroarylboronic acids need a specific order of addition of reagents.[45]

Double Suzuki cross-coupling reaction of compound **8** with 1,3-dibromo-5-butoxybenzene (**5**) was carried out under a variety of reaction conditions including different solvents, bases and catalysts (Table 1). To check the efficiency of different bases, THF was used as a solvent and $Pd(PPh_3)_4$ as a catalyst. When Na_2CO_3, K_2CO_3 and Cs_2CO_3 were used as bases, the reaction produced 1%, 4% and 5%, respectively, of mono-coupled product (**9**), whereas no bis-coupled product (**10**) was isolated (Table 1, entries 1–3). When K_3PO_4 was used as a base under similar conditions, it afforded 3% of compound **10** along with 8% of **9** (Table 1, entry 4). However, use of KF as a base diminished the yields of both compound **9** and compound **10** to 6% and 1%, respectively (Table 1, entry 5). After screening the bases, different solvents were checked for their reaction efficiency. 1,4-Dioxane, Dimethoxyethane (DME), and toluene gave similar results, yielding both mono- and bis-coupled products. It is important to note here that a mixture of 1,4-dioxane with water resulted in a little increase in the yield of either mono and bis-coupled products (Table 1, entry 9). Toluene–water (1:1.3) mixture produced 9% of compound **9** and 7% of compound **10**, respectively (Table 1, entry 10). After getting unsatisfactory results with $Pd(PPh_3)_4$ as a catalyst, it was decided to screen different catalysts in a 1,4-dioxane–water system using K_3PO_4 as a base (Table 1, entries 11–17). By using $Pd(OAc)_2/PCy_3$ as a catalyst system, compound **9** was obtained in 52% yield with 14% of compound **10**. To our delight, when $Pd_2(dba)_3/PCy_3$ was used as catalyst, 50% yield of compound **10** and 15% of (**9**) were isolated. Increase of catalyst quantity from 2 to 5 mol% resulted in an increase of bis-coupled product (**10**) to 72% and a decrease of mono-coupled product (**9**) to 2% (Table 1, entries 15 and 16). However, a further increase in the amount of catalyst to 6 mol % decreased the amount of both compounds **9** and **10** to 0% and 59%, respectively. It should be noted here that by applying different reaction conditions both mono- and bis-coupled products could be obtained as major products. Mono-coupled product (**9**) may further be reacted with other boronic acids to produce unsymmetrical dielectrophiles with a larger difference in their reactivity for desired applications.

After successful synthesis of dielectrophile **10**, it was then reacted with aniline and phenol to test its reactivity with both nitrogen and oxygen nucleophiles (Scheme 4). In the presence of K_2CO_3 in DMSO solvent, both nucleophiles underwent a rapid aromatic nucleophilic substitution reaction with chloropyrimidines of compound **10** at 80°C to afford amino and oxy-substituted compounds **12a** and **12b** with yields of 82% and 87%, respectively.



Scheme 2. Preparation of 5-butoxy-1,3-phenylenebisboronic acid

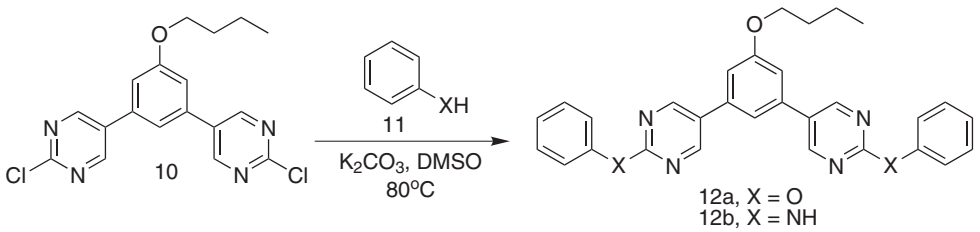


Scheme 3. Synthesis of dielectrophile with alkoxy side chain and reactive chloro substituents

Table 1. Optimization of base, solvent and catalyst for double Suzuki cross-coupling reaction

No.	Solvent	Temp. (°C)	Time (h)	Base	Catalyst	9 (%)[d]	10 (%)[d]
1	THF	Reflux	24	Na_2CO_3	$Pd(PPh_3)_4$	1	0
2	THF	Reflux	24	K_2CO_3	$Pd(PPh_3)_4$	4	0
3	THF	Reflux	24	Cs_2CO_3	$Pd(PPh_3)_4$	5	0
4	THF	Reflux	24	K_3PO_4	$Pd(PPh_3)_4$	8	3
5	THF	Reflux	24	KF	$Pd(PPh_3)_4$	6	1
6	1,4-Dioxane	100	24	K_3PO_4	$Pd(PPh_3)_4$	8	4
7	DME	Reflux	24	K_3PO_4	$Pd(PPh_3)_4$	7	3
8	Toluene	100	24	K_3PO_4	$Pd(PPh_3)_4$	8	3
9	1,4-Dioxane/H_2O	100	24	K_3PO_4	$Pd(PPh_3)_4$	10	8
10	Toluene/H_2O	100	13	K_3PO_4	$Pd(PPh_3)_4$	9	7
11	1,4-Dioxane/H_2O	100	10	K_3PO_4	$Pd(PPh_3)_2Cl_2$	6	9
12	1,4-Dioxane/H_2O	100	11	K_3PO_4	$PdCl_2dppf$	7	10
13	1,4-Dioxane/H_2O	100	12	K_3PO_4	$Pd(OAc)_2/PCy_3$	52	14
14	1,4-Dioxane/H_2O	100	10	K_3PO_4	$Pd_2(dba)_3/PCy_3$	15	50
15[a]	1,4-Dioxane/H_2O	100	08	K_3PO_4	$Pd_2(dba)_3/PCy_3$	7	63
16[b]	1,4-Dioxane/H_2O	100	06	K_3PO_4	$Pd_2(dba)_3/PCy_3$	2	72
17[c]	1,4-Dioxane/H_2O	100	05	K_3PO_4	$Pd_2(dba)_3/PCy_3$	0	59

Entries 1–14; catalyst = 2 mol%.
[a]Catalyst = 3 mol%.
[b]Catalyst = 5 mol%.
[c]Catalyst = 6 mol%.
[d]Isolated yields, 2-chloro-5-pyrimidylboronic acid (**6**) (2.2 equiv.), 1,3-dibromo-5-butoxybenzene (**5**) (1equiv.), base (3.4 equiv.).



Scheme 4. Nucleophilic substitution reaction of dielectrophile with oxygen and nitrogen nucleophiles

Conclusion

We have demonstrated the double Suzuki cross-coupling reaction of 2-chloropyrimidin-5-ylboronic acid (**2**) with 1,3-dibromo-5-butoxybenzene (**5**) to achieve the synthesis of 5,5′-(5-butoxy-1,3-phenylene)bis(2-chloropyrimidine) (**10**) as dielectrophile in good yield. We have also shown the ability of this dielectrophile to undergo nucleophilic substitution reaction with oxygen and nitrogen nucleophiles with the production of desired products in excellent yield. This method of dielectrophile formation with the installation of alkyl chain will provide a route to the construction of giant macromolecules for application in supramolecular and material chemistry. In addition, the presence of two pyrimidine moieties and reactivity towards different kinds of nucleophiles will allow us to prepare derivatives for various medicinal applications.

Experimental

General

NMR spectra were recorded at 300 MHz (Bruker) and chemical shifts are reported in ppm versus tetramethylsilane with either

tetramethylsilane or the residual solvent resonance used as an internal standard. Melting points are uncorrected. Solvents were dried according to standard procedures prior to use. All other major chemicals were obtained from commercial sources and used without further purification.

*Synthesis of 1,3-dibromo-5-butoxybenzene (**5**)*

Sodium *n*-butoxide (1.92 g, 20 mmol) was added to a solution of 1,3,5-tribromobenzene (**4**) (4.72 g, 15 mmol) in DMF (50 ml). The reaction mixture was stirred at 80°C for 10 h, quenched with a 10% aqueous HCl solution (25 ml) and extracted with $CHCl_3$ (3×40 ml). The combined organic layers were washed with brine (50 ml), dried with magnesium sulfate and the solvents evaporated. The crude product was purified by column chromatography using petroleum ether as mobile phase to afford compound **5** (3.64 g, 79%) as a colourless oil. It was characterized by comparing its ^1H and ^{13}C NMR spectra with those of the literature.[53,54]

*Synthesis of 2-chloro-5-pyrimidylboronic acid (**8**)*

To a solution of 5-bromo-2- chloropyrimidine (**2**) (2.5 g, 13.0 mmol) and triisopropyl borate (4.2 ml, 18.2 mmol) in anhydrous THF (20 ml) and toluene (5 ml) at −78°C was added *n*BuLi (2.5 M in hexane, 6.2 ml, 15.6 mmol) dropwise. The reaction mixture was stirred for 4 h at −78°C; it was then quenched with water (40 ml) and warmed to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo*, and the remaining aqueous layer was washed with diethyl ether (3×10 ml) to remove unreacted starting material. The aqueous layer was then acidified to pH 5 (with 48% aqueous HBr) to precipitate **8** as a white solid (1.44 g, 70%). It was characterized by comparing its ^1H and ^{13}C NMR spectra with those of the literature.[45]

*Synthesis of dielectrophile (**10**)*

2-Chloropyrimidin-5-ylboronic acid (**8**) (0.70 g, 4.40 mmol), 1,3-dibromo-5-butoxybenzene (**5**) (0.62 g, 2 mmol), $[Pd_2(dba)_3]$ (92 mg, 0.1 mmol), and PCy_3 (67 mg, 0.24 mmol) were added to a 50 ml round-bottom flask equipped with a stirring bar. The flask was evacuated and refilled with argon three times. 1,4-Dioxane (10 ml) and aqueous K_3PO_4 (1.30 M, 13 ml, 17 mmol) were then added by syringe and heated the mixture at 100°C for 6 h with continuous stirring. The reaction mixture was then filtered and washed thoroughly with chloroform. The filtrate obtained was concentrated under reduced pressure, and the remaining aqueous residue was extracted with $CHCl_3$ (5×25 ml). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was chromatographed on a silica gel column (100–200) with a mixture of petroleum ether and $CHCl_3$ as the mobile phase (5:1) to give pure **10** (0.54 g, 72%) as a white solid: m.p. 252–253°C; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.78$ (s, 4H, pyrimidinyl), 7.15 (t, $J = 1.4$ Hz, 1H, phenyl), 7.07 (d, $J = 1.4$ Hz, 2H, phenyl), 4.03 (t, $J = 6.4$ Hz, 2H, CH_2), 1.85–1.70 (m, 2H, CH_2), 1.54–1.37 (m, 2H, CH_2), 0.94 (t, $J = 7.4$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 160.9$, 160.8, 157.5 (pyrimidinyl), 135.8 (C_5-phenyl), 132.3 (C_1, C_3-phenyl), 117.6 (C_2-phenyl), 113.9 (C_4, C_6-phenyl), 68.3 (CH_2- butyl), 31.1 (CH_2-butyl), 19.26 (CH_2-butyl),13.8 (CH_3-butyl); MS (ESI) *m/z* 375.1 [M + H] (100%), 377.2 (62), 379.1 (9). Anal. Calcd for $C_{18}H_{16}Cl_2N_4O$: C, 57.61; H, 4.30; N, 14.93. Found: C, 57.68; H, 4.28; N, 14.85. Compound **9** (0.013 g, 2%) was also isolated as a white solid from column chromatography. When $Pd(OAc)_2/PCy_3$ was used as catalyst, the reaction gave mono-coupled product **9** (0.35 g, 52%) and bis-coupled product **10** (0.11 g, 14%).

9: m.p. 195–196°C;^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.71$ (s, 2H, pyrimidinyl), 7.18–7.15 (m, 1H, phenyl), 7.09–7.05 (m, 1H, phenyl), 6.92–6.89 (m, 1H, phenyl), 3.94 (t, $J = 6.4$ Hz, 1H, CH_2), 1.83–1.66 (m, 1H, CH_2), 1.51–1.34 (m, 1H, CH_2), 0.92 (t, $J = 7.4$ Hz, 2H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 160.7$, 160.6, 157.4 (pyrimidinyl), 135.6 (C_5-phenyl), 131.8 (C_1-phenyl), 124.0 (C_3-phenyl), 121.9 (C_2-phenyl), 118.0 (C_4-phenyl), 112.7 (C_6-phenyl), 68.3 (CH_2-butyl), 31.1 (CH_2-butyl), 19.1 (CH_2-butyl), 13.7 (CH_3-butyl); MS (ESI) *m/z* 341.0 [M + H] (100%), 343.1 (96), 345.0 (4). Anal. Calcd for $C_{14}H_{14}BrClN_2O$: C, 49.22; H, 4.13; N, 8.20. Found: C, 49.01; H, 4.08; N, 8.34.

General Procedure for the Synthesis of 12

To a solution of **10** (0.19 g, 0.5 mmol) in DMSO (5 ml) at 80°C was added K_2CO_3 (finely ground) (0.14g, 1 mmol) and respective nucleophile **11** (1.1 mmol) with constant stirring. Stirring was continued further for 24 h. The reaction mixture was then partitioned between ethyl acetate (60 ml) and water (50 ml), the resulting mixture separated, and the aqueous layer extracted twice with ethyl acetate (15 ml). The combined organics were washed with brine (60 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was chromatographed on a silica gel column (100–200) with a mixture of petroleum ether and acetone as the mobile phase (3:1) to give pure products **12a**, **12b** as white solids.

12a (0.20 g, 82%): m.p. 225–226°C; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.57$ (s, 4H, pyrimidinyl), 7.26–7.23 (m, 2H, phenyl), 7.43–7.32 (m, 3H, phenyl), 7.12 (t, $J = 1.4$ Hz, 1H, phenyl), 7.05 (d, $J = 1.4$ Hz, 2H, phenyl), 7.04–7.00 (m, 1H, phenyl), 4.02 (t, $J = 6.4$ Hz, 1H, CH_2), 1.85–1.70 (m, 1H, CH_2), 1.53–1.36 (m, 1H, CH_2), 0.93 (t, $J = 7.4$ Hz, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.6$, 168.5, 156.3 (pyrimidinyl), 153.2 (C_5-phenyl), 134.7 (C_1-phenoxy), 131.2 (C_1, C_3-phenyl), 125.3 (C_3, C_5-phenoxy), 120.5 (C_4-phenoxy), 118.7 (C_2, C_6-phenoxy), 116.3 (C_2-phenyl), 112.8 (C_4, C_6-phenyl), 66.2 (CH_2-butyl), 30.9 (CH_2-butyl), 18.2 (CH_2-butyl),12.9 (CH_3-butyl); MS (ESI) *m/z* 491.3 [M + H] (100%), 492.2 (33), 493.3 (7). Anal. Calcd for $C_{30}H_{26}N_4O_3$: C, 73.45; H, 5.34; N, 11.42. Found: C, 73.58; H, 5.26; N, 11.40.

12b (0.21 g, 87%): m.p. 269–271°C; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.66$ (s, 4H, pyrimidinyl), 7.62–7.60 (m, 2H, phenyl), 7.35–7.24 (m, 3H, phenyl), 7.13 (t, $J = 1.4$ Hz, 1H, phenyl), 7.06 (d, $J = 1.4$ Hz, 2H, phenyl), 7.04–7.00 (m, 1H, phenyl), 4.02 (t, $J = 6.4$ Hz, 1H, CH_2), 1.85–1.70 (m, 1H, CH_2), 1.53–1.36 (m, 1H, CH_2), 0.93 (t, $J = 7.4$ Hz, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 163.4$, 163.3, 158.1 (pyrimidinyl), 152.1 (C_5-phenyl), 138.6 (C_1-*N*-phenyl), 132.1 (C_1, C_3-phenyl), 124.3 (C_3, C_5-*N*-phenyl), 120.5 (C_4-*N*-phenyl), 118.6 (C_2, C_6-*N*-phenyl), 116.1 (C_2-phenyl), 112.5 (C_4, C_6-phenyl), 66.1 (CH_2-butyl), 30.8 (CH_2-butyl), 18.1 (CH_2-butyl),12.7 (CH_3-butyl); MS (ESI) *m/z* 489.3 [M + H] (100%), 490.3 (36), 491.2 (5). Anal. Calcd for $C_{30}H_{28}N_6O$: C, 73.75; H, 5.78; N, 17.20. Found: C, 73.83; H, 5.86; N, 16.96.

Acknowledgements

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