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Electronic Supplementary Information

Ultrafast Synthesis of 2-(Benzhydrylthio) benzo[d]oxazole, An Antimalarial Drug, via Unstable Lithium Thiolate Intermediate in a Capillary Microreactor

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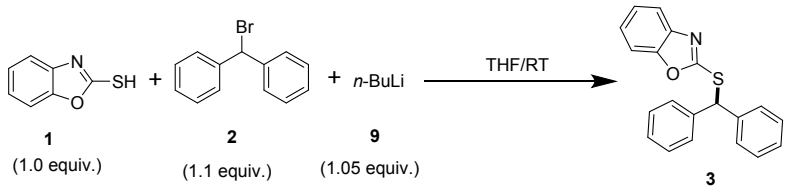
General Information

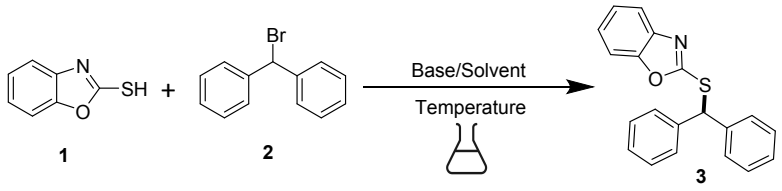
All reactions were performed under N_2 atmosphere employing flame-dried glass wares. Most of the starting materials and reagents were purchased from commercial sources and used as such. *n*-Butyl lithium (1.6 M in hexane), *Sec*-Butyl lithium and solvents such as Tetrahydrofuran (THF, anhydrous), & 2-Methyltetrahydrofuran (2-MeTHF, anhydrous) were purchased from Sigma-Aldrich and used as such. Perfluoroalkoxy alkane (PFA) tubing, T-junctions, and cross-junctions were purchased from IDEX HEALTH & SCIENCE (WA, USA). And syringe pumps (Harvard apparatus, PHD 22/2000 Hpsi, PHD Ultra) were used from commercial sources. Gas tight syringes (50 mL, inner diameter: 27.6 mm) purchased from SGE Analytical Science. ^{1}H, and ^{13}C (proton decoupled) nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance III (500, and 125 MHz respectively). ^{1}H and ^{13}C chemical shifts values are reported in parts per million (ppm) relative to downfield of Me_3SiCl or $CHCl_3$ as a standard in $CDCl_3$ solvent unless otherwise noted and the coupling constants (*J*) are reported in Hz. Multiplicities were reported using the following abbreviations: s = singlet, d= doublet, t = triplet, dd= doublet of doublet, m = multiplet. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 TLC plates and visualization was accomplished with short wave UV light (254 nm). Column chromatography was carried out through silica gel (100-200 mesh) by eluting EtOAc/hexane as eluents.

General procedure for the synthesis of 2-(Benzhydrylthio) benzo[d]oxazole (3) from benzo[d]oxazole-2-thiol (1), benzhydryl bromide (2) and base in batch



In a 25 ml flame-dried round bottom flask equipped with magnetic stirring bar under N_2 atmosphere, benzo[d]oxazole-2-thiol **1** (1.0 mmol) and benzhydryl bromide **2** (1.1 mmol) were added in dry solvent (6.0 ml, THF) at room temperature (23–26 ^oC). And to the stirred solution, base (1.05 mmol) [*n*-Butyl lithium **9** (1.6 M in hexane, 0.66 ml) used as indicated cases] was added slowly about ~20 sec. Then progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with aq. NH_4Cl solution, and then extracted with ethyl acetate (10 ml). The aqueous layer was collected and washed three times with ethyl acetate (3x8 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. To isolate the product **3**, the residue was passed through silica gel (100-200 mesh) column chromatography using petrol ether/ethyl acetate as an eluent.

Table S1: Different equivalents and different solvents study for the synthesis of 2-(Benzhydrylthio) benzo[d]oxazole (**3**) from benzo[d]oxazole-2-thiol (**1**), benzhydryl bromide (**2**) and *n*-BuLi (**9**) in batch[a]



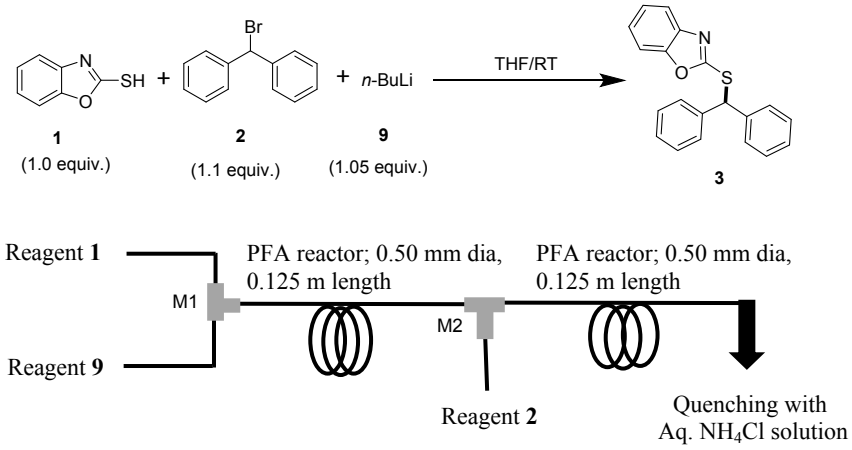
1 2 3

Entry	Equiv. of 1	Equiv. of 2	Equiv. of Base (*n*-BuLi (9))	Solvent	Time	Yield 3 (%)[b]
1	1.0	1.1	1.2	THF	10 min	75
2	**1.0**	**1.1**	**1.05**	**THF**	**10 min**	**75**
3	1.1	1.0	1.05	THF	10 min	68
4	1.0	1.2	1.05	THF	10 min	75
5	1.0	1.1	1.05	2-MeTHF	10 min	64
6[c]	1.0	1.1	1.05	THF	10 min	65

[a] Reaction conditions: 0.16 M in solvent (1 mmol scale) under N_2 atmosphere. THF; Tetrahydrofuran; 2-MeTHF; 2-Methyl tetrahydrofuran; Room temperature 23-26 ^oC. *n*-BuLi (1.6 M in hexane) used. [b] Isolated yields. [c] *Sec*-BuLi reagent was used instead of *n*-BuLi and very small amount of decomposition was observed in this case.

Optimization studies were carried out under various equivalents of reagents **1, 2,** & **9** and different solvents in batch as shown in table S1. Initially, excess amount of base *ie., n*-butyl lithium **9** with respect to reagent **1** was employed at room temperature (entry 1, table S1) and in this case, yield of the product **3** was obtained in 75% after 10 min. In other experiments, the use of excess amount of substrates **1** or **2** (entries 3-4) didn't improve the desired product (**3**) yield as compared to entry 2. When 2-Me THF was employed as reaction solvent, the desired product (**3**) yield was observed lower yield (64%) (entry 5) than the reaction in THF (75%) solvent (entry 2). Note that, decrease in the yield of product **3** was obtained when *sec*-BuLi was employed as a base instead of *n*-BuLi (entry 6, Table S1).

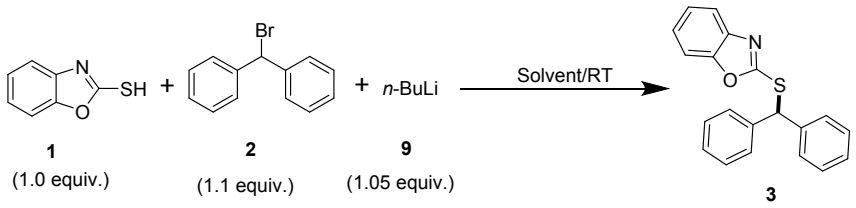
Continuous-flow procedure for the synthesis of 2-(Benzhydrylthio) benzo[d]oxazole (3) from benzo[d]oxazole-2-thiol (1), benzhydryl bromide (2), and *n*-butyl lithium (9) using a Perfluoroalkoxy alkane (PFA) capillary reactor in consisting of two T-micromixers M1 and M2

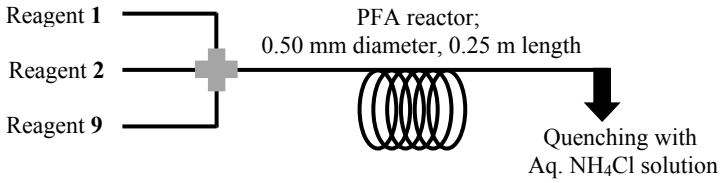


Initially, benzo[d]oxazole-2-thiol (4.0 mmol) **1** in 6.3 ml of anhydrous THF, benzhydryl bromide **2** (4.4 mmol) in 12.6 ml of anhydrous THF, and *n*-butyl lithium (1.6 M in hexane, 4.2 mmol, 2.6 ml) **9** in 3.7 ml of anhydrous THF in an oven-dried three 50 ml flasks equipped with magnetic stirring bar were individually well mixed at room temperature (23–26 ^{o}C) under N_2 atmosphere. And then these three reagents **1, 9** & **2** were taken carefully into 10 ml, 10 ml, & 20 ml NORM-JECT plastic syringes, respectively. Reagents **1** & **9** were introduced into a single perfluoroalkoxy alkane (PFA) coil capillary (0.5 mm diameter, 0.125 m length) through a T-micromixer (M1) for lithiated intermediate generation at the flow rate of 1.9 ml/min (residence time 0.39 sec) for each reagent by one syringe pump, and then third reagent **2** was passed through another T-micromixer (M2) at the flow rate of 3.8 ml/min (residence time 0.19 sec) by another syringe pump (Total flow rate by two syringe pumps; 7.6 ml/min; residence time; 0.58 sec). After reaching steady state, the reaction mixture was quenched with aq. NH_4Cl solution at the end of the coil reactor in a beaker

collection. As soon as the reaction completed, the PFA capillary tube was washed with aq. NH_4Cl solution, water, followed by acetone (2 times) & dried for the next reaction. After completion of the reaction, the volume of collected mixture was measured and then extracted with ethyl acetate (50 ml). The aqueous layer was collected and washed three times with ethyl acetate (3x30 ml) and then the combined organic layer was washed with brine, dried with anhydrous Na_2SO_4. After filtration, organic solvent was evaporated under reduced pressure. Then the resulting residue was purified by column chromatography through silica gel (100-200 mesh) by eluting petrol ether/ethyl acetate as an eluent (by varying ratios). The product **3** was isolated in 75% yield as a white solid.

Table S2. Different solvents studies for the synthesis of 2-(Benzhydrylthio) benzo[d]oxazole (**3**) from benzo[d]oxazole-2-thiol (**1**), benzhydryl bromide (**2**), and *n*-butyl lithium (**9**) in a single perfluoroalkoxy alkane (PFA) capillary reactor by simultaneous injection of three reagents[a]



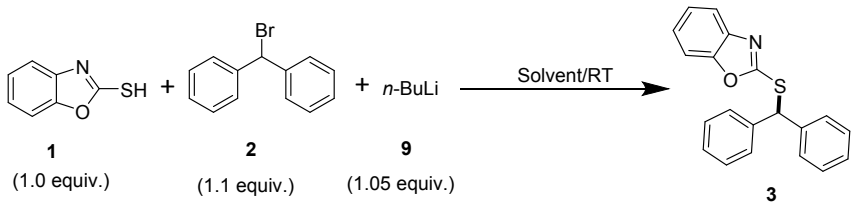


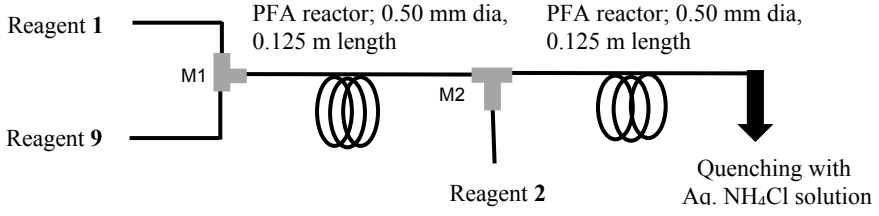
Entry	Solvent (0.16 M)	Total Flow rate (ml/min)	Residence time t^R [s]	Yield (%)[a] **3**[b]
1	THF	1.0	2.95	20
2	THF	1.5	1.96	32
3	THF	1.95	1.51	36
4	THF	3.0	0.98	54
5	**THF**	**4.5**	**0.65**	**60**
6	THF	6.0	0.49	52
7	THF	7.5	0.39	46
8	2-Me THF	1.0	2.95	20
9	2-Me THF	1.5	1.96	28
10	2-Me THF	1.95	1.51	33
11	2-Me THF	3.0	0.98	48
12	2-Me THF	4.5	0.65	55
13	2-Me THF	6.0	0.49	45
14	2-Me THF	7.5	0.39	43

[a] Reaction conditions: Perfluoroalkoxy alkane (PFA) capillary (0.50 mm diameter, 0.25 m length) was used with 0.16 M of **1** (4 mmol scale) in solvent (total volume). 1.1 equiv. of **2** with respect to **1**, and 1.05 equiv. *n*-BuLi (**9**) (1.6 M in hexane) were found to be optimal. RT = 23–26 °C. THF: Tetrahydrofuran, 2-Me THF: 2-Methyltetrahydrofuran. [b] Isolated yields.

As shown in table S2, our flow optimization studies were performed by simultaneous injection of three reagents **1, 2,** & **9** through a cross mixer using a single Perfluoroalkoxy alkane (PFA) coil capillary (0.5 mm diameter, 0.25 m length) in different solvents (THF, 2-Me THF). Our initial attempt using THF as solvent, several reactions were performed by varying flow rates (entry 1-7, table S2) and in all cases, the yield of the product **3** was obtained in moderate to good yields (20-60%). In other experiments, the use of 2-Me THF as solvent also gave the product **3** in low yields (20-55%). In fact, reactions with THF solvent (entry 1-7, table S2) gave better results than the reactions with 2-Me THF solvent (entry 8-14, table S2). Here, it is noteworthy that the reaction at total flow rate of 4.5 ml/min (residence time 0.65 sec) in THF solvent at room temperature (entry 5, table S2) was found to better (60% yield) as compared to several reactions tried (entries 1-4 & entries 6-14 in table S2).

Table S3: Optimization studies at different flow rates in different solvent for the synthesis of 2-(benzhydrylthio) benzo[d]oxazole (**3**) from benzo[d]oxazole-2-thiol (**1**), benzhydryl bromide (**2**) and *n*-BuLi (**9**) in flow using perfluoroalkoxy alkane (PFA) capillary reactor with consisting of two T-micromixers M1 and M2.[a]





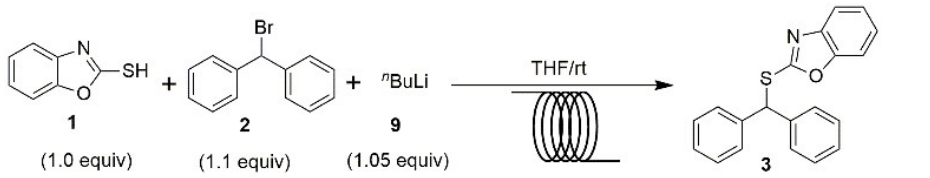
Entry	Solvent	Flow rate of (1+9) (ml/min)	t_1^R [s]	Flow rate of 2 (ml/min)	t_2^R [s]	Total t^R [s]	Yield (%)[a] **3**[b]
1	2- Me THF	0.5+0.5	1.47	1	0.74	2.21	62
2	2- Me THF	1.25+1.25	0.59	2.5	0.30	0.89	68
3	2- Me THF	**1.9+1.9**	**0.39**	**3.8**	**0.19**	**0.58**	**65**
4	2- Me THF	2.1+2.1	0.35	4.2	0.18	0.53	58

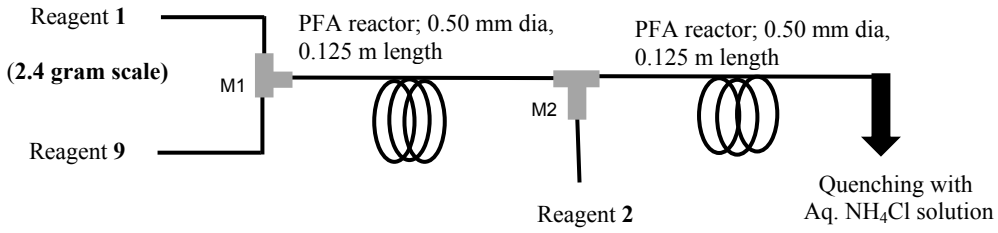
[a] Reaction conditions: Two capillary tubings with inner diameters (0.50 mm diameter, 0.125 m length) used for lithiated intermediate generation, and its decomposition. 0.16 M of **1** (4 mmol scale) in 2-Me THF (total volume). 1.1 equiv. of **2** with respect to **1**, and 1.05 equiv. of n-BuLi (1.6 M in hexane) were found to be optimal. RT = 23–26 °C. [b] Isolated yields.

As shown in table S3, our flow optimization studies were performed in perfluoroalkoxy alkane (PFA) coil capillary (0.5 mm diameter, 0.125 m length) in consisting of two T-micromixers M1 and M2 by introducing three reagents **1, 2,** & **9** in 2-Me THF solvent at room temperature under different flow rates. Reagents **1** & **9** were introduced with the indicated flow rates through a T-mixer using PFA coil capillary (0.5 mm diameter, 0.125 m length) for lithium intermediate generation then third reagent **2** was introduced with the indicated flow rate through another T-

mixer and the resulting reaction mixer was quenched with aq. NH_4Cl at the end of the outlet collection. In this manner, several reactions were performed by varying flow rates (entry 1-4, table S3). When a reaction performed with the total flow rate of 2 ml/min (t^R = 2.21 sec) (entry 1, table S3), the desired product **3** was obtained in 62% yield. Interestingly, when flow rates increased to 5 ml/min (t^R = 0.89 sec) and 7.6 ml/min (t^R = 0.58 sec), the yield of the product **3** was improved to 68% and 65% yields, respectively (entries 2-3, table S3). Excellent mixing efficiency at high flow rates in a confined space of the microfluidic reactor,[1] that could make the reaction efficiency, resulting decrease in the synthesis time to less than one second. Note that, when a reaction was carried out at very high flow rate (8.4 ml/min; residence time; 0.53), the yield of the product **3** was obtained in low yield (58% yield). It was observed that considerable amount of side products was not formed in any of these cases (entries 1-4, table S3).

Continuous-flow procedure for the multi-gram scale synthesis of 2-(Benzhydrylthio) benzo[d]oxazole (3), an antimalarial drug from benzo[d]oxazole-2-thiol (1), benzhydryl bromide (2), and *n*-butyl lithium (9) using a Perfluoroalkoxy alkane (PFA) capillary reactor with consisting of two T-micromixers M1 and M2.



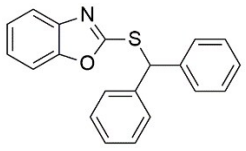


Initially, benzo[d]oxazole-2-thiol **1** (16.0 mmol) in 25 ml of anhydrous THF, *n*-butyl lithium **9** (1.6 M in hexane, 16.8 mmol, 11 ml) in 14 ml of anhydrous THF and benzhydryl bromide **2** (17.6 mmol) in 50 ml of anhydrous THF were individually well mixed in an oven-dried three 100 ml flasks equipped with magnetic stirring bars at room temperature (23–26 ^{o}C) under N_2 atmosphere. And then these three reagents **1, 9** & **2** were taken carefully into 3x50 ml glass syringes, respectively. Reagents **1** & **9** were introduced into a single perfluoroalkoxy alkane (PFA) coil capillary (0.5 mm diameter, 0.125 meter length) through a T-micromixer (M1) for lithiated intermediate generation at the flow rate of 1.9 ml/min (total flow rate; 3.8 ml/min; residence time 0.39 sec) for each reagent by one syringe pump, and then third reagent **2** was passed through another T-micromixer (M2) at the flow rate of 3.8 ml/min (residence time; 0.19 sec) by another syringe pump (Total flow rate by two syringe pumps; 7.6 ml/min; t^R = 580 ms). After reaching

steady state, the reaction mixture was quenched with aq. NH_4Cl solution at the end of the coil reactor in a beaker collection. As soon as the reaction completed, the PFA capillary tube was washed with aq. NH_4Cl solution, water, followed by acetone (2 times) & dried for the next reaction. After completion of the reaction, the volume of collected mixture was measured and then extracted with ethyl acetate (200 ml). The aqueous layer was collected and washed three times with ethyl acetate (3x120 ml) and then the combined organic layer was washed with brine, dried with anhydrous Na_2SO_4. After filtration, organic solvent was evaporated under reduced pressure. Then the resulting residue was purified by column chromatography through silica gel (100-200 mesh) by eluting petrol ether/ethyl acetate as an eluent (by varying ratios).

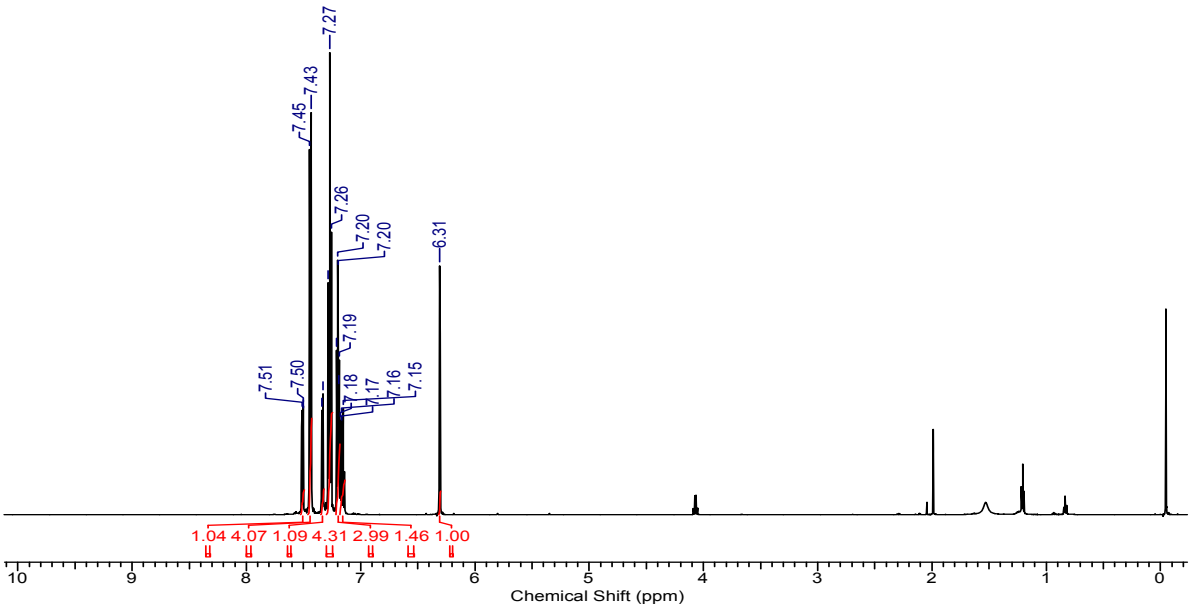
Characterization data of compound (3):

2-(Benzhydrylthio) benzo[d]oxazole (3):[2]

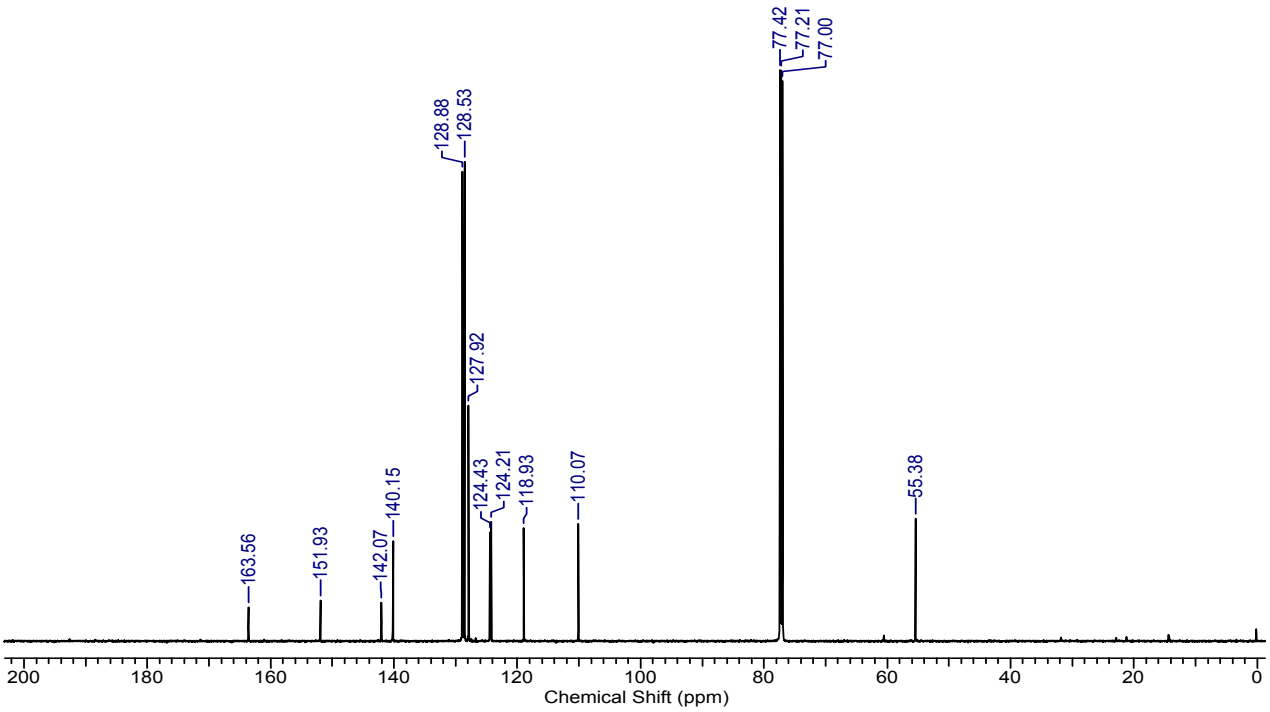


The product **3** was obtained in 75% isolated yield as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.6 Hz, 0.8 Hz,1H), 7.44 (d, *J* = 7.3 Hz, 4H), 7.34-7.33 (m, 1H), 7.28-7.26 (m, 4H), 7.21-7.19 (m, 3H), 7.18-7.15 (m, 1H), 6.31 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.56, 151.93, 142.07, 140.15, 128.88, 128.53, 127.92, 124.43, 124.21, 118.93, 110.07, 55.38.

^{1}H NMR of 2-(Benzhydrylthio) benzo[d]oxazole (3)



^{13}C NMR of 2-(Benzhydrylthio) benzo[d]oxazole (3)



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