

Microwave Irradiation Assisted Synthesis 4-Hydroxy 3-Iodobenzylguanidine(HIBG)

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Abstract

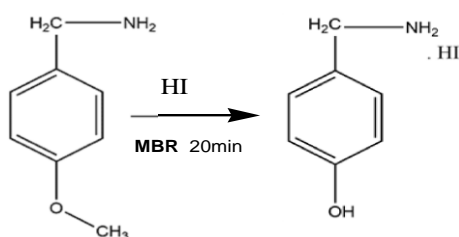
Meta-iodo benzyl guanidine(MIBG) is an analogue of Noradernalin transmitter. When radiolabelled with ¹²³I and ¹³¹I, used for scan and diagnosis Adernal's tumor. Labeled MIBG with ¹³¹I used in therapy of Neuroblastoma, Pheochromocytoma, Carcinoidsyndrome and Neuroendocrine tumors. In our continuing efforts to develop MIBG analogues with higher therapeutic efficacy, we recently evaluated the structure-activity characteristics of several analogues of MIBG. We are interested in developing HIBG analogues containing hydroxyl at the 4-postion of HIBG.generous of the some groups to activate the aromatic ring of a drug towards electrophilic radiodiodination may have merit. The resistance of HIBG to in vivo radiodiodination and amenability to kit production make it a strong candidate for clinical evaluation as a pheochromocytoma and neuroblastoma localzing agent. Microwave assisted heating under controlled conditions has been shown to be an invaluable technology for organic chemistry and during discovery applications since it often rise yield and dramatically reduce reaction times, typically form days or hours to minutes or even seconds.

Microwave Irradiation Assisted Synthesis of HIBG is started to produce 4-methoxybenzylamine. 4-methoxybenzylamine and hydriodic acid are mixed and heated for this purpose. Then under MBR condition 4-Hydroxybenzyl guanidine in sulphate form is prepared with additional Cyanamide and Sulphuric acid. After that Iodination is preformed under MBR condition and 4-Hydroxy-3-iodobenzyl guanidine sulphate formed, that can labeled with ¹³¹I and exchange to labeled 4-Hydroxy-3-iodobenzyl guanidine sulphate.

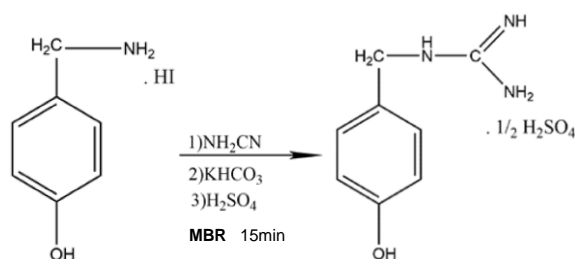
Keywords: Radiolabelling- MIBG- HIBG- Neuroblastoma- Pheochromocytoma- Carrcinoidsyndrome- Microwave Batch Reactor

1. Introduction

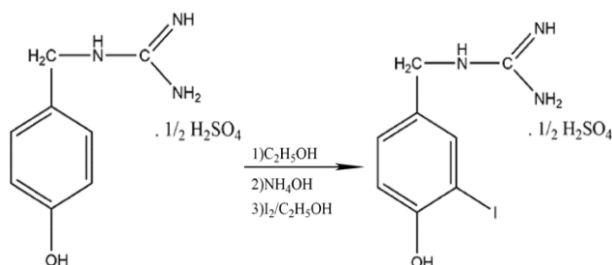
In recent years, Synthesis and labeling of MIBG analogues which are used in scan and diagnosis of adrenal tumors have become highly important. In this research, synthesis of HIBG is examined microwave irradiation assisted that resulted in higher therapeutic effect of HIBG compared to MIBG, plus a faster synthesis and higher efficiency when microwave irradiation assisted than thermal method.



Schema.1



Schema.2



Schema.3

2. EXPERIMENTAL METHOD

Chloramine-T , 4-methoxybenzylamin , sodium iodide , hydriodic acid and Cyanamide were provided in the laboratory microwave from laboratory resources. Proton magnetic resonance (HNMR) and infrared spectrum (IR) of them were obtained.

2.2 TASK PROCEDURE

2.2.1 4-Hydroxybenzylamin hydroiodide

4-methoxybenzylamine(125mg, 1mmol) was MBR irradiation assisted for 20min with hydriodic acid(184mg, 3mmol)(German Merck) . methylode(bp:30°C) was vacuum evaporated and extra HI was isolated with appropriate solvents (methyl acetate , acetic acid)after 3 times of recrystallization. needle crystals of 4-hydroxybenzylaminohydroiodide were appeared .(88% yield) (Shema.1)

m.p:182° C

IR(KBr) $\nu_{\max}/\text{cm}^{-1}$: 3400(OH), 3161.25(NH), 3006.77(NH),3000(sp² C-H, Arom)

2.2.2 4-Hydroxybenzylguanidine sulphate

4-Hydroxybenzylamin hydroiodide (502mg , 2mmol) and Cyanamide (252mg , 0.6mmol) were irradiation at 150°C for 15minutes then they were cool to ambient temperature. The Remaining was solved in boiling water. Dissolved KHCO₃ (220mg , 2.2mmol) in 2ml of water, was added to the solution . The resulting solution was boiled for 2minutes then was left to be cool to ambient temperature. Filtrated product of bicarbonate salt made in 4ml hot water as a suspension . Added H₂SO₄(2N) drop by drop until pH became 2. It boiled to become dense to 1ml, then were cool. Colorless solid filtrated . it was recrystallized once more with water to achieve sulphat solid as a colorless crystal.(380mg , 90%) (Shema.2)

m.p: 260-262 °C

HNMR(300 MHZ ,MeOH) δ : 7.11(d,2H , J=8HZ), 6.74(d,2H , J=8HZ),4.25(S,2H)

2.2.3 4-hydroxy-3-iodobenzylguanidine sulphate

Dissolved 4-Hydroxybenzylguanidine sulphate (225mg , 1.05mmol) in EtOH (30% , 15ml) and dense ammoniac solution and added a solution of I₂ (199.9mg , 0.788mmol) in EtOH(15ml) in 0 °C were mixed. Once more in ambient temperature mixed for 18hours. In vacuum, solvent evaporated and the rest was recrystallized three times with water solvent to achieve (149mg , 82%) (Shema.3)

m.p.:208-210 °C

¹HNMR(300MHz , MeOD)δ:6.76-7.65(m , 6H , ArH,NH₂), 4.10(S,2H,CH₂)

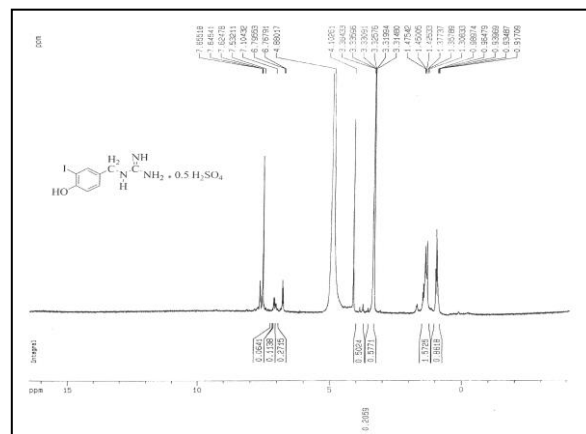


Figure3:¹HNMR of 4-hydroxy-3-iodobenzyl guanidine sulphate

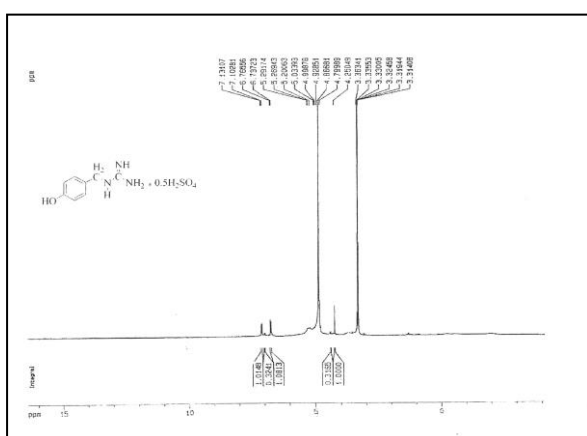


Figure1:¹HNMR of 4-Hydroxybenzylguanidine sulphate

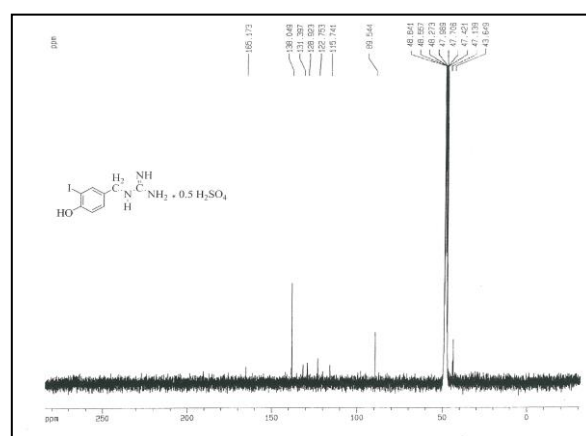


Figure4:¹³CNMR of 4-hydroxy-3-iodobenzyl guanidine sulphate

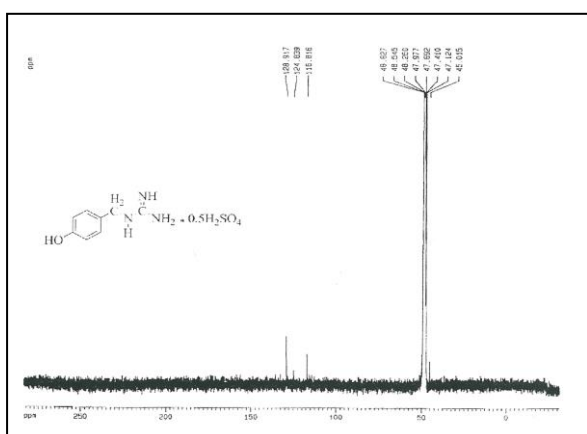


Figure2:¹³CNMR of 4-Hydroxybenzylguanidine sulphate

3. RESULT DISSCUSION

4-hydroxy-3-iodobenzyl guanidine sulphate labeled easily with carrier added and nocarrier added structures. In addition, containing hydroxyl group in para-position , radiation iodo stabled in 3-position . this function reduce large amount of releasing scatter iodine in drug. 4-hydroxybenzyl guanidine sulphate (HBG) is an intermediate that has the ability to be labeled in the clinics by provided kit production. The far hospitals from central nuclear may have merit. Microwave irradiation assisted synthesis reduce reaction time with rise yield.

4. REFERENCES

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