HL
http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 5: (2), 2015, 213-221

GREEN METHODOLOGIES IN ORGANIC SYNTHESIS: MICROWAVE-ASSISTED STUDY ON CARBOSTYRIL DERIVATIVES UNDER PHASE TRANSFER CATALYSIS

Chandra Babu Kollapudi [a,*], Madhusudhan Gutta [a], Buchi Reddy Reguri [a,b]

[a]*Centre for pharmaceutical sciences, JNT University, Kukatpally, Hyderabad 500 072, India*
[b] *IPCA Laboratories Ltd, 142 AB, Kandivli Industrial Estate, Mumbai, India*
E-mail: chandra.kollapudi@gmail.com

Abstract: Green chemistry is the new and rapid emerging field of chemistry. Its growing importance is in utilization of maximum possible resources in such a way that, there is negligible or minimum production of chemical waste. In this paper few derivatives of carbostyril were synthesized by microwave method as well as by green chemistry method. By applying the green synthesis method, we have not only avoided the use of DDQ and benzyl halide which is hazardous one but also the formations of by products are avoided. The quaternary ammonium salts (PTC) under micro wave conditions towards Aripiprazole (carbostyril derivative) act as a reagent and give dehydrogenated and benzylated carbostyril from 3,4-dihydro carbostyril derivatives.

Keywords: Green methodology, Aripiprazole, Microwaves and Quaternary ammonium salts

Introduction:

Quinolin-2(1*H*)-one (carbostyril) derivatives have been proved to possess anti platelet, anti-inflammatory, anti-ulcer, vasodilatory and phosphodiesterase inhibitory activities.[I-XII] The cardiovascular and neuroprotective activities of certain 3,4-dihydroquinolin-2(1*H*)-ones substituted with various side chains have also been reported.[II,VII,X,XI,XIII] Among these heterocycles, quinolin-2(1*H*)-ones proved to be the most active against platelet aggregation [XIIII-XVIII]. One of the most potent antiplatelet agents, CCT-62, has been proved to be an inhibitor of phosphodiesterases, and its antiplatelet effect is mainly mediated by elevation of cyclic-AMP levels.[XVIX]

Microwave have been used to speed up chemical reactions in the laboratories [XX] which led scientists to investigate the mechanism of microwave dielectric heating and to identify the advantages of the technique for chemical synthesis.[XXI] During recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis.[XXII] This is supported by a great number of publications in recent years, particularly in 2003, related to the application of microwaves as a consequence of a great availability of dedicated and reliable microwave instrumentation.[XXIII-XXVI]

The first recorded application of microwave energy in organic synthesis is the aqueous emulsion polymerization using pulsed electromagnetic radiation. The start of the rapid growth of microwave assisted procedures in organic synthesis was ignited in 1986 by pioneering papers by Gedye and co-workers [XXVI] and Giguere and coworkers.[XXVII]

Experimental section:

Materials and methods

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400MHz spectrometer using DMSO-d_6, $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375 °C. All the organic extracts were dried over sodium sulfate after work-up. The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated

Procedure for the preparation of Aripiprazole in conventional method (7-(4-(4-(2,3-dichlorophenyl) piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one), 1:

To a suspension of the crude quaternary spiro ammonium salt (8-(2,3-Dichlorophenyl-8-aza-5-azoniaspiro(4,5) decane Bromide), **3** (200.0 g, 0.54 mol) in MIBK (1000 mL) and DMF (400 mL), were added the 7-hydroxy-4,5-dihydrocarbostyry, **4** (84.6 g,0.51 mol) and TBAB (8.6 g,0.027 mol). The resulting mixture was refluxed under vigorous stirring for 18 hr. The reaction temperature was then adjusted in a manner to distill under a water pump vaccum 800 mL of MIBK with a column-head temperature ranging from 60-70 ° after cooling to room temperature water (1000 mL) and hexane (1000 mL) were added, and the suspension was stirred for 30 min. The medium was filtered and the filter cake washed 4 times with 200 mL water and suctioned to give 230.0 g (94.0%) crude Aripiprazole, **1**.

HPLC at 215 nm (Waters Model Alliance 2695-separation module, Inersil ODS C18, 250mm long, 4.6mm i.d., and 5-m particle diameter column, Mobile phase A was Phosphate buffer (pH 3.0±0.05) and acetonitrile in the ratio of 80:20 [buffer (pH 6.0)], prepared by dissolving 2.72 g of KH_2PO_4 in 1000 ml of water, pH adjusted to 3.0±0.05 with dilute ortho phosphoric acid. Mobile phase B was acetonitrile and methanol in the ratio of 8:2 (v/v) ,flow rate 1.0 ml/min ,45 min, gradient pump, retention time 15.23 min.; 93.97%).

Mp: 136-137.6 ^{o}C; IR (KBr) 3434, 1677, 1234, 1034 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400MHz) δ 10.0 (s, 1H), 7.3 (s, 1H), 7.2 (d, 1H), 7.1 (t, 1H), 7.05 (d, 1H), 6.5 (d, 1H), 6.4 (d, 1H), 4.3 (t, 2H), 3.9 (t, 2H), 2.97 (b, 2H), 2.9 (b, 2H), 2.7 (t, 2H), 2.4 (t, 2H), 2.4 (b, 2H); 2.4 (b, 2H), 1.7 (m, 2H), 1.5 (m, 2H). ES-MS *m/z* 448.4 (M^{+}+1, 100%).

Procedure for the preparation of Impurity in conventional method (7-(4-(4-(2,3-dichloro phenyl)piperazin-1-yl)butoxy) quinolin-2(1H)-one), 2:

A mixture of THF (660.0 mL), Aripiprazole, **1** (20.0 g, 0.045 mol) and dichloro dicyano quinine (DDQ) (40.5 g, 0.1784 mol) was stirred at 25-35 °C for reaction completion. The reaction mass was concentrated at reduced pressure at 50-55 °C to obtained the crude. To the crude, water (660 mL) was added and stirred at 25-35 °C for 15-30 min. The reaction mass pH was adjusted to 8.0-9.0 using caustic lye. The reaction mass was extracted with ethyl acetate and this layer was washed with (2 x 100 mL) water. The organic layer was

concentrated under reduced pressure at 50-55 °C to get the residue. To the residue pet ether (200 mL) was added and stirred for 30-60 min. at 25-35 °C. The isolated solid was filter, washed with ether (20 mL) and dried to constant weight at 25-35 °C to yield 7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2(1H)-one, **2** (Yield 8.5 g, 42.5%)
Mp: 137-139 ^{o}C; IR (KBr) 3450, 1659, 1230, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.60-2.0 (m, 4H), 2.49 (t, 2H), 2.64 (br, 4H), 3.05 (br, 4H), 4.09 (t, 2H), 6.4-7.8 (2H), 6.4-7.9 (m, 3H,Ar-H), 6.45 (d, 1H), 6.77 (s, 1H,Ar-H), 7.73 (D, 1H), 11.8 (br, N-H. ES-MS *m/z* 446.0 (M^{+}+1, 100%).

Procedure for the preparation of dehydro compound in green procedure in microwave method (7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl) butoxy) quinolin-2(1H)-one), 2:
A mixture of compound **1 (**1.0 mol) , DMF (10 Vol), Tetrabutyl ammonium bromide (3.0 mol), KOH (5.0 mol) was irradiated by focused microwave at 150 °C for 30-45 min for product **2**. Completion of reaction was monitored by TLC. After the solid product filtered and product quenched in water then extracted with ethyl acetate. After complete distillation, crude so formed was purified by column chromatography Hexane: EtOAc (1:3) to afford pure compounds **2.**
Mp: 137-139 ^{o}C; IR (KBr) 3450, 1659, 1230, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.60-2.0 (m, 4H), 2.49 (t, 2H), 2.64 (br, 4H), 3.05 (br, 4H), 4.09 (t, 2H), 6.4-7.8 (2H), 6.4-7.9 (m, 3H,Ar-H), 6.45 (d, 1H), 6.77 (s, 1H,Ar-H), 7.73 (D, 1H), 11.8 (br, N-H. ES-MS *m/z* 446.0 (M^{+}+1, 100%).

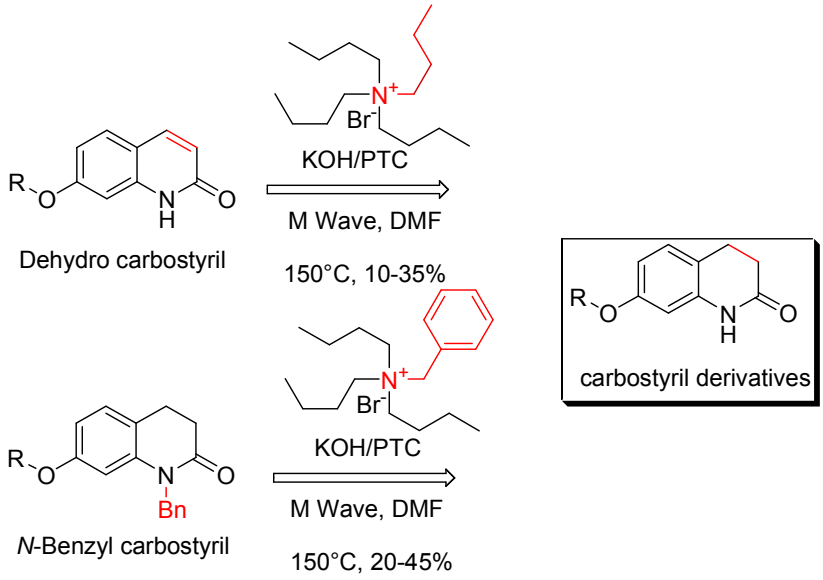
Procedure for the preparation of benzylated compound in green procedure in microwave method 7**-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-1-benzyl-3,4-dihydroquinolin-2(1H)-one, 5:**
A mixture of compound **1 (**1.0 mol) , DMF (10 Vol), Benzyl Tributyl ammonium bromide (3.0 mol), KOH (5.0 mol) was irradiated by focused microwave at 150 °C for 30-45 min for product **5**. Completion of reaction was monitored by TLC. After the solid product filtered and product quenched in water then extracted with ethyl acetate. After complete distillation, crude so formed was purified by column chromatography Hexane: EtOAc (1:5) to afford pure compounds **5.**
IR (KBr) 3434, 1677, 1234, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.3 (m, 2H), 7.3 (m, 2H), 7.15 (m, 2H), 7.05 (d, 1H), 6.95 (d, 1H), 6.45 (m, 2H), 5.2 (s, 2H), 3.2 (m, 4H), 2.97 (b, 1H), 2.9 (b, 2H), 2.7 (t, 2H), 2.4 (t, 2H), 2.4 (b, 2H); 2.4 (b, 2H), 1.7 (m, 2H), 1.5 (m, 2H). ES-MS *m/z* 538.2 (M^{+}+1, 100%).

Procedure for the preparation of dehydro compound in green procedure in microwave method 7-(4-bromobutoxy) quinolin-2(1H)-one, 7:
A mixture of compound **6 (**1.0 mol) , DMF (10 Vol), Benzyl Tributyl ammonium bromide (3.0 mol), KOH (5.0 mol) was irradiated by focused microwave at 150 °C for 30-45 min for product **7**. Completion of reaction was monitored by TLC. After the solid product filtered and product quenched in water then extracted with ethyl acetate. After complete distillation, crude so formed was purified by column chromatography Hexane: EtOAc (1:3) to afford pure compounds **7.**
IR : 1655 cm^{-1}. ^{1}H-NMR: 7.70-7.90 (d, 1H), 7.40-7.50 (d, 1H), 6.70 (m, 1H), 6.80 (d, 1H), 6.45-6.65 (d, 1H), 4.05 (t, 2H), 3.50 (t, 2H), 2.00 (m, 4H). Presence of exchangeable amide NH proton appeared at 12.40-12.60 (s, NH). ES-MS *m/z* 296 (M^{+}+1, 100%).

Procedure for the preparation of benzylated compound in green procedure in microwave method 1-benzyl-3,4-dihydro-7-hydroxyquinolin-2(1H)-one, 8:
A mixture of compound **4 (**1.0 mol) , DMF (10 Vol), Benzyl Tributyl ammonium bromide (3.0 mol), KOH (5.0 mol) was irradiated by focused microwave at 150 °C for 30-45 min for product **8**. Completion of reaction was monitored by TLC. After the solid product filtered and product quenched in water then extracted with ethyl acetate. After complete distillation, crude so formed was purified by column chromatography Hexane: EtOAc (1:5) to afford pure compounds **8.**

Results and discussions:
In general, the dehydrogenation & benzylation of 3,4-dihydro carbostyril (Aripiprazole) have been prepared by treatment of DDQ & Benzyl bromide methods but those procedures suffer from some drawbacks such as the handling of hazardous and highly lachromatric reagents, exact reaction-temperature control and evolution of toxic hydrogen bromide by quenching with water. As previously reported in conventional method TBAB/V_2O_5 or P_2O_5 generate tribromide and form bromination products followed by dehydro halogenation under basic condition [XXIV] give unsaturated products but Reactions of peroxometal intermediates well exploited to generate an active brominating species (Br_3) *in situ* which can also perform bromination of organic substrates very efficiently without compromising with the environmental acceptability.

Retro synthesis:

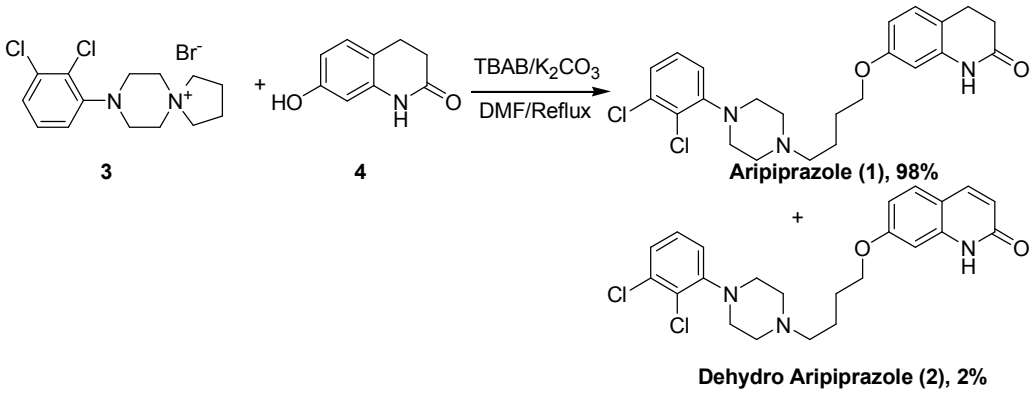


DEHYDROGENATION & BENZYLATION OF CARBOSTYRIL DERIVATIVES USING PTC UNDER MICRO WAVE USING GREEN METHODOLOGY
FIGURE-1
Herein, we wish to report a novel and facile 1) dehydrogenation using quaternary ammonium salt (TBAB/KOH) under microware condition at high temperature and 2) benzylation using benzyl quaternary ammonium salt (BTAB/KOH), here benzyl source is BTAB (**Figure-1**). Microwave conditions under basic conditions (KOH) quaternary ammonium salts (PTC) converted in to *tert*-amine and alkyl halide. In earlier paper we found Phase-transfer catalyzed β -elimination of HBr from trans-*β*-bromostyrene but dehrogenation using Phase-transfer catalyzed not yet reported hence under microwave conditions dehydrogenation of

carbostyril derivatives observed. Using benzylated Phase-transfer catalyzed under microwave form benzylated carbostyril derivatives

$$R_4N^+X^- \underset{\text{KOH/ 150°C}}{\overset{\text{M Wave, DMF}}{\rightleftharpoons}} R_3N + RX$$

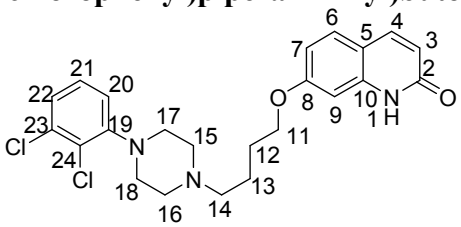
Our research on this starts with synthesis of Aripiprazole (psychotic drug). During the preparation of Aripiprazole in our lab (**Scheme-1**), one unknown impurity was detected in HPLC analysis at levels ranging from 1.0 to 2.0 %. The same unknown impurity was also observed in commercial batches. The unknown impurities have not been reported previously in the preparation of Aripiprazole as a bulk drug synthesis. This new impurity was isolated from crude sample of aripiprazole by preparative HPLC and co-injected with Aripiprazole sample to confirm the retention times in HPLC. This impurity was characterized as, 7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2(1H)-one. Structural elucidation, of this impurity by spectral data (^{1}H NMR, ^{13}C NMR, MS and IR) has been discussed.



Scheme for synthesis of aripiprazole conventional method
SCHEME- 1

Laboratory batches of aripiprazole were analyzed for their impurities identification using the HPLC and isolated by preparative HPLC. These samples were subjected to LC-MS/MS analysis and known impurities and isolated 7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl) butoxy) quinolin-2(1H)-one impurity were co-injected with aripiprazole to confirm the retention times. The impurity was well resolved from aripiprazole peak The chemical structures of impurity conformed by H^1-NMR, Mass, C^{13}-NMR, DEPT. the standard dehydrogenated impurity prepared in large scale using DDQ method and compared with isolated impurity and both spectral data matches.

Table 1
Comparative ^{1}H, ^{13}C (proton decoupled) and DEPT NMR assignments for aripiprazole and impurity 7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2(1H)-one.



Position	Aripiprazole			impurity		
	^{1}H, δ (ppm) Multiplicity	^{13}C, δ (ppm)	DEPT	^{1}H, δ (ppm) multiplicity	^{13}C, δ (ppm)	DEPT
1	10.0 (s, 1H)	--	--	11.8 (s, 1H)	--	--
2	--	170.1	--	----	162.3	---
3	2.4 (t, 2H)	29.3	CH2	6.8 (d, 1H)	121.5	CH
4	2.7 (t, 2H)	26.3	CH2	7.7 (d, 1H)	139.5	CH
5	----	128.3	---	----	110.7	---
6	7.2(d, 1H)	128.5	CH	7.5 (d, 1H)	127.2	CH
7	6.5(d, 1H)	109.9	CH	7.2 (d, 1H)	109.9	CH
8	----	157.7	---	---	159.7	--
9	7.3(s, 1H)	106.2	CH	7.15 (d, 1H)	117.4	CH
10	---	136.6	--	---	137.4	--
11	4.3(t, 2H)	68.4	CH2	4.2(t, 2H)	68.4	CH2
12	1.7(m, 2H)	27.3	CH2	1.9(m, 2H)	27.3	CH2
13	1.5(m, 2H	24.6	CH2	1.7(m, 2H)	24.6	CH2
14	3.9(t, 2H)	54.1	CH2	2.5(t, 2H)	54.1	CH2
15	2.9(Brad, 2H)	48.8	CH2	3.1(Brad, 2H)	48.8	CH2
16	2.9(Brad, 2H)	48.8	CH2	3.1(Brad, 2H)	48.8	CH2
17	2.4(Brad, 2H)	49.3	CH2	2.7(Brad, 2H)	49.3	CH2
18	2.4(Brad, 2H)	49.3	CH2	2.7(Brad, 2H)	49.3	CH2
19	------	150.0	--	------	150.0	--
20	6.4(d, 1H)	117.6	CH	6.5(d, 1H	117.6	CH
21	7.15 (t, 1H)	129.1	CH	6.8 (t, 1H)	129.1	CH
22	7.05(d, 1H)	123.9	CH	6.9(d, 1H)	123.9	CH
23	---	133.3	--	---	133.3	--
24	---	127.2	--	---	127.2	--

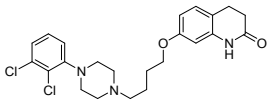
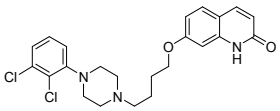
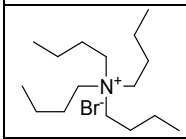
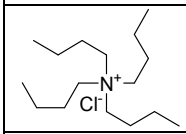
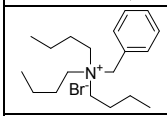
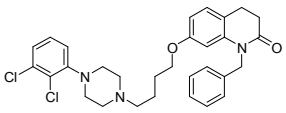
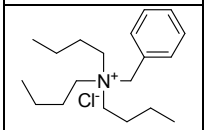
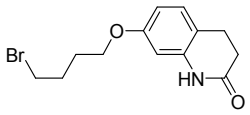
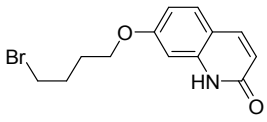
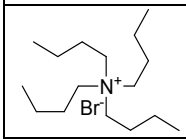
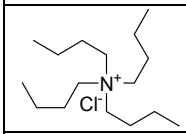
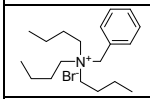
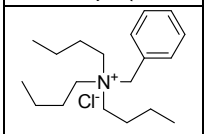
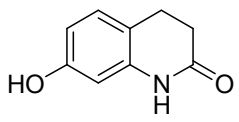
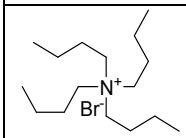
s, singlet; d, doublet; dd, doublet of a doublet; m, multiplet.

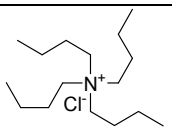
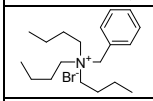
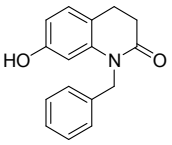
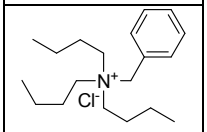
CHEMICAL STRUCTURES OF ARIPIPRAZOLE IMPURITIES
FIGURE- 2

Reason for formation of impurity not known, so some studies conducted in conversional methods using PTC but not enhanced impurity levels. Whereas the forced, drastic conditions like microwave, high basic, high temp, PTC used conditions results surprising results like high flurocent products (dehydrogenated) carbostyril derivatives using TBAB and benzylated products using Benzylated PTC like BTAB or BTAC. Dehydrogenated products all shows good florescence nature in UV light in TLC chamber. During purification of dehydrogenated products by column product contain fractions showy very high florescent nature. We focus on the role of PTC toward carbostyril derivatives under basic microwave conditions.

$$R_4N^+X^- \underset{\text{base/ High temp}}{\overset{\text{M Wave, Solvent}}{\rightleftharpoons}} R_3N + RX$$

From the above equations we focus on PTC (3.0 eq) role under microwave using KOH (5.0 eq)/DMF at reflux temperatures in green chemistry method and results are mentioned in below table

Entry	Substrate	PTC (3.0 Eq) ($R_4N^+ X^-$)	Products	Conventional	Micro wave
				Yield[a] (%)	
1	 **1**	None	 **2**	0	0
2				2.0	35
3				1.0	10
4			 **5**	--	45
5				--	20
6	 **6**	None	 **7**	0	0
7				--	15
8				--	10
9			No required product	--	--
10				--	--
11	 **4**	None	No required product	0	0
12				--	--

13				--	--
14				--	27
15		 **8**		--	20

a Yield after Isolated and purified by column

Aripiprazole react with phase transfer catalyst tetra butyl ammonium bromide or chloride in DMF solvent at reflux temperature using KOH as a base under microwave irradiation after 10-15 min observed highly fluorescent compound in TLC and the compound identified as aromatized quinoline type of dehydrogenated product, after isolation and purification by column observed 10-35% yields and structure conformed by NMR, Mass, C^{13},DEPT. but for this KOH and TBAB required high mole equivalence and more time 10-15 mints for better yield . Similarly same studies continued with other benzylated PTC benzyl tri butyl ammonium bromide and observed *N*-benzylated aripiprazole with isolated yield of 20-45% after column purification. Other intermediate bromo compound results dehydrogenated compound but benzylation not successful, 7-hydroxy carbostyril results N-benzylation with PTC but not give dehydrogenation products. The further studies on this chapter are underway in our lab.

Conclusion:

In conclusion, it must be admit that the results of our endeavour in the field of microwave assistant phase transfer catalysis on carbostyril compounds provided us a lead to develop a clean method for the synthesis of dehydro & benzylated carbostyril using quaternary ammonium salts capable of dehydrogenation & benzylation a wide derivatives of carbostyril organic substrates in a safer way.

Acknowledgements:

K C Babu thanks to JNTU & Buchi Reddy R, Madhusudhan G for there support.

References:

[I]. Tominaga, M.; Tone, H.; Nakagawa K.; Takada, K.; Hoshino, Y.; Watanabe, K. Chem. Pharm. Bull. **1981**, 29, 2166.

[II]. Nishi, T.; Yamamoto, K.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. Chem. Pharm. Bull. **1983**, 31, 798.

[III]. Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. Chem. Pharm. Bull. **1983**, 31,1151.

[IV]. Nishi, T.; Tabusa, F.; Tanaka, T.; Ueda, H.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. Chem. Pharm. Bull. **1983**, 31, 852.

[V]. Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu, T.; Nakagawa, K. Chem. Pharm. Bull. **1985**, 33, 1140.

[VI]. Tominaga, M.; Yo, E.; Ogawa, H.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. Chem. Pharm. Bull. **1984**, 32, 2100.

[VII]. Tominaga, M.; Ogawa, H.; Yo, E.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. Chem. Pharm. Bull. **1987**, 35, 3699.

[VIII]. Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G.M. R.; J. Med. Chem. **1988**, 31, 2048.
[IX]. Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.;Morris, D. S.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; J. Med. Chem. **1989**, 32, 575.
[X]. Fujioka, T.; Teramoto, S.; Mori, T.; Hosokawa, T.; Sumida, T.; Tominaga, M.; Yabuuchi, Y. J. Med. Chem. **1992**, 35, 3607.
[XI]. Uno, T.; Ozeki, Y.; Koga, Y.; Chu, G. N.; Okada,M.; Tamura, K.; Igawa, T.; Unemi, F.; Kido, M.; Nishi, T. Chem. Pharm. Bull. **1995**, 43, 1724.
[XII]. Tzeng, C. C.; Chen, I. L.; Chen, Y. L.;Wang, T. C.; Chang, Y. L.; Teng, C. M. Helv. Chim. Acta **2000**, 83, 349
[XIII]. Desos, P.; Lepagnol, J. M.; Morain, P.; Lestage, P.; Cordi, A. J. Med Chem. **1996**, 39, 197
[XIV]. Tzeng, C. C.; Wang, T. C.; Chen, Y. L.; Wang, C. J.; Chang, Y. L.; Teng, C. M. Helv. Chim. Acta **1997**, 80, 1161.
[XV]. Wang, T. C.; Chen, Y. L.; Tzeng, C. C.; Liou, S. S.; Tzeng,W. F.; Chang, Y. L.; Teng, C. M. Helv. Chim. Acta **1998**, 81, 1038.
[XVI]. Chen, Y. L.; Wang, T. C.; Fang, K. C.; Chang, N. C.; Tzeng, C. C. Heterocycles **1999**, 50, 453.
[XVII]. Chen, Y. L.; Wang, T. C.; Chang, N. C.; Chang, Y. L.; Teng, C. M.; Tzeng, C. C. Chem. Pharm. Bull. **1998**, 46, 962.
[XVIII]. Chen, Y. L.; Wang, T. C.; Liang, S. C.; Teng, C. M.; Tzeng, C. C. Chem. Pharm. Bull. **1996**, 44, 1591.
[XIX]. Liao, C. H. ; Tzeng, C. C. ; Teng, C.M. Eur. J. Pharmacol. **1998**, 349, 107.
[XX]. DMP Mingos;,Chem. Ind.; **1994;** 596-599.
[XXI]. A Hoz de la; A Dfaz; A Moreno; Chem. Soc. Re; **2005;** 34; 164-178.
[XXII]. (a) RN Gedye; JB Wei; Can. J. Chem.; **1998;** 76, 525–527. (b) RS Varma; Green Chem.; **1999;** 1; 43–55.
[XXIII]. (a) DMP Mingos; AG Whittaker; RV Van; C Malik; D. Hubbard; John Wiley and Sons and Spektrum Akademischer Verlag Co- Publication, New York and Heidelberg, **1997**, 479.(b) DMP Mingos; DR Baghurst ; HM Kingston; SJ Hazel; ACS, Washington D. C., **1997**, 455.
[XXIV]. (a) M Nuchter; B Ondruschka; A Jungnickel; U Muller; J Phys. Org. Chem.; **2000;**13; 579–586. (b) M Nuchter; B Ondrushka; W Lautenschlager; Synth. Commun; **2001;** 37; 1277-1283.
[XXV]. JW Vanderhoff; U. S. 3; **1969;** 432- 413; Chem. Abstr. **1969;** 70; 97422v.
[XXVI]. R Gedye; F Smith; K Westaway; H Ali; L Baldisera; L Laberge; J Rousell; Tetrahedron Lett.; **1986;** 27; 279–282.
[XXVII]. RJ Giguere; TL Bray ; SM Duncan; G Majetich; Tetrahedron Lett.; **1986;** 27; 4945–4948.

Received on 2 March 2015.