8 Application of Phase-Transfer Catalysis in the Synthesis of Esters of Some Spasmolytically Active Gamapiperaziny Proponols

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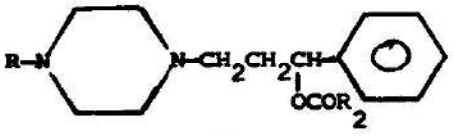
ABSTRACT

The principles of phase-transfer catalysis was applied for the synthesis of some Gamma-piperazinyl propanols of general formula I, which were synthesized for the purpose of studying the



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influence of esterification on their spasmolytic activity. It was found out that, esters of this type can be obtained in very good yields, utilizing the solid-liquid phase-transfer catalyzed (PTC) conditions and not the liquid-liquid PTC conditions. The method and conditions for their successful syntheses are described in this paper.

Key Words - Gamma-piperazinyl alcohols; spasmolytic activity; phase-transfer-catalysed (PTC) esterification procedures; solid-liquid PTC conditions.

INTRODUCTION

Gamma-amino alcohols are very well known for their various pharmacological activities, among which is their activity as spasmolytics (1,2,3,4). Earlier on, we had synthesized a group of gamma - amino alcohols of piperazine series (5) for the purpose of studying the variation of spasmolytic activities among them. Our interest became drawn to what would be the possible effect of esterification of the alcoholic function of these compounds. In search of a suitable synthetic method for these esters, we discovered that they were mostly unknown in literature except the 1, 4 bis product (6) obtained by esterification with acetyl chloride but the yield obtained by the authors above using the normal esterification procedure was not specified.

Theory. The normal method of obtaining esters of carboxylic acids is with either the acids, acid chlorides or the anhydrides (7). Of the above mentioned three methods, the use of the acid chlorides is the most common and the most convenient. However, the use of this normal esterification process is not often particularly effective for many reasons:- there could exist other functionality or compounds that are sensitive to the acidic conditions of the standard procedure (8); product formation may proceed very slowly, which is normally the case when sterically hindered acids or bulky alcohols are in use (9); and in addition the acid - ester equilibrium may be unfavourable (10). Moreover there are also instances when the incoming alcohols can react with the by-product of the normal esterification procedure, HCl, to form stable intermediates.

In order to avoid these problems, convenient ester syntheses using such bases as tertiary amines (like N,N dimethylamine [11,12] and pyridine) and magnesium metal (13) has been reported, in which case the base reacts with the hydrogen chloride being formed. However, the above method requires operating under strictly anhydrous conditions because of the possibility of hydrolysis of the acylating agent.

Several other approaches to esterification have been advanced, but they all have their own limitations either in requiring additional synthetic and purification steps, or in leading to decrease in yield, convenience and/or generality (14,15,16).

The most recent approach to the avoidance of the problems of the normal esterification procedures is by the use of the principles of the phase-transfer catalysis (PTC) (17). This was successfully used in the synthesis of carboxylic acid esters, utilising nucleophilic substitution with the carboxylate anion.

Szeja (18), working on the phase-transfer catalyzed synthesis of esters of carboxylic acids of general formula-R_2-CH(R_1)(COOH), where, R_1 = CH_3 and R_2 = phenyl group, found out that esters

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TABLE 1

No	R_1	R_2	Solvent used	Rxn time (mins)	Mol. ratio alc:cat: a/c	Yield %	M.P°C
1	2	3	4	5	6	7	8
I	CH_3	CH_3	$CHCl_3$	120	1:0.2:1.5	90	187
II	CH_3	C_2H_5	$CHCl_3$	210	1:0.2:1.5	94	212
III	CH_3	C_6H_5	$CHCl_3$	210	1:0.2:1.7	96.5	-
IV	CH_3	$C_6H_5CH_2$	$CHCl_3$	240	1:0.2:1.9	92	-
V	$C_6H_5CH_2$	CH_3	CH_2Cl_2	210	1:0.2:1.7	91.5	222
VI	$C_6H_5CH_2$	C_6H_5	CH_2Cl_2	210	1:0.2:1.7	93	228
VII	$C_6H_5CH_2$	C_6H_5	$CHCl_3$	90	1:0.2:1.7	96	230-2
VIII	$C_6H_5CH_2$	$C_6H_5CH_2$	$CHCl_3$	90	1:02:1.7	92	235-7
IX	$(C_6H_5)_2CH$	C_2H_5	$CHCl_3$	120	1:0.2:1.5	91	-
X	$(C_6H_5)_2CH$	$C_6H_5CH_2$	$CHCl_3$	120	1:0.2:1.7	98.5	80-6
XI	$PhCH(CH_2)_2$ $\vert$ $OCOR_2$	CH_3	CH_2Cl_2	210	1:02:3.5	94	232-4
XII	$PhCH(CH_2)_2$ $\vert$ $OCOR_2$	C_2H_5	$CHCl_3$	180	1:0.2:3.6	92.5	223-4
XIII	$PhCH(CH_2)_2$ $\vert$ $OCOR_2$	C_6H_5	$CHCl_3$	100	1:0.2:3.6	93	220-1
XIV	$PhCH(CH_2)_2$ $\vert$ $OCOR_2$	$C_6H_5CH_2$	$CHCl_3$	120	1:0.2:3.4	93	134-6

alc.= alcohol, cat=catalyst, a/c =acyl chloride. Yields refer to those of the raw products, chromatographically devoid of the alcohol. M.Ps given refer to those of the dihydrochloride salts (with the exception of compounds X and XIV, where those of the bases are given). The 2HCl salts melt with decomposition.

TABLE II

No	H^1NMR Spectral Analysis
II	7.30(s,5H,Ph);5.76(t, H,CH-O);1.00(t,3H,CH_3CH_2); 2.00(m,14H,CH_3N+ CH_2O+CH_2CH_2CH)NCH_2)
V	7.30(s,10H;Ph);5.76(t,1H,CH-O);3.44(t,2H,$PhCh_2$); 1.90(s,3H,CH_3);2.30(s,12H,CH_2-).
VI	7.22(s,10H,Ph);5.78(t,1H,CH-O);3.40(s,2H,$PhCH_2$); 2.12(m,14H,CH_2);1.04(t,3H,CH_3CH_2).
VII	8.00(d,2H,PhCO);7.24(m,13H,Ph);6.00(t,1H,PhCH); 3.44(s,2H,$PhCH_2N$ 2.25(s,12H,CH_2)
VIII	7.22(s,15H,Ph);3.20(s,2H,CH_2OO);3.22(s,2H,NCH_2Ph); 2.10(m,12H;NCH_2); 5.80(t,1H,CH-O);
X	7.20(m,20H;Ph);5.74(t,1H,CH-O);2.12(s,1H,$(Ph)_2CH$); 3.45(s,2H; CH_2CO);2.20(m,12H,N-CH_2):
XI	2.00(s,6H,CH_3CO);2.28(q,4H,CH_2CH_2CH);3.16(t,4H,CH_2N); 3.64(s,8H,CH_2-ring); 5.16(t,2H,PhCH-O);7.32(s,10H,Ph);
XII	7.32(s,10H,Ph);5.76(t,2H,CH-O);2.10(m,20H,CH_2); 1:04(t,6H,CH_3)
XIII	8.00(m,4H,PhCO);7.32(m,16H,Ph);2.40(m,16H,CH_2); 6.00(t,2H,CH-O).
XIV	7.24(s,20H,Ph);5.80(t,2H,CH-O);3.54(s,4H,CH_2CO); 2.20(m,16H,CH_2).

of carboxylic acids can be obtained in high yields, if the reactions of primary and secondary alcohols with acetic anhydride or acetyl, propanoyl or benzoyl chloride is carried out under the liquid-liquid PTC conditions, while the less reactive tertiary alcohols are esterified in good yields using the solid-liquid PTC procedures.

EXPERIMENTAL METHODS

(1) LIQUID - LIQUID PTC PROCEDURE.

The materials involved are secondary gamma-amino alcohol, benzyl triethylammonium chloride (catalyst), acyl Chloride, an organic solvent (chloroform, dichloromethane) and 30% solution of sodium hydroxide (Liquid phase).

Procedure: A mixture of 30 NaOH, benzyltriethylammonium chloride and the parent alcohol was stirred at room temperature (20°C), and a solution of the acylating agent (as the case may be) in chloroform was added in portions; stirring was continued for 2-3 hours. After the third hour, the temperature was increased to 30°C and stirring was continued at this temperature for 30 mins.

The organic phase was separated from the water phase in a separating funnel and washed 3-4 times with water in order to get rid of the catalyst. Washing was continued until a neutral solution was obtained (ascertained by using indicator).

The organic phase was then subjected to TLC to determine the extent of esterification.

(2) SOLID-LIQUID PTC

The major materials involved are anhydrous sodium carbonate as the solid phase, the parent sec. alcohol; and acyl chloride, organic solvent (same as in above), benzyltriethylammonium chloride (catalyst).

Esterification of 1-substituted 4-(3-phenyl-3-hydroxylpropyl piperazine:-

A mixture of the alcohol (2-3g), benzyltriethylammonium chloride (0.24 - 0.3g) and anhydrous Na_2CO_3 in 35 - 40ml of dischloromethane or chloroform were treated under stirring, with a solution of the acyl chloride in the same organic solvent, for periods of up to 4 hours (Note - routine TLC analysis was done at intervals to determine the time of full conversion of the alcohol to ester). After the cooling of the mixture the solids were filtered off and washed with the organic solvent. The organic layer was washed with 25ml of water 3 - 4 times and dried with anhydrous Na_2SO_4 for two days. Purification (where necessary) was achieved either by recrystallisation (from ethanol) of the solid base formed after evaporation of the solvent or by conversion of the oily base to their dihydrochloride salts.

RESULTS AND DISCUSSIONS

Table I shows the results of the various reactions and the reaction conditions for successful preparations of the compounds shown, while table II shows the H^o NMR spectral analysis of some of the compounds.

Since the present work involves the esterification of much more bulkier secondary alcohol than those investigated by Szeja (18), a preliminary investigation was done using a prototype of this series-1-benzhydryl-4-(γ-phenyl-γ-hydroxyl propyl) piperazine. The benzoylation of this alcohol was first examined under the liquid-liquid PTC conditions (as described by SZEJA) using benzyltriethylammonium chloride as the catalyst at O°C, the molar ratio of the alcohol: catalyst: benzoyl chloride being I:0.2:I.4. Using chloroform as the organic solvent and after vigorous stirring for 10 mins., only a small amount of the ester was formed. Vigorous agitation was continued, and samples of the reaction mixture were taken at 20,30,40,50,60,70,90 and120 mins for TLC analysis. It was found out that greater part of the alcohol remained unconverted even after two hours. Raising the reaction temperature did not appear to have improved the yield. On increasing the molar concentration of the benzoyl chloride to 1.7 (while the concentration of the other components remained the same) an improvement in yield was observed, although full conversion of the alcohol still could not be obtained.

On resorting to solid-liquid conditions, using anhydrous sodium carbonate as the solid phase, chloroform or dichloromethane as the organic solvent, benzyltriethylammonium chloride as the catalyst, excellent results were obtained for the compounds synthesized. Complete conversions of the alcohols were observed at reaction times of 120-240 min, depending on the solvent used, the molar ratio of the reaction components and the alcohol itself.

CONCLUSION

It was seen that the reaction conditions of the liquid-liquid PTC esterification procedure are sufficient only for the esterification of low-molecular weight alcohols, devoid of sterically sensitive or bulky groups. Bulkily substituted secondary alcohols,like the type studied in this work require more stringent reaction conditions of the solid-liquid PTC, that is normally used for the less reactive tertiary alcohols (18). The products obtained are new(except one) and were obtained in very good yields.

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