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# SIDE CHAIN BROMINATION OF 3, 4-DIHYDROPYRIMIDINES USING PHENYLTRIMRTHYLAMMONIUM TRIBROMIDE

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**ABSTRACT**

Phenyltrimethylammonium tribromide (PTAB), a stable, crystalline organic ammonium tribromide (OATB), has been used as an alternative electrophilic bromine source for the bromination of methyl group at C-6 position of 3, 4-dihydropyrimidin-2(1H)-thiones and 3, 4-dihydropyrimidin-2(1H)-methylthiols.

**Keywords:** Phenyltrimethylammonium tribromides, 3, 4-dihydropyrimidine, 6-bromomethyl dihydropyrimidines, bromination.

## INTRODUCTION

Pyrimidinones or 3, 4-Dihydropyrimidin-2(1*H*)-thiones (DHPMs) are well known for their wide range of bioactivities and their applications in the field of drug research. This fact has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations. DHPM nucleus with structural variations in the aromatic ring at 4-position as well as the modification of basic pyrimidine skeleton at 2, 3, 5 and 6- positions are known as calcium channel blockers. These dihydropyrimidines have found widespread use in cardiovascular medicine (antihypertensive activity) and have also served as important tools for the study of calcium channel structure and function.[1-3]

In general, acetoacetates are employed in the Biginelli reaction and therefore in most cases a methyl group is placed at the C-6 position of the pyrimidine ring. Functionalization of this methyl group is easily achieved by bromination. There is a wide utility of bromomethyl compound for making functionalized DHPMs nucleus at C-6 position.[4] Functionalization of DHPMs nucleus at C-6 position has been carried out with bromine in acetic anhydride[5], bromine in water[6-7], bromine in DMF[8], N-bromosuccinimide[9], dioxane dibromide.[10] Polymer-supported brominating reagent,[11] and with lithium bromide in presence of ceric ammonium nitrate (CAN)[12-14], bromination of other positions of the pyrimidinone ring has been carried out with phosphorus tribromide[15], through substitution of the carbonyl oxygen by the bromine atom. On the other hand, phenyltrimethylammonium tribromide (PTAB) has been found to be much easier to handle and it maintains the desired stoichiometry in comparison with bromine. The use of PTAB was more advantageous and attractive than that of $Br_2$ in organic synthesis. Hence in this present work, we wish to report a novel methodology for the facile and direct substitution of bromine at C-6 position of DHPMs under mild conditions (Fig.1).

## EXPERIMENTAL

### General Procedure

A reaction mixture of appropriate DHPM (1 mmol) and PTAB (1.5mmol) in $CH_2Cl_2$ (10 mL) was refluxed for time mentioned in Table 2. The reaction mixture soon turned reddish in color and the progress of the reaction was monitored by TLC. After 30 minute of refluxed, solution of $CHCl_3$ (2X10 mL) and water (2X10 mL) was added to cooled reaction mixture. The organic layer was separated from the resulting reaction mixture using separating funnel. The combined organic layer concentrated under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether-ethyl

acetate) to give the corresponding side chain bromination of methyl group at C-6 position of DHPMs in good yield.

**Spectral Analysis**

All reagents were obtained commercially and used without further purification. NMR spectra were recorded at 400 ($^1$H) and 100 ($^{13}$C) MHz, respectively, spectral analysis $^1$H NMR spectra of the products showed a characteristics peak singlet due to two equivalent proton of $CH_2$ group around δ 4.1-4.5 ppm .

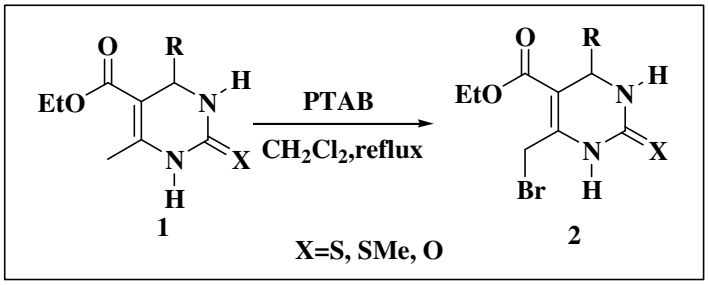


Fig.-1: The general scheme of bromination of DHPMs

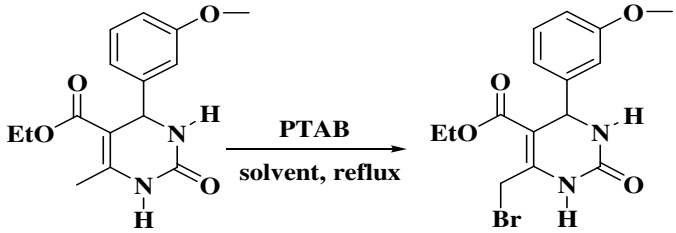


Fig.-2: Reactions of ethyl 1,2,3,4-tetrahydro-4-(3-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate with PTAB: Formation of ethyl 6-(bromomethyl)-1,2,3,4-tetrahydro-4-(3-methoxyphenyl)-2-oxopyrimidine-5-carboxylate

Table -1: Optimization of reaction condition

| Entry | Solvent | Reaction time (min) | Yield (%) |
|---|---|---|---|
| 1 | $CH_3CN$ | 20 | 68 |
| 2 | MeOH | 25 | 65 |
| 3 | $CH_3COCH_3$ | 15 | 70 |
| 4 | $CH_2Cl_2$ | 30 | 84 |

Table-2: Side chain bromination of methyl group at C-6 position of 3,4-dihydropyrimidin-2(1H)-thiones and 3,4-dihydropyrimidin-2(1H)-methylthiols using PTAB in $CH_2Cl_2$

| Entry | DHPM | X | R | Product | Reaction Time (min) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 1a | S | $C_6H_5$- | 2a | 35 | 82 |
| 2 | 1b | S | 4-$ClC_6H_4$- | 2b | 30 | 81 |
| 3 | 1c | S | 3-$O_2NC_6H_4$- | 2c | 35 | 78 |
| 4 | 1d | S | 3,4-$(MeO)_2$ $C_6H_3$ | 2d | 35 | 75 |
| 5 | 1e | S | 4-$MeOC_6H_4$ | 2e | 30 | 75 |
| 6 | 1f | O | 4-$ClC_6H_4$- | 2f | 20 | 80 |
| 7 | 1g | O | 3-$O_2NC_6H_4$- | 2g | 30 | 78 |
| 8 | 1h | O | 3,4-$(MeO)_2$ $C_6H_3$ | 2h | 30 | 75 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | 3a | SMe | 4-$MeOC_6H_4$- | 4a | 35 | 80 |
| 10 | 3b | Sme | 3,4,5-$(MeO)_3$ $C_6H_2$- | 4b | 45 | 79 |
| 11 | 3c | SMe | $(CH_3)_2$ $CHCH_2$- | 4c | 30 | 82 |
| 12 | 3d | Sme | $C_6H_5$- | 4d | 35 | 80 |
| 13 | 3e | Sme | 3-$O_2NC_6H_4$- | 4e | 40 | 78 |
| 14 | 3f | Sme | 4-MeC6H4- | 4f | 35 | 80 |

## RESULTS AND DISCUSSION

The reaction conditions were optimized by investigation of the model bromination of methyl group at C-6 position of 1f using various solvent. The reaction of 1f with PTAB in different solvents such as $CH_3CN$, MeOH, $CH_3COCH_3$ was screened and results are summarized in Table 1. The side chain bromination of methyl group at C-6 position of 1f using $CH_3CN$, MeOH, $CH_3COCH_3$ did not produce the brominating product in satisfactory yield. The $CH_2Cl_2$ was found to be most suitable solvent for the conversion of 1f to 2f in 84 % yield (fig.2) .Thus with the success in the above reaction we extend this reaction to several DHMPs with different substituent at C4 position with high yield of the products and results are summarized in Table 2.

## CONCLUSION

In conclusion, we demonstrated the use of solid brominating agent PTAB for the efficient bromination of methyl group at C-6 position of 3, 4-dihydropyrimidin-2(1H)-thiones and 3, 4-dihydropyrimidin-2(1H)-methylthiols (DHPMs). Mild reaction conditions, high yields of the products and experimental simplicity make it a practical alternative.

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