

SYNTHESIS OF NOVEL PHOSPHONIUM TRIBROMIDE AND ITS APPLICATION AS A CATALYST IN THE ONE-POT SYNTHESIS OF HIGHLY FUNCTIONALIZED PIPERIDINES

Abstract

Green chemistry is a chemical research and engineering concept that promotes the development of products and processes that reduce the usage and manufacture of hazardous substances. The current study concentrated on the synthesis of poly-functionalized piperidines at room temperature utilizing a green catalyst (tribromide) rather than a metal catalyst. By oxidizing bromide to tribromide with sodium hypochlorite, a variety of unique phosphonium tribromides were synthesized from matching phosphonium bromides. Different analytical techniques were used to characterize the synthesized tribromide. The most stable phosphonium tribromide was discovered to be (1-propyl) triphenyl phosphonium tribromide. As synthesized, (1-propyl) triphenyl phosphonium tribromide was proven to be an excellent catalyst for the one-pot synthesis of highly substituted piperidines in ethanol at room temperature employing a combination of 1,3-dicarbonyl compounds, aromatic aldehydes, and different amines. This protocol's key properties include atomic economy, high yields, and mild reaction conditions.

Keywords: Green Chemistry, phosphonium tribromide, bromination, organic ammonium tribromides, functionalized piperidines.

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I. INTRODUCTION

Green chemistry is the improvement of synthetic techniques that do not pollute the environment while simultaneously reducing its cost [1]. Organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, physical chemistry, and even chemical engineering are all part of green chemistry. Tribromides reagents, particularly organic ammonium tribromides, OATBs, are crucial in organic synthesis for a variety of functional group transformations, particularly as mild brominating agents. Because of the increased commercial importance of bromo organics in the synthesis of numerous organic products, as well as the creation of medicines, agrochemical products, as well as other specialized chemicals, the bromination of organic substrates has attracted great attention in recent years. Pesticides, fire retardants, insecticides, herbicides, and other new compounds all have Bromo functionality[2].

Under high reaction conditions, traditional bromination techniques involve the direct or indirect application of elemental bromine. The classic reagent bromine was combined with several new techniques, such as phase-disappearing technologies and fluoros solvents, to improve efficiency and selectivity[3].

However, because bromine is toxic, precautions must be taken when storing and transporting it. Furthermore, elemental bromination of aromatic substrates, which involves an electrophilic aromatic substitution process with the generation of HBr as a byproduct, effectively decreases the efficiency of the atom to 50%. Before it may be discharged as effluent, the HBr waste must be neutralized. To address these issues, some environmentally safer approaches including *in situ* synthesis of positive bromonium species via bromide ion oxidation with suitable oxidants under different homogeneous and heterogeneous reaction conditions have been proposed[4].

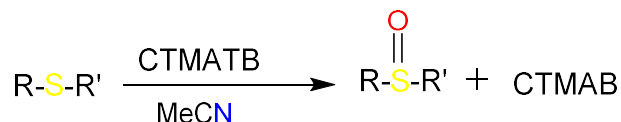
The benefits of OATBs are their crystalline nature, ease of handling, and ability to retain the desired stoichiometry. Organic ammonium tribromides (OATBs) include tetramethylammonium tribromide (TMATB), tetraethylammonium tribromide (TEATB), tetrabutylammonium tribromide (TBATB), benzyl trimethylammonium tribromide (BTMATB), cetyltrimethylammonium tribromide (CTMATB), pyridine hydrobromide perbromide (PyHBPB), etc. These organic ammonium tribromides were employed in a variety of chemical reactions, including dithioacetal deprotection [5], carbonyl compound conversion to 1,3-oxathiolanes, and vice versa [6]. However, their synthesis generally contains elemental bromine and, in some cases, HBr, which are hazardous and pollute the environment.

Tetrabutylammonium tribromide, having the formula $[\text{N}(\text{C}_4\text{H}_9)_4] \text{Br}_3$, is a pale orange solid. It is a salt of the linear tribromide anion and the lipophilic tetrabutylammonium cation. As a readily weighable solid source of bromine, salt is commonly utilized as a reagent in organic synthesis. The compound is prepared by treatment of solid tetrabutylammonium bromide with bromine vapor [3].

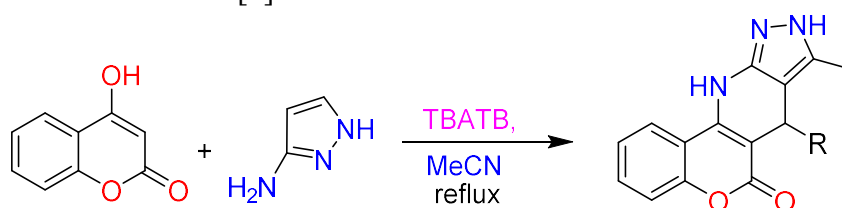


Organic ammonium tribromides have been utilized as catalysts and/or reagents in various synthetically significant reactions. A few examples are provided below:

Cetyl trimethyl ammonium tribromide (CTMATB) might be suitable for sulfide oxidation [7].



Synthesis of densely functionalized dihydro[4, 3-b]pyrazole[4,3-e]pyridine-6(7H)-ones as shown in scheme below[8].



Following the fruitful production of this novel reagent, it is critical to investigate the compound's efficiency as a reagent or catalyst in synthetically relevant transformations. It should be noted that protecting reactive hydroxyl groups is critical in multistep processes for the production of polyfunctional molecules. Silylation is one of the most frequent and simple ways for protecting hydroxyl and thiol groups by converting them into equivalent silyl ethers. A novel synthetic procedure for the synthesis of OATBs in solvents was also introduced. The latest ongoing synthetic green methodology for the solvent-free synthesis of organic ammonium tribromides (OATBs) is reported by reacting the respective organic bromides with hydrogen peroxide as an oxidant in the presence of a tiny amount of sulphuric acid.

These tribromides have served as catalysts/reagents in various organic green transformations [9]. Several homogeneous and heterogeneous catalytic approaches for the production of functionalized piperidines have recently been found. TBATB and a plethora of other catalysts are among them. Due to the tribromide reagent's unusual features, it would be an excellent catalyst for the one-pot synthesis of highly functionalized piperidines from the reaction of 1,3-dicarbonyl compounds, aromatic aldehydes, and amines. In this regard, we report phosphonium-1-propyl ammonium tribromide reagent (catalyst) used in a one-pot (single step) multi-component reaction (MCR) leading to yield highly functionalized piperidine derivatives.

MCRs are a form of convergent reaction in which three or more diverse starting materials react to produce highly selective products in a one-pot method. These are more likely to be a succession of bimolecular reactions. Owing to its significance over traditional multistep synthesis, multicomponent reactions (MCRs) have emerged as efficient and potent techniques in current synthetic organic chemistry for the production of unique and complex molecular structures [10-12]. MCRs provide various advantages, including lower pricing, faster reaction times, great atom economy, energy savings, and the elimination of time-consuming and expensive purification operations[13-14]. It is a fact that MCRs are often

significantly more environmentally benign, providing quick access to huge compound complexes with different capabilities while avoiding protection and deprotection.

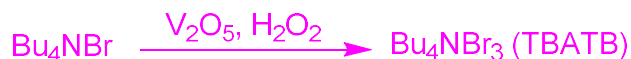
One-pot multicomponent reactions with three different starting materials, such as 1,3-dicarbonyl compounds, aldehydes, and nucleophilic compounds, have risen in popularity in recent years due to their ability to produce several condensation products based on the specific conditions and structures of the building blocks [17]. 1,3-dicarbonyl derivatives are important synthetic intermediates among carbonyl compounds because they contain multiple functionalities that can be used as electrophilic or nucleophilic species in various reactions to create complex heterocyclic structures such as poly-functionalized piperidine derivatives.

Natural alkaloids and manufactured medications both contain poly-functionalized piperidines [18]. Polyfunctionalized heterocyclic compounds play critical roles in drug discovery and research. Piperidine structural motif compounds have antihypertensive [19], antibacterial [20], antimalarial [20], anticonvulsant, and anti-inflammatory activities [21], are therapeutic agents in the curing of influenza infection [22-23], metastasis of cancer [24], and take part key roles in many disease treatment [25-26]. Recently, L-proline/tetrahydrofuran (THF), InCl_3 , bromodimethylsulfonium bromide (BDMS), tetrabutylammonium tribromide (TBATB), iodine, cerium ammonium nitrate (CAN), and $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as a catalyst was used to synthesize functionalized piperidines [27-28]. On the contrary, the use of organic catalysts in organic synthesis has gotten a lot of attention because of their significant advantages, such as the ability to perform reactions in the presence of acid-sensitive substrates, the ability to perform reactions under mild reaction conditions, and selectivity [29].

Organic phosphonium tribromides are chemical analogs of organic ammonium tribromides, and their characteristics are expected to be similar. While organic ammonium tribromides have grown in popularity in recent years, with several reports available discussing their importance in various types of organic transformations, phosphonium tribromides do not appear to have received the same level of attention. Nonetheless, these chemicals demand further exploration, particularly because they are said to be less reactive than organic ammonium tribromides. As a result, efforts were made to synthesize such phosphonium tribromide and subsequently study its reactivity profile. As a result, investigating organic phosphonium tribromide as a novel tribromide-based catalyst for the multicomponent synthesis of functionalized piperidines is desirable.

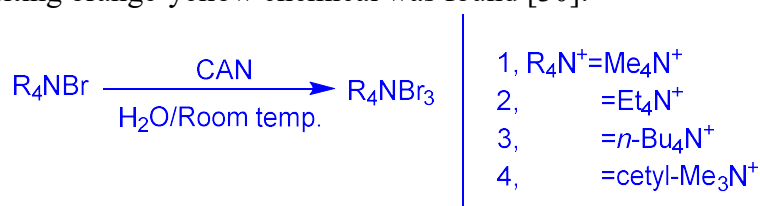
II. HISTORICAL BACKGROUND

Chaudhuri et al. synthesized organic ammonium tribromides in an environmentally friendly manner. They dissolved, V_2O_5 in H_2O_2 while stirring in a normal reaction condition. Water was added to the red solution of tetrabutylammonium bromide, and the reaction was stirred at room temperature. They observed that the reaction proceeded quickly, and the solution turned yellow with the simultaneous precipitation of yellow or orange-yellow tetrabutylammonium tribromide (TBATB), Bu_4NBr_3 . After 15-20 minutes, the product was isolated, washed twice with water, and air-dried [3].



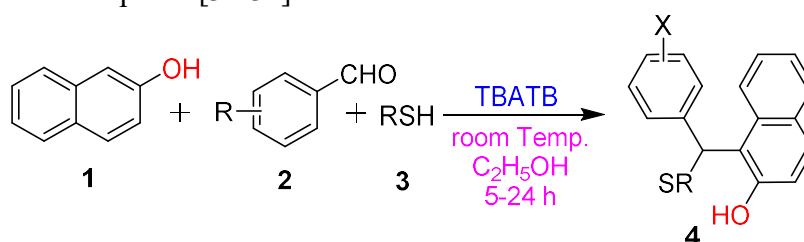
Scheme 1: Organic ammonium tribromide synthesis using V_2O_5 in H_2O_2 .

Borah *et al.* synthesized tetraalkylammonium tribromide in water by oxidizing cerium (IV) ammonium nitrate (CAN). In this approach, tetraalkylammonium tribromides were made by combining a CAN solution and a tetraalkylammonium bromide solution in water at room temperature. Stirring continued for 15 minutes after the CAN solution was added. By filtering, the resulting orange-yellow chemical was found [30].



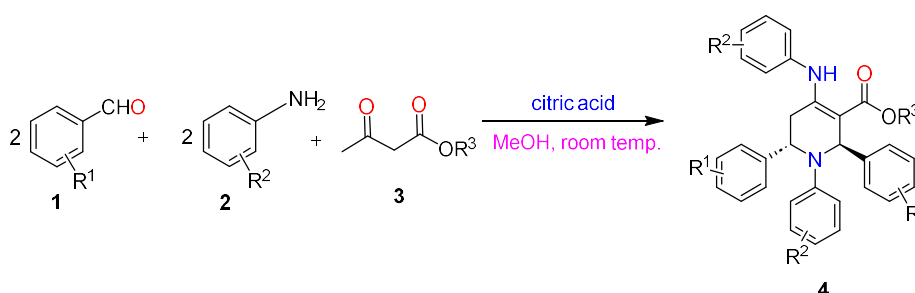
Scheme 2: Synthesized tetraalkylammonium tribromide by using cerium (IV) ammonium nitrate (CAN) as an oxidizing agent in water.

Dar *et al.* synthesized unsymmetrical sulphides by reacting 2-naphthoquinone-1-methide intermediates with thiols in the presence of a catalytic quantity of n-tetrabutylammonium tribromide (TBATB). The synthesized unsymmetrical sulfide can be employed as a mercury(II) ion selective fluorescent probe [31-32].



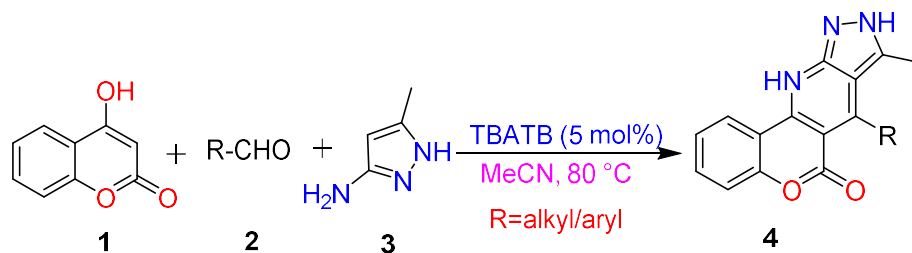
Scheme 3: One-pot three component reaction for the synthesis of unsymmetrical sulfides.

Madanifaret *et al.* employed citric acid as a green and efficient catalyst in the one-pot, multi-component synthesis of substituted piperidines by condensation of aromatic aldehydes, aromatic amines, and β -ketoesters in MeOH at room temperature. This approach has various advantages, including the use of a nonhazardous and low-cost catalyst, simple set-up, clean reaction conditions, and excellent yields [33].



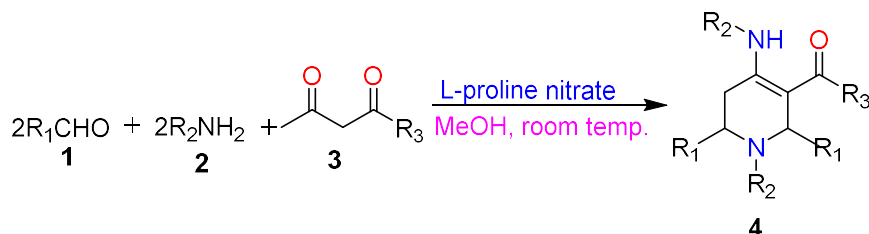
Scheme 4: At room temperature, piperidines are synthesized in MeOH with citric acid as a green catalyst.

Ghosh *et al.* synthesized dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones were synthesized in acetonitrile utilizing a one-pot three-component reaction involving 4-hydroxycoumarin, aldehydes, and 3-amino-5-methyl-pyrazole using a catalyst of 5% TBATB. The product is formed by a tandem Knoevenagel-Michael reaction followed by concurrent cyclization. The presented methodology by Ghosh *et al.* has several notable properties, including a simple reaction procedure, a faster reaction time, acceptable yields, and column chromatographic separation [34].



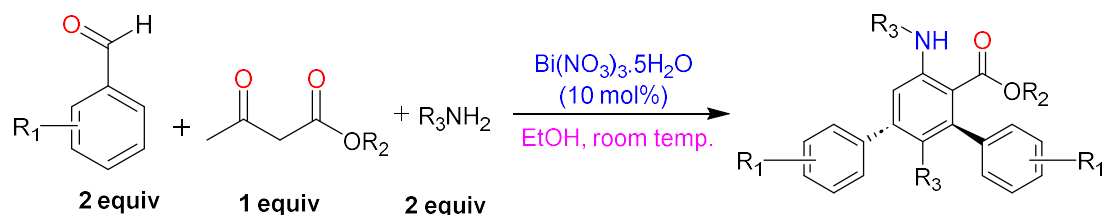
Scheme 5: The synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones.

Agarwal *et al.* recently synthesised highly functionalized piperidines using an organo-catalytic three-component (in situ five-component) reaction of an amine, aldehyde, and 1,3-dicarbonyl molecule. This multi-component imine synthesis was carried out using entirely green L-proline nitrate as a recyclable room-temperature ionic liquid. The catalyst could be recycled up to five times without losing its activity [28].



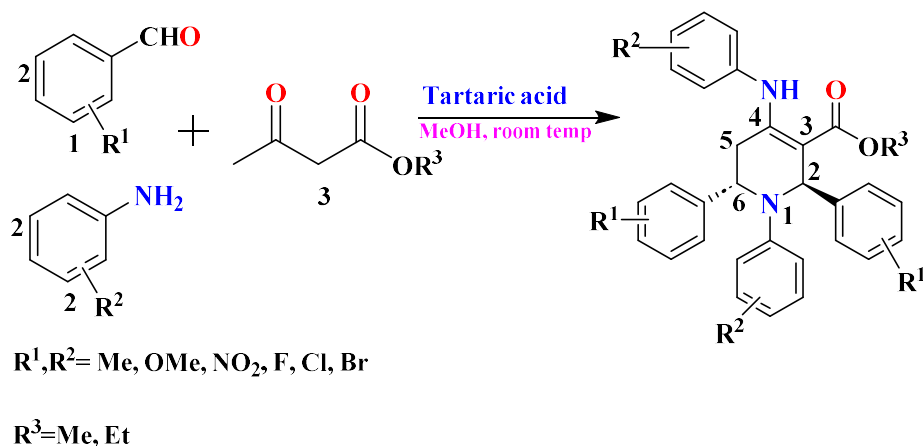
Scheme 6: The synthesis of highly functionalized piperidines is catalyzed by L-proline nitrate.

Brahmachari *et al.* synthesized functionalized piperidine through parallel reactions of 1,3-dicarbonyl compounds, aromatic aldehydes, and various amines in ethanol at room temperature. Hence, a simple and highly efficient diastereoselective multicomponent one-pot synthesis of a group of functionalized piperidine derivatives was produced. They found that this protocol's key advantages are high atom economy, high yields, environmental friendly, and gentle reaction conditions [35].



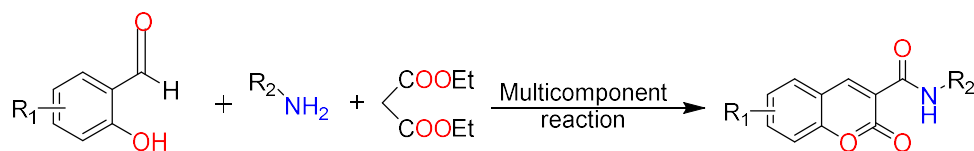
Scheme 7: A viable mechanism for one-pot functionalized piperidine production.

Moreover, Tartaric acid is an extremely powerful and effective catalyst for the one-pot synthesis of highly substituted piperidines in methanol at room temperature using a combination of 1,3-dicarbonyl compounds, aromatic aldehydes, and different amines. Good yields, a quick reaction time, moderate reaction conditions, no requirement for column chromatography, easy access, a basic work-up technique, as well as a low-cost, biodegradable catalyst are all advantages of this protocol[36].



Scheme 8: Synthesis of highly substituted piperidine.

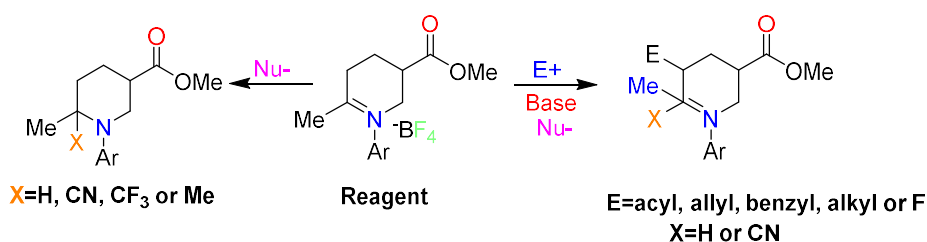
Piperidines, a type of N-heterocycle, are abundant in naturally occurring bioactive chemicals. Because of their anti-cancer, anti-microbial, anti-oxidant, anti-fungal, anti-inflammatory, and acetylcholinesterase (AChE) inhibitory activities, functionalized piperidines, notably 1,2,6-triaryl-4-arylamino-piperidine-3-ene-3-carboxylates, have recently received a lot of attention. As a result, several methods to produce 1,2,6-triaryl-4-arylamino-piperidine-3-ene-3-carboxylates via one-pot pseudo five-component reactions involving aromatic aldehydes, anilines, and -keto esters under varied reaction environment have been reported over the previous decade [37]. Recently Velasco *et al.* provide a straightforward and efficient three-component one-pot synthesis technique by the reaction of salicylaldehyde, aliphatic primary/secondary amines, and diethyl malonate that used piperidine-iodine as a dual catalyst with ethanol as a green solvent. The primary benefits of this technique are that it is a metal-free and clean reaction, has modest catalyst loading, and requires no costly workup [38].



Scheme 9: Depicting the preparation of coumarin-3-carboxamides employing piperidine-iodine as a dual catalyst.

Gadge *et al.* established a high-yielding synthetic process for highly derivatized piperidines using 5-sulfosalicylic acid acting as an organocatalyst in multicomponent reaction at room temperature between aromatic aldehydes, aromatic anilines, and β -ketoesters. They

reported that the new approach has several advantages over earlier methods, including the use of a low-cost, recyclable, non-toxic, and metal-free catalysts, easily available precursors, mild reaction conditions, and simple workup procedures [39]. In addition, Greenwood *et al.* recently described a generic way for the faster synthesis of a variety of highly functionalized N-(hetero)aryl piperidine derivatives employing a familiar iminium ion precursor. The rapid synthesis of cyclic iminium salts using commonly available heteroaryl-amine and keto acrylate feedstocks is described. They demonstrate that these intermediates can be easily functionalized, generating a broad range of complicated piperidines [40].



Scheme 10: Rapid synthesis of complex, highly functionalized N-(hetero)aryl piperidines.

III. RESULT AND DISCUSSION.

Tribromides have generated substantial interest due to their superior properties to liquid bromine. Tribromide's crystalline form makes it a possible reagent and catalyst due to its ability to store, transport, and maintain desired stoichiometry. The current approach is an environmentally friendly procedure for producing innovative phosphonium tribromides and using them to the production of highly functionalized piperidine derivatives. With good yield, a wide range of phosphonium tribromides were synthesised (Table 1).

Table 1: Synthesis of organic phosphonium tribromides using sodium hypochlorite as oxidant.

Serial No.	Substrate	Time (min)	Products	Yields (%)
1	(1-Propyl)triphenylphosphonium bromide	5	(1-propyl)triphenylphosphonium tribromide	99
2	(Methoxycarbonylmethyl)triphenylphosphonium bromide	10	(methoxycarbonylmethyl)triphenylphosphonium tribromide	95
3	(ethoxycarbonylmethyl)triphenylphosphonium bromide	15	(ethoxycarbonylmethyl)triphenylphosphonium tribromide	95

The phosphonium tribromides have a strong absorption band in the 273-276 nm range, which is characteristic for the tribromide ion (Br_3^-). OATB IR spectra show distinctive IR bands in the range 153 to 208 cm^{-1} , which correspond to the literature value

(Table 2). Among all tribromides, (1-propyl) triphenyl phosphonium tribromide has been shown to be the most stable and can be made in high yield.

Table 2: Analysis results of organic ammonium tribromides.

Sl no.	Product	λ_{\max} (nm)	ν (cm^{-1})
1	(1-Propyl)triphenylphosphonium bromide	274	196
2	(Methoxycarbonylmethyl) triphenylphosphonium bromide	276	188
3	(ethoxycarbonylmethyl)triphenyl phosphonium bromide	271	189

In order to evaluate the efficiency of all the as synthesised tribromide, a catalytic reaction for the synthesis of densely functionalized piperidine analogs was performed. In terms of yield and time, tribromide (1-propyl) triphenyl phosphonium tribromide has been shown to be the most effective tribromide. All subsequent reactions were carried out in the presence of (1-propyl) triphenyl phosphonium tribromide.

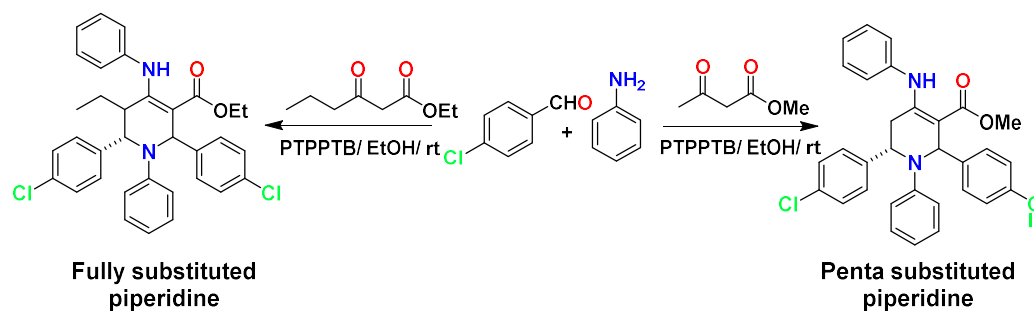
Multicomponent reactions (MCRs) are a popular and effective technique in modern chemical synthesis for obtaining complex heterocyclic compounds in a single step. It is obvious that MCRs are often considerably more environmentally friendly, and provide instant access to enormous compound libraries with varied capabilities, without the need for protection and deprotection procedures, allowing for possible combination of structural variations. As a result, generating novel MCRs and refining existing MCRs are attractive research topics in modern chemical synthesis. In addition, the synthesis of highly substituted piperidines utilising MCRs approach has received a lot of attention, and numerous processes have been developed. In this context, we described a one-pot multicomponent reaction (MCR) that resulted in the synthesis of highly functionalized piperidines with (1-propyl)triphenyl phosphonium tribromide as a catalyst, as well as the mechanistic aspects of the reaction.

We investigated a four-component one-pot reaction of aromatic aldehydes and aromatic amines with methyl acetoacetate (2:2:1) utilising (1-propyl)triphenyl phosphonium tribromide as a catalyst in this study. To begin, a combination of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) in acetonitrile (5 mL) was reacted with 10% PTPPTB (0.1 mmol) at room temperature to optimise the reaction conditions. The reaction was continued until the desired functionalized tetrahydropyridines (as white solid precipitate) were obtained in a moderate yield. The solid product was filtered and washed with ethanol to provide 78% functionalized piperidine 1. The melting point, IR, ^1H NMR, ^{13}C NMR, and elemental analyses were then utilized to characterize the product. To improve yield, the reaction conditions to produce 1 were examined in different solvents (Table 1). Several solvents were tested, and ethanol was shown to be the optimum solvent for these reactions. The product was generated in low yields (51%) under neat reaction, which is most likely because of lack of efficient interaction of reactants and the catalyst.

Table 3: Optimize reaction conditions for the synthesis of functionalized piperidine 1.

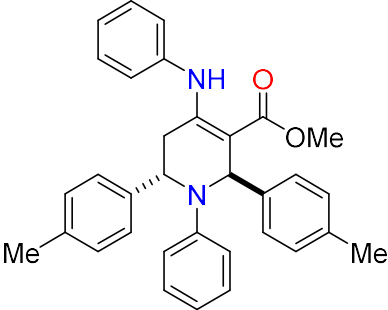
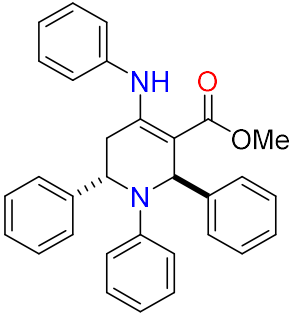
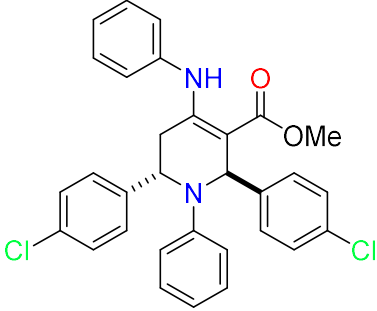
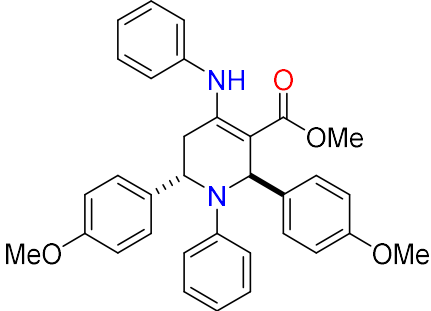
Entry	Solvent	Catalyst(mol %)	Time (h)	Yield (%)
1	CH ₃ CN	No Catalyst	12	0
2	CH ₃ CN	10	12	66
3	EtOH	05	10	56
4	EtOH	10	10	78
5	EtOH	20	10	69
6	CH ₂ Cl ₂	10	10	54
7	CH ₃ OH	10	12	68
8	Neat	10	5	51

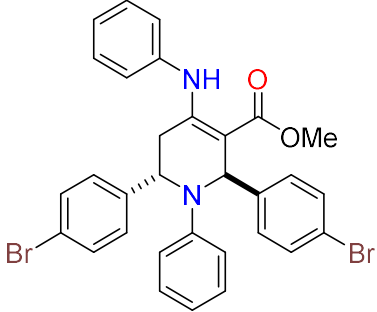
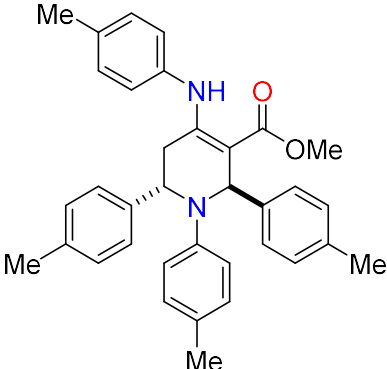
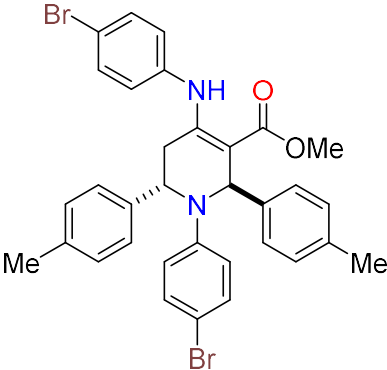
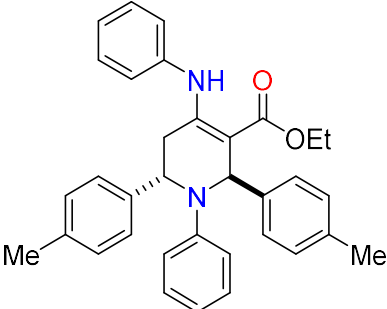
At the same reaction circumstances, several substituted aromatic aldehydes, anilines, and acetoacetates (1,3-dicarbonyl compounds) were reacted. Table 3 displays the reaction time and percentage of yield for the products. However, in the case of 3- and 4-nitrobenzaldehydes, the yield was poor (Table 2, entries 7 and 8). When a nitro group is present, this may result in the production of a more stable imine with an additional conjugation. This stable imine has low reactivity and a lower ethanol solubility. Some aldehydes, namely-naphthaldehyde and n-butanal, have not produced functionalized piperidines. All these reactions proceeded easily, yielding piperidine derivatives in moderate to good yields. The enolizable alkyl group present in the β -position of 1,3-dicarbonyl complexes is adequate for the generation of highly functionalized piperidines employing MCRs (Scheme 4).



Scheme 11: Criteria for the formation of piperidine derivatives.

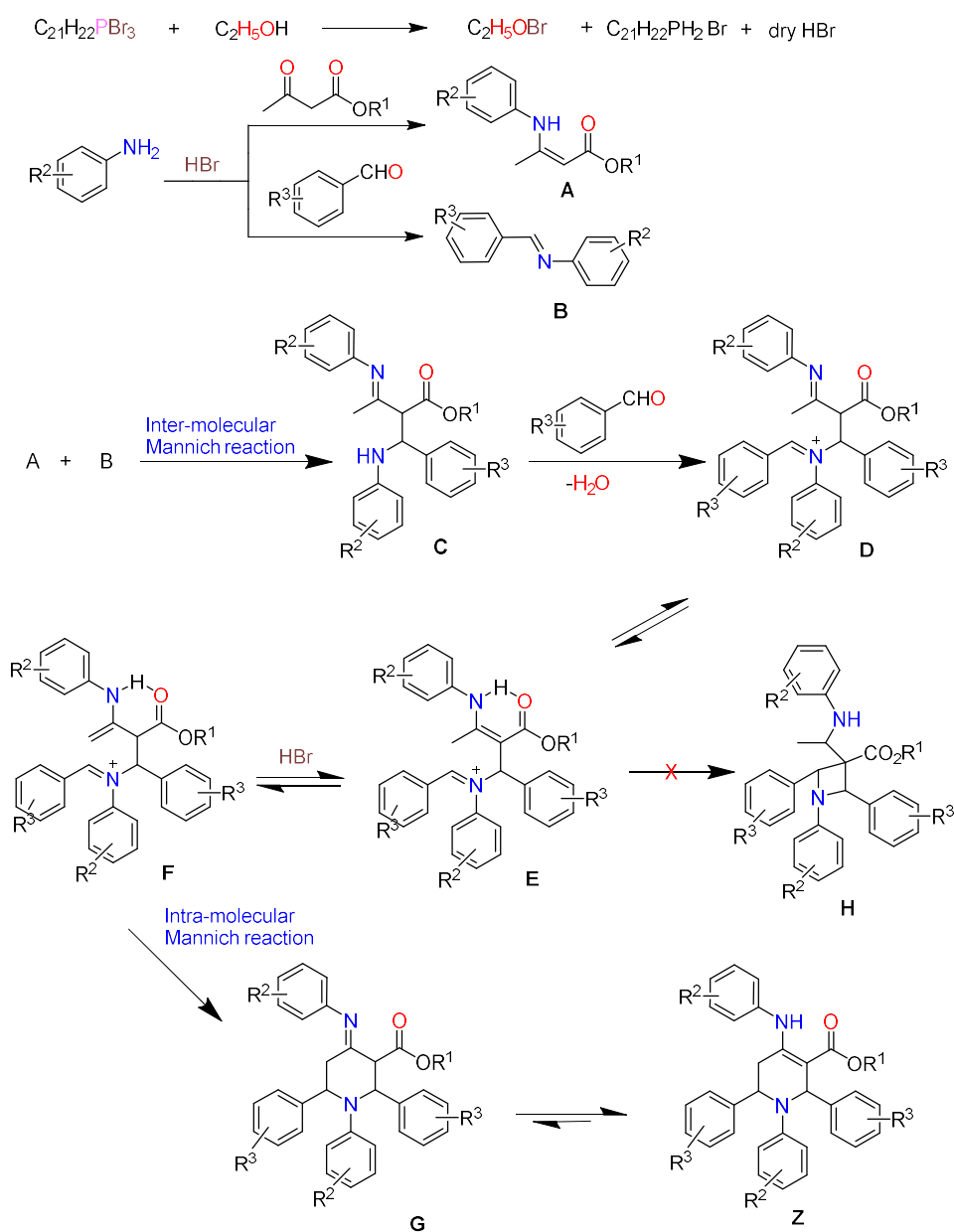
Table 4: Synthesis of functionalized piperidines using (1-propyl)triphenyl phosphonium tribromide in ethanol.

Entry	Product	Time (hr)	Yield (%)
1.		8	78
2.		24	74
3.		10	82
4.		8	80

5.		8	80
6.		12	75
7.		8	63
8.		9	70

Several groups have proposed the synthesis of piperidines using a Knoevenagel-type intermediate followed by the [4+2] aza-Diels-Alder reaction[23, 41-42]. It has been predicted

that keto ester would combine with amine to form enamine A, which would then react with aldehyde to form a Knoevenagel-type compound. As a reactive diene, it undergoes the aza-Diels-Alder reaction with imine B to produce substituted piperidines. To support this mechanism, intermediate diene isolation using other reactive dienophiles such as dimethyl acetylene dicarboxylate and maleic anhydride was attempted but failed. Given the lack of cycloaddition products, an alternative feasible mechanism for the formation of products is provided (Scheme 12). When PTPPTB interacts with ethanol, it produces dry HBr, which leads to the creation of enamine A and imine B (Scheme 12). It is established that enamine A would be a stronger nucleophile and the nucleophilic attack will take place preferably on the activated imine B to give intermediate C through an intermolecular Mannich-type reaction.



Scheme 12: Proposed mechanistic steps for the synthesis of highly substituted piperidines.

By removing a water molecule, intermediate C combines with aldehyde to form intermediate D. There is a natural tendency to give the intramolecular hydrogen bonded species either E or F in the presence of HBr for tautomerization. The tautomer F immediately undergoes intramolecular Mannich-type reaction to produce intermediate G. The tautomer E would give a four-membered ring H, which is inappropriate. The intermediate G tautomerizes to produce the resultant piperidine derivative Z owing to the conjugation with the ester group. At last, the formation of the product is followed by both inter- and intramolecular Mannich-type reactions. In summary, we reported that highly functionalized piperidines can be formed in the presence of PTPPTB as a catalyst in a one-pot five-component process at room temperature using easily obtainable starting materials. This MCRs approach has several advantages, including high yields, gentle reaction conditions, an ecologically friendly catalyst, the absence of time-consuming procedures, excellent atom economy, and low cost. Furthermore, mechanistic studies showed another route for the synthesis of piperidines via double Mannich-type reactions.

IV. CONCLUSION

In summary, three different forms of phosphonium tribromide were successfully synthesized, among them (1-propyl)triphenylphosphonium tribromide was found to be the most efficient phosphonium tribromide. This novel chemical was characterized using a variety of physicochemical techniques. Moreover, in the three-component reaction of aldehyde, amine, and 1,3-dicarbonyl compounds to produce functionalized piperidines, the as-prepared tribromide was used as a recoverable, heterogeneous catalyst. We hope these tribromide reagents are extremely useful in organic synthesis for a variety of functional group transformations, especially as mild brominating agents.

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