CHAPTER- 3:
SYNTHESIS AND
CHARACTERIZATION OF BISINDOLE,
TETRAZOLE AND PYRIMIDONE
COMPOUNDS

Part [A]:
General introduction of
Eaton’s reagent
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General introduction of Eaton’s reagent

3A.1 INTRODUCTION

Eaton’s reagent (1:10 phosphorus pentoxide in methanesulfonic acid) is an inexpensive and commercially available substance synthesized by Philip E. Eaton in 1973 and found to be a good alternative to polyphosphoric acid which enables the drawbacks of many traditional catalysts to be overcome, because it has a much lower viscosity, it is easier to handle, and no complex separation procedures need to be employed. Many processes that employ a mixture of phosphorus pentoxide and methanesulfonic acid ($P_2O_5/MeSO_3H$) are not only more economical, but also they are more environmentally friendly and offer a number of distinct advantages such as chlorine-free, low environmental impact, safe in industrial scale, no additional solvent required, rapid reactions, easy work-up procedures, and high-purity products with excellent yields. Combination $P_2O_5/MeSO_3H$ can also be employed as catalyst for Fisher-Indole synthesis, Beckmann rearrangement and Schmidt rearrangement processes.¹

Eaton’s reagent is colorless, odorless liquid mixture of non-oxidizing methanesulfonic acid and a powerful dehydrating agent phosphorus pentoxide. The addition of phosphorus pentoxide increases the solubility of organic compounds in methanesulfonic acid; this was introduced by Eaton and has been used enormously in organic synthesis.² The important reactant in the phosphorus pentoxide-methanesulfonic acid reagent is not certain; most probably it is a very active mixed anhydride. Although methanesulfonic anhydride is present in phosphorus pentoxide-methanesulfonic acid, a methanesulfonic anhydride-methanesulfonic acid solution is a less effective reagent than phosphorus pentoxide-methanesulfonic acid for
intramolecular acylation and the Beckmann rearrangement, and in other cases such as
the synthesis of 2-phenylbenzoxazole, it does not work at all. Pure methanesulfonic
acid or a mixture of phosphorus pentoxide-sulfuric acid does not promote the
reactions as phosphorus pentoxide-methanesulfonic acid, and therefore it is more
prefered.³

3A.2 APPLICATIONS OF EATON’S REAGENT

The distinctive physical and chemical properties of Eaton’s reagent make it a
very useful substance in many different reactions with different applications. The
mixture of P₂O₅/MeSO₃H is particularly effective for ring closures, but this versatile
reagent is also employed as a catalyst in condensation, cyclization, rearrangement and
polymerization reactions. Furthermore, it also serves as a mild reaction medium in
number of significant reactions. Herein, some reports highlighted the use of this
reagent are as follows.

Zewge and coworkers⁴ used Eaton’s reagent to promote the cyclization of
aniline derivatives to produce 4-quinolones [1] in high yields under mild conditions,
which avoids the use of traditionally used mineral oil, diphenyl ether or Dowtherm at
elevated temperature with inert atmosphere essential for the cyclisation through
Gould-Jacobs reaction (Scheme 3A.1). It was found that dissolution of the requisite
substrates in neat Eaton’s reagent and heating to 50 ºC gave complete conversion and
high yields within 1-3 h. Important to note that, product isolation from these reactions
is straightforward, involving quenching into aqueous base and filtration of the
precipitate. However, this method have some limitations includes a lack of
regioselectivity when meta-substituted anilines are used and its failure to generate a
seven-membered benzoazepine and a five-membered indanone.
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![Eaton's reagent scheme](image)

(Scheme 3A.1)

Pandit et al.\(^5\) use this reagent for the synthesis of 2-substituted oxazole via an improved cyclization of amidoacetals [2] in neat Eaton’s reagent at 130 °C for 7.5 h afforded the corresponding oxazole [3] in good yields. The product was isolated by precipitation upon dilution of the reaction mixture with water. The method is simple, economical, and uses inexpensive, commercially available starting materials and reagents. It is amenable to large scale and complements existing methods of oxazole synthesis. This method is applicable only to those substrates which are tolerant to highly acidic conditions (Scheme 3A.2).

![Scheme 3A.2](image)

The synthesis of dihydrojasmine (\(R_2=C_4H_9\)) and analogues [6] from cyclopropanol derivatives [4] was reported in 55-90 % yield via the intermediacy of cyclobutanones [5]. In this transformation, the ring expansion of cyclobutanones [5] to cyclopentenones [6] was expeditious, completed in 5 min but requires extra amount of \(P_2O_5/MeSO_3H\) in diethyl ether at room temperature (Scheme 3A.3).\(^6\)
Cohen and Matz\(^7\) employed Eaton’s reagent in 1,2- as well as 1,3-rearrangement to produce the spiro and bicyclic compounds respectively. A 1,2-rearrangement of vinylic cyclobutanone [7] to 51% of spiro[4.5]dec-2-en-1-one [8] was observed and accompanied by a minor but significant degree of 1,3-rearrangement (13%) to give bicyclic compound [9]. Whereas, nor-methyl analogue (R = H) yielded no 1,2-rearrangement product; only the 1,3-rearrangement product [9] was formed under the same reaction conditions (Scheme 3A.4).

Tupare et al.\cite{9} synthesize the series of chalcones and bis-chalcones \cite{15} derivatives by condensation reaction of aromatic aldehydes \cite{13} with various ketones such as cyclohexanone \cite{14}, by using catalytic amount Eaton’s reagent under microwave irradiation conditions (Scheme 3A.6).

Kim and his associates\cite{10} reports a new polymerization method for poly(2,5-benzimidazole) (ABPBI) \cite{17} with a novel polymerization medium of methanesulfonic acid and P$_2$O$_5$. A monomer 3,4-diaminobenzoic \cite{16} acid is soluble in the medium and the polymerization was therefore performed in a homogeneous state. This method produces very fine polymer fibers that simplify the work-up process and the polymer obtained either as fibers or a membrane (Scheme 3A.7).
Use of Eaton’s reagent as condensing agent was successfully achieved for the synthesis of poly(phenylene ether sulfones) [19] by direct self-polycondensation of sodium 4-phenoxybenzenesulfonate [18]. These polymers can be prepared by either polyetherification or polysulfonation, and plays an important role as heat-resistant thermoplastics (Scheme 3A.8).\[^{11}\]

\[
\begin{array}{c}
\text{O-S}^\text{Na} \\
\text{O-S}^\text{O}_\text{O} \\
\text{O-S}^\text{O} \\
\text{O-S}^\text{Na}
\end{array}
\xrightarrow{\text{Eaton’s reagent}}
\begin{array}{c}
\text{O-S}^\text{Na} \\
\text{O-S}^\text{O}_\text{O} \\
\text{O-S}^\text{O} \\
\text{O-S}^\text{Na}
\end{array}
\]

(Scheme 3A.8)

Kaboudin and Abedi\[^2\] employed this system for synthesis of aryl mesylates from aryl methyl ethers. In this synthesis, the treatment of a broad range of aryl methyl ethers [20] with a mixture of methanesulfonic acid and phosphorus pentoxide at 80 °C furnishes the corresponding mesylates [21] in 48-95 % yields (Scheme 3A.9).

\[
\begin{array}{c}
\text{R} = \text{CH}_3, \text{Cl}, \text{NO}_2 \text{ etc.}
\end{array}
\xrightarrow{1) \text{MeSO}_3\text{H, 16 h, 80 °C}}
\begin{array}{c}
\text{R} = \text{CH}_3, \text{Cl}, \text{NO}_2 \text{ etc.}
\end{array}
\xrightarrow{2) \text{P}_2\text{O}_5, 2 \text{ h, 80 °C}}
\]

(Scheme 3A.9)

The Grover, Shah and Shah reaction\[^{12}\] is modified by using a mixture of methanesulfonic acid-phosphorus pentoxide, which replaces the use of phosphoryl chloride-zinc chloride as a catalyst. In this GSS reaction, Eaton’s reagent found to be an excellent condensation agent between 3-methyl-salicylic acid [22] and
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\[
\begin{array}{c}
\text{[22]} \quad \text{[23]} \\
\text{Eaton’s reagent} \quad \text{80 °C, 20 min} \\
\text{[24]}
\end{array}
\]

(Scheme 3A.10)

3A.3 PRESENT WORK

Owing to the important properties of Eaton’s reagent, we have taken its application in condensation, [2+3] cycloaddition and cyclization reactions as described in Part [B], Part [C] and Part [D] of this chapter respectively.

i) Part [B] of this chapter explains the efficient synthesis of Bis(indolyl)methane derivatives under solvent free conditions using a mixture of methanesulfonic acid and phosphorus pentoxide at ambient temperature.

ii) Part [C] comprises the use of methanesulfonic acid and phosphorus pentoxide at catalytic amount for the [2+3] cycloaddition reaction between organic nitriles and sodium azide to give the 5-substituted 1H-tetrazoles in high yields.

iii) Part [D] shows application of Eaton’s reagent in one-pot, three-component reaction of ethylacetoacetate, aldehyde and urea in prompt synthesis of 3,4-dihydropyrimidin-2(1H)-ones via Biginelli reaction.
3A.4 REFERENCES


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