REMARKABLE UTILITY OF AROMATIC ALDEHYDES, HALOGENS AND CYANO GROUPS IN THE SYNTHESIS OF PHARMACOLOGICALLY SIGNIFICANT COMPOUNDS: A REVIEW

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ABSTRACT

Synthetic utility of aromatic aldehydes is well known since these played an important role in the synthesis of dyes, chemotherapeutic agents, analytical reagents and variety of compounds. These are important and versatile intermediates in the pharmaceutical industry and organic synthesis. Considerable interest attached with the compounds bearing cyano moiety because they have been used widely as precursors for pharmaceuticals, heterocyclic compounds and biologically active molecules. Compounds with halogen atoms have become of immense importance in the pharmaceutical and agrochemical products. Present communication is an attempt to review the reports on the synthesis of pharmacologically active compounds of non Schiff base or non β-lactams using aromatic aldehydes, halogens and cyano groups.

KEYWORDS: Aromatic aldehydes, tertiaryaminobenzaldehydes, halogen, cyanooethylation and cyano group.

INTRODUCTION

Aromatic aldehydes constitute an important class of organic compounds. Certain substituted aromatic aldehydes have been employed in the detection of urea[1,2] and bile pigment in urine[3] of children, scarlet fever, measles and various infections.[4] Liendo has reported the determination of blood urea level by substituted aromatic aldehydes.[5] Aldehydes have been used as an initiator for the synthesis of the compounds of chemotherapy of laprosy and in the synthesis vast number of azomethines having diverse biological activities.
Antimicrobial efficacy\(^{[6,7]}\) has been evaluated by a series of compounds synthesized from 3-methoxy-4-hydroxy-5-substituted benzaldehydes (1) and 3-methoxy-4-chloroacetyl oxybenzaldehyde (2).

\[
\begin{align*}
    X = \text{Br, I,} \\
    (1) \\
    (2)
\end{align*}
\]

The review of literature suggests that aldehydes having methoxy group exhibits marked pesticidal,\(^{[8,9]}\) antimicrobial,\(^{[10,11]}\) and biological properties.\(^{[12]}\) In addition, a correlation study has been performed on the lipophilic nature of the methoxy group and its effect on bacterial pathogens.\(^{[13]}\) Current literature revealed that various bioactive compounds bearing acetyloxy moiety in aldehydes attracted considerable attention as they are endowed with wide range of anti-inflammatory,\(^{[14,15]}\) anti-tumour\(^{[16]}\) and other biological activities. 2-Oxo-thiazolin hydrazones from 3-methoxy-4-acetyloxybenzaldehydes (3) are endowed with anti-HIV activity.\(^{[17]}\) A new library of compounds synthesised from 2-hydroxy-3-iodo-5-chlorobenzaldehyde (4) and 3-methoxy-4-chloroacetyloxybenzaldehyde (5) indicated that presence of chloro and methoxy group in compounds enhances their antibacterial activity.\(^{[18]}\)

\[
\begin{align*}
    (3) \\
    (4) \\
    (5)
\end{align*}
\]

Substituted azosalicylaldehydes are used as precursor in the synthesis of compounds of therapeutic interest.\(^{[19-23]}\) Pendse\(^{[24]}\) et al. reported the preparation of substituted azo-salicyl aldehydes (6) and screened them in-vitro for evaluation of antibacterial activity against Gram “+”ve and Gram “-”ve strains of bacteria.
Compounds containing chloro substituents showed pronounced biological activities.\textsuperscript{[25]} 2-chloro-3-formylquinolines react with ethyl glycine hydrochlorides in pyridine, to form antifungal\textsuperscript{[26]} quinolin-2-ones. Aldehydes containing methoxy group and their other biodynamic products have shown anticancer potentiality.\textsuperscript{[27]} Various chemotherapeutic agents derived from substituted salicyldehydes have showed DNA cleavage activity,\textsuperscript{[28]} merogenic properties\textsuperscript{[29]} and various pharmaceutical applications.\textsuperscript{[30]}

Aldehydes on condensation with primary amines give numerous applications\textsuperscript{[31-33]} for preparation, detection, determination and purification purposes. Aromatic aldehydes containing additional substituents are important and versatile intermediates in the pharmaceutical industry and for organic synthesis. Ongoing studies on the synthesis of nitrones\textsuperscript{[34]} required the preparation of hetero aromatic aldehydes and dialkoxy benzaldehydes. Hetero aromatic α- and β-carboxaldehydes were prepared by Katritzky\textsuperscript{[35]} et al. via formylation of α-lithiobenzofuran, benzo thiophene, N-methylbenzimidazole and 10-methylphenothiazine by DMF.

HALOGEN SUBSTITUTED COMPOUNDS

Halogenated compounds have become of immense importance in the pharmaceutical and agrochemical products.\textsuperscript{[36]} Compounds containing halogen atoms have shown to play a crucial role in the pharmacological properties.\textsuperscript{[37]} With a view to explore the influence of halogen atoms on the biological activity of compounds, Ankhiwala\textsuperscript{[38]} synthesized halogenated pyrazoline derivatives and tested them for biological potentiality against S. aureus and E. coli. Wolf\textsuperscript{[39]} prepared N1-aryloxyacetal-3-methyl-5-pyroziline which on reactions with pyrazolines gave monoaryllidene derivatives along with bis-pyrazolone. Monoarylidine compounds have been brominated in acetic acid to give 4-bromo-(4-α-bromoaryl)-N1-aryloacetyl-3-methyl-5-pyrazolines. All compounds were screened against A. niger and A. flavus, results showed increased antifungal activity.\textsuperscript{[40]} Keeping the
eyes on excellent biological and clinical potential of pyrazolines, Kumar et al. have reported the synthesis of some new benzothiazole pyrazolines to explore further the effect of bromine on their biological activity.\textsuperscript{[41,42]}

It is well known that the introduction of fluorine atom on organic molecule causes dramatic changes in its biological properties mainly due to high electro negativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids.\textsuperscript{[43]} Fluorine substitution can alter the metabolic stability, hydrogen-bonding capacity, lipophilicity, solubility, conformation and even the fundamental structure of a molecule (e.g., the propensity of fluorinated ketones to hydrate) variations can profoundly influence biological activity.\textsuperscript{[44]}

Fluorine plays a pivotal role in the discovery of novel drug for modulating physical and biological properties of molecules. Incorporation of fluorine atom (s) within the molecule can enhance bio potency, bioavailability, metabolic stability and lipophilicity because of their higher electro negativity. Trifluoromethylation is considered as the most significant strategy to improve pharmacological activity of the molecules due to its high lipophilicity, thereby enhancing the in-vivo uptake and transport of the candidates.\textsuperscript{[45]} A new series of 2-[4-cyano-(3-trifluoromethyl)-phenylamino]-4-(4-quinoline/coumarin-4-yloxy)-6-(fluoropiperazinyl)-s-triazines has been prepared by Patel\textsuperscript{[46]} et al. with screening results of their in-vitro anti-mycobacterium inhibitory effects.

Fluorine substituted organic compounds are of growing interest in modern medicinal chemistry and are ideal for the drug design because of the good biological activity and low toxicity of molecules containing the trifluoromethyl moiety and the easy substitution of a phenyl or heteroaromatic group with trifluoromethyl. Furthermore, trifluoromethyl group bearing compounds possess unexpected biological efficiency.\textsuperscript{[47,48]}

Synthesis and in-vitro antimicrobial screening of a series of compounds derived from 2-hydroxy-3-iodo-5-chlorobenzaldehyde (7) and 3-methoxy-4-chloro-acetyloxy-benzaldehyde (8) indicates that presence of chloro and methoxy moiety in compounds enhances their antibacterial activity.\textsuperscript{[49]}
Waghmare\cite{50} et al. presented an overview of methods used for halogenations of deactivated aryl and N-heteroaryl amines. Polyfluoroaromatic aldehydes are used to produce fluorine-containing products as starting materials that are of considerable interest in agriculture, medicine and electronics. These are prepared mainly from iodo- and bromo-polyfluoroarenes.\cite{51} The fluoro and chloro 2-acetyl benzimidazole derivatives were prepared and screened \textit{in-vitro} by Banda\cite{52} et al., for their antibacterial and analgesic activity.

The compounds containing electron withdrawing (-Cl, -OH) groups in \textit{p}- or \textit{m}-position (-NO$_2$) of the phenyl ring present in the substituted benzimidazole thiazine (9) were found to display potent analgesic and antibacterial activity. Halogen and methoxy group substitution in pyron ring exhibit the biological activity.\cite{53}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure9.png}
\end{center}

\textbf{CYANO SUBSTITUTED COMPOUNDS}

There has been an increasing prevalence over the past decades in different biologically active compounds containing an acrylonitrile moiety.\cite{54-57} Mc Cluskey\cite{58} et al. reported (E)-3-(4-chlorophenyl)-2-(1$H$-pyrrole-2-carbonyl) acrylonitrile (10) as an anticancer compound.

\begin{center}
\includegraphics[width=0.3\textwidth]{figure10.png}
\end{center}

Recently, a family of 2-phenylacrylonitriles possessing novel anticancer activity\cite{59} has been reported which describes pharmacophore an extended conjugation spanning two terminal aromatic rings with one of these rings containing an electron withdrawing group, is important for the maintenance of cytotoxicity. The presence of an acrylonitrile (cyanide) moiety\cite{60} (11) was central to this conjugation.
Considerable attention have been received by 2,3-disubstituted acrylonitriles because of their versatile biological activities.\textsuperscript{[61,62]} A group of authors reported that some 3-heteroaryl acrylonitriles containing triazole or benzimidazole ring possess cytotoxic activity.\textsuperscript{[63,64]} Some acrylonitriles have possessed antibacterial and anti-tuberculostatic activity as well as ability to inhibit tubulin polymerization.\textsuperscript{[65,66]} A project aimed in the synthesis of potential anticancer agents related to benzimidazole derivatives, amidino and cyano substituted- styryl-2-benzimidazoles (12) and benzimidazoquinolines,\textsuperscript{[67,68]} (13) have reported strong inhibitory activities on several human cell lines.

Remarkable interest has been attached with the chemistry of compounds containing cyano aldehyde moiety because they have been used widely as precursors for pharmaceuticals, heterocyclic compounds and biologically active molecules.\textsuperscript{[69,70]} (E)-\(\alpha\)-Cyanocinnamaldehydes are building blocks for the preparation of various N-heterocyclic molecules.\textsuperscript{[71]} Several reports are on the synthesis of (E)-\(\alpha\)-cyanocinnamaldehyde\textsuperscript{[72]} (E)-2-cyanophenylprop-2-enal prepared by Yoshimatsu et al. by \(\alpha\)-cyanofomylation of carbonyl compounds using \(\alpha\)-lithio-\(\beta\)-ethoxyacrylonitrile obtained by lithiation of \(\beta\)-ethoxy acrylonitrile.\textsuperscript{[73]}

(E)-\(\alpha\)-Cyanocinnamaldehydes\textsuperscript{[74]} prepared by the reaction of benzaldehyde with 3,3-di- methoxypropionitrile. Ishii\textsuperscript{[75]} et al. reported synthesis of (E)-\(\alpha\)-cyanocinnamaldehydes (14) from acrylonitrile and benzaldehydes via the Cross-Aldol condensation of diethylacetal derived from acrylonitrile with aldehydes.
The incorporation of dicyano group into organic scaffolds is of immense interest as a result of the varied avenues of further modifications, such group’s allow further interest in biologically relevant molecules containing poly cyano functionalities, which have been shown to possess arthropodicidal, antimicrobial and insecticidal properties. Promising therapeutic potential of cyanoribofuranoses has been attributed to the small size and high electro negativity of the cyano group. The recent findings on 3'-C-cyano and 3'-deoxy-C-cyanopyranonucleosides as cytotoxic agents are based on the fact that various 4'-C substituted nucleosides such as 4'-cyano-thymidine display potential anti-HIV and anti-tumour activity.

The pyridine skeleton containing -CN group is of great importance as it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. Cyano-group is the structural basis of the ricinine 3-cyanopyridin-2-one nucleus which is the first known alkaloid. Cheney et al. reported 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles (15), as inhibitors of the oncogenic serine/threonine kinase PIM-1. Wendt et al. revealed several compounds with the same general formula with higher lipophilic properties (16) can inhibit survivin which is a member of the inhibitor of apoptosis family (IAP).

Chase et al. have synthesized 6-amino-5-phenyl-3-cyanopyridin-2-one by the reaction of 3-isobutoxy-2-phenylacrylonitrile with cyanoacetamide. Alnajjar et al. reported the
conversions of 2-cyano-5-(dimethylamino)-5-phenylpenta-2,4-dienamides into nicotinic nitrile derivatives (17), (18), (19) when 2-cyano-5-(dimethylamino)-5-phenylpenta-2,4-dienamides are heated under reflux in AcOH. Enaminonitrile were readily prepared by reaction of acetonitrile with 4-cyanopyridine in the presence of potassium-t-butoxide.\(^{[89]}\)

\[
\text{N}
\text{H}
\text{N}
\text{H}
\text{CN}
\text{O}
\text{CN}
\text{O}
\text{N}
\text{H}
\text{CN}
\text{O}
\text{NH2}
\text{NH}
\text{CNN}
\text{CN}
\]

(17)  (18)  (19)

Cyanopyridine appeared of considerable interest in possessing antibacterial, anticholesteromic, antifungal, antihypertensive and antidiabetic activities. Thiele\(^{[90]}\) et al. studied the analgesic activity of substituted 3-cyanopyridines. 4-[6-bromo-2,7,8-trichloroquinoline-3-yl]-6-phenyl-2-methoxy-3-cyanopyridine was synthesized by Parikh\(^{[91]}\) et al. via the condensation of malononitrile and sodiummethoxide with 3-[6-bromo-2,7,8-trichloroquinoline-3'-yl]-1-arylprop-2-en-1-one (20).

\[
\text{Br}
\text{Cl}
\text{Cl}
\text{R}
\text{N}
\text{O}
\text{CH3}
\]

(20)

A clinical application of synthetic cyanoacrylate in various medical devices was approved by the US food and drug administration (FDA). It includes cyanoacrylates as liquid bandages and dental cements\(^{[92]}\) etc. A technique of latent fingerprints using controlled cyanoacrylate vapour exposure in fuming cabinets is used for artefacts recovered in investigations of forensic crime-scene. Nanoparticles of poly (isobutylcyanoacrylate) with dispersed insulin in pluronic acid solution have been reported.\(^{[93]}\) Polybutylcyanoacrylate nanoparticles were delivered to the lungs via carrier particles that dissolve after contact with the aqueous environment of lung epithelium.\(^{[94]}\)

Nagai\(^{[95]}\) et al. studied that the reactions of benzaldehyde and analogues with ethyl cyanoacetate in ethanolic ammonia produce \(\alpha\)-cyanohydrocinnamides, 2,6-dihy-droxy-3,5-
dicyano-4-phenopyridines and dimeric products. Le Moal\textsuperscript{(96)} and Nagai\textsuperscript{(97)} et al. reported the Cope-Knoevenagel condensation of \(p\)-substituted benzaldehydes with ethyl cyanoacetate to produce ethyl \(\alpha\)-cyano-\(p\)-substituted cinnamates (21).

![Chemical Structure](image)

(21)

3-Cyano-6-phenyl-4-(3′-pyridyl)pyridine-2(1\textit{H})-thione, 2,2′-bis-pyridyldisulfide, 2-alkylthio pyridines and 2-aminothieno[2,3-b]pyridines were synthesized and their neurotropic activities were examined by Krauze\textsuperscript{(98)} et al., bispyridyldisulfide exhibited low toxicity and selective antiamesic activity. A new series of 2-amino-3-cyano-4-tetrazolo quinolinylpyridine derivatives has been synthesized by Mungra\textsuperscript{(99)} et al. and were subjected to \textit{in-vitro} antimicrobial screening against pathogenic strains of bacteria and fungi, results were found to be equipotent or more potent than commercial antibiotics. Recently, N′-(4-cyanobenzylidene)-2-cyanoacetohydrazide derivatives were prepared by Shah\textsuperscript{(100)} et al. from the cyanoacetohydrazide with the condensation of 4-cyano benzaldehyde (22).

![Chemical Structure](image)

(22)

The pyridine skeleton containing CN group is also of great importance to chemists as well as to biologists because it is found in a variety of naturally occurring compounds as well as in clinically useful molecules having diverse biological activities.\textsuperscript{(101-104)}

Cyano group is the structural basis of the ricinine, 3-cyanopyridin-2-one nucleus which is the first known alkaloid. 4,6-bis[2′-amino-3′-cyano-4′-(substituted phenyl)-6′-pyridyl] has been found to possess antifeedant activity.\textsuperscript{(105)} A series of cyanovinylpyrrole containing aroylhydrazones, derived from ethyl 2-cyano-3-(5-formyl-1\textit{H}-pyrrol-2-yl)-acrylate.\textsuperscript{(106)}

2-Amino-3-cyanopyridines have been identified to possess antimicrobial,\textsuperscript{(107,108)} antifungal,\textsuperscript{(109)} cardiotonic,\textsuperscript{(110)} analgesic,\textsuperscript{(111)} anti-inflammatory\textsuperscript{(112)} and ant-lung-cancer\textsuperscript{(113)}
activities. Many synthetic methods have been used for the preparation of 2-amino-3-cyano pyridine derivatives. \[^{114,115}\] Synthesis of 4, 6-bis[2’-amino-3’-cyano-4’-(substituted-phenyl)-6’-pyridyl]resorcinol derivatives were achieved, with biological screening for their \textit{in-vitro} activity against \textit{Pseudomonas, Bacillus, Streptococcus, Staphylococcus, E. coli, C. albicans and A. niger}. \[^{116}\] 1-Amino-2-cyano-3-methyl-3-ethyl-1, 2-dihydronaphthalene-aminonitrile was synthesized by Markosyan\[^{117}\] et al.

A series of cyano derivatives of N-alkyl and N-arylpiperazine were synthesized by Chaudhary\[^{118}\] et al. and their antimicrobial activities were evaluated as antibacterial and cytotoxic activity. A one-pot procedure has been developed for the synthesis of 2-substituted-3-alkoxyisoindolin-1-imine derivatives via three-component condensation of 2-cyanobenzaldehyde, amine, and alcohol by Shen\[^{119}\] et al. In search of some novel antibacterial agents, synthesis and antibacterial activity of 2-cyano-N’-(1-(4-hydroxy-6-methyl-2-oxo-2\textit{H}-pyran-3-yl)-ethylidene) acetoxydrazide, (23) has been reported by Saini\[^{120}\] et al.

![Structure of 23](image)

A series of C-cyanovinylpyrrole containing aroyldrazones, derived from ethyl- 2-cyano-3-(5-formyl-1\textit{H}-pyrrol-2-yl)-acrylate and acid hydrazides: salicylhydrazide, isoniazid and 3,5-dinitrobenzohydrazide. \[^{121}\] A series of novel pyrrole azomethines were synthesized by reaction of 2-amino-1,5-diaryl pyrrole-3-carbonitrile (24) with different aromatic aldehydes using P\textsubscript{2}O\textsubscript{5} as a catalyst to obtain (25), (2-amino-3-cyano-1,5-diaryl-pyrroles) which were tested against Herpes simplex virus type-1 (HSV-1) by Hilmy\[^{122}\] et al.

![Structure of 24 and 25](image)

Benzothiazoles with a cyanomethyl group at position-2 have been the subject of extensive study in the recent past. Numerous reports have appeared in the literature, which highlight
their chemistry and uses. However, heterocyclic containing cyanoacetyl group are relatively unexplored.

In the last two decades, authors involved in aiming to develop new and simple procedures or novel precursors for the synthesis of heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals.\textsuperscript{123-127} Some heterocyclic compounds containing the benzothiazole nucleus with cyano group, 2-(benzothiazol-2-yl)-3-oxopentanedinitrile (26), synthesised by Abdelrazek\textsuperscript{128} et al. for biological activities.

\[
\text{(26)}
\]

**CYANOMETHYL SUBSTITUTED COMPOUNDS**

Biologically active heterocycles\textsuperscript{129} 2-cyanomethyl-benzoxazole and compounds related to it played a role of extreme importance in pharmaceutical and agricultural fields due to their use as herbicides,\textsuperscript{130,131} bactericides,\textsuperscript{132} fungicides\textsuperscript{133,134} antiviral\textsuperscript{135} and also have been found to be of great interest due to their wide application of biological activities\textsuperscript{136} when connected to pyridine carbonitriles.

Cyanoaclylation of aldehydes and ketones is an important carbon-carbon bond-forming reaction.\textsuperscript{137} Cyanohydrin derivatives are easily converted into a wide variety of compounds, such as \(\alpha\)-amino acids, \(\alpha\)-hydroxy acids, \(\alpha\)-hydroxy aldehydes, \(\alpha\)-hydroxy ketones, \(\beta\)-amino alcohols and vicinal diols.\textsuperscript{138} They are also components of commercially significant compounds such as the pyrethroid insecticides, cypermetrin and fluvalinate.\textsuperscript{139} Among various cyanide ion sources, acyl cyanides and alkyl cyanoformates are safe and commercially available reagents,\textsuperscript{140,141} although cyanoaclylation reactions are very efficient method for the preparation of cyanohydrins.\textsuperscript{142,143}

The reaction of 2-cyanomethylbenzimidazole (27) with substituted benzaldehyde in presence of piperidine afforded a series of new benzimidazolyl acrylonitriles which have pharmacological activity.\textsuperscript{144}
Heterocyclic compounds containing cyanoacetyl group are relatively unexplored.\textsuperscript{[145,146]} Acetyl chloride itself is not particularly useful in this respect since it undergoes dimerization.\textsuperscript{[147]} Cyanoacetylation of uracils, their derivatives\textsuperscript{[148]} and enamines\textsuperscript{[149]} has been reported to be successfully achieved by heating the respective substrate with a mixture of acetic anhydride and cyanoacetic acid as a cyano-acetyling mixture.

The use of this cyanoacetyling mixture (cyanoaceticacid and acetic anhydride) has been used less and instead other less convenient reagents like the pyrrole derivative has been used.\textsuperscript{[150]} In the last two decades, Abdelrazek et al. have been involved in developing simple procedure or novel precursors for the synthesis of heterocyclic compounds of biological interest and evaluated as biodegradable agro-chemicals.\textsuperscript{[151]} In continuation with this, heterocyclic compounds 2-(benzo[d]thiazol-2-yl)-3-oxo-pentanenitrile (28), obtained by cyanoacetylation of a compound containing the benzothiazole nucleus has been synthesized by Abdelrazek\textsuperscript{[152]} et al.

The reactions of acrylonitrile with aldehydes and ketones containing α-hydrogen atoms have been extensively studied by Bruson and co-workers.\textsuperscript{[153]} These reactions results in the attachment of one or more cyanoethyl residues α- to the carbonyl group as shown (29).
Formaldehyde having no active hydrogen atoms shows exceptional behaviour and appears to react through the oxyanion of the hydrated form, giving mono- or bis-cyanoethylation products\cite{154} (30).

\[
\begin{align*}
\text{HOCH}_2\text{OCH}_2\text{=CH}_2\text{CN} & \quad \begin{array}{c}
\text{+} \\
\text{CH}_2\text{(OCH}_2\text{CH}_2\text{CN})_2
\end{array} \\
\text{CH}_2\text{(OH)}_2 \text{+ CH}_2\text{=CH}_2\text{CN} & \quad \begin{array}{c}
\text{+} \\
\text{CH}_2\text{(OCH}_2\text{CH}_2\text{CN})_2
\end{array}
\end{align*}
\]

(30)

In the case of aromatic aldehydes such as benzaldehyde, where there is no active hydrogen, reaction with acrylonitrile takes place under the usual cyanoethylation conditions\cite{155} but the nature of the products formed from these reactions has not previously been established. Wasserman\cite{156} et al. have reinvestigated this reaction and presented evidence for the structures of the various products formed. When acrylonitrile is treated in the cold with benzaldehyde (2:1 molar ratio) using t-butyl alcohol as solvent and in the presence of either Triton B (benzyltrimethylammonium hydroxide) or potassium hydroxide, two major products are formed: A (C\textsubscript{13}H\textsubscript{12}N\textsubscript{2}O) and B (C\textsubscript{20}H\textsubscript{16}N\textsubscript{2}O). Other products formed in smaller yields (in the potassium hydroxide catalyzed reaction) are the alcohol C (C\textsubscript{10}H\textsubscript{9}ON) and an aldehyde D (C\textsubscript{10}H\textsubscript{7}ON).

The synthesis of poly (N-alkyltrimethyleneimines) by a replacement of cyanoethyl group in poly (N-\(\beta\)-cyanoethyltrimethyleneimine) (poly-CET) by other alkyl groups is reported by Yamashita.\cite{157} The poly (N-\(p\)-nitrobenzyltrimethyleneimine was prepared by alkylation of poly-CET with \(p\)-nitrobenzyl bromide, followed by elimination of cyanoethyl groups. Tamelea\cite{158} et al. had cyanoethylated 2-methylpyridine methiodide in good yields, employing weakly basic, triethylamine as catalyst. Investigating its scope, the effect of varying conditions and the nature of the products such a synthesis, proved to be a useful route to the preparation of higher substituted alkyl pyridines, according to the scheme (31).
The cyanoethylation reaction is the addition of the cyanoethyl (-CH₂CH₂CN) group to a molecule in which a cyanoethyl group is added to a compound via a Michael-type reaction. Alcohols\textsuperscript{[159-161]} or water\textsuperscript{[162]} can be cyanoethylated at the oxygen atom; ammonia, amines,\textsuperscript{[163]} amides, imides, and lactams\textsuperscript{[164]} can be cyanoethylated at the nitrogen atom; arsines\textsuperscript{[165]} can be cyanoethylated at the arsenic atom; and inorganic acids also can be cyanoethylated.\textsuperscript{[166,167]}

Adamcik and Miklasiewicz\textsuperscript{[168]} have reported triethylamine as good cyanoethylation catalyst. Triethylamine and water has resulted in an increased yield of dicyanoethylated 2-methylpyridine methiodide. The direct cyanoethylation of alkylpyridines has been demonstrated by Cislak\textsuperscript{[169]}. He used molten sodium as catalyst and claimed to obtain the mono- or di-cyanoethylated product depending on the amount of acrylonitrile used. Cislak\textsuperscript{[170]} was also able to introduce the cyanoethyl group by reacting a monocyanoeethylated alkylpyridine with sodamide followed by reaction with 2-chloropropionitrile.

The cyanomethyl group together with the adjoining formyl group are suitably arranged in a molecule of 2-cyanomethylbenzaldehyde\textsuperscript{[171]} to participate in the formation of fused-ring compounds. Indeed, the reaction of aldehyde with ammonia, primary or secondary amines, catalyzed by trifluoroacetic acid, gives 3-amino substituted isoquinolines, usually in good yields.\textsuperscript{[172]} Mohamed\textsuperscript{[173]} et al. have synthesized a series of 6-aryl-5-cyano-2-thiouracil derivatives by the reaction of ethyl cyanoacetate with thiourea and aldehydes which were used as an intermediate compound for the synthesis of a number of thiouracil derivatives. Pore\textsuperscript{[174]} and co-workers have synthesized a series of 5-cyano N1, 6-disubstituted, 2-thiouracil derivatives exhibiting antinociceptive and analgesic activity with conclusion that compounds bearing bulkier and lipophilic substituents on phenyl group, located at C-6 of thiouracil nucleus, were more active than hydrophilic substituents on phenyl group at the same position.

Dicyanoethylation of m-toluidine was carried out by treating the aromatic primary amine with acryonitrile in acetic acid in presence of cuprous chloride by Arora\textsuperscript{[175]} et al. The
cyanoethylated amine on formylation gave 2-methyl-4-N’N-bis-2’-cyanoethyl amino benzaldehyde. The resulted aldehyde gave azomethines: 2-methyl-4-N’N-bis-2’-cyanoethyl aminobenzylidineaniline, 2-methyl-4-N’N-bis-2’-cyanoethylaminobenzylidine-p-chloroaniline, 2-methyl-4-N’N-bis-2’-cyanoethylaminobenzylidine-p-toludine and 2-methyl-4-N’N-bis-2’-cyanoethylaminobenzylidine-p-fluoroaniline with aniline and three different substituted anilines. Cyano derivatives (32) of N-alkyl and N-aryl piperazine have been synthesized by Kumar\textsuperscript{176} et al. which of them (a), (b) and (c) showed mild to moderate antibacterial and antifungal activity against different pathogenic strains.

\begin{center}
\begin{tabular}{ccc}
& (a) & (b) & (c) \\
\end{tabular}
\end{center}

Synthesis and anti-AIDS, anticancer, anti-tubercular, fungicidal and antibacterial activities of 2-methyl-4-N-2’-cyanoethyl-N-methane/benzenesulphonyl aminobenzaldehyde and their hydrazones (33) bearing 1,3-diketoamino structural analogues to pyrimidine bases as potential biomimetics have been reported by Dhingra\textsuperscript{177} et al.

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\end{tabular}
\end{center}
TERTIARYAMINOBENZALDEHYDE AND THEIR DERIVATIVES

Tertiaryaminobenzaldehydes are useful as photometric reagents\textsuperscript{[178]} in the determination of carboxylic acid hydrazides. Several methods have been developed for the preparation of aromatic aldehydes. A good account on the formation of aldehyde has been given by Ferguson\textsuperscript{[179]} and Patai\textsuperscript{[180]}. \(p\)-N’N-diethylaminobenzaldehyde give a series of reactions with substituted glycines, rhodanine, hydantoin, thiohydantoin, malonanilic acids and substituted malonanilic acid hydrazides, fluorine and cyanoacetamide.

Tertiaryaminobenzaldehydes are of significant importance in synthetic organic chemistry. It is evident from their role in the synthesis of dyes, chemotherapeutic agents, analytical reagents and in various other compounds. The procedure described by Compaigne and Archer\textsuperscript{[181]} offers a convenient and general method for the synthesis of aromatic tertiaryaminoaldehydes. Saxena\textsuperscript{[182]} et al. has adopted the same procedure for the synthesis of substituted \(p\)-N’N-diethylaminobenzaldehyde (34).

\begin{center}
\includegraphics[width=\textwidth]{34.png}
\end{center}

Tertiaryaminobenzaldehydes are significantly important on account of their role in the synthesis of chemotherapeutics\textsuperscript{[183,184]} and analytical reagents.\textsuperscript{[185]}

Numerous and diverse methods have been reported for the preparation of aldehydes from different types of compounds. A review on the synthesis of aromatic aldehydes has been presented by Lioyd N. Ferguson\textsuperscript{[186]} and a good account on the formation of aldehydes has given by S. Patai.\textsuperscript{[187]} Braunholtz and Mann\textsuperscript{[188]} developed an excellent method for the dicyanoethylation of aromatic amines and prepared a large number of dicyanoethylated derivatives. \(m\)-Toluidine and \(m\)-anisidine have been cyanoethylated according to the method recommended by Ittyerah and co-workers.\textsuperscript{[189]} Compaigne and Archer\textsuperscript{[190]} have described a procedure for the synthesis of tertiaryaminobenzaldehydes. 4-N’N-Bis-2’-cyanoethylaminobenzaldehyde, 2-methyl1-4-N’N-bis-2’cyanoethylaminobenzaldehyde and 2-methoxy-4-N’N-bis-2’cyanoethyl aminobenzaldehyde have been prepared according to the procedure reported in the literature\textsuperscript{[191,192]}. Two new aldehydes 2-methyl-4-N-2’-cyanoethyl-N-methane
sulphonylaminobenzaldehyde and 2-methyl-4-N-2’cyanoethyl-N-benzenesulphonylamino benzaldehyde have been synthesised involving monocyanoethylation of \textit{m}-toluidine.\cite{193}

CONCLUSION

Biological activities and the high practical utility of aromatic aldehydes as starting materials to prepare several organic and medicinal compounds bearing halogen atoms and cyano group provided motivation to document the successful achievement of the goals by scientists in the field of research. The synthetic chemists are making efforts to find out newer compounds with active therapeutic values by different possibility of these aldehydes and succeeded in it. Although the significant progress in this area has been made in recent years but further research efforts are needed in order to develop more practical and selective methods for the synthesis of compounds with great medical significance.

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