APPLICATION OF CYANOETHYLATION AND RELATED REACTIONS IN THE SYNTHESIS OF HETEROCYCLES

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CYANOETHYLATION is a versatile reaction and could be successfully utilised to synthesise a variety of organic compounds having different structural features. A number of compounds which readily undergo cyanoethylation include amines, amides, alcohols, phenols, mercaptans, esters, ketones and others such as boranes, arsines, phosphines, and silanes. These are mainly categorized under N-, O-, S-cyanoethylations and nucleophilic or C-cyanoethylation. Several books and reviews have been written on cyanoethylation.

In this article a brief account of the work done in our laboratory has been described, which shows how this reaction could be utilised to synthesise various types of compounds including those which are of pharmacological interest, those which occur in nature and also those possessing novel heterocyclic systems.

Generally, acrylonitrile or a substituted acrylonitrile is employed in this reaction which is carried out in the presence of a base like aqueous sodium hydroxide, saturated sodium bicarbonate, Triton-B, triethylamine, etc., or under acid conditions, as for example acetic acid. The β-propionitriles thus obtained are hydrolysed to the corresponding β-propionic acids which could be cyclised in the presence of PPA to afford cyclised compounds like dihydroquinolones, chromanones, indanones and others.

The above method has certain limitations and drawbacks. For example, due to inaccessibility of substituted acrylonitriles the synthesis of the above heterocycles having substituents becomes almost impossible. Further as their synthesis involves more steps, the yield of the final products get reduced. Often the intermediate β-propionitriles cannot be hydrolysed even under the most drastic conditions and further attempts to obtain the above heterocycles have to be abandoned. Another difficulty encountered is that some of the compounds such as secondary amines, dichlorophenols and others undergo cyanoethylation with great difficulty or not at all.

An elegant and convenient route for the synthesis of the above heterocycles in fairly good yields (25–30%) was developed in this laboratory which involves the direct condensation of the nucleophiles with α,β-unsaturated acids, such as acrylic, α-methylacrylic, crotonic, β, β-dimethylacrylic and cinnamic acids, in the presence of PPA at 100–120° for 4–5 hr. A striking example of this is 4-hydroxycoumarin, which fails to undergo cyanoethylation under various experimental conditions, but easily reacts with α,β-unsaturated acids to afford the corresponding pyranopyranones in fairly good yields.

N-CYANOETHYLATION

Cyanoethylation of aromatic amines has been studied earlier as well as by us using different experimental conditions. The resultant β-propionitriles were hydrolysed to the corresponding β-propionic acids which were cyclised in the presence of PPA to afford dihydroquinolone derivatives.

Chloro- and dichloro-anilines required the use of catalytic amounts of cupric acetate or cupric chloride for cyanoethylation to occur. In the case of o-nitroaniline, the cyanoethylation occurred only in the presence of Triton-B, whereas m-nitroaniline reacted in the presence of cupric acetate in dioxane. The p-isomer however, failed to react at all even under various drastic conditions.

p-Aminoacetophenone afforded the mononitrile in the presence of cuprous chloride whereas the dinitrile was obtained in the presence of Triton-B.
Many other alkyl substituted aromatic amines underwent cyanoethylation in the usual manner, the nitriles thus obtained were utilised to yield different type of heterocycles as shown below.\(^\text{11}\)

\[
\begin{align*}
&\text{R} \quad \text{BrCH₂CO₂Et} \quad \text{R} \quad \text{EtONa} \quad \text{HCO₂NH₂} \\
&\text{H} \quad \text{NC} \quad \text{CN} \quad \text{NH₂} \quad \text{CN} \quad \text{NH₂} \\
&\text{IV} \quad \text{Guanidine} \quad \text{Carbonate} \quad \text{III} \\
&\text{R} \quad \text{NH₂} \quad \text{NH₂} \\
&\text{V} \quad \text{V'} \\
&\text{NH₂} \quad \text{CN} \quad \text{OEt} \quad \text{CN} \quad \text{O} \\
&\text{IV'}
\end{align*}
\]

When 3-amino(3',4'-dimethylphenyl)-4-cyano-3-pyrroline (III, \(R = 3',4'-\text{diMe}\)) was treated with triethylorthoformate, the corresponding 3-ethoxy-methyleneiminopyrroline (IV') was isolated, which was then heated in pyridine in the presence of \(\text{NH}_₃\text{OH} - \text{HCl}\) to afford 4-amino-6,7-dihydro-5H-pyrrolo-(3,4-d)pyrimidine-3-oxide (V)\(^\text{11}\).

Condensation of \(\beta\)-anilinopropionitriles with dicyandiamide in the presence of potassium hydroxide in methyl cellosolve yielded \(\sigma\)-triazine derivatives\(^\text{10}\) (VI), some of which are known to possess interesting pharmacological properties like diuretic\(^\text{12}\).

\[
\text{VI}
\]

Amines react directly with acrylic acid in the presence of PPA to afford the required dihydro-quinolones in one step. This reaction was also carried out with other \(\alpha,\beta\)-unsaturated acids, when in most cases the corresponding amides were isolated, instead of the expected dihydro-quinolones. The amines studied for this reaction were dimethylanilines, dichloroanilines, nitroanilines, aminocoumarins, indolines and carbazoles\(^\text{13-18}\).

The reaction of phenylenediamines with \(\alpha,\beta\)-unsaturated acids in the presence of PPA afforded a variety of interesting compounds as shown below\(^\text{19}\).

\[
\begin{align*}
&\text{IX} + \text{X} + \text{XI} \\
&\text{XII} + \text{XIII} \\
&\text{XIV} + \text{XV} + \text{XVI} \\
&\text{XVII} + \text{XVIII}
\end{align*}
\]

\(\sigma\)-Nitroaniline reacted with acrylic acid in the presence of PPA to give a dihydro-4-quinolone derivative (XX). Reduction of XX yielded 8-amino-2,3-dihydro-4-quinolone (XXI), which was condensed with different acids in the presence of PPA to obtain imidazoquinolone derivatives (XXII)\(^\text{16}\).
In order to investigate the mechanism of this reaction, the benzo(i, j) quinolizine-1-one (XXIV) was reacted with acrylic acid in the presence of PPA. However, the reaction failed to occur, indicating that XXV was formed independently in the reaction. The formation of XXV can be explained by a Michael type of addition on the nitrogen atom followed by ring closure and a Friedel–Craft acylation at the 6′ position of tetrahydroquinoline and subsequent cyclisation to form a cyclopentane ring, both the named reactions occurring concurrently. Heating tetrahydroquinoline with \( \alpha \)-methyl acrylic or crotonic acid in the presence of PPA did not give compounds analogous to XXIV but only compounds similar to XXV were isolated.

\( p \)-Aminoacetophenone reacted with acrylic acid to yield 9-acetylbenzo(i, j)quinolizine-1,7-dione (XXVI). However, with crotonic acid only the corresponding dihydroquinolone was isolated\(^{20}\).

The reaction of indoline and 2-methylindoline with acrylic and crotonic acids yielded two products XXVII and XXVIII (R = H or alkyl)\(^{17,18}\).

Similar results were obtained in the reaction of hexahydrocarbazole with acrylic acid, when two compounds XXIX and XXX were isolated.
However with crotonic acid the reaction failed to take place\textsuperscript{17,18}.

\begin{center}
\includegraphics[width=0.8\textwidth]{chemical结构}
\end{center}

Many N-alkylquinolones are important not only because of their occurrence in nature but also because they exhibit interesting pharmacological properties. The above facts prompted us to investigate the reaction of secondary aromatic amines with \(\alpha,\beta\)-unsaturated acids in the presence of PPA.

The reaction of N-methylaniline with acrylic acid afforded 2,3-dihydro-N-methyl-4-quinolone which on dehydrogenation with Pd on charcoal in diphenyl ether gave N-methyl-4-quinolone (XXXI) which was identical with the alkaloid, echinopsine\textsuperscript{22}.

\begin{center}
\includegraphics[width=0.8\textwidth]{chemical结构}
\end{center}

Similarly, analogs of echinopsine were synthesised using different N-substituted anilines like N-ethyl and N-phenyl anilines with \(\alpha,\beta\)-unsaturated acids.

An interesting reaction is the condensation of N-methylaniline with cinnamic acid in the presence of PPA to afford an indeno(1,2a)indene derivative (XXXII). A reasonable mechanism for its formation is presented below\textsuperscript{23}.

The reaction of cinnamic acid and styrene in the presence of PPA also gave the same compound (XXXII).

Another usefulness of the cyanoethylation reaction is illustrated in the synthesis of aza-steroids as shown below\textsuperscript{24}:

\begin{center}
\includegraphics[width=0.8\textwidth]{chemical结构}
\end{center}

\textbf{O-CYANOETHYLATION}

The O-cyanoethylation of various phenols\textsuperscript{25}, hydroxybiphenyls\textsuperscript{26}, hydroxycoumarins\textsuperscript{27–31}, hydroxylavones\textsuperscript{33}, hydroxychromones\textsuperscript{33}, using different catalysts like Triton-B, sodium hydroxide solution (10%), sodium bicarbonate solution, yielded the o-propionitriles which were
hydrolysed to the corresponding propionic acids which in turn were cyclised to the corresponding chromanone derivatives.

\( \alpha \)-Hydroxyacetophenone with acrylonitrile in the presence of Triton-B gave two products, the corresponding \( \alpha \)-propionitrile (XXXIX) and the cyclised product—a benzopyran derivative (XL), whereas salicylaldehyde under similar conditions afforded three products (XLI-XLIJ)\(^{34}\).

The cyanooethylation of resacetophenone with acrylonitrile was carried out in the presence of anhydrous AlCl\(_3\) and dry HCl gas, when instead of the corresponding dinitrile a dihydrocoumarin derivative (XLIV) was isolated. Similar results were obtained in the case of 2,4-dihydroxy-3-methylacetophenone\(^{20}\).

Similar results were observed in the case of 2,5-dimethylphenol.

The cyclisation of 2,4-, 3,4- and 3,5-dimethylphenols with crotonic acid gave the corresponding 2-methyl-4-chromanones (XLVIII)\(^{36}\).

However, some interesting results were obtained in the reaction of 2,3-dimethylphenol with \( \alpha \)-methylacrylic and crotonic acids, where the cyclopentabenzopyrandiones (XLIX) were isolated\(^{37}\).

The reaction of 2,3-dimethylphenol with acrylonitrile under identical conditions gave a mixture of 2H-1-benzopyran-3,4-dihydro-7,8-dimethyl-6-propionitrile-2-one (XLV) and 3-(2',3'-dimethyl-4'-hydroxy)phenylpropionitrile (XLVI). The former was then hydrolysed and the resulting propionic acid was cyclised to yield cyclopenta(f)-1,3H-benzopyran-1,2-dihydro-5,6-dimethyl-3,9-dione (XLVII)\(^{35}\).

Similar results were obtained in the case of 2,5-dimethylphenol\(^{37}\).

Dichlorophenols which failed to react with acrylonitrile yielded the dichloro-chromanones on direct reaction with acrylic acid in presence of PPA\(^{38}\).
The reaction of 4-hydroxycoumarin with \( \alpha,\beta \)-unsaturated acids yielded 2,3-dihydropyrano-(3,2-C)benzopyran-4,5-diones (L)\(^{39}\).

\[
L
\]

\(a: R_1 = R_2 = R_3 = H; \ b: R_1 = Me, R_2 = R_3 = H; \ c: R_1 = R_3 = H, R_2 = Me; \ d: R_1 = H, R_2 = R_3 = Me; \ e: R_1 = R_2 = H, R_3 = Ph\)

Likewise 6-methyl-, 7-methyl-, 8-methyl-, and 6,8-dimethyl-4-hydroxycoumarins furnished the respective pyrano-benzopyrandiones in good yields\(^{39}\).

The reaction of 6-hydroxy-4-methylcoumarin with acrylic acid yielded two products, one of which was found to be pyrano-pyranide derivative (L1) and the other the corresponding acrylate\(^{40}\).

\[
L1
\]

However, with \( \alpha \)-methylacryl and crotonic acids only the corresponding acrylates were isolated.

7-Hydroxycoumarin with acrylic acid gave two products, one of which was found to be a linear isomer (LII) and the other an angular one (LIII)\(^{40}\).

\[
L II \quad L III
\]

Similarly with crotonic acid only one product analogous to LIII was isolated. However, with \( \alpha \)-methylacryl acid the corresponding acrylate was obtained. The reaction of 7-hydroxycoumarin with \( \beta,\beta \)-dimethylacryl acid in the presence of PPA afforded a brown thick oil which could not be purified. Hence the above reaction was carried out in the presence of anhydrous ZnCl\(_2\) and POCl\(_3\) at room temperature when a compound LIV was obtained\(^{35}\).

\[
L IV
\]

The reaction of 7-hydroxy-4-methylcoumarin with acrylic acid yielded three products LV-LVII.

\[
LV \quad LVI \quad L VII
\]

With \( \alpha \)-methylacryl acid and \( \beta,\beta \)-dimethylacryl acids only the corresponding acrylates were isolated. The use of crotonic acid led to two products, analogous to LVI and LVII respectively\(^{40}\).

The condensation of acrylic and crotonic acids with 7-hydroxy-2-methyl-, 6-hydroxy-2-methylchromones, 7-hydroxy-, 6-hydroxyflavones and 7-hydroxyisoflavone yielded only the corresponding angular benzodipyrandione derivatives\(^{40}\).

When 2,7-dihydroxynaphthalene was reacted with acrylic acid instead of the chromanone
derivative, 1,2,11,12-tetrahydro-3H,10H-naphtho[1,2-b:7,8-b']dipyran-3,10-dione (LVIII, R = H) was isolated. Similarly with crotonic acid LVIII (R = Me) was obtained\(^4\).

![LVIII](image)

The reaction of other dihydroxynaphthalenes failed to occur gives only tarry material.

**S-CYANOETHYLATION**

\(\sigma^-, m^-, p^-\) Thiocresols were cyanoethylated with acrylonitrile in the presence of aqueous sodium hydroxide to afford the corresponding S-propionitriles which were hydrolysed and the resulting acids were cyclised with \(\text{H}_2\text{SO}_4\) to yield the corresponding thiochromanones. In the case of 3-(3'-methylphenyl)thiopropionic acid two thiochromanones (LIX and LX) were isolated\(^4\).

![LIX and LX](image)

**C-CYANOETHYLATION**

The cyanoethylation of the methyl and ethyl ethers of phenols (like cresols, dimethyltrimethylphenols) was investigated using acrylonitrile and \(\epsilon\)-methacrylonitrile in the presence of anhyd.\(\text{AlCl}_3\) and using sym-tetrachloroethane as solvent. The propionitriles (LXI) thus obtained were hydrolysed with hydrochloric acid to the corresponding propionic acids (LXII). Cyclisation of the latter was effected with PPA to obtain the corresponding indanones (LXIII)\(^3\),\(^4\).

![LXI, LXII, LXIII](image)

To study further reactions on indanones, the reaction of a typical indanone, \textit{viz}. 4,5-dimethyl-6-methoxy-indanone (LXIV) with amyl nitrite was carried out, when a 3-isonitroso derivative (LXV) was isolated, which on heating with 35\% formaldehyde and hydrochloric acid yielded the 1,2-indandione (LXVI). The latter reacted with 3-hydroxy-4-methoxy-\(\beta\)-phenylethylamine to afford a spiroisoquinoline derivative (LXVII) which is structurally related to alkaloids like ochotensine\(^5\).

![LXIV, LXV, LXVI, LXVII](image)

The cyanoethylation of dimethoxynaphthalenes was studied under similar reaction conditions. 2,7-dimethoxy- and 2,7-diethoxy-naphthalene reacted with acrylonitrile and \(\epsilon\)-methacrylonitrile to directly yield phenalanone derivatives (LXVIII) instead of the expected dinitriles\(^4\).

![LXVIII](image)
The other dimethoxynaphthalenes (1,5- and 2,3-) gave the corresponding dinitriles which could not be hydrolysed under different experimental conditions\textsuperscript{46,47}.

Reaction of acrylic acid with 2,3-xylendimethyl ether in the presence of PPA afforded the same inden-1-one (LXIX) as that obtained via cyanoethylation, hydrolysis and subsequent cyclisation\textsuperscript{48}.

![Diagram](image)

2,5- and 3,4-Xylendimethyl ethers afforded similar results.

The reaction of acrylic acid with 1,5-dimethoxynaphthalene gave two products, 1,2-dihydro-5,9-dimethoxy-3H-benz(e)inden-3-one (LXXI) and 2,3-dihydro-5,9-dimethoxy-1H-benz(e)inden-1-one (LXXII), whereas with \(\beta\)-methylacrylic and crotonic acids compounds analogous to LXXII could only be isolated\textsuperscript{46}.

![Diagram](image)

The reaction of 2,3-dimethoxynaphthalene with \(\alpha,\beta\)-unsaturated acids gave a mixture of two isomers, identified as dimethoxybenz(c)-indenone (LXXIII) and dimethoxybenz(f)-indenone (LXXIV) derivatives\textsuperscript{47}.

![Diagram](image)

The reaction of 2,7-dimethoxynaphthalene with acrylic acid gave a mixture of two products which were assigned structures as 4-methoxy-1H-phenalene-1-one (LXXV) and 4,9-dimethoxy-1H-phenalene-1-one (LXXVI) on the basis of spectral-analytical data.
procedure employing direct condensation with an \(\alpha,\beta\)-unsaturated acid could be successfully utilised to yield a variety of interesting compounds.

ANNOUNCEMENTS

SEMINAR ON POLYMERS FOR SURFACE COATINGS: RECENT DEVELOPMENTS

The Oil Technologists' Association of India, Southern Zone is organising a seminar on "Polymers for Surface Coatings: Recent Developments" on 27-28 November, 1982 at Hyderabad. The salient topics proposed to be discussed during the seminar are: (i) Polymers and their role in coatings vis-a-vis improved protection against corrosion (ii) Polymers and their status in application to new areas of development like off-shore exploitation, atomic power reactors and space exploration (iii) Newer types of polymers to meet ecological and economy requirements, e.g., water soluble vehicles and powder coatings, UV and electron beam curing systems.

Experts will be invited to give a lead lectures and research papers on original work will also be presented. Abstracts (300 words) of research papers proposed to be presented in the seminar are invited for inclusion in study material. Registration fee for OTAI members is Rs. 50/- and for non-members Rs. 100/- per person. Last date for submitting abstracts and for registrations is 31st August, 1982. Further particulars can be had from Dr. P. S. Sampathkumar, Convener, Seminar on Polymers, OTAI Southern Zone, Regional Research Laboratory, Hyderabad 500 009.

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