Aminomethylation reactions of nitrogen and sulfur five membered heterocyclic compounds

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Five membered nitrogen and sulfur heterocyclic compounds such as isatins, benzimidazole, benzimidazolin-2-thione, benzoazolone-2, benzoazolin-2-thione, benzotriazole, benzothiazolin-2-thione, 1,3,4-oxadiazolin-5-thione and 1,2,4-triazolin-5-thiones have been prepared and subjected to aminomethylation reactions in presence of formaldehyde and amines. Secondary as well as primary aromatic amines bearing different substituents have been successfully utilized in the aminomethylation reaction. The aminomethylated products have been tested for antibacterial, antifungal, antiviral, anticancer, antileishmanial and antifilarial activity. A number of such products have exhibited promising antifungal and antileishmanial activities.

Some of the five membered N and S heterocyclic compounds undergoing aminomethylation reactions are : isatin (1), benzimidazole (2), benzimidazolin-2-thione (3), benzoazolinone-2 (4), benzoazolin-2-thione (5), benzotriazole (6), benzothiazolin-2-thione (7), 1,3,4-oxadiazolin-5-thione (8) and 1,2,4-triazolin-5-thione (9).

Synthesis and aminomethylation of isatins

Isatin (1) can be synthesized conveniently by Sandmeyer isonitrosoacetanilide synthesis4 (Scheme 1). Aniline.HCl, chloral and hydroxyl amine.HCl are dissolved in water and the solution is heated for few minutes. The solution is shaken vigorously and cooled whereby crystals of isonitrosoacetanilide are obtained. The isonitrosoacetanilide is filtered and dried.

The dried isonitrosoacetanilide is then cyclized in conc. H2SO4 at 60–80° to yield isatin. The crude isatin is then recrystallized from glacial acetic acid or purified by dissolving in aq. NaOH and reprecipitating with HCl (Scheme 1).

N, S Heterocycles undergoing aminomethylation

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and formaldehyde leads to aminomethylated product 1-morpholinomethyl-4-chloroisatin (14). Likewise 6-chloroisatin (13) with formaldehyde and morpholine furnishes 1-morpholinomethyl-6-chloroisatin (15).

Scheme 1. Synthesis of isatins.

4-Substituted anilines yield 5-substituted isatins whereas 2-substituted anilines yield 7-substituted isatins. For instance 4-chloroaniline leads to 5-chloroisatin (9). Similarly 2-chloroaniline gives 7-chloroisatin (10). The isonitrosoacetanilide from 3-chloroaniline (11) can undergo cyclization in conc. H₂SO₄ at two different positions - position 2 and 6. Cyclization at position-2 gives 4-chloroisatin (12) and cyclization at position-6 leads to 6-chloroisatin (13). Thus cyclization of the isonitrosoacetanilide from 3-chloroaniline yields a mixture of 4-chloroisatin (70%) and 6-chloroisatin (30%) (Scheme 2).

Scheme 2

The isomeric mixture⁵ of 4 and 6 chloro isatins was dissolved in N/2 NaOH. The solution was filtered. To the filtrate N/2 HCl was gradually added. As the pH dropped below 8 precipitation of 4-chloroisatin commenced which was completed at pH 4.5. The filtrate obtained after removing 4-chloro isomer was further acidified with N/2 HCl when precipitation of 6-chloro isomer commenced which was completed at pH 2.0.

Treatment of 4-chloro isatin⁵ (12) with morpholine

Aminomethylation of 4 and 6 chloroisatin.

The isonitrosoacetanilide from 4-methoxyaniline (16) when cyclised in conc. H₂SO₄ did not yield any isatin. A small amount of 5-methoxyisatin (17) was however isolated when the cyclization was performed in PPA (Scheme 3). The failure of the cyclisation in the present case may
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be due to extensive sulfonation of the aromatic ring due to strong activating influence of methoxy group. With a view to moderating the electron donating influence of methoxy group to a considerable extent, a bromine/chlorine atom has now been introduced at position-3 of \( p \)-anisidine and position-4 of \( m \)-anisidine. The 3-bromo/chloro-4-methoxy and 4-bromo/chloro-3-methoxy anilines, thus obtained, were converted to the corresponding isonitrosoacetanilides, which underwent smooth cyclization in conc. sulphuric acid furnishing the mixtures of isomeric pairs consisting of 4-bromo/chloro-5-methoxy-, 6-bromo/chloro-5-methoxy- and 5-bromo/chloro-4-methoxy-, 5-bromo/chloro-6-methoxy-isatins in 80-85% yields. Thus, mild electron withdrawing or mild electron donating groups give isatins in excellent yields and strong electron donating groups have to be suitably moderated in order to obtain better results (Scheme 4).

During dissolution of isomeric pairs of 4- and 6-substituted isatins in sodium hydroxide solution, the isatin ring opens up resulting in the formation of the sodium salt of the corresponding isatinic acid which on acidification with HCl immediately cyclizes back to isatin (Scheme 4).

The isatinic acid anion corresponding to the 4-substituted isatin is a relatively strong conjugate base, and, therefore, more inclined to accept a proton. It stabilizes at pH 8.0 or above. The lowering of pH value below 8.0 destabilizes the isatinic acid anion resulting in the liberation of isatinic acid which, immediately gets transformed into the 4-substituted isatin. The continuous removal of isatinic acid in the form of 4-substituted isatin prevents the establishment of isatinic acid anion/isatinic acid equilibrium resulting in almost total conversion of isatinic acid anion to the 4-substituted isatin as the pH is progressively brought down to 4.5.

The isatinic acid anion corresponding to the 6-substituted isatin is a relatively weak conjugate base and, therefore, less inclined to accept a proton. It continues to remain stable at pH as low as 4.0. The anion gets destabilized when the pH value is lowered below 4.0 leading to the formation of the corresponding isatinic acid which immediately undergoes cyclisation yielding the 6-substituted isatin. The precipitation is complete as the pH is brought down to 2.0.

It is obvious that the precipitation of 4- and 6-substituted isatins from alkaline solution of their isomeric mixtures over widely differing pH values affords a novel and efficient method for their separation. The method, indeed is of wide applicability as it can be used to separate iso-

| Isatins synthesized |
|---------------------|
| \( R_1 \) | \( R_2 \) | \( R_3 \) | \( R_4 \) |
| H    | H    | H    | H    |
| H    | Cl   | H    | H    |
| H    | H    | H    | Cl   |
| H    | B   | H    | H    |
| H    | M   | H    | H    |
| Br   | OMe  | H    | H    |
| H    | OMe  | Br   | H    |
| Cl   | H    | H    | H    |
| H    | H    | Cl   | H    |
| Cl   | OMe  | H    | H    |
| OMe  | Br   | H    | H    |
| H    | Br   | OMe  | H    |
| OMe  | Cl   | H    | H    |
| H    | Cl   | OMe  | H    |

Scheme 4
meric binary mixtures of organic acids with a marked difference in their relative acidity. This has been experimentally verified by effecting the separation of o-chlorobenzoic acid and p-chlorobenzoic acid from the alkaline solution of their mixtures. As expected the p-chlorobenzoic acid, being relatively week acid, precipitated out at a higher pH while the o-chlorobenzoic acid separated out at a lower pH value.

The substituents at 4/6 position of isatin acquire positions ortho/para to the carbonyl group in the corresponding isatinic acid, respectively. The acidity of isatinic acids is determined to a large extent by the proximity of the carbonyl group to the carboxylic group. The relative acidity of an isatinic acid with a substituent ortho to the carbonyl group is apparently less than its isomer with substituent para to the carbonyl group. This is in contrast to the substituted aromatic acids where the ortho-substituted acids are invariably stronger than their para-isomers.

The relative proximity of the substituent ortho to the carbonyl group, greatly reduces its inductive effect, thus rendering the isatinic acid relatively weak. The substituent para to the carbonyl group, on the other hand, exerts its inductive effect in a normal manner, thereby making the isatinic acid relatively strong.

4-Bromo-5-methoxy (18) and 6-bromo-5-methoxy isatisins\(^6\) (19) thus separated in a pure state were aminomethylated with morpholine in the presence of formalin to yield corresponding 1-aminomethylated products (20, 21).

### Aminomethylated isatin-3-thiosemicarbazones

The striking antiviral activity\(^7\) of N-methyl (22) and N-ethyl isatin-3-thiosemicarbazones (23) led us to replace methyl and ethyl group with an aminomethyl group in order to examine the effect of aminomethyl group on antiviral activity\(^8\),\(^9\). The aminomethylated isatin-3-thiosemicarbazones\(^10\),\(^11\) (25-27) exhibited antiviral activity as well as anticancer, antibacterial and antifungal activity. It is interesting to note that the isatin N-Mannich bases appeared to be more promising as antiviral agents.

Next a series of 4-arylthiosemicarbazides were prepared and condensed with isatins in acidic medium. The 3-arylthiosemicarbazono-2-indolinones thus prepared were then treated with formalin and secondary amines leading to aminomethylated-2-indolinones (28).

### Aminomethylation of 3-arylimino-2-indolinones

Further the isatins were treated with various substituted anilines to yield 3-arylimino-2-indolines (29) which were then aminomethylated with different secondary amines to get the target compounds (30). The compounds were evaluated for their cysticidal activity.

### Aminomethylation of 3-hydracozo-2-indolinones

It has been observed that 2-aminobenzothiazole\(^12\) does
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not react with isatin as a nucleophile\textsuperscript{13}. However when 2-aminobenzothiazole is transformed into 2-hydrazinobenzothiazole, it reacts smoothly with isatin leading to 3-hydrizonobenzothiazolyl-2-indolinones which were conveniently aminomethylated (31) in the presence of formalin and secondary amines.

A number of benzoyl hydrazines, anilino-acetyl hydrazines and phenoxy acetyl hydrazines were prepared by the standard procedures. These hydrazine derivatives were then condensed with isatins as nucleophiles\textsuperscript{14–17}. The products obtained after condensation were subjected to aminomethylation reactions. The aminomethylated products were obtained in excellent yields (32–34, 41) compound (39) was prepared via a number of steps starting from (35) as indicated in the Scheme 5.

Aminomethylation of benzimidazole

Benzimidazole(s) (48) contain an active hydrogen atom attached to nitrogen which can be easily replaced by an aminomethyl group\textsuperscript{18–22} (49) in the presence of formalin and an amine. Many benzimidazoles are available commercially. If desired they are easily prepared from appropriately substituted $o$-phenylene diamine (47) and formic acid. One can also take acetic acid in place of formic acid to get 2-methylbenzimidazole. Thus by taking appropriate carboxylic acid one can get appropriately 2-substituted benzimidazoles. 2-Substituents in benzimidazole bulkier than methyl group create difficulty in aminomethylation reactions (Scheme 6).

Aminomethylation of benzimidazolin-2-thione

Benzimidazolin-2-thione (55) unlike benzimidazole has two active hydrogen atoms attached to each nitrogen. Both these hydrogens have been replaced with aminomethyl groups\textsuperscript{23–26} (57) in the presence of formalin and an amine. Secondary as well as primary aromatic

Scheme 5
Aminomethylation of benzimadazole

The aminomethylation of benzimidazole has been successfully incorporated into benzimidazolin-2-thione molecule (Scheme 7). The benzimidazolin-2-thione (55) may be prepared by the reaction of carbon disulfide on o-phenylenediamine (54).

Aminomethylation of benzoxazolinone-2

Benzoxazolinone-2 (61) is one of the versatile five membered heterocyclic system which undergoes aminomethylation with ease. In order to prepare benzoxazolinone-2, o-aminophenol and urea are fused together at elevated temperature. The crude product is repeatedly recrystallized from water to get pure material.

During fusion with urea considerable decomposition takes place resulting in the lower yields of the material. We have developed a preparative method for benzoxazolinone-2. In this procedure o-aminophenol and urea are heated in dry pyridine. After pyridine is distilled off the residue is poured into water thereby pure benzoxazolinone-2 is obtained in high yields. Aminomethylation of benzoxazolinone-2 has been done in ethanolic medium in the presence of formalin and an amine. Different types of amines have been utilized to obtained the required aminomethylated products (62) (Scheme 8).

Scheme 6. Aminomethylation of benzimadazole.

Scheme 7. Aminomethylation of benzimidazolin-2-thione.

Aminomethylation of benzoxazolinone-2

Next we have taken a closely related system benzoxazolinone-2-thione (64) to be studied for aminomethylation reaction. Its method of preparation is described in organic synthesis. The procedure involves treatment of o-aminophenol (63) with potassium ethylxanthate in ethanol followed by acidification of the reaction mixture with acetic acid. The benzoxazolinone-2-thione (64) thus obtained has been treated with formalin and amines. The reaction takes place both with secondary as well as with primary aromatic amines (69) (Scheme 9).

Aminomethylation of benzotriazole

Benzotriazole, a five membered heterocyclic system with three nitrogen atoms at 1,2,3 positions contains an active hydrogen atom attached to nitrogen atom. It was subjected to aminomethylation reaction with various types of primary aromatic amines. The L-arylamominomethyl-
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benzotriazoles (72) can also be obtained by treating 1-hydroxymethylbenzotriazole (71) with primary aromatic amines, when 1-dimethylaminomethylbenzotriazole (73) was treated with aniline, the dimethylamino group got displaced with aniline (Scheme 10).

Aminomethylation of benzothiazolin-2-thione

The aminomethylation reaction of benzothiazolin-2-thione (79) obtained from o-amino thiophenol (78) and carbon disulfide has been studied in detail. Different types of primary (77) and secondary amines have been taken for aminomethylation reaction (80) (Scheme 11).

Aminomethylation of 1,3,4-oxadiazolin-5-thiones

1,3,4-Oxadiazolin-5-thiones having a variety of substituents at position-2 have been synthesized in order to study their aminomethylation reaction.

Thus 4-butylamino-3-nitro benzoic acid hydrazide was cyclized in the presence of potassium hydroxide and CS₂ to furnish 2-(4'-butylamino-3'-nitrophenyl)-1,3,4-oxadiazolin-5-thione which was amino methylated in presence of morpholine and formaldehyde to yield 4-morpholinomethyl-2-(3'-nitro-4'-butylaminophenyl)-1,3,4-oxadiazolin-5-thione (81).

4-Benzylthio-3-nitrobenzoic acid hydrazide (83) was similarly transformed to 2-(4'-benzylthio-3'-nitrophenyl)-1,3,4-oxadiazolin-5-thione (84) which was again aminomethylated in the usual manner to yield the target compounds (85,86). Another 1,3,4-oxadiazolin-5-thione
Aminomethylation of 1,3,4-oxadiazolin-5-thione

(88) has been obtained from 4-acetylamino-3-chloro-benzoic acid hydrazide (87) which undergoes amino-methylation leading to the desired products (89) in excellent yields (Scheme 13).

Microwave mediated aminomethylation

Microwave mediated synthesis of heterocyclic compounds have attracted more attention of chemists because of shorter reaction time, simple reaction conditions, higher yields and purer products. Many reactions like oxidation, reduction, alkylation, O-benzylation, hydrazinolysis, esterification, aromatic substitution and decarboxylation proceed smoothly under microwave conditions. Aminomethylation was the further addition to the microwave mediated reactions.

Aminomethylation of isatins

1-Morpholinomethyl-4/6-bromo-5-methoxy isatins and 1-morpholino-4/6-chloroisatins have been obtained in excellent yield by irradiating a mixture of isatin, formaldehyde and morpholine (Scheme 15).

Aminomethylation of 3-hydrazone-2-indolinones

A series of 1-aminomethyl-3-[4'- (4''-chlorobenzyl oxy)-benzoyl hydrazone] -indolin-2-ones have been obtained by irradiating compound (96) with formaldehyde and morpholine and piperidine. Compound
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Aminomethylation of 3-hydrazone-benzothiazolyl-2-indolinones

3-(6'-Substituted-2'-hydrazonobenzothiazolyl)-4/6-bromo-5-methoxy-2-indolinones on irradiation in the presence of formaldehyde and secondary amines gave 3-(6'-substituted-2'-hydrazonobenzothiazolyl)-1-aminomethyl-4/6-bromo-5-methoxy-2-indolinones. Compounds were obtained by acid catalysed condensation of 2-hydrazone-6-substituted benzothiazoles with isatins under microwave irradiation (Scheme 17).

Aminomethylation of benzazoles

Aminomethylation of benzazoles was carried by irradiating mixture of benzazoles, formaldehyde and 4-benzylxoy anilines to get 4-(benzyloxy) anilinomethyl benzazoles. 4-Benzylxoyanilines were obtained by O-benzylation of 4-hydroxyacetanilide followed by hydrolysis (Scheme 18).

Mechanism of aminomethylation reaction

The aminomethylation reaction is believed to take place in two steps. Initially the amine reacts with formaldehyde to generate an aminomethylol. The aminomethylol then reacts with active hydrogen containing substrate [say for instance benzoxazolinone-2 (B)] to furnish amino methylated product (C).

Alternatively formaldehyde may react with benzoxazolinone-2 (B) to generate N-hydroxymethyl benzoxazolinone-2 (D) which subsequently reacts with amine (e.g. dimethylamine) to yield N-Mannich bases (C).
Aminomethylated compounds have been primarily synthesised on account of their medicinal importance.

The compounds have been tested for their antiviral activity against

**Viruses**
Polio II

**Parainfluenza**
Antibacterial activity against

**Bacteria**
(i) *Streptococcus faecalis.*
(ii) *Klebsiella pneumoniae.*
(iii) *Escherichia coli.*
(iv) *Pseudomonas aeruginosa.*
(v) *Staphylococcus aureus.*

**Fungi**
(i) *Candida albicans.*
(ii) *Cryptococcus neoformans.*
(iii) *Sporotrichum schenckii.*
(iv) *Trichophyton mentagrophytes.*
(v) *Aspergillus fumigatus.*

Antifungal and antileishmanial activity are listed in Tables 1 and 2.

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**Table 1.**
Compounds showing antifungal activity

| Compounds showing antifungal activity | T. mentagrophytes MIC \( \mu g/ml \) |
|--------------------------------------|--------------------------------------|
| 1.                                   | 50                                   |
| 2.                                   | 50                                   |
| 3.                                   | <12.5                                |
| 4.                                   | 25                                   |
| 5.                                   | 50                                   |

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**Scheme 18.** Microwave mediated aminomethylation of benzazoles.
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Table 2.

| Compounds showing antileishmanial activity | % Inhibition of L. donovani |
|--------------------------------------------|----------------------------|
| 1.                                         | 100                        |
| 2.                                         | 100                        |
| 3.                                         | 100                        |
| 4.                                         | 100                        |
| 5.                                         | 100                        |
| 6.                                         | 100                        |
| 7.                                         | 100                        |
| 8.                                         | 100                        |
| 9.                                         | 100                        |
| 10.                                        | 100                        |
| 11.                                        | 100                        |
| 12.                                        | 100                        |
| 13.                                        | 100                        |

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