SYNTHETIC APPLICATIONS OF
LEWIS ACID-INDUCED N-METHYLENEAMINE EQUIVALENTS

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Abstract - The reactions involving one of the simplest imines, N-methyleneamine (monomeric formaldehyde imine), are very limited from the synthetic viewpoint because it is difficult to generate the N-methyleneamine. In this review are summarized a method and synthetic applications of N-methyleneamine equivalents generated from hexahydro-1,3,5-triazines or N-methoxymethylamines in the presence of a Lewis acid. Reactions with various nucleophiles yield aminomethylated products at the α-position of amines. Lewis acid-induced N-methyleneanilines can also serve as azadienes with electron rich diene for reverse electron demand [4π+2π] cycloaddition reactions.

The Mannich reaction is a well-known synthetic method to be applicable to the syntheses of wide range of nitrogen containing molecules.1,2 This reaction involves iminium ions called as Mannich bases derived from amine and aldehyde under acidic condition to yield the aminomethyalted products. For the successful reaction were used normally secondary amines and formaldehyde with properly activated nucleophiles. Under this condition the preparation of aminomethylated secondary amine products from primary amine via formaldehyde iminium ions is impossible because the aminomethylated secondary amines are more reactive toward iminium ion formation under this reaction condition. Furthermore, the harsh reaction condition limits the applicable nucleophiles that should be free from any acid sensitive functional groups. To avoid these drawbacks, free monomeric N-methyleneamine (1) should be available for the synthetic purpose. However, N-methyleneamine is unstable and it is difficult to be
prepared and to be isolated as its pure form\textsuperscript{3} except only one case as hexakis\(N\)-methyleneamine)-cyclotriphosphazene\textsuperscript{4} that was obtained by addition of paraformaldehyde to phosphonodihydrazides.

\[
\begin{align*}
R^1\text{N} \equiv \text{CH}_2 & & R^1\text{N} = \text{CH}_2 \ X \\
1 & & 3 \ X = \text{Ts} \\
 & & 4 \ X = \text{CN} \\
 & & 5 \ X = \text{OMe}
\end{align*}
\]

\(N\)-Methyleneamine is only known in the gas phase through flash vacuum thermolysis from the corresponding \(\alpha\)-amino nitriles \textsuperscript{4}.\textsuperscript{3} Synthetic efforts enabled to generate \(N\)-methyleneamine as an intermediate from \(N\)-chloroalkylamine \textsuperscript{2},\textsuperscript{3} \(N\)-tosylmethylamide \textsuperscript{3},\textsuperscript{5} \(\alpha\)-cyanomethylamine \textsuperscript{4}\textsuperscript{6} or \(N\)-methoxymethylamine \textsuperscript{5}\textsuperscript{7,8} with strong bases. \(N\)-Trimethylsilyl-\(N\)-methyleneamine-AlCl\(_3\) complex was reported to be obtained \textit{in situ} from (trimethylsilyl)methylazide with AlCl\(_3\).\textsuperscript{9}

1. Characteristics of Lewis Acid-Induced \(N\)-Methyleneamine Equivalents

For the last few years we have found that \(N\)-methyleneamine equivalents can be generated either from 1,3,5-trisubstituted hexahydro-1,3,5-triazines or \(N\)-methoxymethylamines in the presence of a Lewis acid. \(N\)-Methoxymethylamines \textsuperscript{5} have close relationship with 1,3,5-trisubstituted hexahydro-1,3,5-triazines \textsuperscript{6} due to their convertibility (Scheme 1). The reaction for the preparation of \(N\)-methoxymethylamines with an amine, paraformaldehyde, and sodium methoxide in methanol yields either \(N\)-methoxymethylamines or 1,3,5-trisubstituted hexahydro-1,3,5-triazines, or a mixture of both depending on the substituent \(R^1\).\textsuperscript{10,11} In most cases hexahydro-1,3,5-triazines were obtained with an alkylamine while \(N\)-methoxymethylamines were yielded with anilines. Heating of \(N\)-methoxymethylamines under reduced pressure resulted in quantitative transformation into the corresponding hexahydro-1,3,5-triazines. Some of 1,3,5-trisubstituted hexahydro-1,3,5-triazine is also converted to \(N\)-methoxymethylamine under reflux with sodium methoxide in methanol.

\textbf{Scheme 1}
When strong Lewis acid like TiCl$_4$ was added into 1,3,5-trisubstituted hexahydro-1,3,5-triazines (6) or N-methoxymethylamines (5) in CH$_2$Cl$_2$ the color of this reaction mixture became deep wine-red, which indicated the formation of a complex with TiCl$_4$ (Scheme 2). The structure of the complex generated from 1,3,5-trisubstituted hexahydro-1,3,5-triazines is assumed to be 9 or 10 because $N$-methyleneamine peaks in $^1$H and $^{13}$C NMR spectra were observed by mixing 1,3,5-tri-$n$-butylhexahydro-1,3,5-triazine with 5 mol% of TiCl$_4$. This spectral data were also consistent to alternative zwiterion intermediate (11) whose existence was found during the reaction with the nucleophile 1-Boc-2-tert-butyl(dimethyl)siloxypyrrole. The $^1$H and $^{13}$C NMR spectra of the mixture of N-methoxymethylaniline with TiCl$_4$ did not show any peak corresponding to $N$-methylenaniline. This supports tentatively assumed intermediate (7) or (8) with exclusion of the possibility that the C–OMe bond is cleaved to make $N$-methyleneamine type of complex before nucleophile attacks. However, under the reaction condition with a strong Lewis acid like TiCl$_4$ the intermediate (7) or (8) serves as a $N$-methyleneamine equivalent to the coming nucleophile with the removal of the methoxy group.

**Scheme 2**

These synthetic equivalents of $N$-methyleneamines can be used for aminomethylation reactions with various nucleophiles being added to the $\alpha$-position of amines. These reactions would overcome the drawbacks in the classical Mannich reaction as mentioned at the early part of the introduction.

**2. Lewis Acid-Induced $N$-Methyleneamine Equivalents as Mannich Bases**

Utilization of the $N$-methyleneamine equivalents generated either from 1,3,5-trisubstituted hexahydro-1,3,5-triazines (6) or N-methoxymethylamines (5) in the presence of a Lewis acid afforded a facile synthetic route for the various aminomethylated secondary amines (12 - 15). Reactions with heteroatom nucleophiles such as phosphorus and azide from trialkylphosphine and trimethylsilyl azide yielded...
aminomethylphosphonate(12)\textsuperscript{11,13} and aminomethylazide(13)\textsuperscript{14} (Scheme 3). Hydride nucleophile was introduced to envisage the effective monomethylation reactions (14) from either hexahydro-1,3,5-triazines\textsuperscript{15} and (or) \(N\)-methoxymethylamines\textsuperscript{16} in high yield. The reactions with the carbon nucleophiles were also successful. 1,3,5-Trisubstituted hexahydro-1,3,5-triazines or \(N\)-methoxymethylamines were reacted with trimethylsilyl cyanide in the presence of TiCl\(_4\) to give aminoacetonitrile (15) in 40-90\% yield (Scheme 3).\textsuperscript{17}

\[
\text{Scheme 3}
\]

\[
\begin{align*}
R^1\text{NHCH}_2\text{OMe} & \xrightarrow{\text{Nu}} R^1\text{NHCH}_2\text{P(=O)(OR)}_2 \\
& \xrightarrow{\text{Nu}} R^1\text{NHCH}_2\text{N}_3 \\
& \xrightarrow{\text{Nu}} R^1\text{NHCH}_2\text{H} \\
& \xrightarrow{\text{Nu}} R^1\text{NHCH}_2\text{CN}
\end{align*}
\]

\(N\)-Methyleneanilines derived from either 1,3,5-triphenylhexahydro-1,3,5-triazines or \(N\)-methoxymethylanilines were reacted with allyltrimethylsilane to yield a mixture of 1,2,3,4-tetrahydroquinolines (17) and homoallylic anilines (18) arising from the branching reactions from the same silicium cationic intermediate (16) (\(Y = \text{SiMe}_3\)) by the pathway i or ii respectively (Scheme 4).\textsuperscript{18}

\[
\text{Scheme 4}
\]

Changing the allyl nucleophile to allylmagnesium bromide (\(Y = \text{MgBr}\)) and allyltributyltin (\(Y = \text{SnBu}_3\)) led to the reaction proceeding in only one direction for the selective synthesis of homoallylic anilines without the formation of quinolines. The cationic intermediate (16) (\(Y = \text{MgBr, SnBu}_3\)) generated from allylmagnesium bromide or allyltributyltin does not survive long enough for electrophilic aromatic
cyclization as the pathway i with phenyl ring due to the weakness of carbon-magnesium and carbon-tin bonds compared with the carbon-silicon bond. Instead removal of Y according to the pathway ii became dominant. This result supports the reaction involves the formation of the cationic intermediate like 16 instead of $[4\pi+2\pi]$ cycloaddition of N-methyleneaniline with olefin.

The similar reactions with propargyltrimethylsilanes provided N-but-2,3,3-dienylanilines (23), 4-methylene-1,2,3,4-tetrahydroquinolones (21) and its oxidized product 4-methylquinolines (22) (Scheme 5). These products came from branching reactions of electrophilic aromatic substitution (pathway i) and the elimination (pathway ii) from the vinylic cationic intermediate (19). About the mechanistic details of this reaction there is still a possibility that the formation of cyclic product from N-methyleneanilines proceeds by a concerted cyclization followed by the elimination reaction. However, obtaining the mixture of the reaction products (21-23) with dependency of the electronic characteristics of phenyl ring of starting substrate seems more feasible to be explained with the same vinylic cationic intermediate as 19.

Utilization of N-methyleneamine equivalent as an electrophile could afford the synthetic route to aziridine-2-carboxylates. An adduct (24) was yielded from the reaction of the N-methyleneamine equivalents generated from N-methoxymethylamines or 1,3,5-trisubstituted hexahydro-1,3,5-triazines in the presence of catalytic amount of Lewis acid such as BF$_3$·OEt$_2$ or SnCl$_4$ with the nucleophile alkylidiazooacetate. Then the nucleophilic nitrogen of the amine at 24 kicks out N$_2$ as a leaving group with the formation of the three membered aziridine ring (25) (Scheme 6). This reaction can be served as a facile synthetic method to prepare various aziridine-2-carboxylates with diverse substituent on the nitrogen in good yield.
Heterocyclic nucleophile 2-trimethylsilyloxyfuran reacts with the N-methyleneamine equivalents generated either from 1,3,5-trisubstituted hexahydro-1,3,5-triazines (6) or N-methoxymethylamines (5) in the presence of catalytic amount Ti(Oi-Pr)$_4$ to yield 5-aminomethyl-2,5-dihydrofuran-2-ones (26) in high yield (Scheme 7).$^{22}$

Based on the successful reaction with the nucleophile 2-trimethylsilyloxytetrahydrofuran, the similar heterocyclic nucleophile 1-Boc-2-tert-butyldimethylsilyloxyprrole was applied to Lewis acid-induced N-methyleneamine equivalents. These reactions gave insights into the nature of N-methyleneamine equivalents generated from 1,3,5-trisubstituted hexahydro-1,3,5-triazines.

Reactions of N-methoxymethylaniline (5, $R = \text{Ph}$) or 1,3,5-triphenylhexahydro-1,3,5-triazines (6, $R^1 = \text{Ph}$) with 1-Boc-2-tert-butyldimethylsilyloxyprrole yielded the expected aminomethylated product 1-Boc-5-anilinomethyl-2,5-dihydropyrrol-2-ones (27) (Scheme 8) while the same reactions from 1,3,5-trialkylhexahydro-1,3,5-triazines (6, $R^1 = \text{alkyl}$) yielded bicyclic spiro compound 1-Boc-7,9-dialkyl-2-oxo-1,7,9-triaza[4.5]deca-3-nes (28) as the major product with small amount of 1-Boc-5-
alkylaminomethyl-2,5-dihydropyrrol-2-ones (27) in a few cases (Scheme 9).\textsuperscript{12}

Scheme 9

This result was explained by the formation of the intermediate in the way how three carbon-nitrogen bonds consisted of 1,3,5-trisubstituted hexahydro-1,3,5-triazine ring were broken in the presence of Lewis acids.

Scheme 10

When the substituent is aryl \((R^1 = \text{aryl})\) monomeric \(N\)-methyleneanilines equivalents described as 9 and 10 in the Scheme 10 would be the dominant species with all three carbon-nitrogen bonds broken regardless of the Lewis acid used. While only one carbon-nitrogen bond of the ring is broken from
1,3,5-trialkylhexahydro-1,3,5-triazines ($6$, $R^1 = \text{alkyl}$). When the fragmentation of 1,3,5-trialkylhexahydro-1,3,5-triazine is not completed to generate $N$-methyleneamine equivalents as a monomer drawn in the bracket as $9$ or $10$, zwitterionic intermediate like $11$ as a possibly coordinated complex with the Lewis acid can be formed by breaking only one C–N bond. The reaction of this intermediate with the nucleophile 1-Boc-2-tert-butyldimethylsilyloxypyrrole gives an adduct ($29$) bearing an electron rich anionic nitrogen that may complex with the Lewis acid. Immediate abstraction of the proton at C-5 by the basic nitrogen regenerates another type of nucleophile in the intermediate ($30$) with aminomethyl group at C-5. Mannich base is generated again from the intermediate ($30$) in the presence of a Lewis acid with the removal of one amine that is ready to react with internally pre-formed nucleophile with aminomethyl at C-5 as $31$. One more intramolecular aminomethylation at C-5 of the reactive intermediate ($31$) by Mannich base gives a double aminomethylated product of 1-Boc-2-oxo-7,9-dialkyl-1,7,9-triazaspiro[4.5]dec-3-ene ($28$). Under this condition monoaminomethylated product of 1-Boc-5-aminomethyl-2,5-dihydropyrrol-2-ones ($27$) can not be obtained. This reaction revealed the presence of the intermediate $N$-methyleneamines as $11$ besides $9$ and $10$ possibly generated from 1,3,5-trisubstituted hexahydro-1,3,5-triazine ($6$) depending on the characteristics of $R^1$ whether it is alkyl or aryl. For the proper aminomethylation reaction the intermediates ($9$) and ($10$) should be generated and used with nucleophiles while it is not possible with the intermediate ($11$). Lower chemical yield could be explained by the formation of $11$ as the dominant species in the aminomethylation reaction with 1,3,5-trialkylhexahydro-1,3,5-triazine ($6$) with most nucleophiles compared with the $N$-methoxymethylamines ($5$).

The crystalline structure of this novel spirobicyclic compound in Figure 1 shows an interesting feature. The structure of 1-Boc-2-oxo-7,9-dibenzyl-1,7,9-triazaspiro[4.5]dec-3-ene has imposed mirror symmetry and the hexahydropyrimidine ring adopts a chair conformation with two benzyl substituents bonded equatorially to the ring nitrogen atoms. The 3-pyrrolin-2-one is attached as spiro-skeleton to the hexahydropyrimidine ring by one axial C–C bond and one equatorial C–N bond.

While 1,3,5-trialkylhexahydro-1,3,5-triazines ($6$, $R^1 = \text{alkyl}$) yielded the bicyclic spiro compound 1-Boc-7,9-dialkyl-2-oxo-1,7,9-triazaspiro[4.5]dec-3-enes ($28$) as the...
major product with 1-Boc-2-tert-butyldimethyl-silyloxypyrrrole, reactions of 1,3,5-triphenylhexahydro-1,3,5-triazines \(4, R^1 = \text{Ph}\) gave only 1-Boc-5-anilinomethyl-2,5-dihydropyrrol-2-ones \(27\). The reaction proceeded efficiently with various 1,3,5-triphenylhexahydro-1,3,5-triazines containing substituents on the phenyl ring such as \(o\)-Me, \(2,5\)-Cl\(_2\), and \(p\)-F in high yield. This implies the formation of monomeric \(N\)-methyleneanilines equivalents described as \(9\) and \(10\) in the Scheme 10 as the dominant species with all three carbon-nitrogen bonds are broken by conjugative stabilization.

Other carbon nucleophiles of silyl enol ethers as electron rich olefins were reacted with \(N\)-methyleneaniline equivalents from \(N\)-methoxymethylamines or 1,3,5-trisubstituted hexahydro-1,3,5-triazines to afford \(\beta\)-amino aldehyde or ketone \(32, X = H\) or alkyl)\(^{24,25}\). Trimethylsilyloxyketene acetals as a nucleophiles facilitate the synthetic route to aminopropionate \(32, X = \text{OMe, OEt}\) in high yield (Scheme 11)\(^{26,27}\).

### 3. Lewis Acid-Induced \(N\)-Methyleneaniline Equivalents as Azadienes

Imine and iminium ions are well known dienophiles for the synthesis of nitrogen containing bicyclic structures\(^{28,29}\). \(N\)-Trimethylsilylaldimine\(^{30}\) and \(N\)-trimethylsilyl-3-furaldimine\(^{31}\) were reacted with electron rich diene to yield the cycloadduct in the presence of \(\text{ZnCl}_2\). Aldimines derived from aromatic aldehydes and anilines were used as dienes with allylsilane as a dienophile in the presence of a Lewis acid to afford 2-aryl-1,2,3,4-tetrahydroquinolines\(^{32}\). Recent report described the successful intramolecular \([4\pi+2\pi]\) cycloaddition of \(N\)-methyleneanilines with dienes in reverse electron demand mode\(^{33,34}\). \(N\)-Methyleneaniline generated from thermolysis of 1,3,5-triphenylhexahydro-1,3,5-triazines \(6\) or \(N\)-methoxymethylenalanilines \(5\) was reacted with cyclobutadiene to yield not tetrahydropyridine \(34\) but tetrahydroquinoline \(33\) in 67% yield (Scheme 12)\(^{33}\). Lewis acid-derived \(N\)-methyleneaniline equivalent described as \(9\) and \(10\) in Scheme 13 represents the characteristics of imine and iminium ions generated form 1,3,5-triphenylhexahydro-1,3,5-triazine as their
monomeric forms.

All of the reactions developed with \( N \)-methyleneaniline equivalents generated from 1,3,5-triphenylhexahydro-1,3,5-triazines in the presence of a Lewis acid stem from the Mannich base character of 9 and 10 for aminomethylations. No reaction was revealed using \( N \)-methyleneamine equivalents as azadiene\(^{35} \) that may have a chance to react with olefins in reverse electron demand \([4\pi+2\pi]\) cycloaddition to afford 1,2,3,4-tetrahydroquinolines.

The possibility of utilizing \( N \)-methyleneamine equivalents as azadienes was speculated by the early observations that \( N \)-alkyl- or \( N \)-aryliminium ions with the electron-rich olefins in the presence of acids provided \( N \)-alkyl-1,2,3,4-tetrahydroquinolines.\(^{36} \) However, most reactions\(^{36-41} \) claimed \([4\pi+2\pi]\) cycloadditions can also be explained by the step-wise mechanism with the cationic intermediate generated from addition of electron-rich olefins to imine or iminium ions as Mannich bases followed by electrophilic cyclization.\(^{18} \) We described the successful application of \( N \)-methyleneamine equivalents (9, 10) as azadienes for the reactions with 1,2-bistrimethylsilyloxycyclobutene to afford tricyclic 2a,8b-bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[c]quinoline (35) that was further transformed to the heterocycle 1,2,4,5-tetrahydro-1-benzazocine-3,6-diones (Scheme 14). For the cycloaddition
reactions with electron-rich olefin 1,2-bistrimethylsilyloxy-cyclobutene was used with \( N \)-methylenamine equivalents (9 or 10) generated from 1,3,5-triphenylhexahydro-1,3,5-triazine (6) in the presence of various Lewis acids. Most of the Lewis acids we tried gave expected cycloadducts (35) with certain amount of diol (36) losing two TMS that might come from the initial adducts after hydrolysis. TMSCl was the best to provide the tricyclic cycloadduct \( 2a,8b \)-bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[c]quinoline (35) without losing TMS groups in 65% isolated yield with the least amount of the hydrolyzed diol (Scheme 14). This reaction sequence is quite successful to give 40-60% yield of the cyclic adducts starting from 1,3,5-triphenylhexahydro-1,3,5-triazine compounds with various substituents on the benzene ring such as \( p \)-methoxy, \( p \)-fluoro and \( o \)-methyl.42

Scheme 14

![Reaction Scheme](image)

The initial adduct (35) was hydrolyzed with \( K_2CO_3 \) in MeOH to produce the diol (36) in quantitative yield. By further treatment with PDC in \( CH_2Cl_2 \) at room temperature, 1,2-diol group at the junction of the cyclobutane and piperidine rings was oxidatively expanded to give an eight-membered ring product, 1,2,4,5-tetrahydro-1-benzazocine-3,6-dione (37) in 63% yield. Oxidative ring expansion was driven by the ring strain present in the cyclobutane. This reaction may serve as an efficient way to construct 1-benzazocine skeletons, some of which are biologically active43 (Scheme 14).

Once we had 37 in hand, we tried to obtain free benzazocine which has not been obtained in a pure form yet.44 The sequence of transformations includes reduction to the corresponding diol and subsequent dehydration, at which point oxidative conjugation may occur to obtain free benzazocine. Lithium aluminum hydride reduced only one carbonyl at C-3 to give hydroxy ketone that was not further reduced to the diol regardless of the amount LiAlH\(_4\) used. Superhydride reduction was also tried in vain, and gave an unidentified complex mixture of the products. Thus, the synthesis of free benzazocine remains elusive.

To figure out the characteristics of this cycloaddition reaction HOMO and LUMO energies of azadienes as an analog of iminium ion and dienophile were calculated as shown in Figure 1. The energy difference between HOMO of 1,2-bistrimethylsilyloxy-cyclobutene and LUMO of \( N \)-methylenalininium ion is 2.8 eV
which is smaller than 6.6 eV energy difference between HOMO of N-methyleanilinium ion and LUMO of 1,2-bistrimethylsilyloxy cyclobutene. This shows that the reaction is a reverse electron demand Diels-Alder reaction that N-methyleanilinium ion and 1,2-bistrimethylsilyloxy cyclobutene were served as azadiene and dienophile respectively.

Figure 2. Frontier orbitals of N-methyleanilinium ions and 1,2-bistrimethylsilyloxy cyclobutene

In the presence of properly selected Lewis acid the [4π+2π] cycloaddition will be succeeded between Lewis acid-derived N-methyleneaniline equivalent described as 9 and 10 as azadiene and olefin in a reverse electron demand mode.

4. Conclusions

In this review discussions were made about the preparations and synthetic applications of N-methyleneamine equivalents generated from hexahydro-1,3,5-triazines or N-methoxymethylamines in the presence of a Lewis acid. Their reactions show a great deal of utility with wide range of nucleophiles for the synthesis of various aminomethylated products. However, there is short of our understanding about the exact species generated from hexahydro-1,3,5-triazines or N-methoxymethylamines in the presence of a Lewis acid. The success of cycloaddition with N-methyleaniline equivalents from 1,3,5-triphenylhexahydro-1,3,5-triazines being served as azadienes extends the synthetic utility for the preparation of 1,2,3,4-tetrahydroquinolines.

ACKNOWLEDGEMENT

This work was supported by the Korea Science & Engineering Foundation (No.R-01-2000-00048 to HJH
and No. R-01-1999-00044 to WKL) and HUFS Research Fund (2002).

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