N,N-DIMETHYLCHLOROFORMIMINIMUM CHLORIDE IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS.

THE SYNTHESIS OF N-HETEROARYLFORMAMIDINE HYDROCHLORIDES, OXAZOLO/5,4-d/PYRIMIDINES, FUSED IMIDAZOLES AND OTHER SYSTEMS

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Abstract - N,N-Dimethylchloroformiminium chloride (DCFC) was used for preparation of N-heteroarylformamidine hydrochlorides (2), fused oxazoles (4), imidazoles (6, 8) and thiazoles (10). DCFC is advantageous in those cases in which the undesired further methylation of NH, OH, and SH groups could occur by using N,N-dimethylformamide dimethyl acetal (DMFDMA).

N-Heteroaryl formamidines and N-heteroarylformamide oximes have been shown to be extremely useful intermediates in the synthesis of various heterocyclic systems. Recently, we have described a new simple method for the preparation of 2-amino-oxazolo/4,5-c/quinoline and oxazolo/4,5-b/pyridine derivatives by cyclization of the corresponding o-hydroxy-substituted N-heteroarylformamide oximes with N,N-dimethylformamide dimethyl acetal (DMFDMA). However, when we wanted to extend this reaction to the synthesis of oxazolo/4,5-d/pyrimidines starting from 5-amino-uracil, we observed that the limiting step is the preparation of 5-(N,N-dimethylaminomethyleneamino)uracil which can be obtained only in 17% yield under optimal reaction condition by using DMFDMA. The reason for this low yield is further methylation affording 1,3-dimethyl-5-(N,N-dimethylaminomethyleneamino)uracil as the main product.

In order to avoid the methylation of NH groups, N,N-dimethylformamide dineopentyl acetal has been found to be advantageous in comparison to DMFDMA since the big neopentyl group prevents further alkylation during the reaction as observed in fused imidazoles. On the other hand, Vilsmeier reagent, prepared in situ from N,N-dimethylformamide and either thionyl chloride, phosphoryl chloride, or phosphorus pentachloride, can be used for cyclization of a variety of ortho-disubstituted aromatic and heterocyclic compounds. In this manner dioxoles, chromones, isochromones, isoquinolines, 4,7-diazaindole, pyridines, pyrimidines, and quinolines have been prepared. In some instances alkylation, chlorination, and dehydration of amides into nitriles and isonitriles have been observed.
In this communication we would like to report on the transformation of heterocyclic amines into the corresponding N-heteroarylformamidines (usually isolated as hydrochlorides) with N,N-dimethylchloroformiminium chloride (DCFC) (the Vilsmeier reagent) as an alternative to the previously described methods. Furthermore, the reagent can be used also for the cyclization of o-diamino and o-aminomercapto compounds into the corresponding fused imidazoles and thiazoles, respectively.

The reaction between heterocyclic amines and DCFC yielded the corresponding N-heteroaryl-N',N'-dimethylformamidines usually in the form of hydrochlorides. The following heterocyclic amines were converted in this manner: 2-aminopyrimidine (1a), 5-aminouracil (1b), 3-amino-6-chloropyridazine (1c), 3-amino-(1H)-1,2,4-triazole (1e), 2-aminobenzimidazole (1g), and 4-amino-2,1,3-benzothiadiazole (11). The corresponding N-heteroarylformamidine hydrochlorides were easily converted with hydroxylamine into the corresponding N-heteroarylformamide oximes with hydroxylamine in methanol by standing at room temperature for several hours. In some instances, especially when analytically pure samples could not be obtained by usual purification, the crude N-heteroarylformamidine hydrochlorides were converted with hydroxylamine directly into the corresponding N-heteroarylformamide oximes. The compounds 3d, e, f, and h were prepared in this way. (Scheme 1).

\[ \text{Het} \cdot \text{NH}_2 + \text{DCFC} \rightarrow \text{Het} \cdot \text{N} = \text{CH} - \text{NMe}_2 \]

\[ \text{Het} \cdot \text{N} = \text{CH} - \text{NMe}_2 + \text{H}_2\text{NOH} \xrightarrow{(x \text{ HCl})} \text{Het} \cdot \text{NHCH} = \text{NOH} \]

**Scheme 1**

Due to the method described above, the problem around the preparation of 5-(N,N-dimethylaminomethyleneamino)uracil (2b) was satisfactorily solved so that 5-hydroxyaminomethyleneuracil (3b) could be prepared in high yield. The cyclization of the formamide oxime group to the o-hydroxy or potential hydroxy group did not occur under the described reaction conditions. However, the treatment of the compound 3b with DMFDMA afforded most probably 2-(N,N-dimethylaminomethyleneamino-7-methyloxazo/5,4-d/pyrimidin-6(7H)-one (4) (Scheme 2), similarly, as already...
reported for pyridine\textsuperscript{3} and quinoline derivatives.\textsuperscript{2}

\[
\begin{align*}
\text{N} & \text{HCH=NOH} & \text{DMFDMA} & \text{O} \\
\text{N} & \text{Me} & \text{NMe}_2 \\
\end{align*}
\]

\textbf{SCHEME 2}

On the other hand, the treatment of o-diamino and o-aminomercapto compounds resulted in cyclization to give fused imidazoles and thiazoles, respectively. Reactions with DCFC were carried out either in toluene or in \textit{N},\textit{N}-dimethylformamide at the temperatures ranging from 90\textdegree{}C to 130\textdegree{}C. The following compounds

\[
\begin{align*}
\text{Y} & \text{X} & \text{NH}_2 & \text{DCFC} & \text{Y} & \text{X} & \text{N} \\
\text{R} & \text{R} & \text{DCFC} & - & \text{NH}_2 & - & - \\
\end{align*}
\]

\textbf{SCHEME 3}

\texttt{a) } X = Y = CH ; R = H \\
\texttt{b) } X = Y = CH ; R = Cl \\
\texttt{c) } X = Y = CH ; R = NO_2 \\
\texttt{d) } X = N ; Y = CH ; R = H \\
\texttt{e) } X = CH ; Y = N ; R = H
were cyclized in this manner: 1,2-diaminobenzene (5a), 1,2-diamino-4-chlorobenzene (5b), 1,2-diamino-4-nitrobenzene (5c), 2,3-diaminopyridine (5d), 3,4-diaminopyridine (5e), 5,6-diamino-1,3-dimethyluracil (7), and 2-aminothiophenol (9) to give the corresponding benzimidazole (6a), its 5-chloro- (6b), and 5-nitro- (6c) derivatives, 1H-imidazo/4,5-b/pyridine (6d), 1H-imidazo/4,5-c/pyridine (6e), theophylline (8), and benzothiazole (10), respectively. The yields were comparable to those obtained by other methods.30,31 (Scheme 3).

In conclusion, DCFC is comparable to DMFDMA for the preparation of N-heteroarylformamidines from amines and for the cyclization of o-diamino and o-aminomercapto aromatic and heteroaromatic compounds into fused imidazoles and thiazoles. However, DCFC is advantageous to DMFDMA in those cases, in which further methylation of NH, OH, and/or SH groups containing N-substituted formamidines or cyclization of the formamidine group to the o-hydroxy group is not desirable.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage, \(^1\)H nmr spectra were obtained on a JEOL JNM C60-HL spectrometer with TMS as internal standard, ir spectra on PERKIN-ELMER instrument 727B, mass spectra on a HITACHI-PERKIN-ELMER mass spectrometer RMU-6L, and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyzer 240C.

The preparation of N,N-dimethyl-N'-heteroarylformamidine hydrochlorides (2).

General procedure.-

A mixture of heterocyclic amino compound and N,N-dimethylchloroformiminium chloride (DCFC) in an appropriate solvent was left at room temperature for several hours. The excess of the reagent was separated by sublimation (80-90°C, 3 torr), and the residue recrystallized from an appropriate solvent.

In this manner the following compounds were prepared:

2-(N,N-Dimethylaminomethyleneamino)pyrimidine hydrochloride (2a).- This compound was prepared from 2-aminopyrimidine (1a, 330 mg) and DCFC (700 mg) in toluene (6 ml) by heating at reflux for 1 h in 88% yield, mp. 205-210°C (from 2-propanol), nmr (DMSO-d6/TMS) \(\delta\): 3.39 (s) and 3.48 (s) (NMe2); 5.5-6.5 (br, NH\(^+\)); 7.38 (t, H\(5\)); 8.77 (d, H\(4\), H\(6\)); 9.15 (s, CH=N); \(J_{H4,H6}\) = 4.6 Hz. Anal. Calcd. for C\(7\)H\(_4\)N\(_4\)Cl: C, 45.05; H, 5.94; N, 30.02. Found: C, 43.80; H, 5.29; N, 29.28.
5-(N,N-Dimethylaminomethyleneamino)uracil hydrochloride (2b). - This compound was prepared from 5-aminouracil (1b, 185 mg) and DCFC (710 mg) in toluene (7 ml) by heating the reaction mixture at reflux temperature for 2 h in 78% yield, mp 300°C (from methanol), nmr (DMSO-d$_6$/TMS) 5: 3.18 (s) and 3.23 (s) (NMe$_2$); 7.75 (d, H$_6$); 8.35 (s, CH=N); J$_{H_6,NH}$ = 5.0 Hz. Anal. Calcd. for C$_7$H$_{11}$CN$_4$O$_2$: C, 38.45; H, 5.0; N, 25.62. Found: C, 37.53; H, 4.99; N, 25.23.

6-Chloro-3-(N,N-dimethylaminomethyleneamino)pyridazine hydrochloride (2c). - This compound was prepared from 3-amino-6-chloropyridazine (1c, 225 mg) and DCFC (560 mg) in toluene (6 ml) by heating at reflux temperature for 3 h in 90% yield, mp 164-171°C (from 2-propanol), nmr (DMSO-d$_6$/TMS) 5: 3.49 (s, NMe$_2$); 7.98 (s) and 8.28 (s) (H$_4$ and H$_5$); 9.25 (s, CH=N); J$_{H_4,H_5}$ = 9.0 Hz. Anal. Calcd. for C$_7$H$_{10}$N$_4$Cl$_2$: C, 38.03; H, 4.56; N, 33.01. Found: C, 37.99; H, 4.65; N, 34.00.

3-(N,N-Dimethylaminomethyleneamino)-1H-1,2,4-triazole dihydrochloride (2e). - This compound was prepared from 3-amino-1H-1,2,4-triazole (1e, 275 mg) and DCFC (1030 mg) in toluene (6 ml) by heating at reflux temperature for 2 h in 90% yield, mp 123-125°C (from a mixture of ethyl acetate and methanol 3:1), nmr (DMSO-d$_6$/TMS) 5: 3.11 (s) and 5.24 (s) (NMe$_2$); 8.48 (s, H$_5$); 8.82 (s, CH=N). Anal. Calcd. for C$_5$H$_{11}$N$_5$Cl$_2$: C, 28.30; H, 5.18; N, 33.01. Found: C, 28.60; H, 5.47; N, 34.00.

2-(N,N-Dimethylaminomethyleneamino)benzimidazole dihydrochloride (2g). - This compound was prepared from 2-aminobenzimidazole (1g, 130 mg) and DCFC (600 mg) in toluene (6 ml) by standing at room temperature for 3 h in 68% yield, mp 69-72°C (from a mixture of ethyl acetate and methanol 3:1), nmr (DMSO-d$_6$/TMS) 5: 3.10 (s) and 3.22 (s) (NMe$_2$); 7.05-7.50 (m, H$_4$,H$_5$,H$_6$,H$_7$); 8.98 (s, CH=N). Anal. Calcd. for C$_{10}$H$_{14}$N$_4$Cl$_2$: C, 45.99; H, 5.40; N, 21.45. Found: C, 45.62; H, 5.26; N, 22.05.

4-(N,N-Dimethylaminomethyleneamino)-2,1,3-benzothiadiazole hydrochloride (2i). - This compound was prepared from 4-amino-2,1,3-benzothiadiazole (1i, 90 mg) and DCFC (500 mg) in 1,2-dimethoxyethane (6 ml) by standing at room temperature for 24 h in 94% yield, mp 195-199°C (from 2-propanol), nmr (DMSO-d$_6$/TMS) 5: 3.41 (s) and 3.46 (s) (NMe$_2$); 7.65-8.10 (m, H$_5$,H$_6$,H$_7$); 9.68 (s, CH=N). Anal. Calcd. for C$_9$H$_{11}$N$_4$Cl$_2$: C, 44.53; H, 4.57; N, 23.08. Found: C, 43.58; H, 4.71; N, 22.80.
Transformation of $N,N$-Dimethyl-$N'$-heteroarylformamidine hydrochlorides into $N$-heteroarylformamide oximes (3). - General Procedure.

To a solution of $N,N$-dimethyl-$N'$-heteroarylformamidine hydrochloride (0.001 mole) in methanol (4 ml) hydroxylamine (0.0016 mole) was added and the mixture was left at room temperature for 2 h. The solvent was evaporated in vacuo, water (3 ml) was added, the crude product collected by filtration and recrystallized from an appropriate solvent.

In this manner the following compounds were prepared:

2-Hydroxyiminomethyleneaminopyridine (3a). - This compound was prepared from 2-(N,N-dimethylaminomethyleneamino)-pyrimidine in 59% yield, mp 184-186°C lit.26 mp 198-200°C, whose ir spectrum was identical with that of an authentic sample.

5-Hydroxyiminomethyleneaminouracil (3b). - This compound was prepared from 5-(N,N-dimethylaminomethyleneamino)uracil hydrochloride (2b) in 41% yield, mp >300°C (from water); nmr (DMSO-$d_6$) δ: 7.25 (s, $H_6$); 7.23 (CHNH); 6.88 (CHNH); 10.2 (br, OH); $J_{NHCH}$ =10.5 Hz.
Anal.Calcd. for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93; Found: C, 34.59; H, 3.42; N, 31.69.

3-Hydroxyiminomethyleneamino-1H-1,2,4-triazole (3c). - This compound was prepared from 3-(N,N-dimethylaminomethyleneamino)-1H-1,2,4-triazole dihydrochloride (2e) in 70% yield, mp 222-226°C (from water).
Anal.Calcd. for $C_3H_5N_5O$: C, 28.35; H, 3.97; N, 55.10. Found C, 28.60; H, 4.04; N, 55.20.

3-(Hydroxyiminomethyleneamino)-6-chloropyridazine (3d). - This compound was prepared from 3-(N,N-dimethylaminomethyleneamino)-6-chloropyridazine hydrochloride (2c) in 42% yield, mp 207-211°C, lit.26 mp 190-194°C, whose ir spectrum was identical with that of an authentic sample.

4-(Hydroxyiminomethyleneamino)-2,1,3-benzothiadiazole (3e). - This compound was prepared from 4-(N,N-dimethylaminomethyleneamino)-2,1,3-benzothiadiazole hydrochloride (2g) in 66% yield, mp 168-173°C, nmr (DMSO-$d_6$) δ: 7.10-7.62 (m, $H_6,H_6,H_7$); 8.02 (d, CHNH); 8.50 (d, CHNH); 10.42 (s, OH); $J_{CHNH}$ = 10.5 Hz.

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Direct conversion of N,N-dimethyl-N'-heteroarylformamidinium chlorides (2) into N-heteroarylformamide oximes (3).

2-(Hydroxyiminomethyleneamino)-thiazole (3d).- The crude 2-(N,N-dimethylaminomethyleneamino)thiazolium chloride (2d) obtained from 2-aminothiazole (100 mg, 0.001 mole) and N,N-dimethylchloroformiminium chloride (780 mg) after standing for 24 h at room temperature according to the above procedure, was treated with hydroxylamine (40 mg) in methanol (4 ml). The reaction mixture was left at room temperature for 2 h. The solvent was evaporated in vacuo, water (3 ml) was added to the residue, the crude product collected by filtration and recrystallized from methanol. Yield 89%, mp 153-156°C, nmr (DMSO-D$_6$/TMS) $\delta$: 6.88 (d, H$_5$); 7.15 (d, H$_4$); 7.50 (s, N=CX); 10.1 (br, NH, OH). $J_{H_4,H_5} = 2$ Hz.

Anal. Calcd. for C$_4$H$_5$N$_3$O$_3$: C, 33.55; H, 3.52; N, 29.35. Found: C, 33.43; H, 3.60; N, 29.08.

In the same manner the following N-heteroarylformamide oximes 3 were prepared:

3-(Hydroxyiminomethyleneamino)-1H-1,2,4-triazole (3e).- This compound was prepared from the crude 3-(N,N-dimethylaminomethyleneamino)-1H-1,2,4-triazole dihydrochloride (2e), obtained from 3-amino-1H-1,2,4-triazole and DCFC in 90% yield, by treatment with hydroxylamine in methanol after 2 h at room temperature in 80% yield, mp 222-226°C (from water).

Anal. Calcd. for C$_3$H$_5$N$_5$O: C, 28.35; H, 3.97; N, 55.10. Found: C, 28.60; H, 4.04; N, 55.20.

5-(Hydroxyiminomethyleneamino)-pyrazolyl-4-carboxamide oxime (3f).- This compound was prepared from 4-cyano-5-(N,N-dimethylaminomethyleneamino)-pyrazole hydrochloride (2f) (106 mg) prepared from 5-amino-4-cyanopyrazole (1f) and DCFC in 92% yield, by treatment with hydroxylamine (78 mg) in methanol (4 ml) by standing at room temperature for 2 h in 62% yield, mp 300°C (from water).

Anal. Calcd. for C$_5$H$_8$N$_6$O$_2$: C, 32.61; H, 4.38; N, 45.63. Found: C, 32.59; H, 4.53; N, 44.04.

6-(Hydroxyiminomethyleneamino)purine (3h).- This compound was prepared from the crude 6-(N,N-dimethylaminomethyleneamino)purine hydrochloride (2h, 112 mg) prepared from adenine (1h) and DCFC in 87% yield, by treatment with hydroxylamine (56 mg) in methanol (4 ml) for 30 min at room temperature in 68% yield, mp 300°C (from a mixture of ethanol and DMF 3:1), nmr (DMSO-$d_6$) $\delta$: 8.15 (s) and 8.18 (s), (H$_2$H$_8$); 8.33 (s, NH). 

Cyclization of o-diamino substituted compounds with N,N-dimethylchloroformiminium chloride (DCFC). General procedure

A mixture of ortho-diamino compound (0.001 mole) and DCFC (0.005 mole) in toluene (10 ml) was stirred for several hours at room temperature and then heated at reflux temperature for 2 to 9 h. The solvent was evaporated in vacuo, and the dry residue suspended in water (10 ml), neutralized with solid sodium carbonate and extracted with chloroform (3 times, 20 ml each time). The combined extracts were dried with anhydrous sodium sulphate, chloroform evaporated in vacuo and the product purified by crystallization or sublimation.

In this manner the following compounds were prepared:

Benzimidazole (6a).- This compound was prepared from o-phenylenediamine (5a) in 42% yield, mp 172-174°C (sublim. 150°C, 3 torr) (lit. 32 mp 173-174°C). The ir spectrum was identical with that of an authentic sample.

5-Chlorobenzimidazole (6b).- This compound was prepared from 4-chloro-1,2-diamino-benzene (5b) (2 h at room temperature, 2 h at reflux temperature) in 45% yield, mp 122-124°C (from water), lit. 34 mp 125°C, m/e 152 (M^+), nmr (DMSO-d6/TMS) δ: 3.5 (br, NH); 7.12 (dd, H6); 7.53 (m, H4, H7); 8.13 (s, H2); J_H4,H6 = 1.5 Hz.

5-Nitrobenzimidazole (6c).- This compound was prepared from 4-nitro-1,2-diamino-benzene (5c) in 58% yield, mp 206-209°C (from water) (lit. 35 mp 207-209°C).

1H-Imidazo/4,5-b/pyridine (6d).- This compound was prepared from 3,2-diamino-pyridine (5d) in 46% yield, mp 146-150°C (lit. 32 mp 150-152°C), whose ir and nmr spectra were identical with those of an authentic sample.

1H-Imidazo/4,5-c/pyridine (6e).- This compound was prepared from 3,4-diamino-pyridine (5e) in 30% yield, mp 212-218°C (from 2-propanol), lit. 32 mp 210-215°C, ir and nmr spectra were identical with those of an authentic sample.

Theophylline (8).- This compound was prepared from 5,6-diamino-1,3-dimethyluracil (7) in 44% yield, mp 258-263°C (subl. 220-230°C, 3 torr) (lit. 36 mp 269-274°C), whose ir spectrum was identical with that reported in the lit.

Benzothiazole (10).- This compound was prepared from 2-aminothiophenol (9) in 40% yield, bp 222°C (distil. 100°C, 3 torr) (lit. 37 bp 229-231°C), whose ir spectrum was identical with that reported in the lit.

2-(N,N-Dimethylaminomethyleneamino)-7-methyloxazolo/5,4-d/pyrimidin-6(7H)-one (4).- A mixture of 5-hydroxyiminomethyleneaminouracil (3b, 170 mg, 0.001 mole) and DMFDMA (357 mg, 0.003 mole) was heated at 100-110°C for 6 h. The precipitate formed after cooling was collected by filtration and recrystallized from n-propanol, yield 21%, mp 253-255°C, m/e 221 (M^+), nmr (DMSO-d6/TMS) δ: 4.08 (s) and 4.40 (s) (NMe2):
8.0 (s, H_4); 8.45 (s, N=CH).

Anal. Calcd. for C_{11}H_{11}N_5O_2: C, 48.86; H, 5.01; N, 31.66. Found: C, 49.37; H 5.13, N, 31.39.

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