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2, 4, 6-trichloro-1, 3, 5-triazine and N, N'-dimethylformamide as an effective Vilsmeier - Haack reagent for the synthesis of 2-chloro-3-formyl quinolines from acetanilides

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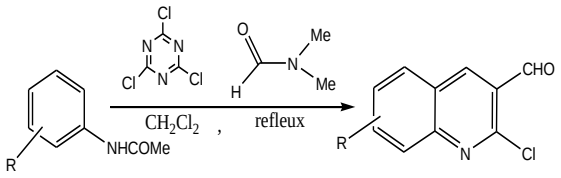
ABSTRACT

TCTA-DMF (2, 4, 6-trichloro-1, 3, 5-triazine / N, N'-dimethylformamide) adduct has been used as a Vilsmeier - Haack type reagent for effective synthesis of 2-chloro-3-formyl quinolines from acetanilides under conventional and ultrasonically assisted conditions. The reaction times under sonication are quite significantly shorter than conventional method even though the yields obtained under sonication are comparable with those obtained under reflux conditions.

Introduction

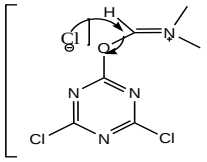
Symmetric 1, 3, 5-triazine derivatives have been known for a long period of time for their widespread pharmaceutical, textile, plastic, and industrial applications. Besides they are also used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents[1-6]. Quinoline is one of the most important heterocyclic compounds, which is used as a feedstock for the preparation of hydroxy quinoline sulfate, niacin; for manufacture of dyes and as a solvent for resins and terpenes. Hydroxy quinolines derived from quinoline are used as versatile chelating agents and precursors; its 2- and 4-methyl derivatives are precursors to cyanine dyes, while 8- hydroxy derivative is a precursor to pesticides[7]. Besides, quinoline derivatives are some of the oldest compounds that are used for the treatment of a variety of diseases[8]. Quite a good number of quinoline derivatives are important constituents of pharmacologically active synthetic compounds, which exhibited a broad spectrum of biological activities [9 -14]. Interesting pharmacological properties such as antimicrobial, antimalarial, anti-inflammatory, antitumor, and anti-parasitic activities have been associated with 2-chloroquinoline-3-carbaldehydes and their derivatives[15-23]. Many 2-chloro-3-formyl-quinolines, 3-formyl-2- mercaptoquinolines and transition metal complexes derived from Schiff bases of these compounds have been reported as potential antifungal and biodynamic agents. Zn (II) complex Schiff bases of 3-formyl-2-mercaptoquinolines has also been found to be a fluorescent compound[24]. Quinoline derivatives such as 2-Chloroquinoline-3-carbaldehyde and their thioanalogues have become back bone for the synthesis of several bioactive agents[25-30]. Govindaraj et al prepared a series of functional polyhedral oligomeric silsesquioxane (POSS)/polyimide (PI) nanocomposites comprising quinoline backbone. Prepared polymer composites exhibited thermal and mechanical properties. Few of these composites exhibited good antimicrobial activity. Shelar et.al developed a novel route for the synthesis of *ortho* amino formyl quinoline (heterocyclic ortho amino aldehyde) which in turn was utilized for the synthesis of series of benzonaphthyridines which exhibited excellent fluorescent properties[32].Over the years, the Vilsmeier-Haack (VH) reagent is used as an efficient, economical and mild reagent for the formylation of aromatic and heteroaromatic substrates. Basically, DMF and oxychloride under chilled conditions[33] in *situ* forms a chloromethyleniminium salt, which is used as a powerful synthetic tool to achieve several aromatic and heterocyclic compounds including quinoline derivatives[34-40]. But the oxychlorides such as phosphoryl chloride, thionyl chloride, or phosgene that are used in the preparation of VH reagents are toxic in nature. Recently Dune-Ren Hour [41] et al used trichlorotriazine (TCTA) or Cyanuric Chloride is used in place of oxychloride for the preparation of VH type reagent during the preparation of α,β-unsaturated enol aldehydes such as 3-Ethoxymethacrolein and 5-formyl-3,4-dihydro-2*H*-pyran from enol ethers. Trichlorotriazine (TCTA) is also earlier used for the synthesis of alcohols, diazo carbonyl, acyl azides, and hydroxamic acids as well as acyl chlorides from carboxylic acids[42]. In addition, it has been shown that TCTA could efficiently promote several reaction protocols[42-45(a)] such as carboxylic acid activation, Swern oxidation, Friedel–Crafts acylation, Beckman rearrangement[44] and Lossen rearrangement[45]. Encouraged by these features, we have embarked on exploring

(TCTA/DMF) adduct for the cyclization of acetanilides under conventional and ultrasonically assisted conditions[31]. Present work is an effort in which TCTA-DMF (2, 4, 6-trichloro-1, 3, 5-triazine / N, N'-dimethylformamide) adduct[46] has been used as a Vilsmeier - Haack type reagent for effective synthesis of 2-chloro-3-formyl quinolines from acetanilides under conventional and ultrasonically assisted conditions.



Scheme 1: Synthesis of 2-chloro-3-formyl quinolines from acetanilides using TCTA/DMF as Vilsmeier-Haack Reagent

The [TCTA/DMF] reactions with acetanilides[47] underwent smoothly at reflux temperatures. The reaction times for most of the studied reactions are in the range of 3 to 18 hrs, depending on the structure **(Table 1)**. Mechanism of the reaction could be explained through the formation of [TCTA-DMF] adduct comprising "chloromethyleniminum" moiety. Formation of Chloro methyleniminum cation intermediate can be supported on the basis of spectroscopic results obtained under different conditions. IR spectrum of DMF (neat), recorded in this study depicted different bands. The bands appeared in 450-1550 cm^{-1} range are attributed to C-N, band at 1675 cm^{-1} corresponds to C=O stretching frequency, which is lower than an unsubstituted C=O bond. The observed reduction in the bond order of the carbonyl C=O bond followed by an increase in the carbon-nitrogen bond order could be explained probably because of the two possible resonance structures of amide. The bands observed beyond 2500 (i.e., 2500- 4000) cm^{-1} are attributed to methyl (C-H) groups respectively. The infrared spectrum of TCTA (KBr disc) indicated three important bands respectively at 536, 764, 1399 cm-1 are explained due to C-Cl, and the four band aggregations in the range 1679-1780 cm^{-1} (1679, 1719,1752 and 1776 cm^{-1}) could be due to C=N stretching. These observations are by and large in agreement with SDBS information for organic compounds. However, the infrared spectrum recorded for the mixture of TCTA/DMF exhibited three overlapping band aggregations in the range 1718-1780 (1718, 1753 and 1779) cm^{-1}, attributed to $C=N^{+}$ stretching vibrations. This observation probably strengthens the interaction of TCTA with DMF to result in [TCTA-DMF] adduct, in the lines of Vilsmeier –Haack (DMF-$POCl_3$) adduct.

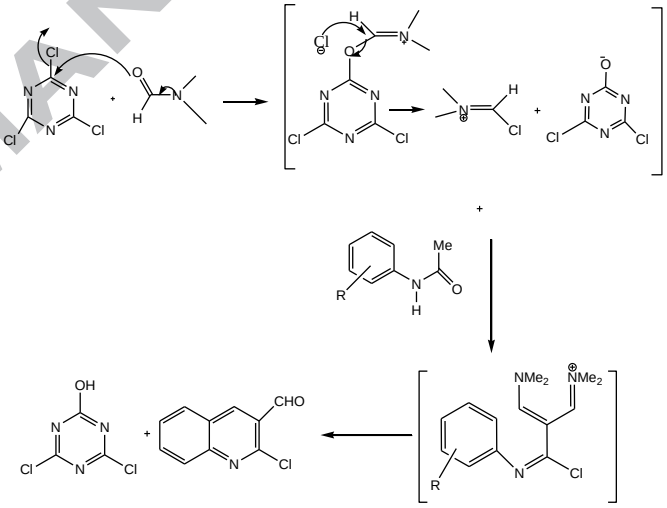


[TCTA-DMF] Adduct

Proton NMR spectrum of DMF(in DMSO-d_6) indicated three peaks on δ –scale, one singlet at δ7.952, attributed to aldehydic proton, and two singlets of 3 protons each at δ 2.891 and 2.731, instead of one singlet of 6 protons. This observation could be explained due to the partial double bond character of C-N, which made the rotation about the C-N axis in DMF slow at room temperature and also the two methyl groups inequivalent on the NMR time scale. In the presence of TCTA, HNMR spectrum of DMF underwent several changes and became more complex. NMR peak corresponding to aldehydic proton observed at δ7.952 almost disappeared. Interestingly, two methyl singlets (observed in DMF spectra) underwent dramatic shifts (δ2.88, 2.72). The signals around δ 2.5 (in both DMF and TCTA-DMF the spectra Fig S4 and S5 of Supplementary data) could be assigned to residual protons of deuterated DMSO. The broad signal at 4.069 may come from water. These observations together with IR spectral results envisage the formation of [TCTA-DMF] adduct and thereby chloro methyleniminum species [45(b)].

Scheme-2: Formation of chloro methyleniminum cation

Chloromethyleniminum cation thus formed in turn reacted with acetanilide to afforded chloro acetyl derivatives as shown in **Scheme -3.** (Spectroscopic data of (isolated products) chloro formyl quinolines are given in supplementary data).



Scheme 3: Mechanism of 2-chloro-3-formyl quinoline formation from acetanilide using TCTA/DMF as Vilsmeier-Haack Reagent

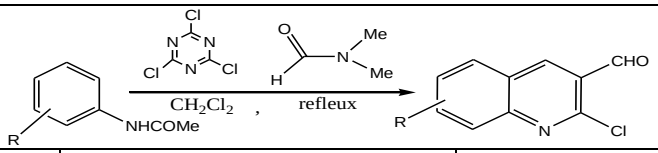
Data presented in table -1shows that some of the conventional reactions are too sluggish. However, under sonication[48] "Reaction Times" reduced amazingly from 3 to 18 hrs under conventional methods to 35 to 90 minutes at room temperature. Observed dramatic sonocatalysis could be attributed to cavitation phenomenon as explained in earlier literature reports by Mason, Suslick and many other pioneers[49, 50].

Conclusions

In summary, in the present work we have developed TCTA-DMF (2, 4, 6-trichloro-1, 3, 5-triazine / N, N'-dimethylformamide) adduct as an efficient and modified form VH reagent for effective synthesis of 2-chloro-3-formyl quinolines from acetanilides. TCTA (2, 4, 6-trichloro-1, 3, 5-triazine) used for the preparation of VH reagent is eco-friendly, readily available and inexpensive compound. The reactions afforded very good yields of under stirred conditions at room temperature. Depending on the structure of acetanilide, reaction times recorded under conventional conditions reduced from (3 to 18) hours to (35 to 90) minutes under sonication. Even the most sluggish reaction (2-nitroacetanilide) underwent rate acceleration from 18 to 1.5 hours (90 min). Product yields are also increased from 6 to 10% under

sonication as compared to conventional procedures. All synthesized compounds were characterized by H NMR and mass spectral studies.

Table 1: Synthesis of 2-chloro-3-formyl quinolines from acetanilides using TCTA/DMF as VH Reagent



S.N.	Acetanilide	2-chloro-3-formyl quinolines	Conventional		Sonication	
			R.T (hr)	Yield (%)	R.T (min)	Yield (%)
1	4-Cl acetanilide	2, 6-dichloroquinoline 3-carbaldehyde	3	89	35	85
2	4-NO_2 acetanilide	2-chloro-6-nitro quinoline-3-carbaldehyde	5	85	40	87
3	2-Cl acetanilide	2, 8- dichloro quinoline-3-carbaldehyde	7	92	50	90
4	4-Me acetanilide	2-chloro-6-methyl quinoline-3-carbaldehyde	10	87	75	85
5	2-ethyl acetanilide	2-chloro-8-ethyl quinoline-3-carbaldehyde	13	85	90	87
6	4-OMe acetanilide	2-chloro-6-methoxy quinoline-3-carbaldehyde	9	88	80	85
7	2-NO_2 acetanilide	2-chloro-8-nitro quinoline-3-carbaldehyde	18	82	95	90
8	3-NO_2 acetanilide	2-chloro-7-nitro quinoline-3-carbaldehyde	5	87	45	90
9	4-Br acetanilide	2-chloro-6-bromo quinoline-3-carbaldehyde	9	86	85	89
10	acetanilide	2-chloroquinoline-3-carbaldehyde	11	88	90	90
11	2-CH_3 acetanilide	2-chloro-8-methyl quinoline-3-carbaldehyde	11	85	85	90

Supplementary Material

All the chemicals were purchased from Aldrich or Arcos Organics and used without further purification. Analytical TLC was carried out using Merck aluminum-backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using Merck silica gel 60 (230-400mesh). Ultrasonically assisted reactions were performed in a Sonicator bath (KQ-250B, China). A flat transducer with a frequency of 40 kHz and voltage of 220 V (with an output of 100 W electric power rating) was mounted at the bottom of the Sonicator. The reaction vessel placed inside the ultrasonic bath containing water. See also separate file for further details.

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46. **Preparation of TCTA-DMF reagent:** All the chemicals were purchased from Aldrich or Arcos Organics and used without further purification. TCTA-DMF reagent was always prepared fresh prior to the reaction. About 0.110mol of TCTA and 0.13mol of DMF were added to 50ml CH_2Cl_2 solvent in a round bottomed flask and stirred for about 3 h at room temperature white colored precipitate formed as [TCTA-DMF] reagent.

47. **Cyclization reaction using TCTA-DMF reagent:** To the prepared TCTA-DMF reagent, 9.8 mmol of the Acetanilide was added and stirred under reflux conditions. Progress of the reaction was checked by TLC till the completion of the reaction. Analytical TLC was carried out using Merck aluminum-backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using Merck silica gel 60 (230-400mesh). After completion of the reaction, water was added to the reaction mixture and stirred for few more minutes to extract inorganic component in to water. Organic layer was separated and the crude product thus obtained was further purified with column chromatography (silica gel, ethyl acetate/n-hexane).

48. **Cyclization reaction using TCTA-DMF reagent under Sonication:** Methodology for the ultrasonically assisted cyclization of substituted Acetanilide by TCTA-DMF under sonication is largely similar to the classical method. After preparing the reaction mixture, as detailed above[47], the reaction flask is clamped in a Sonicator bath (KQ-250B, China). The reaction vessel was placed inside the ultrasonic bath containing water, which was supported at the corner of the ultrasonic cleaning bath 2 cm above from the position of the transducer to get the maximum ultrasound energy. Progress of the reaction was checked by TLC till the completion of the reaction. After completion of the reaction as ascertained by TLC, similar work up procedure mentioned in the above section

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Graphical Abstract

2, 4, 6-trichloro-1, 3, 5-triazine and N, N'-dimethylformamide as an effective Vilsmeier - Haack reagent for the synthesis of 2-chloro-3-formyl quinolines from acetanilides

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