Reactions of aniline in acetic acid solutions containing cyanuric chloride and hydrogen chloride acceptors

Kirill A. Kolmakov

Abstract: Two reaction pathways in acetic acid solution containing cyanuric chloride, aniline, and some hydrogen chloride acceptors (triethylamine, sodium acetate, pyridine) were studied. Both aryl amination and acylation can be performed with high yields under proper reaction conditions. Contrary to the only known literature report on the reactions between carbonic acids and cyanuric chloride in the presence of a hydrogen chloride acceptor (triethylamine), it was established that acid chlorides are not formed. A scheme involving the replacement of chlorine atoms by acetate ion in the initial stage was proposed for the acylation of aniline promoted by cyanuric chloride.

Key words: acetic acid, acylation, aniline, cyanuric chloride, aryl amination.

Résumé : On a étudié deux voies réactionnelles pour les réactions de l'aniline dans des solutions d'acide acétique contenant du chlorure cyanurique et des accepteurs du chlorure d'hydrogène, tels la triéthylamine, l'acétate de sodium et la pyridine. En choisissant les conditions expérimentales appropriées, on peut réaliser aussi bien les réactions d'amination aromatique que celles d'acylation, avec de bons rendements. Contrairement à ce qui a été rapporté dans la seule publication connue sur les réactions entre les acides carboniques et le chlorure cyanurique en présence d'un accepteur de chlorure d'hydrogène (triéthylamine), on a démontré qu'il n'y a pas de formation de chlorures d'acide. On propose un schéma impliquant le remplacement des atomes de chlore par l'ion acétate dans l'étape initiale de la réaction d'acylation de l'aniline catalysée par le chlorure cyanurique.

Mots-clés : acide acétique, acylation, aniline, chlorure cyanurique, amination aromatique.

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Introduction

Acetic acid as solvent has a unique combination of valuable qualities, the most important of which are environmental compatibility, low toxicity, low flammability, and the possibility to recycle. All these are complemented by miscibility with water and most organic solvents, high polarity, and high boiling point. At the same time, its application in preparative organic chemistry is narrow. The reactions of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine (**1**, Scheme 1)) with aniline and with acetic acid, respectively, have been known for more than 60 years (1), while the interactions between *all three* still have not been studied. In our most recent research, we devised an efficient and "green" synthetic approach to aryl amination of cyanuric chloride with various aromatic amines using acetic acid as solvent (2). No attempts to perform amination (or other type of nucleophilic substitution) in acetic acid medium had been reported previously. We found that mono- and di-arylamino derivatives (**2a**, **2b**) are formed smoothly at ambient temperature in the absence of hydrogen chloride acceptors, while conventional procedures utilize bases (1). The final third stage of substitution in **1**, a typically difficult transformation to achieve with aromatic amines, is complete after 30 min heating at 118 °C in acetic acid (2). One needs to know why acetic acid is superior to conventional polar organic solvents in the aryl amination of **1** and why acylation, as an expected side reaction, is eliminated. Apart from acid–base interaction between aniline and acetic acid, it is well known that carbonic acids can act as acylating agents, especially at elevated temperatures (3). One could expect that **1**, with the reactive C-Cl function, may interact with acetic acid and thus promote acylation of aniline. The formation of acetyl chloride and cyanuric acid (Scheme 1, **3a**), as a result of cyanuric chloride dechlorination (solvilysis) in boiling acetic acid, was mentioned in the literature (1*a*, 1*d*). Further, in 1981 Lahoti and Wagle (4) suggested cyanuric chloride as a reagent for preparation of acid chlorides, amides, and esters. The authors claimed that when **1** was treated with a carbonic acid and triethylamine (1 equiv. each) in acetone, the corresponding acid chloride was readily formed. We decided to check whether the recipe (4) worked for acetic acid as substrate. If it did, acetyl chloride could form in the process of aryl amination. This extremely reactive acylating agent definitely would compete with **1** in reaction with aniline. In the context of further utilization of acetic acid for nucleophilic substitution reactions in preparative organic chemistry, we decided to explore the two alternative reaction pathways

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K.A. Kolmakov.[1] Department of Chemistry, University of Toronto, Toronto, ON M5S 3H6, Canada.

[1]Contact (e-mail: kkolmako@chem.utoronto.ca).

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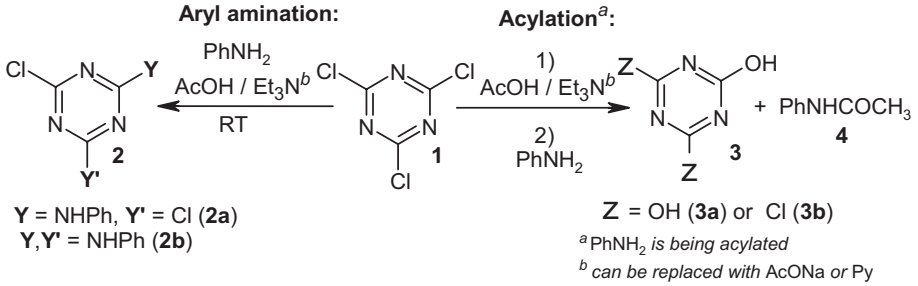
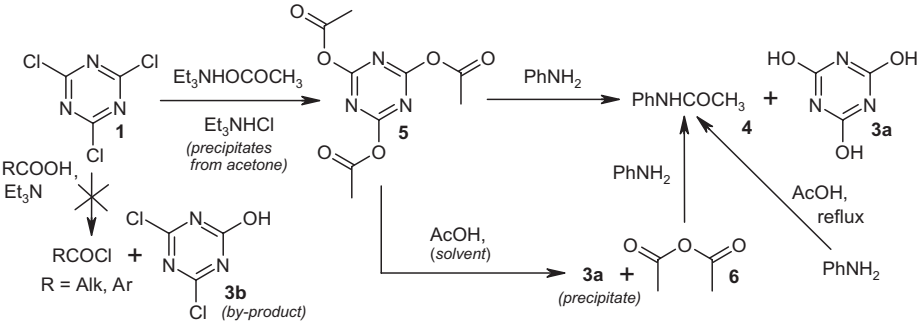
Scheme 1.



Scheme 2.



(aryl amination of **1** and acylation of aniline) in an acetic acid – cyanuric chloride – triethylamine – aniline system with acetic acid as solvent. Even though the two reaction pathways in the system seem to be obvious and involve simple and readily available reagents, no comparative studies have been published. The influence of hydrogen chloride acceptors, especially homogeneous (e.g., triethylamine, pyridine, sodium acetate) acceptors, must be deciding and should also be studied.

Results and discussion

In our initial experiments on acylation assisted by cyanuric chloride, we attempted to follow the recipe suggested by Lahoti and Wagle (4) with acetic acid as a substrate and acetone as solvent. According to the authors, insoluble 4,6-dichloro-[1,3,5]triazin-2-ol (Schemes 1 and 2, **3b**) was formed as a by-product, while acid chlorides were isolated in good and moderate yields by simple evaporation of filtrates that also contained Et_3N.

Regarding the isolation protocol, we considered it unlikely that acid chlorides and a tertiary amine could exist unreacted in the same solution (quarternary ammonium salt has to be formed (3*d*). Note that by-product **3b** is rather acidic (pK = 3.2 (2*d*)) and also would have reacted. When we added Et_3N to an acetone solution containing acetic acid and cyanuric chloride in molar ratio 1:1:1, a precipitate did form, as described, but turned out to be triethylamine hydrochloride ($Et_3N \times HCl$) rather than **3b**. The salt was identified by means of ^1H NMR, mass-spectrometry, and by melting point.

We took two other substrates, i.e., 4-nitrobenzoic and trichloroacetic acids (mentioned in (4) among illustrative examples) and obtained exactly the same salt ($Et_3N \times HCl$) as a by-product. Importantly, acid chlorides were not detected in the reaction mixtures (see Experimental section).

Regarding the reaction scheme in general, we would like to emphasize that 1 equiv. of chlorine (one chlorine atom) goes to form triethylamine hydrochloride, as we established. Logically, acid chlorides cannot be the major reaction products. All of this makes the formation of acid chlorides, as described in the above mentioned paper (4), very doubtful. Further tests showed that amides, namely acetanilide (Scheme 2, **4**), were formed (together with other products including aryl amination products **2a** and **2b**) when aniline (1 equiv.) was added to the reaction mixtures. However, amides proved to be problematic to isolate from reaction mixtures without using preparative chromatography, and we focused on experiments in acetic acid medium. The interaction between carbonic acids and **1** can be illustrated by Scheme 2. It explains the formation of triethylamine hydrochloride. The key point is that in acetic acid – cyanuric chloride – triethylamine system, the only possible nucleophile is acetate ion. Acetate replaces the chlorine atom in the course of aromatic nucleophilic substitution. Chlorine is a leaving group, while 4,6-dichloro-[1,3,5]triazin-2-ol acetate (acetate of compound **3b**) or 1,3,5-triazine-2,4,6-triol acetate (**5**) (when 1 or 3 equiv. of Et_3N is added, respectively) are the products. The presence of **5** in the reaction mixtures was detected by mass spectrometry. Importantly, we established that the reaction does not proceed in the absence of Et_3N. Cyanuric chloride is stable in acetic acid at room temperature; the ^1H NMR or ^{13}C NMR spectra of **1** in CD_3COOD solution are invariant over 2 days. Equilibrium is only shifted when an acetic acid solution of cyanuric chloride is heated to boil so that acetyl chloride distills off. Another way to shift the equilibrium is the introduction of Et_3N (or other HCl acceptors). In this case triethylamine hydrochloride is formed, which binds HCl. In the final stage of the re-

action sequence, 4,6-dichloro-[1,3,5]triazin-2-yl group has to be the leaving group, because the acidity of 4,6-dichloro-[1,3,5]triazin-2-ol **3b** is higher (pK = 3.2 (1*d*)) than that of aliphatic carbonic acids or benzoic acid. As a result, target amides are formed, and compound **3b** is washed off by basic solutions. Cyanuric acid (**3a**), with pK value about 4.7, is acidic enough to be the leaving group. We would prefer to consider the formation of amides promoted by cyanuric chloride as a case of activated ester method (see Scheme 2), which has a wide application in organic (mostly peptide) synthesis (5). The method involves the conversion of acids to esters with hydroxy compounds whose anions are good leaving groups (4-nitrophenol, 1-hydroxybenzitriazole, and many others). The esters then react with amines or amino acids to furnish amides.

To embark on experiments with acetic acid as solvent, we first combined aniline, cyanuric chloride, and Et_3N in the molar ratio 1:1:1 (1 equiv. each). Triethylamine, a strong base, was neutralized with acetic acid, and the mixture was cooled to ambient temperature before being added to the solution of cyanuric chloride. Aniline was also neutralized with acetic acid beforehand (see experimental details later). We tried different sequences of the reagent addition. When aniline (1 equiv.) was added immediately or even 3 h after Et_3N (1 equiv.), aryl amination proved to be the predominant reaction. Only trace amounts of acetanilide **4** were detected. Further experiments showed that the course of the reaction could be changed when no less than 3 eqiuv. of Et_3N was added to the reaction mixture. To completely eliminate the aryl amination, the acetic acid solution of cyanuric chloride and Et_3N must be left for a long time (10–12 h) before the addition of aniline. Aniline was taken in excess (~4 equiv.) to provide maximum yield. Extraction of the reaction mixture with benzene and subsequent treatment with dilute hydrochloric acid and alkali gave a chromatographically pure sample of **4** (the purity and identity was checked by means of ^{1}H NMR and HPLC). The isolated yield was 77%, assuming all three chlorine atoms of **1** reacted. The yield of **4** is slightly higher (81%) when Et_3N is replaced by sodium acetate and is considerably lower (56%) when pyridine is used instead.

The analysis of an acetic acid solution containing cyanuric chloride and Et_3N (in the form of its acetate) revealed some interesting facts. First, a precipitate of cyanuric acid **3a** was formed. It was identified by mass spectroscopy and elemental analysis; the isolated yield was about 72%. Further, triethylamine hydrochloride was isolated with 92% yield from the liquid phase upon diluting with hexane. The formation of this salt confirms the proposed reaction scenario (Scheme 2). Regarding the reactivity of cyanuric chloride in general, our results are consistent with some of the previously reported data, showing that selective substitution of one chlorine atom in cyanuric chloride is often problematic (1*d*). To explain the formation of cyanuric acid (**3a**), one should keep in mind that acetic acid is a protonic solvent. Such solvents must cause solvolysis of the "active ester" **5**. We observed a rapid formation of **3a** when water was added to the solutions of **1** and Et_3N in acetone or acetic acid. In dry acetic acid medium, the only possible solvolysis product was acetic anhydride (Scheme 2, **6**), whose presence in the reaction mixture was confirmed by means of mass spectrometry and ^{1}H NMR. No trace of acetyl chloride was detected. We may assume that the formation of insoluble cyanuric acid **3a** could be an additional driving force of the solvolysis, which leads to the formation of acetic anhydride. Finally, we found it possible to perform acylation of aniline with acetic acid as a "green reaction" simply by heating aniline in a large volume (~ 80 mol excess) of acetic acid under reflux (~1 h) in the absence of catalysts or dehydrating agents, as recommended in (3*a*).

Meanwhile, no trace of **4** was detected when 3 equiv. of all three reagents were mixed simultaneously. Thus, when aniline (3 equiv.) was added to the reaction mixture immediately after Et_3N (3 equiv.), aryl amination prevailed and a precipitate was formed (see Experimental section). The major product (92%, according to HPLC) was 6-chloro-*N*,*N*′-diphenyl-[1,3,5]triazine-2,4-diamine (Scheme 1, di-substituted product **2a**). Up to 66% of this compound was isolated by simple filtration of the reaction mixture after 6 h exposure at ambient temperature. Et_3N can be replaced by sodium acetate or pyridine with the same result. An excellent yield (96%, isolated) of di-substituted product was achieved when water was added to the reaction mixture (together with the reagents), which precipitated the reaction product. To obtain pure mono-substituted product **2b** in the reaction with 1 equiv. of aniline, the temperature should be maintained at about 15 °C and water should also be added. Otherwise, substantial amounts of di-substituted product **2a** are formed.

All these experiments demonstrate that acetate ion, as a weaker nucleophile, fails to compete with aniline in the reaction with cyanuric chloride in acetic acid solutions. It was established in the late 1940s that salts and acids are dissociated to a very little extent (6) in acetic acid medium, in contrast to water solutions. Thus, acetates are barely dissociated in anhydrous acetic acid, and consequently the effective concentration (activity) of the nucleophile is very low. Note that neat acetic acid exists in the form of dimers with strong intramolecular hydrogen bonds and, as acid, dissociates weakly (6).

Conclusions

Two reactions of aniline in acetic acid solutions containing cyanuric chloride and hydrogen chloride acceptors have been established, not considering the acid–base interaction between aniline and acetic acid. Either transformation, aryl amination or acylation, can be performed smoothly and with high yields under proper reaction conditions. The results show that acetic acid can be used as solvent for aryl amination of cyaniric chloride **1** and most probably other heterocyclic halides with no risk of acylation. This is due to the lower nucleophilicity of the acetate ion and a weak dissociation of acetates in anhydrous acetic acid medium. The presence of HCl acceptors (triethylamine, pyridine, sodium acetate) does not influence the aryl amination, which predominates in acetic acid solution. Mono- or di-phenylamino-1,3,5-triazine derivatives (**2a** and **2b**) were obtained in good and excellent yields when acetic acid solutions of cyanuric chloride, aromatic amines (1 or 2 equiv.), and an acetate (1 or 2 equiv., respectively) were combined simultaneously at ambient temperature. On the other hand, a clean procedure

for the preparation of acetanilide **4** promoted by cyanuric chloride has been developed. It is very likely to be applicable to other acids and amines. To achieve acylation, it is first necessary to complete the reaction between cyanuric chloride and 3 equiv. of triethylammonium acetate, which causes the replacement of all three chlorine atoms; sodium or pyridinium acetates can also be used. For acylation, acetic acid has to be dry, while aryl amination is not impeded by the addition of water. Acetyl chloride is never formed in the course of the reaction between cyanuric chloride and acetic acid in the presence of triethylammonium acetate in acetone or acetic acid solutions. In acetic acid solution containing cyanuric chloride and triethylammonium (or sodium) acetate, cyanuric acid **3a** and acetic anhydride **6** are formed as solvolysis products. Acetic anhydride is the actual acylating agent in the subsequent reaction with aniline.

Experimental section

General

All chemicals were purchased from Sigma-Aldrich Chemical Company and used as received. Progress of the reactions was monitored by HPLC or TLC on silica gel SIL G/UV 254 plates and chloroform/acetone (10:1) as mobile phase. HPLC was performed using a 5500 Varian Vista chromatograph equipped with Waters Symmetry C-18 reverse-phase column (4.6/150 mm, 5 μ particle size, methanol/water (80:20 vol.) as mobile phase). Mass spectra were recorded on Micromass 70S-250 sector mass spectrometer; NMR spectra on a Varian spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C). Acetic acid (Sigma-Aldrich, 99.7%, ACS reagent grade) was freshly distilled and subjected to fractional crystallization under inert atmosphere. Triethylamine and pyridine were distilled over KOH and dried over CaH_2. Sodium acetate (anhydrous) was dried at 150 °C under vacuum. All the experiments on acylation and aryl amination were carried out under inert atmosphere, unless otherwise noted.

Aryl amination of cyanuric chloride

*Preparation of 6-chloro-*N,N′*-diphenyl-[1,3,5]triazine-2,4-diamine (di-substituted derivative 2b)*

Method A (in glacial acetic acid medium)

Triethylamine (3.6 mL, 0.025 mol) and aniline (1.95 g, 0.021 mol) were added dropwise upon cooling (t < 35 °C) to 30 mL of acetic acid and the solution was combined with **1** (1.84 g, 0.01 mol) dissolved in 30 mL of AcOH. After 6 h a precipitate was filtered, washed with boiling water (20 mL × 2) to neutral pH, and dried to furnish 1.96 g (66%) of **2b**.

Method B (in the presence of water and with sodium acetate as HCl acceptor)

A solution of **1** (1.84 g, 0.01 mol) in 30 mL of AcOH was combined with a solution of aniline (1.95 g, 0.021 mol) and CH_3COONa (2.0 g, 0.025 mol) in the mixture of AcOH (10 mL) and H_2O (10 mL) at RT without protection from air and then left for 4 h. The precipitate was treated as described above to furnish 2.85 g (96%) of compound **2b**. Melting point (192–194 °C) and spectroscopic data agreed with previoulsy reported data (1*e*).

Preparation of 4,6-dichloro-[1,3,5]triazin-2-yl-phenylamine (mono-substituted derivative 2a)

To a stirred solution of **1** (9.2 g, 0.05 mol) in 150 mL of acetic acid 4.65 g (0.05 mol, 1 equiv.) of aniline and 7.2 mL (0.05 mol, 1 equiv.) of Et_3N in a mixture of 20 mL of AcOH and 80 mL of H_2O was added dropwise within 15 min at 15–17 °C upon cooling with ice water (not letting AcOH to freeze). In the open air, the reaction mixture was left for 1 h at this temperature and then diluted with 1 L of brine. The solid was collected, dried, and recrystallized from 330 mL of heptane (insoluble impurities were filtered off the hot solution) to afford 7.47 g (62%) of pure (HPLC, NMR) compound **2a**, whose melting point (136 to 137 °C) and spectroscopic data was in accordance with that previously reported (1*d*).

Acylation of aniline

Acylation promoted by cyanuric chloride

Et_3N (0.60 mL, 4 mmol) was added dropwise to 5 mL of AcOH, the mixture cooled to RT, combined with a solution of **1** (0.184 g, 1 mmol) in 5 mL of AcOH and left overnight. Aniline (0.370 g, 4 mmol) in 3 mL of AcOH was added and left for 6 h upon stirring. The mixture was diluted with 30 mL of water containing 10 g of NH_4Cl and extracted with benzene (3 × 10 mL). The extract was consequently washed with 10 mL of 0.5 mol/L HCl and 10 mL of 0.5 mol/L NaOH, dried over $MgSO_4$, and evaporated under reduced pressure to furnish 312 mg (77%) of chromatographically pure (~99%, according to HPLC) acetanilide **4**, whose melting point (113 to 114 °C) and ^{1}H NMR agreed well with the literature data (7).

Acylation of aniline with acetic acid as solvent

Aniline (0.93 g, 0.01 mol) was refluxed in 50 mL of glacial acetic acid for 2 h, the solvent evaporated under vacuum, the residue washed with 0.1 N HCl (20 mL), then H_2O (3 × 10 mL) to neutral pH and dried to furnish 1.11g (82%) of pure acetanilide.

Identification of by-products

Triethylamine hydrochloride

Colorless needles, mp 251–253 °C (lit. value 254–260 °C, Merk Index Vol. 13, p. 9740). ^{1}H NMR (300 MHz, D_2O) δ: 1.10 (t, 3H, Et), 3.02 (m, 2H, Et), 4.67 (br. s, H_2O + H^+). HRMS (EI, 70 eV) calcd. for $C_6H_{15}N$ (M^+ – HCl): 101.1204; found: 101.1204.

Cyanuric acid (3a)

Colorless solid, does not have a clear melting point (1*a*). MS (EI, 70 eV) *m*/*z*: 129 (M^+, 100), 86 (M^+ – NHCO, 25), 70 (M^+ – NHCO – O, 20), 58 (NHCONH, 10). HRMS (EI, 70 eV) calcd. for $C_3H_3N_3O_3$: 129.0174; found: 129.0176.

Acetic anhydride (6)

Isolated by fractional distillation of the reaction mixtures under reduced pressure (dry argon atmosphere was maintained), bp 80–83 °C/100mm. ^{1}H NMR (300MHz, $CDCl_3$) showed the characteristic signal of acetyl group protons in Ac_2O at 2.22 ppm (acetyl group protons in AcOH and AcCl

resonated at 2.09 and 2.62 ppm respectively). MS (EI, 70 eV) *m*/*z*: 101 (M^+, 100), 43 (CH_3CO^+, 40).

Acid chlorides

Careful fractional distillation of the reaction mixtures in inert atmosphere did not lead to isolation of the chlorides, as claimed in (4). Because of the extremely high reactivity, no "direct" methods for chromatographic detection of acid chlorides are known. Derivatization, which is normally used in the preparation step of chromatographic analysis (8), fails to distinguish chlorides from anhydrides or other acylating agents. While working with acetic, 4-nitrobenzoic, and trichloroacetic acids as substrates, ^{13}C NMR spectroscopic study of the reaction mixtures showed that they contain several components, including unreacted cyanuric chloride **1**. We compared ^{13}C NMR spectra of authentic samples of 4-nitrobenzoyl chloride, acetyl chloride, and trichloroacetyl chloride with that of reaction mixtures but did not observe the characteristic signals of "acid chloride" carbonyl groups. Mass spectrometric analysis did not reveal any peaks that could be attributed to the acid chlorides either.

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