Synthesis and Characterization of Substituted New 1, 2, 4-Triazines from *p*-Chloroacetophenone

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Summary: Two new 1,2,4-triazines **5a** and **5b** were obtained in a 92 : 8 ratio by condensation of the new amino keto-amide **4** with hydrated hydrazine in the presence of acetic acid. The previously unreported amino keto-amide **4** was obtained from *p*-chloroacetophenone **(1)** in three steps. Both of the triazines were characterized by their spectral data.

Keywords: Hydrated hydrazine, 2-Chloropropanoyl chloride, NBS (*N*-Bromosuccinimide), DIPEA (*N, N*-Diisopropylethylamine), Triphenyphosphine.

Introduction

Triazines are six-membered heterocyclic compounds with three nitrogen atoms in the ring. 1,2,4-Triazine nucleus is an important structural moiety in many biologically interesting compounds [1], including antimicrobial [2], antibacterial [1-6], antiviral [1, 7], antifungal [7], anticancer [1, 7-9], anticonvulsant, antihypertensive, and platelet inhibitors [10, 11].

There are several different methods for the synthesis of Triazines. The first synthesis of this type of triazines, reported by Bamberger in 1892, involved the reaction between an aryl diazonium salt and the hydrazone of pyruvic acid. The resulting azo intermediate was finally converted to the 1,2,4-benzotriazine in sulfuric acid and acetic acid [12]. 1,2,4-Triazines have been synthesized mostly by the reaction of monoamidrazone with α-dicarbonyl and polycarbonyl compounds [13]. In addition, a number of other general methods are reported [14, 15], including the dehydrogenation of dihydrotriazines with potassium dichromate or sulphur, prepared by the condensation of α-acylamino-ketone with hydrazine, followed by ring closure [16].

Recently Bigot *et al.* reported (DAST)-mediated cyclization of α,α-disubstituted-α-acylaminoketones into fluorooxazolines which on treatment with hydrazine hydrochloride provided 1,2,4-triazine [17]. Due to a number of biological activities of triazines are reported in previous literature, we have synthesized triazines starting from acetophenone by using simple and an efficient method. The investigation of the biological activities of these triazines is in progress.

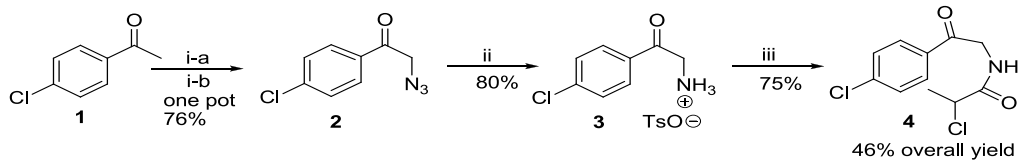
Results and Discussion

We synthesized 2-chloro-*N*-(2-(4-chlorophenyl)-2-oxoethyl)-propanamide **(4)** from *p*-chloroacetophenone **(1)** in three steps in 46% yield. In an attempt to prepare the hydrazone **6** by treating keto-amide **4** with hydrated hydrazine in the presence of acetic acid led to two new compounds, identified by spectral analysis to be 1,2,4-triazines (**5a** ,**5b**). The mass spectrum analysis showed molecular ion at *m/z* 255, which indicated the loss of water from **6**. The ^{13}C-NMR (BB and DEPT) of triazine **5a** showed one methyl, one methylene, five methine (four aromatics) and four quaternary carbons, while triazine **5b** exhibited one methyl, six methine (five aromatics) and four quaternary carbons. The appearance of aliphatic methyl and methine revealed that ring closure does not involve nucleophilic substitution of chlorine atom attached to C-1, but involves amide carbonyl group for ring closure. The main difference between the two triazines was at C-5, which in **5a** appears as a methylene at δ 44.3 while the same carbon in **5b** resonates as a methine at δ 146.9 in the ^{13}C-NMR spectrum. Absence of NH peak in the triazine **5b** also indicated the presence of a double bond in the ring. HREIMS exhibited the molecular ions at *m/z* 255.0313 and 253.0174 for **5a** and **5b** with molecular formulae $C_{11}H_{11}N_3Cl_2$ and $C_{11}H_9N_3Cl_2$, respectively. **5b** was found to be dehydro analog of **5a** (Scheme-2).

Preparation of **4** was commenced with *p*-chloroacetophenone **(1)** which was first converted to 2-Azido-1-(4-chlorophenyl)ethanone **(2)** followed by the formation of 2-(4-chlorophenyl)-2-

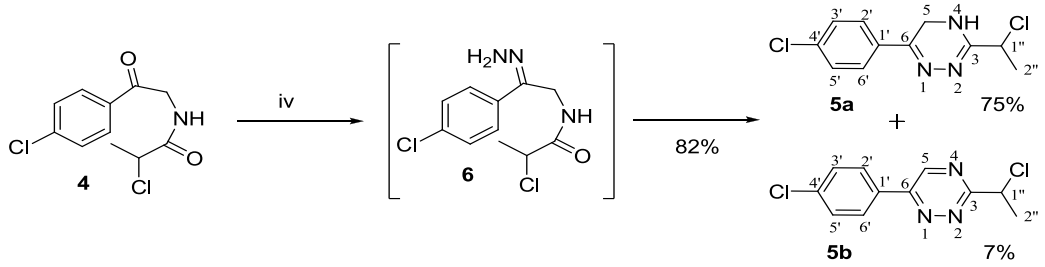
oxoethanaminium 4-methylbenzenesulphonoate **(3)** on treatment with triphenylphosphine. The resulting compound **3** upon reaction with 2-chloropropanoyl chloride provided the novel amide **4** (Scheme-1).

The proposed mechanism involved nucleophillic attack of hydrazine on carbonyl of the ketone **4** to afford amino alcohol, which upon subsequent dehydration gave the corresponding hydrazone **6**. The protonation of the carbonyl oxygen of amide group increased its electrophillicity, causing it to be more susceptible for nucleophillic attack by amino group of hydrazone **6**. The resulting cyclized intermediate upon dehydration gave the triazine **5a**. It was expected that the triazine **5a** undergoes air oxidation to afford **5b** (Fig. 1)**.**



Scheme-1**:** Synthesis of Keto-amide **4.**

Reagents and Conditions: (i) (a) *p*-TsOH, NBS, CH_3CN, Reflux, 1 h; (b) NaN_3, r.t, 4 h, 76%; (ii) PPh_3, *p*-TsOH, THF, 8 h, 80%; (iii) 2-chloropropanoyl chloride, DIPEA, DCM, r.t, 12 h, 75%



Scheme-2**:** Synthesis of triazine **5a** and **5b.**
Reagents and Conditions: (iv) 80% $N_2H_4.H_2O$, AcOH, 80 °C, 1 h, **5a**; 75% and **5b**; 7%.

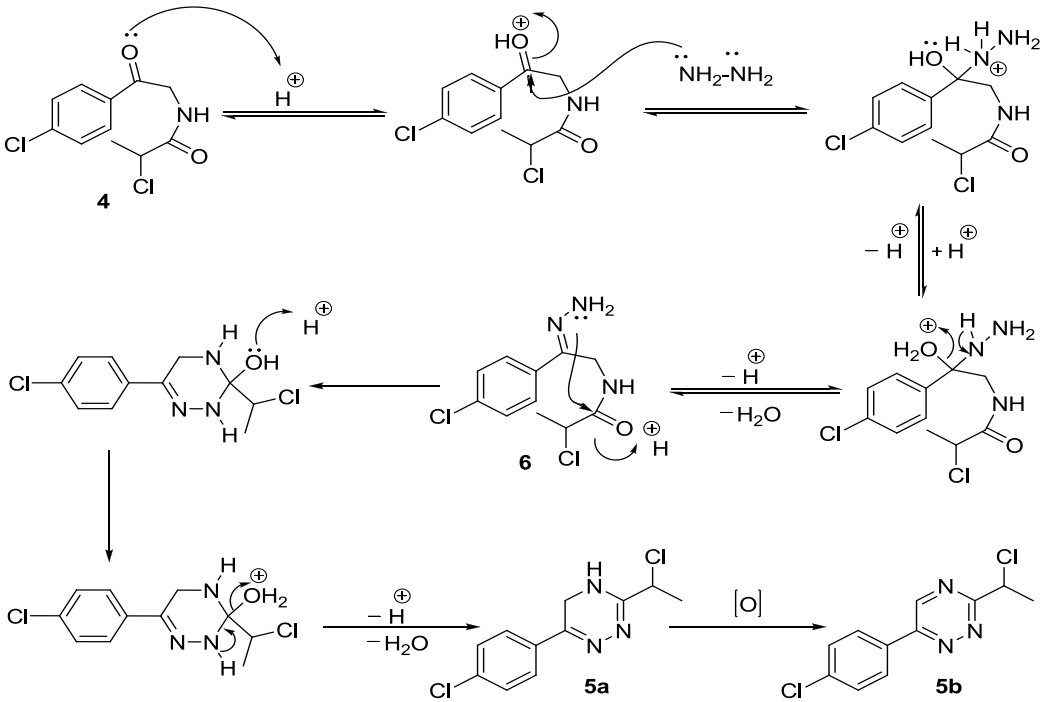


Fig. 1: Proposed mechanism of Triazines formation.

Experimental

General Procedures

The progress of all reactions were monitored by TLC (thin layer chromatography) which was performed on 2.0 × 5.0 cm aluminium sheets, precoated with silica gel $60F_{254}$ to a thickness of 0.20 mm (Merck). The chromatograms were visualized under ultraviolet light (254-366 nm) and vanillin dips. Melting points were determined in open glass capillaries on an electronic melting point apparatus (SMP3). The *p*-chloroacetophenone and all other starting materials were used without purification. ^{1}H and ^{13}C-NMR spectra were obtained on Bruker 300 MHz spectrometers. Coupling constant were calculated in hertz (Hz). Mass spectra were recorded on JEOL MS Route 600 H spectrometer by using (EI^+) techniques. HREIMS was obtained on Thermo Finnigan MAT 95XP instrument. The silica gel 60, E. Merck was used for column chromatography.

2-Azido-1-(4-chlorophenyl)ethanone **(2)**

To a solution of *p*-chloroacetophenone **(1)** (6.46 mmol) in acetonitrile (20 mL), *p*-toluenesulfonic acid (9.69 mmol) and NBS (9.04 mmol) were added and refluxed for 1 hour. TLC showed that the starting material was consumed. The reaction mixture was cooled to room temperature then sodium azide (19.38 mmol) was added and stirred for 4 h. The crude reaction mixture was diluted with cold water and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the crude product was purified by flash silica gel column chromatography by using 5-10 % ethyl acetate in hexane as an eluent. Light yellow solid; yield 76%; m.p.: 160-162 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.83 (2H, d, J = 8.7 Hz, ArH), 7.47 (2H, d, J = 8.7 Hz, ArH), 4.50 (2H, s, CH_2).

2-(4-Chlorophenyl)-2-oxoethanaminium 4-methylbenzenesulphonoate **(3)**

To a solution of **2** (9.90 mmol) in THF (60 mL), triphenyl phosphine (9.90 mmol) was added, followed by the addition of *p*-toluenesulfonic acid (29.71 mmol) under nitrogen atmosphere. The reaction mixture was left for stirring at room temperature for 8 hours. After completion of the reaction, the solid appeared which was filtered and washed with THF to obtain the desired compound **3** as a white solid. Yield; 80%; m.p.: 240-242 ºC; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.20 (3H, br. s, NH_3), 8.01 (2H, d, J = 8.4 Hz, ArH), 7.68 (2H, d, J = 8.4 Hz, ArH), 7.46 (2H, d, J = 7.8 Hz, ArH), 7.10 (2H, d, J = 7.8 Hz, ArH), 4.55 (2H, s, CH_2), 2.27 (3H, s, CH_3).

2-Chloro-N-(2-(4-chlorophenyl)-2-oxoethyl)propanamide **(4)**

To a suspension of compound **3** (3.66 mmol) in 20 mL dichloromethane at room temperature, DIPEA (2.42 mL) was added under an argon environment. To the stirring mixture, 2-chloropropanoyl chloride (7.32 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 12 h, diluted with cold water and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and purified by flash silica gel column chromatography (10-20% ethyl acetate in hexane as an eluent) to afford desired compound **4** in 75% yield. Off white solid; m.p.: 130-132 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.90 (2H, d, J = 8.7 Hz, ArH), 7.50 (1H, br. s, NH), 7.47 (2H, d, J = 8.7 Hz, ArH), 4.70 (2H, d, J = 4.5 Hz, CH_2), 4.47 (1H, q, J = 6.9 Hz, CH), 1.75 (3H, d, J = 6.9 Hz, CH_3); MS (EI, 70 eV): *m/z*: 259 (M^+).

Synthesis of Triazines

To a solution of compound **4** (0.57 mmol) in acetic acid (1.5 mL), 80% hydrated hydrazine (0.1 mL) was added dropwise. The resulting reaction mixture was heated up to 80°C for 1 hour. After the completion of reaction checked by TLC (thin layer chromatography), the reaction mixture was quenched with saturated solution of sodium bicarbonate and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried (anhydrous $MgSO_4$), filtered and concentrated. The mixture was purified by column chromatography by using 5-10 % ethyl acetate in hexane as an eluent to get two triazines **5a** and **5b** in a ratio of 92:8, respectively.

3-(1-Chloroethyl)-6-(4-chlorophenyl)-4,5-dihydro-1,2,4-triazine **(5a)**

Light yellow solid; yield 75%; m.p.: 138-139 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.42 (1H, s, H-4), 7.63 (2H, d, J = 8.7 Hz, H-2',H-6'), 7.35 (2H, d, J = 8.7 Hz, H-3', H-5'), 4.62 (1H, q, J = 6.9 Hz, H-1''), 4.25 (2H, d, J = 2.4 Hz, H-5), 1.77 (3H, d, J = 6.9 Hz, H-2''); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.6 (C-2''), 44.3 (C-5), 54.2 (C-1''), 127.3 (C-3',C-5'), 128.8 (C-2', C-6'), 131.4 (C-1'), 138.0 (C-4'), 155.1 (C-3), 166.8 (C-6); MS (EI, 70 eV): *m/z*: 255 (M^+); HREIMS calcd for $C_{11}H_{11}N_3Cl_2$: 255.0330, found: 255.0313.

3-(1-Chloroethyl)-6-(4-chlorophenyl)-1,2,4-triazine **(5b)**

Off white solid; yield 7%; m.p.: 97-99 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.01 (1H, s, H-5), 8.05 (2H, d, J = 8.7 Hz, H-2', H-6'), 7.52 (2H, d, J = 8.7 Hz, H-3', H-5'), 5.48 (1H, q, J = 6.9 Hz, H-1"), 2.02 (3H, d, J = 6.9 Hz, H-2"); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.0 (C-2"), 56.4 (C-1"), 128.2 (C-3', C-5'), 129.8 (C-2', C-6'), 131.2 (C-1'), 137.9 (C-4'), 146.9 (C-5), 155.3 (C-3), 167.0 (C-6); MS (EI, 70 eV): *m/z*: 253 (M^+); HREIMS calcd for $C_{11}H_9N_3Cl_2$: 253.0174, found: 253.0174.

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