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A NEW SYNTHESIS OF 2-SUBSTITUTED 4*H*-3,1-BENZOXAZIN-4-ONES BY CYANURIC CHLORIDE CYCLODEHYDRATION OF *N*-BENZOYL- AND *N*-ACYLANTHRANILIC ACIDS

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Abstract - A new and a convenient method for the synthesis of aryl- and alkyl-2-substituted 4*H*-3,1-benzoxazin-4-ones by cyclodehydration of *N*-benzoyl- and *N*-acylanthranilic acid by cyanuric chloride is described.

INTRODUCTION

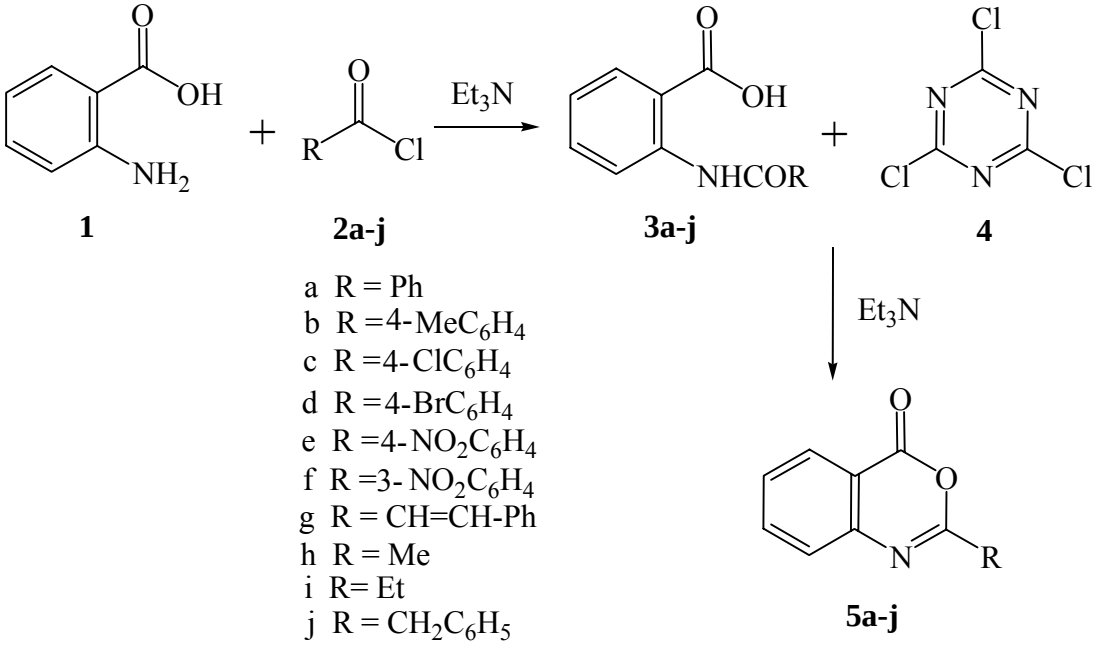
Cyanuric chloride activates carboxylic acids by formation of active esters.[1] These *in situ* prepared active esters can be utilized for the synthesis of a variety of functional groups, such as amides,[2-3] acid chlorides,[3] esters,[3] peptides,[3] macrocyclic lactones,[4] β-lactams,[5-6] acylazides,[7] hydroxamic acids[8] and diazocarbonyl compounds.[9] Also cyanuric chloride has been used for the preparation of nitriles by dehydration of aldoximes,[10] sulfides from sulfoxides,[11] nitriles from amides and thioamides[12] and sulfonyl chlorides.[13] Furthermore, cyanuric chloride has been used to activate other class of organic compounds such as dimethyl sulfoxide in Swern oxidation of alcohols[14-15]or in preparation of disulfides[16] and DMF for the conversion of alcohols into the corresponding formates,[17] alcohols to alkyl chlorides,[18] ketoxime to amides[19-20] and aldoximes to nitrile.[19] Among other applications, the utilization of cyanuric chloride in the field of carbohydrate microarrays for monitoring of carbohydrate-protein interaction,[21] the production of new class of UV filters for use in cosmetic sunscreens[22] and in molecular imprinting can be mentioned.[23] Following our earlier research works on the efficient synthesis of 2-substituted 4*H*-3,1-benzoxazin-4-ones by the condensation of anthranilic acid with various orthoesters under classical heating or microwave irradiation[24] and application of cyanuric chloride in stereospecific synthesis of β-lactams,[5] here we wish to report a convenient procedure for the synthesis of aryl- and alkyl-2-substituted 4*H*-3,1-benzoxazin-4-ones from the readily available *N*-benzoyl- and *N*-acylanthranilic acid by cyanuric chloride (**4**).

4*H*-3,1-benzoxazin-4-ones are an important class of condensed heterocyclic compounds exhibiting a wide spectrum of biological activities. Many compounds containing this core structure have shown interesting biological properties such as anti-neoplastic activity,[25] fungicidal properties,[26] as lipoprotein elevators for the treatment of hyperlipoproteinemia and associated diseases[27] or as serine protease and human leukocyte elastase inhibitors.[28] Furthermore, they are valuable starting materials for the synthesis of a variety of 2,3-disubstituted 4(3*H*)-quinazolinones.[29]

RESULTS AND DISCUSSION

We have found that cyanuric chloride reacts smoothly with *N*-benzoylanthranilic acid (**3a**), which can be readily prepared from anthranilic acid (**1**) and benzoyl chloride (**2a**), in refluxing toluene in the presence of triethylamine to give 2-phenyl-4*H*-3,1-benzoxazin-4-one (**5a**) in 83% yield. During the process of this cyclodehydration reaction cyanuric acid is converted to hydoxydichloro[1,3,5]triazine which can be easily separated from the desired product (due to its solubility in water or its insolubility in non-polar organic solvents). The reaction is very clean and the product can be isolated with high purity by usual workup.

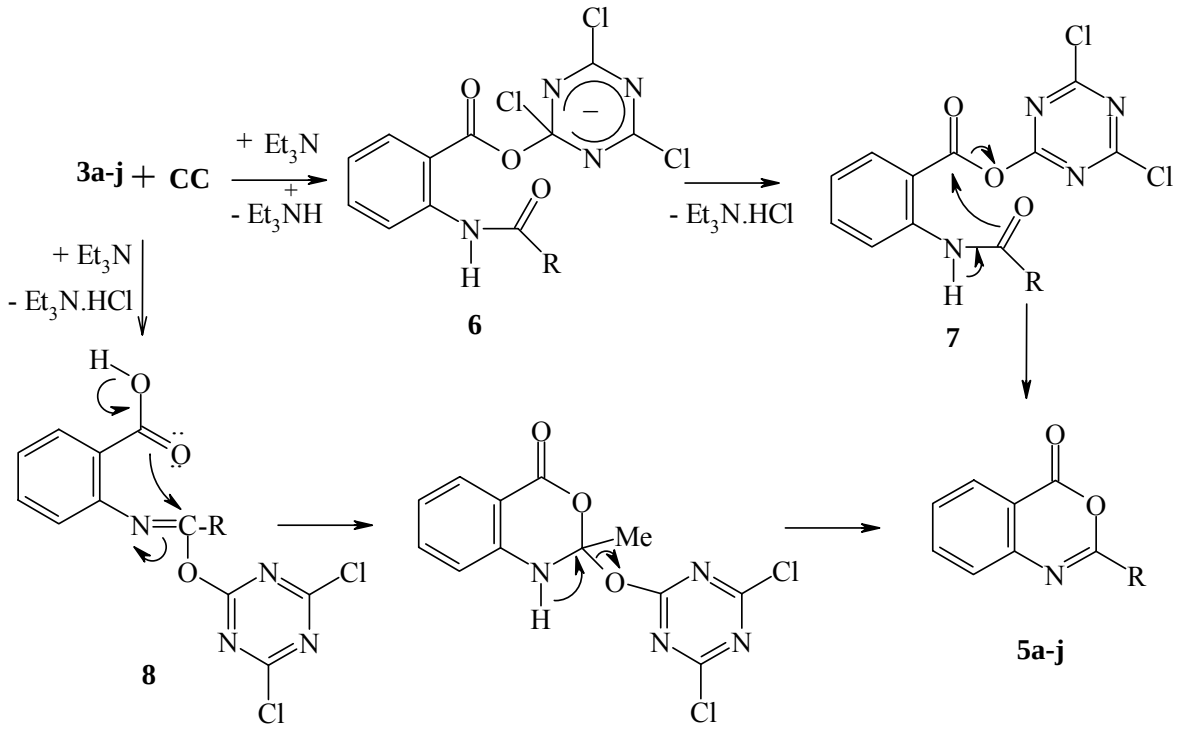
The results with some derivatives of *N*-benzoylanthranilic acid (**3a-f**) for the preparation of 2-aryl-4*H*-3,1-benzoxazin-4-one are summarised in Table1. In all cases the required amide intermediates (**3a-f**) were prepared from aroyl chloride and anthranilic acid.



Scheme 1

The method also works well for the synthesis of 2-alkyl-4*H*-3,1-benzoxazin-4-one (**5h-j**). Since the 2-akyl substituted benzoxazinones are hydroscopic and they are hydrolysed easily to 2-acetaminobenzoic acids we only modified the workup procedure (EXPERIMENTAL) to avoid such kind of hydrolysis during the isolation of the products. The results for the preparation of 2-alkyl-4*H*-3,1-benzoxazin-4-one are summarised in Table 1. Furthermore, the employment of sodium or potassium salt of *N*-benzoylanthranilic acid or its derivatives instead of acid itself in this reaction did not appreciably increase the yields of the products (Method B, see Table 1).

A proposed mechanism for this reaction is depicted in Scheme 2. The nucleophilic attack of the carboxylic group of anthranilic acid to cyanuric chloride (**CC**) *via* formation of the σ adduct (**6**) will produce the active ester (**7**) which in the next step can cyclized to produce (**5**). The alternative pathway of the formation of imidic ester intermediate (**8**) where the carboxylic group attacks to imidate to produce the cyclized product have a lower probability.



Scheme 2

The structures of all synthesized compounds were confirmed by the analyses of their spectra data (IR, ^{1}H and ^{13}C NMR). Products (**3a-j**) and (**5a-j**) are known compounds and their physical properties were identical with those of authentic samples.

Table 1: Reaction of *N*-benzoyl- and *N*-acylanthranilic acid with cyanuric chloride

Entry	Product	R	Method	Yield (%)	Mp (T/°C)	Lit. mp (T/°C)
1	**5a**	Ph	A & B	83[a]	123-124	124-125,[30] 123-124[31]
2	**5b**	4-MeC_6H_4	A & B	75[a]	154-155	154.5,[31] 155[32]
3	**5c**	4-ClC_6H_4	A	81	190-191	190[32]
4	**5d**	4-BrC_6H_4	A	87	183-184	184[32]
5	**5e**	4-$NO_2C_6H_4$	A	82	202-204	203[31]
6	**5f**	3-$NO_2C_6H_4$	A	80	166	166[32]
7	**5g**	CH=CH-Ph	A	78	148-149	148[32]
8	**5h**	Me	C	76	80-82	80-81[31]
9	**5i**	Et	C	72	84-86	85-86[31]
10	**5j**	$CH_2C_6H_5$	C	75	90-91	90.5[33]

[a] Yields of the isolated products with Method A. The yields with Method B were within ± 5 % as of Method A.

In conclusion we have found that cyanuric chloride is an effective reagent for the cyclodehydration of *N*-aroylanthranilic acid and 2-acetamonobenzoic acid. This method is convenient for the synthesis of a variety of aryl- and alkyl-2-substituted 4*H*-3,1-benzoxazin-4-one.

EXPERIMENTAL

IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrophotometer. ^1H and ^{13}C NMR spectra were measured using a JEOL EX-90A spectrometer at 90 and 22.63 MHz respectively. Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. Anthranilic acid, cyanuric chloride and all the acid chlorides were purchased from Aldrich or Fluca and were used without further purification. Toluene was freshly distilled from sodium.

Preparation of 2-aryl-4*H*-3,1-benzoxazin-4-ones – The general procedure is illustrated with 2-phenyl-4*H*-3,1-benzoxazin-4-ones (5a), (Method A): A solution of benzoyl chloride (1.41 g, 10 mmol) in 10 mL of dichloromethane was added dropwise to a stirred solution of anthranilic acid (1.37g, 10 mmol) and triethylamine (1.11 g, 11 mmol) in 40 mL of dichloromethane at rt. After 5 h, the reaction mixture was washed with water, dried ($MgSO_4$). Evaporation of the solvent and recrystallisation from chloroform gave the *N*-benzoylanthranilic acid (2.24 g 93%). A suspension of cyanuric chloride (0.92 g, 5 mmol) in anhydrous toluene (20 mL) was added dropwise over 10 min to a stirred solution of a mixture of *N*-benzoylanthranilic acid (1.20 g, 5 mmol) and triethylamine (0.60 g, 6 mmol) in 30 mL of toluene at rt. Following the addition, the reaction mixture was refluxed overnight and then washed with water, 5%

$NaHCO_3$ solution and at the end with brine and dried with $MgSO_4$. After solvent evaporation the crude product was recrystallised from ether-chloroform (1:2) mixture to afford the title compound (0.93 g 83%), mp 123-124 °C (lit.,124-125[30], 123-124[31]); IR (KBr): ν_{max}/cm^{-1}1769, 1625, 1622, 1600; ^{1}H NMR ($CDCl_3$): δ ppm 7.25-8.51 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$): δ ppm 116.8 (C_{4a}), 126.9 (C_8), 127.9 (C_6), 128.0 ($C_{2'}$), 128.2 (C_5), 128.4 ($C_{3'}$), 129.9 ($C_{1'}$), 132.3 ($C_{4'}$), 136.1 (C_7), 146.6 (C_{8a}), 156.7 (C_2), 158.9 (CO).

Preparation of 2-*p*-tolyl-4*H*-3,1-benzoxazin-4-ones (5b), (Method B): *N*-(*p*-Toluoyl)anthranilic acid was prepared as described for (**3a**). The crystallised compound was treated with equivalent amount of potassium hydroxide dissolved in ethanol. The potassium salt that separated was filtered and washed with ether and air-dried. To a suspension of potassium *N*-(*p*-toluoyl)anthranilate (1.46 g, 5 mmol) in toluene (30 mL) at rt was added dropwise with stirring cyanuric chloride (0.92 g, 5 mmol) in 20 mL of toluene. Stirring is continued at rt for 30 min and then the reaction mixture was refluxed overnight. Workup of the reaction mixture as described for method A gave the crude product which was recrystallised from ether-chloroform (1:2) mixture to give **5b** (0.89 g 75%), mp 154-155°C (lit., 154.5[31], 155[32]); IR (KBr): ν_{max}/cm^{-1} 1767, 1609, 1612, 1604; ^{1}H NMR ($CDCl_3$): δ ppm 2.37 (s, 3H, CH_3), 7.45-8.36 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$): δ ppm 21.5 (CH_3), 116.9 (C_{4a}), 127.2 (C_8) 127.4 ($C_{1'}$), 127.9 (C_6), 128.3 ($C_{2'}$), 128.4 (C_5), 129.5 ($C_{3'}$), 136.5 (C_7), 143.4 ($C_{4'}$), 147.3 (C_{8a}), 157.3 (C_2), 159.8 (CO).

Preparation of 2-alkyl-4*H*-3,1-benzoxazin-4-ones The general procedure is illustrated with 2-methy-4*H*-3,1-benzoxazin-4-one (5h), (Method C): To a stirred solution of anthranilic acid (1.37 g, 10 mmol) and triethylamine (1.11g, 11 mmol) in 40 mL of dichloromethane a solution of acetyl chloride (0.78 g, 10 mmol) in 10 mL of dichloromethane is added. The stirring is continued at rt for 4 h. Then the reaction mixture is poured into a mixture of ice and water. The precipitated material was separated and recrystallised from ethanol to give *N*-acetaminobenzoic acid (1.7 g 95%). To a stirred mixture of *N*-acetaminobenzoic acid (0.89 g, 5 mmol), triethylamine (0.60 g, 6 mmol) and 30 mL of toluene in a flame dried 100 mL flask equipped with a condenser attached to a drying tube filled with dry calcium chloride, was added a suspension of cyanuric chloride (0.92 g, 5 mmol) in toluene (20 mL) at rt. The mixture stirred for 30 min at rt and refluxed overnight. After evaporation of toluene the residue was extracted with petroleum ether (30-60°) and finally recrystallised with heptane to afford the desired compound (**5h**) (0.61 g 76%), mp 80-82°C (lit., 80-81[31]); IR (KBr): ν_{max}/cm^{-1}1755, 1650, 1610; ^{1}H NMR ($CDCl_3$): δ ppm 2.43 (s, 3H, CH_3), 7.40-8.42 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ ppm 21.2 (CH_3), 116.5 (C_{4a}), 126.2 (C_8), 127.9 (C_6), 128.1 (C_5), 136.2 (C_7), 146.3 (C_{8a}), 159.2 (CO), 160.0 (C_2).

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