Synthesis of Some 4-Substituted-2-(*o*-halogenophenyl)-1,2,3-triazoles

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Mesoaldehyde 1,3-dioxime was treated with either 2,4,6-trichlorophenyl- **(a)**, *o*-fluorophenyl- **(b)**, or *o*-bromophenyl- **(c)** hydrazine to give the corresponding mesoaldehyde 1,3-dioxime-2-halogenophenylhydrazones (**1a,b,c**). The latter were *O*-acetylated with acetic anhydride, and cyclized to triazole 4-oximes (**3b, c**) or triazole 4-*O*-acetyloximes (**6a,b,c**) with cesium carbonate, then converted to nitriles (**7a,b,c**) by refluxing with acetic anhydride followed by pyrolysis, or to aldehydes (**4a,b,c**) by hydrolysis. The nitriles (**7a,b,c**) were also converted to acids (**9a,b,c**), esters (**10a,b,c**), amides (**8a,c**), an alcohol (**11a**), and an amine (**12a**). In addition, tetrazoles of two types were prepared. The first (**13d,e**) were obtained from the acid chlorides by the action of 5-aminotetrazole, whereas the second (**14f**) was produced from the respective nitrile by the action of ammonium azide.

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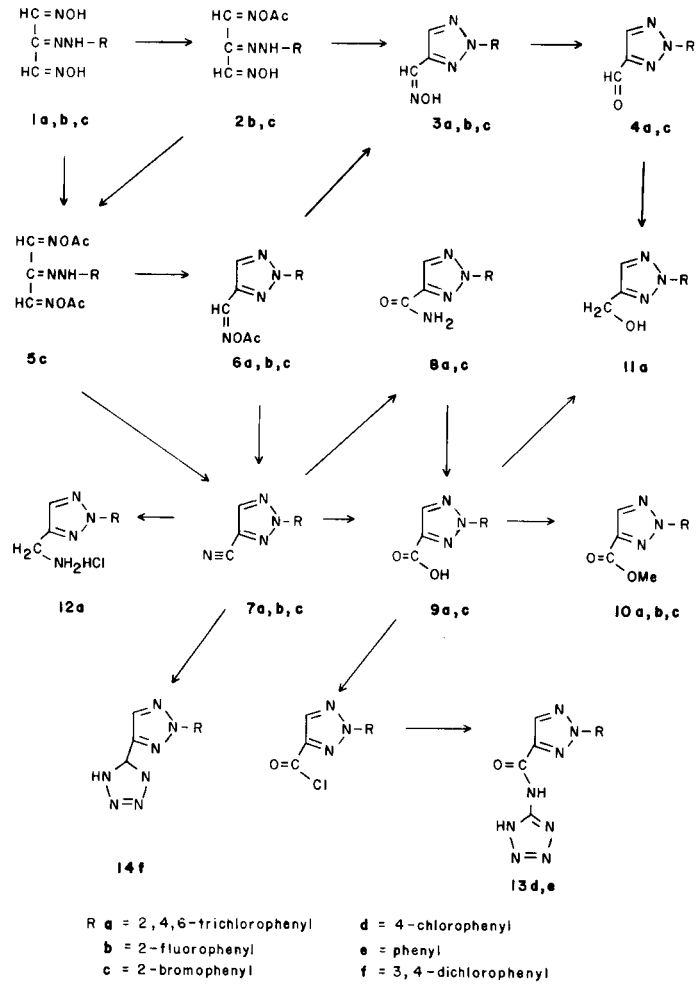
Discussion.

The 4-substituted 2-*o*-, *m*-, and *p*-fluoro- as well as the 2-*m*- and *p*-chloro, bromo- and iodophenyl-1,2,3-triazoles can be readily synthesized from the corresponding sugar *o*-, *m*-, and *p*-fluorophenylosazones or *m*- and *p*-chloro-, bromo-, and iodophenylosazones by cyclization to the corresponding fluoro-, chloro-, bromo- and iodophenylosotriazoles using cupric sulfate [1,2,3]. The resulting osotriazoles can then be subjected to periodate oxidation to convert the hydroxyalkyl chain to a formyl group, or to permanganate oxidation to convert it to a carboxylic group [1,2]. On the other hand, glucose *o*-chloro-, *o*-bromo-, or *o*-iodophenylosazones when treated with cupric sulfate, undergo dehalogenation of the phenyl ring and yield the unsubstituted glucose phenyl osotriazole [1,2]. It seems that the dehalogenation of these *o*-halogenophenyl derivatives is caused by the copper metal precipitated during the cyclization reaction [2,4]. As a result, many 2-halophenyl-4-substituted-1,2,3-triazoles have not been prepared. However, we recently devised a method to overcome this diffi-

Table I

Compound No.	Mp, °C	Yield, %	Molecular Formulla	Analyses % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1a	198	80	$C_9H_7Cl_3N_4O_2$	34.92	2.28	18.10	35.05	2.28	18.25
1b	151	85	$C_9H_9FN_4O_2$	48.22	4.05	24.99	48.12	4.01	24.54
1c	185	85	$C_9H_9BrN_4O_2$	37.92	3.18	19.65	37.89	3.18	19.66
2b	133	34	$C_{11}H_{11}FN_4O_3$	49.63	4.16	21.04	49.47	4.09	21.20
2c	160	55	$C_{11}H_{11}BrN_4O_3$	40.39	3.39	17.13	40.63	3.25	17.02
3a	155	30	$C_9H_5Cl_3N_4O$	37.08	1.73	19.22	37.01	1.72	19.59
3b	105	68	$C_9H_7FN_4O$	52.43	3.42	27.17	52.57	3.54	27.14
3c	183	26	$C_9H_7BrN_4O$	40.47	2.64	20.98	40.30	2.50	20.86
4a	73	95	$C_9H_4Cl_3N_3O$	39.09	1.46	15.20	39.15	1.41	14.97
4c	63	41	$C_9H_6BrN_3O$	42.88	2.40	16.67	42.66	2.32	16.72
5c	115	35	$C_{13}H_{13}BrN_4O_4$	42.30	3.55	15.18	42.09	3.38	15.35
6a	129	90	$C_{11}H_7Cl_3N_4O_2$	39.61	2.11	16.80	39.70	2.11	17.03
6b	116	40	$C_{11}H_9FN_4O_2$	53.23	3.65	22.57	53.71	3.68	22.91
6c	62	72	$C_{11}H_9BrN_4O_2$	42.74	2.93	18.12	42.42	2.93	18.03
7a	87	70	$C_9H_3Cl_3N_4$	39.52	1.11	20.48	39.60	1.10	20.48
7b	40	81	$C_9H_5FN_4$	57.45	2.68	29.77	57.13	2.68	29.91
7c	63	72	$C_9H_5BrN_4$	43.40	2.02	22.49	43.69	2.01	22.73
8a	224	60	$C_9H_5Cl_3N_4O$	37.08	1.73	19.22	37.48	1.64	19.14
8c	135	30	$C_9H_7BrN_4O$	40.47	2.64	20.98	40.27	2.59	20.76
9a	182	70	$C_9H_4Cl_3N_3O_2$	36.96	1.38	14.37	36.93	1.29	14.35
9c	180	80	$C_9H_6BrN_3O_2$	40.33	2.26	15.67	40.34	2.23	16.02
10a	119	40	$C_{10}H_6Cl_3N_3O_2$	39.18	1.97	13.71	38.85	1.93	13.57
10b	55	78	$C_{10}H_8FN_3O_2$	54.30	3.65	19.00	54.04	3.69	19.15
10c	92	79	$C_{10}H_8BrN_3O_2$	42.58	2.86	14.90	42.61	2.83	14.78
11a	71	95	$C_9H_6Cl_3N_3O$	38.81	2.17	15.09	38.49	2.12	15.09
12a		80	$C_9H_8Cl_4N_4$	34.42	2.57	17.84	34.51	2.59	17.93



culty. Instead of carrying out an oxidative cyclization that requires Cu(II) salts to convert the bishydrazones into unstable intermediates that would lose aniline and afford the triazole, we carried out a more facile cyclization involving elimination of an acetate group from hydrazone oxime acetates, using cesium carbonate [5]. This method enabled us to prepare some hitherto unknown *o*-chlorophenyl and 2,6-dichlorophenyl-1,2,3-triazoles, starting with the corresponding *o*-chloro- and 2,6-dichlorophenylhydrazones of mesoaldehyde 1,3-dioxime by reaction with acetic anhydride to form the oxime acetates, then cyclizing the latter with cesium carbonate. This constituted a useful modification of a cyclization first used by von Pechmann [6].

In the present paper, we explored further the scope of the above mentioned cyclization of hydrazone oxime acetates with cesium carbonate, and describe the synthesis of a number of 2-*o*-fluoro-, 2-*o*-bromo- and 2,4,6-trichlorophenyl-1,2,3-triazoles substituted in position 4 of the triazole ring. Some of the triazoles prepared were subsequently linked to tetrazoles affording a new type of phenyltriazolotetrazoles.

To prepare the halophenyl-1,2,3-triazoles, we reacted mesoaldehyde 1,3-dioxime [7,8] with *o*-fluoro-, *o*-bromo-, or 2,4,6-trichlorophenylhydrazine and obtained the respective mesoaldehyde 1,3-dioxime-2-(*o*-halophenyl)hydrazones (**1a, 1b** and **1c**). Treatment of the hydrazones with acetic anhydride at room temperature gave the mono *O*-

Table 2

Compound No.	Mp, °C	Yield, %	Molecular Formula	Analyses, % Calcd. C	H	N	Found C	H	N
13d	279	73	$C_{10}H_7ClN_8O$	41.32	2.43	38.55	40.94	2.36	38.23
13e	289	88	$C_{10}H_8N_8O$	46.88	3.15	43.73	47.09	3.15	43.57
14f	256	45	$C_9H_5Cl_2N_7$	38.32	1.79	34.76	37.89	1.64	34.65

acetyl derivative (**2b** and **2c**), which were cyclized to the triazole oxime (**3b** and **3c**) by the action of cesium carbonate in THF. The triazole oxime were then hydrolyzed to give the desired aldehydes (**4b** [2] and **4c**) in an overall yield of 45% based on the hydrazone. In addition 2-*o*-bromophenylhydrazone-1,3-dioxime and its acetate (**2c**) gave a diacetate (**5c**) when heated with acetic anhydride at 40°. The diacetate was converted to the triazole oxime acetate (**6c**), by cyclization with cesium carbonate in THF. Both the *o*-fluoro and the 2,4,6-trichorophenylhydrazone 1,3-dioximes (**1a** and **1b**) gave directly the triazole oxime acetate (**6a** and **6b**) upon gentle heating with acetic anhydride. For the trichlorophenyl derivative, the acetate group was removed with methanolic hydrogen chloride to give a syrupy oxime (**3a**), which was hydrolyzed to the desired aldehyde (**4a**) in 60% yield based on the hydrazone. The oxime (**3a**) was obtained in a crystalline form after column chromatography.

Other derivatives readily obtained by the above reaction sequence were the nitriles (**7a, 7b**, and **7c**), which were obtained by refluxing the corresponding hydrazones (**1** or **2**), or the triazole oximes (**3** or **6**) with acetic anhydride, followed by pyrolytic distillation. These nitriles (**7a** and **7c**), were hydrolyzed to the amides (**8a** and **8c**) by treatment with concentrated hydrochloric acid at 40° for one hour, or to the acids (**9a, 9b** [2], and **9c**) by refluxing with the same reagent for three hours. Under the mild hydrolysis conditions that usually led to the amide, the *o*-fluoronitrile (**7b**) was hydrolyzed completely to the acid (**9b**). The methyl esters (**10a, 10b**, and **10c**) were formed by the action of methanolic hydrogen chloride on the respective acids. Reduction of the trichlorophenyltriazolenitrile (**7a**) with lithium aluminum hydride resulted in the formation of an amine (**12a**) which was characterized as its hydrochloride salt. Under similar conditions, the *o*-bromonitrile (**7c**) was totally dehalogenated by lithium aluminum hydride. This is certainly because it is much easier to remove a bromine atom than a chlorine atom. The alcohol (**11a**) was obtained by the reduction of the aldehyde (**4a**) with sodium borohydride.

Aminotetrazolecarboxamides (**13d** and **13e**) were formed by reacting the appropriate acid with thionyl chloride, and then treating the resulting acid chlorides with two equivalents of 5-aminotetrazole in toluene. Tetrazole (**14f**) was prepared from the corresponding nitrile by treatment with ammonium azide generated *in situ* from sodium azide and ammonium chloride in DMF.

From the above, it is seen that the cyclization of the aryl hydrazones of mesoaldehyde-1,3-dioxime acetates constitutes an excellent procedure for the synthesis of 1,2,3-triazoles substituted in the 4-position.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Microanalyses were carried out by the Central Analytical Laboratory, Department of Chemistry and Chemical Engineering, Michigan Technological University, or by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. The nmr spectra were measured on Varian T-60 and EM-360A instruments. Infrared spectra were recorded on a Perkin Elmer 735 instrument. All spectral data are consistent with the proposed structures. The melting points, yields, and analyses of the compounds prepared are shown in Tables 1 and 2.

Mesoaldehyde 1,3-Dioxime-2-(halogenophenyl)hydrazone (**1a, 1b, 1c**).

A solution of mesoaldehyde-1,3-dioxime [7] (60 mmoles) in ethanol (70 ml) was treated with the appropriate halogenophenylhydrazino hydrochloride (60 mmoles) and sodium acetate (60 mmoles) and heated to 70° with stirring for 30 minutes. Water (70 ml) was then added and the mixture allowed to cool. The crude hydrazone was filtered and recrystallized by dissolving it in 150 ml of a boiling mixture of ethanol-toluene (1:3), which was distilled until the vapor temperature reached 110° before cooling.

Mesoaldehyde 1-(*O*-Acetyloxime)-2-(halogenophenyl)hydrazone 3-Oxime (**2b, 2c**).

Compound **1** (3.0 g) was stirred in acetic anhydride (30 ml) at room temperature for 30 minutes. The mixture was then poured into water, stirred for 20 minutes, and the product filtered, dried, and recrystallized from benzene-ethyl acetate.

Mesoaldehyde 2-(*o*-Bromophenyl)hydrazone 1,3-Di-*O*-acetyloxime (**5c**).

The hydrazone (**1c**) (5 g) in acetic anhydride (50 ml) was heated with stirring until a clear yellow solution was obtained. It was then stirred for an additional five minutes without heating and poured into water (300 ml). After 20 minutes, the diacetate was extacted with ether, and the latter washed with water and sodium carbonate, dried over sodium sulfate, and evaporated to dryness. The product was crystallized from cyclohexane-benzene.

2-(Halogenophenyl)-4-formyl-1,2,3-triazole *O*-Acetyloxime (**6a, 6b, 6c**).

Method A.

When a solution of the diacetate (**5c**) (3.0 mmoles) in THF (50 ml) was stirred with cesium carbonate (3.3 mmoles), it turned colorless almost immediately. Ether (200 ml) was then added, and the solution was washed with water, dried, and evaporated to dryness. The product was crystallized from cyclohexane.

Method B.

A suspension of the hydrazone (4 g) (**1a, 1b**) was heated in acetic anhydride (40 ml) until a clear solution resulted, then the solution was poured into water (400 ml) and stirred for 20 minutes. The solution was extracted with ether (2 × 100 ml), and the combined extracts washed with sodium carbonate, dried over sodium sulfate, and evaporated to dryness. The product was crystallized from cyclohexane.

2-(Halogenophenyl)-4-formyl-1,2,3-triazole Oxime (**3a, 3b, 3c**).

Method A.

The monoacetate (**2b, 2c**) (5 mmoles) and cesium carbonate (5.5 mmoles) in THF (50 ml) were stirred for one hour. The solution was then filtered, and the filtrate evaporated to dryness under reduced pressure. For crystallization, the residue was dissolved in hot isopropyl ether-cyclohexane (1:2, 60 ml) and evaporated to one-half the original volume.

Method B.

The oxime triazole acetate (**6a**) (2 g) in methanolic hydrogen chloride (5%, 30 ml) was stirred at room temperature for one hour. The solvent was removed under reduced pressure, and the residue applied to a silica gel column (50 × 2.5 cm) and eluted with ethyl acetate. The appropriate fractions crystallized upon evaporation of the solvent.

2-(Halogenophenyl)-4-formyl-1,2,3-triazole (**4a, 4c**).

The oxime (**3a, 3c**) (10 mmoles) and *s*-trioxane (10b mmoles) in 2*N* hydrochloric acid was refluxed for three hours, then extracted with ether. The latter was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of ethanol (3 ml) and cooled in an ice bath. Crystallization was induced by adding water (60 ml) slowly and stirring until the crystals were formed.

2-(Halogenophenyl)-4-cyano-1,2,3-triazole (**7a, 7b, 7c**).

The hydrazone (**1a, 1b, 1c**) (5.0 g) was refluxed in acetic anhydride (50 ml) for 30 minutes. When the solution cooled, it was poured into water (500 ml), stirred for 20 minutes, and extracted with ether. The latter was washed successively with water and sodium bicarbonate, then dried and evaporated to a viscous mass under reduced pressure. The product distilled at 60-90° (0.1 torr) and crystallized upon cooling. It was recrystallized from ethanol-water.

2-(Halogenophenyl)-1,2,3-triazole-4-carboxamide (**8a, 8c**).

The nitrile (**7a** or **7c**) (1.0 g) was hydrolyzed with concentrated hydrochloric acid (100 ml) at 40° for one hour, after which time the mixture was extracted with ether, and the latter washed with water and sodium carbonate. The product was crystallized from benzene, after evaporation of the dried ether solution.

2-(Halogenophenyl)-1,2,3-triazole-4-carboxylic Acid (**9a, 9c**).

The nitrile (**7a, 7c**) (1.0 g) was refluxed for three hours in concentrated hydrochloric acid (100 ml). Upon cooling, the acid was taken in ether and washed with water. The ether layer was shaken with a sodium carbonate solution to form the sodium salt, which upon acidification of the aqueous layer with dilute hydrochloric acid, regenerated the acid. The latter was extracted with ether and washed with water. Evaporation of the ether afforded the desired acid, which was recrystallized from benzene.

Methyl 2-(Halogenophenyl)-1,2,3-triazole-4-carboxylate (**10a, 10b, 10c**).

The acid (**9a, 9b, 9c**) was refluxed overnight in a 1% methanolic hydrogen chloride solution (50 ml), then evaporated to dryness under reduced pressure. The ester crystallized and was recrystallized from cyclohexane.

2-(2,4,6-Trichlorophenyl)-4-(hydroxymethyl)-1,2,3-triazole (**11a**).

To a solution of the aldehyde (**4a**) (200 mg) in ethanol (10 ml) was added sodium borohydride (15 mg), and the mixture stirred for 15 minutes, after which time water was added, and the alcohol extracted with ether. The latter was washed with water, dried over sodium sulfate, and evaporated to dryness to give the product, which was purified by crystallization from benzene.

4-(Aminomethyl)-2-(2,4,6-trichlorophenyl)-1,2,3-triazole Hydrochloride (**12a**).

To a suspension of lithium aluminium hydride (85 mg) in ether (5 ml) was added a solution of nitrile (**7a**) (200 mg) in ether (10 ml). After stirring for 20 minutes, water (5 ml) was added, followed by a 10% sodium hydroxide solution (10 ml). The amine was extracted with ether, and the latter washed with 10% sodium hydroxide, dried, and evaporated to dryness. The syrup was treated with a few drops of concentrated hydrochloric acid. When the latter evaporated at room temperature, it afforded crystals, which were suspended in ether and filtered.

N-(5-Tetrazolyl)-2-(halogenophenyl)-1,2,3-triazole-4-carboxamide (**13d** and **13e**).

An acid (50 mmoles) and thionyl chloride (100 mmoles) are refluxed for two hours. The solution is cooled, toluene (1000 ml) added, and the solution evaporated under reduced pressure. More toluene (100 ml) is added and evaporated under reduced pressure to remove the last traces of hydrogen chloride, and the residue is dissolved in toluene (125 ml). 5-Aminotetrazole (100 mmoles) is then added, and the solution refluxed overnight. Some of the toluene is then distilled off (50 ml), and the product crystallized upon cooling. The resulting crystals were filtered and recrystallized from DMF-water.

2-(3,4-Dichlorophenyl)-4-(5-tetrazolyl)-1,2,3-triazole (**14f**).

A nitrile (50 mmoles) and ammonium chloride (60 mmoles) and sodium azide (60 mmoles) in DMF (100 ml) were refluxed for 24 hours. Most of the solvent was removed under reduced pressure, and the remaining solution poured into water, where the product crystallized. It was recrystallized from DMF-water.

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