Synthesis of 2-(*o*-Chlorophenyl)- and 2-(2′,6′-Dichlorophenyl)-4-formyl-1,2,3-triazoles

David L. Swartz and Hassan S. El Khadem

Department of Chemistry and Chemical Engineering,
Michigan Technological University, Houghton, Michigan 49931

Received January 29, 1979

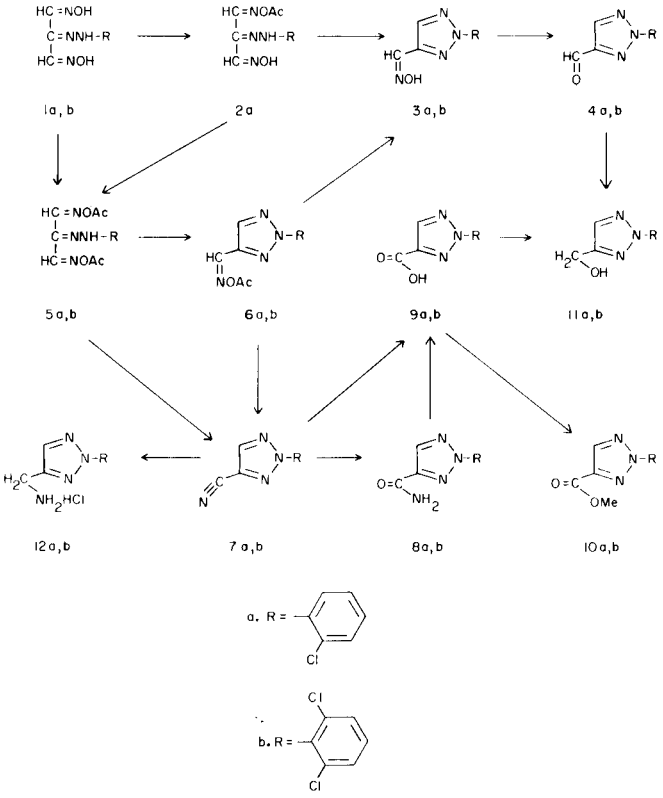
Mesoaldehyde 1,3-dioxime was treated with either *o*-chlorophenyl- or 2,6 dichlorophenylhydrazine to give the corresponding 2-chlorophenylhydrazone. Hydrazones **1a** and **1b** were treated with acetic anhydride and cyclized to triazoles (**3a** and **6a**) with cesium carbonate. These were then hydrolized to the previously unknown chlorophenyltriazole aldehydes (**4a** and **4b**). They were also converted to a number of acid derivatives, alcohols, and amines.

J. Heterocyclic Chem., **16**, 909 (1979).

Discussion.

The 2-*m*- and *p*-chlorophenyl-4-formyl-1,2,3-triazoles have been shown to possess insecticidal properties (1). They can be readily synthesized from the corresponding sugar *m*- and *p*-chlorophenylosazones by cyclization to the chlorophenylosotriazoles, using cupric sulfate. The osotriazoles can then be subjected to periodate oxidation to convert the hydroxylalkyl chain to a formyl group (2). When glucose *o*-chlorophenylosazone was treated with cupric sulfate, the chlorinated phenyl ring was dehalogenated and glucose phenyl osotriazole resulted (3). It seemed that the dehalogenation of these *o*-halogeno derivatives is caused by the copper metal precipitated during the cyclization reaction. This dehalogenation occured with all *ortho*-halogenated phenyl osazones except for the *o*-fluoro derivative (3-6). As a result, the 2-*o*-chloro-, the 2-*o*-bromo-, and the 2-*o*-iodophenyl-4-formyl-1,2,3-triazoles have not been described in the literature. If, like the *meta* and *para* isomers, 2-(*o*-chlorophenyl)-4-formyl-1,2,3-triazole was found to be an active insecticide, the labile halogen atom could render this compound biodegradable. To explore this we have prepared this compound and some other hitherto unknown *o*-chlorophenyl and 2′,6′-dichlorophenyl-1,2,3-triazoles.

Since it was apparent that the usual route for the formation of 2-(*o*-chlorophenyl)-4-formyl-1,2,3-triazole through the corresponding osazone was not available because of dehalogenation, we explored alternate methods. During the course of our work, we found that butandione bisphenylhydrazone could be oxidized with cupric chloride dihydrate in absolute ethanol to 4,5-dimethyl-2-phenyl-1,2,3-triazole in about 95% yield without the formation of copper metal. This suggested that the *ortho*-halogen might not be removed under such reaction conditions. This was confirmed when butandione and glyoxal bis-(*o*-chlorophenyl)hydrazones were treated with cupric chloride dihydrate in ethanol to yield their respective *o*-chlorophenyltriazoles in about 90% yield (7). However, attempts to introduce a formyl group by oxidation of the



methyl groups failed. Similarly, when the synthesis of the desired 2-*o*-chlorophenyl-4-formyl-1,2,3-triazole was attempted by reacting glucose *o*-chlorophenylosazone with cupric chloride in ethanol, the reaction proved to be unsatisfactory because of the numerous side reactions.

It was then decided to try a modification of a procedure used by von Pechmann to synthesize 4-formyl-2-phenyl-1,2,3-triazole from mesoaldehyde 1,3-dioxime (8). We reacted mesoaldehyde dioxime (9,10) with either *o*-chloro- or 2,6-dichlorophenylhydrazine and obtained the respective hydrazones (**1a** and **1b**). Treatment of the hydrazone (**1a**) with acetic anhydride at room temperature gave a monoacetate (**2a**), which was cyclized to the triazole oxime (**3a**) by the action of cesium

0022-152X/79/050909-04$02.25

carbonate in THF. The oxime was readily hydrolyzed to give the desired aldehyde (**4a**) in an overall yield of 45% based on the hydrazone. This reaction sequence proved, however, less satisfactory for the 2,6-dichlorophenylhydrazone (**1b**), which upon similar treatment gave a mixture of products of which the diacetate (**5b**) predominated. The latter compound was obtained in a better yield when the reaction was carried out at a higher temperature. The diacetates (**5a** and **5b**) were converted to the triazole oxime acetates (**6a** and **6b**) by cyclization wiht cesium carbonate in THF. The acetate group was finally removed with methanolic hydrogen chloride to give a syrupy oxime (**3b**), which was hydrolyzed to the desired aldehyde (**4b**) in 60% yield based on the hydrazone. The oxime (**3b**) was obtained in a crystalline form by hydrolysis of the oxime acetate, followed by column chromatography.

Other derivatives readily obtained by the above reaction sequence are the nitriles (**7a** and **7b**), which were obtained by refluxing the hydrazones (**1a** and **1b**) or oximes (**3a** and **3b**) with acetic anhydride. These were hydrolyzed to the amides (**8a** and **8b**) with concentrated hydrochloric acid at 40° for one hour, or to the acids (**9a** and **9b**) by refluxing with the same reagent for three hours. The methyl esters (**10a** and **10b**) were formed by the action of methanolic hydrogen chloride on the respective acids. Reduction of the nitriles by lithium aluminum hydride in diethyl ether gave the amines (**12a** and **12b**), which were characterized as their hydrochloride salts. Reduction of the acid (**9a**) to the alcohol (**11a**) by lithium aluminum hydride in diethyl ether gave the alcohol in small yield due to the insolubility of the acid. For the dichloro acid (**9b**), THF was used as a solvent, and the major product was the same monochlorophenyl alcohol (**11a**). The dichloro alcohol (**11b**) was formed by the reduction of the aldehyde (**4b**) by sodium borohydride in ethanol. When the reduction of the nitrile (**7a**) was carried out with THF instead of ether, the phenyl ring was 25% dehalogenated. This seems to be a solvent effect; in THF the solvation of the aromatic nucleophilic substitution intermediate state is greater than in ether.

In conclusion, we have developed methods to prepare several new substituted 2-*o*-halogenophenyl-1,2,3-triazoles, including the 4-formyl derivatives which are potentially biodegradable insecticides. We have also shown a degree of lability of the *o*-chloro atoms during reduction with lithium aluminum hydride.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Microanalyses were carried out by Mrs. S. Brotherton in the Department of Chemistry and Chemical Engineering, Michigan Technological University, on a Perkin-Elmer 240 Elemental Analyzer. Nmr spectra were measured on Varian T-60 and

Table I

Compound		Yield		Analyses					
				Calcd.			Found		
No.	M.p.°	%	Formula	C	H	N	C	H	N
1a	184	90	$C_9H_9ClN_4O_2$	44.92	3.77	23.28	44.97	3.77	23.16
1b	179	92	$C_9H_8Cl_2N_4O_2$	39.30	2.93	20.37	39.32	2.82	20.42
2a	165	65	$C_{11}H_{11}ClN_4O_3$	46.74	3.92	19.82	46.65	3.87	19.96
3a	123	68	$C_9H_7ClN_4O$	48.55	3.17	25.17	48.91	3.11	25.42
3b	120	30	$C_9H_6Cl_2N_4O$	42.05	2.35	21.79	41.89	2.38	21.80
4a	56	95	$C_9H_6ClN_3O$	52.07	2.91	20.24	51.67	2.80	20.08
4b	94	95	$C_9H_5Cl_2N_3O$	44.66	2.08	17.36	44.27	2.02	17.06
5a	143	70	$C_{13}H_{13}ClN_4O_4$	48.09	4.04	17.25	48.24	4.00	17.27
5b	93	65	$C_{13}H_{12}Cl_2N_4O_4$	43.47	3.37	15.60	43.44	3.29	15.84
6a	159	95	$C_{11}H_9ClN_4O_2$	49.92	3.43	21.17	49.71	3.34	21.28
6b	118	95	$C_{11}H_8Cl_2N_4O_2$	44.17	2.70	18.73	44.31	2.58	18.77
7a	65	80	$C_9H_5ClN_4$	52.83	2.46	27.38	52.69	2.42	27.57
7b	84	75	$C_9H_4Cl_2N_4$	45.22	1.69	23.44	45.14	1.58	23.27
8a	154	80	$C_9H_7ClN_4O$	48.55	3.17	25.17	48.45	2.99	25.18
8b	201	70	$C_9H_6Cl_2N_4O$	42.05	2.35	21.79	41.96	2.31	21.62
9a	172	90	$C_9H_6ClN_3O_2$	48.34	2.70	18.77	48.00	2.66	18.79
9b	213	85	$C_9H_5Cl_2N_3O_2$	41.89	1.95	16.28	42.10	1.75	16.57
10a	85	95	$C_{10}H_8ClN_3O_2$	50.54	3.39	17.68	50.17	3.35	17.85
10b	133	90	$C_{10}H_7Cl_2N_3O_2$	44.14	2.59	15.44	44.46	2.43	15.26
11a	Syrup	40	$C_9H_8ClN_3O$	51.57	3.85	20.04	51.54	3.89	19.73
11b	Syrup	95	$C_9H_7Cl_2N_3O$	44.29	2.89	17.22	44.58	2.90	17.58
12a		95	$C_9H_{10}Cl_2N_4$	44.10	4.11	22.86	44.10	4.16	23.10
12b		95	$C_9H_9Cl_3N_4$	38.67	3.25	20.04	39.00	3.17	20.15

360-A instruments. Infrared spectra were recorded on Perkin Elmer 621 and 717 instruments. All spectral data are consistent with the proposed structures. The melting points, yields, and analyses of of the compounds prepared are shown in Table I.

Mesoaldehyde 1,3-Dioxime 2-(*o*-Chloro-, or 2',6'-Dichlorophenyl)-hydrazone (**1a,1b**).

A solution of mesoaldehyde-1,3-dioxime (9) (60 mmoles) in ethanol (70 ml.) was treated with the appropriate chlorophenylhydrazine 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-(*o*-Chlorophenyl)hydrazone 3-Oxime (**2a**).

Compound **1a** (3.0 g.) was stirred in acetic anhydride 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*-Chloro-, or 2',6'-Dichlorophenyl)hydrazone 1,3-Di-*O*-acetyloxime (**5a,5b**).

The hydrazone (**1a** or **1b**) (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 (**5a** or **5b**) was extracted 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-(*o*-Chloro-, or 2',6'-Dichlorophenyl)-4-formyl-1,2,3-triazole *O*-Acetyloxime (**6a,6b**).

When a solution of the diacetate (**5a** or **5b**) (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 crystallized from cyclohexane.

2-(*o*-Chlorophenyl)-4-formyl-1,2,3-triazole Oxime (**3a**).

The monoacetate (**2a**) (2 g., 7.1 mmoles) and cesium carbonate (7.8 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 ehter-cyclohexane (1:2, 60 ml.), charcoaled, and evaporated to one-half the original volume.

2-(2',6'-Dichlorophenyl)-4-formyl-1,2,3-triazole Oxime (**3b**).

The oxime acetate (**6b**) was refluxed in a water-dioxane (2:1) mixture containing 2*N* hydrochloric acid for one hour. The mixture was then extracted with ether, which was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The resulting syrup was dissolved in benzene, applied to a silica gel column, and washed with benzene to remove unwanted products. The oxime (**3b**) was later eluted with ethyl acetate and was recrystallized from benzene.

2-(*o*-Chlorophenyl)-4-formyl-1,2,3-triazole (**4a**).

The oxime (**3a**) (3.0 g., 13.5 mmoles) and *s*-trioxane (13.5 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 crystals were formed.

2-(2',6'-Dichlorophenyl)-4-formyl-1,2,3-triazole (**4b**).

The oxime acetate (**6b**) (2.8 g., 9.4 mmoles) was refluxed in 0.5% hydrochloric acid in methanol (50 ml.) for 30 minutes and evaporated to a syrup under reduced pressure. The syrup was refluxed with *s*-trioxane (10 mmoles) in 2*N* hydrochloric acid (50 ml.) for three hours and extracted with ether. The latter was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. Aldehyde (**4b**) crystallized from cold ethanol upon the addition of water.

2-(*o*-Chloro-, or 2',6'-Dichlorophenyl)-4-cyano-1,2,3-triazole (**7a,7b**).

The hydrazone (**1a** or **1b**) (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 60-70° (0.1 torr) and crystallized upon cooling. It was recrystallized from ethanol-water.

2-(*o*-Chloro-, or 2',6'-Dichlorophenyl)-1,2,3-triazole-4-carboxamide (**8a,8b**).

The nitrile (**7a** or **7b**) (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 the evaporation of the dried ether solution.

2-(*o*-Chloro-, or 2',6'-Dichlorophenyl)-1,2,3-triazole-4-carboxylic Acid (**9a,9b**).

The nitrile (**7a** or **7b**) (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 crystallized from benzene.

Methyl 2-(*o*-Chloro-, or 2',6'-Dichlorophenyl)-1,2,3-triazole-4-carboxylate (**10a,10b**).

The acid (**9a** or **9b**) 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-(*o*-Chlorophenyl)-4-(hydroxymethyl)-1,2,3-triazole (**11a**).

To a suspension of lithium aluminum hydride (60 mg.) in ether (5 ml.) was added a suspension of acid (**9a**) (200 mg.) in ether (15 ml.), and the mixture stirred for one hour. Water (2 ml.) was then added, followed by a 10% aqueous sulfuric acid solution (10 ml.). The ether layer was washed with water and potassium carbonate, and then dried over sodium sulfate. The syrup obtained upon evaporation was dissolved in benzene and applied to a silica gel column, washed first with benzene-ethyl acetate (3:1) to remove some impurities. The alcohol (**11a**) was eluted with ethyl acetate and distilled under reduced pressure, b.p. 75° (0.1 torr).

2-(2',6'-Dichlorophenyl)-4-(hydroxymethyl)-1,2,3-triazole (**11b**).

To a solution of aldehyde (**4b**) (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 distilled, b.p. 85° (0.1 torr).

4-(Aminomethyl)-2-(*o*-chloro-, or 2',6'-dichlorophenyl)-1,2,3-triazole Hydrochloride (**12a,12b**).

To a suspension of lithium aluminum hydride (85 mg.) in ether (5 ml.) was added a solution of nitrile (**7a** or **7b**) (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.

REFERENCES AND NOTES

(1) H. S. El Khadem, A. M. Kolkaila, and M. H. Meshreki, *J. Chem. Soc.*, 3531 (1963).

(2) B. B. Bishay, H. S. El Khadem, Z. M. El-Shafei and M. H. Meshreki, *ibid.*, 3993 (1962).

(3) H. S. El Khadem, Z. M. El-Shafei and M. H. Meshreki, *ibid.*, 2957 (1961).

(4) H. S. El Khadem and D. L. Swartz, *Carbohydr. Res.*, **30**, 400 (1968).

(5) H. S. El Khadem, Z. M. El-Shafei and Y. S. Mohamed, *J. Chem. Soc.*, 3993 (1960).

(6) G. Henske and Z. Müller, *J. Prakt. Chem.*, **18**, 47 (1962).

(7) D. L. Swartz and D. Jaeger, unpublished work.

(8) A. Jonas and H. von Pechmann, *Ann. Chem.*, **262**, 277 (1891).

(9) H. von Pechmann and K. Wehsarg, *Ber.*, **19**, 2465 (1886).

(10) H. von Pechmann and K. Wehsarg, *ibid.*, **21**, 2989 (1888).