Nonaqueous Diazotization of 4-Amino-3-arylisothiazole-5-carboxylate Esters

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4-Amino-3-arylisothiazole-5-carboxylate esters are converted to the corresponding desamino, chloro, bromo, and iodo esters by processes involving nonaqueous diazotization. These related procedures open up the possibility for the conversion of readily available heterocyclic *ortho*-amino esters and nitriles to related heterocyclic derivatives, which are not easily obtained by alternate routes.

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In recent patents [1] we described the synthesis of 4-amino-3-arylisothiazole-5-carboxylate esters **2** by the reaction of α-aryl-α-cyanooxime tosylates **1** [2] with thioglycolate esters. The derived amino acids were potent inhibitors of the enzyme, xanthine oxidase. This same synthesis was originally described by Gewald and Bellmann in 1979 [3]. We further found that these amino esters could be readily converted to the corresponding desamino and halo esters by processes utilizing nonaqueous diazotization.

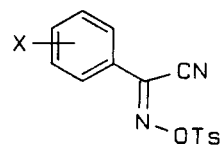
For example, treatment of the amino esters **2** with isopentyl nitrite in refluxing tetrahydrofuran gave the corresponding desamino esters **3a-f** in 45-75% yield (Table I). 3-Phenylisothiazole-5-carboxylic acid was originally synthesized in several steps, the last of which involved carbonation of 5-lithio-3-phenylisothiazole [4]. More recently, mixtures of 3-phenylisothiazole-4- and 5-carboxylate esters were obtained *via* 1,3-cycloaddition of benzonitrile *N*-sulfides with propiolate esters [5a-c].

Reaction of the amino esters **2** with nitrosyl chloride in chloroform gave the corresponding chloro esters **4a-f** in 40-75% yield (Table I). In this case, nitrosyl chloride served both as the diazotizing agent and chlorine source. When methyl 4-amino-3-(3-methoxyphenyl)isothiazole-5-carboxylate was utilized as the starting material in this reaction, the isothiazolo[4,3-*c*]cinnoline derivative **7**, formed by diazo coupling, was isolated as a by-product in 11% yield. Surprisingly, this compound was not detected in the formation of **3e**.

Diazotization of the amino esters **2** with isopentyl nitrite in chloroform in the presence of excess bromine or iodine gave the corresponding bromo (**5a-c**) and iodo (**6a-b**) esters, respectively, in 40-65% yield (Table I). We have recently reported the extension of these reactions to the conversion of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles to the corresponding 5-chloro and 5-bromo derivatives [6].

Nonaqueous diazotizations have been reported for the replacement of the amino function in anilines by hydrogen [7a-b], chlorine and bromine [8a-d], iodine [9], and methylthio [8c,10]. Alkyl nitrites, thionitrites, or thionitrates were used in these aniline studies. Chlorine sources were carbon tetrachloride, chloroform, or copper(II) chloride. Bromine sources were bromoform or copper(II) bromide. In related arylation reactions, the process was reported to involve free radical intermediates [11a-b].

In an attempt to understand the nature of our reactions, the diazotization of the amino amide **8** was investigated. Treatment with aqueous nitrous acid yielded the fused triazinone **9** (79%). Reaction of **8** with excess nitrosyl



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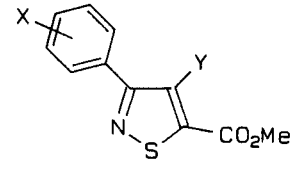
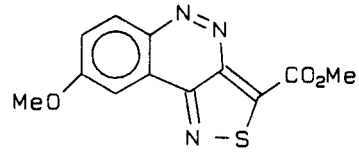


2 Y = NH_2
3 Y = H
4 Y = Cl
5 Y = Br
6 Y = I



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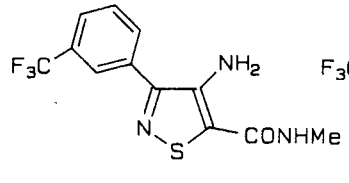

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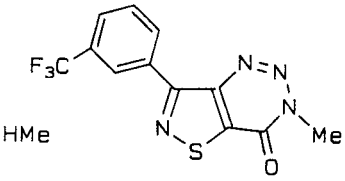

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Table I

Methyl 3-Arylisothiazole-5-carboxylates

Compound	X	Y	Yield %	Mp °C	Calcd. % (Found) C	H	N
3a	3-CF_3	H	66	82-83	50.17	2.81	4.88
					(49.93	2.58	4.73)
3b	H	H	44	73-74	60.26	4.11	6.39
					(60.02	4.01	6.36)
3c	3-Cl	H	64	106-107	52.08	3.18	5.52
					(52.03	2.96	5.49)
3d	4-Cl	H	47	112-113	52.08	3.18	5.52
					(52.26	3.20	5.67)
3e	3-OMe	H	73	95-96	57.82	4.45	5.62
					(57.99	4.43	5.66)
3f	4-OMe	H	62	104-105	57.82	4.45	5.62
					(57.54	4.45	5.84)
4a	3-CF_3	Cl	74	53-54	44.80	2.19	4.35
					(44.90	2.21	4.28)
4b	H	Cl	64	101-102	52.08	3.18	5.52
					(52.15	3.26	5.63)
4c	3-Cl	Cl	57	92-93	45.85	2.45	4.86
					(45.97	2.56	4.98)
4d	4-Cl	Cl	42	104-106	45.85	2.45	4.86
					(45.98	2.40	5.07)
4e	3-OMe	Cl	49	59-60	50.80	3.55	4.94
					(50.59	3.61	5.08)
4f	4-OMe	Cl	73	143-144	50.80	3.55	4.94
					(50.60	3.36	4.90)
5a	3-CF_3	Br	53	54-55	39.36	1.93	3.83
					(39.12	1.96	3.96)
5b	3-Cl	Br	63	99-100	39.72	2.12	4.21
					(39.76	2.10	4.35)
5c	4-Cl	Br	54	127-129	39.72	2.12	4.21
					(39.91	1.86	4.25)
6a	3-CF_3	I	46	92-93	34.89	1.71	3.39
					(35.16	1.69	3.23)
6b	3-Cl	I	53	115-116	34.81	1.86	3.69
					(34.87	1.85	3.80)

chloride in refluxing chloroform for 10 minutes also yielded **9** (83%). When **8** was combined with isopentyl nitrite in refluxing THF, however, a complex mixture was obtained. Repeating the reaction, but first adding dry hydrogen chloride to the solution of **8** in THF, resulted in the clean formation of **9** (80%). These results suggest that the intermediate in the nitrosyl chloride reaction may be cationic, rather than radical, in nature, and that the reaction with isopentyl nitrite in the presence of hydrogen chloride may also involve a cationic intermediate. This hypothesis might also explain the formation of **7** in the synthesis of **4e** and its absence in the synthesis of **3e**.

The significance of our chemistry is that it converts readily available heterocyclic *ortho*-amino esters and nitriles to related desamino and halo esters and nitriles, which are often difficult to synthesize by alternate routes. In addition, our work represents the first use of nitrosyl chloride as both the diazotizing agent and chlorine source and also the first example using bromine as the source of halogen. Similar reactions with chlorine failed.

EXPERIMENTAL [12]

General Synthesis of Methyl 3-Arylisothiazole-5-carboxylates **3a-f**.

To a solution containing 0.01 mole of the appropriate **2** [1] in 30 ml of tetrahydrofuran was added 0.015 mole of isopentyl nitrite. The mixture was stirred and heated to reflux for 20-30 minutes. The solvent was removed *in vacuo*, and the crude product was crystallized from ethanol or ethanol-water to yield the desired product (Table I).

General Synthesis of Methyl 3-Aryl-4-chloroisothiazole-5-carboxylates **4a-f**.

Excess nitrosyl chloride [13] was bubbled into a cold solution containing 0.015-.02 mole of the appropriate **2** in 75 ml. of chloroform for 1-2 minutes. The mixture was heated on the steam bath in an open flask for 5 minutes. The solution was dried with Woelm silica gel and filtered. The solvent was removed *in vacuo*, and the crude product was crystallized from ethanol or ethanol-water to yield the desired product (Table I).

8-Methoxyisothiazolo[4,3-*c*]cinnoline-3-carboxylic Acid, Methyl Ester (**7**).

Methyl 4-amino-3-(3-methoxyphenyl)isothiazole-5-carboxylate (4.0 g, 0.015 mole) [1] was subjected to the above general synthesis. Crystallization of the crude product from ethanol yielded 0.5 g of a bright yellow product, mp 190° dec. Recrystallization from ethyl acetate gave 0.45 g. (11%) of **7**, mp 207-210° dec; ms: m/e 275 (M^+).

Anal. Calcd. for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.30; N, 15.26; S, 11.65. Found: C, 52.39; H, 3.39; N, 15.10; S, 11.53.

The mother liquor from the original ethanol crystallization above was concentrated and water was added. Thus obtained was 2.1 g of **4e** (49%), mp 56-57°. An analytical sample, mp 59-60°, was recrystallized from ethanol-water.

General Synthesis of Methyl 3-Aryl-4-bromoisothiazole-5-carboxylates **5a-c**.

To a solution containing 0.015 mole of the appropriate **2** and 3 ml of bromine in 50 ml of chloroform was added 0.022 mole of isopentyl nitrite. The mixture was stirred and refluxed for 15 minutes. Woelm silica gel was added and the mixture was filtered. The solvent and excess bromine was removed *in vacuo*, and the crude material was crystallized from ethanol or ethanol-water (Table I).

General Synthesis of Methyl 3-Aryl-4-iodoisothiazole-5-carboxylates **6a-b**.

A solution containing 0.015 mole of the appropriate **2**, 0.08 mole of iodine, and 0.022 mole of isopentyl nitrite in 100 ml. of chloroform was stirred and refluxed for 30 minutes. The cooled mixture was washed with aqueous sodium thiosulfate solution and then water. The organic layer was dried with magnesium sulfate. Removal of the solvent *in vacuo* and crystallization from ethanol yielded the desired product (Table I).

3-Methyl-7-[3-(trifluoromethyl)phenyl]isothiazolo[4,5-*d*]-1,2,3-triazin-4(3*H*)-one (**9**).

Method A.

To a cold solution containing 0.8 g of sodium nitrite (0.012 mole) in 20 ml of concentrated sulfuric acid was added dropwise a solution containing 3.0 g of **8** (0.01 mole) [1] in 20 ml of acetic acid. The mixture was stirred in the cold for 30 minutes and allowed to come to ambient temperature during 1 hour. It was poured into ice-water, collected, and crystallized from ethanol to yield 2.45 g (79%) of **9**, mp 133-134°; nmr (deuteriochloroform) δ 4.1 (s, 3H), 7.6-7.8 (m, 2H), 8.7-8.8 (m, 2H).

Anal. Calcd. for $C_{12}H_7F_3N_4OS$: C, 46.16; H, 2.66; N, 17.94. Found: C, 46.30; H, 2.50; N, 18.08.

Method B.

Into a suspension of 4.0 g of **8** (0.013 mole) in 70 ml of chloroform was bubbled excess nitrosyl chloride [13] for several minutes. The mixture was heated on the steam bath in an open flask for 10 minutes. The sol-

vent was removed *in vacuo*, and the product was crystallized from ethanol to yield 3.45 g (83%) of **9**, mp 134-135°.

Method C.

Into a solution containing 1.5 g of **8** (0.005 mole) in 25 ml of tetrahydrofuran was bubbled hydrogen chloride gas for 1-2 minutes. Isopentyl nitrite (1 ml) was added and the mixture was stirred and refluxed for 2 hours. Ethyl acetate (25 ml) was added and the mixture was washed twice with water. The organic layer was dried with magnesium sulfate and filtered. Removal of the solvent and crystallization from ethanol yielded 1.25 g (80%) of **9**, mp 134-135°.

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