Synthesis of 2-Aryl-6-carbethoxythiazolo[4,5-*c*]pyridine and 7-Chloro-2-phenylthiazolo[5,4-*c*]pyridine [1]

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Starting from readily available 2-aryl-5-formyl-4-mehtylthiazole, 2-aryl-6-carbethoxythiazolo[4,5-*c*]pyridine was prepared. β-(2-Phenylthiazol-4-yl)acrylic acid was converted to the corresponding azide (VI). Cyclization of compound VI afforded 2-phenylthiazolo[5,4-*c*]pyridin-7(6*H*)-one. Reaction of the latter with phosphorous oxychloride gave 7-chloro-2-phenylthiazolo[5,4-*c*]pyridine.

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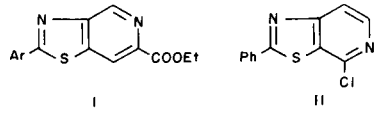
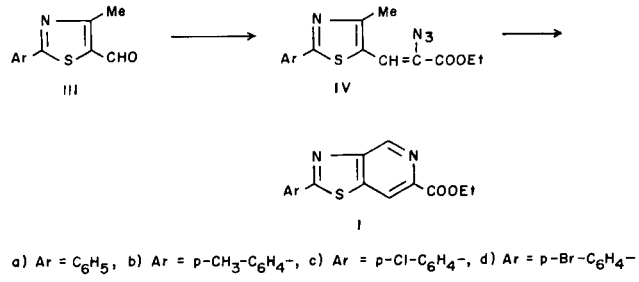
In continuation of our research interest in the synthesis of fused heterocycles [2], it was of interest to synthesize2-aroyl-6-carbethoxythiazolo[4,5-*c*]pyridine (I) and 7-chloro-2-phenylthiazolo[5,4-*c*]pyridine (II).



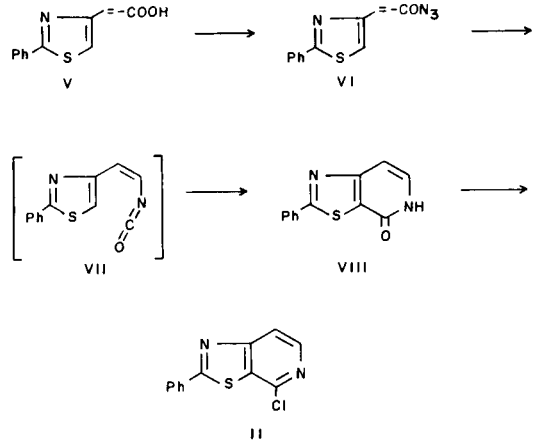
I II

2-Substitutedthiazolo[4,5-*c*]pyridine was prepared through cyclization of 3-amino-4-mercaptopyridine with acids [3]. The synthesis of 2-substitutedaminothiazolo-[4,5-*c*]pyridine, through the reaction of 4-chloro-3-aminopyridine with substituted isothiocyanates, has been reported [4]. 2-(2-Pyridyl)thiazolo[4,5-*c*]pyridine was prepared through oxidation-cyclization of *N*-(3-pyridyl)thiopicolinamide [5]. We have developed a new scheme for the synthesis of compound I (Scheme I).

Scheme I



a) Ar = C_6H_5, b) Ar = p-CH_3-C_6H_4-, c) Ar = p-Cl-C_6H_4-, d) Ar = p-Br-C_6H_4-



II

Reaction of 2-aryl-formyl-4-methylthiazole (III) [6] with ethyl azidoacetate, under the conditions reported [7], afforded ethyl *a*-azido-β-(2-aryl-4-methylthiazol-5-yl)acrylate (IV).

The nmr spectrum of compound IV was in agreement with the suggested structure. In the nmr spectrum of compound IV, the β vinylic proton appeared at 7.16 ppm. This value is similar to the one reported for the thiazole, selenazole [7] and thiophene analogs of compound IV [8].

Cyclization of compound IV to the desired compound I was accomplished through heating the former in xylene. The physical data of the compounds prepared are summarized in Tables I and II.

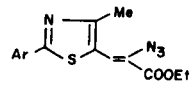
7-Chloro-2-phenylthiazolo[5,4-*c*]pyridine (II) was prepared according to Scheme I. Reaction of β-(2-phenylthiazol-4-yl)acrylic acid (V) [9] with ethyl chloroformate in acetone in the presence of triethylamine and subsequent addition of sodium azide afforded β-(2-phenylthiazol-4-yl)-acryloyl azide (VI). Cyclization of compound VI, through the intermediate VII, to the desired compound VIII was accomplished by heating compound VI in diphenyl ether [10]. Reaction of compound VIII with phosphorus oxychloride gave 7-chloro-2-phenylthiazolo[5,4-*c*]pyridine (II).

The nmr spectrum of compound II was in agreement with the suggested structure. H_4 and H_5 appeared as two doublets at 7.91 and 8.53 ppm with $J_{4,5}$ = 5.5 Hz. The structure of all compounds were confirmed by spectroscopic methods (ir, nmr and ms) and chemical analysis.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide discs). The nmr spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

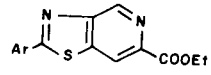
Table I



Compound No.	Ar	MP°C [a]	Yield (%)	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
IVa	C_6H_5-	115-116	70	$C_{15}H_{14}N_4O_2S$	57.32	57.51	4.46	4.35	17.83	17.68
IVb	p-$CH_3C_6H_4$-	117-119	40	$C_{16}H_{16}N_4O_2S$	58.54	58.61	4.88	4.72	17.07	16.91
IVc	p-ClC_6H_4-	114-115	30	$C_{15}H_{13}ClN_4O_2S$	51.65	51.48	3.73	3.59	16.07	16.18
IVd	p-BrC_6H_4-	119-120	35	$C_{15}H_{13}BrN_4O_2S$	45.80	45.71	3.31	3.50	14.25	14.40

[a] All compounds were crystallized from ether.

Table II



Compound No.	Ar	MP°C [a]	Yield (%)	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
Ia	C_6H_5-	124-126	30	$C_{15}H_{12}N_2O_2S$	63.38	63.21	4.23	4.08	9.86	9.95
Ib	p-$CH_3C_6H_4$-	162-164	25	$C_{16}H_{14}N_2O_2S$	64.43	64.58	4.70	4.58	9.40	9.56
Ic	p-ClC_6H_4-	191.193	15	$C_{15}H_{11}ClN_2O_2S$	56.51	56.45	3.45	3.51	8.79	8.85
Id	p-BrC_6H_4-	200-202	30	$C_{15}H_{11}BrN_2O_2S$	49.59	49.63	3.03	3.21	7.71	7.85

[a] All compounds were crystallized from ether.

Ethyl α-Azido-β-(4-methyl-2-phenylthiazol-5-yl)acrylate (IV).

To a stirring solution of sodium (276 mg, 12 mmoles) in absolute ethanol (9 ml) at 0° was added dropwise a solution of IIIa (609 mg, 3 mmoles) and ethyl azidoacetate (1548 mg, 12 mmoles) in 10 ml of absolute ethanol. After two hours at 0°, the mixture was added to a saturated solution of ammonium chloride. The mixture was extracted with ether. The organic layer was washed once with water and dried (anhydrous sodium sulfate). The ether was evaporated and the residue was purified by tlc (silica gel, chloroform) to give 660 mg, (70%) of IVa, mp 115-116° (ether); ir: 2100 (azide), 1695 and 1260 cm^{-1} (ester); nmr (deuteriochloroform): 8.0-7.56 (m, 2H, aromatic), 7.50-7.20 (m, 3H, aromatic), 7.16 (s, 1H, Hβ), 4.35 (q, 2H, OCH_2), 2.56 (s, 3H, CH_3) and 1.40 ppm (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.32; H, 4.46; N, 17.83. Found: C, 57.51; H, 4.35; N, 17.68.

Other ethyl α-azido-β-(2-aryl-4-methylthiazol-5-yl)acrylates IVb-IVd were prepared similarly (Table I).

6-Carbethoxy-2-phenylthiazolo[4,5-*c*]pyrimidine (Ia).

A solution of IVa (314 mg, 1 mmole) in xylene (10 ml) was refluxed for 45 minutes. The solvent was evaporated. The tlc of the residue (silica gel, chloroform:ether:petroleum ether; 70:15:15) gave 115 mg (30%) of Ia, mp 124-126°; ir: 1700 and 1250 cm^{-1} (ester); nmr (deuteriochloroform): 9.65 (s, 1H, H_4), 8.93 (s, 1H, H_7), 8.46-7.93 (m, 2H, aromatic), 7.90-7.26 (m, 3H, aromatic), 4.65 (q, 2H, OCH_2) and 1.53 ppm (t, 3H, CH_3); ms: m/e (%) 284 (M^+, 20), 240 (37), 212 (100), 121 (10), 108 (48), 82 (14), 43 (21).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.38; H, 4.23; N, 9.86. Found: C, 63.21; H, 4.08; N, 9.95.

Other 2-aryl-6-carbethoxythiazolo[4,5-*c*]pyridines Ib-Id were prepared similarly (Table II).

β-(2-Phenylthiazol-4-yl)acryloyl Azide (VI).

To a stirring solution of β-(2-phenylthiazol-4-yl)acrylic acid (924 mg, 4 mmoles) (9), triethylamine (540 mg.) in acetone (10 ml) at 0° a solution of ethyl chloroformate (542 mg, 4 mmoles) in acetone (2 ml) was added dropwise. After stirring 1 hour at 0°, water (20 ml) was added and the precipitate was filtered to give 1.015 g (99%) of VI, mp 122-123°; ir: 2120 (azide), 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_8N_4OS$: C, 56.25; H, 3.13; N, 21.88. Found: C, 56.15; H, 3.01; N, 21.69.

2-Phenylthiazolo[5,4-*c*]pyridine-7(6*H*)-one (VIII).

A solution of VI (256 mg, 1 mmole) in diphenyl ether (5 ml) was heated at 220° for half an hour. After standing overnight, the precipitate was filtered and crystallized from ethyl acetate to give 205 mg (90%) of VIII, mp 299-300°; ir: 3440 (NH), 1650 cm^{-1} (C=O); ms: m/e (%) 228 (M^+, 100), 200 (20), 70 (33).

Anal. Calcd. for $C_{12}H_8N_2OS$: C, 63.15; H, 3.51; N, 12.28. Found: C, 63.01; H, 3.64; N, 12.34.

7-Chloro-2-phenylthiazolo[5,4-*c*]pyridine (II).

A stirring mixture of VIII (228 mg, 1 mmole) and phosphorus oxychlor-

ide (1.8 ml) was heated at 135° for 1.5 hours. After cooling ice-water was added. The organic layer was extracted with chloroform. The chloroform was washed with water and evaporated. The residue was purified by tlc (silica gel, chloroform) and the desired compound was crystallized from ether to give 104 mg. (42%) of II, mp 122-124°; nmr (deuteriochloroform): 8.53 (d, 1H, H_5, $J_{4,5}$ = 5.5 Hz), 8.16 (m, 2H, aromatic), 7.91 (d, 1H, H_4, $J_{4,5}$ = 5.5 Hz) and 7.63 ppm (m, 3H, aromatic); ms: m/e (%) 248 (M^+ +2, 33), 246 (M^+, 100), 211 (26), 143 (8), 108 (20), 82 (32), 81 (13), 77 (21), 64 (16), 57 (10).

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[1] A. preliminary account of this work was submitted to the Xth ICHC, Waterloo, Canada, August, 1985.

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