A New, Convenient Synthesis of 7*H*-Thiazolo[3,2-*a*]pyridine Derivatives from α-Cyanocinnamic Esters and Mercaptoacetic Ester

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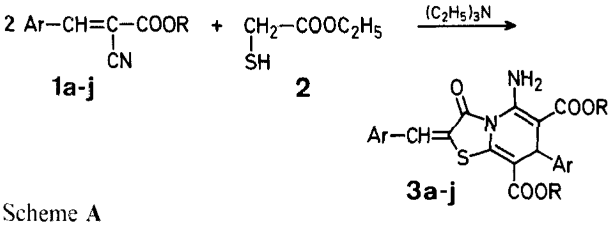
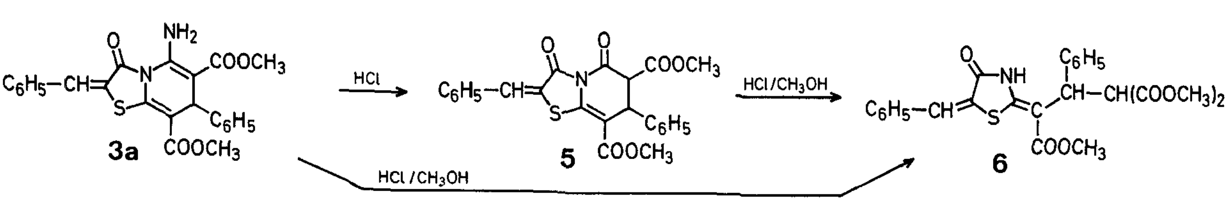
Although a number of papers[1,2,3] have been published concerning the syntheses of thiazolo[3,2-*a*]pyridines, no syntheses from α-cyanocinnamic esters **1** and mercaptoacetic ester **2** have been reported. We wish now to report a one-step synthesis of hitherto unknown 7*H*-thiazolo[3,2-*a*]pyridine derivatives from **1** and **2** in the presence of triethylamine.



Scheme A

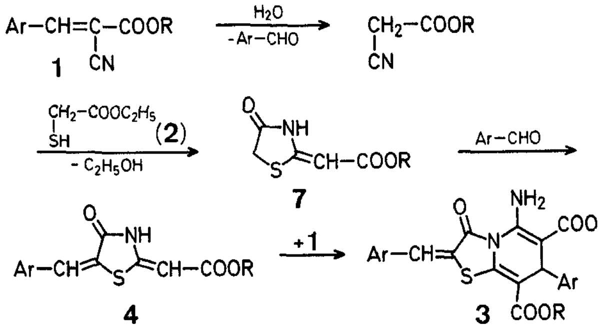
The reaction was performed by refluxing a mixture of **1** and **2** in a suitable alcohol containing triethylamine. For example, the reaction of **1f** with **2** in ethanol containing triethylamine afforded a yellow solid melting at 207 208° which was identified as 5-amino-2-benzylidene-6,8-diethoxycarbonyl-3-oxo-7-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine (**5f**). The microanalysis, I.R., N.M.R., and mass spectral data of this product are compatible with the structure **5f**. For the structural confirmation of **5f**, an authentic sample was prepared by the treatment of **1f** with 5-benzylidene-2-ethoxycarbonylmethylene-4-oxotetrahydrothiazole (**4**) which was synthesized from benzaldehyde and 2-ethoxycarbonylmethylene-4-oxotetrahydrothiazole (**7**)[4]. These products were proved to be identical by mixture melting point determination and by I.R., N.M.R., and mass spectral studies.

In addition, 7*H*-thiazolo[3,2-*a*]pyridine derivatives **3** could be obtained by the reaction of substituted α-cyanocinnamic esters with **2**. On the treatment with hydrochloric acid, **3a** is converted into 2-benzylidene-6,8-dimethoxycarbonyl-3,5-dioxo-7-phenyl-2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyridine (**5**) which did not show an amino group absorption. On the other hand, **5** was hydrolyzed with hydrochloric acid/methanol to give 5-benzylidene-4-oxo-2-(1,3,3-tris-[methoxycarbonyl]-2-phenylpropylidene)-tetrahydrothiazole (**6**). Furthermore, **6** was prepared directly by the hydrolysis of **3a** with hydrochloric acid/methanol (Scheme **B**).



Scheme B

Although we have not undertaken a mechanistic investigation of the reaction, the reaction should be considered to proceed as shown in Scheme C.



Scheme C

General Method for the Preparation of 5-Amino-7-aryl-2-arylidene-6,8-dialkoxycarbonyl-3-oxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines (3):
A mixture of the α-cyanocinnamic ester (**1**; 0.01 mol) and mercaptoacetic ester (**2**; 0.005 mol) in a suitable alcohol (10 ml) containing triethylamine (0.005 mol) is refluxed for 3 5 h. The yellow crystals which precipitate during the reaction are collected and washed with water and ether. Recrystallization from acetic acid gives **5**. The experimental results and spectral data are summarized in Tables 1 and 2. Reaction solvent: **3a–3e**, methanol; **3f–3j**, ethanol.

Preparation of 5-Benzylidene-2-ethoxycarbonylmethylene-4-oxotetrahydrothiazole (4; Ar = C_6H_5, R = C_2H_5):
A mixture of benzaldehyde (0.02 mol) and 2-ethoxycarbonylmethylene-4-oxotetrahydrothiazole[4] (0.02 mol) in ethanol (20 ml) containing triethylamine (0.01 mol) is refluxed for 4 h. After cooling, the resultant precipitate is collected and recrystallized from ethanol to give **4**; yield: 65%; m.p. 193 194°.

$C_{14}H_{13}NO_2S$	calc.	C 61.09	H 4.76	N 5.09	S 11.63
(275.3)	found	61.07	4.77	5.02	11.68

I.R. (Nujol): ν_{max} = 3250; 1710; 1685; 1595 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 12.15 (br, 1H, =N$\underline{H}$); 7.75 7.37 (m, 5H$_{arom}$, 1H, =C$\underline{H}$–C_6H_5); 5.65 (s, 1H, =C$\underline{H}$–$COOC_2H_5$); 4.35 3.90 (q, 2H, –C$\underline{H}_2$–CH$_3$); 1.40 1.15 ppm (t, 3H, –CH$_2$–C$\underline{H}_3$).

Preparation of 5-Amino-2-benzylidene-6,8-diethoxycarbonyl-3-oxo-7-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine (3f) from 1f and 4:
A mixture of **1f** (0.001 mol) and **4** (0.001 mol) in ethanol (5 ml) containing triethylamine (0.001 mol) is refluxed for 20 min. A yellow crystalline matter precipitates out during the reaction. This is collected and recrystallized from acetic acid to afford **3f**; yield: 83%; m.p. 207 208°.

Hydrolysis of 3a with Hydrochloric Acid:
Product **3a** (0.001 mol) is heated with concentrated hydrochloric acid (20 ml) for 2 h. The yellow solid deposited is collected and recrystallized from THF/ethanol to give **5**; yield: 72%, m.p. 212 213°.

$C_{24}H_{19}NO_6S$	calc.	C 64.14	H 4.26	N 3.12	S 7.12
(449.4)	found	63.99	4.27	3.10	7.06

M.S.: *m/e* (relative intensity) = 449 (M$^+$, 11); 390 (100); 358 (21); 340 (17).

I.R. (Nujol): ν_{max} = 1800; 1725; 1690; 1610 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 7.75 (s, 1H, =C$\underline{H}$–C_6H_5); 7.65 7.15 (m, 10H$_{arom}$); 4.65 (d, 1H, =C$\underline{H}$–CH=); 4.05 (d, 1H, =CH–C$\underline{H}$=); 3.65 (s, 3H, –C$\underline{H}_3$); 3.65 ppm (s, 3H, –CH$_3$).

Table 1. Preparation of 5-Amino-7-aryl-2-arylidene-6,8-dialkoxycarbonyl-3-oxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines **3**

Product No.	Ar	R	Yield [%]	m.p.	Molecular formula[a]
3a	C_6H_5	CH_3	32	221–222°	$C_{24}H_{20}N_2O_5S$ (448.4)
3b	$4\text{-}H_3C—C_6H_4$	CH_3	27	199–200°	$C_{26}H_{24}N_2O_5S$ (476.5)
3c	$4\text{-}H_3CO—C_6H_4$	CH_3	25	223–224°	$C_{26}H_{24}N_2O_7S$ (508.5)
3d	$4\text{-}Cl—C_6H_4$	CH_3	28	229–230°	$C_{24}H_{18}Cl_2N_2O_2S$ (517.4)
3e	$4\text{-}O_2N—C_6H_4$	CH_3	15	192–193°	$C_{24}H_{18}N_4O_9S$ (538.5)
3f	C_6H_5	C_2H_5	35	210–211°	$C_{26}H_{24}N_2O_5S$ (476.5)
3g	$4\text{-}H_3C—C_6H_4$	C_2H_5	30	206–207°	$C_{28}H_{28}N_2O_5S$ (504.6)
3h	$4\text{-}H_3CO—C_6H_4$	C_2H_5	27	219–220°	$C_{28}H_{28}N_2O_7S$ (586.6)
3i	$4\text{-}Cl—C_6H_4$	C_2H_5	24	235–236°	$C_{26}H_{22}Cl_2N_2O_5S$ (545.4)
3j	$4\text{-}O_2N—C_6H_4$	C_2H_5	17	255–256°	$C_{26}H_{22}N_4O_9S$ (566.5)

[a] All products gave satisfactory microanalyses (C ± 0.30%, H ± 0.15%, N ± 0.33%, S ± 0.11%).

Table 2. Spectral Data for Products **3a–j**

Product	I.R. (nujol)[a] ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[b] δ [ppm]	M.S.[c] *m/e* (relative intensity)
3a	3400; 3270; 1705; 1695; 1660; 1618	8.60 (br, 2H, $—N\underline{H}_2$); 7.75 (s, 1H, $=C\underline{H}—$); 7.60–7.20 (m, $10H_{arom}$); 4.95 (s, 1H, ring $=C\underline{H}—$); 3.70 (s, 3H, $—C\underline{H}_3$); 3.60 (s, 3H, $—C\underline{H}_3$)	448 (M^+, 4); 416 (3); 389 (5); 371 (100); 339 (11); 311 (9)
3b	3400; 3250; 1710; 1700; 1665; 1620	8.65 (br, 2H, $—N\underline{H}_2$); 7.75 (s, 1H, $=CH—$); 7.65–7.20 (m, $8H_{arom}$); 4.95 (s, 1H, ring $=C\underline{H}—$); 3.75 (s, 3H, ester $—C\underline{H}_3$); 3.65 (s, 3H, ester $—C\underline{H}_3$); 2.40 (s, 3H, substituted $—C\underline{H}_3$); 2.25 (s, 3H, substituted $—C\underline{H}_3$)	476 (M^+, 4); 417 (6); 385 (100); 353 (6); 325 (9); 293 (2)
3c	3400; 3250; 1710; 1690; 1660; 1610	8.65 (br, 2H, $—N\underline{H}_2$); 7.67 (s, 1H, $=C\underline{H}—$); 7.50–6.68 (m, $8H_{arom}$); 5.86 (s, 1H, ring $=C\underline{H}—$); 3.85 (s, 3H, ester $—C\underline{H}_3$); 3.76 (s, 6H, ester $—C\underline{H}_3$, $—OC\underline{H}_3$); 3.65 (s, 3H, $—OC\underline{H}_3$)	508 (M^+, 21); 449 (26); 401 (100); 369 (23); 341 (23); 309 (10)
3d	3375; 3250; 1710; 1690; 1655; 1610	8.60 (br, 2H, $—N\underline{H}_2$); 7.63 (s, 1H, $=C\underline{H}—$); 7.47–7.17 (m, $8H_{arom}$); 4.87 (s, 1H, ring $=C\underline{H}—$); 3.73 (s, 3H, $—C\underline{H}_3$); 3.63 (s, 3H, $—C\underline{H}_3$)	516 (M^+, 5); 457 (8); 405 (100); 373 (23); 345 (22); 257 (11)
3e	3400; 3275; 1705; 1690; 1660; 1625; 1525	8.71–7.45 (m, $8H_{arom}$, 1H, $=C\underline{H}—$); 5.35 (s, 1H, ring $—C\underline{H}=$); 4.95 (br, 2H, $—N\underline{H}_2$); 4.95 (s, 6H, 2 × $—C\underline{H}_3$)[d]	538 (M^+, 7); 479 (10; 416 (100); 353 (6); 325 (9); 293 (2)
3f	3395; 3250; 1710; 1690; 1660; 1615	8.65 (br, 2H, $—N\underline{H}_2$); 7.70 (s, 1H $=CH—$); 7.60–7.25 (m, $10H_{arom}$); 4.90 (s, 1H, ring $=C\underline{H}—$); 4.35–3.85 (m, 4H, 2 × $—C\underline{H}_2—CH_3$); 1.35–1.05 (m, 6H, 2 × $—CH_2—C\underline{H}_3$)	476 (M^+, 4); 403 (6); 399 (100); 375 (5); 353 (5); 325 (3)
3g	3390; 3275; 1710; 1690; 1655; 1615	8.70 (br, 2H, $—N\underline{H}_2$); 7.75 (s, 1H, $=CH—$); 7.65–7.20 (m, $8H_{arom}$); 4.90 (s, 1H, ring $=C\underline{H}—$); 4.40–3.90 (m, 4H, 2 × $—C\underline{H}_2—CH_3$); 2.45 (s, 3H, $—C\underline{H}_3$); 2.30 (s, 3H, $—C\underline{H}_3$); 1.40–1.03 (m, 6H, 2 × $—CH_2—C\underline{H}_3$)	504 (M^+, 10); 456 (6); 431 (23); 413 (100); 385 (31); 367 (24)
3h	3395; 3250; 1710; 1690; 1660; 1610	8.70 (br, 2H, $—N\underline{H}_2$); 7.75 (s, 1H, $=CH—$); 7.50–6.72 (m, $8H_{arom}$); 4.90 (s, 1H, ring $=C\underline{H}—$); 4.40–3.75 (m, 10H, 2 × $—C\underline{H}_2—CH_3$, 2 × $—OC\underline{H}_3$); 1.95–1.50 (m, 6H, 2 × $—CH_2—C\underline{H}_3$)	536 (M^+, 15); 488 (20); 463 (20); 429 (100); 401 (13); 383 (13)
3i	3350; 3250; 1710; 1690; 1660; 1615	8.75 (br, 2H, $—N\underline{H}_2$); 7.70 (s, 1H, $=C\underline{H}—$); 7.55–7.25 (m, $8H_{arom}$); 4.90 (s, 1H, ring $=C\underline{H}—$); 4.30–4.00 (m, 4H, 2 × $—C\underline{H}_2—CH_3$); 1.35–1.05 (m, 6H, 2 × $—CH_2—C\underline{H}_3$)	544 (M^+, 11); 471 (27); 433 (100); 505 (30); 387 (29); 359 (20)
3j	3400; 3200; 1710; 1690; 1655; 1625; 1524	8.65–7.55 (m, $8H_{arom}$, 1H, $=C\underline{H}—$); 5.35 (s, 1H, ring $=C\underline{H}—$); 4.99 (br, 2H, $—N\underline{H}_2$); 4.75–4.30 (q, 4H, 2 × $—C\underline{H}_2—CH_3$); 1.60–1.30 (t, 6H, 2 × $—CH_2—C\underline{H}_3$)[d]	566 (M^+, 4); 493 (7), 444 (100); 416 (13); 398 (14); 370 (7)

[a] All I.R. spectra were measured with a Shimadzu I.R.-27G spectrometer.

[b] All ^{1}H-N.M.R. spectra were measured with a JEOL JNM-MH-60 using TMS as internal standard.

[c] Mass spectra were taken with a Hitachi M-52 GC-MS instrument operating at 70 eV.

[d] Measured in CF_3COOH.

Hydrolysis of 3a with Hydrochloric Acid/Methanol:

To a solution of concentrated hydrochloric acid (10 ml) and methanol (20 ml) is added **3a** (0.001 mol), then the mixture is refluxed for 5 h. The yellow solid which is deposited is collected and recrystallized from chloroform/methanol to give **6**; yield 68%; m.p. 195–196°.

$C_{25}H_{23}NO_7S$	calc.	C 62.36	H 4.81	N 2.91	S 6.65
(481.4)	found	61.98	4.80	2.92	6.61

M.S.: m/e (relative intensity) = 481 (M^+, 16); 449(14); 421(14); 390(21); 362(18); 350(100); 318(24); 156(21); 134(27).

I.R. (Nujol): ν_{max} = 3250; 1760; 1720; 1665; 1605 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 11.35 (br, 1H, =N$\underline{H}$); 7.85–7.25 (m, 1H, =C$\underline{H}$—C_6H_5, 10H_{arom}); 4.90 (d, 1H, =C$\underline{H}$—CH=); 4.40 (d, 1H, =CH—C$\underline{H}$=); 3.70 (s, 3H, —C$\underline{H}_3$); 3.60 (s, 3H, —C$\underline{H}_3$); 3.55 ppm (s, 3H, —C$\underline{H}_3$).

Hydrolysis of 5:

The procedure used is essentially the same as described above. Recrystallization from THF/methanol gives **6**; yield 88%; m.p. 195–196°.

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[1] D. H. Reid et al., *Organic Compounds of Sulphur, Selenium, and Tellurium*, The Chemical Society, London, 1970, Vol. 1, p. 429.

[2] D. H. Reid et al., *Organic Compounds of Sulphur, Selenium, and Tellurium*, The Chemical Society, London, 1973, Vol. 2, p. 695.

[3] D. H. Reid et al., *Organic Compounds of Sulphur, Selenium, and Tellurium*, The Chemical Society, London, 1974, Vol. 3, p. 653.

[4] J. L. Isidor et al., *J. Org. Chem.* **38**, 3615 (1973).