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STUDY ON THIAZOLOPYRIDINES PART (7) : SYNTHESIS OF NOVEL THIAZOLIDINONE AND THIAZOLO[3,2-A]PYRIDINE DERIVATIVES

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Abstract

A novel 2-ethoxycarbonyl methylidine-4,5-dihydo-4-oxo-5-arylmethylidine-1,3-thiazole derivatives **(2a-c)** are obtained via the reaction of 4-thiazolinone derivative **(1)** with different aromatic aldehydes. Cyclization of 4-thiazolidinone derivatives **(2a-c)** with various α–cyanocinnamonitriles afforded the corresponding thiazolopyridine derivatives (**5a-r).** Thiazolopyridine derivatives **(5a,b)** are refluxed with acetic anhydride, and gave N,N-diacetyl amino derivatives **(8a,b)**.

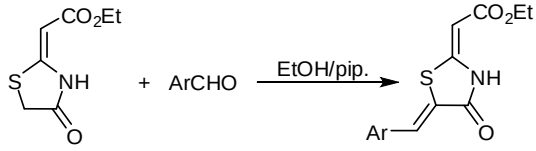
Introduction

In the last decade, much attention have been devoted to construct a new thiazolidinone and thiazolopyridine derivatives and reported their biological activities. A series of novel 4-thiazolidinone and thiazolopyridine derivatives are reported to have diverse biological and medicinal activities as antibacterial[1-4], antimicrobial[5-7], antifungal[8], anticonvulsant[9], anticancer[10], antituberculosis[11], antihypertensive, coronary dilator and muscle relxant[12-14] activities. Thus, we devoted the synthesis of heterocyclic compounds from readily available starting materials[15-21]. We reported here the synthesis of some novel thiazolidinone **(2a-c)**, thiazolo[3,2-a]pyridine (**5a-r),** and **(8a,b)** derivatives from 2-ethoxycarbonyl-methylidine-4,5-dihydro-4-thiazolidinone **(1)** as starting material[22].

Keywords: *5-Arylmethylidine-4-thiazolinones, thiazolo[3,2-a] pyridines.*

Results And Discussion

4,5-Dihydro-2-ethoxycarbonylmethylidine-4-oxo-1,3-thiazole**(1)** was condensed with different aromatic aldehydes in absolute ethanol catalyzed with piperidine to give the corresponding 4-thiazolidinone derivatives **(2a-c)**, **(Scheme 1).**

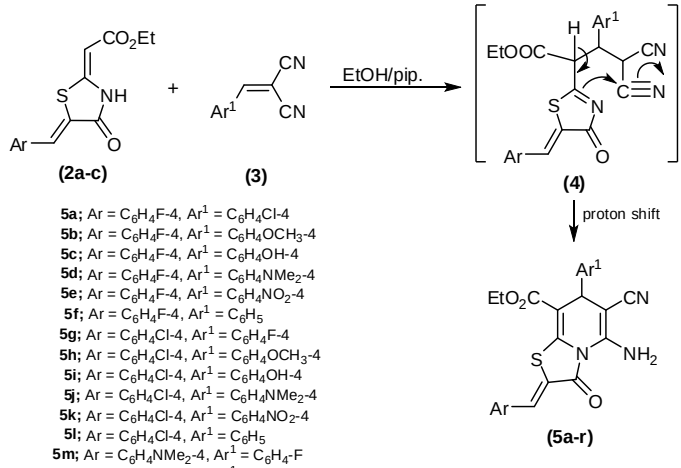


(1) **(2a-c)**

a; Ar = C_6H_4F-4
b; Ar = C_6H_4Cl-4
c; Ar = $C_6H_4NMe_2$-4

(Scheme 1)

The structure of compounds **(2a-c),** were established by the correct elemental and spectral data. Infrared spectra of thiazolidinone derivatives **(2a-c)** showed absorption signals corresponding to (NH, C=O thiazolidinone and ester). ^{1}HNMR Spectrum of **(2a)** recorded on (DMSO-d_6) revealed signals at δ 1.22 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.62 (s, 1H, methylidene-H), 7.35-7.72 (m, 5H, Ar-H + benzylidene-H) and 12.26 (s, 1H, OH-enolic). Also,^{1}HNMR spectrum of **(2b)** recorded on (DMSO-d_6) displayed signals at δ 1.03 (t, 3H CH_3), 4.10 (q, 2H, CH_2), 5.62 (s, 1H, methylidene-H), 7.35-7.72 (m, 5H, Ar-H + benzylidene, and 12.26 (s, 1H, OH-enolic). Mass spectrum of thiazolidinone derivative **(2c**, $C_{16}H_{18}N_2O_3S$**)** displayed a molecular ion peak at m/z 318 (23.5%) and a base peak was found in the spectrum at m/z 177. Reaction of 5-arylmethylidene-4,5-dihydro-4-thiazolidinone **(2a-c)** with α-cyanocinnamo-nitriles **(3)** in ethanol in presence of a few drops of piperidine led to the formation of the novel thiazolo[3,2-a] pyridines **(5a-r)** in good yields. The reaction was assumed to proceed via *Michael* addition of methylene group of 4-thiazolidinone to β- carbon atom of α-cyanocinnamonitrile, and followed by intermolecular cyclization **(Scheme 2)**.



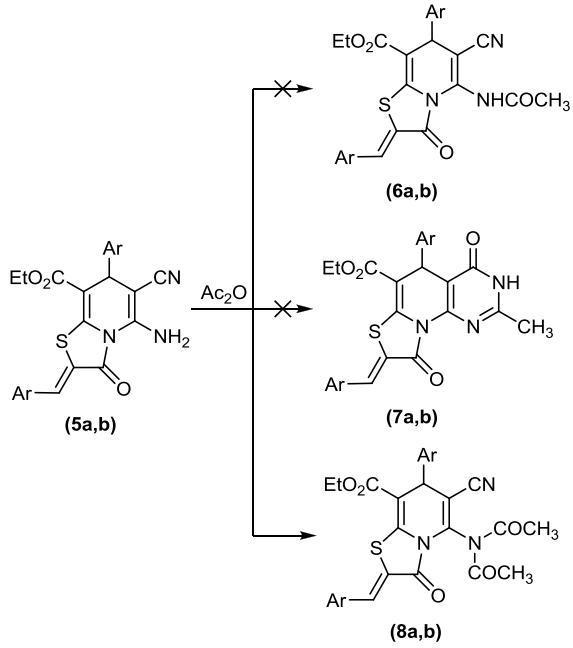
(2a-c) **(3)** **(4)** **(5a-r)**

5a; Ar = C_6H_4F-4, Ar^1 = C_6H_4Cl-4
5b; Ar = C_6H_4F-4, Ar^1 = $C_6H_4OCH_3$-4
5c; Ar = C_6H_4F-4, Ar^1 = C_6H_4OH-4
5d; Ar = C_6H_4F-4, Ar^1 = $C_6H_4NMe_2$-4
5e; Ar = C_6H_4F-4, Ar^1 = $C_6H_4NO_2$-4
5f; Ar = C_6H_4F-4, Ar^1 = C_6H_5
5g; Ar = C_6H_4Cl-4, Ar^1 = C_6H_4F-4
5h; Ar = C_6H_4Cl-4, Ar^1 = $C_6H_4OCH_3$-4
5i; Ar = C_6H_4Cl-4, Ar^1 = C_6H_4OH-4
5j; Ar = C_6H_4Cl-4, Ar^1 = $C_6H_4NMe_2$-4
5k; Ar = C_6H_4Cl-4, Ar^1 = $C_6H_4NO_2$-4
5l; Ar = C_6H_4Cl-4, Ar^1 = C_6H_5
5m; Ar = $C_6H_4NMe_2$-4, Ar^1 = C_6H_4-F
5n; Ar = $C_6H_4NMe_2$-4, Ar^1 = C_6H_4-OCH_3-4
5o; Ar = $C_6H_4NMe_2$-4, Ar^1 = C_6H_4OH
5p; Ar = $C_6H_4NMe_2$-4, Ar^1 = C_6H_4Cl-4
5q; Ar = $C_6H_4NMe_2$-4, Ar^1 = $C_6H_4NO_2$-4
5r; Ar = $C_6H_4NMe_2$-4, Ar^1 = C_6H_5

(Scheme 2)

The structure of thiazolo[3,2-a] pyridines **(5a-r)** were established by the correct analytical and spectral data. The infrared spectra of 1,3-thiazolo[3,2-a] pyridine derivatives (**5a-r)** exhibited absorption bands corresponding to (NH_2, C≡N and C=O thiazolidinone and ester functional groups). ^{1}HNMR spectra of thiazolopyridines **(5a-r)** in (DMSO-d_6) revealed a signal characteristic for pyridine-H. The mass spectrum of compound **(5a**; $C_{24}H_{17}N_3FClO_3S$**)** showed a molecular ion peak at m/z 481 (10.8%) and a base peak was found in the spectrum at m/z 370. Also, a molecular ion peak of thiazolopyridine **(5i**; $C_{24}H_{18}N_3ClO_4S$**)** was observed at m/z 480 (5.1%) and a base peak was found in spectrum at m/z 386. The mass spectrum of thiazolopyridine derivative **(5l**; $C_{24}H_{18}N_3ClO_3S$**)** exhibited a molecular ion peak at m/z 464 (11.11%) and the base peak was found in the spectrum at m/z 386. Finally, the mass spectrum of compound **(5n**; $C_{27}H_{26}N_4O_4S$**)** exhibited a molecular ion peak at m/z 502 (14.1%) and a base peak at m/z 177.

Refluxing of 2-arylmethylidine-2,3,7-trihydro-3-oxo-5-amino-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridines **(5a,b**) with acetic anhydride for 4 hrs furnished the corresponding 5-*N*,*N*-diacetyl amino derivatives **(8a,b)** and the other possible structures **(7a,b)** and **(6a**,**b)** were excluded on the basis of analytical and spectral data **(Scheme 3)**.



(Scheme 3)

The formation of 5-*N*,*N*-diacetylamino derivatives **(8a,b)** are assumed to proceed via nucleophilic addition of amino group to the deficient carbonyl carbon of acetic anhydride followed by elimination of two moles of acetic acid.

The infrared spectra of **(8a,b)** displayed a lack of absorption band corresponding to amino group and presence of absorption signals for cyano and carbonyl functional groups and thus the structure of thiazolopyridines **(7a,b**) was excluded. ^{1}HNMR spectra of (**8a,b)** recorded on (DMSO-d_6) revealed characteristic signals at δ 2.22, 2.20 corresponding to $2COCH_3$ and excluded the structure of thiazolopyridines **(6a,b)**. The mass spectrum of compound (**8b**; $C_{29}H_{24}N_3FO_6S$) exhibited a molecular ion peak at m/z 561 (19.4%) and a base peak at m/z 370.

Table I: Physical data of the synthesized compounds.

Compd. No.	Yield [%]	Cryst. Solvent	M.P [ºC]	Mol. Formula (M. Wt.)	Elemental analysis Calcd./Found[%]		
					C	H	N
2a	70	EtOH	191-93	$C_{14}H_{12}FNO_3S$	57.33	4.09	4.77
				(293)	57.42	4.10	4.63
2b	60	EtOH	207-09	$C_{14}H_{12}ClNO_3S$	54.28	3.87	4.52
				(309.5)	53.92	3.82	4.67
2c	55	EtOH	234-36	$C_{16}H_{18}N_2O_3S$	60.37	5.66	8.80
				(318)	60.50	5.48	8.91
5a	76	EtOH	246-48	$C_{24}H_{17}ClFN_3O_3S$	59.81	3.53	8.72
				(481.5)	59.72	3.64	8.80
5b	58	$CHCl_3$	237-39	$C_{25}H_{20}FN_3O_4S$	62.89	4.19	8.80
				(477)	63.00	4.27	8.65
5c	65	$CHCl_3$	240-42	$C_{24}H_{18}FN_3O_4S$	62.20	3.88	9.07
				(463)	62.09	4.00	9.26
5d	58	$CHCl_3$	173-75	$C_{26}H_{23}FN_4O_3S$	63.67	4.69	11.42
				(490)	63.82	4.52	11.63
5e	60	$CHCl_3$	260-62	$C_{24}H_{17}FN_4O_5S$	58.53	3.45	11.38
				(492)	58.40	3.62	11.10
5f	55	$CHCl_3$	257-59	$C_{24}H_{18}FN_3O_3S$	64.42	4.02	9.39
				(447)	64.59	3.92	9.21
5g	62	EtOH	270-72	$C_{24}H_{17}ClFN_3O_3S$	59.81	3.53	8.72
				(481.5)	60.00	3.53	8.90
5h	73	EtOH	217-19	$C_{25}H_{20}ClN_3O_4S$	60.79	4.05	8.51
				(493.5)	60.80	3.91	8.52
5i	55	EtOH	249-51	$C_{24}H_{18}ClN_3O_4S$	60.06	3.75	8.75
				(479.5)	60.20	3.61	8.60
5j	57	EtOH	225-27	$C_{26}H_{23}ClN_4O_3S$	61.59	4.54	11.05
				(506.5)	61.52	4.52	10.99
5k	74	EtOH	187-89	$C_{24}H_{17}ClN_4O_5S$	56.63	3.34	11.01
				(508.5)	56.60	3.50	11.02
5l	63	EtOH	249-51	$C_{24}H_{18}ClN_3O_3S$	62.13	3.88	9.06
				(463.5)	62.20	3.82	9.05
5m	46	EtOH	242-44	$C_{26}H_{23}FN_4O_3S$	63.67	4.69	11.42
				(490)	63.70	4.52	11.30
5n	69	EtOH	193-95	$C_{27}H_{26}N_4O_4S$	64.54	5.17	11.15
				(502)	64.42	5.20	11.20
5o	71	EtOH	230-32	$C_{26}H_{24}N_4O_4S$	63.93	4.91	11.47
				(488)	64.20	4.80	11.62
5q	71	EtOH	223-25	$C_{26}H_{23}N_5O_5S$	60.34	4.44	13.53
				(517)	60.40	4.60	13.60
5r	73	EtOH	210-12	$C_{26}H_{24}N_4O_3S$	66.10	5.08	11.86
				(472)	65.92	5.12	11.90
8a	65	EtOH	140-42	$C_{28}H_{21}ClFN_3O_5S$	59.41	3.71	7.42
				(565.5)	60.01	3.76	7.33
8b	63	EtOH	150-52	$C_{29}H_{24}FN_3O_6S$	62.03	4.27	7.48
				561	62.01	4.30	7.41

Table II : Spectral data of some synthesized compounds.

Compd. No.	IR (KBr, cm^{-1})	^{1}HNMR (DMSO-d_6) (δ, ppm)
2a	3172 (NH), 2988 (CH-aliph.), 1700 (C=O thiazolidinone and ester).	1.23 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.62 (s, 1H, methylidene-H), 7.35-7.73 (m, 5H, Ar-H + benz-ylidene-H), 12. 26 (s, 1H, OH enol).
2b	3132 (NH), 2980 (CH-aliph.), 1686 (C=O thiazolidinone and ester)	1.03 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.62 (s, 1H, methylidene-H), 7.52-7.61 (m, 5H, Ar-H + benzylidene-H), 12.26 (s, 1H, OH enol)
5a	3344, 3379 (NH_2), 2194 (C≡N), 1691 (C=O thiazolidinone and ester).	1.02 (t, 3H, CH_3), 4.08 (q, 2H, CH_2), 4.51 (s, 1H, pyridine-H) 6.79-7.72 (m, 10H, Ar-H + NH_2), 8.64 (s, 1H, methine-H)
5b	3335, 3376 (NH_2), 2190 (C≡N), 1688 (C=O thiazolidinone and ester).	1.03 (t, 3H, CH_3), 3.85 (s, 3H, OCH_3) 4.05 (q, 2H, CH_2), 4.51 (s, 1H, pyridine-H), 6.84-7.75 (m, 11H, Ar-H + NH_2 + methine-H)
5d	3415, 3315 (NH_2), 2193 (C≡N), 1687 (C=O thiazolidinone and ester).	1.06 (t, 3H, CH_3), 3.05 (s, 6H, $N(CH_3)_2$), 4.08 (q, 2H, CH_2), 4.48 (s, 1H, pyridine-H), 6.83-7.86 (m, 10H, Ar-H + NH_2), 8.05 (s, 1H, methine-H)
5f	3344, 3379 (NH_2), 2194(C≡N), 1691(C=O thiazolidinone and ester).	1.05 (t, 3H, CH_3), 4.03 (q, 2H, CH_2), 4.51 (s, 1H, pyridine-H), 6.62-7.92 (m, 10H, Ar-H + NH_2), 8.62 (s, 1H, methine-H)
5h	3330, 3315 (NH_2), 2184 (C≡N), 1689 (C=O thiazolidinone and ester).	1.03 (t, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.05 (q, 2H, CH_2), 4.52 (s, 1H, pyridine-H), 6.85-7.69 (m, 11H, Ar-H + NH_2 + methine-H)
5j	3412, 3371 (NH_2), 2193 (C≡N), 1687 (C=O thiazolidinone and ester).	1.01 (t, 3H, CH_3), 3.05 (s, 6H, $N(CH_3)_2$), 3.97 (q, 2H, CH_2), 4.52 (s, 1H, pyridine-H), 6.85-8.07 (m, 11H, Ar-H + NH_2 + methine-H)
5m	3376, 3283 (NH_2), 2193 (C≡N), 1688 (C=O thiazolidinone and ester).	1.04 (t, 3H, CH_3), 3.00 (s, 6H, $N(CH_3)_2$), 4.03 (q, 2H, CH_2), 5.62 (s, 1H, pyridine-H), 6.79-8.01 (m, 11H, Ar-H + NH_2 + methine-H)
5o	3355, 3315 (NH_2), 2197 (C≡N), 1688 (C=O thiazolidinone and ester).	1.03 (t, 3H, CH_3), 3.02 (s, 6H, $N(CH_3)_2$), 3.99 (q, 2H, CH_2), 4.39 (s, 1H, pyridine-H), 6.60-7.62 (m, 11H, Ar-H + NH_2 + methine-H), 9.34 (s, 1H, OH)
8a	2193 (C≡N), 1688 (C=O thiazolidinone and ester).	1.02 (t, 3H, CH_3), 2.22, 2.20 (2s, 6H, $2COCH_3$), 4.01 (q, 2H, CH_2), 4.47 (s, 1H, pyridine-H), 7.33-7.74 (m, 11H, Ar-H + NH_2 + methine-H),
8b	2193 (C≡N) 1688 (C=O thiazolidinone and ester).	1.02 (t, 3H, CH_3), 2.22, 2.20 (2s, 6H, $2COCH_3$), 3.85 (s, 3H, OCH_3), 4.09 (q, 2H, CH_2), 4.92 (s, 1H, pyridine-H), 6.92-7.78 (m, 11H, Ar-H + NH_2 + methine-H),

Experimental

Melting points are recorded on a Fisher-John melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrometer using KBr pellets. ^{1}HNMR spectrum were recorded on a Varian Gemini spectrometer 200 (200 MHz) using TMS as internal standard and mass spectra on a Jeol-JMS-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C micro-analyzer. The physical and spectral data are collected in Tables I and II, respectively.

4,5-Dihydro-2-ethoxycarbonylmethylidine-5-arylmethylidene-4-thiazolidinone (2a-c)

To a solution of 4-thiazoloidinone **(1)** (0.01mol), the aromatic aldehydes were added (0.01mol) in presence of absolute ethanol (20mL) having few drops of piperidine. The mixture was refluxed for 4h, then allowed to cool. The solid product was collected and recrystallized from ethanol to give **(2a-c)**.

2,3,7-Trihydro-2-arylmethylidene-4-oxo-5-amino-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridine (5a-r)

A mixture of 4-thiazolidinone **(2a-c)** and α-anocinnamonittiles (3), (0.01 mol) in presence of absolute ethanol (20 mL) having few drops of piperidine was refluxed for 4 h, then allowed to cool. The solid product was collected and recrystallized from ethanol to give **(5a-r)**.

2,3,7-Trihydro-2-arylmethylidene-4-oxo-5-*N,N*-diacetylamino-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridine (8a,b)

A mixture of thiazolopyridine derivative **(5a,b)** (0.01 mol) was refluxed with acetic anhydride for 4h. The solid product that obtained was allowed to cool, collected and recrystallized from ethanol to give **(8a,b)**.

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