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SYNTHESIS OF 2-ARYL-2,3-DIHYDRO-4H-[1,3]THIAZINO[3,2-*a*]BENZIMIDAZOL-4-ONES AND 7-ARYL-2,3,6,7-TETRAHYDRO-5H-IMIDAZO[2,1-*b*]-1,3-THIAZIN-5-ONES

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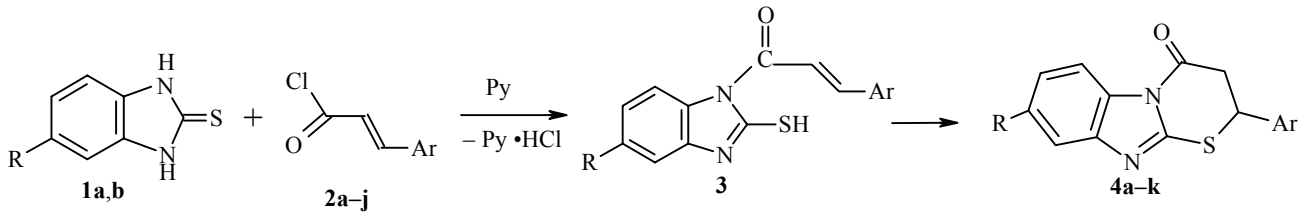
The reaction of 2-mercaptobenzimidazole, 5-ethoxy-2-mercaptobenzimidazole, and 2-mercaptoimidazoline with cinnamoyl chloride, its derivatives, and heteroanalogs was studied. Convenient methods were found for the synthesis of 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-a]benzimidazol-4-ones and 7-aryl-2,3,6,7-tetrahydro-5H-imidazo[2,1-b]-1,3-thiazin-5-ones.

Keywords: 2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones, 7-aryl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]thiazin-5-ones.

4H-1,3-Thiazin-4-one derivatives have various types of biological activity and may be used as pesticides and herbicides [1], fungicides [2], and antituberculosis agents [3]. Condensed heterocyclic systems containing the 4H-1,3-thiazin-4-one structure such as derivatives of 2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-one and 2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-one hold promise in this regard. These compounds are obtained as a rule through multistep syntheses [4-8]. Information on the single-step synthesis of these compounds by the reaction of 2-mercaptobenzimidazole (**1a**) and 2-mercaptoimidazoline (**5**) with the acid chloride of acrylic acid is very limited [9, 10].

2-Aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones **4a-k** were obtained in our single-step method by the reaction of 2-mercaptobenzimidazole (**1a**) and 5-ethoxy-2-mercaptobenzimidazole (**1b**) and substituted **2b-g** and heteroanalogs **2h-j** without isolation of intermediate N-cinnamoylimidazoles **3**.



1a,**b** **2a–j** **3** **4a–k**

1 a R = H, **b** R = EtO; **2, 4 a-j** R = H, **a** Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-FC_6H_4, **d** Ar = 3-$O_2NC_6H_4$, **e** Ar = 3,4-$(MeO)_2C_6H_3$, **f** Ar = 3,4,5-$(MeO)_3C_6H_2$, **g** Ar = 2-$MeOC_6H_4$, **h** Ar = 2-thienyl, **i** Ar = 2-furyl, **j** Ar = 1-(3,4-methylenedioxy)phenyl; **4k** R = EtO, Ar = Ph; **3** R = H, Ar = 2-$MeOC_6H_4$

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The elemental analysis data, melting points, and product yields are given in Table 1. The ^{1}H NMR spectra of these compounds are given in Table 2. This reaction may be followed conveniently using ^{1}H NMR spectroscopy since signals at 3.3-5.5 ppm (an ABX proton system for the thiazine ring) appear during the reaction instead of the two doublets at 7.6-7.9 ppm (signals for the protons of the double bond in starting acid chlorides **2a-j**).

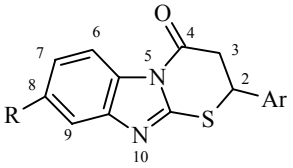
Availability of the starting compounds, experimental simplicity, and high product yields are advantages of our single-step method. The reaction proceeds under mild conditions by heating the reagents in pyridine–benzene at reflux for 2 h. The highest yields (69-82%) were obtained with cinnamoyl chloride **2a** and its *para*- and *meta*-phenyl derivatives **2b-d**. The yields of the desired products were somewhat lower using 3-heterylacryloyl chlorides **2h-j** (61-72%).

TABLE 1. Characteristics of Compounds Synthesized

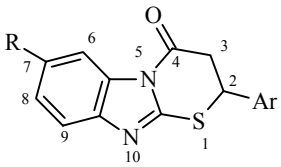
Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
3	$C_{17}H_{14}N_2O_2S$	65.90 / 65.80	4.61 / 4.52	9.08 / 9.03	206-208	52
4a	$C_{16}H_{12}N_2OS$	68.65 / 68.57	4.34 / 4.29	10.20 / 10.00	121-123	73
4b	$C_{17}H_{14}N_2O_2S$	65.91 / 65.80	4.33 / 4.52	9.09 / 9.03	140-143	69
4c	$C_{16}H_{11}FN_2OS$	64.31 / 64.44	3.61 / 3.69	9.53 / 9.40	135-138	71
4d	$C_{16}H_{11}N_3O_3S$	59.24 / 59.08	3.17 / 3.38	13.12 / 12.92	192-195	82
4e	$C_{18}H_{16}N_2O_3S$	63.54 / 63.53	4.58 / 4.70	8.40 / 8.23	170-173	67
4f	$C_{19}H_{18}N_2O_4S$	61.54 / 61.62	4.98 / 4.86	7.50 / 7.57	215-218	68
4g	$C_{17}H_{14}N_2O_2S$	65.62 / 65.80	4.35 / 4.52	9.18 / 9.03	100-103	53
4h	$C_{14}H_{10}N_2OS_2$	58.99 / 58.74	3.66 / 3.50	9.71 / 9.79	120-123	72
4i	$C_{14}H_{10}N_2O_2S$	62.03 / 62.22	3.51 / 3.70	10.17 / 10.37	130-133	63
4j	$C_{17}H_{12}N_2O_3S$	62.71 / 62.96	3.93 / 3.70	8.52 / 8.64	157-160	61
4k	$C_{18}H_{16}N_2O_2S$	65.87 / 66.66	4.78 / 4.94	8.83 / 8.64	152-155	68
6a	$C_{21}H_{18}N_2O_2S$	69.87 / 69.61	4.48 / 4.97	7.51 / 7.73	197-200	49
6b	$C_{23}H_{22}N_2O_4S$	65.28 / 65.40	5.06 / 5.21	6.48 / 6.63	184-185	50
6c	$C_{21}H_{16}N_4O_6S$	55.60 / 55.75	3.68 / 3.54	12.57 / 12.39	207-210	52
8a	$C_{12}H_{13}ClN_2OS$	53.88 / 53.63	4.71 / 4.84	10.30 / 10.43	142-145	50
8b	$C_{13}H_{15}ClN_2O_2S$	52.47 / 52.26	5.21 / 5.03	9.47 / 9.38	175-179	49
8c	$C_{12}H_{12}ClN_3O_3S$	45.47 / 45.93	3.71 / 3.83	13.17 / 13.40	205-208	54
8d	$C_{10}H_{11}ClN_2OS_2$	43.57 / 43.72	4.22 / 4.01	10.43 / 10.20	153-156	47

* Products **4a,c,g-i,** and **8a** were recrystallized from ethanol, **4b,e,j,k, 8b,d** were recrystallized from ethanol–pyridine, and **3, 4d,f, 6a-c,** and **8c** were recrystallized from pyridine.

The formation of isomers A and B is possible in the reaction of **1b** and **2a**.



A

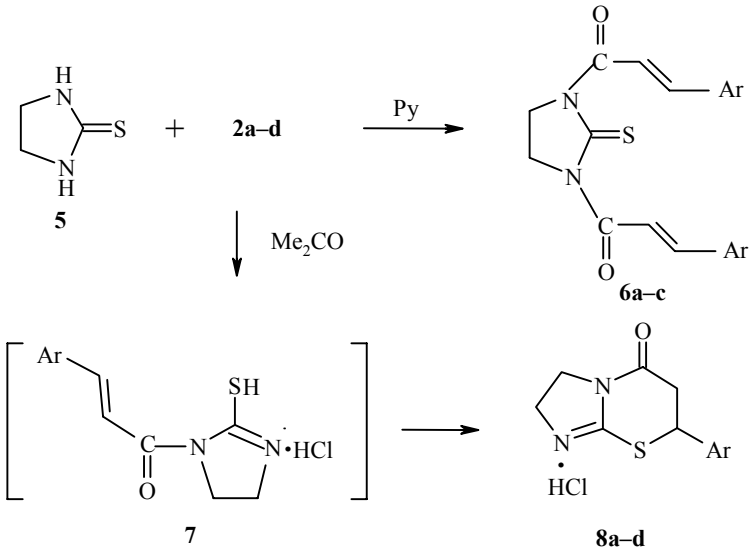


B

^{1}H NMR spectroscopy showed that **4k** is one of these isomers. Since the ethoxy group is a type-1 substituent, we should propose that the acylation should proceed predominantly at the nitrogen atom at position 5 to give isomer A. In order to clarify the isomer type of **4k**, we assigned the signals of 6-H and 9-H in the spectra of **4a** and **4k**. The signal for 6-H in **4a** affected by the amide group lies downfield at 8.16 ppm, while the signal for 9-H is at 7.42 ppm. The doublet for of 6-H in **4k** is at 7.99 ppm (J = 8.7 Hz), while the singlet for 9-H is at 7.13 ppm, which corresponds to structure A.

Experimentally, this is a single-step process though, in fact, it is a sequence of at least two reactions, namely, N-acylation and addition of the mercapto group at the double bond. It is unclear which of these reactions is primary and which secondary. Thus, we attempted to determine the probable scheme for this reaction. The reaction of **1a** with *o*-methoxycinnamoyl chloride **2g**, whose methoxy group sterically hinders heterocyclization, was selected for study. Product **3** (R = H) was isolated from the reaction mixture. Since signals of the double bond protons of this compound are at 7.72 and 7.94 ppm as in starting **2**, this compound is the product of N-acylation. The IR spectrum of this product has bands for both NH (3100-2900 cm^{-1}) and SH groups (2600-2450 cm^{-1}). Product **3** (R = H) probably exists as a mixture of thione and thiol forms, while the heterocyclization, in all likelihood, proceeds through the thiol form. Thus, we may assume that N-acylation is the primary reaction followed by conversion of the thione form into the thiol and reaction of the thiol group with the activated double bond to give the thiazine ring.

The direction of the reaction of cinnamoyl chloride and its derivatives with 2-mercaptoimidazoline **5** depends significantly on the nature of solvent used. Thus, only N-acylation products are formed in pyridine (analogously to the acylation of 2-mercaptoimidazoline by acetic anhydride [11]), while heterocyclization proceeds smoothly in acetone (probably through intermediate **7**) to give the acid chlorides of 7-aryl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-ones (**8a-d**):



2, 6, 8 a Ar = Ph, **b** Ar = 4-MeOC$_6$H$_4$, **c** Ar = 3-O$_2$NC$_6$H$_4$; **2**, **8 d** Ar = 2-thienyl

TABLE 2. ^{1}H NMR Spectral Data for **3, 4a-4k, 6a-6c,** and **8a-8d**

Com-pound	Chemical shifts, δ, ppm
3	3.94 (3H, s, CH_3O); 7.17-7.58 (7H, m, Ar); 7.72 (1H, d, Ar); 7.94 (1H, d, Ar); 8.22 (1H, d, Ar)
4a	3.14 (1H, m, H-3); 3.85 (1H, m, H-3); 5.40 (1H, m, CH-2); 7.35-7.60 (8H, m, Ar); 8.16 (1H, d, Ar)
4b	3.75 (3H, s, CH_3O); 3.85 (1H, m, H-3); 5.37 (1H, m, H-2); 7.00-7.52 (6H, m, Ar); 7.62 (1H, d, Ar); 8.17 (1H, d, Ar)
4c	3.43 (1H, m, H-3); 3.80 (1H, m, H-3); 5.41 (1H, m, H-2); 7.26-7.59 (7H, m, Ar); 8.16 (1H, d, Ar)
4d	3.55 (1H, m, H-3); 3.93 (1H, m, H-3); 5.59 (1H, m, H-2); 7.39-8.40 (8H, m, Ar)
4e	3.24 (1H, m, H-3); 3.73 (6H, d, $2CH_3O$); 3.85 (1H, m, H-3); 5.31 (1H, m, H-2) 6.99-7.36 (5H, m, Ar); 8.17 (1H, d, Ar); 8.18 (1H, d, Ar)
4f	3.67 (3H, s, CH_3O); 3.79 (6H, s, $2CH_3O$); 3.93 (1H, m, H-3); 5.31 (1H, m, H-2); 6.80 (2H, s, Ar), 7.38 (2H, m, Ar); 7.63 (1H, d, Ar); 8.18 (1H, d, Ar)
4g	3.42 (1H, m, H-3); 3.71 (1H, m, H-3); 3.91 (3H, s, CH_3O); 5.55 (1H, m, H-2); 7.02-7.57 (7H, m, Ar); 8.18 (1H, d, Ar)
4h	3.65 (2H, m, CH_2); 5.67 (1H, m, H-2); 7.03-7.65 (6H, m, Ar); 8.16 (1H, d, Ar)
4i	3.61 (2H, m, CH_2); 5.44 (1H, m, H-2); 6.46 (2H, s, Ar); 7.36-7.66 (4H, m, Ar); 8.19 (1H, d, Ar)
4j	3.17 (1H, m, H-3); 3.79 (1H, m, H-3); 5.33 (1H, m, H-2); 6.05 (2H, s, OCH_2O); 6.96-7.37 (5H, m, Ar); 7.60 (1H, d, Ar); 8.17 (1H, d, Ar)
4k	1.35 (3H, t, $\underline{CH_3}CH_2O$); 3.40 (1H, m, H-3); 3.78 (1H, m, H-3); 4.06 (2H, q, $CH_3\underline{CH_2}O$); 5.37 (1H, m, H-2); 6.90 (1H, d, Ar); 7.13 (1H, s, Ar); 7.31-7.60 (5H, m, Ar); 7.99 (1H, d, Ar)
6a	4.30 (4H, s, $2CH_2$); 7.47 (6H, m, Ph); 7.60 (2H, d, 2 =CH–CO–); 7.68 (4H, m, Ph); 8.08 (2H, d, 2Ar–CH=)
6b	3.80 (6H, s, $2CH_3O$); 4.38 (4H, s, $2CH_2$); 7.04 (4H, d, *p*-C_6H_4); 7.61 (6H, m, Ar); 7.98 (2H, d, 2Ar–CH=)
6c	4.11 (4H, s, $2CH_2$); 7.72-8.08 (8H, m, Ar); 8.27 (2H, d, *m*-$NO_2C_6H_4$); 8.49 (2H, s, *m*-$NO_2C_6H_4$)
8a	3.22 (1H, m, H-6); 3.41 (1H, m, H-6); 3.92-4.20 (4H, m, $2CH_2$); 5.29 (1H, m, H-7); 7.47 (5H, m, Ph); 8.05 (1H, br. s, NH)
8b	3.13 (1H, m, H-6); 3.53 (1H, m, H-6); 3.76 (3H, s, CH_3O); 3.81-4.20 (4H, m, $2CH_2$); 5.25 (1H, m, H-7); 7.17 (2H, d, *p*-C_6H_4); 7.44 (2H, d, *p*-C_6H_4); 8.10 (1H, br. s, NH)
8c	3.36 (1H, m, H-6); 3.58 (1H, m, H-6); 3.85-4.18 (4H, m, $2CH_2$); 5.47 (1H, m, H-7); 7.76 (1H, t, *m*-$NO_2C_6H_4$); 7.94 (1H, d, *m*-$NO_2C_6H_4$); 8.23 (1H, d, *m*-$NO_2C_6H_4$); 8.35 (1H, s, *m*-$NO_2C_6H_4$); 8.18 (1H, br. s, NH)
8d	3.32 (1H, m, H-6); 3.63 (1H, m, H-6); 3.67-4.13 (4H, m, $2CH_2$); 5.46 (1H, m, H-7); 7.04 (1H, t, Het); 7.16 (1H, d, Het); 7.59 (1H, d, Het); 8.15 (1H, br. s, NH)

Compounds **1a** and **5** can exist in both the thione and thiol forms. The difference in their reactivity may be attributed to the likelihood that **1a** exists significantly as the thiol, while the thione form is more characteristic for **5**. Furthermore, the content of the thiol form of **5** increases with increasing solvent polarity [12]. Thus, the heterocyclization of **5** to give **8** occurs only under conditions enhancing the content of the thiol form, which corresponds to the structure of salt **7**.

Therefore, the reactions of cinnamoyl chloride, its derivatives and heteroanalogs with **1a** and **5** are simimilar in nature and serve as a convenient method for the synthesis of 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones (**4a-k**) and hydrochloride salts of 7-aryl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-ones (**8a-d**). A scheme for heterocyclization has been proposed. The structures of these products were demonstrated using ^{1}H NMR and IR spectroscopy, and their composition was shown by elemental analysis.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian-300 spectrometer at 300 MHz in DMSO-d_6 with TMS as the internal standard. The IR spectra were obtained on Specord IR-75 spectrometer for KBr pellets.

1-[3-(2-Methoxyphenyl)acryloyl]benzimidazole-2-thiol (3). A solution of 3-(2-methoxyphenyl)-acryloyl chloride (**2g**) (1.96 g) in benzene (4 ml) was added to a solution of **1a** (1.6 g, 10 mmol) in pyridine (5 ml) at 20°C and stirred for 20 min. Then, water (30 ml) was added. The precipitate formed was filtered off, washed with ethanol, and dried. IR spectrum, ν, cm^{-1}: 3000 (NH), 2500 (SH), 1690 (C=O), 1600 (C=N), 1510 (NH–C=S).

2-Aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazole-4-thiones (4a-k) and 1,3-Di(3-arylacryloyl)imidazoline-2-thiones (6a-c). A solution of 3-arylacryloyl chloride **2** (10 mmol) in benzene (4 ml) was added to a solution of 2-mercapto derivative **1a, 1b,** or **5** (10 mmol) in pyridine (5 ml) and heated at reflux for 2 h (12 h for **4g**). The solution was cooled and water (30 ml) was added. The precipitate formed was filtered off, washed with ether, dried, and recrystallized from the solvent indicated in Table 1.

7-Aryl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazine-5-ones Hydrochlorides (8a-d). 3-arylacryloyl chloride **2** (10 mmol) was added to a mixture of 2-mercaptoimidazoline **5** (10 mmol) and acetone (20 ml), heated at reflux for 4 h, and cooled. The precipitate formed was filtered off, washed with acetone, and dried.

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