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Synthesis of 2-N-Acylamino-4-Arylthiazole-5-Acetic acids/ esters for Their Anti-inflammatory and Analgesic Activities

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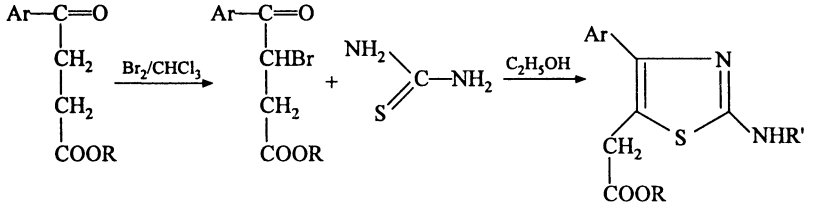
Condensation of thiourea with 3-bromo-3-aryl propionates yielded 2-amino-4-aryl thiazole-5-acetates (**3a–c**). The compounds (**3a–c**) were hydrolyzed to thiazole-5-acetic acids (**3d–f**). The esters (**3a–c**) and acids (**3d–f**) were subjected to acylation with acetic anhydride and succinic anhydride to give the title compounds (**4a–d** and **5a–f**). Arti-inflammatory and analgesic activities of some compounds have been evaluated.

Key Words: Synthesis, Thiazole acetic acids, Anti-inflammatory and Analgesic Activity.

Succinamic acid derivatives[1, 2] of aromatic amino acids are documented for their anti-inflammatory and analgesic activities. Some reports from our laboratories[3] and elsewhere[4–6] have shown that derivatives of thiazole acetic acids/esters are also associated with anti-inflammatory and analgesic activities. In continuation of these studies attention has been directed towards succinamic acid group linked to some substituted thiazole acetic acids/esters in an attempt to generate useful anti-inflammatory and analgesic agents. The synthesis of 2-N-acetylamino- and N-succinamic acid derivatives of 4-arylthiazole-5-acetic acids/esters and their associated anti-inflammatory and analgesic activities are reported **(Scheme 1)**



R = H | CH_3 | C_2H_5 (1) R = H | CH_3 | C_2H_5 (2) R′ = H, R = | CH_3 | C_2H_5 (3)
Ar = 2-thienyl, *p*-Cl, R′ = $COCH_3$, R = | CH_3 | C_2H_5 (4)
—C_6H_4, —C_6H_5 R′ = $COCH_2CH_2COOH$,
R = | CH_3 | C_2H_5 (5)

(Scheme 1)

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were run on Shimadzu FTIR spectrophotometer in KBr pellets. ^1H NMR and ^{13}C NMR were obtained using Jeol GSX-400 FT NMR 400 MHz in $CDCl_3$/DMSO-d_6 solvent using TMS as internal reference. Mass spectra were

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recorded by Jeol-JMS-300 spectrometer at 70 eV. The compounds were analyzed for C, H and N analyses and the values were found within ±0.4% of the calculated values. The Physical data of synthesized compounds are given in Table-1.

3-Benzoyl, 3-(4-chlorobenzoyl) and 3-(2-thienyl) propionic acids **(1a–c: R=H)** were prepared by Friedel Crafts acylation and were esterified using alcohol-sulphuric acid method to get respective propionates **(1a–c: R=Me/Et).**

Ethyl 3-bromo-3-(2-thienyl) propionate (2a: R=Et)

To a solution of ethyl 3-(2-thienyl) propionate **(1a: R=Et)** (2.12 g, 0.01 mol) in warm chloroform (20 mL), bromine (1.76 g, 0.011 mol) was added dropwise with stirring. After the addition, the reaction mixture was stirred for another 2 h. The reaction mixture was washed with water, dried over anhydrous sodium sulphate and the solvent removed to get the bromoester **(2a)** as a viscous oil which was used immediately as such for the next step.

Ethyl 4-(2-thienyl)-2-aminothiazole-5-acetate (3a)

A mixture of bromoester **(2a)** (2.9 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in ethanol (20 mL) was refluxed for 15 min. Therefore anhydrous sodium carbonate (0.25 g) was added and the reaction mixture was refluxed for 1 h. The precipitation of the base thiazole acetate **(3a)** occurred with addition of water; this was filtered, dried and crystallized from aqueous ethanol. Yield 72%, m.p. 119–120°C.

Other thiazole acetates **(3b–c)** were prepared similarly.

The formations of the compounds **(3a–c)** were confirmed by the m.p. R_f values, presence of important IR bands at 3392, 3305 ν(—NH_2) 1720 ν(C=O), 1645 ν(—C=N— and /or NH_2 def.), 1564, 1531 cm^{-1} ν(—C=C— aromatic), and ^1H NMR spectra as follows:

3a: 7.80–7.22 (m, 3H, arom), 6.43 (s, 2H, —NH_2), 4.16 (q, 2H, J 7.1 Hz, CH_2CH_3), 3.79 (s, 2H, CH_2), 1.27 (t, 3H, J = 7.1 Hz, CH_3).

3c: 7.53–7.29 (m, 5H, arom), 6.96 (s, 2H, NH_2), 3.74 (s, 2H, —CH_2—), 3.62 (s, 3H, —CH_3).

4-(2-Thienyl)-2-aminothiazole-5-acetic acid (3d)

A mixture of thiazoleacetate **(3a)** (2 g), 10% NaOH (10 mL) and ethanol (5 mL) was heated under reflux for 2 h, cooled to room temperature, filtered and by acidification precipitated the thiazole acid **(3d)**, which was filtered, washed with water, dried and crystallized from ethanol. Yield: 66%, m.p. 201–202°C.

The formation and purity of the thiazole acetic acids **(3d–f)** were confirmed by m.p., R_f values, IR peaks at 3420–3200 ν(—NH_2), 2900–2400 ν(hydrogen bonded COOH), 1680 ν(—COOH), 1640–1620 ν(—C=N— and/or NH_2 def.), 1600–1500 ν(Ar—C=C—), ^1H NMR and mass spectra as follows:

3f: 9.2–9.0 (br, 2H, —NH_2), 7.51 (m, 5H, arom), 3.62 (s, 2H, —CH_2).

3f: MS: m/z 234 (M^+, 36), 189 (76), 162 (8), 147 (100), 103 (26), 89 (6), 77 (23), 60 (7), 51 (7), 45 (15).

Ethyl 2-acetylamino-4-(2-thienyl)thiazole-5-acetate (4a)

Method A: A mixture of ethyl 4-(2-thienyl)-2-aminothiazole-5acetate **(3a)** (2 g) and acetic anhydride (10 mL) was heated under reflux for 1 h. The reaction

mixture was cooled and added to water. The separated solid was filtered, washed with water, dried and crystallized from aqueous ethanol to give ethyl 2-acetylamino-4-(2-thienyl) thiazole-5-acetate (**7a**). Yield 68%, m.p. 145–146°C.

Method B: To a mixture of ethyl 4-(2-thienyl)-2-aminothiazole-5-acetate (**3a**) (2 g) suspended in dioxane (8 mL), acetic anhydride (2 mL) was added and heated under reflux for 1 h, worked up as above. Yield 75%, m.p. 145–146°C.

TABLE-1
PHYSICAL DATA AND PHARMACOLOGICAL ACTIVITY OF ACYLAMINOTHIAZOLES

S. No.	Compd. No.	Substituents		Yield (%)	m.p. (°C)	% A.A.	% Analgesic activity
		Ar	R				
1.	**3a**	2-thienyl	C_2H_5	72	119–120	55.0	46.0
2.	**3b**	*p*-Cl C_6H_4	CH_3	70	157	46.4	41.5
3.	**3c**	C_6H_5	CH_3	83	157–158	37.0	36.0
4.	**3d**	2-thienyl	H	66	201–202	60.0	NS
5.	**3e**	*p*-ClC_6H_4	H	68	221–223	NS	NS
6.	**3f**	C_6H_5	H	61	214–215	NS	NS
7.	**4a**	2-thienyl	C_2H_5	78	145–146	49.2	NS
8.	**4b**	*p*-ClC_6H_4	CH_3	60	171–173	41.0	34.0
9.	**4c**	C_6H_5	CH_3	78	165–166	NS	26.0
10.	**4d**	C_6H_5	H	70	255–256	NS	NS
11.	**5a**	2-thienyl	C_2H_5	74	196–197	64	51.3
12.	**5b**	2-thienyl	H	63	250–252	NS	NS
13.	**5c**	*p*-ClC_6H_4	CH_3	74	210–211	48	45.7
14.	**5d**	*p*-ClC_6H_4	H	65	>255	NS	NS
15.	**5e**	C_6H_5	CH_3	80	195–197	46	39.0
16.	**5f**	C_6H_5	H	65	>255	NS	NS
17.	**Std.**	Ibuprofen	—	—	—	75	—
18.	**Std.**	Aspirin	—	—	—	—	54.0

AA: Anti-inflammatory activity. NS: Not screened.

Other acetyl derivatives (**4b–d**) reported in Table-1 were prepared in the same manner. The formation and purity of the acetyl derivatives (**4a–d**) were confirmed by m.p. R_f values, important IR peaks at 3226 ν(—N—H—), 3062 ν(—C—H—), 1732 ν(C=O ester and —$COCH_3$), ν(—C=N—), 1558, 1421 ν(Ar—C=C—) and ^1H NMR as follows,

4a: 1.3 (t, 3H, —CH_2CH_3), 1.98 (s, 3H, CH_3), 3.9 (s, 2H, CH_2), 4.2 (q, 2H, CH_2CH_3), 7.1–7.4 (m, 3H, arom), 10.6 (br, 1H, —NH—).

4b: 2.15 (s, 3H, CH_3), 3.7 (s, 2H, CH_2), 7.2–7.6 (m, 4H, arom), 11.8–12.0 (br, 2H, —NH— and COOH).

4d: MS: m/z 276 (M^+, 54), 254 (12), 234 (100), 216 (8), 189 (92), 162 (7), 147 (66), 135 (18), 93 (13), 77 (16), 51 (5).

Ethyl 2-succininoylamino-4-(2-thienyl) thiazole-5-acetate (5a)

A mixture of ethyl 4-(2-thienyl) thiazole-5-acetate (**3a**) (2.44 g, 0.01 mol) and succinic anhydride (1.0 g, 0.01 mol) in dioxane (10 mL) was refluxed for 3 h,

cooled and poured into water. The solid which separted was filtered, dried and crystallized from ethanol to give ethyl 2-succninoylamino-4-(2-thienyl) thiazole-5-acetate **(5a).** Yield: 74% m.p. 196–197°C.

Other 2-succininoylaminothiazoles **(5b–f)** were similarly prepared from corresponding esters and acids. The formations of these compounds were confirmed by the difference in m.p., R_f values and IR peaks at 3267 ν(—N—H—), 3300–3000 ν(COOH), 1733 and 1685 ν(>C=O), 1591, 1552 cm^{-1} ν(Ar—C=C—) and ^1H NMR, ^{13}C NMR and mass spectra of compound acetate **5a.**

^1H NMR (DMSO-d_6): 1.2 (t, 2H, CH_2CH_3), 2.6 (t, 4H, 2 × CH_2), 4.05 (s, 2H, CH_2), 4.1 (q, 3H, Ar-H-3), 7.56 (1H, d, Ar-H-5), 12.2–12.35 (2H, br, NH & COOH).

^{13}C NMR (DMSO-d_6): 152.8 (C-2); 140.1 (C-4); 116.4 (C-5); 170.6 (C-7); 60.8 (C-8); 14.0 (C-9); 169.8 (C-10); 28.4 (C-11); 29.8 (C-12); 173.4 (C-13); 137.7 (C-2′); 127.9 (C-3′); 126.1 (C-4′); 124.8 (C-5′).

5a: MS: m/z 368 (M^+, 3), 350 (36), 277 (71), 268 (17), 195 (100), 168 (12), 153 (2), 139 (4), 109 (19), 69 (6), 55 (15).

5e: MS: m/z 349 (M^{+1}, 1), 330 (0.5), 313 (1), 271 (1), 262 (1), 189 (1.5), 147 (3), 111 (2.5), 97 (6), 85 (5), 81 (7), 77 (2), 69 (12), 54 (33), 44 (100), 43 (50).

Pharmacological Studies: The newly synthesized compounds were screened for anti-inflammatory activity by carrageenan induced rat hind paw oedema method[7] using ibuprofen as standard and analgesic activity by acetic acid induced writhing method in mice[8] against aspirin as positive control. All the tested compounds are significantly active. Introduction of chloro group in the *para* position of 4-phenyl group increased the anti-inflammatory and analgesic activities. Replacement of phenyl group by thienyl group further increased the activity. N-succinylamino derivatives are more active than the amino thiazole acetic acids/esters, but acetylation of amino group reduced the activity (Table-1).

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