SYNTHESIS OF NOVEL 5-METHYLINDENO[2,1-e][1,3]THIAZOLO[3,2-a]PYRIMIDINE-1,6(2H,10bH)-DIONES

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Abstract
Treatment of ethyl 5-aryl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **1(a-h)**, with aluminum chloride and acetyl chloride in nitrobenzene gave the corresponding 5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione derivatives **2(a-h)**. Yields of the products, after recrystallizing with acetic acid, were of the order of 46-67%. ^{1}H-NMR and ^{13}C-NMR spectroscopy, and elemental analysis were used for identification of these compounds.

Keywords: Pyrimidine, Indeno, Dione , Thiazolo

Introduction
The pyrimidine nucleus is embedded in a large number of compounds with broad diverse pharmacological activities such as antitumo (1), antiviral (2), anticancer (3), anti-inflammatory (3), antifolate (4), antimicrobial (5), antifungal (6) and antiproliferative (7) activities. Over the past decade many pyrimidines with appropriate functional groups have emerged as antihypertensive agents (8-11) and potent calcium channel blockers (12-13). Furthermore, several marine alkaloids containing the dihydropyrimidine core have been used to inhibit the binding HIV gp-120 to CD4 cells (9). Although there are several modified preparative methods for the preparation of simple pyrimidines which known as Biginelli compounds (14-19), due to incessant interest in this field, substantial attention should be paid to synthesis novel fused pyrimidine derivatives. In view of these reports and continuation of our interest in the synthesis of pyrimidines (20-28), we wish to report the synthesis of some novel fused pyrimidines using an oxidizing reagent.

Experimental
All used chemicals were prepared from Merck or Fluka Company. Melting points were determined on an electrothermal digital melting point apparatus. Microanalyses were performed by the Microanalytical Lab at the Arak petrochemical company. The results were agreed favorably with the calculated values. NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referenced to the internal standards tetramethylsilane (TMS). Reactions were monitored by thin layer chromatography. Starting pyrimidine compounds **1(a-h)** were prepared using the literature procedures (27).

General procedure for the synthesis of 2
To a solution of **1** (0.001 mol) in 4 mL nitrobenzene, aluminum trichloride (0.6 g) and acetyl chloride (0.007 mol, 0.5 ml) was added. The mixture was heated under stirring for 9-12 h. The solution was then poured into 30 ml ice-water

containing 2 ml concentrated hydrochloric acid and 10 ml ligroin. The mixture was stirred for 2 h and filtered. The precipitate was recrystallized twice with acetic acid.

5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2a)
Yield 62%, mp 204-205 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.31 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 5.91 (s, 1H, CH), 7.25-7.50 (m, 4H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 20.2, 31.3, 50.3, 121.2, 128.1, 128.7, 129, 131.1, 135.4, 145.3, 155.4, 164.2, 171.8, 186.1. Anal cald for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36%. Found: C, 62.46; H, 3.61; N, 10.45%.

5,8-Dimethylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2b)
Yield 67%, mp 223-224 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.30 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 5.81 (s, 1H. CH), 7.45-7.68 (m, 3H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 21, 24.3, 30.8, 53.4, 127, 128.1, 128.8, 130.4, 134.6, 134.8, 144.5, 155.8, 165, 172.1, 186.6. Anal cald for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85%. Found: C, 63.51; H, 4.20; N, 10.06%.

8-Bromo-5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2c)
Yield 58%, mp 248-249 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.37 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 5.96 (s, 1H, CH), 7.55-1.74 (m, 3H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 21.3, 31, 53.1, 125.6, 128, 129.4, 131.3, 134.2, 139.2, 146.3, 156.1, 164.1, 171.1, 187.2.Anal cald for $C_{14}H_9BrN_2O_2S$: C, 48.15; H, 2.60; N, 8.02%. Found: C, 47.89; H, 2.78; N, 8.22%.

8-Chloro-5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2d)
Yield 50%, mp 215-216 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.36 (s, 3H, CH_3),3.92 (s,2H, CH_2), 5.94 (s, 1H, CH), 7.59-7.78 (m, 3H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 21.1, 30.8, 51.6, 125.2, 127.3, 129.8, 130.5, 135.5, 140, 145.7, 155.4, 164.9, 171.6, 186.4. Anal cald for $C_{14}H_9ClN_2O_2S$: C, 55.18; H, 2.98; N, 9.19%. Found: C, 55.02; H, 3.17; N, 9.01%.

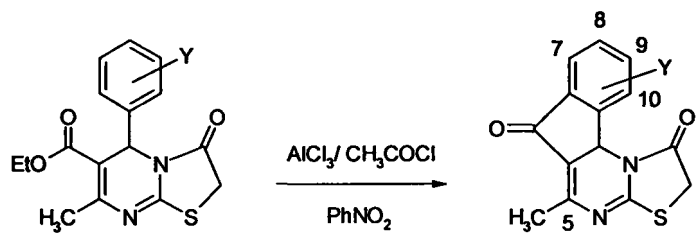
8-Fluoro-5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2e)
Yield 49%, mp 241-242 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.40 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 5.97 (s, 1H, CH), 7.62-7.82 (m, 4H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 21.8, 31.2, 53.4, 123.8, 124.3, 128.2, 130, 132.4, 147.1, 150.4, 155.8, 165.1, 172, 185.9. Anal cald for $C_{14}H_9FN_2O_2S$: C, 58.28; H, 3.12; N, 9.71%. Found: C, 58.05; H, 3.22; N, 9.52%.

9-Chloro-5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2f)
Yield 56%, mp 219-220 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.35 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 5.80 (s, 1H, CH), 7.74-7.92 (m, 3H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 20.9, 31.3, 53.2, 125.1, 127.2, 128.2, 131.6, 134.3, 138.9, 145.3, 154.9, 165.1, 171.8, 185.6. Anal cald for $C_{14}H_9ClN_2O_2S$: C, 55.18; H, 2.98; N, 9.19%. Found: C, 55.34; H, 3.24; N, 9.28%.

5-Methyl-10-nitroindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2g)
Yield 46%, mp 257-258 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.34 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 5.82 (s, 1H, CH), 7.52-7.65 (m, 3H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 20.7, 31.2, 52.2, 125.1, 127.7, 128.9, 129.2, 136.4, 139, 145.1, 156.2, 164.8, 171.9, 185.8. Anal cald for $C_{14}H_9N_3O_4S$: C, 53.33; H, 2.88; N, 13.33%. Found: C, 53.25; H, 2.96; N, 13.43%.

5-Methyl-9-nitroindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione (2h)
Yield 60%, mp 229-230 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.31 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 5.84 (s, 1H, CH), 7.74-7.90 (s, 3H, H_{arom}). ^{13}C-NMR (DMSO-d_6): δ (ppm) = 21.8, 31.1, 53.8, 124.8, 126.1, 127.6, 130, 131.2, 135.2, 147.6, 155.2, 164.6, 172.1, 186.6. Anal cald for $C_{14}H_9N_3O_4S$: C, 53.33; H, 2.88; N, 13.33%. Found: C, 53.58; H, 2.85; N, 13.54%.

Results and Discussion
Compounds **2(a-h)** were synthesized via an intramolecular Friedel-Crafts acylation of corresponding pyrimidine compound in the presence of $AlCl_3$ and acetyl chloride (28, 29) as shown in **Scheme 1**.



1 **2**

1a) Y= H **1e)** Y= 4-F
1b) Y= 4-CH_3 **1f)** Y=3-Cl
1c) Y= 4-Br **1g)** Y= 2-NO_2
1d) Y= 4-Cl **1h)** Y= 3-NO_2

Scheme 1

The Lewis acid, $AlCl_3$, is used as a catalyst in this reaction to produce acilium ion as electrophilic species. The intramolecular electorphilic reaction of these acilium ions with phenyl ring produce desired compounds. However the role of acetyl chloride in this reaction is unknown. It has been reported that the presence of an excess of acetyl chloride increases the yield of the product. This may be due to an interaction between OEt group and acetyl chloride which makes it as a better leaving group. The NMR spectra and elemental analysis data of all synthesized compounds are consistent with the expected structures. For example the ^{1}H NMR spectrum of **2a** shows three singlets at 2.31, 3.88, 5.91 ppm, which attributed to the resonance of the methyl group, thiazole and pyrimidine ring protons respectively. Four aromatic protons are appeared as multiplet at 7.25-7.50 ppm. These signals are shifted downfield with respect to those of starting material due to lose of the electron releasing OEt group. Also the absence of the ^{1}H- NMR signals related to the OEt group resonance is a good support to the expected reaction.

Conclusion
Some novel 5-Methylindeno[2,1-e][1,3]thiazolo[3,2-a]pyrimidine-1,6(2H,10bH)-dione derivatives were synthesized via an intramolecular Friedel-Crafts reaction between phenyl ring and the ester group under mild conditions. The Lewis acid, $AlCl_3$, was used as a catalyst in this reaction to produce the acilium ion.

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