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One-pot synthesis of novel 2-arylnaphtho[2',3':4,5] thieno[2,3-*d*][1,3]pyrimidine-4,5,10(3*H*)-triones

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ABSTRACT

The synthesis of new 2-arylnaphtho[2',3':4,5]thieno[2,3-d][1,3]pyrimidine-4,5,10(3H)-triones was carried out by the interaction of 2-aryl-4H-naphtho[2',3':4,5]thieno[2,3-d][1,3]oxazine-4,5,10-triones and ammonia in ethanol with the subsequent alkaline hydrolysis as one-pot reaction.

Keywords: 2-aryl-4H-naphtho[2',3':4,5]thieno[2,3-d][1,3]oxazine-4,5,10-triones, 2-arylnaphtho [2',3':4,5] thieno [2,3-d][1,3]pyrimidine-4,5,10(3H)-triones, ammonium hydroxide, alkaline hydrolysis.

INTRODUCTION

The chemistry of pyrimidines and its derivatives has been studied for over a century due to their diverse biological activities. Pyrimidine derivatives as purine analogs exhibit a variety of biological activities [1-7]. They possess antibacterial, antiviral, antitumor and anti-inflammatory [8] activities. Recently, 3,4-dihydropyrimidine-2(1H)-ones have attracted great attention of synthetic organic chemists due to their anti-hypertensive activities as well behaving as calcium channel blockers, α-1a-antagonists and neuropeptides-Y antagonists [9-11]. Thienopyrimidines, formed by the fusion of thiophene moiety with pyrimidine ring, have been reported to be chemotherapeutically more active [8]. Though many synthetic strategies [12-14] have been reported for the preparation of thiopheno-pyrimidine derivatives, most of them include use of expensive, commercially non-available or hazardous reagents, drastic reaction conditions, longer reaction time and difficult work-up. From other side, 1,4-naphthoquinone structure is common in various natural products and is associated with biological activities including enzyme inhibition and antifungal, antibacterial, anticancer, anti-proliferative, antiplatelet, anti-inflammatory, antiallergic, and antimalarial activities [15]. Taking into account expressed biological properties of 1,4-naphthoquinone, thiophene and pyrimidines derivatives, it seems appropriate to design hybrid structures, which include naphthoquinonic and thiopheno-pyrimidine cycles.

EXPERIMENTAL SECTION

All the chemicals used for the synthesis of the compounds were purchased from Aldrich, Merck AG and Acros Chemicals. Melting points of the compounds were recorded on an electrothermal-9200 digital melting points apparatus and are uncorrected. NMR spectra ^{1}H and ^{13}C are recorded on the device Varian Mercury-400 (400 and 100 MHz respectively) under 25^{o}C in the solution DMSO-d_6 (dimethylsulfoxide), internal standard TMS

(tetramethylsilane). IR-spectra are obtained on spectrophotometer Specord M80 in KBr tablets. Reaction path was controlled by TLC (thin layer chromatography) method on UV-254 plates in the system of eluents Benzene-Acetonitrile, 10:1. Element analysis was carried out on the analyzer Thermo Finnigan Flash EA 1112.

2-Arylnaphtho[2',3':4,5]thieno[2,3-d]pyrimidine-4,5,10(3*H*)-triones (General procedure). Mixture of **1 a-d** (5 mmol) in 20 ml of ethanol with 10 ml of concentrated ammonium hydroxide was suspended, heated for 2 h and evaporated in vacuum. The residue was boiled for 30 min with 5 % water solution of KOH. Then the reaction mixture was acidified and filtered. The residue was crystallized from ethanol.

2-(4-Chlorophenyl)naphtho[2',3':4,5]thieno[2,3-d]pyrimidine-4,5,10(3*H*)-trione 2a. Yield 78%, mp >250 ^{o}C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.40 (1H, s, NH); 8.27-7.99 (2H, m, CH_{Ar}), 7.77-7.66 (2H, m, CH Ar); 7.51-7.53 (2H, m, CH Ar); 7.37-7.39 (2H, m, CH Ar). ^{13}C NMR spectrum, δ, ppm: 179.79, 177.12, 165.85, 158.15, 151.19, 139.20, 136.40, 134.13, 133.83, 133.39, 133.15, 131.26, 129.66, 129.43, 128.49, 127.90, 127.28, 126.21. IR spectra, ν, см$^{-1}$: 3128 (NH); 1687, 1673, 1667 (C=O). Found, %: C 61.20; H 2.42; N 7.29; S 8.28; Cl 9.10. $C_{20}H_9N_2SO_3Cl$. Calculated, %: C 61.15; H 2.31; N 7.13; S 8.16; Cl 9.03.

2-(4-*p*-Tolyl)naphtho[2',3':4,5]thieno[2,3-d]pyrimidine-4,5,10(3*H*)-trione 2b. Yield 72%, mp >250 ^{o}C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.41 (1H, s, NH); 8.25-7.99 (2H, m, CH_{Ar}), 7.90-7.68 (4H, m, CH_{Ar}); 7.21-7.24 (2H, m, CH_{Ar}); 2.05 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 179.72, 177.17, 165.78, 159.60, 151.23, 141.50, 139.22, 134.17, 133.76, 133.05, 131.91, 131.32, 129.43, 129.38, 129.38, 127.94, 127.94, 127.91, 127.21, 126.19, 21.33. IR spectra, ν, см$^{-1}$: 3129 (NH); 1688, 1678, 1663 (C=O). Found, %: C 67.83; H 3.31; N 7.39; S 8.69. $C_{21}H_{12}N_2SO_3$. Calculated, %: C 67.73; H 3.25; N 7.52; S 8.61.

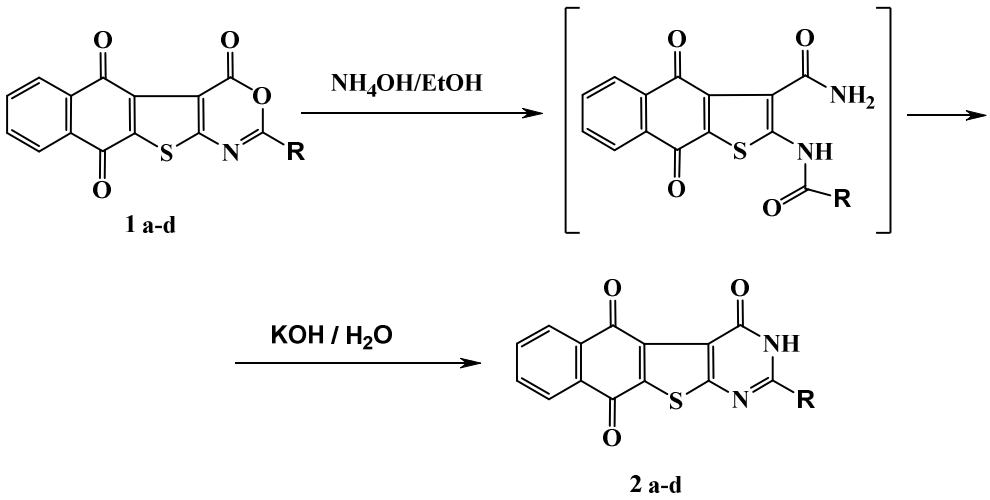
2-(4-Nitrophenyl)naphtho[2',3':4,5]thieno[2,3-d]pyrimidine-4,5,10(3*H*)-trione 2c. Yield 79%, mp >250 ^{o}C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.39 (1H, s, NH); 8.25-7.99 (6H, m, CH_{Ar}), 7.78-7.68 (2H, m, CH_{Ar}). ^{13}C NMR spectrum, δ, ppm: 179.76, 177.08, 165.89, 159.31, 151.15, 150.80, 140.93, 139.23, 134.11, 133.79, 133.15, 131.26, 129.54, 129.36, 127.94, 127.28, 126.26, 123.78. IR spectra, ν, см$^{-1}$: 3124 (NH); 1689, 1678, 1663 (C=O). Found, %: C 65.59; H 2.45; N 10.52; S 8.05. $C_{20}H_9N_3SO_5$. Calculated, %: C 59.55; H 2.25; N 10.42; S 7.95

2-Phenylnaphtho[2',3':4,5]thieno[2,3-d]pyrimidine-4,5,10(3*H*)-trione 2d. Yield 82%, mp >250 ^{o}C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.41 (1H, s, NH); 8.27-7.99(2H, m, CH_{Ar}); 7.77-7.66 (2H, m, CH_{Ar}); 7.42-7.50 (5H, m, CH_{Ar}). ^{13}C NMR spectrum, δ, ppm: 177.48, 176.92, 162.81, 161.76, 149.42, 139.71, 135.92, 133.65, 132.93, 132.88, 130.66, 130.59, 128.79, 128.63, 127.78, 127.60, 127.10, 126.20. IR spectra, ν, см$^{-1}$: 3131 (NH); 1688, 1681, 1665 (C=O). Found, %: C 67.12; H 2.84; N 7.96; S 9.01. $C_{20}H_{10}N_2SO_3$. Calculated, %: C 67.03; H 2.81; N 7.82; S 8.95.

RESULTS AND DISCUSSION

In this work, some novel 2-arylnaphtho[2',3':4,5]thieno[2,3-d][1,3]pyrimidine-4,5,10(3*H*)- triones **2 a-d** are synthesized from previously described 2-aryl-4*H*-naphtho[2',3':4,5]thieno[2,3-*d*][1,3]oxazine-4,5,10-triones **1 a-d** [14] using one-pot synthesis (Scheme 1).

Obtain of pyrimidinetriones **2 a-d** was carried out by the interaction of oxazines **1 a-d** and alcohol solution of ammonium hydroxide at 78-80 ^{o}C (without isolation of intermediate compounds) with the subsequent alkaline hydrolysis by 5% solution KOH during 1 h. Yields of products are 72-82%. Structures of obtained 2-arylnaphtho[2',3':4,5]thieno[2,3-d][1,3]pyrimidine-4,5,10(3*H*)-triones **2 a-d** were confirmed by data of ^{1}H and ^{13}C NMR spectra, IR and element analysis. In the ^{1}H NMR spectra of compounds **2 a-d** along with the signals of aromatic protons, singlets of NH-group of pyrimidine cycle are present at 10.39-10.41 ppm. In the IR spectra of the synthesized compounds are present characteristic absorption bands of three carbonyl groups of naphthoquinone and pyrimidineone fragments within the 1663–1689 cm^{-1} and the ones for the NH group of pyrimidine cycle at 3124–3131 cm^{-1} are present.



R= *p*-ClC$_6$H$_4$-(a); *p*-CH$_3$C$_6$H$_4$-(b); *p*-NO$_2$C$_6$H$_4$-(c); Ph-(d)

Scheme 1

CONCLUSION

Therefore, new 2-arylnaphtho[2',3':4,5]thieno[2,3-d][1,3]pyrimidine-4,5,10(3H)-triones was obtained as one-pot reaction by the interaction of 2-aryl-4H-naphtho[2',3':4,5]thieno[2,3-d][1,3]oxazine-4,5,10-triones and ammonia in ethanol with the subsequent alkaline hydrolysis.

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