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Synthesis and antibacterial evaluation of new pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hybrids linked to different heteroarene units

Sherif M. H. Sanad* and Ahmed E. M. Mekky

Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt.
E-mail: sherif_hamed1980@yahoo.com

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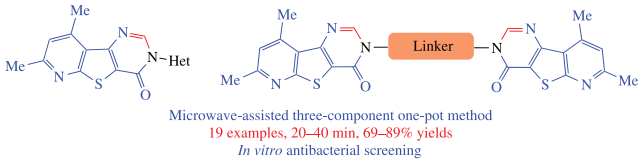
A three-component protocol involving the reaction of 3-aminothieno[2,3-*b*]pyridine-2-carboxylate, $Me_2NCH(OMe)_2$ and heteroaryl (bis)amines in dioxane under microwave irradiation yielded a new series of pyrimidinones. The target hybrids were formed by an initial formamidine formation, followed by cross-imidination and [5+1] heterocyclization. Pyrazole-linked pyrimidinones displayed the best antibacterial activity against all the gram-positive and negative strains tested.



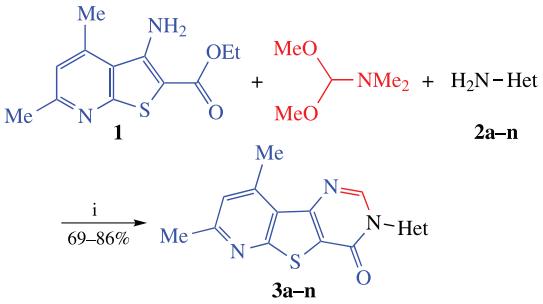
Keywords: cross-imidination, formamidines, [5+1] heterocyclization, *in vitro* antibacterial screening, microwave-assisted reactions, multicomponent reactions, pyrimidinones, tandem reactions, thieno[2,3-*b*]pyridines.

One of the remarkable tasks for researchers is the rapid synthesis of heterocyclic hybrids with promising medicinal effectiveness.[1] Multi-component reactions have been developed in recent years as effective procedures for synthesis of diverse heterocyclic hybrids.[2] Such an approach provides simplicity, shorter time of reaction and reducing the production of by-products with the formation of diverse 'drug-like' hybrids.[3]

Several attempts have recently been made to examine the medicinal applications of pyrimidinone hybrids. The prior hybrids displayed potent anticancer,[4] antioxidant,[5] anti-hypertensive,[6] antiviral,[7] antidiabetic,[8] anti-inflammatory,[9] antibacterial,[10] and antimalarial activities.[11] Pyrimidine hybrids with related fused thienopyridine units are considered as fluorene analogues with hetero-subunits.[12,13] They exhibited promising inhibitory efficacy of mGluR1,[14] and phosphodiesterase IV.[15] Also, they act as potent antimicrobial,[16] anticancer,[17] and antitumor agents.[18] Owing to the wide spectrum of biological applications of the prior hybrids, several publications reported their synthesis.[19–22] Bohm *et al.*[23] reported the synthesis of pyrimidinone derivatives utilizing 3-aminothieno[2,3-*b*]-pyridine-2-carboxylate **1**[24] through a three-step procedure. The authors suggested alkaline hydrolysis of ester **1** followed by acid anhydride cyclocondensation to give oxazinones that then reacted with primary amines.

In this work, we aimed to prepare the target pyrimidinone hybrids linked to different heteroarene units utilizing a three-component one-pot procedure. For this purpose, a ternary equimolar mixture of ester **1**, $Me_2NCH(OMe)_2$ and aminopyrazole **2a** was subjected to microwave irradiation to afford the corresponding pyrimidinone hybrid **3a** as a sole product (Scheme 1). The reaction conditions were optimized using different solvents, temperature and reaction time, taking the synthesis of **3a** as a typical example (see Online Supplementary Materials), the best conditions having comprised 110 °C for 30 min. The reaction may begin with the formation of either of two formamidine intermediates, which are formed by the condensation of $Me_2NCH(OMe)_2$ with substrate **1** or **2a**, respectively.[25] Each corresponding formamidine intermediate was then combined with the amino group of the other substrate. Both pathways produce the same intermediate, which is then cyclocondensed to yield the desired product **3a** (for mechanistic details, see Online Supplementary Materials).

Using ester **1**, $Me_2NCH(OMe)_2$ and several aminopyrazoles **2b–g**, aminothiazoles **2h–l** and benzo-fused heteroaryl amines **2m**,**n** in dioxane under the optimized conditions, the feasibility of the above one-pot protocol has been established. In each case,



2a–l, **3a–l**

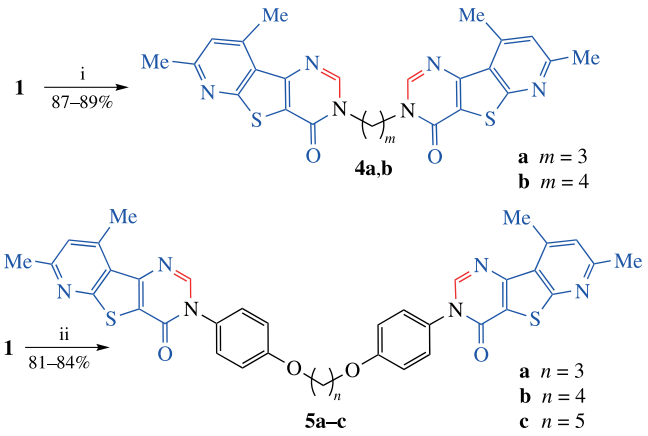
Het =

m Het =

n Het =

a X = CH, Y = NH, Z = N, R = Me
b X = CPh, Y = NH, Z = N, R = Me
c X = CH, Y = NH, Z = N, R = Ph
d X = CH, Y = NH, Z = N, R = 4-ClC_6H_4
e X = CH, Y = NH, Z = N, R = 4-MeC_6H_4
f X = CH, Y = NH, Z = N, R = 4-$MeOC_6H_4$
g X = CH, Y = NH, Z = N, R = 4-$O_2NC_6H_4$
h X = N, Y = S, Z = CH, R = Ph
i X = N, Y = S, Z = CH, R = 4-ClC_6H_4
j X = N, Y = S, Z = CH, R = 4-MeC_6H_4
k X = N, Y = S, Z = CH, R = 4-$MeOC_6H_4$
l X = N, Y = S, Z = CH, R = 4-$O_2NC_6H_4$

Scheme 1 *Reagents and conditions*: i, dioxane, MW (300 W), 110 °C, 30–40 min.



Scheme 2 *Reagents and conditions*: i, $H_2N(CH_2)_mNH_2$, $Me_2NCH(OMe)_2$, dioxane, MW (300 W), 110 °C, 20 min; ii, 4-$H_2NC_6H_4O(CH_2)_nOC_6H_4NH_2$-4, $Me_2NCH(OMe)_2$, dioxane, MW (300 W), 110 °C, 40 min.

the reaction afforded a sole product in good to excellent yields that were assigned as pyrimidinone hybrids **3b–n** (see Scheme 1).

We extended our study to synthesize new bis(pyrimidinone) hybrids **4a**,**b** linked to aliphatic cores by employing bis(amines) in the same protocol, the reaction having required 20 min (Scheme 2). Similarly, we adopted the synthesis of bis(pyrimidinone) hybrids **5a–c** linked to aliphatic cores *via* phenoxy linkage using the appropriate bis(anilines); in this case the reaction was complete in 40 min.

The *in vitro* antibacterial activity of the new pyrimidinones was examined against Gram-positive bacteria such as *Staphylococcus aureus* (ATCC:6538), *Streptococcus mutans,* (ATCC:25175) and *Enterococcus faecalis* (ATCC:29212), as well as Gram-negative bacteria such as *Escherichia coli* (ATCC:9637), *Pseudomonas aeruginosa* (ATCC:27953) and *Klebsiella pneumoniae* (ATCC:10031). To evaluate the MIC values of new pyrimidinones, the microbroth serial dilution method was used with Ciprofloxacin as a reference (MIC of 2.7 μM against all the tested strains).[26,27] The values of MIC of the new pyrimidinones are given in Table 1.

Table 1 Minimum inhibitory concentration of new hybrids.

Compound	MIC/μM					
	S. aureus	*S. mutans*	*E. faecalis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
3a	12.5	200.7	25.0	25.0	200.7	25.0
3b	10.0	80.6	10.0	10.0	80.6	10.0
3c	5.2	83.6	10.4	10.4	83.6	5.2
3d	4.7	76.6	4.7	4.7	76.6	4.7
3e	2.5	40.3	2.5	2.5	40.3	2.5
3f	2.4	38.7	2.4	2.4	38.7	2.4
3g	9.3	149.3	18.6	18.6	149.3	18.6
3h	83.5	>300	83.5	167.0	>300	167.0
3i	73.5	>300	73.5	147.0	>300	147.0
3j	38.6	>300	77.2	77.2	>300	38.6
3k	37.1	>300	74.3	74.3	>300	37.1
3l	143.5	>300	143.5	287.5	>300	287.5
3m	171.5	>300	171.5	>300	>300	>300
3n	22.4	>300	44.8	22.4	>300	22.4
4a	>300	>300	>300	>300	>300	>300
4b	>300	>300	>300	>300	>300	>300
5a	>300	>300	>300	>300	>300	>300
5b	>300	>300	>300	>300	>300	>300
5c	>300	>300	>300	>300	>300	>300
Ciprofloxacin	2.7	2.7	2.7	2.7	2.7	2.7

Regarding the *S. aureus*, *E. faecalis*, *E. coli* and *K. pneumoniae* bacterial strains, pyrazole-linked pyrimidinone hybrids **3a–g** displayed the best antibacterial activity. Hybrids **3e**,**f** showed MIC values of 2.4–2.5 μM, which exceed Ciprofloxacin. Hybrid **3d** was the second-best antibacterial agent with MIC value of 4.7 μM against these four strains. Additionally, hybrids **3b** and **3c** exhibited reduced antibacterial activity with MIC values ranging from 5.2 to 10.4 μM. Among the pyrazole-linked hybrids, compounds **3a** and **3g** showed the least antibacterial activity with MIC values ranging from 9.3 to 25.0 μM. In general, pyrimidinone hybrids **3h–n** linked to thiazole or benzo-fused units showed reduced antibacterial activity when compared to those hybrids linked to pyrazole units. Thus, hybrids **3j**,**k**,**n** exhibited MIC values in the range of 22.4 to 77.2 μM, while other thiazole or benzothiazole-linked hybrids **3h**,**i**,**l**,**m** displayed MIC values ranging from 73.5 to more than 300 μM. Furthermore, bis(pyrimidinone) hybrids **4** and **5** showed fair antibacterial activity with MIC values more than 300 μM.

Despite the fact that all of the hybrids tested showed reduced antibacterial activity against *S. mutans* and *P. aeruginosa* bacterial strains, pyrazole-linked pyrimidinone hybrids **3a–g** demonstrated the best antibacterial activity. Hybrids **3e**,**f** showed MIC values of 38.7–40.3 μM, while other pyrazole-linked hybrids demonstrated MIC values ranging from 76.6 to 200.7 μM. Other pyrimidinones **3h–n** as well as bis(pyrimidinones) **4** and **5** exhibited fair antibacterial activity with MIC values more than 300 μM.

To summarize, we designed an efficient three-component one-pot method for the synthesis of mono- and bis(pyrimidinones). The protocol involved the reaction of thieno[2,3-*b*]pyridine, $Me_2NCH(OMe)_2$ and the appropriate heteroaryl amine or bis(amine) in dioxane under microwave irradiation at 110 °C. In general, the tested hybrids showed enhanced antibacterial efficacies against the *S. aureus*, *E. faecalis*, *E. coli* and *K. pneumoniae* bacterial strains. Pyrazole-linked pyrimidinone hybrids displayed the best antibacterial activity against all the strains tested.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.031.

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