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Design and an efficient synthesis of new thiorotenone derivatives

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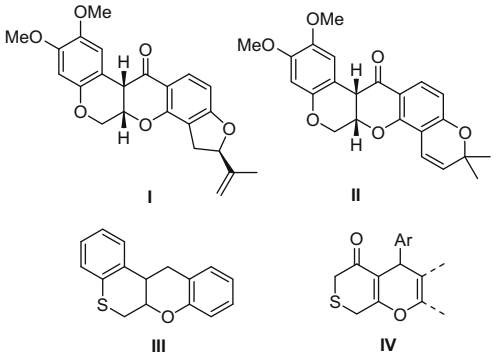
ABSTRACT

A series of novel 4-aryl-thiopyrano[3,4-*b*]pyran-5-one derivatives were synthesized through an efficient one-pot three-component reaction under solvent-free conditions. This work provides a new series of derivatives of thiorotenone with potential biological activity for biomedical screening.

Pyran and fused pyran derivatives show diverse pharmacological properties such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities,[1] antihyperglycemic activity,[2] antiproliferative activity.[3] For example, rotenone (**I**) and deguelin (**II**) and related compounds (rotenoids) are the active ingredients of botanical insecticides used for at least 160 years to control crop pests.[4,5] The results of bioassay test show that rotenoids are known not only as toxicants but also as candidate anticancer agents.[6–9] In past decades, much effort has been devoted to the study on the synthesis and bioactivity of rotenoids.[10–12] However, only a few studies on the synthesis and bioactivity of thiorotenoids based on core structure **III** have been documented in the literature, for example, the multi-step synthesis from thiochromanone,[13,14] the cyclization of (2-hydroxyphenyl)(2*H*-thiochromen-2-yl)methanone obtained via Wadsworth-Emmons reaction and Mukaiyama directed aldol cyclization from 2-((2,2-diethoxyethyl)thio)benzaldehyde and diethyl (methoxy(2-methoxyphenyl)methyl)phosphonate,[15–17] and the tandem reactions of dihydro-2*H*-thiopyran-3(4*H*)-one and 4-(2-hydroxyphenyl)but-3-en-2-one.[18] Given the biological importance of the rotenoids, it is valuable to modify this important scaffold further. So the fused phenyl rings were removed to give thiopyrano[3,4-*b*]pyran scaffold and aryl substituents and a carbonyl group were introduced at position 4 and 5, respectively (**IV**). These variations may contribute to the bioactivity differences and provide new compound library with potential biological activity for biomedical screening.



The known synthesis methods of thiorotenoids suffered from many drawbacks, including long reaction time, complex steps, drastic reaction conditions, low yields, generating limited diversity and the use of catalyst and organic solvent. Recently, the progress in the field of solvent-free reactions is gaining significance because of their high efficiency, operational simplicity and environmentally benign processes. Many organic reactions and complex transformations have been reported to proceed under solvent-free conditions.[19–25] Besides, the diversity generating potential of multicomponent reactions (MCRs) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated.[26] In continuing our work on the design and efficient synthesis of potential biologically active heterocyclic compounds,[27] herein we report a simple work-up, three-component and catalyst-free synthesis of a range of novel thiopyrano[3,4-*b*]pyran derivatives: 2-amino-4,5,6,8-tetrahydro-4-aryl-5-oxothiopyrano[3,4-*b*]pyran-3-carbonitrile and ethyl 2-ami-

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no-4-aryl-4,5,6,8-tetrahydro-5-oxothiopyrano[3,4-*b*]pyran-3-carboxylate (Scheme 1) and 4-arly-3,4-dihydrothiopyrano[3,4-*b*]pyran-2,5(6*H*,8*H*)-dione (Scheme 2) under solvent-free conditions. These novel thiopyrano[3,4-*b*]pyran derivatives may prove to be of biological interest.

The effect of solvent on the reaction was initially examined by reacting 4-bromophenyl aldehyde (1 mmol), 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (1 mmol) and malononitrile (1 mmol) without catalyst. It was found that if the synthesis was performed in the organic solvent it gave the expected product, **4b**, in moderate to high yield (47–80%) (Table 1). However, solvent-free reaction exhibited higher yield (85%) than its liquid-phase counterparts. So we carried out the solventless reaction to synthesize the desired products.

To screen for the practical temperature for the solvent-free synthesis, the previous reaction was run in 1 mmol scale of substrate at different temperature (Table 2). As shown in Table 2, the reaction at 85 °C proceeded in highest yield among the seven reaction temperatures tested. So 85 °C was chosen for this reaction.

Based on the optimized reaction conditions, a series of 2-amino-4,5,6,8-tetrahydro-4-aryl-5-oxothiopyrano[3,4-*b*]pyran-3-carbonitrile were synthesized. As shown in Table 3, the reaction under solvent-free and catalyst-free conditions gave the corresponding products in moderate to good yields.

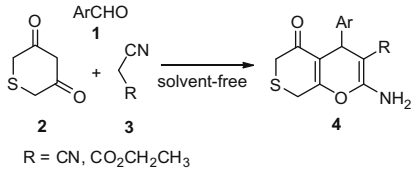
The effect of electron and nature of substituents on the aromatic ring did not show strongly obvious difference in terms of yields. This protocol can be applied not only to aromatic aldehydes either with electron-withdrawing groups (such as a nitro group, halogen) or electron-donating groups (such as a methoxy group) but also heteroaromatic aldehydes with moderate to excellent yields under the same conditions, which highlighted the wide scope of this condensation. In order to check the versatility of the procedure, malononitrile were replaced with other active methylene compounds such as ethyl cyanoacetate and meldrum's acid. To our delight, under the above optimized conditions, a series of ethyl 2-amino-4-aryl-4,5,6,8-tetrahydro-5-oxothiopyrano[3,4-*b*]pyran-3-carboxylate and 4-arly-3,4-dihydrothiopyrano[3,4-*b*]pyran-2,5(6*H*,8*H*)-dione were also synthesized, respectively, in moderate to good yields (Tables 3 and 4).

All the products were characterized by IR, ^{1}H NMR and HRMS data.[28] The structure of **4i** was also established by X-ray crystallographic analysis (Fig. 1).[29]

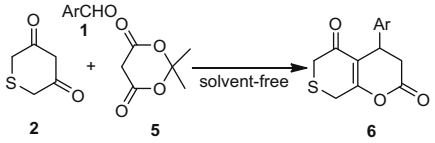
Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of 2-amino-4,5,6,8-tetrahydro-4-aryl-5-oxothiopyrano[3,4-*b*]pyran-3-carbonitrile or ethyl 2-amino-4-aryl-4,5,6,8-tetrahydro-5-oxothiopyrano[3,4-*b*]pyran-3-carboxylate **4** and 4-arly-3,4-dihydrothiopyrano[3,4-*b*]pyran-2,5(6*H*,8*H*)-dione **6** could be explained by the reaction sequence presented in Scheme 3 and 4.

To test the proposed mechanism, we carried out the synthesis of **4b** and **6c** in two steps, first of which was to get the pure 2-(4-bromobenzylidene)malononitrile **7b** and **11c**, and then reacted with **2** under similar conditions (Schemes 5 and 6). The target compound of **4b** and **6c** were obtained with yield similar to the one-pot version. The fact supported the proposed mechanism.

In conclusion, we have provided an effective three-component route using inexpensive starting materials for the synthesis of a



Scheme 1.



Scheme 2.

Table 1
Solvent effect on the synthesis of **4b**

Entry	Solvent	*T* (°C)	Time (h)	Yield (%)
1	CH_3CN	Reflux	3	68
2	$CHCl_3$	Reflux	5	55
3	EtOH	Reflux	2.5	80
4	HOAc	85	4	65
5	H_2O	85	3	47
6	Solvent-free	85	2	85

Table 2
Temperature optimization for the synthesis of **4b**

Entry	T (°C)	Time (h)	Yield (%)
1	25	8.5	Trace
2	45	6.0	45
3	65	4.5	68
4	75	4.0	80
5	85	2.0	85
6	95	2.0	82
7	105	2.0	76

Table 3
Synthesis of product **4** under solvent-free condition at 85 °C[a]

Entry	Product	Ar	R	Time (h)	Yield[b](%)
1	**4a**	C_6H_5	CN	1	83
2	**4b**	4-BrC_6H_4	CN	2	85
3	**4c**	2-FC_6H_4	CN	2.5	83
4	**4d**	3-FC_6H_4	CN	1	86
5	**4e**	4-FC_6H_4	CN	1.3	84
6	**4f**	3-$NO_2C_6H_4$	CN	1.6	87
7	**4g**	2-ClC_6H_4	CN	1.1	81
8	**4h**	3-ClC_6H_4	CN	0.9	82
9	**4i**	4-$OCH_3C_6H_4$	CN	5	80
10	**4j**	2-SC_4H_3	CN	2	85
11	**4k**	3-BrC_6H_4	COOEt	3	80
12	**4l**	3-$NO_2C_6H_4$	COOEt	4	81
13	**4m**	4-BrC_6H_4	COOEt	3.5	82
14	**4n**	3-FC_6H_4	COOEt	2.9	82
15	**4o**	4-$NO_2C_6H_4$	COOEt	4	84
16	**4p**	3-ClC_6H_4	COOEt	3	80

[a] General procedure: 1 mmol **1** and 1 mmol **3** were triturated together for 30 min. Then 1 mmol **2** was added and mixed thoroughly. The mixture were kept at 85 °C until completion (monitored by TLC).
[b] Isolated yield.

Table 4
Synthesis of product **6** under solvent-free condition at 85 °C[a]

Entry	Product	Ar	Time (h)	Yield[b] (%)
17	**6a**	2-ClC_6H_4	1	85
18	**6b**	3,4-(OCH_2O)C_6H_3	3	83
19	**6c**	4-$CH_3OC_6H_4$	2.5	80
20	**6d**	4-$CH_3C_6H_4$	3.5	82
21	**6e**	3,4,5-$(CH_3O)_3C_6H_2$	4	85

[a] General procedure: 1 mmol **1** and 1 mmol **5** were triturated together for 30 min. Then 1 mmol **2** was added and mixed thoroughly. The mixture were kept at 85 °C until completion (monitored by TLC).
[b] Isolated yield.

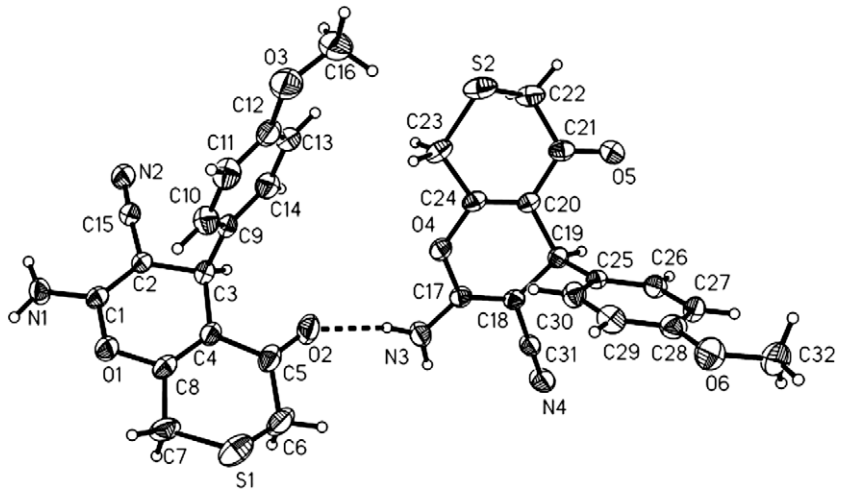
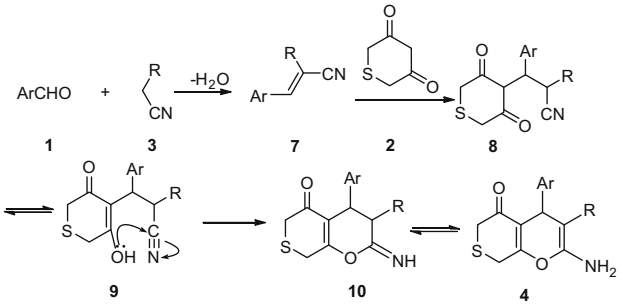
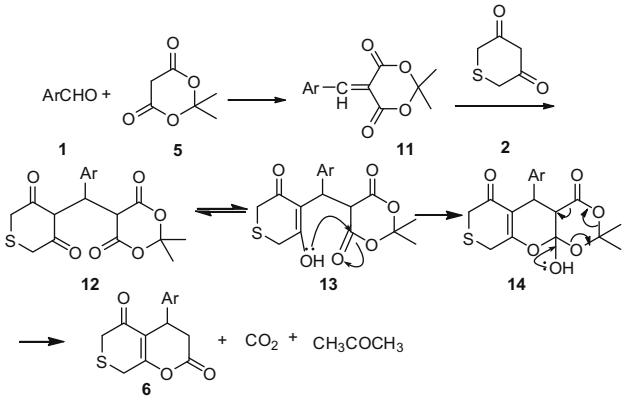


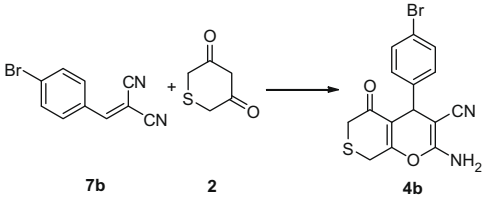
Figure 1. Crystal structure of **4i**.



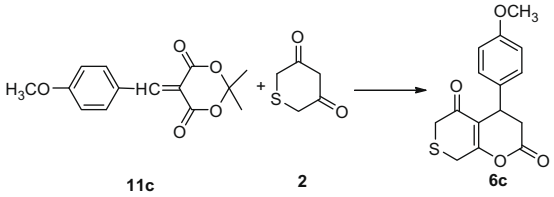
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

series of thiopyrano[3,4-*b*]pyran derivatives under solvent-free and catalyst-free conditions. The experimental simplicity, higher yields, short reaction time, eco-friendly and the simple work-up procedure, makes the procedure attractive to synthesize a variety of these derivatives. The series of novel thiopyrano[3,4-*b*]pyran derivatives may prove to be of biological interest and provide new classes of compounds with potential biological activity for biomedical screening.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.036.

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28. The experimental procedures of synthesis and the spectroscopic data of the synthesized compounds are available in the Supplementary data.
29. The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed using a Rigaku Saturn diffractometer. Crystal data for **4i**: $C_{16}H_{14}N_2O_3S$, colorless, crystal dimension $0.283 \times 0.058 \times 0.052$ mm, monoclinic, space group $C2/c$, $a = 31.5225(13)$, $b = 8.7710(3)$, $c = 23.3362(9)$ Å, $\beta = 107.586(2)^\circ$, $V = 6150.5(4)$ Å^3, $Mr = 314.35$, $Z = 16$, $D_c = 1.358$ g/cm^3, $\lambda = 0.71073$ Å, μ(Mokα) = 0.224 mm^{-1}, $F(0\,0\,0) = 2624$, $S = 0.991$, $R_1 = 0.0560$, $wR_2 = 0.1072$. CCDC 751279 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.