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Synthesis of thio- and furan-fused heterocycles: furopyranone, furopyrrolone, and thienopyrrolone derivatives

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ABSTRACT

We report herein the synthesis of a novel class of compounds, ethyl 4-oxo-4*H*-furo[3,2-*c*]pyran-6-yl carbonate, (7*E*)-7-[(dimethylamino)methylene]-4*H*-furo[3,2-*c*]pyran-4,6(7*H*)-dione, 5-oxo-*N*-phenyl-2,5-dihydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxamide, and 5-oxo-*N*-phenyl-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrole-4-carboxamide starting from the corresponding acid derivatives. Intramolecular cyclization in the presence of thionyl chloride formed the target fused ring systems. Additional transformation was seen in the cyclization of furan-fused heterocycle. A mechanism was proposed based on experimental and computational findings.

1. Introduction

Furan and thiophene derivatives are of great importance due to their crucial role in synthetic organic chemistry.[1–6] They have been proven to exhibit a wide range of biological activities and so they exist in a number of commercially available pharmaceuticals such as furazolidone (**1**),[7] ranitidine (**2**),[8] and tioconazole (**3**) (Fig. 1).[9]

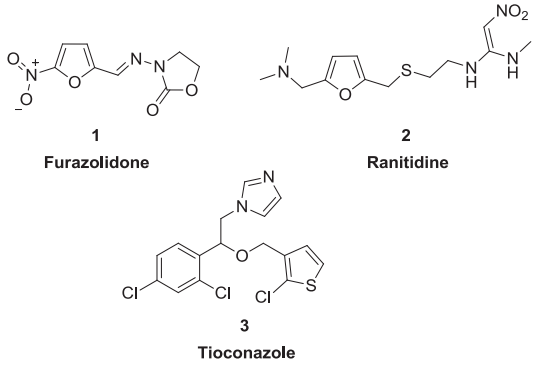

Fig. 1. Structures of some commercially available drugs containg furan or thiophene ring.

Fusing furan rings with other heterocycles results in new characteristics. Furopyranones (**4**) and furopyrrolones (**5**) are key examples of furan-fused heterocyclic systems that have crucial roles (Fig. 2).[10–14] For instance neo-tanshinlactone (**6**), a furopyranone derivative, is reported to be 20 times more selective than anti-estrogenic tomoxifen citrate, which is clinically used in breast cancer therapies.[15]

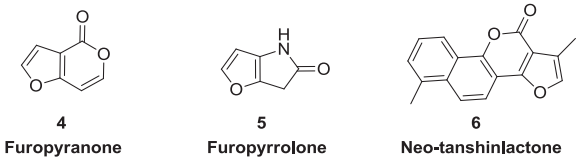

Fig. 2. Structures of some furan-fused heterocycles.

Based on known examples,[9,16] thio- and furan-fused heterocycles have the potential to possess biological activities.

Therefore we were inspired to work on the development of new synthetic methodologies for thio- and furan-fused heterocycles. Starting from diacid **7**, we aimed here to prepare of the furopyranone **8** and furopyrrolone **9** derivatives (Scheme 1).

2. Results and discussion

The starting compounds **12** and **13** were synthesized using previous methodologies in which commercially available dimethyl

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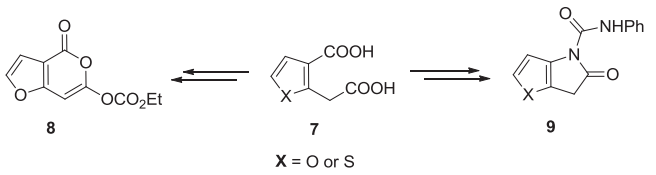
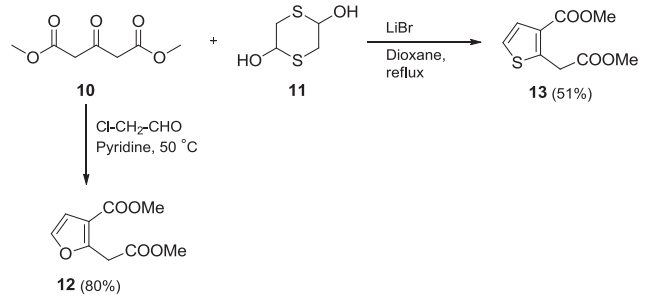


8 7 9

Scheme 1. The synthetic strategy for furopyranone **8** and furopyrrolone **9** derivatives.

1,3-acetonedicarboxylate (**10**) was reacted with chloroacetaldehyde in pyridine to yield furan diester **12**,[17] and with 2,5-dihydroxy-1,4-dithiane (**11**) and lithium bromide in dioxane to yield thiophene diester **13**[18] (Scheme 2).[19]

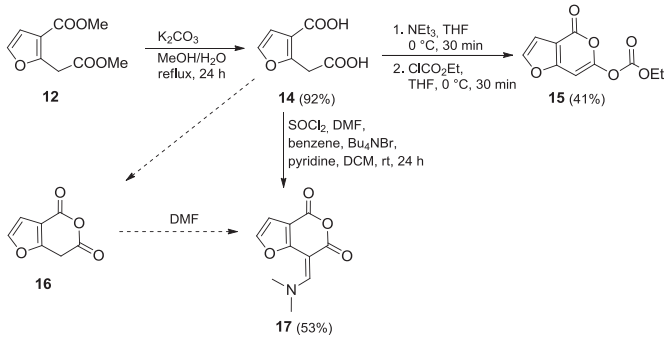


10 **11** **13** (51%)

12 (80%)

Scheme 2. Synthesis of furan and thiophene diesters **12** and **13**.

For the synthesis of furopyranone derivatives, the key compound was the furan diacid **14**. A previously published method by Balci et al.[20] was applied to the furan diacid **14**, which was obtained by the reaction of furan diester **12** with potassium carbonate in a methanol/water mixture.[21] According to this method, furan diacid **14** was then treated with triethylamine and then with ethyl chloroformate, which yielded the cyclization product furopyranone **15**. For the synthesis of further furopyranone derivatives, a modified Vilsmeier–Haack reaction was applied to diacid **14**. Treatment of furan diacid **14** with thionyl chloride, dimethyformamide, pyridine and tetrabutylammonium bromide as a catalyst in dichloromethane resulted in the formation of **17** (Scheme 3). We assume that the diacid **14** first undergoes a cyclization reaction to form the anhydride **16** followed by a condensation reaction of the methylene functionality in **16** with the dimethyl formamide to give **17**. The confirmation of the structure of furopyrandione **17** was achieved by X-ray analysis (Fig. 3).



12 **14** (92%) **15** (41%)

16 **17** (53%)

Scheme 3. Synthesis of furopyranone **15** and furopyrandione **17**.

After the synthesis of furopyranone **15** and furopyrandione **17**, we turned our attention to furo- and thienopyrrolone **9** framework construction, starting from diacid **7**, for which a nitrogen atom must be inserted into the molecule.

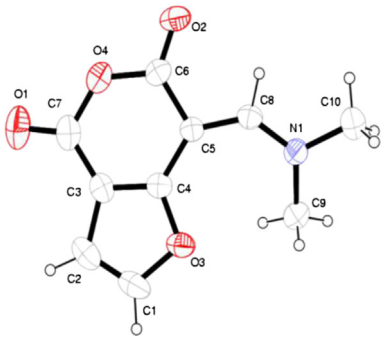
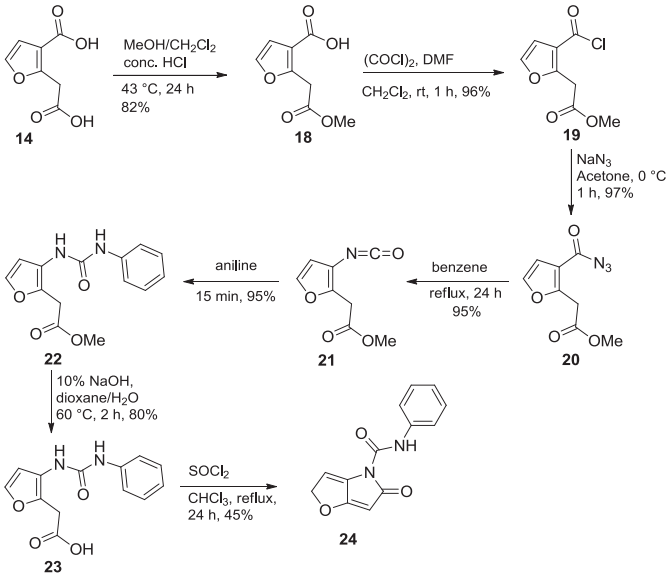


Fig. 3. ORTEP drawing of furopyrandione **17**. Thermal ellipsoids are shown at 40% probability level.

In order to achieve this goal, furan diacid **14** was reacted with concentrated HCl in dichloromethane from which the carboxylic acid group connected to the methylene group in **14** was selectively converted to ester functionality to form monoester **18**.[22,23] The monoester **18** was then reacted with oxalyl chloride in dichloromethane to give the acyl chloride **19**. To introduce the nitrogen atom into the molecule, Curtius rearrangement,[24–28] one of the most convenient methods to generate urea and urethane derivatives, was performed on acyl azide **20** in benzene, which was generated by the reaction of acyl chloride **19** with sodium azide in acetone. The isocyanate **21** formed by the Curtius rearrangement, was mixed with aniline to yield the corresponding urea ester **22**. Then the ester functionality of the molecule **22** was hydrolyzed with 10% NaOH in a dioxane/water mixture to give urea acid **23**. Finally the intramolecular cyclization of the molecule **23** was achieved by adding thionyl chloride in chloroform forming the rearranged product **24** (Scheme 4). The structure of **24** was established by ^{1}H and ^{13}C NMR spectra. Finally X-ray diffraction analysis of **24** confirmed unambiguously the proposed structure (Fig. 4).



14 **18** **19** **20** **21** **22** **23** **24**

Scheme 4. Attempt to synthesize target furopyrrolone derivative **9**.

After the characterization of the unexpected product **24**, we also aimed to apply the same methodology to synthesize the corresponding thienopyrrolone derivative starting from thiophene diacid **25**. For regiospecific formation of the monoester **26**, diacid **25** was treated with HCl in methanol at 40 °C (Scheme 5).[29] The