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Furan ring opening–furan ring closure: cascade rearrangement of novel 4-acetoxy-9-furylnaphtho[2,3-*b*]furans

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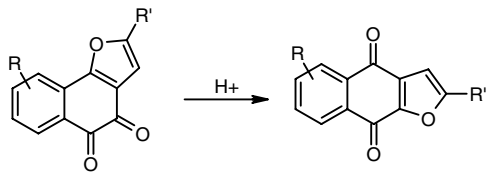
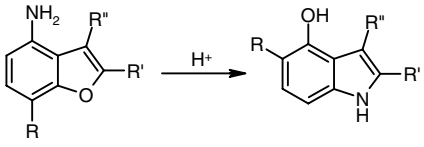
Abstract—The cascade rearrangement of novel 4-acetoxy-9-furylnaphtho[2,3-*b*]furans leading to tetracyclic naphthodifurans derivatives has been developed. The reaction proceeds via double recyclization of both furan rings of the initial molecule, one of the furan rings serving as a 1,3-dicarbonyl compound equivalent.

The rearrangement of 3-acetylfurans, where furan acid catalyzed or thermally induced ring opening leads to the formation of a new furan ring with participation of a carbonyl group at C-3, is well known.[1] Such rearrangements have been widely employed in the synthesis of *para*-naphthofuroquinone derivatives possessing different types of biological activities. These reactions represent the acid catalyzed isomerization of angular naphtho[1,2-*b*]furan-4,9-diones into linear naphtho[2,3-*b*]-furan-4,9-diones (Scheme 1).[2]

Rearrangements of furan rings annulated with an aromatic nucleus with participation of a nucleophilic functional group in one of the β-positions of the furan have also been disclosed in the literature. Thus, Guiotto et al.[3] reported the isomerization of 4-aminobenzofuran derivatives into the corresponding 4-hydroxyindoles.



Scheme 1.



Scheme 2.

The authors demonstrated that this transformation proceeds smoothly with high yields in refluxing acetic acid in the presence of sufficient amounts of protic acids such as concentrated HCl, CF_3COOH or 70% $HClO_4$ (Scheme 2). If the furan ring is susceptible to nucleophilic attack due to electron withdrawing substituents, then this rearrangement can also proceed under basic conditions. The isomerization of linear 4-hydroxy-3-benzoylnaphtho[2,3-*b*]furans into angular naphthofurans in the presence of diethylamine has also been reported.[4] These parent rearrangements are similar to furan ring opening and ring closing into new heterocycles where the furan serves as a masked 1,4-dicarbonyl compound.

In this letter we report our preliminary results on the cascade acid catalyzed rearrangement of 4-acetoxy-9-furylnaphtho[2,3-*b*]furans **1**, which were synthesized according to the method reported earlier.[5] Compounds **1** were refluxed in ethanol saturated with hydrogen chloride under essentially the same conditions that were employed earlier for the recyclization of *ortho*-substituted benzylfurans.[6] The reaction was complete

Keywords: Furan; Recyclization; Rearrangement; Naphtho[2,3-*b*]-furans.
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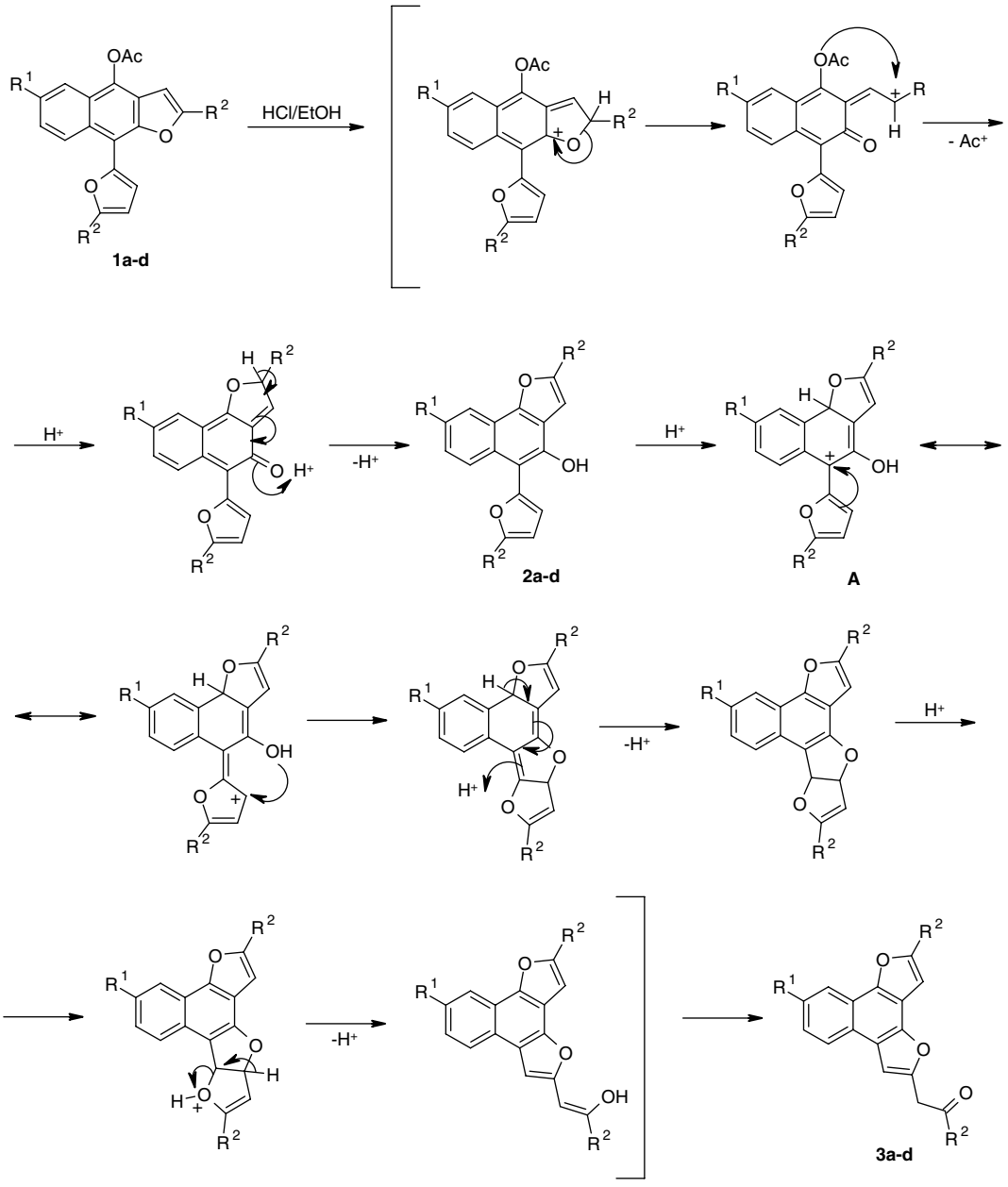


1, 3	R^1	R^2	Yield **3** (%)
a	H	Me	40
b	Cl	Me	42
c	Br	Me	42
d	Br	Et	37

Scheme 3.

within 20–60 min and gave rise to compounds **3** rather than the expected products **2** (Scheme 3).[7] For unambiguous structure confirmation, X-ray analysis was performed on compound **3c** (Fig. 1).[8]

Evidently, the reaction commences with isomerization of linear 4-acetoxy-9-furylnaphtho[2,3-*b*]furan **1** into the angular isomer of 4-hydroxy-5-furylnaphtho[1,2-*b*]-furan **2** as a result of recyclization of the furan ring annulated to the naphthalene framework (Scheme 3). Subsequently, a rearrangement similar to the rearrangement of 2-tosylaminoarylfurans into indole derivatives occurs as was reported earlier from our laboratory.[9] However, the reaction conditions are milder: reflux in ethanolic hydrogen chloride solution versus perchloric acid in glacial acetic acid for the analogous reaction of

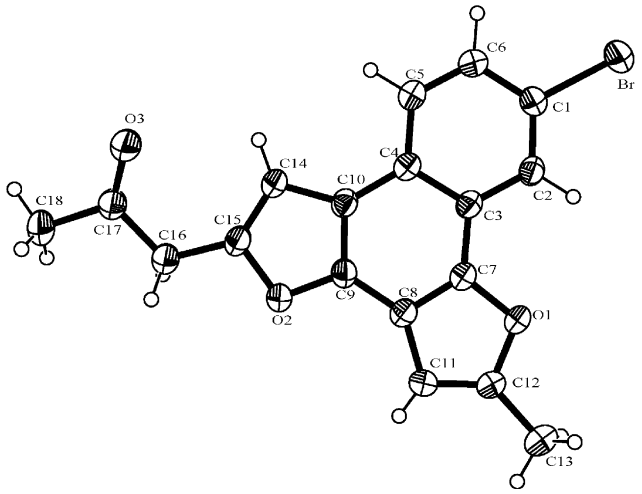


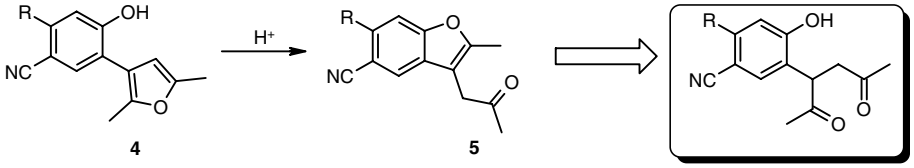
Figure 1. ORTEP diagram of **3c**.

2-tosylaminoarylfurans. This fact allowed us to assume that in this case protonation of the substrate most likely proceeds on the furonaphthalene fragment rather than on the furan ring[9] leading to the formation of the stable aryl(furyl)methyl cation **A**. Delocalization of the positive charge in this cation is favorable for the intramolecular interaction with the hydroxyl group leading eventually to the product **3**.

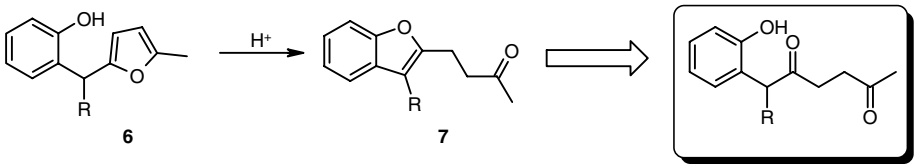
In conclusion, we have developed a novel rearrangement of 4-acetoxy-9-furylnaphtho[2,3-*b*]furans **1** leading to naphthodifuran derivatives. It should be noted that this rearrangement is a result of recyclization of two furan cycles. While the first step of the transformation involves recyclization of linear 4-acetoxy-9-furylnaphtho[2,3-*b*]-furan **1** into its angular isomer, 4-hydroxy-5-furylnaphtho[1,2-*b*]furan **2** is similar to transformations documented in the literature,[1–3] the second recyclization of the 2-alkyl-5-(2-hydroxyaryl)furan **2** into the product **3** is unprecedented.

At present only two examples of furan into benzofuran recyclization are known. It was reported that recyclization of 3-(2-hydroxyaryl)furans **4** in the presence of acid leads to benzofurans **5** (Scheme 4).[10] We showed earlier that 2-hydroxybenzylfurans **6** were transformed into benzofurans **7** under the action of mineral acids (Scheme 5).[6a] Retrosynthetic analysis of compounds **5** and **7** reveals that they can be synthesized from the corresponding 1,4-diketones (Schemes 4 and 5), thus the furan in these transformations can be considered to be 1,4-diketone equivalent.

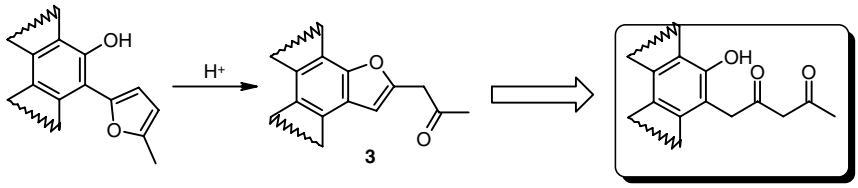
Additionally, retrosynthetic analysis of the final product **3** of the observed rearrangement shows that this compound can be prepared from a corresponding 1,3-diketone (Scheme 6) and hence we consider the furan ring to be a formal equivalent of a 1,3-diketone. To the best of our knowledge this is only the second example of this furan ring behavior which we named second type rearrangement in our previous letter.[9] We believe that such unusual furan chemistry will find broad application in constructing various benzannelated heterocycles.



Scheme 4.



Scheme 5.



Scheme 6.

Acknowledgements

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7. A typical procedure is as follows: A suspension of compound **1c** (2 g, 5.01 mmol) in ethanolic HCl (130 ml) prepared by saturation of 200 g of ethanol with 100 g of gaseous HCl was refluxed until complete dissolution of the starting compound. After completion of the reaction (TLC monitoring), the reaction mixture was poured into 500 ml of water and neutralized with sodium carbonate to pH 7. The resulting precipitate was filtered off, dried, dissolved in benzene/hexane (1:1) mixture and passed through a pad of silica gel. The refined solution was evaporated under reduced pressure and the residue was recrystallized from ethanol to afford yellow crystals of compound **3c** 0.75 g, (42%). MP = 135–137 °C. Anal. found: C, 60.58; H, 3.61%. $C_{18}H_{13}BrO_3$ requires: C, 60.53; H, 3.67%; ν_{max} (KBr): 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (3H, s, CH_3), 2.57 (3H, s, CH_3), 3.96 (2H, s, CH_2), 6.66 (1H, s, H_{Fur}), 7.00 (1H, s, H_{Fur}), 7.53 (1H, dd, $J = 2.0$, 8.7 Hz, H_{Ar}), 7.86 (1H, d, $J = 8.7$ Hz, H_{Ar}), 8.38 (1H, d, $J = 2.0$ Hz, H_{Ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.30, 29.56, 43.73, 100.23, 104.82, 114.22, 118.52, 118.94, 120.00, 122.63, 123.06, 125.59, 128.04, 145.81, 148.05, 149.40, 155.64, 203.62; MS (EI) m/z: 356/358 (13/13, M^+), 313/315 (100/100), 235 (45), 234 (65), 205 (17), 176 (17).
8. Crystal data of compound **3c**: $C_{18}H_{13}BrO_3$, triclinic, space group P-1; $a = 4.9020(10)$ Å, $b = 8.247(2)$ Å, $c = 18.976(4)$ Å, $\alpha = 78.02(3)°$, $\beta = 86.83(3)°$, $\gamma = 78.82(3)°$, $V = 736.1(3)$ $Å^3$, $Z = 2$, $D_{calcd} = 1.612$ Mg/m^3, $F(000) = 360$; 2973 reflections collected, 2637 unique ($R_{int} = 0.0221$); final R indices (2637 observed collections $I > 2\sigma I$): $R_1 = 0.0236$, $wR_2 = 0.0563$; final R indices (all data): $R_1 = 0.0904$, $wR_2 = 0.0613$. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 296395. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this letter.
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