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Oxidative Furan-to-Indole Rearrangement. Synthesis of 2-(2-Acylvinyl)indoles and Flinderole C Analogues

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Supporting Information

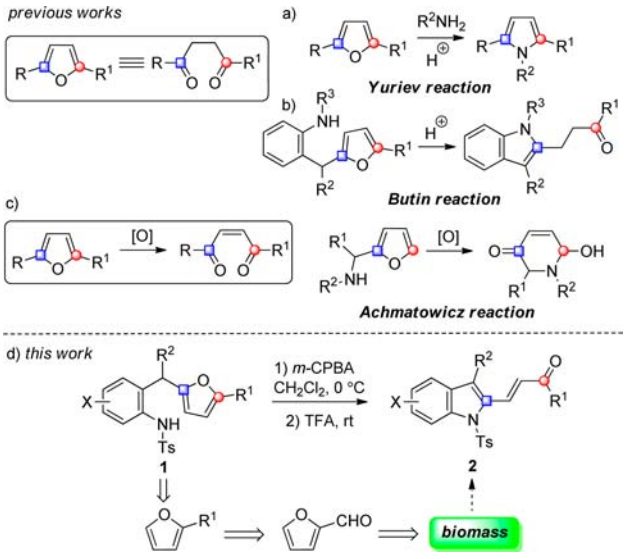
ABSTRACT: Oxidative rearrangement of 2-(2-aminobenzyl)furans affording 2-(2-acylvinyl)indoles in a stereocontrolled manner in good-to-excellent yields has been developed. Thus, (2-aminobenzyl)furans with electron-releasing alkoxy substituents in the phenyl group form only *E*-isomers of 2-(2-acylvinyl)indoles. Conversely, substrates without such substituents produce target products as *Z*-isomers exclusively. A short diastereoselective method for the transformation of the obtained 2-(2-acylvinyl)indoles into antimalarial bisindole alkaloid flinderole A−C analogues has been developed.

The increasing use of biomass as a renewable source of raw materials is one of the imperatives of modern industrial organic chemistry due to the restricted supply of fossil resources. The most important products of biomass processing are referred to as "molecular platforms".[1] Among these platforms, there are three furan derivatives (furfural, 5-hydroxymethylfurfural, and furan-2,5-dicarboxylic acid). Their aromatic reactivity and side chain functionalization are used to produce a wide range of furan derivatives, including medicines, photomaterials, and diesel fuel.[2,3]

The promising extension of "furan platform" utilization is their transformations into other heterocyclic compounds, especially various azaheterocycles.[4] The low aromaticity energy of the furan ring is responsible for the possibility of such transformations, thereby providing diverse furan reactivities.[5] The reactivity of furans as a synthetic equivalent of 1,4-diketones[6] is the most studied. Ammonia or primary amines can react with both masked carbonyl groups, affording pyrrole derivatives (Yuriev reaction, Scheme 1a). Otherwise, azaheterocycles can be formed as a result of the intramolecular reaction of a nitrogen nucleophile, with a single latent ketone function while a second masked carbonyl group evolves in a free form (Butin reaction, Scheme 1b). Moreover, under oxidative conditions, furan can react as synthetic equivalent of 2-ene-1,4-dione; corresponding reactions of furfurylamines afford pyridine derivatives (Scheme 1c, aza-Achmatowicz reaction).[7] In the last process, the nitrogen nucleophile, separated from the furan ring by a single carbon atom, can react with the remote masked carbonyl group only. Nevertheless, if nitrogen and α-carbon are tethered by three atoms, the nucleophile can react with the proximal latent carbonyl group, affording a five-membered azaheterocycle.

Inspired by this idea, we devised a new oxidative rearrangement of 2-(2-aminobenzyl)furans **1**, which can be synthesized from furfural in a straightforward manner,[8] into 2-(2-acylvinyl)-indoles **2**[9] (Scheme 1d). Herein, we report the results of our investigation of this reaction, which opens a simple path from primary products of biomass processing to indoles constituting the most privileged class of heterocyclic compounds due to a broad range of their bioactivities.[10] The presence of an α,β-

Scheme 1. Furan-to-Azaheterocycle Transformations: Previous Approaches and This Work



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unsaturated ketone in indole **2** also opens up opportunities for diverse and useful transformations.[11]

Antimalarial bisindole alkaloid flinderoles A−C (Figure 1), were recently isolated from *Flindersia* sp.[12] To synthesize

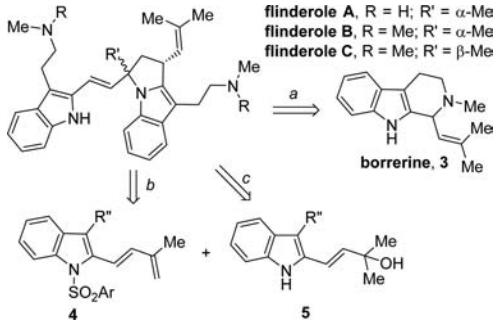
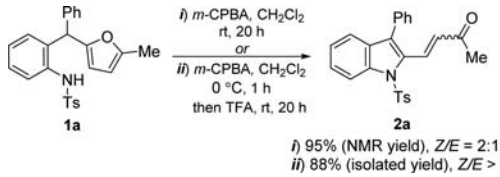


Figure 1. Antimalarial alkaloid flinderoles A−C.

flinderoles and their analogues, three "biomimetic" methods were used.[13] The first one is based on the acid-induced dimerization of borrerine **3** or its derivatives (Figure 1, path a).[14] The key step of the second approach is the acid-catalyzed reaction of diene **4** with 4-(2-indolyl)-2-methylbut-3-enols **5** (Figure 1, path b).[15] Third, a flinderole scaffold was obtained by dimerization of alcohols **5** (Figure 1, path c).[15] Both **4** and **5** can be easily obtained from the corresponding enones **2**. Accordingly, aimed at expansion of the Flinderole-type products, we first developed a short diastereoselective method for the transformation of the obtained 2-(2-acylvinyl)indoles **2** into flinderole A−C analogues.

We started this work with a search for optimal reaction conditions using 5-methyl-2-[(2-tosylamino)benzhydryl]furan **1a** as a model substrate. A diversity of reagents (Oxone, $NaClO_2$, Br_2, *N*-bromosuccinimide, etc.), used previously for oxidation of furans, were studied.[16,17] After extensive experiments, we found that treatment of **1a** with *m*-CPBA at room temperature[18] affords the desired indole **2a** in excellent yield as a 2:1 mixture of *Z*- and *E*-isomers (Scheme 2). During further tuning of the reaction

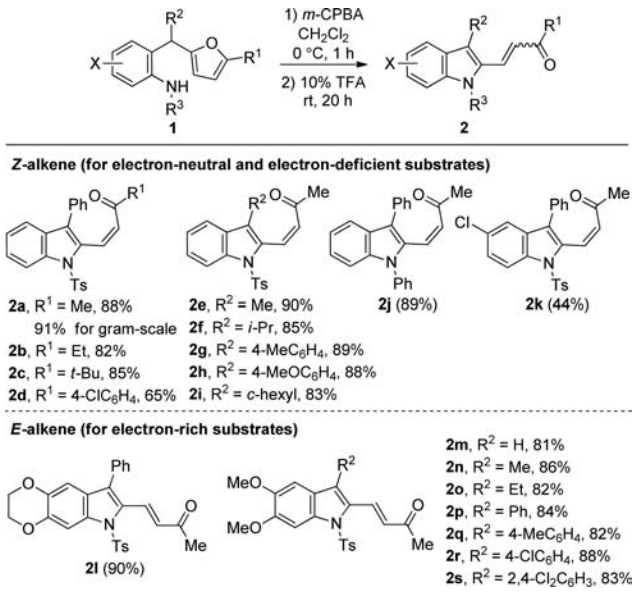
Scheme 2. *m*-CPBA-Induced Oxidative Rearrangement of 1a to 2a



conditions, we found that indole **2a** can be obtained as the *Z*-isomer exclusively in 88% isolated yield under **1a** oxidation at 0 °C followed by treatment of the reaction mixture with 10 mol % of TFA.

With the optimized conditions in hand, we studied the scope of the disclosed reaction (Scheme 3). A broad variety of 2-(2-aminobenzyl)furans **1** were shown to afford the corresponding indoles **2** in good-to-excellent yields. A single exception was compound **2k**, which was obtained in 44% yield only. The presence of the electron-withdrawing substituent in the *para*-position to the nucleophilic nitrogen is responsible for the low yield in this case. The corresponding substrate with a nitro group in the *para*-position of the tosylamine moiety failed to produce the corresponding indole. The presence of a substituent at the C5

Scheme 3. Scope of *m*-CPBA-Induced Rearrangement of Furans 1 to Indoles 2[a]



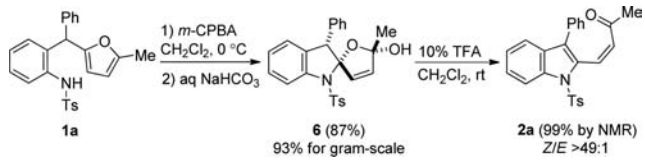
[a]Conditions: benzylfuran (0.5 mmol), *m*-CPBA (0.6 mmol), CH_2Cl_2 (2 mL), 0 °C, 1 h; then TFA (0.05 mmol), rt, 20 h.

atom of the furan ring and at the nitrogen atom (R^1, $R^3 \neq H$) is also crucial for a good yield of **2**. Significant tarring was observed for substrates without substituents at these atoms (R^1, $R^3 = H$). Nevertheless, substrates with diverse alkyl substituents in the furan ring were found to react with a similar efficiency. The nature of the substituent at the benzylic position (R^2) has no significant influence on the reaction yield.[19]

If electron-withdrawing groups in the phenyl ring hamper the studied rearrangement, electron-releasing substituents change process stereoselectivity. Namely, 5,6-dialkoxyindoles **2l−s** were obtained as *E*-isomers exclusively. Evidently, electron-donating substituents in the phenyl ring accelerate acid-induced *Z*/*E*-isomerization in the formed indole **2**.[17] On the contrary, (*Z*)-**2a** was not converted into an *E*-isomer even under higher loading (0.3 equiv) of TFA. Nevertheless, we found that this isomerization proceeds quantitatively under heating with iodine (see below).

During optimization of the reaction conditions, we found that quenching of the reaction mixture with aq $NaHCO_3$ produces an unusual spiroindoline **6** (Scheme 4), structure of which was

Scheme 4. Formation of the 6 in the *m*-CPBA-Induced Oxidative Transformation of Furan 1a



unambiguously proven by single-crystal X-ray analysis.[20] It is noteworthy that the treatment of **6** with TFA furnished indole **2a** quantitatively. This indicates that **6** is a tentative reaction intermediate.

The proposed reaction mechanism for the title rearrangement includes an epoxidation of the furan ring in **1** with *m*-CPBA to form intermediate epoxide **A**[21] followed by an intramolecular

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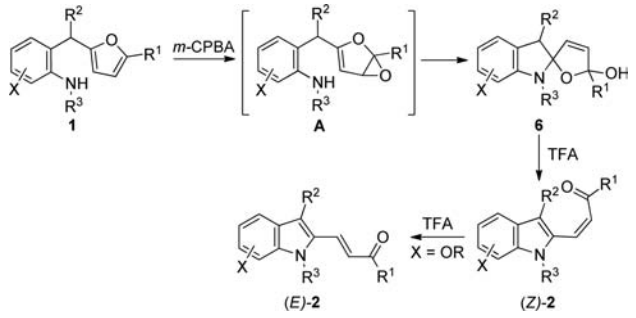
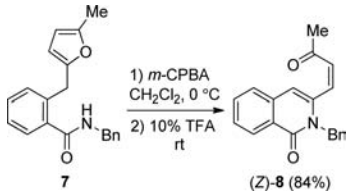
nucleophilic attack of the amine moiety, producing **6**. Subsequent protonation of **6** induces dihydrofuran ring opening and indole moiety aromatization to form (*Z*)-**2** or (*E*)-**2** (Scheme 5).[17]

Scheme 5. Proposed Mechanism for the Formation of Indoles 2



With the aim to extend the scope of the reaction applicability, we decided to study 2-benzylfurans with a nucleophilic moiety separated from the phenyl group by one or more carbon atoms. Indeed, we found that *N*-benzyl-2-(5-methylfurfuryl)benzamide **7** rearranged into the target isoquinolone (*Z*)-**8** in 84% yield (Scheme 6).[22] This demonstrates that the disclosed oxidative

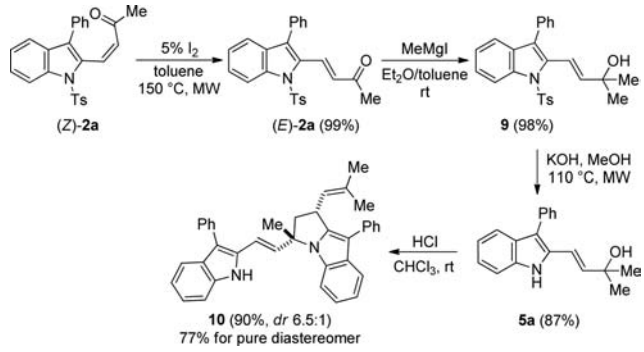
Scheme 6. Oxidative Rearrangement of 2-Furfurylbenzamide 7



rearrangement has a general character and can be used for the transformation of a broad variety of furans bearing a nucleophilic moiety separated from the furan ring by three or more atoms in the corresponding heterocyclic compounds.

Finally, we studied the transformation of indoles **2** into the Flindersial alkaloid analogues using **2a** as a model substrate. Heating of toluene solution of (*Z*)-**2a** with iodine induced its quantitative isomerization to (*E*)-**2a**. A subsequent treatment of (*E*)-**2a** with MeMgI afforded the corresponding tertiary allyl alcohol **9**. Its deprotection with methanolic KOH furnished *N*-unsubstituted indole **5a** in 87% yield. The indole **5a** underwent acid-induced dimerization to 3-[2-(2-indolyl)vinyl]pyrrolo[1,2-*a*]indole derivative **10**. The dimerization yield and stereoselectivity were found to depend on the conditions applied. Acidic agents, applied earlier for the dimerization of borrerine **3**[14] and indoles **5b,c** (R″ = Me,[15a] CH_2CH_2OH),[15b] afford flinderoles and their analogues with low diastereoselectivity. Similarly, under these reaction conditions, dimer **10** was formed as a mixture of two isomers in a ratio of ca. 1:1. Fortunately, we have found that use of concentrated HCl in $CHCl_3$ allows target compound **10** to be produced in excellent yield and a *cis*/*trans* diastereomeric ratio of 6.5:1 (Scheme 7). Moreover, the major isomer of **10** can be isolated by simple crystallization from DMSO. It is noteworthy that single-crystal X-ray analysis of **10** revealed that its stereochemistry corresponds to that of flinderole C,[20] while the reported methods usually produced a small excess

Scheme 7. Synthesis of Flinderole C Analogue 10



of the opposite diastereomers.[14,15,17] The predominant formation of the isomer with *cis*-arrangement of two alkenyl groups in the HCl-induced reaction is consistent with the stability of **10** being higher than that of its *trans*-isomer. Our quantum-chemical calculations showed that **10** is more stable by 7.5 kJ mol^{-1} at HF/6-31G level and 6.2 kJ mol^{-1} at the B3LYP/6-311G** level.[17] Different stereochemical results in the dimerizations of **3** and **5a−c** under the effect of other initiators used can be attributed to the coordination of a catalyst to both molecules in the dimerization transition state,[15a] providing greater decrease of the energy barrier for the formation of *trans*-**10**.

In conclusion, we have developed the *m*-CPBA-induced rearrangement of 2-(2-aminobenzyl)furans **1** to 2-(2-acylvinyl)-indoles **2**. The disclosed reaction provides a shortcut to polyfunctionalized indoles in up to 90% yield starting from furans **1**, which can be easily synthesized from the molecular platforms of biomass processing. It was found that the reaction stereoselectivity is governed by substituents in the phenyl group. Extension of the developed oxidative recyclization for the synthesis of isoquinolones from the corresponding 2-furfurylbenzamides was demonstrated. A simple, efficient transformation of the obtained indole-derived enones **2** into analogues of bisindole alkaloid flinderoles A−C was developed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00805.

Experimental procedures and NMR, IR, MS spectra, elemental analyses (PDF)
X-ray data for **6** (CIF)
X-ray data for **10** (CIF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to the memory of Prof. Alexander V. Butin (1962−2015), mentor, colleague, and friend.

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(19) Related 2-(2-acylvinyl)-*NH*-indoles were synthesized by thermolysis of the corresponding 2-(2-azidobenzyl)furans bearing a broader scope of substituents in the phenyl ring.[9f] On the other hand, only indoles bearing a (hetero)aryl substituent at the C(3) position were prepared by these methods. Moreover, only *E*-isomers were obtained in high yields. Thus, these two methods are complementary.

(20) CCDC 1426892 (**6**) and 1444841 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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