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A Simple Route to Polysubstituted Indoles Exploiting Azide Induced Furan Ring Opening

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Supporting Information

ABSTRACT: A straightforward, efficient indole synthesis based on thermolysis of 2-(2-azidobenzyl)furans with attack of the formed nitrene moiety onto the *ipso* position of furan ring has been developed. The cyclization is accompanied by furan ring opening and affords indoles with a 2-acylvinyl substituent suitable for further modifications.

Indoles belong to the most privileged heterocyclic structures. To date, more than 4000 indole alkaloids were isolated from different natural sources; there is a myriad of synthetic indole derivatives demonstrating a broad range of physiological activities. The indole scaffold is present in a multitude of medicines, such as anticancer prodrug apaziquone,[1] fluvastatin,[2] which is utilized to treat hypercholesterolemia, (Figure 1), and

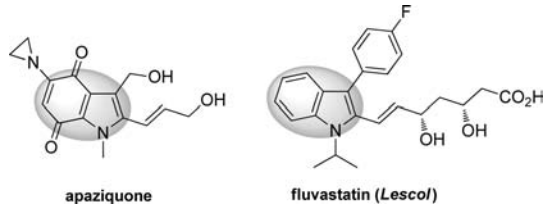


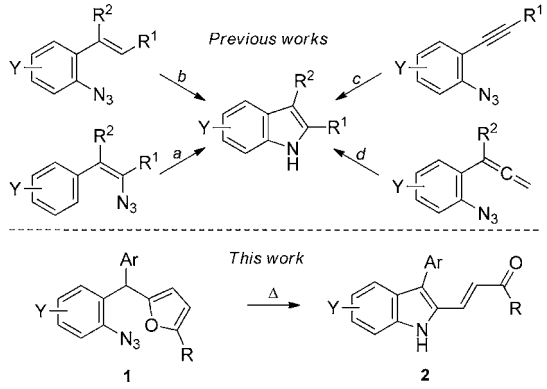
Figure 1. Examples of indole-based drugs.

many others. New indole derivatives are continuously approved for application in medicine. It stimulates the development of novel methods for indole preparation and modification.[3] Syntheses of the indole core bearing functional groups suitable for further transformations are especially attractive approaches.

Organic azides are excellent sources of electrophilic nitrene acting as a counterpart with an appropriate functionality in the synthesis of heterocycles.[4] In particular, indoles are synthesized from azides by four principal methods: (1) thermolysis of 2-arylvinyl azides (Hemetsberger−Knittel indole synthesis, path *a* in Scheme 1);[5] (2) transformation of 2-azidostyrenes under heating[6] or treatment with transition metal complexes[7] (Sundberg synthesis, path *b*); (3) Au(I)-catalyzed cyclization of (2-azidoaryl)acetylenes[8] (path *c*); (4) related cyclization of (2-azidoaryl)allenes (path *d* in Scheme 1).[9]

If there is a gap in conjugation between the azide group and double bond, selectivity is lost as in the case of 2-azidodiphenylmethanes which thermolysis produced indoles

Scheme 1



only as components of complex mixtures due to nitrene attack onto both *ortho*- and *ipso*-positions of a neighboring ring.[10] However, we reasoned that the thermolysis of 2-(2-azidobenzyl)furans **1** should afford indoles **2** selectively (Scheme 1) because of the known tendency of furans to provide an *α* carbon atom for reactions with electrophiles even if this position is substituted; in the latter case the reaction is accompanied by furan ring opening.[11] 2-(2-Azidobenzyl)furans can be synthesized from 2-substituted furans which are easily produced from furfural, one of the biomass platform molecules.

Here we report our investigation of this transformation of inexpensive biomass processing products into indoles bearing functionalities which can be further manipulated in a simple and predictable manner for the syntheses of bioactive compounds.

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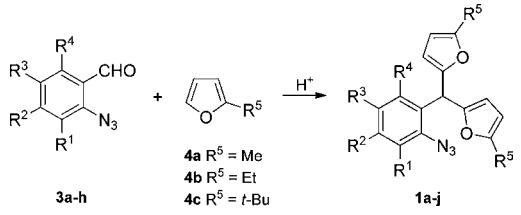
The preparation of 2-(2-azidobenzyl)furans **1** constitutes a significant synthetic challenge in itself. Thus, diazotization/azidation of the corresponding aniline was found to be efficient for **1** bearing an ester group in the furan ring;[12] however, failure occurred for 2-(2-azidobenzyl)furans without an acceptor substituent.[13] To exclude strong mineral acid as a possible reason for the tar formation, we employed nonaqueous conditions (i-$C_5H_{11}ONO$, Me_3SiCl, MeCN) to generate diazonium ions, but only cinnolines were isolated (Scheme 2).[14] So, we started with the development of approaches to various 2-(2-azidobenzyl)furans **1**.

Scheme 2

One of the general methods for the synthesis of 2-(2-substituted benzyl)furans is the Friedel−Crafts reaction of furans with the corresponding benzaldehydes. Surprisingly, this approach had not been reported for the substrates bearing the azide moiety hitherto. The possible reason is the prejudice about the instability of aryl azides in acidic media.[15] After some experimentation, 2-azidobenzaldehyde (**3a**) was found to react with 2-methylfuran (**4a**) in the presence of $HClO_4$ in dioxane affording (2-azidophenyl)difurylmethane **1a** in 76% yield (Table 1, entry 1). Other 2-alkylfurans were also involved into this reaction (Table 1, entries 2, 3). 2-Azidobenzaldehydes **3** with various substituents in the aromatic ring tolerated the reaction conditions that allowed for synthesizing 2-(2-azidobenzyl)furans **1a**−**g** in good isolable yields. Nevertheless, benzaldehydes **3f**−**h** bearing two or more electron-releasing substituents produced benzylfurans **1** in lower yields (50%−60%) due to the partial destruction of the reaction products.

Table 1. Synthesis of (2-Azidoaryl)difurylmethanes 1a−j from 2-Azidobenzaldehydes 3 and Furans 4[a]



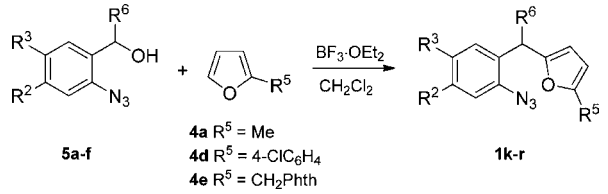
entry	3	R^1	R^2	R^3	R^4	R^5	1	yield, %[b]
1	**a**	H	H	H	H	Me	**a**	76
2	**a**	H	H	H	H	Et	**b**	79
3	**a**	H	H	H	H	*t*-Bu	**c**	75
4	**b**	H	H	NO_2	H	Me	**d**	84
5	**c**	H	H	Br	H	Me	**e**	88
6	**d**	OMe	H	NO_2	H	Me	**f**	92
7	**e**	Br	H	NO_2	H	Me	**g**	85
8	**f**	OMe	H	Me	OMe	Me	**h**	89
9	**g**	OMe	OMe	H	H	Me	**i**	85
10	**h**	OMe	H	H	OMe	Me	**j**	83

[a]Reaction conditions: (a) for **1a**−**g**: aldehyde **3** (10 mmol), furan **4** (22 mmol), $HClO_4$ (6 mmol), and 1,4-dioxane (10 mL), 5−10 °C; (b) for **1h**−**j**: aldehyde **3** (10 mmol), furan **4** (22 mmol), Me_3SiPPA (16.5 mmol), and CH_2Cl_2 (10 mL), 5−10 °C. [b]Isolated yield.

Reoptimization of the reaction conditions revealed that the utilization of polyphosphoric acid trimethylsilyl ester[16] enables products **1h**−**j** to be obtained in high yields (Table 1, entries 9−13).

The reaction between furans and aldehydes is a stepwise process, the intermediate being the corresponding aryl(furyl)-methanol. Under that logic, the reaction of furans with other diarylmethanols should also be an efficient method for the synthesis of 2-(2-azidobenzyl)furans **1**. We prepared a series of 2-azidobenzhydrols **5** and introduced them into the reaction with 2-methylfuran (**4a**). This reaction was found to be inefficient under the above-mentioned applied conditions. However, utilization of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 allowed for performing this condensation in reasonable to excellent yields (Table 2, entries 1, 4−8). 1-(2-Azidoaryl)ethanol **5d** with the electron-enriched aromatic group also gave the corresponding benzylfuran **1p** in good yield (Table 2, entry 7). The furan **4e** with the masked aminomethyl substituent (Table 2, entry 3) and 2-arylfuran **4d** (entry 2) were also successfully introduced into this condensation.

Table 2. Synthesis of (2-Azidoaryl)difurylmethanes 1k−r from 2-Azidobenzyl Alcohols 5 and Furans 4[a]



entry	5	R^2	R^3	R^6	R^5	1	yield, %[b]
1	**a**	H	H	Ph	Me	**k**	82
2	**a**	H	H	Ph	4-ClC_6H_4	**l**	79
3	**a**	H	H	Ph	CH_2Pht[c]	**m**	74
4	**b**	H	H	4-FC_6H_4	Me	**n**	83
5	**c**	H	Cl	Ph	Me	**o**	88
6	**d**	OMe	OMe	Me	Me	**p**	84
7	**e**	OMe	OMe	Ph	Me	**q**	73
8	**f**	OCH_2CH_2O		Ph	Me	**r**	69

[a]Reaction conditions: benzyl alcohol **5** (10 mmol), furan **4** (20 mmol), $BF_3{\cdot}OEt_2$ (15 mmol), and CH_2Cl_2 (25 mL), 5−10 °C. [b]Isolated yield. [c]Pht = Phthalimido.

The starting 2-azidobenzaldehydes and 2-azidobenzyl alcohols can be prepared in a straightforward manner from commercially available reagents. Thus, we have developed efficient procedures for synthesis of 2-(2-azidobenzyl)furans **1** with a broad variety of substituents.

With a series of 2-(2-azidobenzyl)furans **1** in hand, we turned our attention to their thermolysis producing **2**. Screening various solvents revealed that the heating of **1a** under reflux in PhBr, DMSO, DMF, Ph_2O, and propionic acid afforded the target indole **2a**. However, significant tarring was found in these solvents. Better results were obtained when the thermolysis was carried out in *p*-xylene. (*E*)-**2a** was precipitated from the reaction mixture and isolated in 52% yield by simple filtration. Moreover, (*Z*)-**2a** was also obtained in 32% yield.

We believe that indole **2a** formation proceeds through the electrophilic attack of nitrene generated under thermolysis onto the C(2) atom of the furan ring producing spiro zwitterionic intermediate **A** (Scheme 3, path *a*). Then, furan ring opening leads to 4-[3-furyl-3*H*-indol]but-3-en-2-one **B** aromatization

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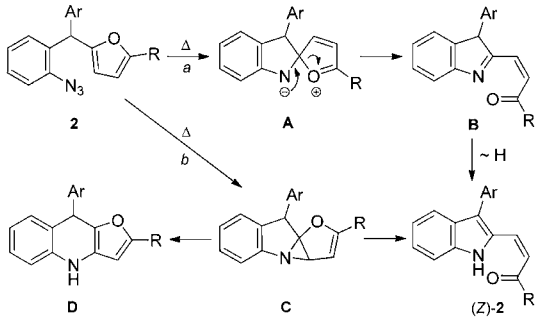
Scheme 3. Possible Mechanism of Indoles 2 Formation



which accomplishes (*Z*)-**2a** formation. A similar mechanism was proposed earlier for the related thermolysis of compounds wherein the 2-azidophenyl moiety was separated from another (het)arene fragment by a one-atom linker.[10b,12,17]

The alternative mechanism consisting of aziridine **C** formation (Scheme 3, path *b*) can be also considered by analogy with mechanism proposed for (2-azidobenzyl)-thiophenes thermolysis.[18] However, in that case thieno[3,2-*b*]quinolines were formed as a single products or along with indoles. We did not identify furoquinoline derivatives **D** in the reaction mixtures obtained after thermolysis of compounds **1**. So, we consider this mechanism to be unlikely.

(*E*)-**2a** is a secondary product resulting from isomerization of the initially formed (*Z*)-**2a**. To manage the stereochemistry of the reaction we reasoned that a higher temperature for the nitrene generation should allow for shortening the reaction time in favor of (*Z*)-isomers at the expense of (*E*)-ones. Indeed, we found that only 2−3 min are sufficient for the full conversion of 2-(2-azidobenzyl)furan **1a** into indole **2a** in the refluxing dodecane (210 °C). Under these conditions, (*Z*)-**2a** was isolated in 60% yield while (*E*)-**2a** was obtained in 26% yield. On the other hand, (*E*)-**2a** was exclusively obtained in 84% yield when products of **1a** thermolysis in dodecane were heated with 4-(dimethylamino)pyridine (DMAP) in refluxing DMF to accelerate *Z*- to *E*-isomerization.[19]

To determine the scope of the disclosed reaction, we investigated the transformation of a series of 2-(2-azidobenzyl)-furans **1** into the corresponding indoles using thermolysis in the dodecane/DMAP-induced isomerization sequence (Scheme 4). We found that 2-(2-acylvinyl)indoles **2a**−**j** were isolated in excellent yields and stereoselectivity independently of substitution pattern in the starting **1**.

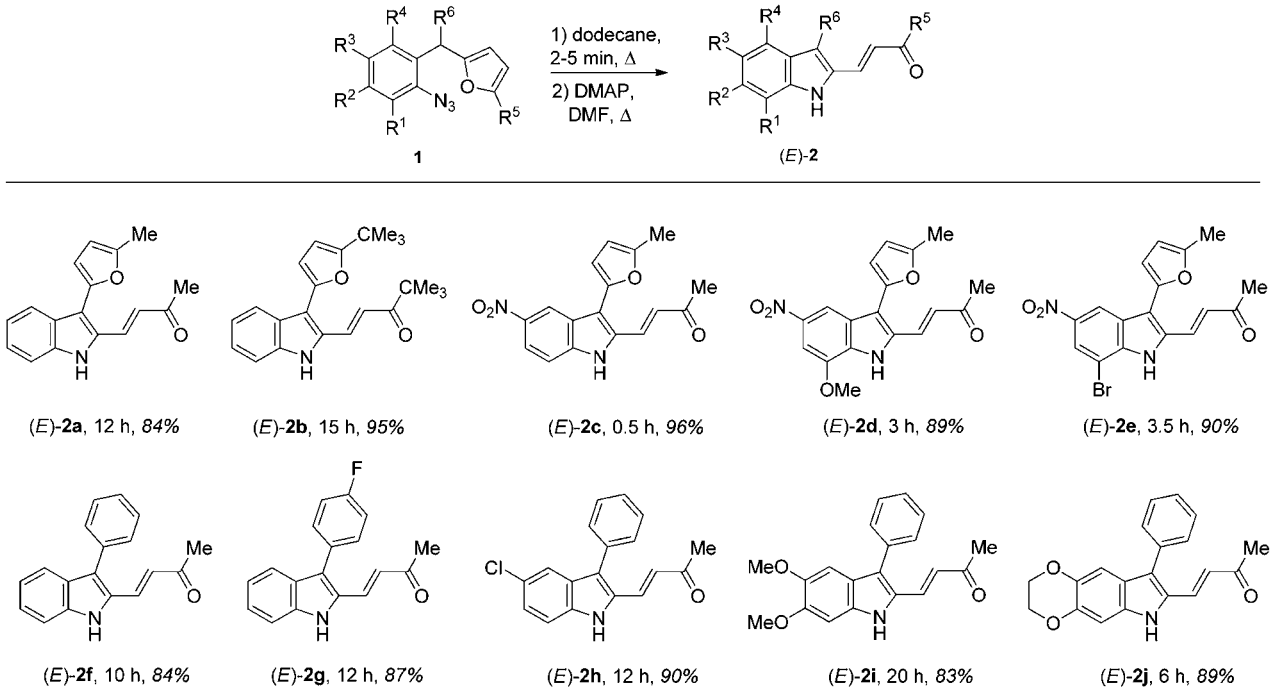
In conclusion, we proposed a conceptually new synthetic approach to 2-(2-acylvinyl)indoles based on thermolysis of 2-(2-azidobenzyl)furans in dodecane for 2−5 min and then in DMF in the presence of DMAP. Indoles are obtained in excellent yields and stereoselectivity. To realize this approach, we developed methods for the preparation of a broad series of starting 2-(2-azidobenzyl)furans from 2-azidobenzaldehydes or 2-azidobenzyl alcohols and 2-substituted furans. The latter are direct products of biomass processing. The reported procedures contribute to the solution of the vital problem of the biorefinery and extend the utilization of the furan-based biomass platform molecules for the production of valuable indoles. For example, indole **2g** can be straightforwardly transformed into fluvastatin (Figure 1). The investigation of other transformations of the synthesized indoles is in progress now.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR, IR, MS spectra, and elemental analyses are given in the Supporting Information.

Scheme 4. Substrate Scope for 2-(2-Azidobenzyl)furan 1 into 2-(2-Acylvinyl)indole 2 Transformation[a,b]



[a]Reaction conditions: 2-Azidobenzylfuran **1** (3 mmol) was refluxed in dodecane (10−15 mL) for 2−5 min. Reaction mixture was evaporated in vacuo to dryness; DMAP (0.15 mmol) and DMF (15 mL) were added; reaction mixture was refluxed for specified time. [b] Isolated yield.

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Notes

The authors declare no competing financial interest.

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