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Furan ring opening—indole ring closure: a new modification of the Reissert reaction for indole synthesis†

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Abstract—A new modification of the Reissert reaction is reported. On treatment of 2-tosylaminobenzylfurans with ethanolic HCl, some indole derivatives have been obtained. The furan ring served as the origin of a carbonyl group in this reaction.

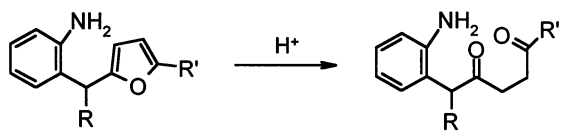
The indole ring system is a major part of a large number of pharmacologically active compounds; thus, the development of new conditions for synthesis of highly functionalized indole derivatives is always of interest. Among a large variety of methods for indole synthesis,[2] the Reissert method has not lost its topicality. In support of this view are recent investigations using this method for the synthesis of alkaloids and other natural compound syntheses.[3]

A

The key intermediate for indole synthesis under Reissert conditions is *o*-aminobenzylcarbonyl compound **A**. Because of the rapid spontaneous reaction of an amino group with a carbonyl group, with subsequent aromatization, compound **A** is not usually isolated from the reaction mixture but generated in situ.

Two general ways for obtaining compound **A** are described: the first is to reduce a nitro group of *o*-nitrobenzylcarbonyl compounds or their derivatives;[4] the other is to generate a carbonyl group either by oxidation of appropriate alcohols[5] or alkenes,[6] or by partial reduction of cyano group in *o*-aminophenylacetonitriles.[7]

Various alkylfurans can serve as the source of the carbonyl group, as it is well known that under the conditions of the Marckwald reaction furans undergo ring cleavage to form 1,4-dicarbonyl compounds.[8] This implies that benzylfurans, which have a nitrogen function in the *o*-position of the aromatic ring, can be useful synthons for indole synthesis.



Earlier, the synthesis of indole derivatives from *o*-nitrophenyldifurylalkanes **1** was described.[9,10] Jones and McKinley reported that as a result of deoxygenation of compounds **1a–c** with triethylphosphite the dibenzopyrroles **2a–c**[9] were obtained. The authors suspected that indoles **3a–c** were intermediate compounds of the transformation.

Later we isolated compound **3a** after reduction of compound **1a** with $SnCl_2$ in the presence of $(CH_3)_3SiCl$.[10] We proved that the transformation proceeded by an oxidative fission of the furan ring and involved a 2,5-cycloaddition of the nitroso-group to one of furan rings. However, such a method of indole synthesis has an essential limitation. The introduction of donor substituents (for example, a methoxy group) in the *p*-position to the nitro group prevents the reaction due to the decrease of the nitroso-group reactivity as a dienophile.

Keywords: furans; Reissert reactions; indoles.

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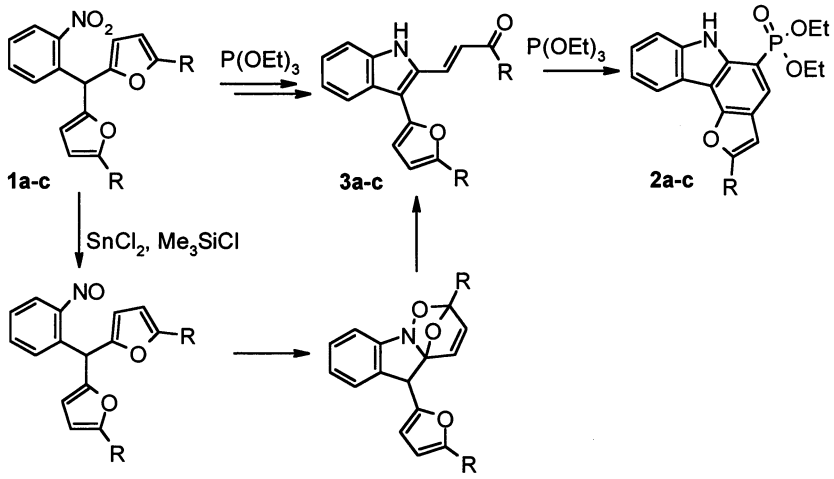
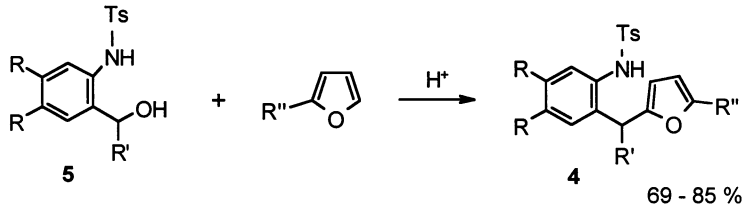
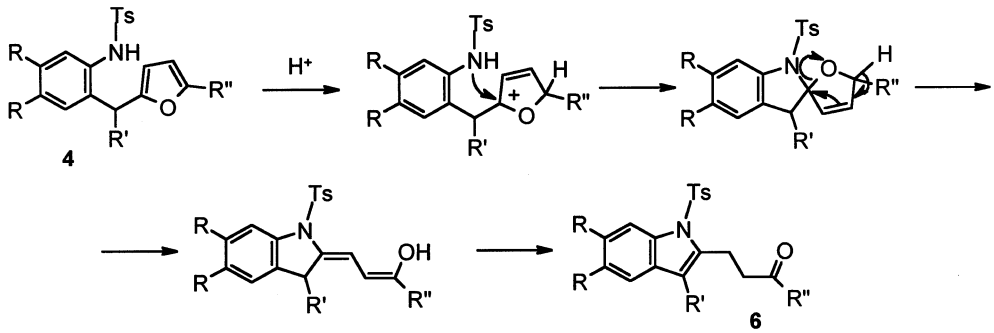


1-3 a) R = Me; **b)** R = Et; **c)** R = i-Pr

In this line of study, we attempted to study the reaction of furan ring opening–indole ring closure under conditions of hydrolytic cleavage of the furan ring for the purpose of developing more general methods for indole synthesis. We showed a similar type of transformation in the case of the synthesis of benzofuran derivatives from 2-hydroxybenzylfurans.[11]



Scheme 1.



4, 5, 6	R	R′	R″	Yield, % 4	6
a	H	Ph	Me	80	82
b	H	4-MeC$_6$H$_4$	Me	75	85
c	H	4-Cl C$_6$H$_4$	Me	78	81
d	OMe	Ph	Me	82	80
e	OMe	Ph	Et	80	79
f	OMe	4-MeC$_6$H$_4$	Me	78	84
g	OMe	3-BrC$_6$H$_4$	Me	85	77
h	OMe	Me	Me	69	78

Scheme 2.

The *o*-tosylaminobenzylfurans **4** were obtained via the well-known alkylation reaction of furans with the appropriate alcohols **5**[12] in high yields (Scheme 1).

Compounds **4**, when heated in ethanolic HCl, were converted into indoles **6** in good yields[13] (Scheme 2). We believe that the mechanism of the reaction is similar to one described earlier for benzofuran derivatives.[11,14]

In conclusion, we would like to point out that this method of indole synthesis is general and allows variation of the substituents R, R′ and R″. Additionally the presence of the alkanone side chain in the indoles **6** substantially extends the possibilities for their synthetic application. Thus, for example, compounds **6** can be utilized as convenient intermediates for the synthesis of mytomicin and mitosene derivatives and new synthetic analogs of the antitumor drug EO-9.[15]

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12. Typical procedure is as follows: To a boiling solution of **5d** (4.13 g, 10 mmol) in CH_2Cl_2 (120 mL), *p*-TsOH (40 mg) and 2-methylfuran (3.7 mL, 40 mmol) were added. The reaction mixture was heated to reflux for 3–5 min, then cooled and washed with $NaHCO_3$ solution, water, dried over Na_2SO_4, evaporated to one-third its initial volume. After addition of hexane the residue obtained was crystallized to afford **4d** as colorless crystals (3.9 g, 82% yield). Mp 125–126°C (hexane/CH_2Cl_2); anal. found: C, 67.63; H, 5.51; N, 3.27. $C_{27}H_{27}NO_5S$ requires: C, 67.90; H, 5.70; N, 2.93%; ν_{max} (Nujol): 3300 cm^{-1}; δ_H (60 MHz, CCl_4): 2.15 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.47 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 4.90 (1H, s, CH), 5.48 (1H, d, $J=3.2$ Hz, 3-H_{Fur}), 5.67 (1H, d, $J=3.2$ Hz, 4-H_{Fur}), 6.15 (1H, s, H_{Ar}), 6.32 (1H, s, NH), 6.57–6.82 (3H, m, H_{Ar}), 6.92–7.25 (5H, m, H_{Ar}), 7.52 (2H, d, $J=8.5$ Hz, H_{Ar}).
13. Typical procedure is as follows: A solution of **4d** (4.77 g, 10 mmol) in ethanolic HCl (150 mL) was heated to reflux for 15 min, cooled and then poured into water. The crystalline product was filtered off, washed with water, air-dried and recrystallized from hexane/CH_2Cl_2 mixture to give indole **6d** (3.8 g, 80% yield). Mp 175–176°C; anal. found: C, 68.15; H, 5.44; N, 2.61. $C_{27}H_{27}NO_5S$ requires: C, 67.90; H, 5.70; N, 2.93%; ν_{max} (Nujol): 1700 cm^{-1}; δ_H (60 MHz, $CDCl_3$): 2.07 (3H, s, $COCH_3$), 2.27 (3H, s, CH_3), 2.70–2.93 (2H, m, -CH_2), 3.02–3.24 (2H, m, -CH_2), 3.73 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 6.68 (1H, s, H_{Ind}), 7.07–7.67 (9H, m, H_{Ar}), 7.83 (1H, s, H_{Ind}).
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