

Furan ring opening—indole ring closure: pseudooxidative furan ring opening in the synthesis of indoles

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Abstract—A new approach to the synthesis of 4-(2-indolyl)-3-buten-2-ones is described based on condensation of 2-tosylamino-benzyl alcohols with *N*-tosylfurfurylamine. Pseudooxidative furan ring opening occurred via protolytic elimination of tosylamide from the side chain of the 2-tosylaminoaryl(5-tosylaminomethylfurf-2-yl)methanes formed in situ.

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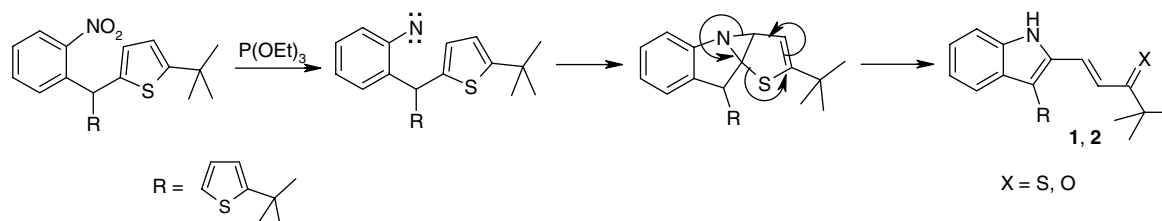
Indole derivatives are of paramount importance in the chemistry of heterocyclic compounds due to their widespread occurrence in Nature and the wide spectrum of pharmacological activity of indoles. Recently, the synthetic chemistry of indole has undergone considerable advancement, with the development of new and modified known approaches, for the synthesis of this class of compounds.¹

4-(2-Indolyl)-3-buten-2-ones, being representatives of α,β -unsaturated ketones, for which considerable synthetic value is well known,² represent versatile building blocks for the synthesis of indole derivatives. For example, 4-(2-indolyl)-3-buten-2-ones can serve as starting materials for the synthesis of carbazoles.³

Most of the existing methods for the synthesis of indole α,β -unsaturated ketones start with precursors with a

preformed indole nucleus. This approach is exemplified by the interaction of 2-silylindoles with methyl vinyl ketone in the presence of $\text{Pd}(\text{OAc})_2$,⁴ *N,N*-dimethyleneaminoketones with 2-lithioindoles,⁵ and methyllithium and 2-indolylacrylic acid.⁶ However, the most common methods are aldol condensation⁷ and Wittig reactions.^{3a,8}

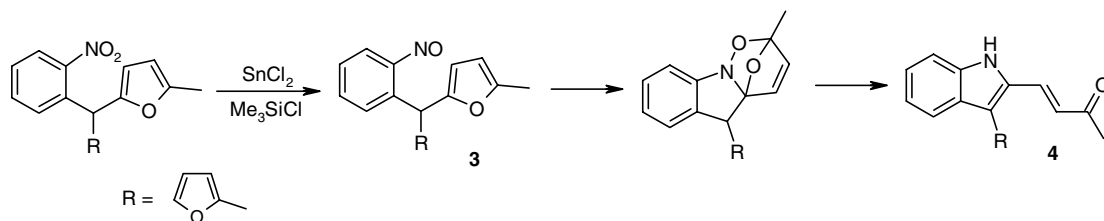
Only two examples are known, which employ simultaneous formation of indole and enone fragments as a result of oxidative heterocyclic ring opening in *ortho*-substituted aryldihetarylmethanes. Thus, Jones et al.⁹ reported that deoxygenation of 2-nitrophenyl-bis(5-*tert*-butylthien-2-yl)methane with triethyl phosphite led to the isolation of unsaturated thioketone **1** ($\text{X} = \text{S}$) and ketone **2** ($\text{X} = \text{O}$) along with the expected thieno[3,2-*b*]quinoline derivative (Scheme 1). It was suggested that these compounds resulted from rearrangement



Scheme 1.

Keywords: Furan; Recyclization; Indole.

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Scheme 2.

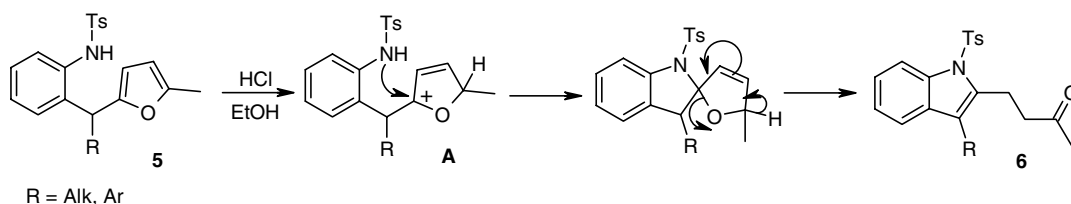
of an intermediate formed by electrophilic attack by a nitrene on the thiophene ring.

Earlier, we demonstrated¹⁰ that reduction of 2-nitrophenyl-bis(5-methylfurfuryl)methane with stannous chloride in the presence of Me₃SiCl also gave 2-indolyl- α,β -unsaturated ketone **4** via oxidative ring opening. In model experiments, it was revealed that the key step of this transformation involves intramolecular [4+2]-cycloaddition of the intermediate nitroso compound (Scheme 2).

Neither the first nor second examples are general, as in one case the title compounds were minor products, and in the second the reaction failed with donor substituents on the benzene ring due to the lowered reactivity of the nitroso group as a dienophile.¹⁰

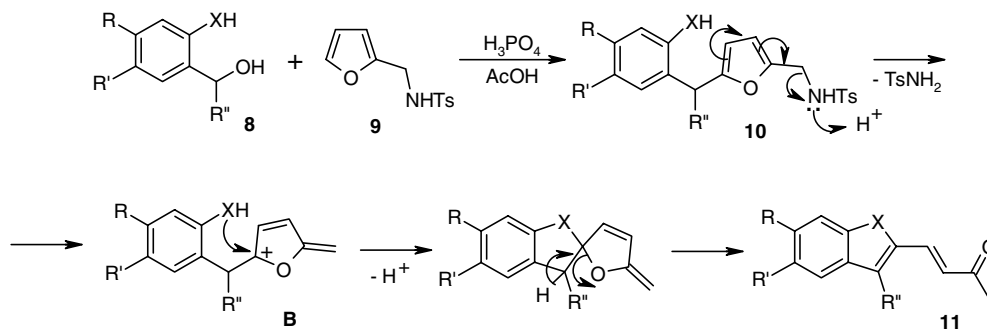
Later, we developed a simple method for the synthesis of 4-(2-indolyl)-3-butan-2-ones **6**, starting from the corresponding 2-tosylaminobenzylfurans **5** (Scheme 3).¹¹ It was postulated that the reaction started with protonation of the furan ring at C5 with the formation of cation **A** and then subsequent nucleophilic attack by the *ortho*-substituent. The generality of this methodology was proven by obtaining of a number of benzannulated heterocycles.¹²

To study the scope of this new reaction and to modify the indole derivative, we attempted the alkylation of *N*-tosylfurfurylamine **9** with benzyl alcohols **8** in acetic acid in the presence of H₃PO₄. However, unexpectedly, 4-(2-indolyl)-3-buten-2-ones **11**¹³ were isolated rather than the desired benzylfurans **10** indicating that formal oxidative furan ring opening had occurred.



Scheme 3.

Table 1.



8, 11	R	R'	R''	X	Yield (%) 11
a	OMe	OMe	H	NTs	28
b	OMe	OMe	Me	NTs	46
c	OMe	OMe	Et	NTs	30
d	OMe	OMe	Ph	NTs	39
e	OMe	OMe	4-MeC ₆ H ₄	NTs	37
f	OMe	OMe	4-BrC ₆ H ₄	NTs	27
g	OCH ₂ CH ₂ O		Me	NTs	37
h			Ph	NTs	6
i	H	OMe	Me	O	18

This result, in the absence of any oxidant, can be ascribed to acid catalyzed elimination of tosylamide¹⁴ with the formation of cation **B** (Table 1 compared with Scheme 3). Further nucleophilic attack by the *ortho*-tosylamino function on the cation, with elimination of a proton, completes the formation of the α,β -unsaturated ketone. In contrast to our proposed mechanism of pseudooxidative furan ring opening via elimination of tosylamide, the common reactions of furan derivatives giving rise to the unsaturated 1,4-diketones reported so far employ electrophilic attack on the furan ring with typical oxidants like molecular oxygen, bromine, pyridinium chlorochromate, and magnesium peroxyphthalate.¹⁵ Intermolecular oxidative fission of the furan ring also starts with electrophilic attack on the furan ring.¹⁶

Although the unoptimized yields of ketones **11** are poor to moderate (6–46%), this simple reaction allows the construction of rather complex indole derivatives in one step. The drawback of the method is that it only works well with benzyl alcohols with donor substituents. In the opposite case, tarry materials are formed and the yields were dramatically reduced. For example, ketone **11h** was isolated in only 6% yield. The reason for this is probably due to the relative stability of the corresponding benzyl cations.

We hypothesized that the introduction of other suitable nucleophiles to the *ortho*-position of the benzyl alcohol could extend the scope of the reaction. This possibility was demonstrated in the reaction of the tosylfurfurylamine and saligenol derivative **8i** which gave 4-(2-benzofuryl)-3-buten-2-one **11i**.¹⁷

Acknowledgements

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References and notes

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- A typical procedure is as follows: A mixture of **8d** (4.13 g, 10 mmol), 2-(4-methylphenylsulfonamidomethyl)furan (3.01 g, 12 mmol), 30 ml of acetic acid and 3 ml of phosphoric acid was heated at reflux for 11 h. The mixture was poured into 500 ml of water and neutralized with the solid NaHCO₃. The precipitate formed was filtered off, washed with water, and dried. The product was isolated by column chromatography (adsorbent silica gel 50/160, eluent acetone/methylene chloride/hexane 5:3:20). Yield of compound **11d** 1.85 g (39%). Mp 172–173 °C; Anal. found: C, 68.01; H, 5.53%. C₂₇H₂₅NO₅S requires: C, 68.19; H, 5.30%; ν_{\max} (KBr): 1666 cm⁻¹; δ_{H} (200 MHz, CDCl₃): 2.29 (3H, s, CH₃), 2.36 (3H, s, CH₃), 3.77 (3H, s, OCH₃), 4.05 (3H, s, OCH₃), 6.01 (1H, d, *J* = 16.5 Hz, =CH), 6.62 (1H, s, H_{Ind}), 7.17 (2H, d, *J* = 8.2 Hz, H_{TS}), 7.19–7.26 (2H, m, H_{Ph}), 7.40–7.47 (3H, m, H_{Ph}), 7.55 (2H, d, *J* = 8.2 Hz, H_{TS}), 7.86 (1H, s, H_{Ind}), 8.09 (1H, d, *J* = 16.5 Hz, =CH).
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- Mp 90–91 °C; Anal. found: C, 72.85; H, 6.38%. C₁₄H₁₄O₃ requires: C, 73.03; H, 6.13%; ν_{\max} (KBr): 1660 cm⁻¹; δ_{H} (250 MHz, CDCl₃): 2.35 (3H, s, CH₃), 2.42 (3H, s, CH₃), 3.87 (3H, s, OCH₃), 6.83 (1H, d, *J* = 15.6 Hz, =CH), 6.93 (1H, d, *J* = 2.4 Hz, H_{Br}), 6.99 (1H, dd, *J* = 2.4, 8.8 Hz, H_{Br}), 7.32 (1H, d, *J* = 8.8 Hz, H_{Br}), 7.49 (1H, d, *J* = 15.6 Hz, =CH).