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Tetrahedron Letters 47 (2006) 4113–4116

Tetrahedron Letters

Furan as a 1,3-diketone equivalent: the second type furan recyclization applied to indole synthesis

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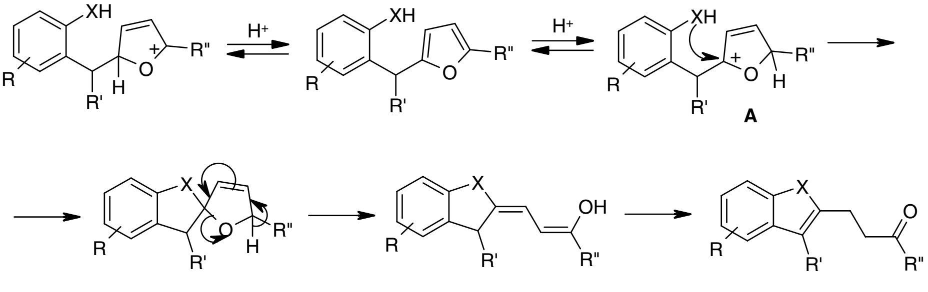
Received 23 January 2006; revised 8 April 2006; accepted 19 April 2006

Abstract—A new approach for the synthesis of indole derivatives based on protolytic recyclization of 2-alkyl-5-(2-tosylaminoaryl)-furans is described. The furan ring in this unusual transformation formally serves as a 1,3-diketone equivalent.

During recent years we have been involved in the elaboration of a general method for the synthesis of benzannelated heterocycles based on recyclization of *ortho*-substituted benzylfurans under protolytic conditions.[1] By varying the substituent at the *ortho*-position of the benzylfuran, different types of heterocyclic systems as benzofurans,[2] indoles,[3] isocoumarins,[4] isoquinolones[5] and isochromenes[6] (Scheme 1) can be obtained. The method is based on the ability of the furan ring, in acidic media, to serve as a 1,4-diketone equivalent. Such reactions are well known and are widely used in synthetic organic chemistry.[7]

In continuation of our ongoing interest in furan recyclization reactions we studied the behavior of 2-alkyl-5-(2-tosylaminoaryl)furans under the acidic conditions, which are commonly used for the recyclization of 2-tosylaminobenzylfurans into indole derivatives. In this case indole derivatives were obtained as well. As a starting material we employed carbonyl derivatives of 2-nitroarylfurans **1**, readily available by arylation of furfural and acetylfuran.[8] Reduction of compounds **1** with $NaBH_4$ in the presence of an equimolar quantity of $AlCl_3$ in dry tetrahydrofuran gave 2-alkyl-5-(2-nitroaryl)-furans **2**.[9] Subsequent reduction of the nitro group with Raney-Ni[10] and tosylation of the resulting anilines **3** gave compounds **4**[11] with good overall yields (Scheme 2).

Refluxing compounds **4** in ethanol saturated with hydrogen chloride afforded indole derivatives **5** in moderate yields (Scheme 3). However, unlike the



X = O, NTs, NAc, COO, CONAlk, CH_2O

Keywords: Furan; Recyclization; Indole.

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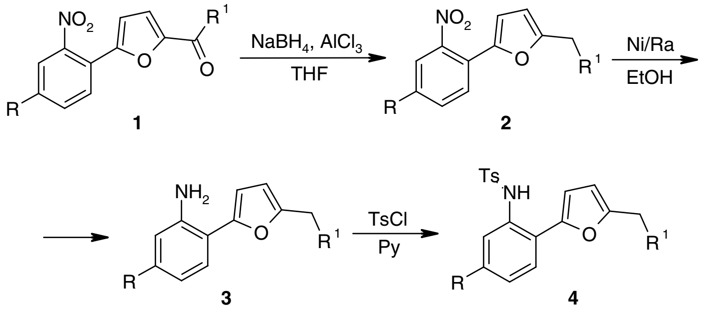
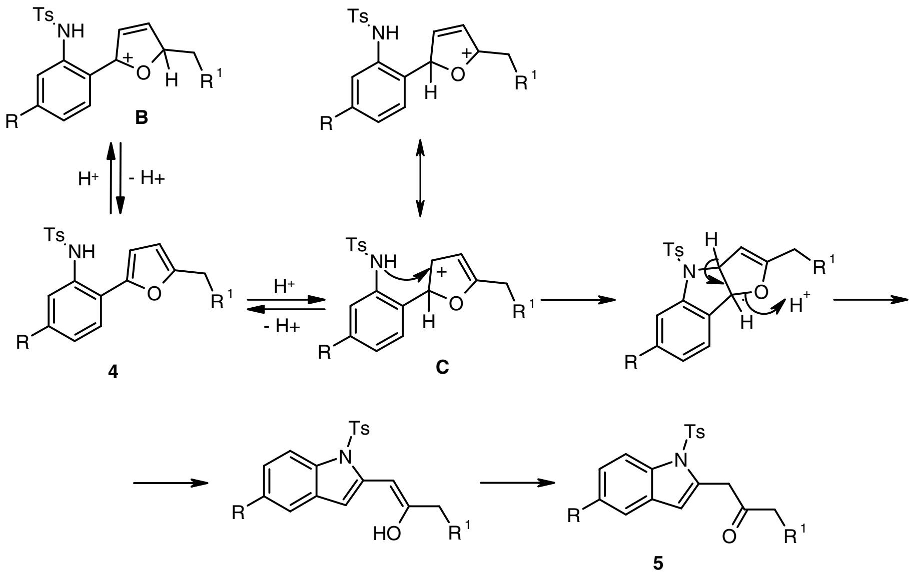
doi:10.1016/j.tetlet.2006.04.080



1-4	R	R^1	Yield **4** (%)
a	H	H	43
b	Me	H	40
c	Cl	H	48
d	OCH_3	H	50
e	H	Me	46

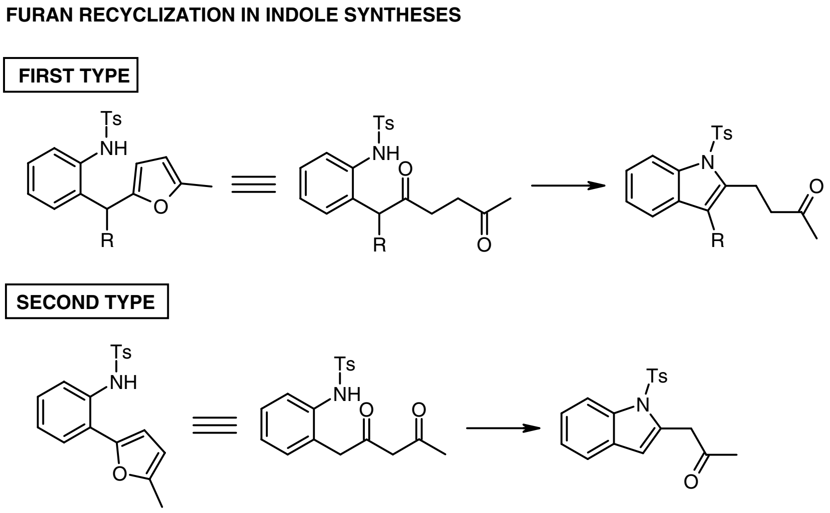
Scheme 2.



4, 5	R	R^1	Yield **5** (%)
a	H	H	83
b	Me	H	75
c	Cl	H	85
d	OCH_3	H	64
e	H	Me	80

Scheme 3.

2-tosylaminobenzylfurans which recyclize within 10–40 min under these conditions,[3] 2-tosylaminoarylfurans **4** required much longer reaction times (4–12 h) with incomplete conversion of the starting compounds **4**. Evidently, both transformations proceed via furan ring protonation with intermediate formation of furyl cations (Schemes 1 and 3). Consideration of the structures of these cations in both cases allowed us to assume a reason for such a striking difference in the duration of the reaction. Thus the substituents in positions 2 and 5 of the furan ring in the case of the corresponding benzylfurans have approximately the same electronic properties and protonation at either alpha position of the furan ring is equally probable. This leads to a sufficiently



Scheme 4.

high concentration of the furyl cation **A**, amenable to the formation of the final product (Scheme 1). In the case of 2-tosylaminoarylfurans **4**, protonation can result in two furyl cations sufficiently different in their stability. Evidently furyl cation **B** must be more thermodynamically stable than cation **C** due to additional delocalization of the positive charge on the aryl substituent. Consequently, a low equilibrium concentration of the cation **C**, which is an intermediate in indole **5** formation leads to a considerable increase in reaction time. Bearing this in mind we attempted a reaction under much more severe conditions hoping that an increase in the acidity would raise the concentration of the requisite cation **C** under kinetic control conditions. In fact, carrying out the reaction in boiling acetic acid in the presence of sufficient amounts of 72% $HClO_4$ allowed us to shorten the reaction time to 10–15 min and improve the yields of the indoles **5** (Scheme 3).[12]

In conclusion, we have reported a new approach to substituted indoles based on the recyclization of 2-tosylaminoarylfurans. The method developed is of preparative value in indole chemistry since all the steps are high yielding and reproducible. Indole derivatives available by this reaction possess an active carbonyl group in the side chain and a free position at C-3, which makes them attractive for further transformations. In addition, this transformation is of interest for improved understanding of furan chemistry as the furan ring here formally acts as a 1,3-dicarbonyl compound equivalent. As was noted previously,[2–6] the furan ring in the benzylfuran acid-catalyzed rearrangement plays the role of a latent 1,4-dicarbonyl compound and we named this process recyclization of the first type. Thus we have named the rearrangement discussed in this work as the recyclization of the second type (Scheme 4). To the best of our knowledge recyclizations of this type in acidic media are unknown.

The study of the scope of this reaction is in progress as it can be successfully applied to the synthesis of other heterocycles by introduction of a suitable nucleophilic group to the *ortho*-position of the aryl ring as was the case for recyclization of benzylfurans.

Acknowledgements

Financial support was provided by Bayer HealthCare AG and the Russian Foundation of Basic Research (grant 03-03-32759).

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8. Compounds **1** were prepared using the Meerwein method. For a typical procedure see: Janda, L.; Voticky, Z. *Chem. Zvesti* **1984**, *38*, 507–513. A general method for the arylation reaction is as follows: A mixture of 2-nitroaniline derivative (0.3 mol), 400 ml of water and 200 ml of 36% hydrochloric acid was stirred for 30 min at 80 °C. To the resulting suspension of aniline hydrochloride, under stirring and cooling (−10 to 0 °C), a solution of $NaNO_2$ (25 g, 0.36 mol) in 120 ml of water was added gradually. The resulting solution of the diazonium salt was stirred for another 40 min at −5 to 0 °C, then filtered, and a solution of furfural (0.3 mol) in 150 ml of acetone was added followed by a solution of $CuCl_2$ (8 g, 0.06 mol) in 100 ml of water. The reaction mixture was stirred for 12 h at room temperature. After completion of the reaction, the resulting precipitated product was filtered off and recrystallized from ethanol/acetone mixture. Yields of 5-arylfurfurals **1a**–**d** were 45–53%. The yield of 2-acetyl-5-phenylfuran **1e** was 41%.
9. Compounds **2** were synthesized according to the procedure reported earlier: Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* **1987**, 736–738. A typical procedure is as follows: To a stirred and cooled solution (0–5 °C) of aldehyde **1a** in tetrahydrofuran (8.68 g, 0.04 mol), anhydrous aluminum chloride (9.58 g, 0.072 mol) and sodium borohydride (2.74 g, 0.072 mol) were added portionwise and the resulting suspension was stirred at 0–5 °C for 20 min and then brought to reflux. After 1–2 h (TLC monitoring) the reaction mixture was cooled and poured into 700 ml of water. The product was extracted with ether (3 × 50 ml) and the combined ethereal extract was dried over sodium sulfate, treated with active charcoal and evaporated under reduced pressure. The obtained residue **2a** was used in the next step as such.
10. A typical procedure is as follows: To an ethanolic solution of compound **2a** (8.12 g, 0.04 mol) active Raney nickel was added (4 g) along with 10 ml of hydrazine hydrate and the reaction mixture refluxed for 1–2 h. After completion of the reaction (TLC monitoring) the nickel was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in benzene/hexane mixture (1:1) and filtered through a pad of silica gel and evaporated under reduced pressure. The obtained residue **3a** was used in the next step. *Warning*: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.
11. A typical procedure is as follows: To a solution of amine **3a** (6.09 g, 0.035 mol) in 15 ml of pyridine under stirring and cooling in a water bath, *para*-toluenesulphonyl chloride (10.07 g, 0.053 mol) was added gradually. The mixture was stirred for 0.5 h and after completion of the reaction (TLC monitoring), the mixture was poured into 1 l of 6 M hydrochloric acid. The oil which separated was washed with water until it crystallized. The crystals were filtered off, dried, dissolved in benzene/hexane mixture (1:1) and passed through a pad of silica gel. The refined solution was evaporated under reduced pressure and the residue crystallized from ethanol. The yield of the compound **4a**, based on starting material **1a**, was 43% as colorless crystals. Mp 88 °C. Anal. Found: C, 66.22; H, 5.07%. $C_{18}H_{17}NO_3S$ requires: C, 66.03; H, 5.23%; δ_H (250 MHz, $CDCl_3$): 2.32 (3H, s, C*H*$_3$), 2.38 (3H, s, C*H*$_3$), 5.99 (1H, d, *J* = 3.0 Hz, 4-H_{Fur}), 6.22 (1H, d, *J* = 3.0 Hz, 3-H_{Fur}), 7.08–7.14 (1H, m, H_{Ar}), 7.09 (2H, d, *J* = 8.3 Hz, H_{Ts}), 7.21–7.24 (1H, m, H_{Ar}), 7.31–7.34 (1H, m, H_{Ar}), 7.32 (2H, d, *J* = 8.3 Hz, H_{Ts}), 7.61–7.64 (1H, m, H_{Ar}), 7.86 (1H, s, N*H*). *Warning*: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.
12. A typical procedure is as follows: To a solution of compound **4a** (3 g, 0.009 mol) in 30 ml of glacial acetic acid, 3 ml of 70% perchloric acid was added and the mixture refluxed for 10 min. After completion of the reaction (TLC monitoring) the mixture was poured into 500 ml of water and brought to pH = 7 with sodium carbonate. The resulting precipitate was filtered off, dried, dissolved in benzene/hexane mixture (1:1) and passed through a pad of silica gel. The refined solution was evaporated under reduced pressure and the residue recrystallized from ethanol. The yield of compound **5a** was 83% as colorless crystals. Mp 95 °C. Anal. Found: C, 65.89; H, 5.12%. $C_{18}H_{17}NO_3S$ requires: C, 66.03; H, 5.23%; ν_{max} (KBr): 1700 cm^{-1}; δ_H (250 MHz, $CDCl_3$): 2.31 (3H, s, C*H*$_3$), 2.34 (3H, s, C*H*$_3$), 4.13 (2H, s, C*H*$_2$), 6.52 (1H, s, 3-H), 7.20–7.23 (3H, m, H_{Ar}), 7.25 (2H, d, *J* = 8.5 Hz, H_{Ts}), 7.44–7.45 (1H, m, H_{Ar}), 7.68 (2H, d, *J* = 8.5 Hz, H_{Ts}), 7.93–7.96 (1H, m, H_{Ar}). *Warning*: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.