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The effect of an N-substituent on the recyclization of (2-aminoaryl)bis(5-*tert*-butyl-2-furyl)methanes: synthesis of 3-furylindoles and triketoindoles

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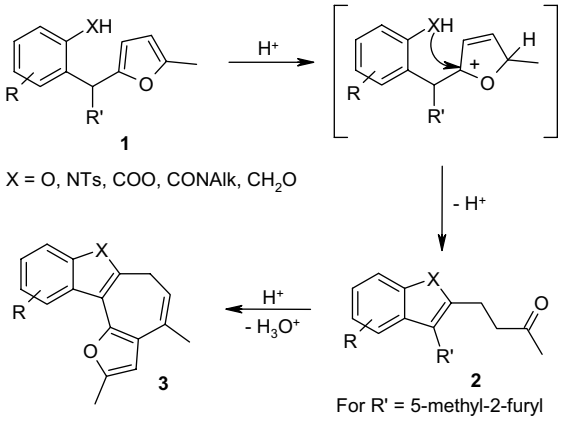
Abstract—The recyclization of (2-aminophenyl)bis(5-*tert*-butyl-2-furyl)methane derivatives has been studied. It was shown that the acid-catalyzed recyclization of *N*-tosylamides leads to the formation of 2-(3-oxoalkyl)-3-(2-furyl)indoles. In contrast, under the same reaction conditions, acetamides are transformed into indoles containing three keto groups. The acid-catalyzed removal of the acetyl group from these substrates facilitated protolytic furan ring opening. The same triketones can be directly obtained from (2-aminoaryl)bis(5-*tert*-butyl-2-furyl)methanes.

3-Furylindoles are poorly explored heterocyclic compounds. Only fragmentary publications dealing with their synthesis are known to date.[1] At the same time, some of these compounds display different types of physiological activity and, therefore, are of interest for biological screening.[2] For this screening, the possibility of modification of the lead molecule is very desirable. The introduction of reactive functional groups into the pharmacophore-containing scaffold is the simplest way for such modification. Earlier, we developed a general approach to benzannelated heterocycles based on the recyclization of *ortho*-substituted benzylfurans (Scheme 1).[3–6] As a continuation of these studies, we decided to elaborate the synthesis of 3-furylindoles possessing a keto group, which is appropriate for further modifications.



Scheme 1.

During our previous studies we showed that the direction of the recyclization depends on the nature of substituent R′ at the benzyl carbon atom (Scheme 1). When R′ = alkyl or aryl, the recyclization affords ketones **2** in good yields.[3] However, for benzylfurans **1** with R′ = 2-furyl, this rearrangement was usually accompanied by secondary cyclization leading to tetracyclic products **3**.[4] For example, treatment of (2-acetylaminoaryl)difurylmethanes **4** with ethanolic hydrogen chloride gave rise to tetracyclic salts **5** (Scheme 2).[5] Variation of the hydrogen chloride concentration, replacement of the acetyl protecting group by benzoyl or sulfonyl, the use of other Bronsted and Lewis acids and variation of the reaction conditions did not prevent the secondary

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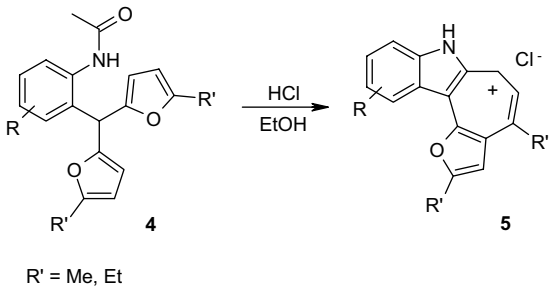


R' = Me, Et

Scheme 2.

cyclization. At the same time, in some cases, careful optimization of the reaction conditions resulted in the target furyl-containing ketones **2** from aryldifurylmethanes.[4d,e] Moreover, our investigation of the (2-carboxyaryl)difurylmethane to isochromone recyclization showed that the presence of a *tert*-butyl group at C5 atom of the furan ring prevented the secondary cyclization due to significant steric hindrance.[4d,6]

Therefore, for the synthesis of ketone-containing 3-furylindoles we used the derivatives of (2-aminophenyl)-bis(5-*tert*-butyl-2-furyl)methane as starting compounds which were synthesized by the reaction sequence shown in Scheme 3. The perchloric acid-catalyzed condensation of 2-nitrobenzaldehydes **6** with 5-*tert*-butylfuran **7** yielded (2-nitroaryl)difurylmethanes **8a–d**,[7] reduction of which with hydrazine hydrate/Raney nickel in refluxing ethanol led to amines **9a–d**[8] (Scheme 3, Table 1). These amines were transformed into the corresponding amides **10a–d**[9] and **11a–d**[10] by tosylation or acetylation of **9**, respectively (Scheme 4, Table 1).

The behavior of compounds **9–11** in the recyclization experiments differed significantly. When tosylamides **10** were heated at reflux in ethanol saturated with hydrogen chloride, 3-furylindoles **12a–d**[11] were isolated as single reaction products (Scheme 5, Table 2). The secondary cyclization was not observed for these substrates even after prolonged heating. This result is in full accordance with the effect of the *tert*-butyl group found earlier for the recyclization of (2-carboxyaryl)difurylmethanes.[4b,6] However, acetamides **11** were transformed into triketones **13a–d**[12] by keeping them either in ethanolic hydrogen chloride for 1 week or in acetic acid in the presence of hydrochloric acid for 24 h at room temperature[13] (Scheme 6, Table 2). In contrast, even in the case of prolonged heating of tosylamides **10** in ethanolic

Table 1. Synthesis of starting compounds **8–11**

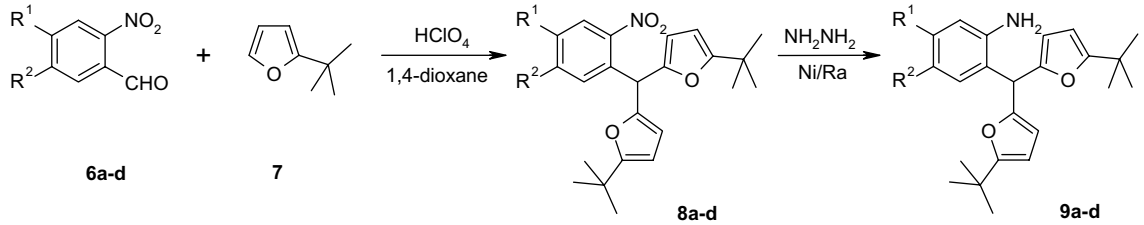
Entry	R^1	R^2	Yield (%)			
			8	**9**	**10**	**11**
a	H	H	92	86	58	53
b	OMe	OMe	94	83	61	57
c	OCH_2O		90	89	65	58
d	OCH_2CH_2O		88	81	68	62

HCl, the corresponding triketones were not observed in the reaction mixture. All these data together allow us to conclude that triketones **13** are formed as a result of a reaction sequence including acetamide deacetylation,[3c] recyclization, and protolytic furan ring opening of the 3-furyl-1*H*-indole intermediates. Indeed, we showed that amines **9** were also converted under the same reaction conditions into the corresponding triketones (Scheme 6).[14]

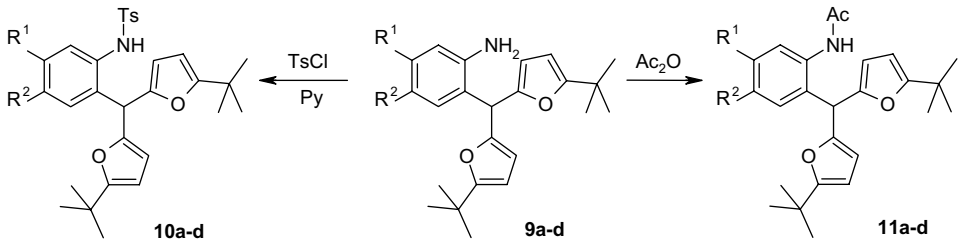
Thus, protolytic opening of the furan ring appeared to be impossible for the deactivated *NTs*-indoles but proceeded readily with *NH*-indoles. To prove this, we synthesized indole **14b**[15] and showed that its treatment with ethanolic hydrogen chloride gave triketone **13b** (Scheme 7).[16]

The crucial difference in the reactivity of compounds **12** and **14** in the acid-catalyzed furan ring opening is determined by the nature of the substituents at C2 of the furan. Indole **12b** is a typical example of a 2-aryl-5-alkylfuran, which are known to be much more resistant to hydrolytic ring opening than 2,5-dialkylfurans due to conjugation between the two aromatic rings. The ready acid-catalyzed furan opening in **14b** can be explained by reversible protonation at C3 of the indole moiety with the formation of tautomeric 3-furyl-3*H*-indole (**A**). In this tautomer, conjugation between the indole and furan counterparts does not exist, so, formally it can be considered as an acid-labile 2,5-dialkylfuran (Scheme 8).

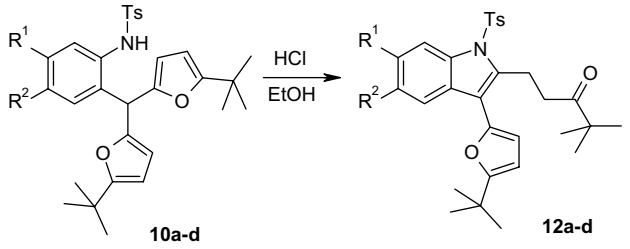
In summary, the direction of the recyclization of (2-aminophenyl)bis(5-*tert*-butyl-2-furyl)methane derivatives depends on the nature of the substituents on the nitrogen atom. The use of tosylamides allows the synthesis of ketone-containing 3-furylindoles as potential physiologically active agents. In contrast, N-unsubstituted derivatives and acetamides form the corresponding triketones as a result of protolytic opening of the furan



Scheme 3.



Scheme 4.

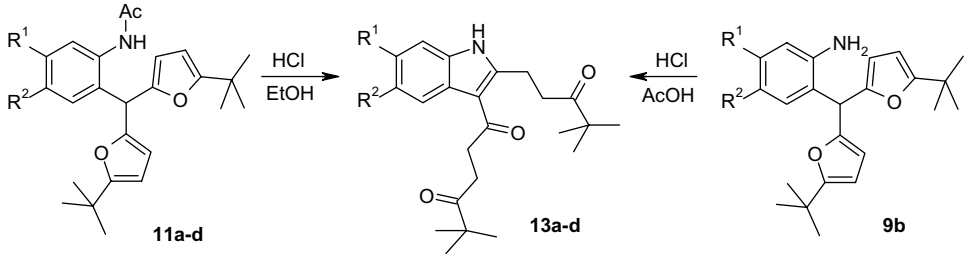


Scheme 5.

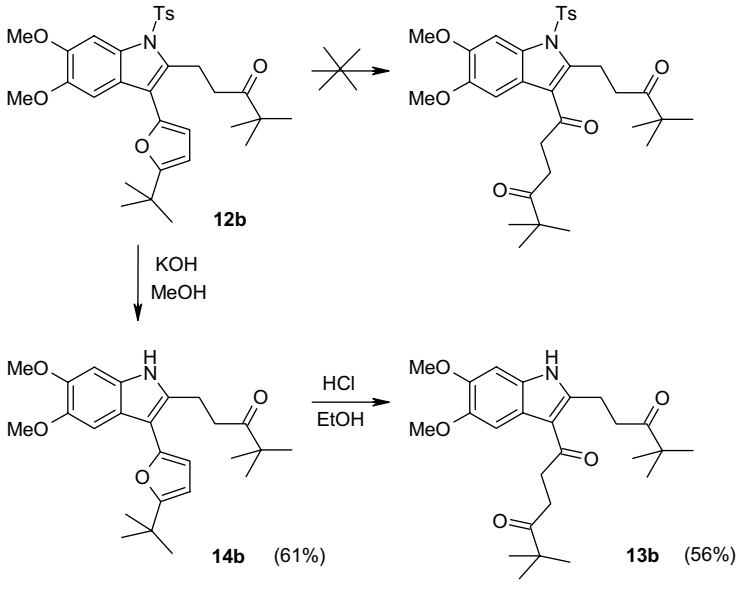
ring in the 3-furyl-3*H*-indole tautomeric form of intermediates. The last transformation can be valuable for preparative chemistry of indoles due to possible transformations of the 1,4-dioxoalkyl substituent at C3 into a variety of 3-hetaryl- and other 3-substituted indoles.

Table 2. Synthesis of 3-furylindoles **12** and triketones **13**

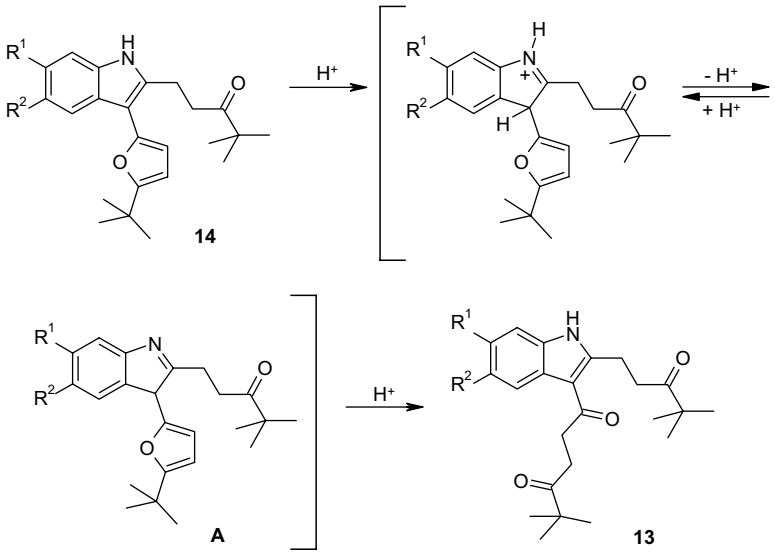
Entry	R^1	R^2	Yield (%)	
			12	**13**
a	H	H	59	42
b	OMe	OMe	62	51
c	OCH_2O		61	56
d	OCH_2CH_2O		65	49



Scheme 6.



Scheme 7.



Scheme 8.

Acknowledgments

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7. A typical procedure is as follows: To a solution of 2-nitrobenzaldehde **6b** (6.33 g, 30 mmol) and 2-*tert*-butylfuran **7** (9.3 g, 75 mmol) in 1,4-dioxane (25 mL), 70% $HClO_4$ (1 mL) was added. The reaction mixture was stirred at 65–70 °C until all the starting compound had been consumed (TLC monitoring), then poured into water, neutralized with $NaHCO_3$, and left overnight at room temperature. The product was extracted with CH_2Cl_2 (2×100 mL). The organic layer was separated, washed with water (2×50 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in hexane, and the resultant solution was filtered through a pad of silica gel (5–40 μm), and evaporated under reduced pressure to dryness. The resulting yellow oil, **8b** (12.44 g, 94%) was used as such in the next step.
8. A typical procedure is as follows: To an ethanolic solution (60 mL) of compound **8b** (6.17 g, 14 mmol), active Raney nickel (4 g) was added along with 5 mL of hydrazine hydrate and the reaction mixture refluxed for 1 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 CH_2Cl_2/hexane mixture and filtered through a pad of silica gel

(5–40 μm) and evaporated under reduced pressure to dryness. The obtained residue, **9b** (4.78 g, 83%) was used as such in the next step.

9. A typical procedure is as follows: *p*-Toluenesulfonyl chloride (1.06 g, 5.6 mmol) was added to a solution of compound **9b** (1.64 g, 4 mmol) in pyridine (7 mL) at room temperature and the mixture was left for 40 min. Then, it was poured into an excess of water and the precipitate was filtered off, washed with water, and dried. Recrystallization from CH_2Cl_2–hexane (1:6) afforded product **10b** as a white solid (1.38 g, 61%). Mp = 117–119 °C. Anal. Calcd for $C_{32}H_{39}NO_6S$: C, 67.94; H, 6.95; N, 2.48. Found: C, 68.05; H, 7.01; N, 2.45; ν_{max} (KBr): 3282, 2959, 1600, 1513, 1462, 1387, 1342, 1207, 1161, 1091, 1008, 904, 784, 678 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (18H, s, *t-Bu*), 2.42 (3H, s, *Me*), 3.68 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 4.79 (1H, s, C*H*), 5.67 (2H, d, *J* 3.1 Hz, H_{Fur}), 5.83 (2H, d, *J* 3.1 Hz, H_{Fur}), 6.42 (s, 1H, H_{Ar}), 6.58 (1H, br s, N*H*), 7.02 (s, 1H, H_{Ar}), 7.27 (2H, d, *J* 8.2 Hz, H_{Ts}), 7.63 (2H, d, *J* 8.2 Hz, H_{Ts}).
10. A typical procedure is as follows: A mixture of compound **9b** (5.34 g, 13 mmol) in acetic anhydride (2.5 mL) was left at 55–60 °C for 15 min. Then, it was poured into an excess of water; the precipitate was filtered off, washed with water, and dried. Recrystallization from CH_2Cl_2–hexane (1:8) afforded compound **11b** as a white solid (3.36 g, 57%). Mp = 122 °C. Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09. Found: C, 71.70; H, 7.69; N, 3.02; ν_{max} (KBr): 3294, 2968, 1658, 1533, 1257, 1208, 1103, 1014, 785 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (18H, s, *t-Bu*), 2.03 (3H, s, *Me*), 3.76 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 5.38 (1H, s, C*H*), 5.89 (1H, br s, N*H*), 5.90–5.92 (4H, m, H_{Fur}), 6.58 (1H, s, H_{Ar}), 7.41 (1H, s, H_{Ar}).
11. A typical procedure is as follows: Ethanolic HCl (25 mL) prepared by saturation of 200 g of EtOH with 100 g gaseous HCl was added to a solution of compound **10b** (2.26 g, 4 mmol) in EtOH (20 mL). The reaction mixture was refluxed until all the starting compound had been consumed (TLC monitoring). The reaction mixture was poured into water and the precipitate obtained was filtered off, washed with water, and dried. Recrystallization from CH_2Cl_2–hexane (1:3) afforded compound **12b** as a white solid (1.40 g, 62%). Mp = 138–139 °C. Anal. Calcd for $C_{32}H_{39}NO_6S$: C, 67.94; H, 6.95; N, 2.48. Found: C, 68.16; H, 7.11; N, 2.51; ν_{max} (KBr): 2961, 1701, 1489, 1365, 1307, 1157, 1059, 1013, 848, 783 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (9H, s, *t-Bu*), 1.34 (9H, s, *t-Bu*), 2.35 (3H, s, *Me*), 2.99–3.07 (2H, m, CH_2), 3.33–3.41 (2H, m, CH_2), 3.93 (3H, s, O*Me*), 4.00 (3H, s, O*Me*), 6.09 (1H, d, *J* 3.2 Hz, H_{Fur}), 6.39 (1H, d, *J* 3.2 Hz, H_{Fur}), 7.19 (2H, d, *J* 8.2 Hz, H_{Ts}), 7.35 (1H, s, H_{Ind}), 7.60 (2H, d, *J* 8.2 Hz, H_{Ts}), 7.88 (1H, s, H_{Ind}); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.6, 22.4, 26.5 (3C), 29.1 (3C), 32.7, 37.6, 44.1, 56.0, 56.4, 99.0, 102.1, 103.7, 108.2, 113.7, 121.2, 126.2 (2C), 130.0 (2C), 130.9, 135.0, 135.9, 144.9, 146.1, 147.4, 147.8, 163.5, 214.9; MS (EI) *m/z*: 565 (3, M^+), 412 (29), 411 (100), 397 (23), 396 (81), 326 (12), 313 (15), 312 (70), 297 (14), 296 (33), 92 (18), 91 (34), 57 (53).
12. A typical procedure is as follows: A suspension of compound **11b** (2.04 g, 4.5 mmol) in ethanolic HCl (50 mL) prepared by saturation of 200 g of EtOH with 100 g gaseous HCl was left at room temperature until all the starting compound had been consumed (TLC monitoring). The reaction mixture was poured into water, neutralized with $NaHCO_3$; the precipitate was filtered off, washed with water, and dried. Compound **13b** was isolated by column chromatography (silica gel, 50–160 μm; eluent: hexane–acetone–CH_2Cl_2, 15:5:3) as a white solid. Yield of **13b** (0.98 g, 51%). Mp = 138–139 °C. Anal. Calcd for $C_{25}H_{35}NO_5$: C, 69.90; H, 8.21; N, 3.26. Found: C, 69.96; H, 8.05; N, 3.11; ν_{max} (KBr): 3344, 2969, 1702, 1693, 1625, 1480, 1462, 1127, 1015, 856, 817, 756 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.09 (9H, s, *t-Bu*), 1.23 (9H, s, *t-Bu*), 2.97–3.06 (m, 4H, CH_2), 3.21–3.26 (m, 2H, CH_2), 3.33–3.38 (m, 2H, CH_2), 3.91 (s, 3H, O*Me*), 3.96 (s, 3H, O*Me*), 6.86 (s, 1H, H_{Ind}), 7.46 (s, 1H, H_{Ind}), 9.07 (br s, 1H, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.3, 26.4 (3C), 26.7 (3C), 30.8, 36.2, 36.6, 44.1 (2C), 56.1, 56.5, 94.6, 103.5, 113.5, 119.1, 128.9, 145.5, 146.2, 146.9, 195.3, 215.2, 217.8; MS (EI) *m/z*: 429 (36), 344 (14), 288 (13), 272 (10), 244 (12), 204 (16), 190 (15), 141 (85), 113 (48), 58 (100), 57 (54).
13. Refluxing of **11** in ethanolic HCl led to significant decomposition and, as a result, to lower yields of the reaction products.
14. Thirty-five percent of hydrochloric acid (7 mL) was added to a cooled solution (10–12 °C) of compound **9b** (1.0 g, 2.4 mmol) in AcOH (25 mL). The reaction mixture was left at room temperature for 24 h. After completion of the reaction (TLC monitoring), the mixture was poured into water, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and evaporated to dryness. Compound **13b** was isolated as described in Ref. 12. Yield of **13b** (0.44 g, 43%).
15. Compound **12b** (1.13 g, 2 mmol) was added to solution of KOH (5.6 g, 100 mmol) in MeOH (23 mL) and the mixture was refluxed for 4 h. After completion of the reaction (TLC monitoring), the mixture was poured into 200 mL of water and the product was extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was washed with water (3 × 100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was recrystallized from CH_2Cl_2–hexane (1:10). Yield of **14b** (0.50 g, 61%) as a white solid. Mp = 140–141 °C. Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 73.01; H, 8.09; N, 3.42; ν_{max} (KBr): 3356, 2964, 1704, 1488, 1456, 1336, 1220, 1200, 1188, 1132, 1008; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (9H, s, *t-Bu*), 1.39 (9H, s, *t*-Bu), 2.96–3.00 (m, 2H, CH_2), 3.19–3.23 (m, 2H, CH_2), 3.90 (s, 3H, O*Me*), 3,95 (s, 3H, O*Me*), 6.08 (1H, d, *J* 3.1 Hz, H_{Fur}), 6.27 (1H, d, *J* 3.1 Hz, H_{Fur}), 6,83 (s, 1H, H_{Ind}), 7,36 (s, 1H, H_{Ind}), 8,53 (br s, 1H, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 26.5 (3C), 29.2 (3C), 32.7, 36.9, 44.2, 56.2, 56.3, 94.4, 101.9, 103.2, 104.1, 104.9, 118.8, 129.4, 134.2, 145.1, 146.7, 149.1, 161.8, 217.4; MS (EI) *m/z*: 411 (100, M^+), 396 (42), 57 (70).
16. Transformation of **14b** into **13b** was performed analogously to the preparation of **13b** from **11b** (see Ref. 12).