Synthesis of (indol-2-yl)furazans

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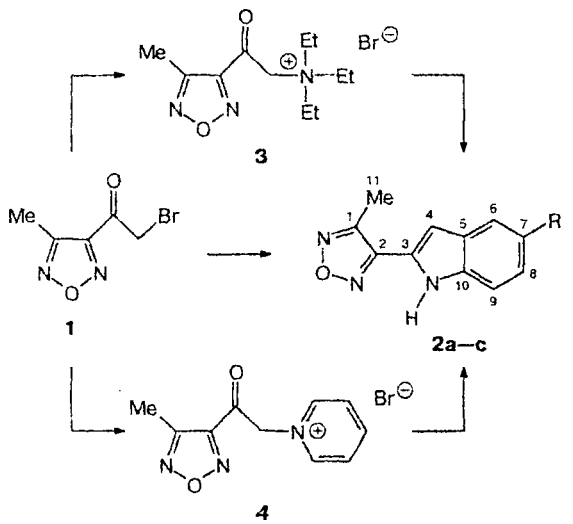
The Bischler reaction and some its modifications were used for the synthesis of derivatives of (indol-2-yl)furazans starting from 3-bromoacetyl-4-methylfurazan and substituted anilines.

Key words: furazans, indoles, Bischler reaction, 3-bromoacetyl-4-methylfurazan, anilines.

Azoles containing the indole fragment as a substituent attract considerable attention of specialists in the chemistry of physiologically active compounds. Of numerous procedures for the synthesis of indole derivatives, only a few of them are used for preparing compounds containing azole residues. The introduction of the indol-2-yl substituent into the azole molecule was performed only by the Fischer—Arbuzov reaction. All aspects of the chemistry and applications of azolylindoles were summarized in the review.[1]

We established for the first time that 2-azolylindoles can be prepared by the Bischler reaction,[2] which has been previously used for the synthesis of 2-alkyl- and 2-arylindoles only. Thus, refluxing of 3-bromoacetyl-4-methylfurazan (**1**) [3] with aniline afforded compound **2a** in 11% yield. The known modification[4] of the Bischler reaction, *viz.*, the use of trialkylammonium derivatives of the initial α-bromo ketones (in our case, compound **3**), allowed us to obtain indole **2a** in 19% yield. When pyridinium salt **4** was used as the starting compound, the yield of **2a** was 33%.

Схема 1



R = H (**a**), Me (**b**), F (**c**)

The use of anilines devoid of electron-withdrawing substituents in this reaction makes it possible to prepare indoles with the corresponding substituents in the benzene ring (Scheme 1).

Attempts to carry out the reaction with nitro- and trifluoromethylanilines as well as with methyl 4-aminobenzoate failed.

It is known that the Bischler reaction can afford either 2- or 3-substituted indoles.[2] The formation of a particular positional isomer in this reaction depends on the structure of the initial bromoacetyl compound. In the case of aryl bromomethyl ketones, 2-substituted indoles were formed, while the reactions with their alkyl analogs afforded 3-substituted indoles. To date, the participation of α-bromo ketones of the heterocyclic series in this reaction has not been reported.

The conclusions about the structures of the indole derivatives prepared in this work were made based on the ^{13}C NMR spectral data. According to the published data, the characteristic chemical shifts of the C(2) and C(3) atoms of indole are δ 121.6—133.4 and 101.6—119.8, respectively.[5] In the spectra of compounds **2a—c** the CH groups of the pyrrole ring give signals at δ 104—105, which suggests that the furazanyl substituent is attached to the C(2) atom of the indole.

Experimental

The mass spectra were obtained on a Varian MAT-311A instrument at 70 eV. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (at 300 and 75 MHz, respectively) in DMSO-d_6 and $CDCl_3$. The assignment of the signals in the ^{13}C NMR spectra was made based on the double heteronuclear resonance and selective polarization transfer from hydrogen nuclei.

The purity of the resulting compounds was monitored by TLC on Silufol UV-254 plates using a 5 : 2 CH_2Cl_2—pentane system.

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3-Bromoacetyl-4-methylfurazan (1) was prepared according to a known procedure.[3] Freshly distilled aniline derivatives were used. Pyridine and triethylamine were distilled over KOH.

***N*-[2-(4-Methylfurazan-3-yl)-2-oxoethyl]triethylammonium bromide (3).** Triethylamine (1.01 g, 0.01 mol) was added dropwise with stirring to a solution of 3-bromoacetyl-4-methylfurazan (**1**) (2.05 g, 0.01 mol) in anhydrous diethyl ether (30 mL) cooled to 0 °C. The reaction mixture was stirred for 2 h with warming to ~20 °C. The precipitate that formed was filtered off and washed with ether and pentane. Salt **3** was obtained in a yield of 2.98 g (97%) and was immediately used for subsequent transformations without additional purification. Salt **3** is unstable and rapidly decomposes.

***N*-[2-(4-Methylfurazan-3-yl)-2-oxoethyl]pyridinium bromide (4)** was prepared as described above in 97% yield. This compound was also used for subsequent transformations without additional purification.

3-(Indol-2-yl)-4-methylfurazan (2a). Method *A*. A mixture of 3-bromoacetyl-4-methylfurazan (**1**) (2.05 g, 0.01 mol) and aniline (8 mL) was refluxed under an atmosphere of argon for 3.5 h. The reaction mixture was cooled to 20 °C and poured into 5% hydrochloric acid. The reaction mixture was stirred for 30 min and extracted with a 5 : 1 CH_2Cl_2—pentane mixture. The extract was dried with $MgSO_4$ and filtered through a layer of silica gel. Then the solvent was removed. The residue was recrystallized from hexane to give white flocculent product **2a** in a yield of 0.22 g (11%), m.p. 184—185 °C. ^{1}H NMR ($CDCl_3$), δ: 2.7 (s), 7.0 (s), 7.2 (t), 7.3 (t), 7.5 (d), 7.7 (d), 9.0 (q). ^{13}C NMR ($CDCl_3$), δ: 9.7 (CH_3); 105.0 (C(4)); 111.4 (C(9)); 120.9, 121.6 (C(6), C(7)); 123.2 (C(3)); 124.8 (C(8)); 128.1 (C(5)); 137.0 (C(10)); 147.5 (C(2)); 149.2 (C(1)). MS, *m/z*: 199 $[M]^+$, 169 $[M - NO]^+$.

Method *B*. Analogously, indole **2a** was prepared from salt **3** (3.06 g, 0.01 mol) and aniline (5 mL) in a yield of 0.38 g (19%).

Method *C*. The analogous reaction of salt **4** (2.84 g, 0.01 mol) with aniline afforded indole **2a** in 33% yield.

3-(5-Methylindol-2-yl)-4-methylfurazan (2b). A mixture of *N*-[2-(4-methylfurazan-3-yl)-2-oxoethyl]pyridinium bromide (**4**) (2.84 g, 0.01 mol) and *p*-toluidine (10 mL) was refluxed under argon for 3.5 h and treated as described above. After recrystallization from a hexane—CCl_4 mixture, compound **2b** was obtained as elongated white crystals in a yield of 0.79 g (37%), m.p. 213—214 °C. ^{1}H NMR (DMSO-d_6), δ: 2.35 (s), 2.65 (s), 7.0 (d), 7.1 (d), 7.4 (s), 7.4 (d), 11.7 (q). ^{13}C NMR (DMSO-d_6), δ: 9.1 (CH_3); 20.9 ($\underline{C}H_3$—Ar); 104.3 (C(4)); 111.6 (C(9)); 120.3 (C(6)); 122.4 (C(3)); 125.4 (C(8)); 127.7 (C(5)); 128.5 (C(7)); 135.9 (C(10)); 147.8 (C(2)); 149.9 (C(1)). MS, *m/z*: 213 $[M]^+$, 183 $[M - NO]^+$.

3-(5-Fluoroindol-2-yl)-4-methylfurazan (2c) was prepared analogously to compound **2b** starting from *p*-fluoroaniline. The yield was 31%. Colorless crystals, m.p. 244—245 °C (from CCl_4). ^{1}H NMR (DMSO-d_6), δ: 2.6 (s), 7.0 (s), 7.1 (dt), 7.3 (dd), 7.5 (dd). ^{13}C NMR (DMSO-d_6), δ: 9.26 (CH_3); 104.8 (d, C(4)); 105.5 (d, C(6)); 112.4 (d, C(8)); 113.1 (d, C(9)); 124.4 (C(3)); 127.7 (C(5)); 134.3 (C(10)); 147.8 (C(2)); 150.2 (C(1)); 157.2 (d, C(7)). MS, *m/z*: 217 $[M]^+$, 187 $[M - NO]^+$.

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