Reaction of 3-trifluoroacetylchromones with diamines

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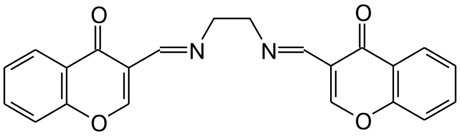
Reaction of 3-(trifluoroacetyl)chromones with ethylenediamine and *o*-phenylenediamine depending on the nature of substituents and the reaction conditions afforded either mono-adducts, 3-[(2-aminoethyl)aminomethylidene]- and 3-[(2-aminophenyl)aminomethylidene]-2-hydroxy-2-(trifluoromethyl)chroman-4-ones, or bis-adducts, *N,N´*-ethylenebis- and *N,N´-o*-phenylenebis[3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-ones].

Key words: 3-(trifluoroacetyl)chromones, imines, ethylenediamine, *o*-phenylenediamine, organofluorine compounds, heterocyclization.

Recently,[1—3] we described the synthesis of 3-(polyfluoroacyl)chromones, the highly reactive compounds, which due to the presence of three electrophilic centers (C(2), C(4), and R^FCO atoms) can serve as the starting materials in the synthesis of a broad variety of new R^F-containing heterocycles.[4,5] (Polyfluoroacyl)chromones react with aliphatic and aromatic amines by the mechanism of nucleophilic 1,4-addition, accompanied by the opening of the pyranone ring and cyclization to 3-alkyl- and 3-arylaminomethylidene-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones.[2—4] The present work deals with the reaction of 3-(trifluoroacetyl)chromones with diamines, such as ethylenediamine and *o*-phenylenediamine. It is known[6-10] that 3-formylchromones react with these diamines to form compounds **1—4**.



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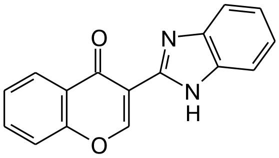

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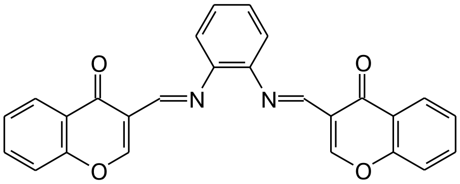

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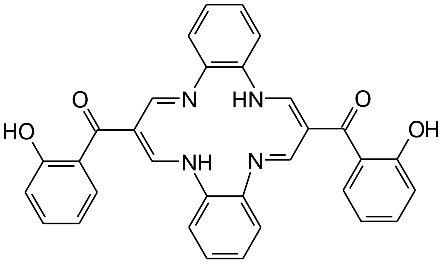

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Results and Discussion

Taking into account that CF_3 group stabilizes the cyclic hemi-ketal form, making the dehydration step difficult, it can be assumed that, in comparison with 3-formylchromones, the reaction of ethylenediamine and *o*-phenylenediamine with 3-(trifluoroacetyl)chromones **5** would stop at a stage of 3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-ones, as it occurred in case of primary aliphatic and aromatic monoamines described earlier.[2—4] In fact, we found that the reaction of 3-(trifluoroacetyl)chromones **5a—d** with ethylenediamine and *o*-phenylenediamine, depending on the reaction conditions and the nature of the substituents in benzene ring of chromones, afforded either mono-adducts, *viz.*, 3-[(2-aminoethyl)aminomethylidene]-2-hydroxy-2-(trifluoromethyl)chroman-4-ones (**6b**,**d**) and 3-[(2-aminophenyl)aminomethylidene)]-2-hydroxy-2-(trifluoromethyl)chroman-4-ones (**7a**,**b**), or bis-adducts, *viz.*, *N,N´*-ethylene-bis(3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-ones) (**8a**,**c**) and

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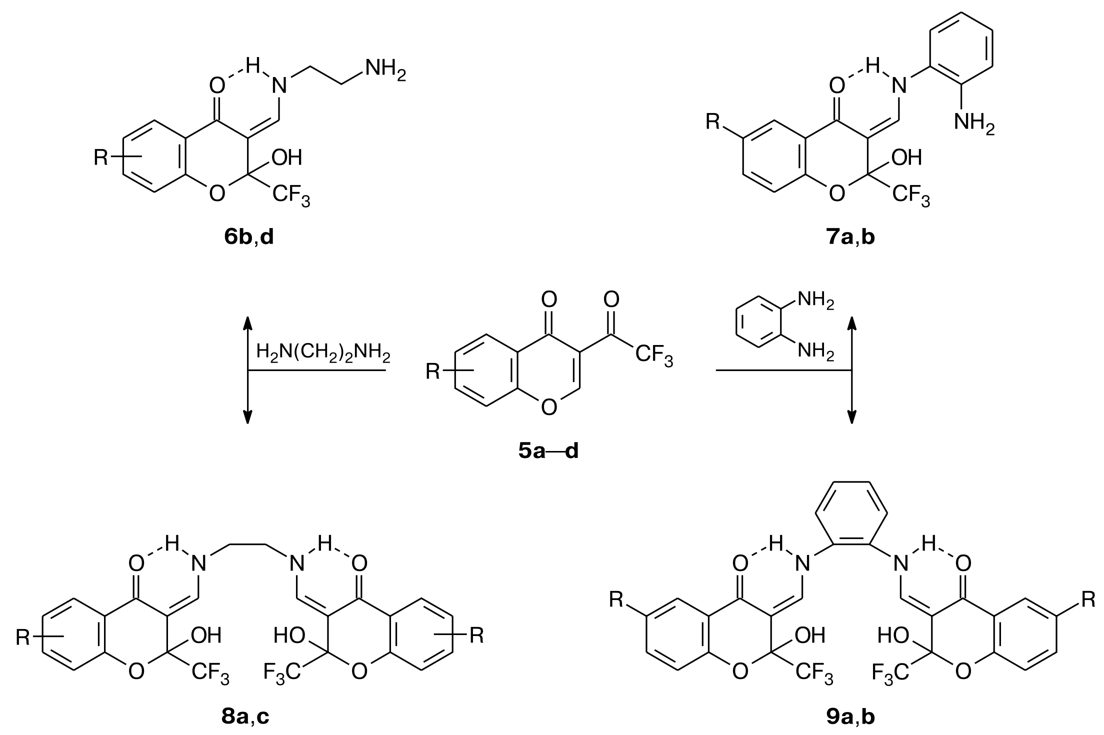
Scheme 1



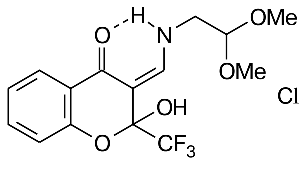
R = H (**a**), 6-Me (**b**), 6-Cl (**c**), 7-OMe (**d**)

N,*N*′-*o*-phenylene-bis(3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-ones) (**9a**,**b**) (Scheme 1).

The reaction with the more basic ethylenediamine was carried out in methanol at −10 °C, nevertheless, even under such mild conditions, a remarkable cleavage of chromones **5** to the corresponding 2-hydroxyacetophenones was observed, resulting in no more than 32% yield of products **6** and **8**. Chromones **5b**,**d** with electron-donating groups gave mono-adducts **6b**,**d** only, whereas under similar conditions, unsubstituted chromone **5a** and 6-chlorochromone **5c** afforded only bis-adducts **8a**,**c**, which points to the significant influence of substituents in benzene ring of chromones **5** on the reactivity of C(2) atom, an attack of which triggers these transformations. All attempts to obtain bis-adducts from chromones **5b**,**d**, as well as mono-adducts from **5a**,**c** failed. Treatment of chromones **5b**,**c** with trimethylenediamine gave the negative results, too.

In contrast to ethylenediamine, the reaction course of the less basic *o*-phenylenediamine with chromones **5a**,**b** can be easily controlled by the reaction conditions. Thus mono-adducts **7a**,**b** are formed by the reaction with the excess of *o*-phenylenediamine in methanol at ~20 °C, whereas a reflux in methanol with the excess of chromone gave bis-adducts **9a**,**b** (the yields were 62—65%). Compounds **8a**,**c** and **9a**,**b** are formed as mixtures of two diastereomers in the ratio 1 : 1, this follows from the ^{1}H NMR spectra, in which the two sets of signals, mostly overlapped, are observed (see Experimental).

It should be finally noted that functionalized amines and amines of naphthalene series, such as aminoacetaldehyde dimethyl acetal and α-naphthylamine, react with chromones **5a**,**c** to form 3-aminomethylidenechroman-4-ones **10** and **11**, which are of interest for further transformations in this series.



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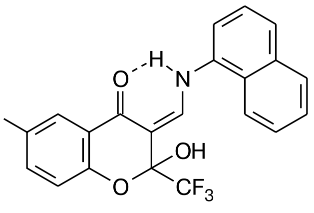

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In conclusion, the reaction of ethylenediamine and *o*-phenylenediamine with 3-(trifluoroacetyl)chromones stops at the stage of re-cyclization to 3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-ones and, depending on the structure of the substrate and the reaction conditions, can lead both to the mono- and to the bis-adducts. Due to the presence of CF_3 group, the dehydration to the corresponding aldimines, as it occurred in case of 3-formylchromones, does not take place.

Experimental

IR spectra were recorded on a Perkin-Elmer Spectrum BX-II spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer (400.1 MHz) in DMSO-d$_6$ with Me_4Si as the internal standard. Chromones **5a—d** were obtained according to the described earlier procedure.^{3}

3-[(2-Aminoethyl)aminomethylidene]-2-hydroxy-6-methyl-2-(trifluoromethyl)chroman-4-one (6b). Ethylenediamine (90 mg, 1.5 mmol) was added to a cooled to −10 °C solution of chromone **5b** (250 mg, 1.0 mmol) in methanol (4 mL) and the mixture was kept at this temperature for 2 days. The formed precipitate was filtered off, washed with methanol, and dried to obtain compound **6b** (90 mg, 30%) as colorless crystals, m.p. 161—162 °C. Found (%): C, 53.26; H, 4.71; N, 8.79. $C_{14}H_{15}F_3N_2O_3$. Calculated (%): C, 53.17; H, 4.78; N, 8.86. IR, ν/cm^{-1}: 3359, 3270, 3210, 1649, 1619, 1595, 1558, 1526, 1485. ^{1}H NMR, δ: 2.27 (s, 3 H, Me); 2.71 (t, 2 H, CH_2, J = 5.9 Hz); 2.8—4.0 (br.s, 3 H, NH_2, OH); 3.33—3.39 (m, 2 H, CH_2); 6.87 (d, 1 H, H(8), J_o = 8.3 Hz); 7.24 (dd, 1 H, H(7), J_o = 8.3 Hz, J_m = 2.0 Hz); 7.50 (d, 1 H, =CH, J = 13.3 Hz); 7.53 (d, 1 H, H(5), J_m = 2.0 Hz); 10.8—10.9 (br.m, 1 H, NH).

3-[(2-Aminoethyl)aminomethylidene]-2-hydroxy-7-methoxy-2-(trifluoromethyl)chroman-4-one (6d) was obtained similarly to compound **6b**. The yield was 28%, m.p. 167—168 °C, light yellow powder. Found (%): C, 50.42; H, 4.56; N, 8.31. $C_{14}H_{15}F_3N_2O_4$. Calculated (%): C, 50.61; H, 4.55; N, 8.43. IR, ν/cm^{-1}: 3352, 3278, 1648, 1640, 1614, 1591, 1555. ^{1}H NMR, δ: 2.69 (t, 2 H, CH_2, J = 5.9 Hz); 2.8—4.0 (br.s, 3 H, NH_2, OH); 3.30—3.37 (m, 2 H, CH_2); 3.79 (s, 3 H, MeO); 6.51 (d, 1 H, H(8), J_o = 2.4 Hz); 6.64 (dd, 1 H, H(6), J_o = 8.7 Hz, J_m = 2.4 Hz); 7.45 (d, 1 H, =CH, J = 13.3 Hz); 7.65 (d, 1 H, H(5), J_o = 8.7 Hz); 10.7—10.8 (br.m, 1 H, NH).

3-[(2-Aminophenyl)aminomethylidene]-2-hydroxy-2-(trifluoromethyl)chroman-4-one (7a). *o*-Penylenediamine (160 mg, 1.5 mmol) was added to a solution of chromone **5a (**250 mg, 1.0 mmol) in methanol (4 mL) and the mixture was kept at room temperature for 1 day. The formed precipitate was filtered off, washed with methanol, and dried to obtain compound **7a** (220 mg, 63%) as orange crystals, m.p. 197—198 °C. Found (%): C, 58.18; H, 3.68; N, 7.92. $C_{17}H_{13}F_3N_2O_3$. Calculated (%): C, 58.29; H, 3.74; N, 8.00. IR, ν/cm^{-1}: 3421, 3358, 3252, 1651, 1608, 1592, 1533, 1479, 1465. ^{1}H NMR, δ: 5.09 (s, 2 H, NH_2); 6.75 (ddd, 1 H, H(5′), J_o = 7.1 Hz, J_m = 1.3 Hz); 6.89 (dd, 1 H, H(3′), J_o = 8.0 Hz, J_m = 1.3 Hz); 6.99 (ddd, 1 H, H(4′), J_o = 8.0 Hz, 7.1 Hz, J_m = 1.3 Hz); 7.07 (d, 1 H, H(6′), J_o = 8.2 Hz); 7.14 (ddd, 1 H, H(6), J_o = 7.9 Hz, J = 7.2 Hz, J_m = 1.0 Hz); 7.19 (d, 1 H, H(8), J_o = 8.3 Hz); 7.53 (ddd, 1 H, H(7), J_o = 8.3 Hz, J_o = 7.2 Hz, J_m = 1.7 Hz); 7.85 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.6 Hz); 7.89 (d, 1 H, =CH, J = 12.8 Hz); 9.06 (s, 1 H, OH); 12.45 (d, 1 H, NH, J = 12.8 Hz).

3-[(2-Aminophenyl)aminomethylidene]-2-hydroxy-6-methyl-2-(trifluoromethyl)chroman-4-one (7b) was obtained similarly to compound **7a**. The yield was 65%, m.p. 193—194 °C, orange crystals. Found (%): C, 59.29; H, 4.11; N, 7.57. $C_{18}H_{15}F_3N_2O_3$. Calculated (%): C, 59.34; H, 4.15; N, 7.69. IR, ν/cm^{-1}: 3422, 3356, 3255, 1650, 1611, 1604, 1534, 1480, 1453. ^{1}H NMR, δ: 2.30 (s, 3 H, Me); 5.06 (s, 2 H, NH_2); 6.74 (ddd, 1 H, H(5′), J_o = 8.3 Hz, J_o = 7.1 Hz, J_m = 1.3 Hz); 6.88 (dd, 1 H, H(3′), J_o = 8.0 Hz, J_m = 1.3 Hz); 6.95 (d, 1 H, H(6′), J_o = 8.3 Hz); 6.98 (ddd, 1 H, H(4′), J_o = 8.0 Hz, J_o = 7.1 Hz, J_m = 1.2 Hz); 7.17 (d, 1 H, H(8), J_o = 8.3 Hz); 7.33 (dd, 1 H, H(7), J_o = 8.3 Hz, J_m = 2.2 Hz); 7.62 (br.s, 1 H, H(5), J_m = 1.7 Hz); 7.86 (d, 1 H, =CH, J = 12.8 Hz); 8.96 (s, 1 H, OH); 12.41 (d, 1 H, NH, J = 12.8 Hz).

***N,N′*-Ethylene-bis[3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-one] (8a).** Ethylenediamine (90 mg, 1.5 mmol) was added to a cooled to −10 °C solution of chromone **5a** (250 mg, 1.0 mmol) in methanol (4 mL) and the mixture was kept at this temperature for 2 days. Then, the mixture was poured into water (15 mL), acidified with conc. HCl (0.5 mL). The formed precipitate was filtered off, washed with methanol, and dried to obtain compound **8a** (90 mg, 32%) as colorless powder, m.p. 243—245 °C (decomp.). Found (%): C, 53.20; H, 3.27; N, 5.05. $C_{24}H_{18}F_6N_2O_6$. Calculated (%): C, 52.95; H, 3.33; N, 5.15. IR, ν/cm^{-1}: 3248, 1648, 1610, 1592, 1546, 1469. ^{1}H NMR, δ: 3.60—3.64 (m, 4 H, 2 CH_2); 6.97 (d, 1 H, H(8), J_o = 7.8 Hz); 6.98 (d, 1 H, H(8′), J_o = 7.8 Hz); 7.05—7.10 (m, 2 H, H(6), H(6′), J_o = 7.5 Hz); 7.42—7.48 (m, 2 H, H(7), H(7′)); 7.54 (d, 1 H, =CH, J = 13.1 Hz); 7.57 (d, 1 H, =CH, J = 13.1 Hz); 7.75 (br.s, 2 H, H(5), H(5′), J_o = 7.6 Hz); 8.70 (br.s, 2 H, 2 OH); 10.74 (br.d, 1 H, NH, J = 13.1 Hz); 10.76 (br.d, 1 H, NH, J = 13.1 Hz).

***N,N′*-Ethylene-bis[3-aminomethylidene-6-chloro-2-hydroxy-2-(trifluoromethyl)chroman-4-one] (8c)** was obtained similarly to compound **8a**. The yield was 27%, m.p. 204—205 °C, colorless powder. Found (%): C, 46.97; H, 2.66; N, 4.51. $C_{24}H_{16}Cl_2F_6N_2O_6$. Calculated (%): C, 47.00; H, 2.63; N, 4.57. IR, ν/cm^{-1}: 3249, 1645, 1606, 1593, 1540, 1469. ^{1}H NMR, δ: 3.62—3.66 (m, 4 H, 2 CH_2); 7.04 (d, 1 H, H(8), J_o = 8.7 Hz); 7.05 (d, 1 H, H(8′), J_o = 8.7 Hz); 7.48 (dd, 1 H, H(7), J_o = 8.7 Hz, J_m = 2.5 Hz); 7.50 (dd, 1 H, H(7′), J_o = 8.7 Hz, J_m = 2.5 Hz); 7.56 (d, 1 H, =CH, J = 13.4 Hz); 7.60 (d, 1 H, =CH, J = 13.4 Hz); 7.65—7.67 (m, 2 H, H(5), H(5′)); 8.88 (br.s, 2 H, 2 OH); 10.74 (br.d, 1 H, NH, J = 13.3 Hz); 10.76 (br.d, 1 H, NH, J = 13.3 Hz).

***N,N′-o*-Phenylene-bis[3-aminomethylidene-2-hydroxy-2-(trifluoromethyl)chroman-4-one] (9a).** *o*-Penylenediamine (55 mg, 0.5 mmol) was added to a solution of chromone **5a** (250 mg, 1.0 mmol) in methanol (4 mL) and the mixture was refluxed for 2 h. The formed precipitate was filtered off, washed with methanol, and dried to obtain compound **9a** (190 mg, 62%) as fine bright yellow crystals with m.p. 242—243 °C. Found (%): C, 56.72; H, 2.99; N, 4.57. $C_{28}H_{18}F_6N_2O_6$. Calculated (%): C, 56.76; H, 3.06; N, 4.73. IR, ν/cm^{-1}: 3307, 1637, 1606, 1589, 1566, 1551. ^{1}H NMR, δ: 7.09 (d, 2 H, H(8), H(8′), J_o = 8.2 Hz); 7.14 (t, 2 H, H(6), H(6′), J_o = 7.5 Hz); 7.35—7.46 (m, 4 H, C_6H_4); 7.56 (ddd, 2 H, H(7), H(7′), J_o = 8.2 Hz, J_o = 7.3 Hz, J_m = 1.7 Hz); 7.80—7.85 (m, 4 H, 2 =CH, H(5), H(5′)); 9.14 (s, 1 H, OH); 9.15 (s, 1 H, OH); 12.48 (d, 2 H, 2 NH, J = 12.5 Hz).

***N,N′-o*-Phenylene-bis[3-aminomethylidene-2-hydroxy-6-methyl-2-(trifluoromethyl)chroman-4-one] (9b)** was obtained similarly to compound **9a**. The yield was 65%, m.p. >250 °C (decomp.), fine bright yellow crystals. Found (%): C, 58.05; H, 3.56; N, 4.30. $C_{30}H_{22}F_6N_2O_6$. Calculated (%): C, 58.07; H, 3.57; N, 4.51. IR, ν/cm^{-1}: 3412, 3196, 1642, 1620, 1600, 1568, 1552, 1489. ^{1}H NMR, δ: 2.30 (s, 6 H, 2 Me); 6.99 (d, 2 H, H(8), H(8′), J_o = 8.3 Hz); 7.34—7.45 (m, 6 H, H(7), H(7′), C_6H_4); 7.60 (d, 1 H, H(5), J_m = 1.8 Hz); 7.62 (d, 1 H, H(5′), J_m = 1.8 Hz); 7.81 (d, 2 H, 2 =CH, J = 12.4 Hz); 9.08 (s, 1 H, OH); 9.09 (s, 1 H, OH); 12.46 (d, 2 H, 2 NH, J = 12.4 Hz).

3-[(2,2-Dimethoxyethyl)aminomethylidene]-2-hydroxy-2-(trifluoromethyl)chroman-4-one (10). The product was obtained from chromone **5a** according to the described earlier procedure.[2,3] The yield was 60%, m.p. 115—116 °C, colorless crystals. Found (%): C, 51.92; H, 4.54; N, 3.74. $C_{15}H_{16}F_3NO_5$. Calculated (%): C, 51.88; H, 4.64; N, 4.03. IR, ν/cm^{-1}: 3173, 1648, 1610, 1594, 1543, 1470. ^{1}H NMR (CDCl$_3$), δ: 3.09 (ddd, 1 H, C$\underline{H}$H, J = 13.8 Hz, J = 5.8 Hz, J = 6.8 Hz); 3.21 (dt, 1 H, CH$\underline{H}$, J = 13.8 Hz, J = 5.3 Hz); 3.37 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 4.31 (t, 1 H, CH, J = 5.3 Hz); 5.47 (br.s, 1 H, OH); 6.95 (dd, 1 H, H(8), J_o = 8.3 Hz, J_m = 1.0 Hz); 7.04 (td, 1 H, H(6), J_o = 7.6 Hz, J_m = 1.0 Hz); 7.28 (d, 1 H, =CH, J = 13.3 Hz); 7.39 (ddd, 1 H, H(7), J_o = 8.3 Hz, J_o = 7.3 Hz, J_m = 1.7 Hz); 7.85 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.7 Hz); 10.79 (dt, 1 H, NH, J = 13.0 Hz, J = 6.4 Hz).

6-Chloro-2-hydroxy-3-[(1-naphthylamino)methylidene]-2-(trifluoromethyl)chroman-4-one (11). The product was obtained from chromone **5c** according to the described earlier procedure.[2,3] The yield was 95%, m.p. 216—217 °C, yellow crystals. Found (%): C, 60.03; H, 2.97; N, 3.13. $C_{21}H_{13}ClF_3NO_3$. Calculated (%): C, 60.08; H, 3.12; N, 3.34. IR, ν/cm^{-1}: 3265, 1637, 1603, 1582, 1557, 1479. ^{1}H NMR, δ: 7.18 (d, 1 H, H(8), J_o = 8.8 Hz); 7.61 (t, 1 H, arom., J_o = 7.8 Hz); 7.62 (dd, 1 H, H(7), J_o = 8.8 Hz, J_m = 2.7 Hz); 7.67 (ddd, 1 H, arom., J_o = 8.0 Hz, J_o = 7.1 Hz, J_m = 1.0 Hz); 7.71 (d, 1 H, arom., J_o = 7.2 Hz); 7.77 (ddd, 1 H, arom., J_o = 8.2 Hz, J_o = 7.0 Hz, J_m = 1.3 Hz); 7.87 (d, 1 H, H(5), J_m = 2.7 Hz); 7.88 (d, 1 H, arom., J_o = 8.2 Hz); 8.06 (d, 1 H, arom., J = 8.1 Hz); 8.09 (d, 1 H, arom., J = 8.4 Hz); 8.29 (d, 1 H, =CH, J = 12.4 Hz); 9.36 (s, 1 H, OH); 13.59 (d, 1 H, NH, J = 12.4 Hz).

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References

1. V. Ya. Sosnovskikh and R. A. Irgashev, *Synlett*, 2005, 1164.
2. V. Ya. Sosnovskikh, R. A. Irgashev, M. A. Barabanov, and V. S. Moshkin, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 572 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 593 (Engl. Transl.)].
3. V. Ya. Sosnovskikh, R. A. Irgashev, and M. A. Barabanov, *Synthesis*, 2006, 2707.
4. V. Ya. Sosnovskikh and R. A. Irgashev, *Heteroat. Chem.*, 2006, **17**, 99.
5. V. Ya. Sosnovskikh, V. S. Moshkin, and R. A. Irgashev, *Tetrahedron Lett.*, 2006, **47**, 8543.
6. A. O. Fitton, P. G. Houghton, and H. Suschitzky, *Synthesis*, 1979, 337.
7. C. K. Ghosh and S. Khan, *Synthesis*, 1980, 701.
8. I. Sigg, G. Haas, and T. Winkler, *Helv. Chim. Acta*, 1982, **65**, 275.
9. G. Rihs, I. Sigg, G. Haas, and T. Winkler, *Helv. Chim. Acta*, 1985, **68**, 1933.
10. F. Ristiano, G. Grassi, and F. Foti, *Heterocycl. Chem.*, 2001, **38**, 1083.

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