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Synthesis and fungicidal activity of new 4-hydroxy-6-trifluoromethyl-2-phenylindoles

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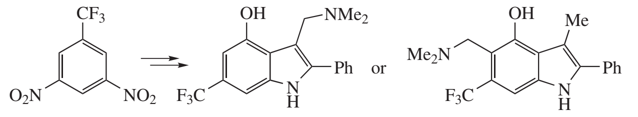
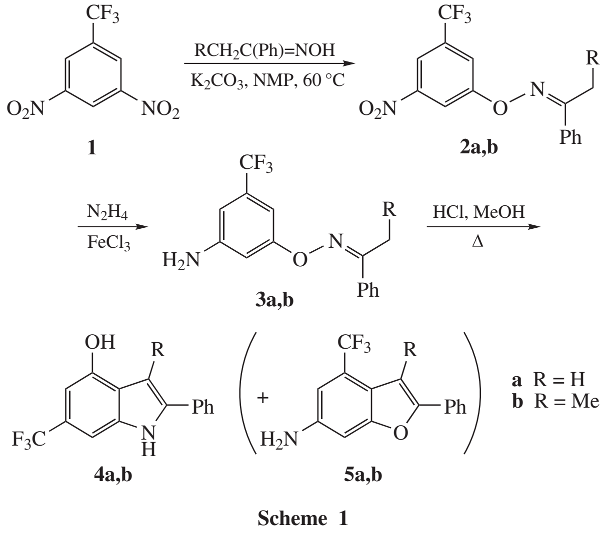
Starting from 1,3-dinitro-5-trifluoromethylbenzene, a pioneering synthesis and dimethylaminomethylation of new 2-aryl-4-hydroxy-6-trifluoromethylindoles have been performed. The study of fungicidal activity has revealed the effect of dimethylaminomethyl group position on fungitoxic properties.



Organofluorine compounds have been in the focus of classical organic chemistry and, in particular, of medical chemistry.[1–3] The introduction of fluorine atoms into a molecule often gives rise to dramatic changes in biological activity. Introduction of trifluoromethyl group enhances amphiphilic properties of a biologically active substance and, consequently, leads to a bioavailability increase.[4]

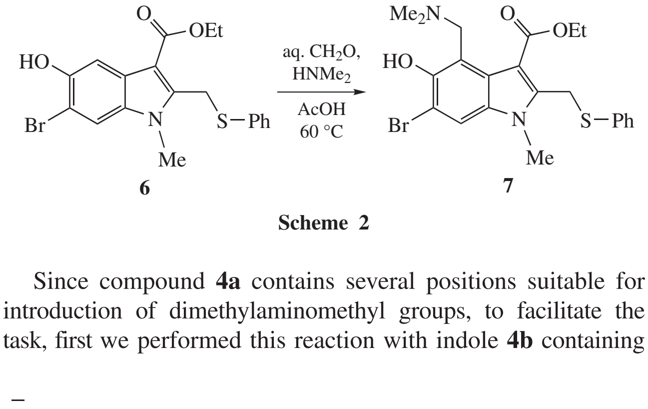
We previously developed a synthesis of 2-aryl-4-hydroxy-6-nitroindoles[5] and demonstrated[6] their high fungicidal activity (the lead compound was 2-phenyl-4-hydroxy-6-nitroindole). However, the presence of nitro group in a molecule, as a rule, negatively affects useful properties of pharmaceuticals which can be sourced from them. Exchange of the nitro group at the 6-position with another electronegative group is one of the means to modify the structure of the lead compound. Therefore, it seems necessary to obtain a number of similar compounds with the 6-positioned CF_3 group. Hence herein, starting from 1,3-dinitro-5-trifluoromethylbenzene **1** (Scheme 1) we prepared trifluoromethyl-equipped 2-aryl-4-hydroxyindoles **4a**,**b**, analogues of 2-aryl-4-hydroxy-6-nitroindoles with close electronegativity. The synthetic sequence comprised preparation of O-arylated oximes **2** and their amino analogues **3** which were subjected to heterocyclization into indoles **4**. The structure of product **4a** was proved by ^{1}H, ^{19}F, ^{13}C NMR spectroscopy. All assignments of carbon and hydrogen atoms in the molecule were based on the ^{1}H and ^{13}C{^{1}H} spectra and data of 2D heteronuclear correlation experiments ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC (Table S1, see Online Supplementary Materials).



Scheme 1

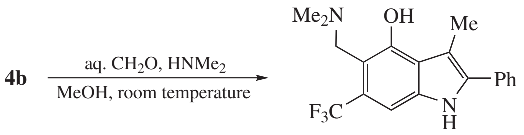
Along with target hydroxyindoles **4**, formation of side aminobenzofurans **5** and some other by-products occurred. Extraction of benzene residue from the evaporated reaction mass made it possible to isolate hydroxyindoles **4**. Since it is known from our previous experiments that the aminobenzofuran-type **5** do not possess fungicidal activity, we discarded their isolation in this study.

With a view to expand a scope of substances with potential fungicidal activity, in addition to hydroxyindoles **4a**,**b**, we studied their more readily soluble in water derivatives. To increase their water solubility, we chose the lead structure modification (Scheme 2) that had been used for the similar purpose[7] in designing Arbidol **7**, namely, the insertion of the dimethylaminomethyl group into the starting indole **6** at the final step.



Scheme 2

Since compound **4a** contains several positions suitable for introduction of dimethylaminomethyl groups, to facilitate the task, first we performed this reaction with indole **4b** containing



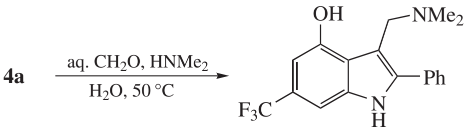
8, 45%

Scheme 3

3-positioned methyl group. Under conditions outlined in Scheme 2, indole **4b** gave a mixture of products which we failed to separate. We studied the influence of the ratio of the reagents, temperature, solvent, and modes of introducing formaldehyde and dimethylamino components. Eventually, we succeeded in inserting the dimethylaminomethyl group at 5-position when the reaction was carried out under milder conditions compared to those applied for Arbidol (Scheme 3). In fact, dimethylaminomethylation of hydroxyindole **4b** in MeOH proceeded at room temperature, and product **8** was isolated in 45% yield after column chromatography.

The structure of indole **8** was confirmed using 2D spectroscopy ROESY (Figure S7, see Online Supplementary Materials). The found correlation of the NH proton with *ortho*-protons of the phenyl substituent and with the aromatic signal from the phenyl moiety of the heterocycle indicated that the 7-position of the indole ring was vacant.

The conditions found for dimethylaminomethylation of compound **4b** appeared inapplicable for introducing the dimethylaminomethyl group into homologue **4a**. However, in water at 50 °C the substitution occurred at 3-position (not 5) thus affording derivative **9** in 50% yield after column chromatography (Scheme 4).



9, 50%

Scheme 4

The fine interpretation of the proton spectra of indole **9** was difficult due to the presence of the trifluoromethyl group (far SSC interactions were implied). However, one of the two signals from the phenyl moiety of the indole cycle at 6.48 ppm had a pronounced doublet pattern with the constant 1.0 Hz, which evidenced that positions 5 and 7 were vacant, *i.e.* the dimethylaminomethyl group had entered into 3-position.

2-Aryl-4-hydroxy-6-trifluoromethylindoles thus obtained were *in vitro* tested for fungicidal activity according to the common conventional procedure[8–11] with six phytopathogenic fungi from different taxonomic classes: *Venturia inaequalis* (*V.i.*), *Rhizoctonia solani* (*R.s.*), *Fusarium oxysporum* (*F.o.*), *Fusarium moniliforme* (*F.m.*), *Bipolaris sorokiniana* (*B.s.*), and *Sclerotinia sclerotiorum* (*S.s.*) (Table 1). The effect of the tested compounds on mycelium radial growth in potato-saccharose agar with triadimefon, a widely used fungicide, taken as a reference compound, was measured in the 30 mg dm^{-3} concentration. The tests in the concentration range 1–60 μg cm^{-3} allowed us to evaluate EC$_{50}$ for the two most potent fungicidal substances **4a** and **4b** (Table 2).

Table 1 Growth inhibition of the mycelium of the pathogenic fungi by 2-aryl-4-hydroxy-6-trifluoromethylindoles **4**, **8** and **9** *in vitro* (c = 30 mg dm^{-3}).

Entry	Compound	Mycelial growth inhibition (%)					
		V.i.	*R.s.*	*F.o.*	*F.m.*	*B.s.*	*S.s.*
1	**4a**	71 ± 10	62 ± 11	77 ± 7	74 ± 11	95 ± 7	100 ± 8
2	**4b**	69 ± 12	53 ± 8	79 ± 5	75 ± 11	93 ± 7	100 ± 8
3	**8**	29 ± 9	16 ± 9	11 ± 8	17 ± 9	51 ± 10	20 ± 6
4	**9**	51 ± 7	40 ± 10	39 ± 6	36 ± 13	69 ± 7	58 ± 7
5	Lead compound[a]	65 ± 8	100 ± 6	64 ± 4	88 ± 10	56 ± 12	71 ± 6
6	Reference compound[b]	55 ± 10	47 ± 11	71 ± 9	65 ± 6	65 ± 8	44 ± 7

[a] 2-Phenyl-4-hydroxy-6-nitroindole. [b] Triadimefon, 1-(1,2,4-triazol-1-yl)-1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one.

Table 2 Fungicidal activity (EC$_{50}$) of 2-phenyl-4-hydroxy-6-trifluoromethylindoles **4a** and **4b**.

Compound	EC$_{50}$/μg cm^{-3}					
	V.i.	*R.s.*	*F.o.*	*F.m.*	*B.s.*	*S.s.*
4a	12.3	2.05	8.66	7.08	5.26	5.92
4b	12.4	2.05	8.97	12.2	5.26	6.38
Triadimefon	19.9	13.4	9.18	9.62	11.1	43.2

Exchange of the nitro group with the trifluoromethyl group entailed some decline in activity, although it was all the same either higher than fungitoxicity of reference triadimefon or comparable with it. As follows from the results, the introduction of methyl group at 3-position of the indole moiety does not essentially affect fungicidal activity (EC$_{50}$ values for **4a** and **4b**). These compounds show higher fungicidal properties for *V.i.*, *S.s.* than triadimefon. Note that this pair of compounds is somewhat more effective than 2-phenyl-4-hydroxy-6-nitroindole *vs. B.s.* and *S.s.* This can be explained by the fact that changing electron-withdrawing nitro group to trifluoromethyl group leads to higher lipophilicity of compounds **4a**,**b**. Introduction of the dimethylaminomethyl group into benzene ring of the indole moiety brought about a strong fungitoxicity decrease (**4b** *cf.* **8**). Modification of indole **4a** with dimethylaminomethyl group had a less dramatic impact on fungitoxicity (**4a** *cf.* **9**). Therefore, it is possible to conclude that the presence of the dimethylaminomethyl group in the heterocyclic moiety of indole is preferable.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.033.

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