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Rhodium(III)-catalyzed C–H annulation for the construction of antifungal agents based on isocoumarin framework

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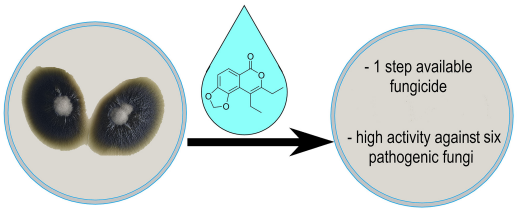
A series of hydroxy- and alkoxy-substituted isocoumarins were synthesized in one step by the rhodium-catalyzed C–H annulation of benzoic acids with alkynes. 8,9-Diethyl-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-one and its isoquinolone analog have effectively inhibited the growth of six types of phytopathogenic fungi at 30 mg dm^{-3} concentration, the activity exceeding that of the commercial Triadimefon.

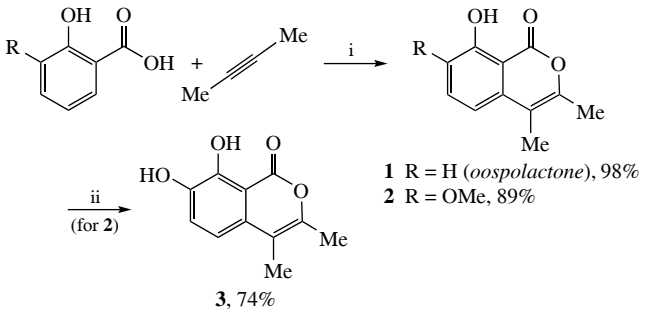


Keywords: antifungal agents, C–H activation, C–H annulation, isocoumarins, benzoic acids, alkynes, homogeneous catalysis, rhodium complexes.

Metal-catalyzed C–H activation of aromatic compounds followed by annulation with alkynes is a simple and efficient approach to the creation of numerous heterocyclic and carbocyclic scaffolds,[1,2] with the half-sandwich cyclopentadienyl rhodium complexes being the best catalysts for these reactions.[3–5] As being involved into the synthesis of multifunctional compounds ranging from drugs and natural products[6] to organic luminophores and semiconductors,[7–9] rhodium-catalyzed C–H annulations became part of the toolkit of modern organic chemistry. For example, this approach has opened an easy access to natural lactones such as isocoumarins, allowing the synthesis of their 3,4-substituted derivatives from aryl carboxylic acids and internal alkynes in one step.[10–12] In contrast to previously known methods,[13,14] this protocol is very simple and tolerant to many functional groups.

Isocoumarins are of particular interest due to their unique photophysical[15,16] and biochemical activities.[17] To date, more than 300 isocoumarins isolated from living organisms (fungi, plants, insects) have been described, most of which exhibit a wide range of biological activities.[18–20] However, 3,4-disubstituted derivatives are the least common structures among natural isocoumarins,[21] and their biological activity is still poorly studied (see, *e.g.*, refs. 22–24). At the same time, the development of new antifungal compounds is an important task of modern chemistry.[25] Herein we report the synthesis of a series of 3,4-disubstituted isocoumarins using rhodium-catalyzed C–H annulation of benzoic acids and alkynes, as well as data on their antifungal activity.

We initiated our investigation with a naturally occurring isocoumarin oospalactone **1** whose antifungal activity has been described earlier.[23] A modified previously known procedure was used for its preparation from salicylic acid and dimethylacetylene using complex $[Cp^{Ph_3}RhCl_2]_2$ as a catalyst (Scheme 1).[26] The 7-methoxy substituted derivative **2** was synthesized in a similar manner starting from 2-hydroxy-3-methoxybenzoic acid. Subsequent demethylation of **2** using boron tribromide afforded 7-hydroxy substituted isocoumarin **3**, whose structure was confirmed by X-ray diffraction study (Figure 1).† Compounds **2** and **3** have been previously isolated from a marine sponge *Paraphoma* sp. CUGBMF180003.[27]



Scheme 1 *Reagents and conditions*: i, $[Cp^{Ph_3}RhCl_2]_2$ (1 mol%), AgOAc (1 equiv.), MeOH, 80 °C, 8 h; ii, BBr_3 (2.5 equiv.), PhH, 60 °C, 2 h, then H_2O, 90 °C, 1 h.

† *Crystal data for* **3**. $C_{11}H_{10}O_4$, M_r = 206.19, monoclinic, space group C_2/c, Mo-Kα radiation (λ = 0.71073 Å), at 100 K, a = 11.853(6), b = 14.981(8) and c = 10.767(6) Å, β = 108.589(6)°, V = 1812.0(17) Å^3, Z = 8, d_{calc} = 1.512 g cm^{-3}, μ = 1.16 cm^{-1}, $F(000)$ = 864. Total of 8400 reflections were measured and 2381 independent reflections (R_{int} = 0.0745) were used. The refinement converged to wR_2 = 0.1421 and GOF = 1.035 for all independent reflections [R_1 = 0.0507 was calculated for 1729 observed reflections with $I > 2\sigma(I)$].

Crystal data for **12**. $C_{14}H_{14}O_3S$, M_r = 262.31, triclinic, space group $P\bar{1}$, Mo-Kα radiation (λ = 0.71073 Å), at 100 K, a = 7.899(5), b = 8.852(5) and c = 10.051(6) Å, α = 114.282(7), β = 106.279(7) and γ = 93.792(7)°, V = 601.6(6) Å^3, Z = 2, d_{calc} = 1.448 g cm^{-3}, μ = 2.66 cm^{-1}, $F(000)$ = 276. Total of 3919 reflections were measured and 2008 independent reflections (R_{int} = 0.1309) were used. The refinement converged to wR_2 = 0.2443

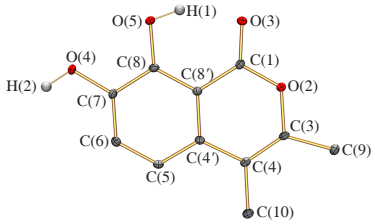


Figure 1 Molecular structure of **3** in the representation of atoms as 50% probability ellipsoids; hydrogen atoms (except two at the O(4) and O(5) atoms) are omitted. Selected bond lengths (Å): C(1)–O(2) 1.3408(19), C(4′)–C(5) 1.394(2), C(1)–O(3) 1.2392(19), C(4′)–C(8′) 1.419(2), C(1)–C(8′) 1.442(2), C(4)–C(10) 1.505(2), O(2)–C(3) 1.4020(19), O(5)–C(8) 1.3541(19), C(3)–C(4) 1.344(2), C(5)–C(6) 1.388(2), C(3)–C(9) 1.491(2), C(6)–C(7) 1.392(2), O(4)–C(7) 1.3586(19), C(7)–C(8) 1.397(2), C(4′)–C(4) 1.457(2), C(8)–C(8′) 1.406(2).

To estimate antifungal activity of compounds **1**–**3**, we investigated their ability to inhibit the growth of six types of phytopathogenic fungi, which infect various agricultural plants, such as cucumbers, tomatoes, onions (*Fusarium oxysporum*); cereals (*Bipolaris sorokiniana*), corn (*Fusarium moniliforme*); cereals and potatoes (*Rhizoctonia solani*); apples (*Venturia inaequalis*) and beans (*Sclerotinia sclerotiorum*). Triadimefon was used as the standard commercially available fungicide for comparison. In general, compounds **1**–**3** showed moderate activity, which was considerably inferior in activity to Triadimefon (Table 1, entries 1–3 *vs*. 20). The exception was isocoumarin **3** which effectively inhibited the growth of the *F. moniliforme* fungi similar to Triadimefon.

Table 1 Inhibition of growth of the pathogenic fungi in the presence of the compounds (c = 30 mg dm^{-3}).

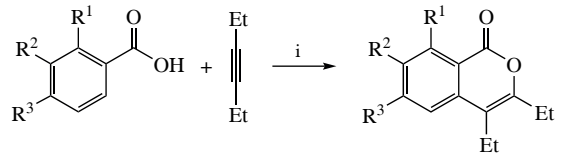
Entry	Compound	Inhibition growth (%) for pathogenic fungi					
		S.s.[a]	*F.o.*[b]	*V.i.*[c]	*F.m.*[d]	*B.s.*[e]	*R.s.*[f]
1	**1**	4	33	28	33	32	23
2	**2**	26	28	37	41	24	39
3	**3**	22	54	22	79	63	58
4	**4**	24	36	42	58	52	65
5	**5**	21	23	45	44	49	54
6	**6**	37	44	56	53	88	71
7	**6′**	8	7	29	37	58	58
8	**7**	2	8	32	29	35	21
9	**8a**	51	80	96	89	97	99
10	**8′a**	8	13	23	26	44	59
11	**8b**	18	49	61	49	48	82
12	**8c**	5	23	38	35	30	66
13	**8d**	8	13	19	13	48	73
14	**8e**	15	17	13	20	51	35
15	**9**	30	31	50	55	53	51
16	**10**	20	20	73	48	50	42
17	**11**	26	52	29	71	61	70
18	**12**	24	26	53	55	58	79
19	**13**	45	80	83	81	90	97
20	Triadimefon	65	68	58	85	69	70

[a] *Sclerotinia sclerotiorum*. [b] *Fusarium oxysporum*. [c] *Venturia inaequalis*. [d] *Fusarium moniliforme*. [e] *Bipolaris sorokiniana*. [f] *Rhizoctonia solani*.

and GOF = 0.994 for all independent reflections [R_1 = 0.0880 was calculated for 1127 observed reflections with $I > 2\sigma(I)$].

Crystal data for **13**. $C_{14}H_{15}NO_3$, M_r = 245.27, orthorhombic, space group *Pbca*, synchrotron radiation (λ = 0.7527 Å), at 100 K, a = 16.613(3), b = 16.788(3) and c = 17.172(3) Å, V = 4789.3(17) Å^3, Z = 16, d_{calc} = 1.361 g cm^{-3}, μ = 1.09 cm^{-1}, $F(000)$ = 2080. Total of 27055 reflections were measured and 5818 independent reflections (R_{int} = 0.0757) were used. The refinement converged to wR_2 = 0.1215 and GOF = 1.027 for all independent reflections [R_1 = 0.0452 was calculated for 4103 observed reflections with $I > 2\sigma(I)$].

CCDC 2434090 (**3**), 2434089 (**12**) and 2434091 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

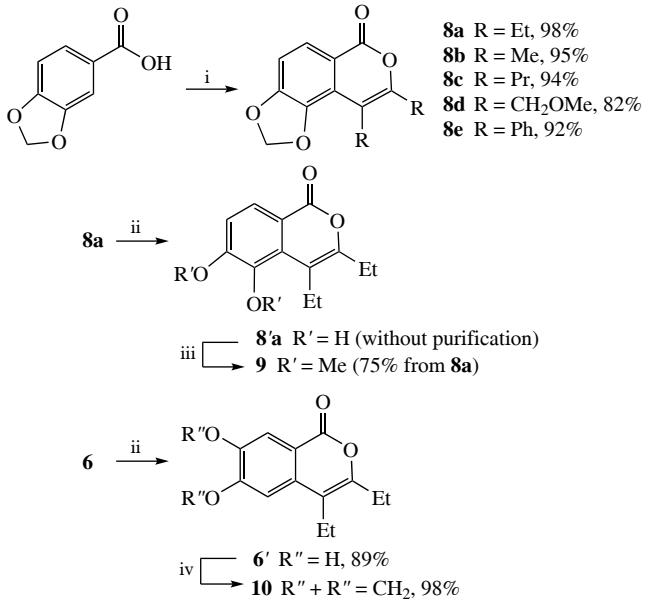


4 R^1 = OH, R^2 = OMe, R^3 = H, 85%
5 R^1 = R^2 = OMe, R^3 = H, 90%
6 R^1 = H, R^2 = R^3 = OMe, 94%
7 R^1 = R^3 = OMe, R^2 = H, 93%

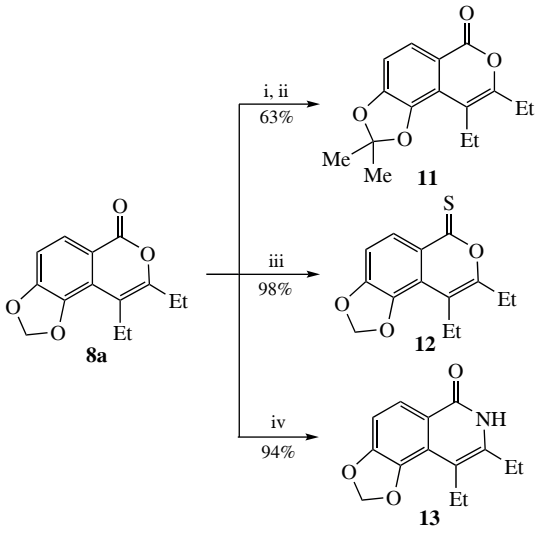
Scheme 2 *Reagents and conditions*: i, [Cp^{Ph_3}RhCl$_2$]$_2$ (1 mol%), AgOAc (1 equiv.), MeOH, 80 °C, 8 h.

To clarify the effect of the location and type of substituents in the isocoumarin framework on its antifungal activity, we synthesized 3,4-diethylisocoumarins **4**–**7** with various positions of methoxy substituents starting from hex-3-yne (Scheme 2). Compounds **4**–**6** demonstrated slightly higher activity against all tested fungi as compared with **1** and **2** (see Table 1, entries 4–6 *vs*. 1 and 2). In particular, compound **6** demonstrated the same and even higher activity against *V. inaequalis*, *B. sorokiniana*, *R. solani* fungi compared to Triadimefon. At the same time, isocoumarin **7** had very low activity. These results showed that the replacement of methyl groups at the positions 3 and 4 with ethyl ones, as well as the absence of a methoxy substituent at position 8 of isocoumarin framework, have a positive impact on the antifungal activity.

We have previously shown that isomeric to compounds **5**–**7** 5,6-dimethoxy analog could not be synthesized directly from 3,4-dimethoxybenzoic acid due to steric repulsion of the two methoxy groups.[28] Therefore, for its preparation the three-step synthetic pathway was developed (Scheme 3). In the first step, isocoumarin **8a** was synthesized by a rhodium-catalyzed coupling of piperonylic acid with hex-3-yne, then the dioxolane fragment in **8a** was destroyed by BBr_3. Finally, the obtained



Scheme 3 *Reagents and conditions*: i, RC≡CR, [Cp^{Ph_3}RhCl$_2$]$_2$ (1 mol%), AgOAc (1 equiv.), MeOH, 80 °C, 8 h; ii, BBr_3 (2.5 equiv.), PhH, 60 °C, 2 h, then H_2O, 90 °C, 1 h; iii, MeI (2.1 equiv.), NaH, DMF, room temperature, ~18 h; iv, CH_2I_2 (1.5 equiv.), KF (5 equiv.), DMF.



Scheme 4 *Reagents and conditions*: i, BBr_3 (2.5 equiv.), PhH, 60 °C, 2 h, then H_2O, 90 °C, 1 h; ii, $Me_2C{=}O$, P_2O_5, PhH; iii, Lawesson's reagent, PhMe; iv, NH_4HCO_2 (3 equiv.), DMSO, 110 °C, 2 h.

crude 5,6-dihydroxy derivative **8′a** was methylated with MeI in DMF giving the target 5,6-dimethoxy isocoumarin **9** in high yield. Although compound **9** demonstrated moderate antifungal activity, its precursor **8a** proved to be more effective in inhibiting fungal growth than Triadimefon (see Table 1, entries 9 and 15). Interestingly, isocoumarin **10** being a 'linear isomer' of **8a** with the 6,7-fused dioxolane ring was found to be less active against fungi (see Table 1, entry 16 *vs*. 9). For its synthesis, two-step procedure based on demethylation of **6** followed by alkylation with CH_2I_2 was used (see Scheme 3).

Inspired by success with compound **8a**, we varied internal alkynes in the reaction with piperonylic acid to synthesize other analogous isocoumarins **8b**–**e** with different substituents in positions 3 and 4 (see Scheme 3). However, these compounds showed lower antifungal activity than **8a** (see Table 1, entries 11–14 *vs*. 9). It should be particularly noted that elongation of the chain of alkyl substituents or introducing methoxy groups leads to a sharp drop in activity.

Direct modification of isocoumarin **8a** using known methods[29,30] allowed us to prepare the dimethyldioxolane derivative **11**, thioisocoumarin **12** and isoquinolone **13** (Scheme 4). The latter inhibits the growth of fungi with the same high efficiency as **8a** (see Table 1, entries 19 *vs*. 9). Structures **12** and **13** were confirmed by X-ray diffraction (Figures 2 and 3).†

In summary, we have developed two new promising antifungal agents (isocoumarin **8a** and isoquinolone **13**), which effectively inhibit the growth of six types of phytopathogenic fungi and

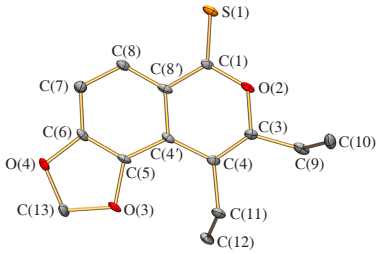


Figure 2 Molecular structure of **12** in the representation of atoms as 50% probability ellipsoids; hydrogen atoms are omitted. Selected bond lengths (Å): S(1)–C(1) 1.655(5), C(4)–C(4′) 1.442(8), C(1)–O(2) 1.349(7), C(4)–C(11) 1.519(6), C(1)–C(8′) 1.451(7), C(4′)–C(5) 1.397(7), O(2)–C(3) 1.397(6), C(4′)–C(8′) 1.442(6), O(3)–C(5) 1.394(5), C(5)–C(6) 1.355(8), O(3)–C(13) 1.434(7), C(6)–C(7) 1.391(7), C(3)–C(4) 1.337(7), C(7)–C(8) 1.386(7), C(3)–C(9) 1.491(9), C(8)–C(8′) 1.375(8), O(4)–C(6) 1.370(6), C(9)–C(10) 1.537(8), O(4)–C(13) 1.429(6), C(11)–C(12) 1.543(6).

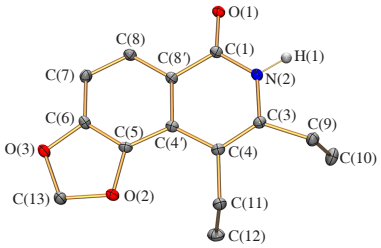


Figure 3 Molecular structure of **13** in the representation of atoms as 50% probability ellipsoids; hydrogen atoms (except one at the nitrogen atom) are omitted. Selected bond lengths (Å): O(1)–C(1) 1.2518(19), C(1)–N(2) 1.355(2), C(1)–C(8′) 1.457(2), O(2)–C(5) 1.3814(19), O(2)–C(13) 1.432(2), N(2)–C(3) 1.396(2), O(3)–C(6) 1.3706(19), O(3)–C(13) 1.431(2), C(3)–C(4) 1.357(2), C(3)–C(9) 1.512(2), C(4′)–C(4) 1.451(2), C(4′)–C(5) 1.403(2), C(4′)–C(8′) 1.429(2), C(4)–C(11) 1.512(2), C(5)–C(6) 1.378(2), C(6)–C(7) 1.379(2), C(7)–C(8) 1.382(2), C(8′)–C(8) 1.400(2), C(9)–C(10) 1.534(9), C(9)–C(10′) 1.527(10), C(11)–C(12) 1.527(2).

exceed the commercial fungicide Triadimefon in their activity. It is important to note that they are easily available and can be synthesized with excellent yields in one or two steps from piperonylic acid and 3-hexyne.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7777.

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