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Synthesis of spiro[chromane-2,4′-pyrimidines] by condensation of 6-styryldihydropyrimidin-2-ones with resorcinols

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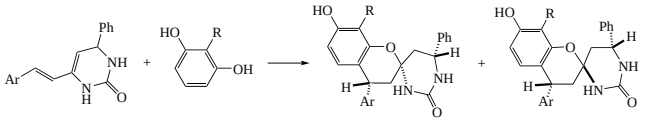
Substituted spiro[chromane-2,4′-pyrimidines] were obtained by the acid-catalyzed reaction between 4-aryl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-ones and resorcinols. The structure of the resulting diastereomeric 4,6′-diaryl-7-hydroxy-5′,6′-dihydro-1′*H*-spiro[chromane-2,4′-pyrimidin]-2′(3′*H*)-ones has been determined by 2D spectroscopy and single-crystal X-ray diffraction analysis.



Keywords: 6-styryl-4-aryldihydropyrimidin-2-ones, resorcinol, 2-methylresorcinol, acid catalysis, substituted spirochromane-2,4′-pyrimidines.

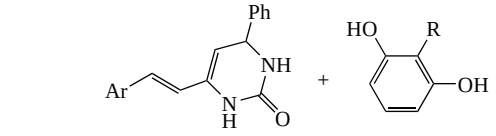
Spirochromanes, fairly well known heterocycles,[1] are of interest as potential biologically active compounds[2] with numerous kinds of pharmacologic activity, including a promising antitumor potential.[3] They are usually synthesized by acid-catalyzed condensations of various CH-acids with phenols[4] and resorcinols.[5] Reactions of styryldihydropyrimidines with resorcinols to give spiro-linked chromane-pyrimidine systems, usually as two diastereomers, are also known.[6] These compounds are of interest since they exhibit various effects[7(a)] including antibacterial activity.[7(b),(c)]

Substituted 4-aryl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-ones became available from heating the products of the Biginelli reaction with aromatic aldehydes in aqueous alkaline solutions.[8] These compounds seem promising for the cyclization with resorcinols since their structures are similar to those of styrylpyrimidines studied previously.[6]

The purpose of this work was to synthesize new substituted spiro[chromane-2,4′-pyrimidines] by the condensation of substituted 4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-ones **1a**–**d** with resorcinols **2a**,**b** (Scheme 1). The latter reactants are most active in this type of reactions (the coordinated orientation of the hydroxy groups would facilitate electrophilic substitution in positions 2 and 4). The required substrates **1a**–**d** were prepared as reported previously.[8(a)]

Various Brønsted and Lewis acids were studied as the catalysts: citric acid, HCl, L-proline, HCl + L-proline, TsOH, $BF_3{\cdot}Et_2O$, $MeSO_3H$, and H_2SO_4 (Table 1). The condensation in the presence of various catalysts gave the anticipated products **3a**–**e** and **3′a**–**c** (see Scheme 1), however, the reaction was often accompanied by significant resinification, which hindered the isolation of the target products. The best results were obtained when TsOH was applied in chloroform with the addition of water and heating at *ca.* 40 °C for 1–3 h. The water additive promoted significant increase in the yield of the product. This caused formation of a two-phase system when dihydropyrimidin-2-ones **1a**–**d** were present mainly in chloroform while resorcinols **2** were mainly located in water. This not only improved the yield of the target product but also significantly minimized the formation of side compounds. Similarly to the previous works,[6] the attempted use of 4-chlororesorcinol or pyrogallol did not afford the desired products, probably due to the insufficient reactivity of compounds **1a**–**d** towards those co-reactants.

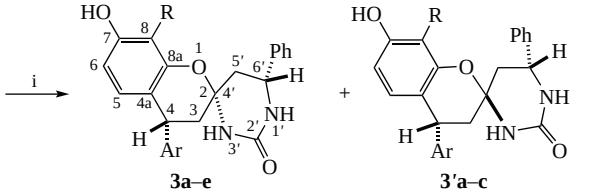
Since the product molecule has three diastereomeric centers, it can in principle be formed as a mixture of at least six diastereomers. However, the formation of only two diastereomers



1a–d **2a,b**

a Ar = Ph
b Ar = 4-ClC_6H_4
c Ar = 4-MeC_6H_4
d Ar = 4-$MeOC_6H_4$

a R = H
b R = Me



3a–e **3′a–c**

a Ar = Ph, R = H, 25 + 17%
b Ar = 4-ClC_6H_4, R = H, 52 + 18%
c Ar = 4-ClC_6H_4, R = Me, 58 + 14%
d Ar = 4-MeC_6H_4, R = H, 36%
e Ar = 4-$MeOC_6H_4$, R = H, 18%

Scheme 1 *Reagents and conditions*: i, TsOH, $CHCl_3$, H_2O, 40 °C, 1–3 h.

Table 1 Selection of the reaction conditions.[a]

Entry	Solvent	Catalyst (mM)	*t*/h	*T*/°C	Yield of **3b** + **3′b** (%)	Ratio **3b**/**3′b**[b]
1	$CHCl_3$, H_2O	TsOH (0.3)	2.5	40	70	1 : 1
2	CCl_4, H_2O	TsOH (0.9)	3	40	–	–
3	$CHCl_3$, H_2O	Citric acid (0.8)	50	60	–	–
4	$CHCl_3$, AcOH	$MeSO_3H$ (2.4)	3.5	~20	30	6 : 1
5	$CHCl_3$, AcOH	H_2SO_4 (2.9)	3	~20	15	1 : 0
6	$CHCl_3$	$BF_3{\cdot}Et_2O$ (12.5)	5	~20	–	–
7	$CHCl_3$, H_2O	10% HCl (8.9)	10	~20	17	3 : 1
8	$CHCl_3$, H_2O	5% HCl (4.4), L-proline (1.4)	15	~20	–	–
9	$CHCl_3$, H_2O	10% HCl (17.9), L-proline (1.4)	31	~20	40	1 : 1
10	$CHCl_3$, H_2O	10% HCl (8.9), L-proline (1.4)	22.5	60	52	2 : 1
11	$CHCl_3$, H_2O	20% HCl (9.4), L-proline (1.4)	7.5	~20	44	1 : 1

[a] Conditions: 1 mmol of **1b**, 2 mmol of **2a**, 5 ml of the solvent (entry 6) or a solvent–cosolvent system in 5 : 1 ratio (entries 1–5, 7–11). [b] From ^{1}H NMR data.

was actually detected (see Scheme 1). In the beginning of the reaction, diastereomer **3** was predominantly formed; it manifested more upfield chemical shifts for the protons at the aromatic substituents in the ^{1}H NMR spectra. It can be isolated in a low yield after the reaction is stopped in 1 h. If the reaction time was prolonged to 3 h, mixtures of **3a–c**/**3′a–c** diastereomers in up to 1 : 1 ratios were isolated. These diastereomers were separated by fractional crystallization in ethyl acetate: diastereomer **3′** is dissolved in ethyl acetate on boiling whereas diastereomer **3** can be separated by hot filtration. Effect of the catalytic system on the diastereomer ratio **3**/**3′** is noticeable but not crucial (see Table 1) except for the case in entry 4.

The probable mechanism for the formation of diastereomers **3**/**3′** is obvious and may consist in the initial Michael addition of resorcinol at the electron-deficient styryl fragment and subsequent cyclization involving the double bond of the pyrimidine ring.

According to ^{1}H NMR spectroscopic data, the chemical shifts of protons at aryl substituents in diastereomers **3**/**3′** differed noticeably. Diastereomer **3** was found to be predominant and showed stronger upfield chemical shifts of the 4-H and 6′-H protons in the δ 4.0–4.5 region. Both diastereomers had large coupling constants (about 12.5–13.0 Hz) of the 4-H and 6'-H protons with the corresponding axial methylene protons. This indicates that the benzylic protons are arranged axially with respect to the heterocycle plane. Hence, the **3**/**3′** diastereomers only differ in the position of substituents at the 2/4′-C carbon. The structure of the diastereomers was determined by analysis of two-dimensional spectroscopy data (NOESY and HMBC) for compounds **3b** and **3′b**. For both diastereomers, 6′-H is the most-downfield aliphatic proton, since 6′-H/1′-NH cross-peaks were observed in the NOESY spectra. Moreover, a cross-peak of 3-H/3′-NH protons was detected in the spectrum of compound **3b**, in contrast to **3′b**, which indicates their spatial proximity. Based on these facts, structures **3** were categorized as (2*R**,4*R**,6′*R**)-diastereomers. For diastereomers **3′**, the (2*S**,4*R**,6′*R**)-configuration was found to be more probable, since the NOESY spectrum of compound **3′b** contains a cross-peak of 4-H/3′-NH protons. The HMBC spectral data do not contradict these structures. The structure of **3b** was ultimately established by single crystal X-ray diffraction (Figure 1).[†] Single crystals of **3b** were obtained by crystallization from methoxyacetic acid as 1 : 1 solvates.

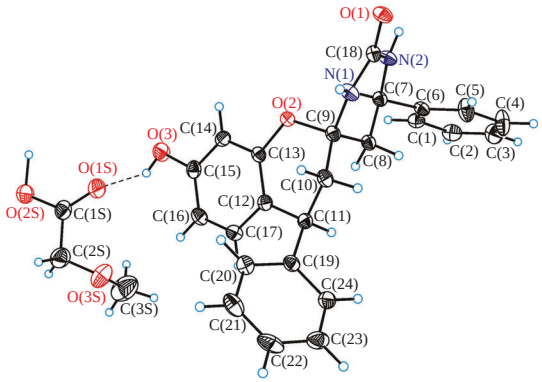


Figure 1 General view of compound **3b**·$MeOCH_2CO_2H$. Thermal ellipsoids are given at 50% probability level.

In conclusion, a method for synthesizing (2*R**,4*R**,6′*R**)/(2*S**,4*R**,6′*R**)-diastereomers of substituted spiro[chromane-2,4′-pyrimidin]-2′(3′*H*)-ones by the reaction of 4-aryl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-ones with resorcinol and 2-methylresorcinol has been developed.

The X-ray diffraction study was supported by the Ministry of Science and Higher Education of the Russian Federation (grant no. 075-03-2023-642) and was carried out using the equipment of the Center for Molecular Structure Studies of the A. N. Nesmeyanov Institute of Organoelement Compounds.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.013.

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† *Crystal data for* **3b**. $C_{24}H_{22}N_2O_3 \cdot C_3H_6O_3$, M = 476.51, monoclinic, space group $P2_1/n$, a = 10.0703(4), b = 10.5940(4) and c = 22.7934(8) Å, β = 92.8542(11)°, V = 2428.7(2) Å^3, Z = 4, d_{calc} = 1.303 g cm^{-3}. wR_2 = 0.1092 calculated on F^2_{hkl} for all 4795 independent reflections with $2\theta < 52.2°$ [GOF = 1.067, R = 0.0399 calculated on F_{hkl} for 3717 reflections with $I > 2\sigma(I)$].

Single crystal X-ray diffraction experiment was carried out using SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scans] at 120 K. Collected data were processed by the SAINT and SADABS programs incorporated into the APEX2 program package.[9(a)] The structures were solved by the direct methods and refined by the full-matrix least-squares procedure against F^2 in anisotropic approximation. The refinement was carried out with the SHELXTL program.[9(b)]

CCDC 2277019 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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