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PII:S0040-4039(18)30741-XDOI:https://doi.org/10.1016/j.tetlet.2018.06.012Reference:TETL 50050To appear in:Tetrahedron LettersReceived Date:26 March 2018

Revised Date:31 May 2018Accepted Date:4 June 2018



Please cite this article as: Levchenko, K.S., Chudov, K.A., Zinoviev, E.V., Lyssenko, K.A., Demin, D.U., Poroshin, N.O., Shmelin, P.S., Grebennikov, E.P., Synthesis of unsymmetrical 4-oxo-2-vinyl-4H-chromene-3-carbonitrile dyes via Knoevenagel reaction, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.012

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Tetrahedron Letters journal homepage: www.elsevier.com

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online New 4-oxo-2-vinyl-4H-chromene-3-carbonitrile derivatives have been synthesized by the Knoevenagel reaction of 2-methyl-4-oxo-4H-chromene-3-carbonitrile with aromatic and heteroaromatic aldehydes. Spectral properties of the obtained compounds have been studied.

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Keywords: 4-Oxo-4H-chromene-3-carbonitrile Knoevenagel reaction Dyes Chromophores

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Over the past decades the development of organic dyes has generated a huge interest owing to their potential applications in a variety of areas: photoelectronics, nonlinear optical (NLO) devices, information processing, fiber communications, optical switching and information storage¹⁻⁶. They widely used as key material for dye-sensitized solar cells⁷, colorants in the industry, in biological reactions, printing systems, food chemistry⁸. Benzopyrane dyes are widely used as a near-infrared fluorescent dyes for rapid detection of hydrogen peroxide in living cells⁹, quantification of alkaline phosphatase in living cells¹⁰, nearinfrared fluorescent probe for biothiols¹¹ for hydrogen polysulfides¹², as photoactive components in optical memory devices^{13,14}, etc. The improvement of the properties of organic dyes is carried out continuously. No matter in what field they are applied. Dye molecules have been studied to improve the efficiency of the solar energy to electricity conversion in dyesensitized solar cells, to improve nonlinear optical properties of chromophores, to increase the sensitivity of analytical methods, increase stability colorants, to of etc. The search for new acceptor or donor fragments for push-pull dyes is one of the strategies of dyes development. Successful combination of the donor and acceptor fragments connected by a p-conjugated bridge (D- π -A) allows to achieve the necessary physical and chemical properties of dyes such as optical properties, solubility, thermal stability, etc.

In this paper, the synthesis of new class of dyes based on 4oxo-4H-chromene-3-carbonitril-2-yl acceptor fragments is considered. It should be noted, that there is no information about the methods of preparation and optical properties of that dyes. Therefore, studies in this area look very attractive. The results of the research will open up access to a new class of dyes for NLO devices and other applications.

The starting 2-methyl-3-cyanochromone was prepared according to the method¹⁵ from 2-hydroxyacetophenone (Scheme 1). In the first step, readily available 2-hydroxyacetophenone was converted into the corresponding dimethylaminomethylene derivative 2 in quantitative yield under reflux in DMF-DMA. Compound 2 was then refluxed in ethanol with hydroxylamine hydrochloride to give 2-(isoxazol-5-yl)phenol 3 in 80% yield. Upon treatment with aqueous-ethanolic NaOH solution at room temperature and neutralization of alkaline solution with acetic acid, the isoxazole ring of compound 3 was cleaved to form 3-(2hydroxyphenyl)-3-oxopropionitrile (4) in 75% yield. Too fast neutralization of alkaline solution with acetic acid at high temperatures (>10°C) led to undesirable by-product 6. 2-Methyl-4-oxo-4H-chromene-3-carbonitrile (5) was prepared by optimized method of acylation of 4 with acetyl chloride at 0-20 C. The introduction of the donor fragments into position 2 of the 2-methyl-4-oxo-4H-chromene-3-carbonitrile (5) was carried out under Knoevenagel reaction conditions. Aldehydes 7 a-h were used as model compounds for investigation of 2-methyl-4-oxo-4H-chromene-3-carbonitrile (5) reactivity (Scheme 2).



Scheme 1. Reagents and conditions: (i) DMF-DMA reflux, 1 h; (ii) NH₂OH·HCl, EtOH, reflux, 2 h; (iii) NaOH, EtOH/H₂O (1:3), r.t., 24 h, AcOH, 0-10 °C; (iv) MeCOCl, pyridine, 0-20 °C, 2 h.

In Knoevenagel reaction we found the problem of selectivity of the reaction flow. It is known that chromone cycle is very sensitive towards nucleophiles and bases, which cause ringopening reaction¹⁵⁻¹⁶ Therefore we investigated organic bases with different basicity and nucleophilicity. Organic bases such as piperidine (Pip), tetraethylenediamine (TMEDA), and 1,8diazabicyclo[5.4.0]undec-7-ene (DBU) were used as reaction catalysts with ethanol and acetonitrile as solvents. The best results were obtained in the case of Pip and TMEDA. The worst yields were obtained with DBU. In all cases, several by-products were formed. Lowering of the reaction temperature decreased byproducts formation but significantly increased time of the process. Reactions proceeded more smoothly in the case of fivemembered heterocyclic aldehydes. The yields of reactions were 55-87%.



Scheme 2. *Reagents and conditions* (i) EtOH or CH₃CN, catalyst, r.t.-reflux, 1,5 h - 5 d.

The worst results were obtained in the cases of 4-fluoro-, 4chloro- and 4-bromo- benzaldehydes **7 f-h**. The title compounds **8 f-h** were obtained in 20-42% yields. Amino derivatives **8 i-m** were obtained in moderate to good yields. All of isolated compounds were only in the *trans* form. The structure of **8k** was confirmed by XRD with all atoms of conjugated system lining in one plane (Figure 1).

The results of Knoevenagel reactions are presented in Table 1. It should be noted that reaction speed and yields were not reliant directly on the aldehydes reactivity. That can be explained by occurrence of several side reactions which colorless and slightly colored by-products were detected by TLC analysis. Obviously, these substances were the by-products of the benzopyranes cycle destruction of 2-methyl-4-oxo-4H-chromene-3-carbonitrile followed by reaction with aldehydes (Scheme 3).



Figure 1. The general view of **8k** in representation of atoms by thermal ellipsoids (p = 50%).

Similar behavior was observed in the case of 3-acyl flavones. On heating under reflux with an aqueous solution of 5% potassium carbonate, 3-acyl flavones produce flavones with moderate yields¹⁷.

Table 1. Reagents and conditions of Knoevenagel reaction^a

Compound	Catalyst	Time	Temperature	Yield %	M.p.°C	
0	Pip	5 d	r.t	74%	100 102	
8a	TMEDA	5 d	r.t	72%	180-182	
	DBU	DBU 5 d r.t.		<10%		
8h	Pip	3 h	reflux	62%	156-158	
80	TMEDA	5 h ^b	reflux	55%		
8c	Pip	1,5 h	reflux	65%	237-238	
	TMEDA 5 h ^b		reflux	87%		
8d	Pip	4 h	reflux	65% 224-22	224-226	
	TMEDA	5 h ^b	reflux	55%		
8e	Pip	3 h	reflux	75%	252-254	
8f	pip	36 h	reflux	20%	226-228	
8g	Pip	28 h	reflux	42%	242 245	
	TMEDA	TMEDA 12 h r.t		22%	243-245	
	Pip	28 h	reflux	40,6%		
8h	pip	5 d	r.t	28.4% 23%	235-237	
	TMEDA	10 h ^c	reflux			
	Pip (CH ₃ CN)	8 h	reflux	27%		
8 i	Pip	2 h	reflux	67%	214	
8j	Pip	$4 h^{d}$	reflux	80%	254-256	
8k	Pip	10 h	reflux	56,7%	>250	
81	Pip	6 h	reflux	23%	-	
8m	Pip (CH ₃ CN)	13 h ^b	reflux	68,7%	219-220	

^a General reaction conditions. One drop of catalyst was added to a mixture of 2-methyl-4-oxo-4H-chromene-3-carbonitrile **5** (185 mg, 0,1 mmol) and aldehyde **7 a-m** (0,1 mmol) in ethanol or CH₃CN. After stirring at appropriate temperature and time, the precipitate that formed was filtered off, washed with ethanol, and dried in air. In case of absence of a solid precipitate the solvent was distilled off under reduced pressure. The residue was separated by column chromatography.

^bMixture was first stirred for three days at room temperature.

^cMixture was first stirred for two days at room temperature.

^d Mixture was first stirred for 14 h at room temperature.

The authors suggested that it is entirely possible for 3-acyl flavones to transform into tri- and diketones (similar to the Baker-Venkataraman reaction) via ring opening reaction followed by cyclization back into flavone.



Scheme 3. *Reagents and conditions* (i) 71, EtOH, piperidine, reflux, 6 h.

To confirm the above hypothesis in our case, we isolated and analyzed the uncolored by-product from synthesis of **81**. In this reaction, we observed the greatest amount of by-products and the minimum yield of the desired compound **81**. ¹H, ¹³C, HRMS and XRD (Figure 2) analyses confirmed the structure **9** shown in Scheme 3.



Figure 2. The general view of 9 in representation of atoms by thermal ellipsoids (p=50%).

In the case of reaction of 2-methyl-4-oxo-4H-chromene-3carbonitrile (5) with 7c another highly colored product was observed. We proposed it to be the by-product of the reaction of the in situ formed 2-[2-(5-bromo-furan-2-yl)-vinyl]-4-oxo-4Hchromene-3-carbonitrile with piperidine used as catalyst. It was confirmed by reaction of isolated 8c with an excess of piperidine (Scheme 4).



Scheme 4. Reagents and conditions (i) EtOH, piperidine, reflux.

The absorption and fluorescence spectral data of the synthesized products **8a-m** are summarized in Table 2. Groups of compounds **8a-e** and **8f-h** have insignificant fluorescence and absorption in UV area due to a weak donor substituent in position 2 of 4-oxo-4H-chromene-3-carbonitrile. Compounds **8i-m** with stronger donor substituents have absorption maxima at 474-513 nm and

strong fluorescence at 547-580 nm. All the compounds are characterized by a large Stokes shift (60-103 nm). Compound **10** has the smallest Stokes shift value among the obtained compounds and absorption maxima at 536 nm.

Table 2. The absorption and fluorescence spectral data and molecular hyperpolarizability (β) estimated at M052X/ 6-31+G(d) level for of the synthesized products **8a-m** and **10**

Compound	λ^{abs}	ε*10 ⁵	λ^{em}	SS	$I_{\rm fl}^{\rm max}$	$\phi^{\mathrm{fl}d}$	β (a.u.) ^e
	(nm)	$(M^{-1}.cm^{-1})$	(nm)	(nm)	(a.u.)		
8a ^b	406	0,39	496	90	23	-	-
8b ^c	382	0,27	452	60	20	-	-
8c ^b	392	1,14	493	101	22	-	-
8d °	380	0,63	469	89	31	-	-
8e ^c	392	0,35	480	78	18	-	-
8f ^c	348	0,41	-	-	-	-	-
$8g^{c}$	350	0,23	-	-	-	-	5005
8h ^c	352	0,17	-	-	-	-	-
8i ^c	487	0,25	547	60	329	0,15	15432
8j°	474	0,11	577	103	491	0,34	20493
8k ^c	513	0,56	571	68	958	0,25	16186
81 °	510	0,40	574	64	524	0,20	14568
8m ^c	500	0,41	564	64	242	0,20	15645
10 ^c	536	0,18	572	36	200	0,18	12819
8h ^c 8i ^c 8j ^c 8k ^c 8l ^c 8m ^c 10 ^c	 352 487 474 513 510 500 536 	0,17 0,25 0,11 0,56 0,40 0,41 0,18	- 547 577 571 574 564 572	- 60 103 68 64 64 36	- 329 491 958 524 242 200	- 0,15 0,34 0,25 0,20 0,20 0,18	- 15432 20493 16186 14568 15645 12819

 $^a\lambda^{abs}$, and λ^{em} are the wavelengths of the maxima of the absorption bands, and fluorescence spectra of compounds **8a-1**, respectively; ϵ - molar extinction coefficient; SS - Stokes shift; ϕ^{fl} is the fluorescence quantum yield; I_{fl}^{max} - fluorescence intensity at the maximum of the fluorescence band of compounds **8a-1**.

^bSolution in DMSO (λ^{em} at c = 0,003 mg/ml);

^c Solution in chlorobenzene (λ^{em} at c = 0,003 mg/ml).

^d The fluorescence quantum yield was determined using a relative optical method¹⁸.

 e β is the calculated using M052X functional and 6-31+G(d) basis set first hyperpolarizability.

Figures 3 and 4 show the absorption and fluorescence spectra of the compounds **8d**, **i-m** and **10**. It was found that obtained compounds have similar spectral properties with dimethyl-[4-(4-nitro-phenylazo)-phenyl]-amine (DR1) or tricyanovinylidenediphenylaminobenzene (TCVDPA) derivatives, that are used as electro-optic chromophores in NLO devices^{1,19,20}.



Figure 3. Absorption spectra of **8d** in DMSO (c = 0.05 mg/ml), **8i** in chlorobenzene (c = 0.2 mg/ml); **8j** in chlorobenzene (c = 0.25 mg/ml); **8k,l,m** in chlorobenzene (c = 0.05 mg/ml) and **10** in DMSO (c = 0.05 mg/ml).



Figure 4. Fluorescence spectra of **8d**, **8i-m**, **10** in chlorobenzene at concentrations 0,003 mg/ml. The fluorescence excitation wavelengths are at the maximum of absorption.

Solvatochromism was investigated for compounds **8k-m** in solvents of low (dioxane, chlorobenzene, methylene chloride) and high polarity (acetone, acetonitrile). A positive solvatochromism was observed in low-polarity solvents for compounds **8k-m**, while in high-polarity solvents they displayed an anomalous solvatochromism. In other words, in a low regime of solvent polarity such as from 1,4-dioxane ($E_T(30) = 36.0$) to dichloromethane ($E_T(30) = 40.7$), absorption area is red-shifted (25-27 nm) with increasing solvent polarity, whereas in a higher-polarity acetone (ET(30) = 42.2) or acetonitrile ($E_T(30) = 45.6$) absorption area is blue-shifted (5-10 nm) relative to that in dichloromethane (Figure 5).



Figure 5. Absorption spectra of 8k in different solvents (c = 0,05 mg/ml).

Fluorescence area (Figure 6) for all of compounds is red-shifted with increasing solvent polarity from 1,4-dioxane to acetonitrile (35-42 nm). This may indicate that the excited state of chromophores has larger dipole moment than in the ground state. And larger shift of the emission to lower energy is due to stabilization of the excited state by the more polar solvent molecules. It is interesting to note that fluorescence quenching is observed in polar solvent (acetone or acetonitrile).

The first hyperpolarizability (β) for **8h-8m** and **10** molecules was calculated using M052X functional and 6-31+G(d) basis set (see SI) that were shown to be adequate for calculation of conjugated molecules consisted from different building blocks²¹⁻²⁴. The results show that value of β for calculated molecules is 2-3 times higher than that for 4,4'-hydroxy-nitrostilbene (HONS)²⁵, and more than order of magnitude higher than that of pNA that is standard benchmark NLO molecule²⁶. It is noteworthy that β values are proportional to λ^{abs} .

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Figure 6. Fluorescence spectra of **8k** in different solvents (c = 0,003 mg/ml).

In conclusion, we have developed efficient methods of synthesis and modification of new 4-oxo-2-vinyl-4H-chromene-3carbonitrile derivatives by the Knoevenagel reaction of 2-methyl-4-oxo-4H-chromene-3-carbonitrile with aromatic and heteroaromatic aldehydes. Experimental solvatochromic data and calculated first hyperpolarizability (β) of obtained chromophores demonstrates the prospects of their use in NLO devices and other applications.

Acknowledgments

This work was supported by RSF 17-73-10433. The X-ray diffraction data were obtained using the equipment of Center for molecules composition studies of INEOS RAS.

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Supplementary Data

Supplementary data containing methods of synthesis and characterization data of synthesized compounds (2-6, 7j-m, 8a-m, 9 and 10), solvatochromism investigation as well as details of DFT calculations are available online. Crystallographic data for the structures reported in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary no.: CCDC - 1828944 (for 8k) and CCDC - 1828945 (for 9). These data can be obtained free of charge from The Cambridge Crystallographic Data via www.ccdc.cam.ac.uk/data request/cif.

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Methods of synthesis of new chromophores by the Knoevenagel reaction were developed Side process in Knoevenagel reaction was found

Acception New potential chromene based non-linear optical (NLO) dyes were prepared