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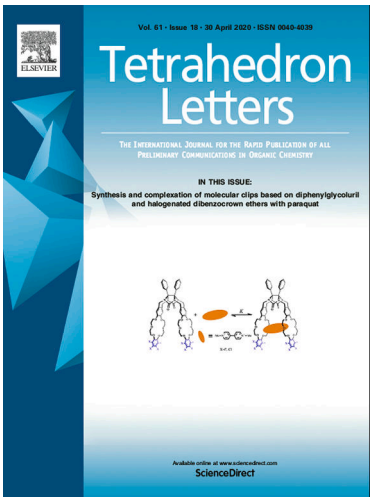

Synthesis and Solid-State Luminescence of Highly-Substituted 6-Amino-*2H*-pyran-2-one Derivatives

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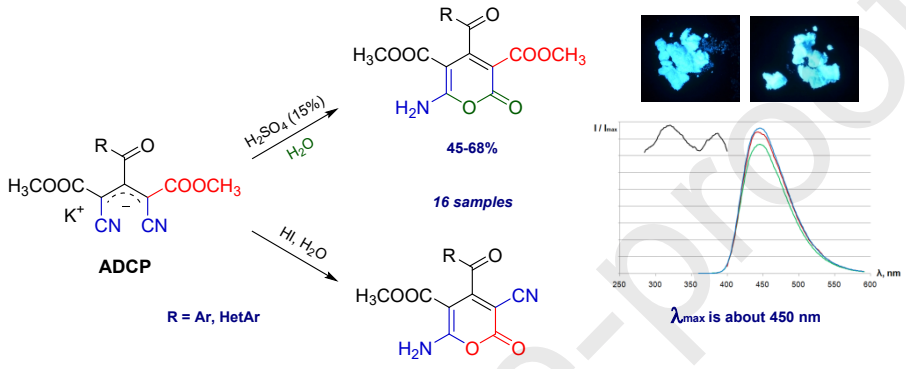
Graphical Abstract

Synthesis and solid-state luminescence of highly-substituted 6-amino-2*H*-pyran-2-one derivatives

Sergey Vladimirovich Karpov, Yakov Sergeevich Kayukov, Arthur Aleksandrovich Grigor'ev, Oleg Evgen'evich Nasakin, Olga Varsanof'evna Kayukova, Viktor Aleksandrovich Tafeenko



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Synthesis and Solid-State Luminescence of Highly-Substituted 6-Amino-*2H*-pyran-2-one Derivatives

Sergey Karpov[a*], Yakov Kayukov[a], Arthur Grigor'ev[a], Oleg Nasakin[a], Olga Kayukova[b] and Viktor Tafeenko[c]

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ABSTRACT

A fast and convenient synthesis and solid-state luminescence properties of new highly-substituted 6-amino-*2H*-pyran-2-one derivatives is described. These compounds were obtained from inexpensive and available 2-acyl(aroyl)-1,3-dicyano-1,3-bis-methoxycarbonylpropenides *via* regioselective heterocyclization under the action of sulfuric and hydroiodic acid. Compounds containing 6-amino-*2H*-pyran-2-one moiety are nearly unstudied, but are of interest for obtaining condensed biologically active compounds based on this scaffold.

Currently, the non-fused 6-amino-2*H*-pyran-2-one derivatives are nearly unstudied. Only two compounds of this type are known,[1] one of them exhibited moderate antimicrobial activity against *S. aureus*, *E. coli* and *P. aeruginosa*.[1a] However, a number of fused compounds, containing this scaffold are described. Among them, are known an effective nicotinic acid receptor agonists,[2] fluorophores,[3] and photobiological active compounds.[4]

In this work, we report a fast and convenient synthesis and solid-state luminescent properties of novel 6-amino-2*H*-pyran-2-ones, obtained from readily available 2-acyl(aroyl)-1,3-dicyano-1,3-*bis*-methoxycarbonylpropenides (ADCP).

The starting ADCP **1** are new representatives of stable organic salts, containing polycyano-substituted allyl anion that have gained interest as bridging ligands for the construction of various 1D, 2D and 3D supramolecular structures.[5] In organic synthesis, the promising precursors for five- and six-membered heterocycles are alkali metals and ammonia 2-acyl-1,1,3,3-tetracyanopropenides (ATCN), preparation[6] and some chemical properties[7] of which we have previously described. The ADCP **1** are close structural analogues of ATCN (Figure 1) containing two ester groups in addition to two cyano groups. At the same time, their chemical properties have not been previously studied.

The potassium ADCP salts **1** were first obtained using a arylglyoxale hydrates, methyl cyanoacetate and bromine as starting compounds.[8] (Scheme 1)

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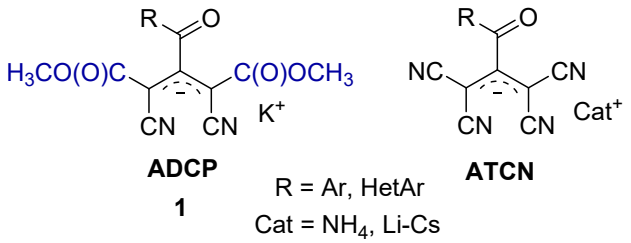
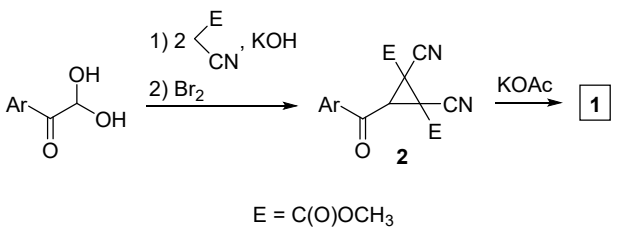


Figure 1. Structures of ADCP and ATCN salts.



Scheme 1. First synthesis of potassium ADCP.

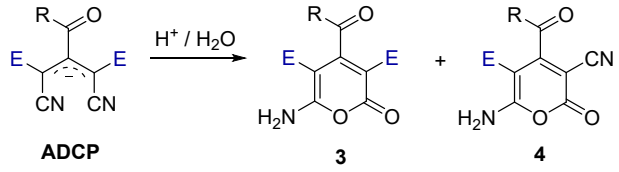
The required arylglyoxale hydrates were obtained by oxidation of acetophenones with selenium dioxide in medium yields.[9] Due to it, the total yield of ADCP based on starting acetophenones did not exceed 37-43%. Later, we described more convenient method for oxidation of acetophenones to arylglyoxales based on readily available reagents such as DMSO, NaBr and sulphuric acid.[6] The resulting arylglyoxales can be

inv ents

consequently the total yields of ADCP increases up to 80% (Table 1).

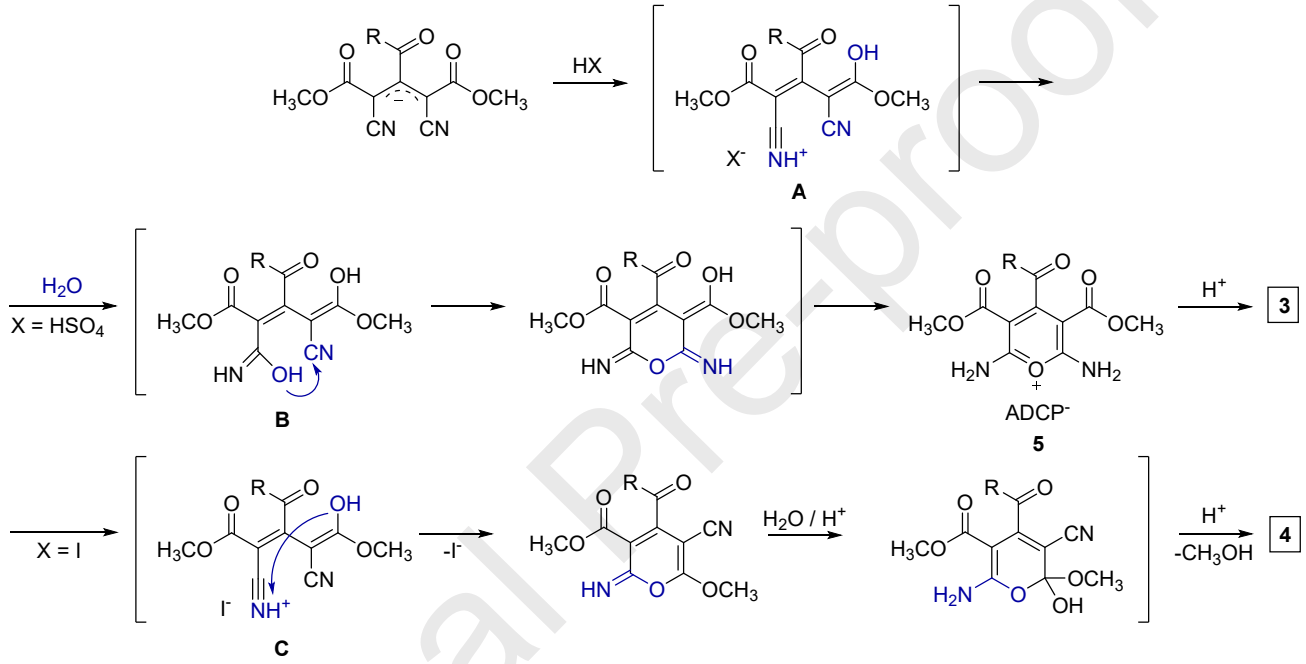
It is noteworthy that the dimethyl 3-acyl(aroyl)-1,2-dicyanocyclopropane-1,2-dicarboxylates **2** were obtained in one stereoisomeric form (mixture of *cis*- and *trans*-isomers), but ADCP, derived from them have only a *cis* -arrangement of the aroyl group and two ester groups.[8]

The potassium ADCP **1** are stable pale-yellow or yellow crystalline powders with a good solubility in water and polar organic solvents. In contrast to ATCP, salts **1** does not undergo heterocyclization under the action of nucleophiles in the base media. However, we have found that ADCP easily forms 6-amino-2*H*-pyran-2-one derivatives **3** and **4** in an acidic media (Scheme 2). In according to ^{1}H NMR data, the ADCP forms mixture of **3** and **4** in aqueous solution of HCl, HBr, nitric and trifluoroacetic acid. This mixture is difficultly separable due to and close retention factors.



Scheme 2. Heterocyclization of ADCP in acidic media.

Nevertheless, we have found that using of aqueous sulphuric acid (10-15%) or hydroiodic acid leads to the predominant formation of pyran-2-ones **3** or **4** correspondingly. Subsequent recrystallization allows to isolate pure compounds in 55-68% yields (Table 1). The possible mechanism for this transformations is shown in Scheme 3.



Scheme 3. The possible mechanism for heterocyclization of ADCP in the presence of sulphuric and hydroiodic acid

The proposed mechanism for this reaction involves preliminary charge neutralization in anion and protonation of one of cyano groups with formation of intermediate **A**. Subsequent route for heterocyclization depends of its stability.

In the case of using sulphuric acid, the protonated cyano group is easily hydrolyzed with formation of intermediate **B**. Subsequent heterocyclization leads to the pyrilium salts **5**, which can be isolated from reaction mass at r.t. Heating of the reaction mass leads to further hydrolysis of **5** and formation of pyran-2-ones **3**. Salts **5** have law solubility in water and to prevent their precipitation a some acetic acid should be added to the reaction mass. The ORTEP image of **5c** (R = 4-$CH_3OC_6H_4$) is shown on Figure 2.

In the case of using hydroiodic acid, the intermediate **C** is more resistant to intermolecular hydrolysis but undergoes intramolecular heterocyclization which leads to compounds **4**.

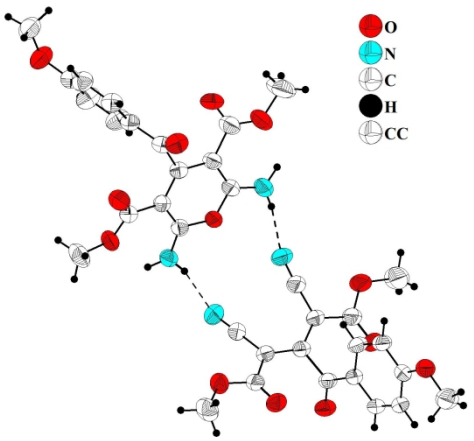


Figure 2. The ORTEP image of pyrilium salt **5c** with 50% probability ellipsoids.[10]

Tab
3 and **4**

Entry	R	Yield (%), ADCP **1**	Yield (%), compd. **3**	Yield (%), compd. **4**
a	Ph	78	64	51
b	4-MeC_6H_4	70	56	62
c	4-MeOC_6H_4	72	68	46
d	4-ClC_6H_4	58	55	58
e	4-BrC_6H_4	65	59	64
f	3-$NO_2C_6H_4$	59	45	47
g	2-MeC_6H_4	74	60	53
h	2-Thienyl	81	61	70

All the investigated pyrane-2-ones **3** and **4** possess no visible fluorescence in solution. However, in the solid state, these compounds possesses visible fluorescence in about 430-450 nm. All emission fluorescence spectra have one optical center (Figures 3 and 4). Fluorescence excitation and emission maxima for the compounds **3** and **4** are presented in Table 2.

Table 2. Fluorescence excitation and emission maxima for the compounds **3** and **4**.

Compound	$\lambda^{ex}{}_{max}$ (λ_{reg}), nm	$\lambda^{em}{}_{max}$ (λ_{ex}), nm
3a	318, 387 (453)	453 (380)
3b	312, 372 (438)	435 (380)
3c	316, 383 (445)	445 (380)
3d	317, 375 (450)	449 (380)
3e	322, 386 (451)	451 (380)
3f	336, 375 (458)	436 (380)
3g	318, 386 (446)	451 (380)
3h	310, 374 (431)	431 (380)
4a	311, 383 (483)	483 (380)
4b	308, 376 (434)	434 (380)
4c	323, 385 (425)	425 (380)
4d	317, 394 (455)	455 (380)
4e	322, 381 (440)	439 (380)
4f	318, 398 (454)	454 (380)
4g	331, 374 (432)	432 (380)
4h	421, 393 (463)	463 (380)

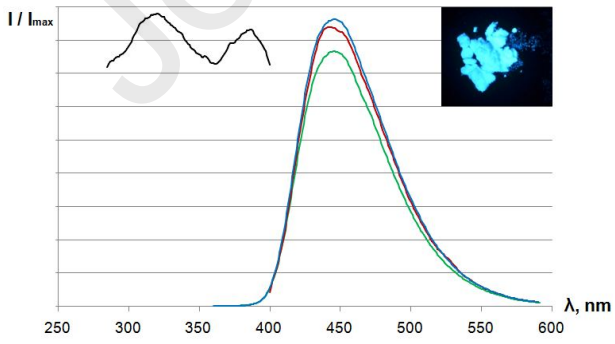


Figure 3. Solid state **3c** emission and excitation spectra; excitation wavelength is 445 nm (black curve), registration wavelength is 350 nm (green curve), 386 (blue curve) and 320 nm (red curve)

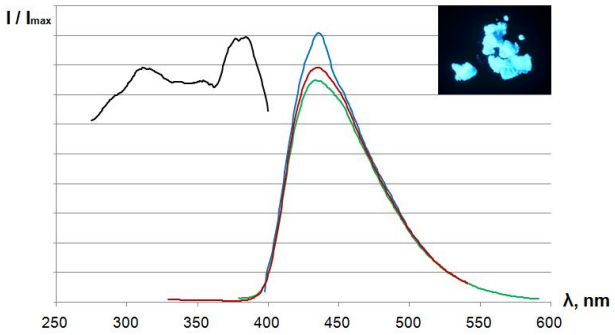


Figure 4 Solid state **4b** emission and excitation spectra; excitation wavelength is 434 nm (black curve), registration wavelength is 350 nm (green curve), 383 (blue curve) and 313 nm (red curve)

In conclusion, ADCP[11] undergo intramolecular heterocyclization in aqueous solution in the presence of strong acids with formation of two 6-amino-2*H*-pyran-2-one derivatives. The ratio of this reaction products is not depends on concentration of acid but depends on its type. Using of 10-15% H_2SO_4 leads to preferential formation of dimethyl 6-amino-4-aroyl(heteroaroyl)-2-oxo-2*H*-pyran-3,5-dicarboxylates **3**,[12] but using hydroiodic acid leads to the formation of methyl 6-amino-4-aroyl(heteroaroyl)-3-cyano-2-oxo-2*H*-pyran-5-carboxylates **4**.[13] The obtained compounds possesses visible fluorescence in about 450 nm in solid state.

Acknowledgments

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10. CCDC 1960984 contain the supplementary crystallographic data for **5c**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures/
11. *Synthesis of dimethyl 3-acyl(aroyl)-1,2-dicyanocyclopropane-1,2-dicarboxylates **2** (General procedure)*. Aryl(heteroaryl)methylketone (0.1 mol) was oxidized to corresponding aryl(heteroaryl)gyoxale via described method[6] using DMSO-NaBr-H_2SO_4 mixture. When the reaction is finished, the formed yellow-orange reaction mass was cooled to r.t. and dissolved in 100 ml of ethanol with methyl cyanoacetate (19.8 g, 0.2 mol). To the resulting solution was added dropwise a concentrated solution of KOH in ethanol under stirring until the reaction mass becomes alkaline. The mixture was stirred for 15 min then neutralized by addition of 20% H_2SO_4 and cooled to r.t. Bromine (16.0 g, 0.1 mol) was added dropwise to the reaction mass with vigorous stirring. After decoloration of bromine, the mixture was poured into 700 ml of distilled water and stay for 30 min. The pale-brown oil which formed was separated from the solution and dissolved in 80 ml of boiling EtOH. After cooling, the formed white solid precipitate was filtered, washed by cold ethanol and dried in air. If necessary, cyclopropanes **2** could be purificated via reprecipitation from a benzene solution by hexane or heptane.
*Synthesis of ADCP **1*** was realized via described method[8] using potassium acetate as a base.
12. *Synthesis of dimethyl 6-amino-4-aroyl(heteroaroyl)-2-oxo-2H-pyran-3,5-dicarboxylates **3** (General procedure).*
ADCP (0.12 mmol) was dissolved in 5 ml of mixture water-acetic acid (3:1) with heating. To the resulting solution under stirring was added dropwise 15% H_2SO_4 (2 ml), then the mixture was heated at 70-80°C until it discolored (3-5 min). After cooling, water (6 ml) was added to the reaction mass and stay for 4-5 hours. The resulting white solid precipitate was filtered and recrystallized from methanol.
Notes: 1) The reaction mass should not be stayed overnight or longer due to resinification. 2) In the case using water instead of mixture water-acetic acid and caring out the reaction at r.t., the yellow precipitate of unpured pirilium salts **5** will form immediately. These compounds are unstable when heated, in air and daylight so we were not able to purify them using recrystallization or column chromatigraphy. For the XRD analysis, the single crystal of **5c** was obtained by evaporation of acetonitrile solution in dark at -18°C.
*Dimethyl 6-amino-4-benzoyl-2-oxo-2H-pyran-3,5-dicarboxylate (**3a**).*
Compound **3a:** white solid, mp 171 - 172 ºC. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 3.34 (3H, s, CH_3), 3.40 (3H, s, CH_3), 7.49 (2H, t, ^3J = 7.7 Hz, Ar), 7.58 (2H, t, ^3J = 7.4 Hz, Ar), 7.83 (1H, d, ^3J = 7.2 Hz, Ar), 9.05 (1H, s, NH_2), 9.79 (1H, s, NH_2). ^{13}C NMR (121 MHz, DMSO-*d6*): δ 51.2, 51.3, 86.5, 98.1, 127.7, 128.4, 136.5, 154.6, 162.9, 163.5, 163.6, 166.0, 192.2. MS (EI, 70 eV): *m/z* (%) 331 (24) $[M]^+$, 105 (100) $[ArCO]^+$, 77 (61) $[Ar]^+$. Anal. Calcd for $C_{16}H_{13}NO_7$: C, 58.01; H, 3.96; N, 4.23. Found: C, 56.82; H, 4.03; N, 4.13.
13. *Synthesis of methyl 6-amino-4- aroyl(heteroaroyl)-3-cyano-2-oxo-2H-pyran-5-carboxylates **4** (General procedure).*
ADCP (0.12 mmol) was dissolved in 6 ml of boiling concentrated (56%) hydroiodic acid. After cooling, water (6 ml) was added to the reaction mass and stay for 2 hours. The resulting white solid precipitate was filtered and recrystallized from acetic acid.
*Methyl 6-amino-4-benzoyl-3-cyano-2-oxo-2H-pyran-5-carboxylate (**4a**).*
Compound **4a:** white solid, mp 262 - 263 ºC. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 3.43 (3H, s, CH_3), 7.57 (2H, t, ^3J = 7.7 Hz, Ar), 7.71 (1H, t, ^3J = 7.3 Hz, Ar), 7.97 (2H, d, ^3J = 7.2 Hz, Ar), 9.31 (1H, NH_2), 10.22 (1H, NH_2). ^{13}C NMR (121 MHz, DMSO-*d6*): δ 52.1, 80.1, 88.0, 115.0, 129.1, 129.3, 134.5, 134.8, 156.7, 163.1, 165.1, 166.3, 191.4. . MS (EI, 70 eV): *m/z* (%) 298 (24) $[M]^+$, 105 (100) $[ArCO]^+$, 77 (61) $[Ar]^+$. Anal. Calcd for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39. Found: C, 59.85; H, 3.44; N, 9.23.

Contains ^{1}H, ^{13}C NMR data for compounds **3**, **4** and ORTEP image of **3d**.

- The [illegible] pyran-2-one derivatives is described.
- A mechanism for ADCP heterocyclization in acidic media is proposed.
- The one key intermediate was isolated and characterized by XRD.