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Reversible condensation of 4-arylidene-1,2-dimethyl-1*H*-imidazol-5(4*H*)-ones with aromatic acyl chlorides

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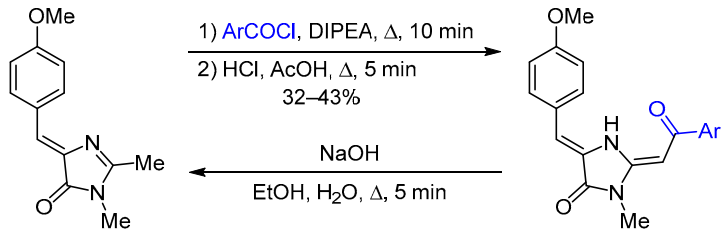


(*Z*)-1,2-Dimethyl-4-(4-methoxybenzylidene)-1*H*-imidazol-5(4*H*)-one underwent a condensation reaction with aromatic acyl chlorides, forming keto derivatives that were structurally similar to chromophores of red fluorescent proteins, as well as to the products of their maturation and/or degradation. The reverse reaction of the obtained products was observed upon treatment with aqueous alkali.

Keywords: imidazolones, chromophores, fluorescent proteins, condensation.

Various 4-arylidene-1*H*-imidazol-5(4*H*)-ones, which are the basis of chromophores in fluorescent proteins, have been attracting the attention of researchers for a long time. On one hand, the synthesis of their derivatives has allowed to characterize the structure and properties of fluorescent proteins, leading to a better understanding of the maturation mechanisms.[1] On the other hand, their various intense colors, small size, and highly hydrophilic nature has enabled a range of useful applications, including RNA tagging,[2] design of two-photon,[3] solid phase,[4] polymeric,[5] and other[6] fluorescent dyes.

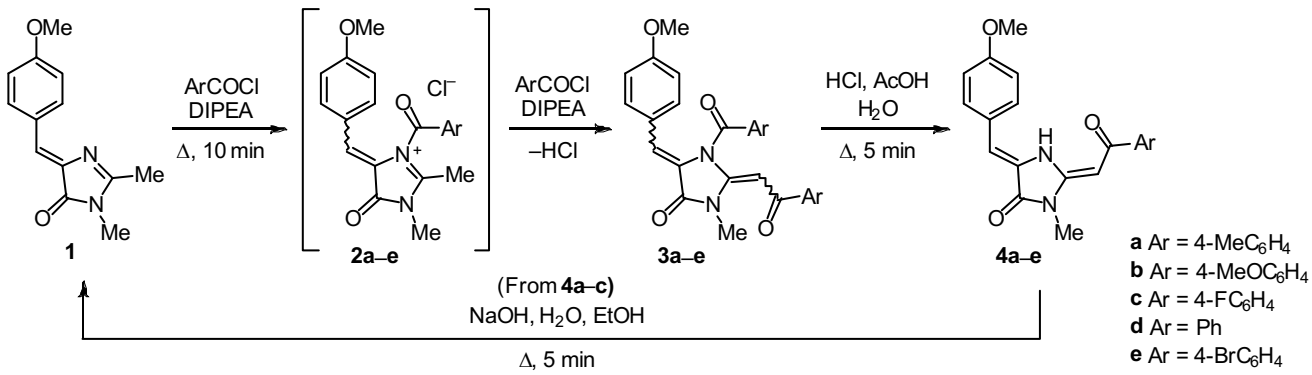
During our work dedicated to studying the chemistry of compounds derived from the chromophore of green fluorescent protein, we found that acyl chlorides reacted with derivatives of 4-arylidene-1*H*-imidazol-5(4*H*)-ones containing a methyl group at position 2 of the imidazole ring, leading to a condensation reaction that produced ketones. A similar reaction giving enols was so far demonstrated only for a few derivatives of 2-methylimidazole, primarily nitro derivatives[7] and benzimidazoles,[8] as well as a small number of other compounds.[9]

At the same time, based on the example of (*Z*)-1,2-dimethyl-4-(4-methoxybenzylidene)-1*H*-imidazol-5(4*H*)-one (**1**), we were able to demonstrate not only the high efficiency of this process, but also the possibility of achieving the reverse reaction (Scheme 1).

We established that the reaction of imidazolone **1** with aromatic acyl chlorides was most effective upon heating with excess acyl chloride in the presence of diisopropylethylamine (DIPEA).

The mechanism of such transformation most likely included the initial acylation of the starting imidazolone at the N-3 atom with the formation of quaternary salts **2a**–**e**. It has been already shown that a similar reaction with Lewis acids enables, for example, the condensation of imidazolones with aromatic aldehydes.[10,11] A further acylation likely results in the formation of amides **3a**–**e**, which could be isolated only as mixtures of *Z*- and *E*-isomers. The isomerization of benzylidene moiety in compounds analogous to imidazolone **1** has been previously observed in basic media,[1] but in this case the formation of isomers occurred simultaneously at two multiple bonds, leading to a mixture of two to four compounds (Scheme 1).

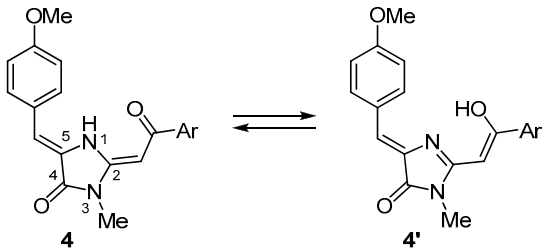
Scheme 1



Nevertheless, the subsequent treatment with hydrochloric acid led to the removal of one aroyl group, as well as isomerization of multiple bonds with the formation of pure (2*E*,5*Z*)-2-(2-aryl-2-oxoethylidene)-5-(4-methoxybenzylidene)-3-methylimidazolidin-4-ones **4a**–**e**.

Obviously, the structure of compounds **4a**–**e** suggests the possible existence of different tautomers: ketone (structure **4**) and enol (structure **4'**), the formation of which was postulated earlier[7–9] (Scheme 2).

Scheme 2



Actually, it was found that compounds **4a**–**e** existed in DMSO solutions exclusively in the ketone form with a double *exo* bond. Such a structure in the case of compound **4a** was confirmed by two-dimensional ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{15}N HSQC, and ^{1}H–^{15}N HMBC NMR experiments, while the double bond configuration was confirmed with two-dimensional ^{1}H–^{13}C HSQMBC (the coupling constant of the 4-CO carbon atom and the =C<u>H</u>Ar proton was equal to 5.4 Hz) and ROESY experiments (the =C<u>H</u>COAr proton gave a cross peak with the protons of 3-CH_3 group, but no cross peak with the 1-NH proton).

During the study of deprotonation in compounds **4a**–**c**, it was found that they were readily converted by the action of base to the starting imidazolone **1** in 56% to 76% yields (Scheme 1).

The study of optical properties of derivatives **4** showed very low quantum yields of fluorescence (less that 5%) in all cases, which was in a good agreement with the data previously obtained for other free chromophores of fluorescent proteins.[1] At the same time, it was also found that the nature of aroyl moiety had a very slight effect on the position of absorption maxima of compounds **4**. Thus, UV spectra of compounds **4a**–**e** contained two absorption maxima in the regions of 300 nm and 430 nm, the position of which shifted by no more than by 5 nm, depending on the aroyl substituent.

Thus, we propose a method for the synthesis of 2-(2-aryl-2-oxoethylidene)-5-(4-methoxybenzylidene)-3-methylimidazolidin-4-ones with unexpected structure, containing a multiple *exo* bond at position 2 of the imidazolone ring. These compounds serve as good models for the study of physicochemical properties of fluorescent proteins and their chromophores.

Experimental

UV spectra were recorded on a Varian Cary 100 Bio spectrophotometer in EtOH. ^{1}H, ^{13}C, and ^{15}N NMR spectra were acquired on a Bruker Avance III instrument (700, 175, and 70 MHz, respectively) in DMSO-d_6. The internal standard for ^{1}H and ^{13}C nuclei was TMS, the external standard for ^{15}N nuclei was liquid ammonia (0.0 ppm). High-resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap instrument (capillary voltage 2 kV, nanospray, needle temperature 200°C). Melting points were determined on an SMP 30 apparatus and were uncorrected. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates.

Reagents from Acros Organics were used without additional purification, and reactions were performed in freshly prepared solvents. Compound **1** was obtained according to a published procedure.[12]

(2*E*,5*Z*)-2-(2-Aryl-2-exoethylidene)-5-(4-methoxybenzylidene)-3-methylimidazolidin-4-ones 4a–e (General method). A suspension of imidazolone **1** (1.15 g, 5 mmol) in (*i*-Pr)$_2$NEt (20 ml) was treated with the appropriate acyl chloride (20 mmol). The obtained mixture was refluxed for 10 min at 130°C. The solvent was removed on a rotary evaporator, the residue was diluted with EtOAc (250 ml), and the solution was washed with 3% HCl solution (3×50 ml). The organic phase was washed with water, NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by silica gel flash chromatography (eluent 20:1 $CHCl_3$–MeOH), collecting the colored fractions with $R_f \sim 0.3$. The obtained product was complex mixture of *Z*- and *E*-isomers of compounds **3a**–**e** (from two to four compounds according

to ^{1}H NMR data), dissolved in AcOH (10 ml) and diluted with 10% HCl (10 ml). The mixture was refluxed for 5 min, dissolved in EtOAc (250 ml), washed with saturated $NaHCO_3$ solution (3×50 ml), water, and NaCl solution. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by silica gel column chromatography (eluent 50:1 $CHCl_3$–MeOH), collecting the colored fractions with $R_f \sim 0.4$.

(2*E*,5*Z*)-5-(4-Methoxybenzylidene)-3-methyl-2-[2-(4-methylphenyl)-2-oxoethylidene]imidazolidin-4-one (4a). Yield 750 mg (43%),* yellow powder, mp 191–193°C. UV spectrum, λ_{max}, nm (log ε): 301 (4.26), 431 (4.43). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, ArC<u>H</u>$_3$); 3.23 (3H, s, NCH_3); 3.84 (3H, s, OCH_3); 6.19 (1H, s, =C<u>H</u>COAr); 6.66 (1H, s, =C<u>H</u>Ar); 7.15 (2H, d, ^3J = 8.7, H-3,5 CHAr); 7.32 (2H, d, ^3J = 7.9, H-3,5 COAr); 7.59 (2H, d, ^3J = 8.6, H-2,6 CHAr); 7.97 (2H, d, ^3J = 7.9, H-2,6 COAr); 12.35 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.0 (Ar<u>C</u>H$_3$); 25.9 (NCH_3); 55.3 (OCH_3); 77.3 (=<u>C</u>HCOAr); 110.3 (=<u>C</u>HAr); 114.9 (C-3,5 CHAr); 124.4 (C-5); 126.0 (C-1 CHAr); 127.2 (C-2,6 COAr); 129.0 (C-3,5 COAr); 130.3 (C-2,6 CHAr); 136.1 (C-1 COAr); 141.7 (C-4 COAr); 154.6 (C-2); 159.8 (C-4 CHAr); 163.1 (4-CO); 187.1 (=CH<u>C</u>OAr). ^{15}N NMR spectrum, δ, ppm: 109.0 (N-1); 135.5 (N-3). Found, *m*/*z*: 349.1547 $[M+H]^+$. $C_{21}H_{21}N_2O_3$. Calculated, *m*/*z*: 349.1552.

(2*E*,5*Z*)-5-(4-Methoxybenzylidene)-2-[2-(4-methoxyphenyl)-2-oxoethylidene]-3-methylimidazolidin-4-one (4b). Yield 580 mg (32%), yellow powder, mp 176–179°C. UV spectrum, λ_{max}, nm (log ε): 299 (4.29), 434 (4.41). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.23 (3H, s, NCH_3); 3.84 (6H, s, 2OCH_3); 6.16 (1H, s, =C<u>H</u>COAr); 6.63 (1H, s, =C<u>H</u>Ar); 7.04 (2H, d, ^3J = 8.9, H-3,5 CHAr); 7.15 (2H, d, ^3J = 8.8, H-3,5 COAr); 7.57 (2H, d, ^3J = 8.8, H-2,6 CHAr); 8.05 (2H, d, ^3J = 8.8, H-2,6 COAr); 12.25 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 25.9; 55.3; 55.4; 77.1; 109.9; 113.6; 115.0; 124.5; 126.1; 129.3; 130.3; 131.4; 154.3; 159.8; 162.1; 163.1; 186.6. Found, *m*/*z*: 365.1495 $[M+H]^+$. $C_{21}H_{21}N_2O_4$. Calculated, *m*/*z*: 365.1501.

(2*E*,5*Z*)-5-(4-Methoxybenzylidene)-2-[2-(4-fluorophenyl)-2-oxoethylidene]-3-methylimidazolidin-4-one (4c). Yield 650 mg (37%), yellow powder, mp 184–186°C. UV spectrum, λ_{max}, nm (log ε): 302 (4.27), 427 (4.42). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.23 (3H, s, NCH_3); 3.84 (3H, s, OCH_3); 6.20 (1H, s, =C<u>H</u>COAr); 6.67 (1H, s, =C<u>H</u>Ar); 7.14 (2H, d, ^3J = 8.7, H-3,5 CHAr); 7.32 (2H, br. t, ^3J = 8.7, H-3,5 COAr); 7.58 (2H, d, ^3J = 8.8, H-2,6 CHAr); 8.13 (2H, dd, ^3J = 8.6, $^4J_{HF}$ = 5.7, H-2,6 COAr); 12.25 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 26.0; 55.4; 77.3; 110.7; 115.0; 115.3 (d, $^2J_{CF}$ = 21.6, C-3,5 COAr); 124.2; 125.9; 129.9 (d, $^3J_{CF}$ = 8.8, C-2,6 COAr); 130.4; 135.4; 154.8; 159.9; 163.1; 164.2 (d, $^1J_{CF}$ = 249.9, C-4 COAr); 186.0. Found, *m*/*z*: 353.1295 $[M+H]^+$. $C_{20}H_{18}FN_2O_3$. Calculated, *m*/*z*: 353.1301.

(2*E*,5*Z*)-5-(4-Methoxybenzylidene)-2-(2-oxo-2-phenylethylidene)-3-methylimidazolidin-4-one (4d). Yield 580 mg (35%), yellow powder, mp 188–190°C. UV spectrum, λ_{max}, nm (log ε): 300 (4.25), 431 (4.39). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.24 (3H, s, NCH_3); 3.85 (3H, s, OCH_3); 6.18 (1H, s, =C<u>H</u>COAr); 6.67 (1H, s, =C<u>H</u>Ar); 7.15 (2H, d, ^3J = 8.8, H-3,5 CHAr); 7.51 (2H, t, ^3J = 7.5, H-3,5 COPh); 7.55 (1H, t, ^3J = 7.5, H-4 COPh); 7.59 (2H, d, ^3J = 8.8, H-2,6 CHAr); 8.05 (2H, d, ^3J = 7.5, H-2,6 COPh); 12.31 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 25.8; 55.2; 77.3; 110.6; 114.9; 124.3; 125.9; 126.9; 128.2; 130.2; 131.4; 138.7; 154.7; 159.8; 163.0; 187.2. Found, *m*/*z*: 335.1385 $[M+H]^+$. $C_{20}H_{19}N_2O_3$. Calculated, *m*/*z*: 335.1396.

(2*E*,5*Z*)-2-[2-(4-Bromophenyl)-2-oxoethylidene]-5-(4-methoxybenzylidene)3-methylimidazolidin-4-one (4e). Yield 660 mg (32%), yellow powder, mp 175–178°C. UV spectrum, λ_{max}, nm (log ε): 307 (4.31), 433 (4.42). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.22 (3H, s, NCH_3); 3.84 (3H, s, OCH_3); 6.19 (1H, s, =C<u>H</u>COAr); 6.67 (1H, s, =C<u>H</u>Ar); 7.13 (2H, d, ^3J = 8.8, H-3,5 CHAr); 7.57 (2H, d, ^3J = 8.8, H-2,6 CHAr); 7.69 (2H, d, ^3J = 8.3, H-3,5 COAr); 8.00 (2H, d, ^3J = 8.3, H-2,6 COAr); 12.26 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 25.8; 55.2; 77.2; 110.9; 114.9; 124.1; 125.2; 125.8; 129.0; 130.3; 131.2; 137.8; 154.9; 159.8; 162.9; 185.9. Found, *m*/*z*: 413.0498 $[M(^{79}Br)+H]^+$, 415.0476 $[M(^{81}Br)+H]^+$. $C_{20}H_{18}BrN_2O_3$. Calculated, *m*/*z*: 413.0501, 415.0480.

Preparation of (*Z*)-4-(4-methoxybenzylidene)-1,2-dimethyl-1*H*-imidazol-5(4*H*)-one (1) by hydrolysis of imidazolidinones 4a–c. An aqueous 1 N solution of sodium hydroxide (10 ml, 10 mmol) was added to a solution of imidazolidinone **4a**–**c** (1 mmol) in EtOH (20 ml). The obtained mixture was refluxed for 5 min, cooled to room temperature, and the product was extracted with $CHCl_3$ (3×30 ml). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was separated by silica gel column chromatography (eluent 10:1 $CHCl_3$–MeOH), collecting the fraction with R_f 0.40. Yield 155 mg (67%, from compound **4a**), 130 mg (56%, from compound **4b**), 175 mg (76%, from compound **4c**), yellow powder, mp 126–128°C (mp 128–129°C[12]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, 2-CH_3); 3.09 (3H, s, 1-CH_3); 3.81 (3H, s, OCH_3); 6.93 (1H, s, =C<u>H</u>Ar); 7.01 (2H, d, ^3J = 8.8, H Ar); 8.19 (2H, d, ^3J = 8.8, H Ar).

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* Here and further for compounds **4a**-**e** the total yield of two steps based on the starting imidazolone **1** is shown.

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