Cascade reactions of diazocarbonyl compounds with pyridinium aroylmethylides accompanied by water or benzoic acid elimination in the cyclocondensation step

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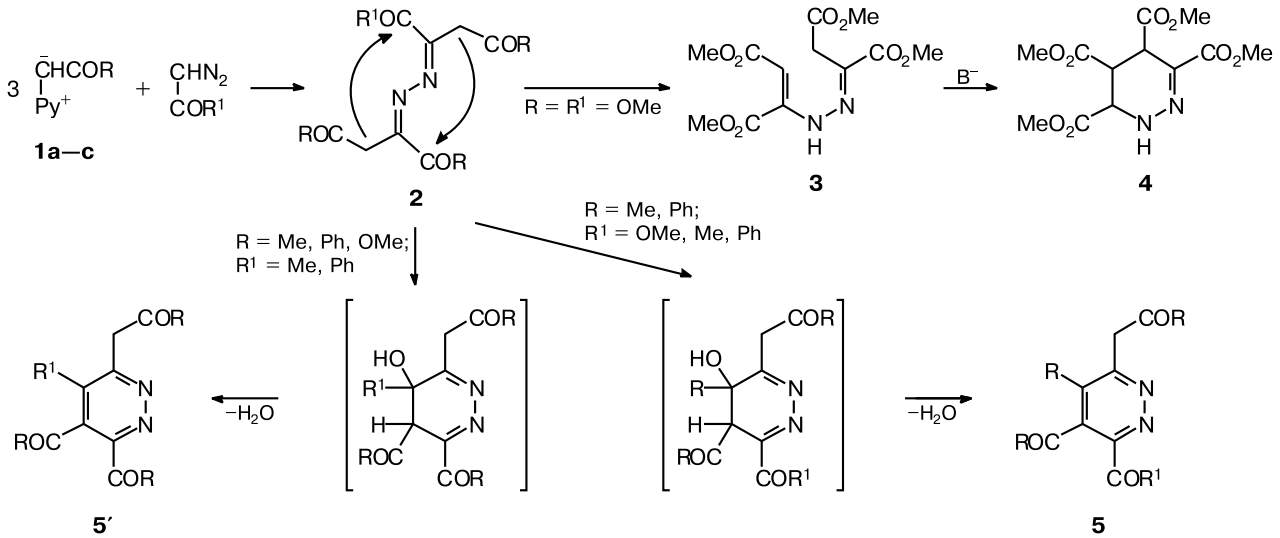
The reaction of pyridinium aroylmethylides with diazocarbonyl compounds proceeds as a multistep process involving three ylide molecules and one diazo compound molecule. As a result, intermediate functionally substituted azines, if they contain carbonyl groups and reactive methylene fragment, undergo intramolecular cyclocondensation to form tri- and tetrasubstituted pyridazines. Depending on stereochemistry of cyclic ketols formed, water or benzoic acid is eliminated to form tetra- or trisubstituted pyridazines, respectively. The regularities of reactions of pyridinium ylides with diazo compounds are discussed depending on the nature of substituents in the both substrates and reaction conditions.

Key words: methyl diazoacetate, diazoacetophenone, pyridinium ylides, pyridazines, addition and elimination reactions, NMR spectra.

Pyridinium ylides containing the carbonyl or carboxyl group at the ylidic carbon atom react with diazocarbonyl compounds involving three ylide molecules in the reaction to form 1,4,5,6-tetrahydropyridazine-3,4,5,6-tetracarboxylates[1,2] or polysubstituted pyridazines.[3,4] The processes involving pyridinium ylides **1** and diazo compounds containing carboxyl or carbonyl groups differ, as a rule, by the heterocyclization step (Scheme 1). In the case of intermediately formed diazadiene **2** containing four ester groups, cyclization proceeds through the corresponding

Scheme 1



R = OMe (**a**), Me (**b**), Ph (**c**)

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ene-hydrazone **3**, in which the nucleophilic moiety of the molecule attacks the electron-deficient C atom of the double bond to form tetrahydropyridazine tetracarboxylate **4** (see Ref. 1). If diazadiene **2** contains the conjugated carbonyl group, cyclization proceeds directly at this group and affords, after elimination of the H_2O molecule, tetrasubstituted pyridazines **5** and/or **5′** (see Ref. 4 and Scheme 1).

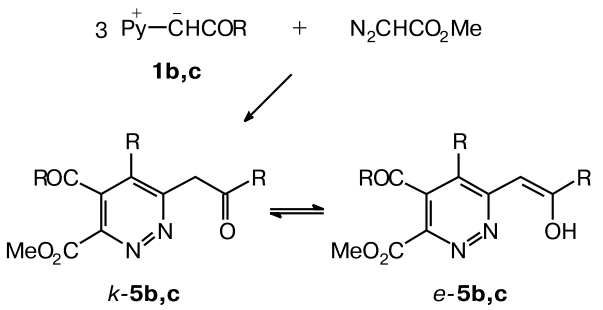
Ylides were generated, as a rule, by the dehydrohalogenation of the corresponding pyridinium salts with wet potassium carbonate in acetonitrile. For the reaction of pyridinium benzoylmethylide (**1c**) with methyl diazoacetate (MDA), we found along with the predominant formation of pyridazine **5** (R = Ph, R^1 = OMe)[4] the presence of one more compound, whose amount changed noticeably depending on the water content in the reaction mixture.

In the present work, we studied in detail the influence of water on the composition of the reaction products of some carbonyl-containing ylides with MDA and with diazoacetophenone and determined the structures of the compounds formed.

Results and Discussion

We have earlier shown[3,4] that the reaction of MDA with pyridinium acetylmethylides in acetonitrile *via* the dehydrobromination of acetonyl- or phenacylpyridinium bromides by K_2CO_3 containing ~20 mol.% H_2O affords substituted pyridazine-3-carboxylates **5b,c** in 65—71% yields. Since position 6 of the pyridazine cycle of the both compounds has the reactive methylene moiety, in solution they exist as ketone and enol forms. According to the ^1H and ^{13}C NMR spectra, the enol form substantially predominates in chloroform, whereas in DMSO the ketone form prevails (Scheme 2).

Scheme 2

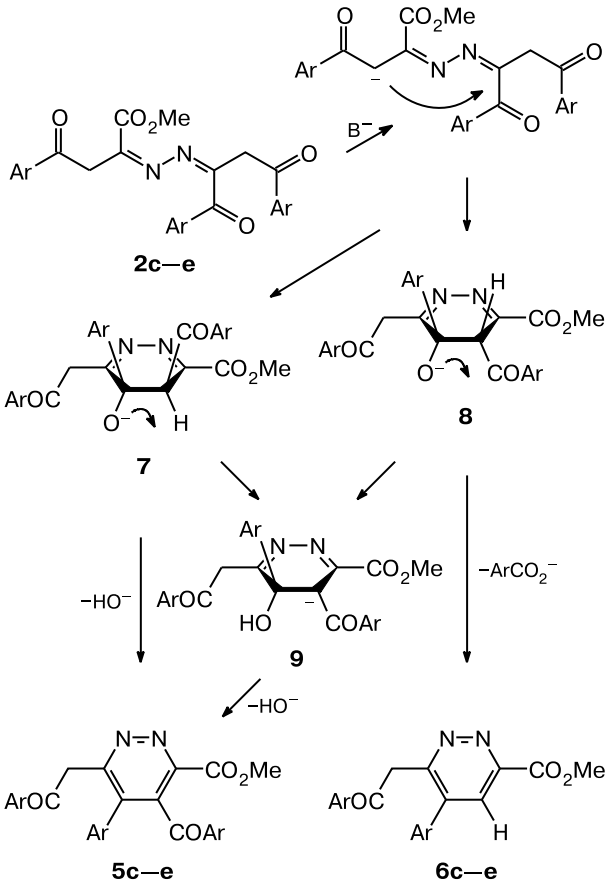


R = Me (**b**), Ph (**c**)

In the case of the reaction of MDA with pyridinium ylide **1c**, the ^1H NMR spectrum ($CDCl_3$) of the reaction mixture contains, along with singlet signals at δ 4.68 (CH_2 group of the ketone form) and 5.77 (=CH group of the enol form)[4] corresponding to pyridazine **5c**, singlets at δ 4.77 and 5.89 with the total integral intensity fourfold lower than that for tautomers **5c**. This ratio did not change with a change in the type of solvent; however, it changed noticeably inside each pair of products, indicating that the content of their tautomeric forms depends on the nature of solvents used. Since we failed to isolate from this mixture the minor product in the analytically pure state because of close values of R_f, we attempted to increase the yield of the minor compound by changing the reaction conditions. It turned out that the desired result can easily be achieved by using water as the main solvent. For instance, the dissolution of phenacylpyridinium bromide, MDA, and potassium carbonate (molar ratio 3 : 1 : 6) in a water—acetonitrile (10 : 1) mixture and storage of the reaction mixture at 20 °C for 2 days gave the former minor compound as the main product. Appropriate crystals of the main compound were obtained by double recrystallization from chloroform, and the structure of the compound was determined by X-ray diffraction analysis.

It turned out that the obtained compound was trisubstituted pyridazine **6c** that differs from pyridazine **5c** by the absence of the benzoyl substituent in position 4 of the pyridazine cycle (Scheme 3). Moreover, a comparison of

Scheme 3



Ar = Ph (**c**), 4-FC_6H_4 (**d**), 4-BrC_6H_4 (**e**)

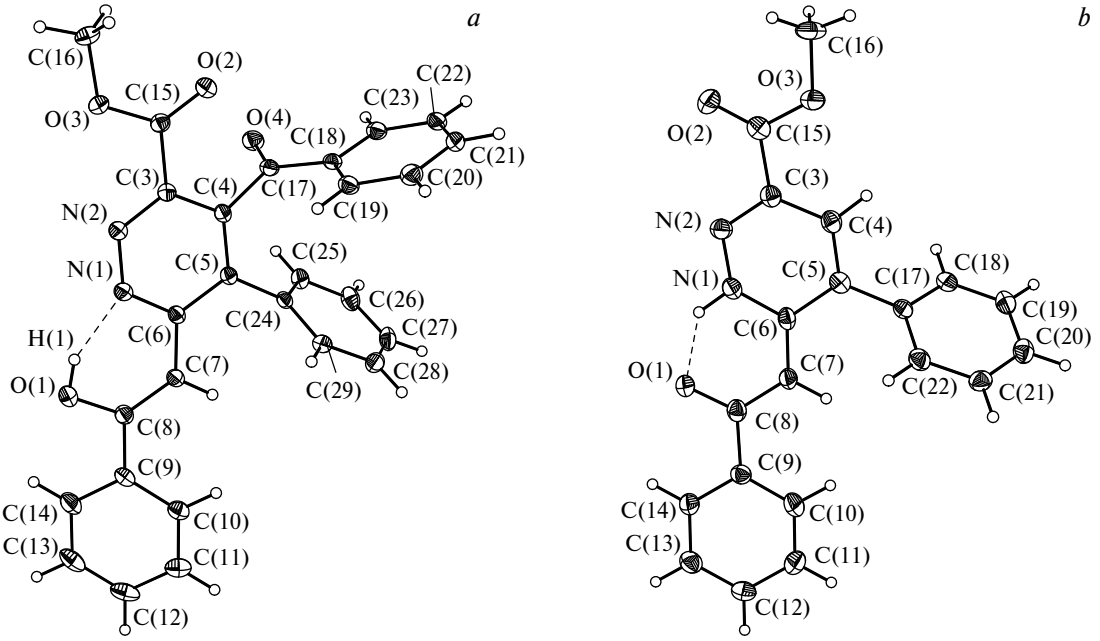


Fig. 1. General view of molecules **5c** (*a*) and **6c** (*b*) in representation of atoms as thermal ellipsoids ($p = 50\%$).

the C(6)—C(7) and C(7)—C(8) bond lengths showed that in single crystal trisubstituted pyridazine **6c** exists in the enamine form (Fig. 1, *b*, Table 1), whereas tetrasubstituted pyridazine **5c** exists in the enol form (Fig. 1, *a*, Table 1). The X-ray diffraction data for crystals of both pyridazines showed that in molecule **5c** the C(6)—C(7) bond is longer than the C(7)—C(8) bond, while an opposite dependence is observed for molecule **6c**.

Unlike the solid phase, in solution both pyridazines **5c** and **6c** exist as the corresponding mixtures of the ketone and enol forms, whose ratio is determined by the nature of solvents used. The ^{1}H and ^{13}C NMR spectra exhibit a correlation of chemical shifts and integral intensities of signals of the protons and carbon atoms in the fragments $COCH_2$ and (HO)C=CH for each pair of tautomers (Table 2).

We did not observe an analogous process leading to the formation of trisubstituted pyridazines in the case of pyridinium acetylmethylide **1a**. An attempt to carry out the reaction of MDA with ylide **1b** generated by the dehydrobromination of acetonylpyridinium bromide with K_2CO_3 in a water—acetonitrile (9 : 1) mixture did not result in the formation of trisubstituted pyridazine and, moreover, pyridazine **5b** described earlier[3] was formed in 10—12% yield only. It is most likely that pyridinium acetylmethylide **1b** is much more easily hydrolyzed with water than ylide **1c** and has no time to react with diazo compound.

Table 1. Bond lengths in molecules of pyridazines **5c** and **6c**

Bond	*d*/Å	
	5c	**6c**
C(6)—C(7)	1.442(2)	1.389(3)
C(7)—C(8)	1.368(2)	1.412(3)
N(1)—C(6)	1.354(2)	1.369(2)
N(1)—N(2)	1.338(1)	1.347(2)
C(8)—O(1)	1.338(2)	1.278(2)

Then we studied the reaction of MDA with *p*-substituted pyridinium benzoylmethylides **1d,e** generated by dehydrobromination of the corresponding phenacylpyridinium bromides with K_2CO_3. Acetonitrile or water containing ~10% acetonitrile were used to provide solubility of the reactants. As should be expected, for the reaction in acetonitrile the major reaction products were tetrasubstituted pyridazines **5d** or **5e** (see Scheme 3 and Table 3), which were isolated (purity >95%) by double recrystallization from methanol.

When the reaction was carried in water, unlike unsubstituted pyridinium benzoylmethylide **1c**, although the amount of trisubstituted pyridazines **6d,e** increased but insignificantly (see Table 3), which did not allow us to separate them completely from tetrasubstituted pyridazines **5d,e**. The structures of pyridazines **6d,e** were determined by the ^{1}H and ^{13}C NMR spectra, subtracting the signals of pyridazines **5d** or **5e**, respectively, and comparing the remained signals with the signals of pyridazine **6c**. In solution both tetra- (**5d,e**) and trisubstituted pyridazines **6d,e** exist as keto-enol tautomers, the equilibrium between which in chloroform is shifted to enol forms (see Table 2).

As mentioned earlier,[4] the formation of pyridazine **5** proceeds *via* successive addition of three molecules of ylide **1** to a diazo ester molecule. As a result, diazadiene **2** formed

Table 2. Chemical shifts of the key signals of the ketone and enol forms of tri- and tetrasubstituted pyridazines in the ^{1}H and ^{13}C NMR spectra ($CDCl_3$)

Compound	Ketone : enol	^{1}H NMR, δ						^{13}C NMR, δ						
		Ketone			Enol			Ketone			Enol			
		CH_2	H(4)	OMe	=CH	H(4)	OMe	CH_2	HC(4)	C(6)	=CH	=C(OH)	HC(4)	C(6)
5c (Ref. 4)	1 : 4	4.68	—	3.91	5.77	—	3.88	44.5	—	157.1	89.2	178.7	—	156.8
6c	1 : 5	4.81	8.10	4.09	6.16	7.73	4.02	44.4	127.7	158.8	88.1	179.8	126.1	156.1
6c*	1 : 1.4	4.90	8.02	3.97	6.07	7.68	3.91	44.6	127.9	159.4	87.6	178.6	126.9	156.2
5d	1 : 5.5	4.65	—	3.95	5.65	—	3.89	44.4	—	156.9	88.5	179.2	—	155.2
6d	1 : 7.3	4.77	8.08	4.08	6.01	7.67	4.03	44.3	128.0	158.8	87.3	180.2	126.2	155.3
5e	1 : 7.2	4.63	—	3.98	5.67	—	3.90	44.4	—	159.4	88.9	178.4	—	156.4
6e	1 : 8	4.77	8.08	4.10	6.04	7.69	4.06	44.2	126.2	159.1	87.6	179.4	126.3	155.5

* Spectra in $(CD_3)_2SO$.

undergoes cyclization of the aldol condensation type. The cyclization can afford two diastereomeric ketols or their anions **7** and **8** (see Scheme 3), which are responsible for the formation of substituted pyridazines **5** and **6** due to the elimination of water or benzoic acid.

Since we could not observe ketol formation in the reaction mixture, it is difficult to make certain conclusions about the step of their aromatization to pyridazines. However, taking into account that the cyclization of the anion of triketones **2c—e** leads to the generation of stereoisomeric anions **7** and **8**, we may assume that the formed nucleophilic oxygen atom will further attack the neighboring proton (isomer **7**) or benzoyl group (isomer **8**) followed by the *cis*-elimination of hydroxyl or benzoate and the formation of tetra- or trisubstituted pyridazines **5** or **6**. Meanwhile, if ketols themselves are formed due to cyclization, their deprotonation will give the same anions **9c—e**, from which only tetrasubstituted pyridazines **5c—e** are formed after hydroxyl group elimination. Indeed, pyridazines **5c—e** are the major reaction products in most cases. Thus, the composition of the final pyridazines can depend on both stereochemistry of the intermediate ketols and diverse variants of their aromatization, which is determined, to a certain extent, by the nature (polarity) of solvents used.

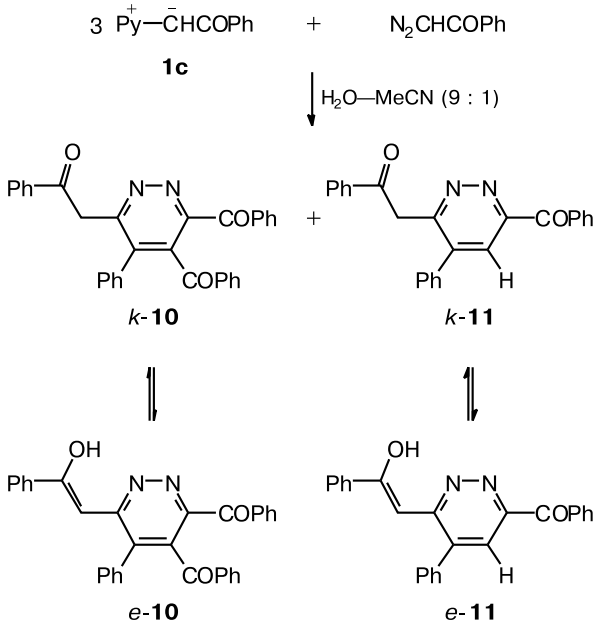
The possibility of elimination of benzoic acid molecule instead of H_2O has earlier been established[5] for the intramolecular cyclocondensation of 5-methyl-1,3,5,7-tetraphenylhept-2-ene-1,7-dione to 5-methyl-1,3,5-triphenylcyclohexa-1,3-diene.

Table 3. Yields and the ratio of pyridazines **5c—e** and **6c—e** depending on the solvent nature

Product	Ar (%)	Solvent **5** : **6**	Yield	Ratio
5c + **6c**	Ph	MeCN	70	4 : 1
		H_2O	73	1 : 3.9
5d + **6d**	4-C_6H_4F	MeCN	69	5.3 : 1
		H_2O	72	2.8 : 1
5e + **6e**	4-C_6H_4Br	MeCN	68	5 : 1
		H_2O	70	1.9 : 1

It has been shown earlier[4] that the reaction of pyridinium benzoylmethylide **1c** with diazoacetophenone in acetonitrile (the amount of water in the reaction mixture did not exceed 5%) affords only 3,4-dibenzoyl-6-phenacyl-5-phenylpyridazine **10**, which exists in solution as keto-enol tautomers. Unlike the reaction with methyl diazoacetate, performing the same reaction in a water—acetonitrile mixture (volume ratio 9 : 1) exerts no principal effect on the formation of pyridazine **10**, but the ^{1}H and ^{13}C NMR spectra make it possible, in this case, to observe also the formation of trisubstituted pyridazine **11**, whose yield is 5—6% (Scheme 4). In a $CDCl_3$ solution,

Scheme 4



pyridazine **11**, as well as pyridazine **10**, exists as ketone and enol forms in a ratio of ~1 : 6.

Thus, we showed that the cascade reactions of pyridinium benzoylmethylides with methyl diazoacetate and diazoacetophenone afford not only tetrasubstituted pyridazines (due to water elimination from intermediate ketols in the step of cyclocondensation), but also trisubstituted pyridazines, *viz.*, products of elimination of benzoic acids, which is determined, most likely, by both different stereochemistry of formed cyclic ketols and different modes of their aromatization.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE II 300 (300 and 75.5 MHz) and Bruker DRX-500 (500 MHz and 125.3 MHz, respectively) spectrometers for $CDCl_3$ solutions containing 0.05% Me_4Si as an internal standard. Mass spectra were obtained on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct inlet). Thin layer chromatography was carried out on Silicagel 60 (Merck) plates with development in an iodine chamber. Column chromatography (silica gel 60, 0.040—0.063 mm, Merck) was used for preparative separation. Solvents were distilled prior to use. Diazoacetophenone was synthesized according to a standard procedure by treatment of benzoyl chloride with diazomethane.[6,7] 4-Halosubstituted phenacylpyridinium bromides were synthesized by quaternization of pyridine by the corresponding α-bromo-4-fluoro- or -bromoacetophenones in acetone.[8] Methyl 4-benzoyl-6-benzoylmethyl-5-phenylpyridazine-3-carboxylate (**5c**) was synthesized by us earlier.[4]

X-ray diffraction studies of pyridazines **5c** and **6c** were carried out on a SMART APEX II CCD diffractometer (MoKα-radiation, graphite monochromator, ω scan mode) at 100 K. The starting arrays of measured intensities were processed using the APEX2 program.[9] The structures were solved by a direct method and refined by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms on F^2_{hkl}. Hydrogen atoms were placed in geometrically calculated positions, except for the hydrogen atoms at the nitrogen and oxygen atoms, whose positions were localized from the difference electron density synthesis and then were normalized to the distance 0.90 Å for the N atoms and 0.85 Å for the O atoms. All hydrogen atoms were refined using the riding model (U_{iso}(H) = nU_{eq}(C,N), where n = 1.5 for the carbon atoms of the methyl groups, n = 1.2 for other C atoms and nitrogen atoms). The structures were decoded and refined using the SHELXTL program.[10] Selected crystallographic data and refinement parameters are listed in Table 4.

Methyl 4-aroyl-6-aroylmethyl-5-arylpyridazine-3-carboxylates (5c—e) (general procedure). Potassium carbonate (1.04 g, 6 mmol) containing ~20 wt.% water was added to a solution of methyl diazoacetate (100 mg, 1 mmol) and 4-fluoro- or 4-fluorophenacylpyridinium bromide (3 mmol) in acetonitrile (30 mL) with vigorous stirring for 16 h at 20 °C. Then the reaction mixture was evaporated to 1/3 of the starting volume, water (50 mL) was added, extracted with CH_2Cl_2 (3×30 mL), and dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo*, the residue was washed with methanol (15 mL), and the obtained product was analyzed using ^{1}H and ^{13}C NMR spectroscopy (the total yield and the ratio of pyridazines **5** and **6** are given in Table 3).

Table 4. Selected crystallographic data for pyridazines **5c** and **6c**

Parameter	**5c**	**6c**
Molecular formula	$C_{27}H_{20}N_2O_4$	$C_{20}H_{16}N_2O_3$
Molecular weight	436.45	332.35
T/K	100(2)	100(2)
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
a/Å	9.9116(11)	7.4968(10)
b/Å	10.5403(12)	10.3702(14)
c/Å	12.2947(13)	10.7176(15)
α/deg	65.012(2)	78.362(3)
β/deg	89.898(2)	85.591(3)
γ/deg	67.270(2)	74.434(3)
V/Å^3	1053.6(2)	785.93(19)
Z	2	2
d_{calc}/g cm^{-3}	1.376	1.404
μ/cm^{-1}	0.93	0.96
F(000)	456	348
Scan range, θ/deg	1.86—28.99	1.94—28.43
Number of measured reflections	12574	9032
Number of independent reflections	5552	3919
R_{int}	0.0225	0.0683
Number of refined parameters	299	227
Number of reflections with $I \geq 2\sigma(I)$	4480	1883
Completeness of reflection array (%)	99.1	99.4
GOOF	1.036	0.965
$R_1(F)^a$ on reflections with $I \geq 2\sigma(I)$	0.0426	0.0549
$wR_2(F^2)^b$ on all reflections	0.1124	0.1060
Residual electron density (min/max)/$e \cdot$ Å^{-3}	0.475/−0.247	0.234/−0.219

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma(F_o)$;
[b] $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$.

Target pyridazines **5c—e** were isolated as orange crystals by double recrystallization from methanol.

Methyl 4-(4-fluorobenzoyl)-6-(4-fluorobenzoyl)methyl-5-(4-fluorophenyl)pyridazine-3-carboxylate (5d). A mixture of pyridazines **5d** and **6d** in the molar ratio 5.3 : 1 were obtained from 4-fluorophenacylpyridinium bromide (0.89 g, 3 mmol) and methyl diazoacetate (0.10 g, 1 mmol) in acetonitrile (see Table 3). Recrystallization from methanol gave 0.25 g (52%) of pyridazine **5d**, m.p. 195—197 °C. Found (%): C, 65.88; H, 3.50; N, 5.82. $C_{27}H_{17}F_3N_2O_4$. Calculated (%): C, 66.12; H, 3.49; N, 5.71. ^{1}H NMR ($CDCl_3$), δ: *enol form* (85%): 3.89 (s, 3 H, OMe); 5.65 (s, 1 H, =CH); 7.02, 7.11, and 7.65 (all m, 3 C_6H_4); 15.9 (br.s, 1 H, OH); *ketone form* (15%): 3.95 (s, 3 H, OMe); 4.65 (s, 2 H, CH_2); 6.86 (br.dd, 2 H, 2 H_m, $^3J_{H,H} \approx {}^3J_{H,F}$ = 8.7 Hz); 7.59 and 7.90 (both m, 2 H each, 4 H_o, $^3J_{H,H}$ = 8.7 Hz, $^4J_{H,F}$ = 5.5 Hz); other signals from aromatic protons lie in the range of signals of the protons of the enol form. ^{13}C NMR ($CDCl_3$), δ: *enol form*: 53.5 (OMe); 88.5 (=CH); 115.6, 116.1 and 116.3 (all d, C_m,

$^2J_{C,F}$ ≈ 22.0); 126.9, 132.5 and 133.4 (all д, C_i, $^4J_{C,F}$ ≈ 3.0); 129.2, 131.2 (br.s) and 131.4 (all d, C_o, $^3J_{C,F}$ ≈ 9.0); 136.6 and 137.8 (C(4) and C(5)); 140.3 (C(3)); 155.2 (C(6)); 163.0 (COO); 163.1, 164.7, and 166.0 (all d, C_p, $J_{C,F}$ = 248—254); 179.2 (=COH); 190.5 (C=O); *ketone form*: 44.4 (CH_2); 53.7 (OMe); 115.8, 116.1, and 116.4 (all d, C_m, $^2J_{C,F}$ ≈ 20); 132.4, 133.2, and 134.2 (all d, C_i, $^4J_{C,F}$ ≈ 2.9 Hz); 131.0, 131.2 (br.s) and 131.5 (all d, C_o, $^3J_{C,F}$ ≈ 9.0 Hz); 136.7 and 138.2 (C(4) and C(5)); 147.2 (C(3)); 156.9 (C(6)); 163.0, 164.5 and 166.1 (all d, C_p, $J_{C,F}$ = 248—254 Hz); 164.5 (COO); 190.6 and 194.0 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): *enol form*: −103.6, −109.0, and −110.7 (all tt, 1 F each, $^3J_{H,F}$ ≈ 8.7 Hz, $^4J_{H,F}$ ≈ 5.5 Hz); *ketone form*: −103.5, −104.2, and −111.3 (all tt, 1 F each, $^3J_{H,F}$ ≈ 8.7 Hz, $^4J_{H,F}$ ≈ 5.5 Hz).

Methyl 4-(4-bromobenzoyl)-6-(4-bromobenzoyl)methyl-5-(4-bromophenyl)pyridazine-3-carboxylate (5e). A mixture of pyridazines **5e** and **6e** in the molar ratio 5 : 1 was obtained from 4-bromophenacylpyridinium bromide (1.07 g, 3 mmol) and methyl diazoacetate (0.10 g, 1 mmol) (see Table 3). Recrystallization from methanol gave 0.36 g (54%) of pyridazine **5e**, m.p. 214—216 °C. Found (%): C, 47.89; H, 2.67; N, 4.48. $C_{27}H_{17}Br_3N_2O_4$. Calculated (%): C, 48.18; H, 2.55; N, 4.16. ^{1}H NMR ($CDCl_3$), δ: *enol form* (88%): 3.90 (c, 3 H, OMe); 5.67 (s, 1 H, =CH); 7.00 (br.d, 2 H, 2 H_m, ^3J = 8.2 Hz); 7.32—7.58 (m, 2 C_6H_4 and 2 H_o); 15.9 (br.s, 1 H, OH); *ketone form* (12%): 3.98 (s, 3 H, OMe); 4.63 (s, 2 H, CH_2); 6.91 (br.d, 2 H, 2 H_m, ^3J = 8.2 Hz); 7.32—7.58 (m, 2 C_6H_4 and 2 H_o). ^{13}C NMR ($CDCl_3$), δ: *enol form*: 53.5 (OMe); 88.9 (=CH); 124.3, 126.1, and 129.4 (C_p); 128.4, 130.0, 130.7 (br.s); 131.8, 132.1, and 132.3 (C_o and C_m); 129.8, 134.9, and 135.8 (C_i); 136.4 and 137.7 (C(4) and C(5)); 140.6 (C(6)); 156.4 (C(3)); 163.1 (COO); 178.4 (=COH); 190.8 (C=O); *ketone form*: 44.4 (CH_2); 53.7 (OMe); 124.4, 126.2, and 129.6 (C_p); 128.4, 129.8, 130.1, 130.7 (br.s); 131.9 and 132.4 (C_o and C_m); 130.2, 134.7, and 135.7 (C_i); 136.2 and 137.5 (C(4) and C(5)); 145.0 (C(3)); 159.4 (C(6)); 163.3 (COO); 190.7 and 193.0 (C=O).

Methyl 6-benzoylmethyl-5-phenylpyridazine-3-carboxylate (6c). A solution of methyl diazoacetate (0.50 g, 5 mmol) in acetonitrile (11 mL) was added to a solution of phenacylpyridinium bromide (4.17 g, 15 mmol) in water (100 mL), and potassium carbonate (6.90 g, 50 mmol) containing 20% water was added by portions of 1—1.5 g with stirring, waiting for the complete dissolution of each portion. The reaction mixture was stirred for 15 h at 20 °C, extracted with ethyl acetate (3×50 mL), and dried with anhydrous $MgSO_4$. The solvents were removed *in vacuo*, the solid residue was treated with hot methanol (15 mL), and cooled, and an orange finely crystalline precipitate was filtered off. The filtrate was evaporated to half a volume and cooled to −5 °C and the precipitate formed was joined with the previous portion of the precipitate. The obtained product was analyzed by ^{1}H and ^{13}C NMR spectroscopy (the total yield and the ratio of pyridazines **5c** and **6c** are given in Table 3). Then trisubstituted pyridazine **6c** was isolated as yellow crystals by double recrystallization from chloroform, m.p. 149—151 °C. Found (%): C, 72.64; H, 4.91; N, 8.20. $C_{20}H_{16}N_2O_3$. Calculated (%): C, 72.28; H, 4.85; N, 8.43. MS, m/z (I_{rel} (%)): 332 $[M]^+$ (3), 255 $[M - Ph]^+$ (5), 227 $[M - COPh]^+$ (10), 195 (7), 167 (15), 105 (100). ^{1}H NMR ($CDCl_3$), δ: *enol form* (84%): 4.02 (s, 3 H, OMe); 6.16 (s, 1 H, =CH); 7.73 (s, 1 H, H(4)); 7.37—7.55 (m, 2 Ph of both tautomers); 7.74 (d, 2 H, J = 7.9 Hz, H_o of one of Ph); 16.2 (OH); *ketone form* (16%): 4.09 (s, 3 H, OMe); 4.81 (s, 2 H, CH_2); 8.08 (s, 1 H, H(4)); 7.10—7.90 (m, 2 Ph of both tautomers). ^{13}C NMR ($CDCl_3$), δ: *enol form*: 53.0 (OMe); 88.1 (=CH); 126.1 (C(4)); 126.7, 128.2, 128.3, and 129.1 (C_o and C_m); 129.7 and 130.8 (C_p); 134.8 and 137.8 (C_i); 140.5 (C(5)); 143.0 (C(3)); 156.1 (C(6)); 163.6 (COO); 179.8 (=COH); *ketone form*: 44.4 (CH_2); 53.1 (OMe); 127.7 (C(4)); 126.8, 128.6, 128.9, and 129.3 (C_o and C_m); 130.7 and 133.4 (C_p); 133.3 and 136.2 (C_i); 141.9 (C(5)); 150.8 (C(3)); 158.8 (C(6)); 164.5 (COO); 194.5 (C=O); ^{13}C NMR (DMSO-d_6), δ: *enol form*: 53.2 (OMe); 87.6 (=CH); 126.1 (C(4)); 126.7, 128.9, 129.0 and 129.6 (C_o and C_m); 130.2 and 131.4 (C_p); 134.6 and 137.6 (C_i); 140.4 (C(5)); 144.0 (C(3)); 156.2 (C(6)); 163.3 (COO); 179.0 (=COH); *ketone form*: 44.6 (CH_2); 53.4 (OMe); 127.9 (C(4)); 128.5, 128.8, 129.2, and 129.3 (C_o and C_m); 129.6 and 134.0 (C_p); 135.6 and 136.5 (C_i); 141.6 (C(5)); 150.8 (C(3)); 159.4 (C(6)); 164.5 (COO); 196.8 (C=O).

Reaction of methyl diazoacetate with 4-fluorophenacylpyridinium bromide in an aqueous solution. A solution of methyl diazoacetate (1.56 g, 9 mmol) in acetonitrile (2 mL) was added to a solution of 4-fluorophenacylpyridinium bromide (1.33 g, 4.5 mmol) in water (18 mL), and potassium carbonate (1.56 g, 9 mmol) containing 20% water was added. The reaction mixture was stirred for 15 h at 20 °C, then extracted with ethyl acetate (3×20 mL), and dried with anhydrous $MgSO_4$. The solvents were removed *in vacuo*, the solid residue was washed with methanol (2 mL) at 0 °C, and 0.50 g of a mixture of pyridazines **5d** and **6d** were obtained, which were analyzed by ^{1}H and ^{13}C NMR spectroscopy (the total yield and the ratio of pyridazines **5d** and **6d** are given in Table 3). Then double recrystallization from chloroform gave orange-yellow crystals enriched in trisubstituted pyridazine **6d** to ~65%. Methyl 6-(4-fluorobenzoyl)methyl-5-(4-fluorophenyl)pyridazine-3-carboxylate (**6d**) was identified by the ^{1}H and ^{13}C NMR spectra by subtracting the signals of the described above pyridazine **5d**. ^{1}H NMR ($CDCl_3$), δ: *enol form* (88%): 4.03 (s, 3 H, OMe); 6.01 (s, 1 H, =CH); 7.00—7.29 (m, 6 H, 4 H_m and 2 H_p); 7.48 and 7.77 (both dd, 2 H each, 4 H_o, $J_{H,H}$ = 8.9 Hz, $J_{H,F}$ = 5.6 Hz); 7.67 (s, 1 H, H(4)); 16.2 (OH); *ketone form* (12%): 4.08 (s, 3 H, OMe); 4.77 (s, 2 H, CH_2); 7.00—7.31 (m, 6 H, 4 H_m and 2 H_p); 7.56 and 7.95 (both dd, 2 H each, 4 H_o, $J_{H,H}$ = 8.8 Hz, $J_{H,F}$ = 5.5 Hz); 8.08 (s, 1 H, H(4)). ^{13}C NMR ($CDCl_3$), δ: *enol form*: 53.3 (OMe); 87.3 (=CH); 115.5 and 116.5 (both d, C_m, $^2J_{C,F}$ ≈ 21.5 Hz); 126.2 (C(4)); 129.1 and 130.3 (both d, C_o, $^3J_{C,F}$ = 8.6 Hz); 131.7 and 133.2 (both d, C_i, $^4J_{C,F}$ ≈ 3.0 Hz); 139.9 C(5)); 142.5 (C(3)); 155.3 (C(6)); 163.5 (COO); 163.6 and 166.1 (both d, C_p, $J_{C,F}$ = = 250—254 Hz); 180.2 (=COH); *ketone form*: 44.3 (CH_2); 53.6 (OMe); 115.8 and 116.2 (both d, C_m, $^2J_{C,F}$ ≈ 21 Hz); 128.0 (C(4)); 133.2 and 134.2 (both d, C_i, $^4J_{C,F}$ ≈ 3.0 Hz); 130.8 and 131.6 (both d, C_o, $^3J_{C,F}$ ≈ 9.0 Hz); 138.2 C(5)); 147.2 (C(3)); 158.8 (C(6)); 164.5 and 166.1 (both d, C_p, $J_{C,F}$ ≈ 250 Hz); 164.5 (COO); 194.3 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): *enol form*: −109.6 and −110.9 (both tt, 1 F each, $^3J_{H,F}$ ≈ 8.7 Hz, $^4J_{H,F}$ ≈ 5.5 Hz); *ketone form*: −104.6 and −111.8 (both tt, 1 F each, $^3J_{H,F}$ ≈ 8.6 Hz, $^4J_{H,F}$ ≈ 5.5 Hz).

Reaction of methyl diazoacetate with 4-bromophenacylpyridinium bromide in an aqueous solution. Similarly to the previous experiment, the reaction of 4-bromophenacylpyridinium bromide (1.07 g, 3 mmol) and methyl diazoacetate (0.10 g, 1 mmol) in an H_2O—MeCN mixture (14 mL, 9 : 1) afforded 0.61 g of a mixture of pyridazines **5e** and **6e**, which were analyzed using the ^{1}H and ^{13}C NMR spectra (the total yield and the ratio of pyridazines **5e** and **6e** are listed in Table 3). Methyl 6-(4-bromo-

benzoyl)methyl-5-(4-bromophenyl)pyridazine-3-carboxylate (**6e**) was identified by the ^{1}H and ^{13}C NMR spectra, subtracting the signals of above described pyridazine **5e**. ^{1}H NMR ($CDCl_3$), δ: *enol form* (89%): 4.06 (s, 3 H, OMe); 6.04 (s, 1 H, =CH); 7.36 and 7.69 (both d, 2 H each, 2 H_o and 2 H_m, J = 8.3 Hz); 7.52 and 7.62 (both d, 2 H each, 2 H_o and 2 H_m, J = 8.4 Hz); 7.69 (s, 1 H, H(4)); 16.2 (OH); *ketone form* (11%): 4.10 (s, 3 H, OMe); 4.77 (s, 2 H, CH_2); 7.25—7.70 (m, 8 H, 2 C_6H_4); 8.08 (s, 1 H, H(4)). ^{13}C NMR ($CDCl_3$), δ: *enol form*: 53.3 (OMe); 87.6 (=CH); 125.8 and 129.3 (C_p); 126.3 (C(4)); 128.4, 130.0, 131.7 and 132.6 (C_o and C_m); 133.5 and 136.6 (C_i); 139.6 C(5)); 142.9 (C(3)); 155.5 (C(6)); 163.1 (COO); 179.4 (=COH); *ketone form*: 44.2 (CH_2); 53.5 (OMe); 124.2 and 128.3 (C_p); 126.3 (C(4)); 129.9, 130.3, 131.8, and 132.2 (C_o and C_m); 133.3 and 136.8 (C_i); 137.0 C(5)); 145.0 (C(3)); 156.4 (C(6)); 163.2 (COO); 193.3 (C=O).

3,4-Dibenzoyl-6-phenacyl-5-phenylpyridazine (10) and 3-benzoyl-6-phenacyl-5-phenylpyrazine (11). Diazoacetophenone (0.15 g, 1 mmol) in acetonitrile (2 mL) was added to a solution of phenacylpyridinium bromide (0.84 g, 3 mmol) in water (18 mL) and then potassium carbonate (1.40 g, 8 mmol) containing 20% water was added. The mixture was stirred for 48 h at 20 °C and extracted with CH_2Cl_2 (3×20 mL). The solvent was removed *in vacuo* and the residue was washed with methanol (8 mL). A mixture of compounds **10** and **11** in the ratio ~12 : 1 was obtained in a yield of 0.33 g (~70%) as an orange finely crystalline powder. Minor product **11** was identified by ^{1}H and ^{13}C NMR spectroscopy, subtracting the signals of pyridazine **10** (see Ref. 4). ^{1}H NMR ($CDCl_3$), δ: *ketone form* (15%): 4.77 (s, 2 H, CH_2); 7.10—7.80 (m, 4 Ph of both tautomers); 7.86 and 8.18 (both br.d, 4 H, H_o (2 Ph), ^3J = 8.0 Hz); *enol form* (85%): 5.89 (s, 1 H, CH); 7.10—7.80 (m, 4 Ph of both tautomers); 8.09 (br.d, 2 H, H_o, ^3J = 8.2 Hz); 11.9 (br.s, 1 H, OH). ^{13}C NMR ($CDCl_3$): *ketone form*: 44.4 (CH_2); 127.0—139.5 (C atoms of pyridazine ring and phenyl groups); 158.8 (C(6)); 191.8, 193.8, and 196.0 (C=O); *enol form*: 88.9 (=CH); 127.0—139.5 (C atoms of pyridazine ring and phenyl groups); 147.6 (C(3); 153.9 (C(6)); 182.0 (=COH); 189.6 and 193.4 (C=O).

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