Synthesis of 1-mono- and 1,2-bisacylpyrazolidines and 1-arylsulfonylpyrazolines*

V. Yu. Petukhova, V. A. Maslennikov, V. V. Kuznetsov, N. N. Makhova, and S. A. Serkov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: pvyu@ioc.ac.ru

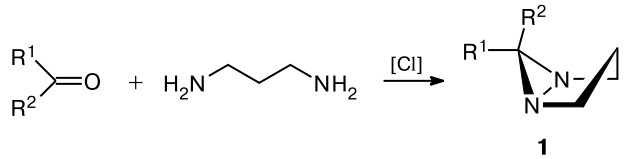
Study of a reaction of 1,5-diazabicyclo[3.1.0]hexanes with acyl and sulfonyl chlorides in organic or aqueous organic media in the presence of inorganic bases resulted in development of new simple one-step methods for the preparation of 1-mono- and 1,2-bisacylpyrazolidines and 1-arylsulfonylpyrazolines.

Key words: 1,5-diazabicyclo[3.1.0]hexanes, ketenes, 1-monoacylpyrazolidines, 1,2-bisacylpyrazolidines, 1-acylpyrazolines, 1-arylsulfonylpyrazolines, arenesulfonyl chlorides, acyl chlorides, mechanism.

It is known that compounds containing a pyrazolidine ring possess a wide range of biological activity.[2,3] In addition, certain pyrazolidine derivatives are used as starting compounds in the synthesis of important biologically active substances, in particular, 1-acylpyrazolidines are used for the preparation of new TNF-α-inhibitors.[4—6] The known approaches to the synthesis of 1-acylpyrazolidines are based on the three-, four-step procedures,[7—10] therefore, a search for new simple methods for obtaining compounds of this type remains an actual problem.

Earlier, we have developed an improved method for the synthesis of 6-substituted 1,5-diazabicyclo[3.1.0]-hexanes **1**, whose structure already contained a pyrazolidine fragment.[11,12] Compounds **1** were obtained in one step from a carbonyl compound, 1,3-diaminopropane, and sodium hypochlorite in water in virtually quantitative yields. In the case of carbonyl compounds insoluble in water, Bu^tOCl was used as a chlorinating agent and organic solvents (MeOH, $CHCl_3$) as a reaction medium (Scheme 1). Compounds **1** were chosen for the search of convenient method for the preparation of pyrazolidine derivatives.

Scheme 1



1

R^1 = H, Alk, Ar
R^2 = H, Alk

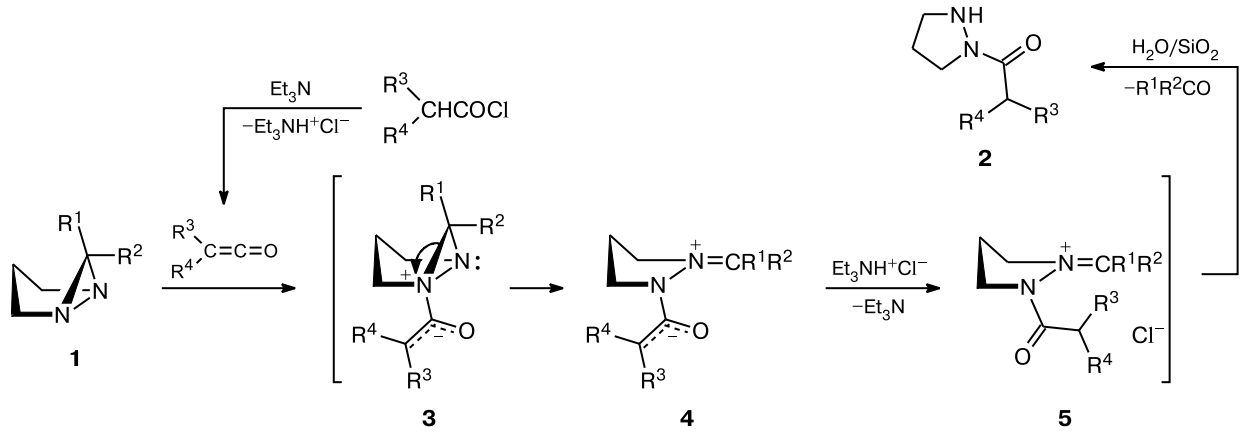
Recently,[13] we have reported on the results of the reaction of 6-unsubstituted, 6-alkyl- and 6,6-dialkyl-substituted 1,5-diazabicyclo[3.1.0]hexanes **1** with arylketenes, which were generated *in situ* from arylacetyl chlorides and Et_3N. It was found that the synthesis of 1-acylpyrazolidines **2** is the main and predominant direction of this reaction (Scheme 2). The reaction was carried out in anhydrous organic solvents (diethyl ether, benzene) in the flow of an inert gas. The following mechanism has been suggested for the formation of 1-acylpyrazolidines **2** in this reaction. The first step of the reaction of arylketene with 1,5-diazabicyclo[3.1.0]hexanes **1** gives zwitterionic intermediates **3**, which undergo the cleavage of C—N bond of the three-membered ring to generate new zwitterionic intermediates **4**. The enolate ion in these intermediates, being a strong base, combines with the HCl molecule from $Et_3N \cdot HCl$, formed during obtaining arylketene, which converts zwitterions **4** to salts **5**, hydrolysis of the latter under isolation conditions on a column with SiO_2 leads to 1-acylpyrazolidines **2.** On the whole, this reaction can be considered as the sequence of acylation and hydrolysis steps.

This approach to the synthesis of 1-arylacetylpyrazolidines **2** is a good supplement to the known methods, but it requires anhydrous reaction medium. Proceeding from the mechanism suggested, in order to prepare compounds of pyrazolidine series it was logically to carry out the reaction of 1,5-diazabicyclo[3.1.0]hexanes **1** with acyl chlorides **6** in aqueous organic medium in the presence of a base. In fact, treatment of **1** with arylacetyl, benzoyl, and other acyl chlorides **6** under conditions of the dichloromethane—aqueous NaOH two-phase system leads to 1,2-bis(arylacetyl)-, 1,2-bisaroyl- and a number of other 1,2-bisacylpyrazolidines **7** in 53—94% yields (Scheme 3). The formation of 1,2-bisacylpyrazolidines **7** under these

* For preliminary communication, see Ref. 1.

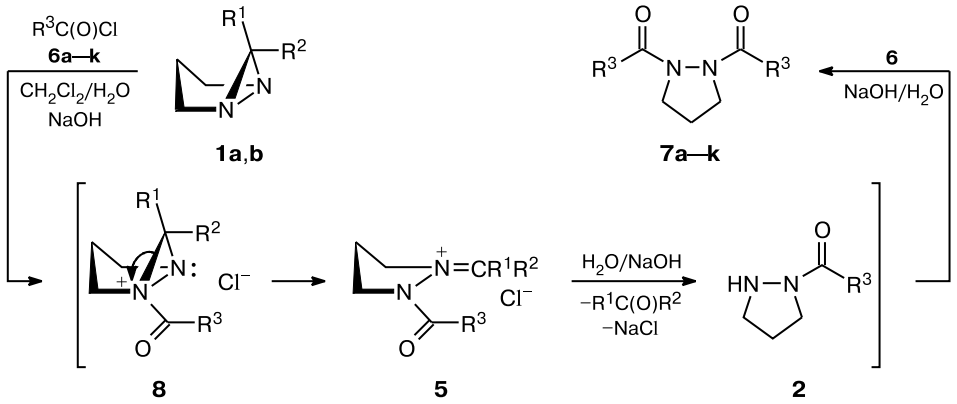
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1388—1394, July, 2010.

Scheme 2



R^1, R^2 = H, Alk
R^3 = Ar; R^4 = H, Alk, Ph

Scheme 3

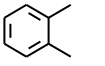


$R^1 = R^2$ = Me (**a**)
R^1 = Pr^i, R^2 = H (**b**)

conditions proceeds, by all accounts, through the intermediates **8**, which after the C—N bond cleavage are converted to compounds **5** similar to compounds **5** in the reaction of compounds **1** with arylketenes (see Scheme 2). Since the reaction was carried out in water, the intermediates **5** were hydrolyzed to 1-acylpyrazolidines **2**, which then were involved into the reaction with the second molecule of acyl chloride **6** to form the final products **7**, with 1,2-bisacylpyrazolidines **7** being the major products at any ratio **1** : **6**. The best yields were obtained for the ratio **1** : **6** = 1 : 2 (see Scheme 3). Table 1 summarizes the data on the starting compounds and yields of 1,2-disubstituted pyrazolidines **7** obtained.

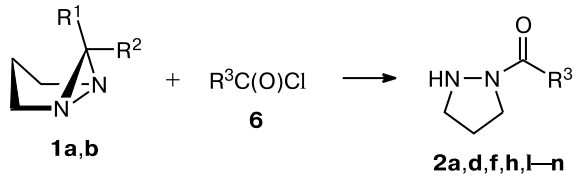
For the selective formation of 1-arylacetyl- and 1-aroylpyrazolidines **2**, the reaction of two moles of 1,5-diazabicyclo[3.1.0]hexanes **1** and one mole of arylacetyl or benzoyl chlorides **6** in organic solvent (toluene) at

Table 1. Starting 1,5-diazabicyclo[3.1.0]hexanes **1**, acyl chlorides **6**, and yields of 1,2-bisacylpyrazolidines **7** obtained

Starting compounds	R^3 in compounds **6** and **7**	Product and its yield (%)
6a + **1a**	4-$FC_6H_4CH_2$	**7a** (53)
6b + **1a**	2-F-6-$ClC_6H_3CH_2$	**7b** (91)
6c + **1a**	$PhCH_2$	**7c** (65)
6d + **1b**	$4ClC_6H_4$	**7d** (90)
6e + **1a**	4-$MeOC_6H_4$	**7e** (84)
6f + **1a**	4-$NO_2C_6H_4$	**7f** (64)
6g + **1b**	Ph	**7g** (84)
6h + **1a**	4-$ClC_6H_4OC(Me)_2$	**7h** (94)
6i + **1a**		**7i** (72)
6k + **1a**	2-$ClC_6H_4CH{=}CH$	**7k** (75)

−18÷−15 °C with subsequent treatment of the reaction mixture with aqueous solution of sodium bicarbonate turned out to be efficient. The final products were isolated by column chromatography on SiO_2. The yields of compounds **2** were 36—59% (Scheme 4, Table 2).

Scheme 4



$R^1 = R^2 = Me$ (**a**)
$R^1 = Pr^i$, $R^2 = H$ (**b**)

Reagents and conditions: 1) toluene, −15 °C; 2) $NaHCO_3/H_2O$.

Isolation of the product of the reaction of 6-isopropyl-1,5-diazabicyclo[3.1.0]hexane **1b** with 4-chlorobenzoyl chloride **6d** by column chromatography on SiO_2 gives, together with desired 4-chlorobenzoylpyrazolidine **2d**, 1-(4-chlorobenzoyl)-2-(2-methylpropen-1-yl)pyrazolidine **9** in low yield (8%), whose formation confirms the reaction mechanism suggested in Scheme 3. Apparently, intermediate **5d** in alkaline medium is transformed to product **9** with the double bond migration and elimination of the HCl molecule (Scheme 5).

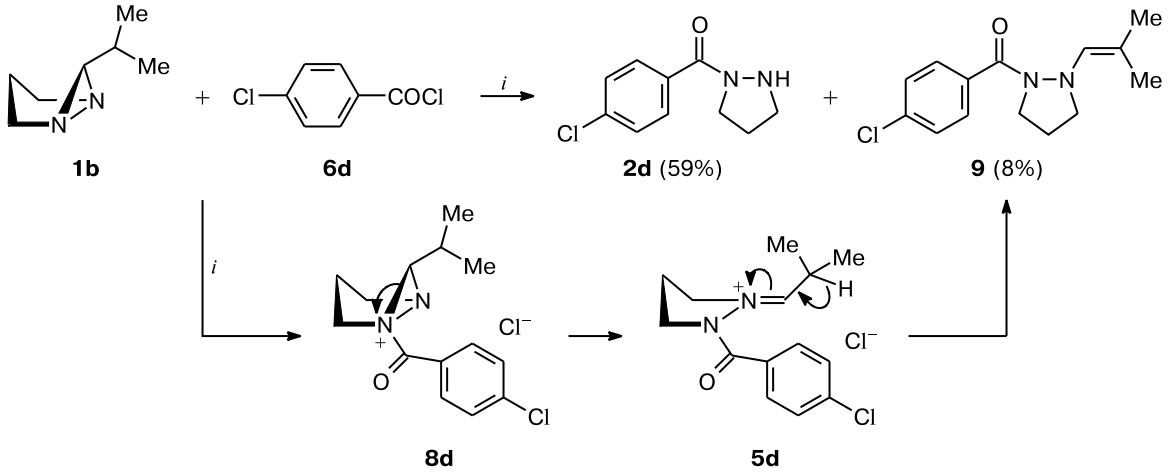
When products of the reaction of 6,6-dimethyl-1,5-diazabicyclo[3.1.0]hexane **1a** with 2-(4-chlorophenoxy)-2-methylpropionyl chloride **6h** under indicated conditions were separated, the corresponding pyrazoline **10** was isolated along with monosubstituted pyrazolidine **2h**, the formation of which can be explained by the oxidation of pyrazolidine **2h** with air oxygen in the process of its isolation on a column with SiO_2 (analogous reactions are described in the literature[14]) (Scheme 6).

Table 2. Starting compounds and yields of 1-monoacylpyrazolidines **2** obtained

Starting compounds	R^3 in compounds **6** and **2**	Product and its yield (%)
6a + **1a**	$4\text{-}FC_6H_4CH_2$	**2a** (52)
6d + **1b**	$4\text{-}ClC_6H_4$	**2d** (59)
6f + **1a**	$4\text{-}NO_2C_6H_4$	**2f** (42)
6h + **1a**	$4\text{-}ClC_6H_4OC(Me)_2$	**2h** (36)
6l + **1a**	$4\text{-}ClC_6H_4CH_2$	**2l** (41)
6m + **1a**	$4\text{-}BrC_6H_4CH_2$	**2m** (45)
6n + **1b**	$2,4\text{-}(NO_2)_2C_6H_3$	**2n** (37)

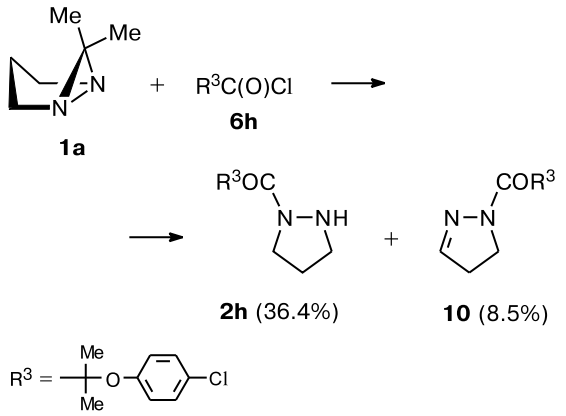
To sum up, this stage of the study resulted in the development of simple two-step methods for obtaining 1-acyl- (**2**) and 1,2-bisacylpyrazolidines (**7**), including in the first step the synthesis of 1,5-diazabicyclo[3.1.0]hexanes **1** and in the second step, their reaction with acyl chlorides **6**. For simplification of these procedures, a possibility of the preparation of 1,2-bisacylpyrazolidines **7** by a *one-pot* reaction was studied, which excluded the isolation of compounds **1**. As it was mentioned above, 1,5-diazabicyclo-[3.1.0]hexanes **1** were obtained by the action of NaOCl on a mixture of 1,3-diaminopropane and the corresponding carbonyl compound in water at reduced temperature.[11] For obtaining compounds **7** by the *one-pot* reaction, we carried out the synthesis of bicycle **1a** without isolation (TLC monitoring, iodometric titration). The reaction mix-

Scheme 5



i. 1) Toluene, −15 °C; 2) $NaHCO_3/H_2O$.

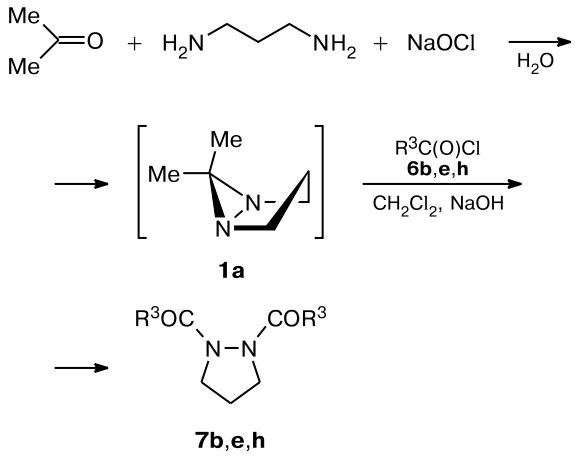
Scheme 6



Reagents and conditions: toluene, –15 °C.

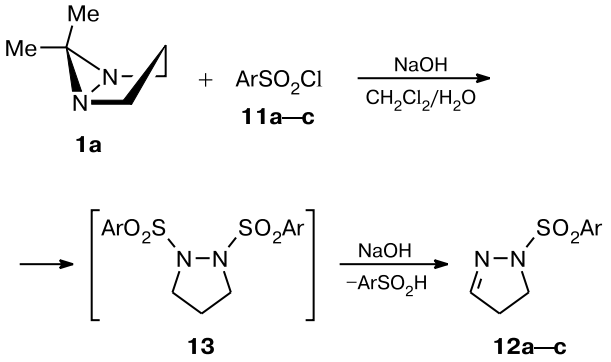
ture obtained was diluted with the equal volume of CH_2Cl_2, followed by addition of calculated amount of NaOH, and, on cooling, the corresponding acyl chloride. In fact, in all the cases the desired compounds were obtained in preparative yields (Scheme 7). The yields were calculated on 1,3-diaminopropane.

Scheme 7



In order to broaden preparative application of the reactions found under conditions of obtaining 1,2-bisacylpyrazolidines **7**, a reaction of 6,6-dimethyl-1,5-diazabicyclo[3.1.0]hexane **1a** with arenesulfonyl chlorides **11** was studied. In this case, 1-arylsulfonylpyrazolines **12** were isolated as the reaction products in 13—78% yields (Scheme 8). Probably, the formation of the desired 1,2-bis(arylsulfonyl)pyrazolidines **13** occurs in the first step of the reaction. However, in the presence of a strong base (NaOH), elimination of arenesulfinic acid takes place with the formation of pyrazoline derivative **12**. Such an elimination of arenesulfinic acids has been already observed in the synthesis of various heterocyclic compounds, for example, in obtaining 1,2,3-triazol-4-ine.[15]

Scheme 8



Ar = 4-MeC_6H_4(**a**), 4-FC_6H_4 (**b**), 4-BrC_6H_4 (**c**)

Product	**12a**	**12b**	**12c**
Yield (%)	26.7 (16)	78.0 (54)	21.5 (13.2)

This process was also carried out under conditions of the *one-pot* reaction. It turned out that arylsulfonylpyrazolines **12a—c** are formed in this case as well, but in considerably lower yields than in the two-step version (see Scheme 8, the numbers in parentheses).

In conclusion, the studies performed resulted in the development of simple and accessible methods for the preparation of 1-mono- and 1,2-bisacylpyrazolidines and 1-arylsulfonylpyrazolines by the reaction of 1,5-diazabicyclo[3.1.0]hexanes with acyl chlorides and arenesulfonyl chlorides in preparative yields. It was shown that 1,2-bisacylpyrazolidines and 1-arylsulfonylpyrazolines can be obtained by *one-pot* reactions, that considerably simplifies procedure for their synthesis.

Experimental

IR spectra were recorded on a UR-20 spectrometer in KBr pellets, ^1H NMR spectra were recorded on a Bruker WM-250 (250 MHz), Bruker AM-300 (300 MHz), and Bruker AC-200 (200 MHz) spectrometers, ^{13}C NMR spectra, on a Bruker AM-300 (75.5 MHz) spectrometer, chemical shifts are given with respect to the signal of $SiMe_4$. The reaction course and purity of the products obtained were monitored by TLC on Silufol UV_{254} plates with visualization under a UV lamp and in I_2 vapors. Melting points were determined on a Sanyo GALLENKAMP instrument.

6,6-Dimethyl-1,5-diazabicyclo[3.1.0]hexane (**1a**) (see Ref. 16), 6-isopropyl-1,5-diazabicyclo[3.1.0]hexane (**1b**) (see Ref. 12), carboxylic acyl chlorides and arenesulfonyl chlorides[17—22] were obtained according to the known procedures.

Synthesis of 1-acylpyrazolidines 2 (general procedure). A solution of the corresponding benzoyl or arylacetyl chloride **6** (2 mmol) in toluene (20 mL) was slowly added dropwise to a solution of the corresponding 1,5-diazabicyclo[3.1.0]hexane (**1a**

Table 3. Yields and some physico-chemical characteristics of compounds synthesized

Compound	M.p./°C[a]	R_f	Found (%) / Calculated				Molecular formula	Yield[b] (%)
			C	H	N	Cl (S)		
1b	—[c]	—	66.40 66.62	11.23 11.18	22.39 22.20	—	$C_7H_{14}N_2$	98
2a	75—76 [76—77][13]	—	—	—	—	—	—	52
2d	140—141 [139—140][23]	—	—	—	—	—	—	59
2f	103—105 [106][7]	—	—	—	—	—	—	42
2h	—[d]	0.47[e]	58.22 58.10	6.10 6.38	10.63 10.42	13.00 13.19	$C_{13}H_{17}ClN_2O_2$	36.4
2l	105—106 [104—105][13]	—	—	—	—	—	—	41
2m	102—103 [102—103][13]	—	—	—	—	—	—	45
2n	119—120 (with decomp.) [119—125][13] (with decomp.)	—	—	—	—	—	—	37
7a	127—128	0.34[f]	66.50 66.27	5.21 5.27	8.00 8.14	11.21 11.03	$C_{19}H_{18}F_2N_2O_2$	53
7b	111—112	0.36[f]	55.30 55.22	4.01 3.90	6.63 6.78	17.09 17.16	$C_{19}H_{16}Cl_2F_2N_2O_2$	91 (72)
7c	79—80 [78—79][24]	—	—	—	—	—	—	65
7d	95—96 [92—93][4]	—	—	—	—	—	—	90
7e	112—114	0.41[f]	67.22 67.05	5.87 5.92	8.02 8.23	— —	$C_{19}H_{20}N_2O_4$	84 (72)
7f	236—238	0.41[f]	55.31 55.14	3.54 3.81	14.99 15.13	— —	$C_{17}H_{14}N_4O_6$	64
7g	145—146 [146—147][25]	—	—	—	—	—	—	84
7h	155—157	0.67[e]	59.68 59.36	5.32 5.63	5.96 6.02	15.56 15.24	$C_{23}H_{26}Cl_2N_2O_4$	97 (74)
7i	202—204 [205—206][26]	—	—	—	—	—	—	72
7k	144—147	0.40[f]	63.01 62.85	4.90 4.52	7.14 6.98	17.32 17.67	$C_{21}H_{18}Cl_2N_2O_2$	75
9	93—94	0.52[e]	63.76 63.51	6.52 6.47	10.79 10.58	13.18 13.39	$C_{14}H_{17}ClN_2O$	8.5
10	56—58	0.73[e]	58.69 58.54	5.23 5.67	10.27 10.50	13.10 13.29	$C_{13}H_{15}ClN_2O_2$	8.5
12a	163—164	0.62[e]	53.30 53.55	5.71 5.39	12.76 12.49	(14.08) (14.30)	$C_{10}H_{12}N_2O_2S$	36.7 (16)
12b	75—77	0.65[e]	47.80 47.36	4.09 3.97	12.59 12.27	(14.43) (14.05)	$C_9H_9FN_2O_2S$	78 (54)
12c	160—162	0.50[e]	37.18 37.38	3.43 3.14	9.23 9.69	(11.53) (11.09)	$C_9H_9BrN_2O_2S$	21.5 (13)

[a] The data from the present work. Literature data are given in square brackets.
[b] The yield of the product obtained by the *one-pot* reaction is given in brackets.
[c] Boiling point is 70—71 °C (13 Torr), $n_D^{20} = 1.4600$.
[d] Crystallizing oil.
[e] An ethyl acetate—hexane (1 : 1) solvent mixture was an eluent, visualization was performed under the UV light.
[f] Ethyl acetate was an eluent.

or **1b**) (4 mmol) in anhydrous toluene (30 mL) under argon at −15—−10 °C with constant and vigorous stirring. The reaction mixture was kept at room temperature and vigorous stirring for 3 h, followed by addition of 20% aqueous $NaHCO_3$ (30 mL). The organic layer was separated, dried with $MgSO_4$, the solvent was evaporated *in vacuo* of a water-jet pump. An oil obtained was purified by column chromatography on SiO_2 using hexane—ethyl acetate (1 : 1 → 0 : 1) mixture as an eluent. The solvent was evaporated *in vacuo* of a water-jet pump.

Compound **1a** gave rise to 1-(4-fluorophenylacetyl)pyrazolidine (**2a**), 1-(4-nitrobenzoyl)pyrazolidine (**2f**), 1-[2-(4-chlorophenoxy)-2-methylpropionyl]pyrazolidine (**2h**), 1-[2-(4-chlorophenoxy)-2-methylpropionyl]pyrazoline (**10**), 1-(4-chlorophenylacetyl)pyrazolidine (**2l**), and 1-(4-bromophenylacetyl)-pyrazolidine (**2m**).

Compound **1b** gave rise to 1-(4-chlorobenzoyl)pyrazolidine (**2d**), 1-(4-chlorobenzoyl)-2-(2-methylpropen-1-yl)pyrazolidine (**9**), 1-(2,4-dinitrophenylacetyl)pyrazolidine (**2n**).

Table 4. The IR spectral data

Compound	IR, ν/cm^{-1}
1b	—
2h	668, 736, 796, 832, 892, 940, 972, 1008, 1092, 1124, 1156, 1240,1284, 1364, 1380,1488, 1596, 1628, 1640, 1720, 1736, 2890, 3250
7a	—
7b	—
7e	768, 844, 1008, 1052, 1088, 1112, 1172, 1256, 1308, 1360, 1420, 1440, 1460, 1512, 1548, 1576, 1608, 1640, 1668, 2360, 2840, 2892, 2936, 2972
7f	716, 732, 708, 720, 840, 860,912, 964, 1012, 1112, 1144, 1240, 1292, 1316, 1344, 1396, 1420, 1492, 1524, 1604, 1648, 1650
7h	492, 508, 526, 572, 594, 664, 704, 740, 832, 848, 896, 936, 964, 1008, 1088, 1108, 1164, 1236, 1280, 1304, 1360, 1388, 1440, 1468, 1492, 1524, 1580, 1592, 1656, 1688
7k	—
9	628, 696, 752, 836, 848, 892, 932, 972, 1012, 1088, 1116, 1132, 1184, 1216, 1256, 1280, 1308, 1328, 1420, 1452, 1472, 1488, 1508, 1564, 1608, 1680, 1704, 2324, 2896, 2980, 3060, 3240
10	668, 704, 760, 796, 832, 872, 932, 944, 972, 1008, 1020, 1088, 1104, 1124, 1156, 1204, 1240, 1280, 1332, 1368, 1384, 1404, 1432, 1448, 1472, 1492, 1544, 1600, 1628, 1884, 2992, 3064
12a	664, 708, 732, 800, 824, 840, 856, 928, 980, 1008, 1016, 1100, 1120, 1164, 1184, 1224, 1256, 1292, 1352, 1400, 1436, 1468, 1492, 1520, 1560, 1596, 1644, 1944, 2924, 3000, 3080
12b	664, 712, 829, 840, 928, 980, 1012, 1088, 1144, 1176, 1236, 1292, 1336, 1356, 1360, 1408, 1496, 1592, 2964
12c	704, 748, 820, 828, 840, 928, 980, 1008, 1068, 1080, 1096, 1168, 1176, 1232, 1256, 1280, 1292, 1336, 1356, 1392, 1436, 1468, 1572, 1596, 3000, 3084

Table 5. The ^{1}H and ^{13}C NMR spectral data ($CDCl_3$) for the compounds synthesized*

Compound	δ, *J*/Hz	
	^{1}H NMR	^{13}C NMR
1b	0.68 (d, 6 H, Me, ^3J = 6.3); 1.09 (m, 1 H, CHMe, ^3J = 7.5); 1.49 (m, 1 H, $H_{ax}(3)$); 1.55 (m, 1 H, $H_{eq}(3)$, ^2J = −11.8); 1.70 (d, 1 H, CHC_{ring}, ^3J = 7.5); 2.68 (m, 2 H, $H_{ax}(2)$, $H_{ax}(4)$, ^2J = −12.0, $^3J_{H_{ax}(2)(4),H_{eq}(3)}$ = 8.7, $^3J_{H_{ax}(2)(4),H_{ax}(3)}$ = 11.3); 3.04 (m, 2 H, $H_{eq}(2)$, $H_{eq}(4)$, $^3J_{H_{eq}(2)(4).H_{ax}(3)}$ = 8.7)	18.01 (Me); 22.24 ($C\underline{C}H_2C$); 30.65 ($\underline{C}Me_2$); 51.58 ($N\underline{C}H_2$); 62.84 (C_{ring})
2h	10.38 (s, 6 H, Me); 1.65 (br.m, 2 H, $CC\underline{H}_2C$); 2.67 (br.m, 2 H, $HNC\underline{H}_2$); 3.28 (br.m, 2 H, $CONC\underline{H}_2$); 4.63 (br.s, 1 H, NH); 6.56, 6.99 (both d, Ar, ^3J = 8)	24.00 (Me); 31.25 ($C\underline{C}H_2C$); 45.19, 47.85 ($N\underline{C}H_2$); 80.22 ($\underline{C}Me$); 118.40, 128.61 (C(2), C(3), C(5), $C_{Ar}(6)$); 148.51 (CCl); 153.92 ($C_{Ar}(1)$); 170.82 (CO)
7a	1.87 (q, 2 H, $CC\underline{H}_2C$, ^2J = 18.0, ^3J = 9.0); 2.67 (m, 2 H, $NC\underline{H}_2$); 3.63 (m, 4 H, $C\underline{H}_2CO$); 4.15 (m, 2 H, $NC\underline{H}_2$); 6.99—7.25 (m, 8 H, Ar)	—
7b	2.12 (m, 2 H, $CC\underline{H}_2C$, ^2J = 18.0, ^3J = 9.0); 3.13 (m, 2 H, $NC\underline{H}_2$); 4.05 (m, 4 H, $C\underline{H}_2CO$); 4.38 (m, 2 H, $NC\underline{H}_2$); 7.02 (t, 2 H, Ar); 7.22 (d, 8 H, Ar)	—
7e	2.09 (m, 2 H, $CC\underline{H}_2C$, ^3J = 9.9); 3.48 (m, 2 H, $NC\underline{H}_2$); 3.77 (s, 6 H, MeO); 3.99 (m, 2 H, $NC\underline{H}_2$); 6.82, 7.57 (both d, 8 H, Ar, ^3J = 8.3)	24.99 ($C\underline{C}H_2C$); 47.34 ($N\underline{C}H_2$); 55.32 (OMe); 113.63 (CH_{Ar}); 126.06 (C(1)); 130.10 (CH_{Ar}); 161.98 (C(4)); 171.50 (CO)
7f	2.209 (m, 2 H, $CC\underline{H}_2C$, ^3J = 7.15); 3.79 (br.m, 4 H, $NC\underline{H}_2$); 7.80, 8.23 (both d, 8 H, Ar, ^3J = 8.3)	24.29 ($\underline{C}H_2$); 39.92 (NCH_2); 123.38, 129.06 (CH_{Ar}); 140.00 ($\underline{C}CO$); 148.68 (CNO_2); 169.00 (CO)
7h	1.61 (s, 12 H, Me); 1.92 (m, 2 H, $CC\underline{H}_2C$); 3.32 (m, 2 H, $NC\underline{H}_2$); 4.35 (m, 2 H, $NC\underline{H}_2$); 7.15, 7.49 (both d, 8 H, Ar, ^3J = 8.1)	24.85 ($\underline{C}H_3C$); 25.14 ($\underline{C}H_3C$); 25.96 ($C\underline{C}H_2C$); 46.05 ($N\underline{C}H_2$); 80.47 ($\underline{C}Me_2$); 120.04 (CH_{Ar}); 127.05 (C^i_{Ar}); 128.99 (CH_{Ar}); 153.40 (CCl); 170.0 (CO)

(*to be continued*)

Table 5 (*continued*)

Compound	δ, *J*/Hz	
	^{1}H NMR	^{13}C NMR
7k	1.95 (m, 2 H, CC$\underline{H}_2$C); 3.45 (m, 2 H, NC$\underline{H}_2$); 4.25 (m, 2 H, NC$\underline{H}_2$); 6.93 (d, 2 H, CHCO, ^2J = 14.0); 8.23 (d, 2 H, ArCH, ^2J = 14.0); 7.23 (t, 2 H, Ar); 7.28 (t, 2 H, Ar); 7.39 (d, 2 H, Ar); 7.55 (d, 2 H, Ar)	—
9	1.44 (s, 3 H, Me); 1.48 (s, 3 H, Me); 2.01 (m, 2 H, CC$\underline{H}_2$C, ^3J = 6.9, ^3J = 7.3); 2.96 (m, 2 H, CH_2NC=, ^3J = 6.9); 3.73 (m, 2 H, CH_2NCO, ^3J = 7.3); 5.57 (s, 1 H, C$\underline{H}$=); 7.22, 7.64 (both d, 4 H, Ar, ^3J = 8.3)	16.73 (Me); 21.64 (Me); 23.70 (C$\underline{C}H_2$C); 43.28 ($\underline{C}H_2$NCO); 56.24 ($\underline{C}H_2$C=N); 124.34 (CH_2=$\underline{C}Me_2$); 127.36, 130.09 ($\underline{C}H_{Ar}$); 133.25 ($\underline{C}$H=C); 135.77 (C^i_{Ar}); 154.00 (CCl); 168.30 (C=O)
10	1.68 (s, 6 H, Me); 2.53 (m, 2 H, CC$\underline{H}_2$C, ^3J = 9.8); 3.57 (m, 2 H, CH_2N, ^3J = 10.0); 6.76, 8.18 (both d, 4 H, Ar, ^3J = 8.9); 7.98 (s, 1 H, C$\underline{H}$=N)	25.02 (Me); 31.62 (C$\underline{C}H_2$C); 43.12 (N$\underline{C}H_2$); 80.58 ($\underline{C}Me_2$); 119.07 ($\underline{C}H_{Ar}$); 126.05 (C_{Ar}(4)); 128.92 ($\underline{C}H_{Ar}$); 148.77 ($\underline{C}$=N); 154.0 (CCl); 170.98 ($\underline{C}$=O)
12a	2.4 (s, 3 H, Me); 2.75 (t, 2 H, CC$\underline{H}_2$C, ^3J = 8.8); 3.5 (t, 2 H, C$\underline{H}_2$N, ^3J = 8.1); 7.0 (br.s, 1 H, C$\underline{H}$=N); 7.35, 7.75 (both d, 4 H, Ar, ^3J = 9.0)	21.5 (Me); 34.13 (C$\underline{C}H_2$C); 45.49 ($\underline{C}H_2$N); 128.77, 129.53 ($\underline{C}H_{Ar}$); 131.06, 144.45 (C_{Ar}(4)); 150.21 ($\underline{C}$=N)
12b	2.77 (t, 2 H, CC$\underline{H}_2$C, ^3J = 9.2, ^3J = 9.8); 3.50 (t, 2 H, C$\underline{H}_2$N, ^3J = 9.8); 7.02 (br.s, 1 H, C$\underline{H}$=N); 7.22 (dd, 2 H, C_{Ar}(3), C_{Ar}(5), $^3J_{P,H}$ = 8.5, $^3J_{H,F}$ = 4.3); 7.90 (dd, 2 H, C_{Ar}(2), C_{Ar}(6), $^3J_{H,H}$ = 5.3, $^3J_{H,F}$ = 3.2)	34.24 (CC$\underline{H}_2$C); 46.60 ($\underline{C}H_2$N); 116.09, 116.54 (d, C_{Ar}(2), C_{Ar}(6), $^3J_{C,F}$ = 11.03); 130.65, 131.60 (dd, C_{Ar}(3), C_{Ar}(5), $^2J_{C,F}$ = 20.7); 150.32 ($\underline{C}$=N); 163.22, 168.32 (d, C_{Ar}(4), $J_{C,F}$ = 96.6)
12s	2.77 (t, 2 H, CC$\underline{H}_2$C, ^3J = 9.2, ^3J = 9.9); 3.50 (t, 2 H, C$\underline{H}_2$N, ^3J = 9.9); 7.02 (s, 1 H, C$\underline{H}$=N); 7.71 (both d, 4 H, Ar, ^3J = 7.9)	34.33 (C$\underline{C}H_2$C); 46.58 ($\underline{C}H_2$N); 128.82 (C_{Ar}(4)); 130.33, 132.02 ($\underline{C}H_{Ar}$); 133.35 (C_{Ar}(1)); 150.46 ($\underline{C}$=N)

* The ^{1}H and ^{13}C NMR spectra of compound **7f** were recorded in DMSO-d_6.

Synthesis of 1,2-bisacylpyrazolidines 7 and 1-arylsulfonylpyrazolines 12 (general procedure). Dichloromethane (20 mL) and the corresponding 1,5-diazabicyclo[3.1.0]hexane (**1a** or **1b**) (2 mmol) were added to a solution of NaOH (4 mmol) in water (30 mL) at 0 °C (ice bath) with vigorous stirring, followed by a dropwise adition over 5 min of a solution of the corresponding acyl chloride **6** or arenesulfonyl chloride **11** (4 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was vigorously stirred for 1 h, while the temperature rised to ambient. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). A combined organic phase was dried with $MgSO_4$, the solvent was evaporated *in vacuo* of a water-jet pump. The residue obtained was dissolved in acetone (5—10 mL) and reprecipitated with 10% aq. $NaHCO_3$ (1-arylsulfonylpyrazolines were reprecipitated with water), filtered off, washed with water, and dried in air.

Compound **1a** gave rise to 1,2-bis(4-fluorophenylacetyl)-pyrazolidine (**7a**), 1,2-bis[(2-chloro-6-fluorophenyl)acetyl]-pyrazolidine (**7b**), 1,2-bis(phenylacetyl)pyrazolidine (**7c**), 1,2-bis-(4-methoxybenzoyl)pyrazolidine (**7e**), 1,2-bis(4-nitrobenzoyl)-pyrazolidine (**7f**), 1,2-bis[2-(4-chlorophenoxy)-2-methylpropionyl]pyrazolidine (**7h**), 2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (**7i**), 1,2-bis[(2*E*)-3-(2-chlorophenyl)propen-2-yl]pyrazolidine (**7k**), 1-[(4-methylphenyl)sulfonyl]pyrazoline (**12a**), 1-[(4-fluorophenyl)sulfonyl]pyrazoline (**12b**), and 1-[(4-bromophenyl)sulfonyl]pyrazoline (**12c**).

Compound **1b** gave rise to 1,2-bis(4-chlorobenzoyl)pyrazolidine (**7d**) and 1,2-bisbenzoylpyrazolidine (**7g**).

***One-pot* synthesis of 1,2-bisacylpyrazolidines 7 and 1-arylsulfonylpyrazolines 12.** Acetone (0.1 mol, 5.8 r, 7.3 mL) was added to 1,3-diaminopropane (0.1 mol, 7.4 g, 8.4 mL) in water (50 mL). The reaction mixture was stirred for 10 min, cooled to 0—−5 °C, followed by a dropwise addition of freshly prepared aq. sodium hypochlorite (40 mL) containing active chlorine (0.1 mol) and having residual alkalinity of 10—15%. The reaction mixture was kept for 1 h at 0—5 °C and 12 h at room temperature. The yield of 6,6-dimethyl-1,5-diazabicyclo[3.1.0]hexane **1a** (96—100%) was determined by iodometris titration with addition of Cu^{2+} salts. An aliquot of the solution containing 2 mmol of **1a** was taken. The pH of the aliquot taken was raised to 14 by addition of aq. NaOH. An equal volume of CH_2Cl_2 was added and a solution of the corresponding acyl or sulfonyl chloride (4 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min with vigorous stirring at 0 °C (ice bath). The reaction mixture was vigorously stirred for 1 h, while the temperature rised to ambient. The organic layer was separated, the aqueous was extracted with CH_2Cl_2 (2×20 mL). A combined extract was dried with $MgSO_4$, the solvent was evaporated *in vacuo* of a water-jet pump. The residue obtained was dissolved in acetone (5—10 mL) and reprecipitated with 10% aq. $NaHCO_3$ (1-arylsulfonylpyrazolines were reprecipitated with water), filtered off, washed with water, and dried in air to obtain 1,2-bis[(2-chloro-6-fluorophenyl)acetyl]pyrazolidine (**7b**), 1,2-bis(4-methoxybenzoyl)pyrazolidine (**7e**), 1,2-bis[2-methyl-2-(4-chlorophenoxy)propionyl]pyrazolidine (**7h**), 1-[(4-methylphenyl)sulfonyl]pyrazoline (**12a**), 1-[(4-fluorophenyl)sulf-

onyl]pyrazoline (**12b**), 1-[(4-bromophenyl)sulfonyl]pyrazoline (**12c**).

The yields, physico-chemical and spectral characteristics of compounds obtained are given in Tables 3—5.

References

1. A. V. Shevtsov, A. A. Kislukhin, V. V. Kuznetsov, V. Yu. Petukhova, V. A. Maslennikov, A. O. Borissova, K. A. Lyssenko, N. N. Makhova, *Mendeleev Commun.*, 2007, **17**, 119.
2. L. N. Jungheim, S. K. Sigmund, *J. Org. Chem.*, 1987, **52**, 407.
3. L. N. Jungheim, *Tetrahedron Lett.*, 1989, **30**, 1889.
4. T. Toya, K. Yamaguchi, Ya. Endo, *Bioorg. Med. Chem.*, 2002, **10**, 953.
5. M. J. Laufersweiler, T. A. Brugel, M. P. Clark, A. Golebiowski, R. G. Bookland, S. K. Laughlin, M. P. Sabat, J. A. Townes, J. C. VanRens, B. De, L. C. Hsieh, S. A. Heitmeyer, K. Juergens, K. K. Brown, M. J. Mekel, R. L. Walter, M. J. Janusz, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4267.
6. M. P. Clark, S. K. Laughlin, M. J. Laufersweiler, R. G. Bookland, T. A. Brugel, A. Golobiowski, M. P. Sabat, J. A. Townes, J. C. VanRens, J. F. Djung, M. G. Natehus, B. De, L. C. Hsieh, S. C. Xu, R. L. Walter, M. J. Mekel, S. A. Heitmeyer, K. K. Brown, K. Juergens, Ye. O. M. J. Janusz, *J. Med. Chem.*, 2004, **47**, 2724.
7. M. D. Curtis, N. C. Hayes, P. A. Matson, *J. Org. Chem.*, 2006, **71**, 5035.
8. R. G. Crawford, A. Mishra, R. J. Dummel, *J. Am. Chem. Soc.*, 1966, **88**, 3959.
9. L. A. Banuelos, P. Cuadrado, A. M. Gonzales-Nogal, I. Lopez-Solera, F. J. Pulido, P. R. Raithby, *Tetrahedron*, 1996, **52**, 9193.
10. P. Cuadrado, A. M. Gonzales-Nogal, S. Martinez, *Tetrahedron*, 1997, **53**, 8585.
11. V. V. Kuznetsov, N. N. Makhova, L. I. Khmelrnitskii, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1410 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1997, **46**, 1354].
12. N. N. Makhova, A. N. Mikhailyuk, V. V. Kuznetsov, S. A. Kutepov, P. A. Belyakov, *Mendeleev Commun.*, 2000, 182.
13. A. V. Shevtsov, V. V. Kuznetsov, A. A. Kislukhin, V. Yu. Petukhova, Yu. A. Strelenko, N. N. Makhova, K. A. Lyssenko, *J. Heterocycl. Chem.*, 2006, **43**, 881.
14. S. D'Andrea, Z. B. Zheng, K. DenBleyker, J. C. Fung-Tomc, H. Yang, J. Clark, D. Taylor, J. Bronson, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2834.
15. G. Beck, D. Gunter, *Chem. Ber.*, 1973, **106**, 2758.
16. G. V. Shustov, S. N. Denisenko, I. I. Chervin, N. L. Asfandiarov, R. G. Kostyanovsky, *Tetrahedron*, 1985, **41**, 5719.
17. L. Ch. Raiford, J. N. Wickert, *J. Am. Chem. Soc.*, 1931, **53**, 3143.
18. G. A. Olah, A. E. Pavlath, J. A. Olah, F. Herr, *J. Org. Chem.*, 1957, **22**, 879.
19. C. Almansa, L. A. Gomez, F. L. Cavalkanti, A. F. Arriba, J. Garcia-Rafanell, J. Forn, *J. Med. Chem.*, 1997, **40**, 547.
20. P. T. Flaherty, T. D. Greenwood, A. L. Manheim, J. F. Wolfe, *J. Med. Chem.*, 1996, **39**, 1509.
21. C. H. Fawcett, R. L. Wain, F. Wightman, *Ann. Appl. Biology*, 2008, **43**, 342.
22. N. J. Turro, C. Gregory, *J. Am. Chem. Soc.*, 1983, **105**, 1861.
23. Yu. S. Syroeshkina, V. Yu. Petukhova, V. V. Kachala, Yu. V. Nelyubina, N. N. Makhova, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 1401 [*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 1433].
24. Ya. Endo, U. Takuya, K. Yamaguchi, *Heterocycl.*, 2000, **53**, 151.
25. E. L. Buhle, A. M. Moore, F. Y. Wiselogle, *J. Am. Chem. Soc.*, 1943, **65**, 29.
26. A. Csámpai, K. Körmendy, F. Ruff, *Tetrahedron*, 1991, **47**, 4457.

Received July 2, 2009;
in revised form February 16, 2010