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SYNTHESIS AND HETEROCYCLIZATION OF β-AROYL-α-DIPHENYL-PHOSPHORYLPROPIONIC ACIDS

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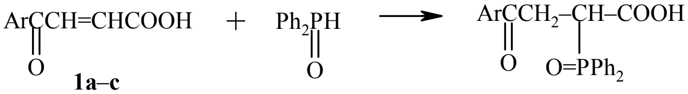
It has been established that diphenylphosphine oxide reacts smoothly with β-aroylacrylic acids with the formation of β-aroyl-α-diphenylphosphorylpropionic acids, which were cyclized under the action of hydroxylamine, hydrazine hydrate, and phenylhydrazine hydrochloride into phospho derivatives of dihydrooxazinone and tetrahydropyridazinone respectively. It was shown that imidazole may serve as nucleophilic protection for the synthesis of dihydropyridazinone derivatives from β-aroylacrylic acids.

Keywords: β-aroylacrylic acids, dihydropyridazinones, diphenylphosphine oxide, diphenylphosphoryl-dihydrooxazinones, diphenylphosphoryltetrahydropyridazinones, imidazole, pyrazolinecarboxylic acids.

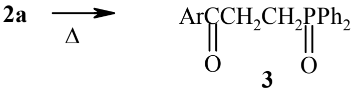
Due their high electrophilicity aroylacrylic acids react readily with nucleophiles, including primary and secondary amines, but, as was shown by one of us, do not interact with diethyl phosphite in the absence of catalysts. The reaction was successfully effected in an alcoholic solution of sodium ethylate or under conditions of interphase catalysis [1]. A conclusion on the order of addition has been made by analogy with amines and on the basis of the results of quantum chemical calculations [2].

The present work is devoted to the study of the interaction of aroylacrylic acids **1a-c** with diphenylphosphine oxide. It was established that the reaction proceeded smoothly on heating the reactants and the addition products **2a-c** are formed in high yield (70-81%, Table 1). The structures of the latter were established on the basis of the exclusive formation of β-(benzoylethyl)diphenylphosphine oxide (**3**), on decarboxylation of acid **2a** and not the isomeric α-(benzoylethyl)diphenylphosphine oxide.



$$\mathrm{Ar\underset{\underset{O}{\|}}{C}CH{=}CHCOOH}\ (\mathbf{1a{-}c}) + \mathrm{Ph_2\underset{\underset{O}{\|}}{P}H} \longrightarrow \mathrm{Ar\underset{\underset{O}{\|}}{C}CH_2{-}\underset{\underset{O{=}PPh_2}{|}}{C}H{-}COOH}$$

2a–c



$$\mathbf{2a} \xrightarrow[\Delta]{} \mathrm{Ar\underset{\underset{O}{\|}}{C}CH_2CH_2\underset{\underset{O}{\|}}{P}Ph_2}$$

3

Here and subsequently: **a** Ar = Ph, **b** Ar = C_6H_4Me-4, **c** Ar = C_6H_4Br-4

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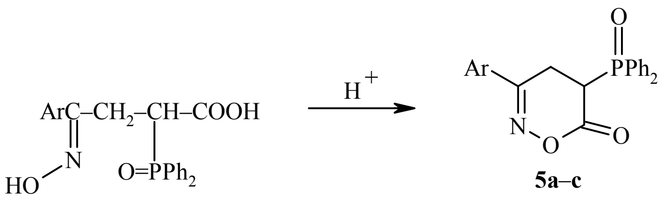
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	P		
2a	$C_{22}H_{19}O_4P$	69.79 69.84	4.98 5.03	—	8.16 8.20	154-155	81
2b	$C_{23}H_{21}O_4P$	70.36 71.41	5.28 5.36	—	7.93 7.91	190-192	70.5
2c	$C_{22}H_{18}BrO_4P$	57.72 57.76	3.89 3.94	—	6.81 6.78	204-205	76.5
3	$C_{21}H_{19}PO_2$	75.38 75.45	5.71 5.69	—	9.32 9.28	131-133	48
4a	$C_{22}H_{20}NO_4P$	67.21 67.17	5.11 5.09	3.49 3.56	7.88 7.89	211-212	81.5
4b	$C_{23}H_{22}NO_4P$	67.79 67.81	5.39 5.41	3.46 3.44	7.67 7.62	214-216	87.3
4c	$C_{22}H_{19}BrNO_4P$	55.89 55.93	3.98 4.03	3.01 2.96	6.54 6.57	210-211	76
5a	$C_{22}H_{18}NO_3P$	70.43 70.40	4.69 4.80	3.76 3.73	8.30 8.27	172-173	54
5b	$C_{23}H_{20}NO_3P$	70.91 70.95	5.09 5.14	3.58 3.60	7.89 7.97	179-180	52
5c	$C_{22}H_{17}BrNO_3P$	57.98 58.15	3.79 3.74	3.12 3.08	6.85 6.83	176-177	71
6a	$C_{22}H_{19}N_2O_2P$	70.54 70.59	5.11 5.08	7.46 7.49	8.26 8.29	240-241	57.7
6b	$C_{23}H_{21}N_2O_2P$	71.17 71.13	5.39 5.41	7.19 7.22	7.94 7.99	231-232	78.6
6c	$C_{22}H_{18}BrN_2O_2P$	58.26 58.28	3.94 3.97	6.16 6.18	6.82 6.84	245-246	65.7
7a	$C_{28}H_{23}N_2O_2P$	74.62 74.66	5.09 5.11	6.18 6.22	6.84 6.88	201-203	93.1
7b	$C_{29}H_{25}N_2O_2P$	74.96 75.00	5.35 5.39	6.00 6.03	6.68 6.68	195-197	78
7c	$C_{28}H_{22}BrN_2O_2P$	63.49 63.52	4.09 4.16	5.27 5.29	5.89 5.86	204-205	74.4
9b	$C_{11}H_{10}N_2O$	70.93 70.97	5.29 5.37	14.95 5.05	—	242-243	64.5
9c	$C_{10}H_7BrN_2O$	47.76 47.81	2.81 2.79	11.14 11.15	—	235-237	51.6
10a	$C_{10}H_{10}N_2O_2$	63.12 63.15	5.29 5.26	14.72 14.74	—	203-204	53.1
10b	$C_{11}H_{12}N_2O_2$	64.74 64.71	5.89 5.88	13.69 13.72	—	173-175	56.2
10c	$C_{10}H_9BrN_2O_2$	44.59 44.61	3.38 3.35	10.42 10.41	—	205-206	46.3

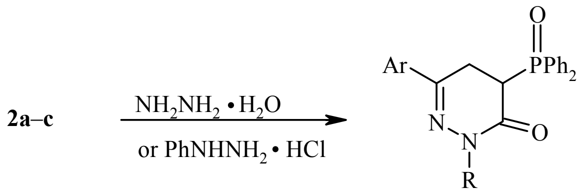
It is known that heterocyclic compounds with a phosphorus atom in the side chain possess high biological activity and belong to a new generation of pesticides.

With the aim of transferring to compounds of this type we have obtained oximes **4a-c** of the synthesized β-aroyl-α-diphenylphosphorylpropionic acids **2a-c** and have heterocyclized them by heating with a catalytic amount of sulfuric acid. As a result phospho derivatives of 3-aryl-4,5-dihydro-1,2-oxazin-6-one **5a-c** were obtained in 52-71% yield (Table 1).



4a–c
5a–c

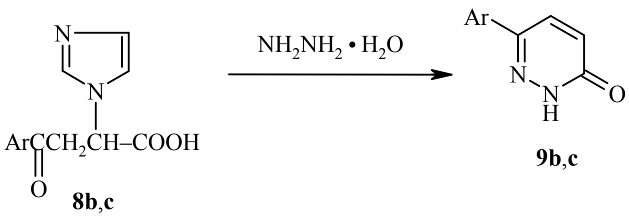
The similarly constructed 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones **6a-c** and **7a-c** were obtained by heating the same α-phosphorylaroylpropionic acids **2a-c** with hydrazine hydrate or phenylhydrazine hydrochloride respectively.



6a–c, 7a–c

6 R = H; **7** R = Ph

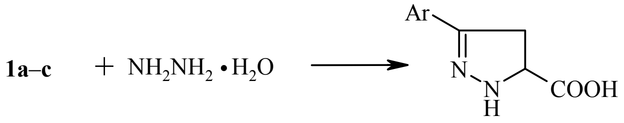
Interesting results were obtained by us on boiling β-aroyl-α-(N-imidazolyl)propionic acids **8b,c**, synthesized by one of us previously [3], with an aqueous solution of hydrazine. In place of the expected aminotetrahydropyridazinones the reaction products proved to be the 6-aryl-2,3-dihydropyridazin-3-ones **9b,c**.



8b,c

9b,c

The latter might have been formed as a result either of preliminary fission of imidazole with subsequent heterocyclization or by initial heterocyclization with subsequent fission of imidazole. Specially designed experiments showed that the interaction of aroylacrylic acids **1a-c** with hydrazine hydrate leads not to the formation of pyridazinone derivatives but to pyrazolinecarboxylic acids **10a-c**.



10a–c

Analogous results have been obtained by several authors studying the reaction of aroylacrylic acids and their esters with phenylhydrazine [4-6].

It can therefore be assumed that dihydropyridazinones **9** owe their origin to the fission of imidazole from the initially formed imidazolo derivatives of tetrahydropyridazinone. The results obtained permit the conclusion that imidazole may serve as nucleophilic protection for the synthesis of pyridazinone derivatives from β-aroylacrylic acids.

The composition and structure of all the compounds obtained were confirmed by the results of elemental analysis (Table 1) and data of NMR spectra (Table 2, the spectra of compounds **8b,c** missing from [3] are also given in this Table).

TABLE 2. ^{1}H, ^{13}C* , and ^{31}P*^{2} NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (coupling constants, J, Hz)*^{3}
1	2
2a	12.35 (1H, br. s, CO_2H); 7.91 (6H, m, C_6H_5); 7.40-7.58 (9H, m, C_6H_5); 4.26 (1H, ddd, J_1 = 13.5, J_2 = 11.0, J_3 = 2.7, CH); 3.81 (1H, ddd, J_1 = 18.3, J_2 = 11.0, J = 5.4, CH_2); 3.03 (1H, ddd, J_1 = 18.3, J_2 = 9.0, J_3 = 2.8, CH_2)
2b	12.37 (1H, br. s, COOH); 7.90 (4H, m, C_6H_5); 7.80 (2H, d, J = 8.1, Ar); 7.51 (6H, m, C_6H_5); 7.23 (2H, d, J = 8.1, Ar); 4.23 (1H, ddd, J_1 = 13.2, J_2 = 11.1, J_3 = 2.8, PCH); 3.76 (1H, ddd, J_1 = 18.0, J_2 = 11.1, J_3 = 5.4, CH_2); 2.98 (1H, ddd, J_1 = 18.0, J_2 = 9.0, J_3 = 2.8, CH_2); 2.40 (3H, s, CH_3)
2c	12.3 (1H, br. s, CO_2H); 7.91 (4H, m, C_6H_5); 7.84 (2H, d, J = 8.5, Ar); 7.60 (2H, d, J = 8.5, Ar); 7.45-7.55 (6H, m, C_6H_5); 4.26 (1H, ddd, J_1 = 13.2, J_2 = 10.5, J_3 = 2.9, CH); 3.78 (1H, ddd, J_1 = 18.3, J_2 = 10.5, J_3 = 5.7, CH_2); 3.01 (1H, ddd, J_1 = 18.3, J_2 = 8.7, J_3 = 2.9, CH_2)
3	7.91 (2H, d, J = 8.1, C_6H_5); 7.80 (4H, m, C_6H_5); 7.40-7.57 (9H, m, C_6H_5); 3.20 (2H, m, CH_2); 2.66 (2H, m, CH_2)
4a	12.19 (1H, br. s, CO_2H); 11.27 (1H, s, NOH); 7.79-7.94 (4H, m, C_6H_5); 7.43-7.59 (8H, m, C_6H_5); 7.22-7.35 (3H, m, C_6H_5); 4.09 (1H, td, J_1 = 10.8, J_2 = 3.3, CH); 3.32 (1H, ddd, J_1 = 13.8, J_2 = 11.1, J_3 = 6.3, CH_2); 2.90 (1H, ddd, J_1 = 13.8, J_2 = 10.2, J_3 = 3.3, CH_2)
4b	12.18 (1H, br. s, CO_2H); 11.14 (1H, s, NOH); 7.86 (4H, m, C_6H_5); 7.45-7.57 (6H, m, C_6H_5); 7.42 (2H, d, J = 8.2, Ar); 7.06 (2H, d, J = 8.2, Ar); 4.06 (1H, td, J_1 = 10.8, J_2 = 3.2, PCH); 3.31 (1H, ddd, J_1 = 13.8, J_2 = 11.1, J_3 = 6.0, CH_2); 2.87 (1H, ddd, J_1 = 13.8, J_2 = 10.2, J_3 = 3.2, CH_2); 2.33 (3H, s, CH_3)
4c	12.17 (1H, br. s, CO_2H); 11.23 (1H, s, NOH); 7.91 (4H, m, C_6H_5); 7.83 (2H, d, J = 8.5, Ar); 7.62 (2H, d, J = 8.5, Ar); 7.45-7.56 (6H, m, C_6H_5); 4.05 (1H, td, J_1 = 10.8, J_2 = 3.2, PCH); 3.32 (1H, ddd, J_1 = 13.8, J_2 = 11.1, J_3 = 6.2, CH_2); 2.89 (1H, ddd, J_1 = 13.8, J_2 = 10.2, J_3 = 3.2, CH_2)
5a	7.91 (2H, d, J = 8.1, C_6H_5); 7.80 (4H, m, C_6H_5); 7.40-7.57 (9H, m, C_6H_5); 4.29 (1H, ddd, J_1 = 15.0, J_2 = 8.3, J_3 = 4.2, PCH); 3.68 (1H, ddd, J_1 = 17.3, J_2 = 12.5, J_3 = 4.2, CH_2); 3.19 (1H, ddd, J_1 = 26.4, J_2 = 17.3, J_3 = 8.3, CH_2)
5b	8.00-7.78 (6H, m, C_6H_5); 7.60-7.40 (6H, m, C_6H_5); 7.20 (2H, m, Ar); 4.25 (1H, ddd, J_1 = 15.0, J_2 = 8.4, J_3 = 3.6, PCH); 3.80 (1H, ddd, J_1 = 17.3, J_2 = 12.8, J_3 = 4.2, CH_2); 3.05 (1H, ddd, J_1 = 27.3, J_2 = 17.3, J_3 = 8.3, CH_2)
5c	7.60-7.85 (6H, m, C_6H_5); 7.40-7.62 (9H, m, C_6H_5); 4.39 (1H, ddd, J_1 = 15.0, J_2 = 8.4, J_3 = 3.6, PCH); 3.85 (1H, ddd, J_1 = 17.3, J_2 = 12.9, J_3 = 3.6, CH_2); 3.15 (1H, ddd, J_1 = 27.3, J_2 = 17.3, J_3 = 8.4, CH_2)
6a	10.87 and 10.73 (1H, s, NH); 7.00-8.00 (15H, m, C_6H_5); 4.70 (0.5H, dd, J_1 = 11.7, J_2 = 8.4, PCH); 4.02 (0.5H, ddd, J_1 = 13.8, J_2 = 8.1, J_3 = 5.4, CH_2); 3.35 (0.5H, ddd, J_1 = 17.1, J_2 = 12.9, J_3 = 5.4, CH_2); 3.78-3.16 (1H, m, CH_2); 2.53 (0.5H, dd, J_1 = 17.1, J_2 = 13.2, PCH)
6b	11.01 (1H, s, NH);7.89 (2H, m, C_6H_5);7.73 (2H, m, C_6H_5); 7.37-7.65 (6H, m, C_6H_5); 7.40 (2H, d, J = 8.4, Ar); 7.19 (2H, d, J = 8.4, Ar); 4.26 (1H, m, PCH); 2.95-3.25 (2H, m, CH_2); 2.32 (3H, s, CH_3)
6c	10.93 and 10.81 (1H, s, NH); 7.97 (2H, m, Ar); 7.10-7.70 (12H, m, Ar and C_6H_5); 4.71 and 4.02 (1H, m, CH); 2.43-3.41 (2H, m, CH_2)
7a	8.05 (2H, m, C_6H_5); 7.12-7.76 (18H, m, C_6H_5); 4.29 (1H, ddd, J_1 = 15.0, J_2 = 8.3, J_3 = 4.2, PCH); 3.69 (1H, ddd, J_1 = 17.3, J_2 = 12.5, J_3 = 4.2, CH_2); 3.29 (1H, ddd, J_1 = 26.4, J_2 = 17.3, J_3 = 8.3, CH_2)
7b	8.20 (2H, m, C_6H_5); 7.72 (2H, d, J = 8.1, Ar); 7.44-7.64 (6H, m, C_6H_5); 7.15-7.35 (7H, m, C_6H_5); 7.06 (2H, m, Ar); 3.96-4.11 (2H, m, CH_2); 3.24 (1H, m, PCH); 2.43 (3H, s, CH_3)
7c	8.03 (2H, dd, J_1 = 11.7, J_2 = 7.8, Ar); 7.46-7.66 (10H, m, C_6H_5); 7.08-7.39 (7H, m, C_6H_5 and Ar); 4.31 (1H, ddd, J_1 = 15.0, J_2 = 8.4, J_3 = 3.6, PCH); 3.65 (1H, ddd, J_1 = 17.3, J_2 = 12.9, J_3 = 3.6, CH_2); 3.30 (1H, ddd, J_1 = 27.3, J_2 = 17.3, J_3 = 8.4, CH_2)
8b	7.35-7.78 (7H, m, Ar, Het); 5.75 (1H, dd, J_1 = 8.4, J_2 = 4.2, CH); 4.05 (1H, dd, J_1 = 18.9, J_2 = 8.4, CH_2); 3.89 (1H, dd, J_1 = 18.9, J_2 = 4.2, CH_2); 2.35 (3H, s, CH_3)
8c	7.38-7.71 (7H, m, Ar, Het); 5.78 (1H, dd, J_1 = 8.4, J2 = 4.2, CH); 4.07 (1H, dd, J_1 = 18.9, J_2 = 8.4, CH_2); 3.91 (1H, dd, J_1 = 18.9, J_2 = 4.2, CH_2)

TABLE 2 (continued)

1	2
9b	12.97 (1H, br. s, NH); 7.80 (1H, d, *J* = 9.9, Het) 7.68 (2H, d, *J* = 8.1, Ar); 7.20 (2H, d, *J* = 8.1, Ar); 6.86 (1H, d, *J* = 9.9, Het); 2.38 (3H, s, CH_3)
9c	13.09 (1H, br. s, NH); 7.87 (1H, d, *J* = 9.9, Het); 7.77 (2H, d, *J* = 8.4, Ar); 7.56 (2H, d, *J* = 8.4, Ar); 6.89 (1H, d, *J* = 9.9, Het)
10a	9.00 (1H, br. s, NH); 7.59 (2H, d, *J* = 7.5, C_6H_5); 7.32 (2H, t, *J* = 7.5, C_6H_5); 7.25 (1H, t, *J* = 7.2, C_6H_5); 4.23 (1H, dd, J_1 = 10.5, J_2 = 9.5, CH); 3.21 (1H, m, J_1 = 16.5, J_2 = 10.5, CH_2); 3.19 (1H, m, J_1 = 16.5, J_2 = 9.5, CH_2)
10b	8.95 (1H, br. s, NH); 7.47 (2H, d, *J* = 8.1, Ar); 7.11 (2H, d, *J* = 8.1, Ar); 4.20 (1H, dd, J_1 = 11.1, J_2 = 9.3, CH); 3.18 (1H, m, J_1 = 16.5, J_2 = 11.1, CH_2); 3.16 (1H, m, J_1 = 16.5, J_2 = 9.3, CH_2)
10c	9.03 (1H, br. s, NH); 7.51 (2H, d, *J* = 8.7, Ar); 7.46 (2H, d, *J* = 8.7, Ar); 4.24 (1H, t, *J* = 10.2, CH); 3.18 (2H, d, *J* = 10.2, CH_2)

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* ^{13}C NMR spectrum of **6b** (DMSO–CCl_4, 1:3), δ, ppm (*J*, Hz): 163.07 (CO, d, *J* = 3.0); 147.94 (d, *J* = 5.0); 138.92 (4-C_{Ar}); 132.95 (2C, 4-CPh); 132.19 (d, *J* = 99.5); 131.89 (d, *J* = 99.1); 131.92 (d, *J* = 2.7); 131.65 (d, *J* = 2.7); 130.99 (2C, d, *J* = 9.4); 130.90 (2C, d, *J* = 9.4); 128.95 (2C, 3-, 5-C_{Ar}); 128.66 (2C, d, *J* = 11.7); 128.04 (2C, d, *J* = 12.0); 125.45 (2C, 2-, 6-C_{Ar}); 37.41 (CH, d, *J* = 62.8); 22.53 (CH_2, d, *J* = 2.4); 20.76 (CH_3).

*[2] ^{31}P NMR spectrum (DMSO–CCl_4, 1:3), δ, ppm: **6a** 33.84 and 33.03 (1:1 mixture of two tautomers); **6c** 34.03 and 32.91 (1:1 mixture of two tautomers).

*[3] Solvents: DMSO–CCl_4, 1:3 (**2-7a**, **9**, **10**); $CDCl_3$ (**7b**); DMSO–CF_3COOD, 1:3 (**8b,c**).

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra of the synthesized compounds were taken on a Varian Mercury-300 instrument (300, 75, and 121 MHz respectively).

β-Aroyl-α-(diphenylphosphoryl)propionic Acids (2a-c). A solution of diphenylphosphine oxide (10 mmol) and β-aroylacrylic acid (10 mmol) in dry benzene (10 ml) was boiled for 6 h. After cooling, the resulting precipitate of product **2** was filtered off, washed with benzene, and dried in vacuum.

Decarboxylation of β-Benzoyl-α-(diphenylphosphoryl)propionic Acid 2a. Compound **2a** (1 g) was kept at 140°C (5 mm Hg) for 5-10 min. After cooling, the resulting product was recrystallized from acetone. (β-Benzoylethyl)diphenylphosphine oxide (**3**) (0.4 g) was obtained.

Oximes of β-Aroyl-α-(diphenylphosphoryl)propionic Acids (4a-c). A solution of hydroxylamine hydrochloride (36 mmol) in the minimum amount of water was added to a saturated solution of compound **2a-c** (3 mmol) in methanol and the mixture obtained was boiled for 30 h. The resulting precipitate of oxime **4a-c** was filtered off, washed sequentially with methanol, and with water, and dried in vacuum.

3-Aryl-5-diphenylphosphoryl-4,5-dihydro-1,2-oxazin-6-one (5a-c). A solution of compound **4a-c** (15 mmol) in acetone (8 ml) containing a catalytic amount of conc. H_2SO_4 was boiled for 3 h. After cooling, the reaction mixture was poured into water, the precipitate of product **5a-c** formed was filtered off, washed with water, and recrystallized from acetone.

6-Aryl-4-diphenylphosphoryl-2,3,4,5-tetrahydropyridazin-3-ones (6a-c). A solution of compound **2a-c** (2.9 mmol) and 60% aqueous hydrazine hydrate solution (4 ml) in alcohol (5 ml) was boiled for 8 h. After cooling, the resulting solid was filtered off, washed with alcohol, and dried in vacuum.

6-Aryl-4-diphenylphosphoryl-N-phenyl-2,3,4,5-tetrahydropyridazin-3-ones (7a-c). A solution of compound **2a-c** (1.5 mmol) and phenylhydrazine hydrochloride (1.5 mmol) in alcohol (10 ml) was boiled for 6 h. The reaction mixture was treated similarly to that described above for compounds **6a-c**.

6-Aryl-2,3-dihydropyridazin-3-ones (9b,c). A mixture of acid **8b,c** (2.5 mmol) and 60% aqueous hydrazine hydrate solution (4 ml) was boiled for 4 h. After cooling, the precipitate of product **9b,c** formed was filtered off, washed with alcohol, and dried in vacuum.

3-Aryl-2-pyrazoline-5-carboxylic Acids (10a-c). A mixture of acid **1a-c** (5 mmol), 60% aqueous hydrazine hydrate solution (3 ml), and alcohol (3 ml) was boiled for 6 h. After cooling, the precipitate of product **10a-c** was filtered off, washed with alcohol, and dried in vacuum.

REFERENCES

1. R. J. Khachikyan, S. Yu. Kotikyan, and S. G. Agbalyan, *Khim. Zh. Armen.*, **52**, 90 (1999).
2. N. P. Churkina, N. P. Gambaryan, D. A. Bochvar, and S. G. Agbalyan, *Arm. Khim. Zh.*, **30**, 370 (1977).
3. R. J. Khachikyan, G. V. Grigoryan, and S. G. Agbalyan, *Arm. Khim. Zh.*, **39**, 373 (1986).
4. E. A. Soliman, *Rev. Roum. Chem.*, **23**, 159 (1978).
5. A. A. Nada, *Egypt. J. Chem.*, **19**, 621 (1978).
6. A. W. Nineham and R. A. Raphael, *J. Chem. Soc.*, 118 (1949).