Brief Communications

Reactions of β-aroylacrylic acids with N-nucleophiles

R. Dj. Khachikyan,[a] N. V. Karamyan,[a]★ H. A. Panosyan,[b] and M. H. Injikyan[a]

[a]Institute of Organic Chemistry, National Academy of Sciences,
167-A ul. Z. Sarkavag, 375091 Yerevan, Republic of Armenia.
Fax: (374 1) 28 3511. E-mail: Nara7777@mail.ru
[b]Molecular Structure Research Center,
Yerevan, Republic of Armenia

Reactions of $NH_2OH \cdot HCl$ with β-aroylacrylic acids proceed ambiguously: a nucleophile attacks either the carbonyl group or the C=C bond. In the latter case, the resulting α-hydroxylamino derivative converts into enamine, probably *via* dehydration followed by isomerization. Addition of 1,2,4-triazole to the C=C bond of β-(*p*-toluyl)acrylic acid followed by refluxing of their adduct with 60% $NH_2NH_2 \cdot H_2O$ gave a dihydropyridazinone derivative.

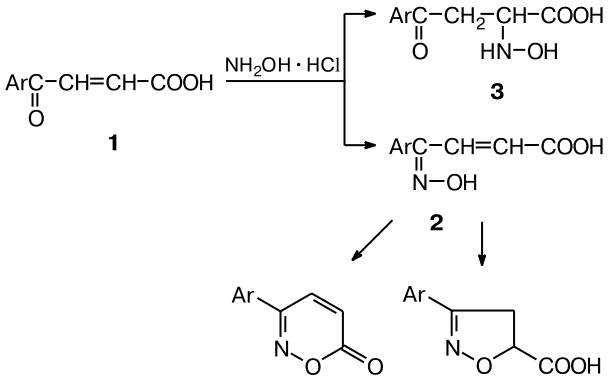
Key words: β-aroylacrylic acids, hydroxylamine hydrochloride, carbonyl group, double bond, enamine, oxime, triazole.

A large number of studies devoted to reactions of β-aroylacrylic acids with nucleophiles have been published to date. It is known[1—8] that in reactions with water and NH, SH, CH, and PH acids, a nucleophile attacks the C_α atom to form α-substituted β-aroylpropionic acids. Quantum-chemical[9] and experimental data are in agreement. It should be noted that β-aroylacrylic acids form salts with heterocyclic amines, thiourea, and thiosemicarbazide.[10,11]

We studied reactions of β-aroylacrylic acids **1** with hydroxylamine; the expected products were either oximes **2**, which undergo subsequent cyclization into isoxazole or oxazinone derivatives, or β-aroyl-α-hydroxylaminopropionic acids **3** (Scheme 1).

However, the reaction of β-(*p*-toluyl)acrylic acid (**1a**) with $NH_2OH \cdot HCl$ in aqueous methanol gave no oxime **2a** or products of its subsequent transformations; instead, a 1 : 3 mixture of α-amino-β-(*p*-toluyl)acrylic acid (**4**) and its methyl ester **5a** was unexpectedly obtained in 70% yield (Scheme 2).

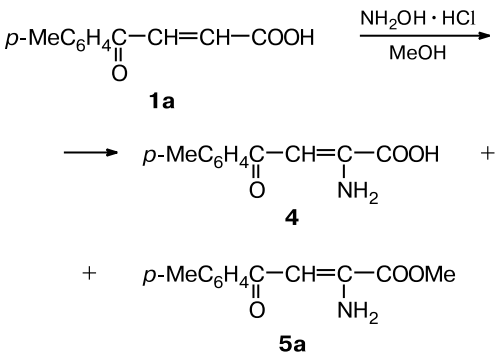
Scheme 1



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1923—1927, August, 2005.

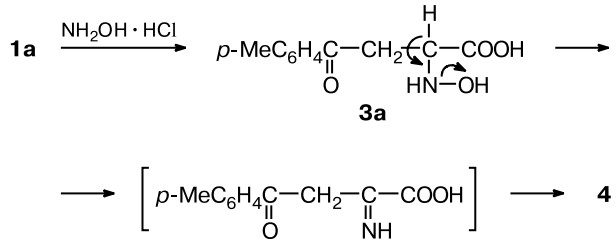
1066-5285/05/5408-1982 © 2005 Springer Science+Business Media, Inc.

Scheme 2



Apparently, the reaction involves addition of NH_2OH to the double bond to form compound **3a**, its dehydration, and isomerization of the resulting imine into enamine **4** (Scheme 3).

Scheme 3

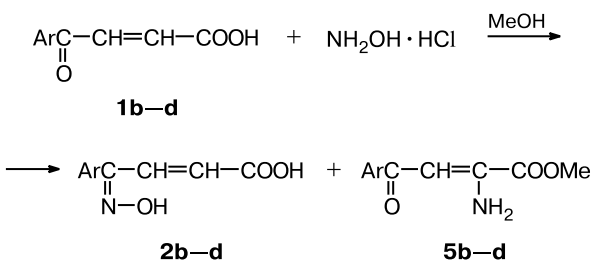


The reaction of methyl β-(*p*-toluyl)acrylate with hydroxylamine in the presence and in the absence of Et_3N afforded ester **5a** in 58 and 61% yields, respectively.

The structures of compounds **4** and **5a** were determined by ^1H NMR spectroscopy and confirmed by 2D NOESY NMR spectroscopy: the presence of a cross peak between the *ortho*-protons of the aromatic ring and the H atom at the C=C bond unambiguously indicates that the nucleophile attacks the α-position relative to the carboxyl group.

A different pattern was observed with β-benzoyl-, β-(*p*-chlorobenzoyl)-, and β-(*p*-bromobenzoyl)acrylic acids **1b**—**d**. In all the cases, the corresponding oximes **2b**—**d** were obtained as the major reaction products in 71, 45, and 50% yields, respectively (Scheme 4). Minor methyl α-amino-β-aroylacrylates **5b**—**d** were obtained in 19, 21, and 15.5% yields, respectively.

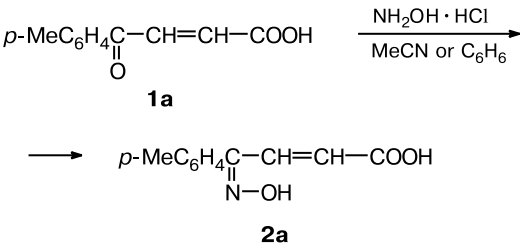
Scheme 4



1, 2, 5: Ar = Ph (**b**), *p*-ClC_6H_4 (**c**), *p*-BrC_6H_4 (**d**)

With β-(*p*-toluyl)acrylic acid (**1a**) as an example, we found that the reaction pathway is decisively influenced by the solvent nature. For instance, the reaction in acetonitrile or benzene rather than methanol gave the corresponding oxime **2a** as the only product (Scheme 5).

Scheme 5

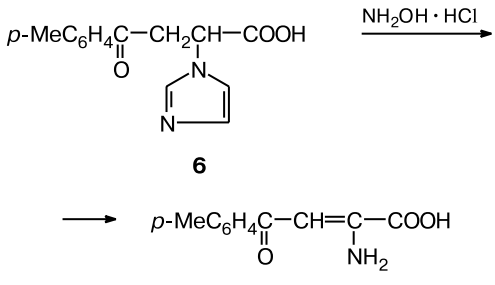


Thus, the reactions of $NH_2OH \cdot HCl$ with β-aroylacrylic acids can follow alternative pathways, with an attack of the nucleophile on either the carbonyl group or the C=C bond.

It is known[12—14] that reactions of β-aroylacrylic acids with hydrazines yield pyrazolinecarboxylic acids; dihydropyridazinone derivatives cannot be obtained with the use of $NH_2NH_2 \cdot H_2O$. Recently,[15] we found that the imidazolyl protection of the C=C bond in β-aroylacrylic acids allows the synthesis of 2,3-dihydropyridazin-3-one derivatives.

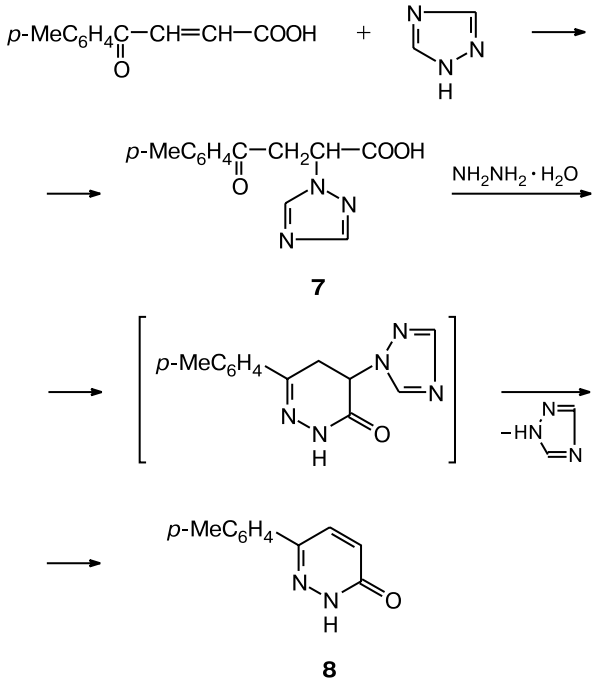
To verify the possibility of employing imidazole for the synthesis of oxazinone derivatives from β-aroylacrylic acids, we studied the reaction of adduct **6** (synthesized from imidazole and β-(*p*-toluyl)acrylic acid) with NH_2OH. However, the only product was α-amino-β-(*p*-toluyl)acrylic acid (**4**); *i.e.*, in contrast to the reactions with hydrazine, the attack by the nucleophile is preceded by elimination of imidazole (Scheme 6).

Scheme 6



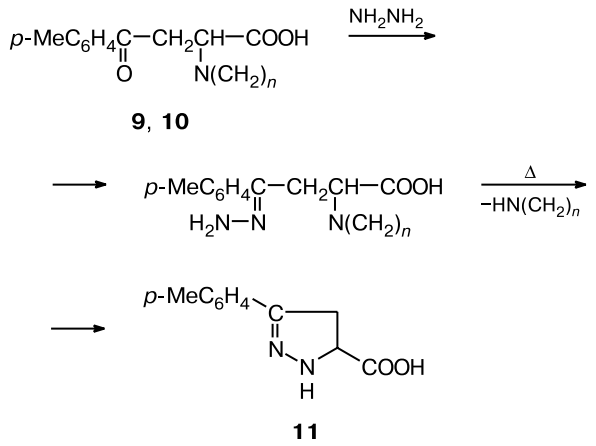
In continuation of the previous investigations, here we studied reactions of hydrazine hydrate with adducts of β-aroylacrylic acids with some other amines. It was demonstrated that 1,2,4-triazole behaves like imidazole; its adduct with β-(*p*-toluyl)acrylic acid **7** in the presence of hydrazine hydrate undergoes cyclization followed by elimination of the triazole to give the corresponding dihydropyridazinone **8** [15] (Scheme 7).

Scheme 7



We found that the reactions of hydrazine hydrate with pyrrolidine and piperidine adducts of β-(*p*-toluyl)acrylic acid (**9**, **10**)[16] occurs in a different way: elimination of the amine precedes cyclization to give 3-(*p*-tolyl)pyrazoline-5-carboxylic acid (**11**)[15] (Scheme 8).

Scheme 8



n = 4 (**9**), 5 (**10**)

Experimental

^{1}H NMR spectra were recorded on a Mercury-300 Varian instrument. A mass spectrum was recorded on an MX-1321 instrument (direct inlet probe, ionizing voltage 70 eV).

Reaction of β-(*p*-toluyl)acrylic acid (1a) with $NH_2OH \cdot HCl$. Aqueous $NH_2OH \cdot HCl$ (8.34 g, 0.12 mol) was added to a saturated solution of acid **1a** (1.9 g, 0.01 mol) in MeOH. The reaction mixture was refluxed in a water bath for 30 h and then treated with water. The precipitate was filtered off, washed with water, and treated with 1 *M* KOH. The alkaline solution was acidified with dilute HCl. The precipitate that formed was filtered off, washed with water, dried *in vacuo*, and refluxed in $CHCl_3$ for purification. The yield of **α-amino-β-(*p*-toluyl)acrylic acid (4)** was 0.43 g (23%), m.p. 189—190 °C. Found (%): C, 64.91; H, 5.43; N, 6.92. $C_{11}H_{11}NO_3$. Calculated (%): C, 64.39; H, 5.37; N, 6.83. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 3)), two isomers **4** and **4′** (60 : 40), δ: **4**, 2.41 (s, 3 H, Me); 4.15 (br.s, 3 H, COOH + NH_2); 7.26 (d, 2 H, *p*-C_6H_4, J = 8.1 Hz); 7.39 (s, 1 H, =CH); 7.75 (d, 2 H, *p*-C_6H_4, J = 8.1 Hz); **4′**, 2.42 (s, 3 H, Me); 4.15 (br.s, 3 H, COOH + NH_2); 7.01 (s, 1 H, =CH); 7.29, 7.73 (both d, 2 H each, *p*-C_6H_4, J = 8.1 Hz).

The precipitate that did not dissolve in KOH was filtered off, washed with water, dried *in vacuo*, and refluxed in $CHCl_3$ for purification to give **methyl α-amino-β-(*p*-toluyl)acrylate (5a)** (0.89 g, 47%), m.p. 111—112 °C. Found (%): C, 64.43; H, 5.90; N, 6.32. $C_{12}H_{13}NO_3$. Calculated (%): C, 64.39; H, 5.93; N, 6.39. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 3)), two isomers **5a** and **5a′** (40 : 60), δ: **5a**, 2.40 (s, 3 H, Me); 3.10 (br.s, 2 H, NH_2); 3.96 (s, 3 H, OMe); 7.09 (s, 1 H, =CH); 7.29, 7.74 (both d, 2 H each, *p*-C_6H_4, J = 8.2 Hz); **5a′**, 2.40 (s, 3 H, Me); 3.10 (br.s, 2 H, NH_2); 3.97 (s, 3 H, OMe); 7.27 (d, 2 H, *p*-C_6H_4, J = 8.2 Hz); 7.53 (s, 1 H, =CH); 7.76 (d, 2 H, *p*-C_6H_4, J = 8.2 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 219 $[M]^+$ (132).

Reaction of methyl β-(*p*-toluyl)acrylate with $NH_2OH \cdot HCl$. Aqueous $NH_2OH \cdot HCl$ (8.34 g, 0.12 mol) was added to a saturated solution of methyl β-(*p*-toluyl)acrylate (2.04 g, 0.01 mol) in MeOH. The reaction mixture was refluxed in a water bath for 30 h and then treated with water. The precipitate was filtered off, washed with water, dried *in vacuo*, and recrystallized from MeOH to give ester **5a** (1.34 g, 61%), m.p. 111—112 °C. Its ^{1}H NMR spectrum agrees with the data given above.

Under analogous conditions but in the presence of an equimolar (with respect to $NH_2OH \cdot HCl$) amount of Et_3N, the yield of ester **5a** was 1.27 g (58%), m.p. 112—113 °C. Its ^{1}H NMR spectrum agrees with the data given above.

Reactions of β-aroylacrylic acids 1b—d (Ar = Ph, *p*-ClC_6H_4, and *p*-BrC_6H_4) with $NH_2OH \cdot HCl$ were carried out as described for acid **1a**. The water-insoluble precipitate was filtered off to give **methyl α-amino-β-aroylacrylates 5b—d (Ar = Ph, *p*-ClC_6H_4, and *p*-BrC_6H_4)**. Acidification of the alkaline solution gave **β-aroylacrylic acid oximes 2b—d (Ar = Ph, *p*-ClC_6H_4, and *p*-BrC_6H_4)** (Tables 1, 2).

β-(*p*-Toluyl)acrylic acid oxime (2a). Aqueous $NH_2OH \cdot HCl$ (8.34 g, 0.12 mol) was added to a saturated solution of β-(*p*-toluyl)acrylic acid (1.9 g, 0.01 mol) in MeCN. The

Table 1. Physicochemical parameters and elemental analysis data for compounds **2b—d** and **5b—d**

Compound	Ar	Yield (%)	M.p. /°C	Found / Calculated (%)					Molecular formula
				C	H	Cl	Br	N	
2b	Ph	71	199—200	62.64	4.89	—	—	7.45	$C_{10}H_9NO_3$
				62.83	4.71			7.33	
2c	*p*-ClC_6H_4	45	196—197	53.32	3.49	15.69	—	6.33	$C_{10}H_8ClNO_3$
				53.22	3.55	15.74		6.21	
2d	*p*-BrC_6H_4	56	208—209	44.51	2.88	—	29.62	5.27	$C_{10}H_8BrNO_3$
				44.44	2.96		29.69	5.18	
5b	Ph	19	32—33	64.48	5.41	—	—	6.76	$C_{11}H_{11}NO_3$
				64.39	5.36			6.83	
5c	*p*-ClC_6H_4	21	169—170	55.02	4.27	14.71	—	5.93	$C_{11}H_{10}ClNO_3$
				55.11	4.18	14.82		5.85	
5d	*p*-BrC_6H_4	15.5	132—133	46.31	3.64	—	28.16	4.92	$C_{11}H_{10}BrNO_3$
				46.48	3.58		28.29	4.82	

Table 2. ^{1}H NMR spectra (DMSO-d_6—CCl_4) of compounds **2b—d** and **5b—d**

Compound	δ (*J*/Hz)
2b	5.96 (d, 1 H, =CHCOOH, *J* = 16.4); 7.38—7.55 (m, 5 H, Ph); 7.84 (d, 1 H, =CHC(NOH), *J* = 16.4); 12.0 (br.s, 2 H, COOH + NOH)
2c	5.90 (d, 1 H, =CHCOOH, *J* = 16.4); 7.83 (d, 1 H, =CHC(NOH), *J* = 16.4); 7.30—7.60 (m, 4 H, *p*-C_6H_4); 11.95 (br.s, 2 H, COOH + NOH)
2d	5.96 (d, 1 H, =CHCOOH, *J* = 16.4); 7.84 (d, 1 H, =CHC(NOH), *J* = 16.4); 7.38 (d, 2 H, *p*-C_6H_4, *J* = 16.4); 7.55 (d, 2 H, *p*-C_6H_4, *J* = 8.5); 12.0 (br.s, 2 H, COOH + NOH)
5b	3.00 (br.s, 2 H, NH_2); 3.97 (s, 3 H, OMe); 7.31 (s, 1 H, =CH); 7.66—7.84 (m, 5 H, Ph)
5b´	3.00 (br.s, 2 H, NH_2); 3.98 (s, 3 H, OMe); 7.62 (s, 1 H, =CH); 7.69—7.86 (m, 5 H, Ph)
5c	3.00 (br.s, 2 H, NH_2); 3.97 (s, 3 H, OMe); 7.31 (s, 1 H, =CH); 7.66, 7.84 (both d, 2 H each, *p*-C_6H_4, *J* = 8.6)
5c´	3.00 (br.s, 2 H, NH_2); 3.98 (s, 3 H, OMe); 7.62 (s, 1 H, =CH); 7.69, 7.86 (both d, 2 H each, *p*-C_6H_4, *J* = 8.6)
5d	3.00 (br.s, 2 H, NH_2); 3.97 (s, 3 H, OMe); 7.31 (s, 1 H, =CH); 7.66, 7.84 (both d, 2 H each, *p*-C_6H_4, *J* = 8.6)
5d´	3.00 (br.s, 2 H, NH_2); 3.98 (s, 3 H, OMe); 7.62 (s, 1 H, =CH); 7.69, 7.86 (both d, 2 H each, *p*-C_6H_4, *J* = 8.6)

alkaline solution was acidified and treated as described above. The yield of oxime **2a** was 1.4 g (68%), m.p. 204 °C. Found (%): C, 64.47; H, 5.26; N, 6.95. $C_{11}H_{11}NO_3$. Calculated (%): C, 64.39; H, 5.37; N, 6.83. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 3)), δ: 2.35 (s, 1 H, Me); 5.98 (d, 1 H, =CHCOOH, *J* = 16.4 Hz); 7.11, 7.47 (both d, 2 H each, *p*-C_6H_4, *J* = 8.1 Hz); 7.90 (d, 1 H, =CHC(NOH), *J* = 16.4 Hz); 12.0 (br.s, 2 H, COOH + NOH).

Reaction of α-(imidazol-1-yl)-β-(*p*-toluyl)propionic acid (6) with $NH_2OH \cdot HCl$. Aqueous $NH_2OH \cdot HCl$ (2.65 g, 0.038 mol) was added to a saturated solution of acid **6** (0.82 g, 0.0032 mol) in MeOH. The reaction mixture was refluxed in a water bath for 30 h and then treated with water. The precipitate was filtered off, washed with water, and dried *in vacuo*. To remove impurities, the precipitate was recrystallized from EtOH. The yield of acid **4** was 0.45 g (68.6%).

Reaction of β-(*p*-toluyl)acrylic acid (1a) with 1,2,4-triazole. A mixture of acid **1a** (1.9 g, 0.01 mol) and 1,2,4-triazole (0.69 g, 0.01 mol) in aqueous KOH (0.56 g, 0.01 mol) was allowed to stand at room temperature for 3 days. The reaction mixture was acidified with dilute HCl and the precipitate that formed was filtered off, washed with water, and dried *in vacuo*. To remove impurities, the precipitate was refluxed in ether and dried *in vacuo* to give **β-(*p*-toluyl)-α-(1,2,4-triazol-1-yl)propionic acid (7)** (1.9 g, 73%), m.p. 203 °C. Found (%): C, 60.39; H, 5.10; N, 16.13. $C_{13}H_{13}N_3O_3$. Calculated (%): C, 60.23; H, 5.02; N, 16.22. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 3)), δ: 2.43 (s, 3 H, Me); 3.88 (m, 2 H, CH_2); 5.73 (t, 1 H, N=CH, *J* = 6.5 Hz); 7.27 (d, 2 H, 3.5 *p*-C_6H_4, *J* = 8.0 Hz); 7.73 (s, 1 H, N=CH); 7.87 (d, 2 H, 2.6 *p*-C_6H_4, *J* = 8.0 Hz); 8.47 (s, 1 H, N=CH); 12.7 (br.s, 1 H, COOH).

6-Tolyl-2,3-dihydropyridazin-3-one (8). A mixture of acid **7** (0.6 g, 0.0023 mol) and 60% $NH_2NH_2 \cdot H_2O$ (4 mL) was refluxed for 4 h. The precipitate that formed was filtered off, washed with EtOH, and dried *in vacuo* to give compound **8** (0.24 g, 50.5%). Its physicochemical constants were identical with our previous data.[15]

Reactions of adducts 9 and 10 with $NH_2NH_2 \cdot H_2O$. A mixture of compound **9** or **10** (0.005 mol) in EtOH and 60% $NH_2NH_2 \cdot H_2O$ (4 mL) was refluxed for 2 h. The precipitate that formed was filtered off, washed with EtOH, and dried *in vacuo* to give pyrazolinecarboxylic acid **11** in 45 and 48% yields, respectively. Its physicochemical constants were identical with our previous data.[15]

References

1. R. A. Raphael, *Nature*, 1947, **160**, 261.
2. A. N. Nesmeyanov, M. I. Rybinskaya, and A. N. Rybin, *Usp. Khim.*, 1967, **36**, 1089 [*Russ. Chem. Rev.*, 1967, **36** (Engl. Transl.)].
3. M. M. Frazer and R. A. Raphael, *J. Chem. Soc.*, 1950, 2245.
4. R. C. Moreau and P. Loiseau, *Compt. Rend. Acad. Sci.*, 1976, **283**, 589.
5. N. H. Cromwel, P. L. Greger, and K. E. Cook, *J. Am. Chem. Soc.*, 1956, **78**, 4412.
6. M. T. Bogert and J. J. Ritter, *J. Am. Chem. Soc.*, 1925, **47**, 526.
7. E. P. Kohler and H. Engelbrecht, *J. Am. Chem. Soc.*, 1919, **41**, 764.
8. J. Bougault, *Ann. Chim. Phys.*, 1908, **15**, 491.
9. G. V. Grigoryan and S. G. Agbalyan, *Khim. Geterotsikl. Soedin.*, 1979, 348 [*Chem. Heterocycl. Compd.*, 1979 (Engl. Transl.)].
10. R. Dj. Khachikyan, S. Yu. Kotikyan, and S. G. Agbalyan, *Khim. Zh. Armen.* [*Armenian Chem. J.*], 1999, **52**, 90.
11. N. P. Churkina, N. P. Gambaryan, D. A. Bochvar, and S. G. Agbalyan, *Khim. Zh. Armen.* [*Armenian Chem. J.*], 1977, **30**, 370.
12. R. Dj. Khachikyan, G. V. Grigoryan, and S. G. Agbalyan, *Khim. Zh. Armen.* [*Armenian Chem. J.*], 1986, **39**, 452.
13. R. Dj. Khachikyan, G. V. Grigoryan, and S. G. Agbalyan, *Khim. Zh. Armen.* [*Armenian Chem. J.*], 1986, **39**, 373.
14. E. A. Soliman, *Rev. Roum. Chem.*, 1978, **23**, 1597.
15. R. A. Khachatryan, R. Dj. Khachikyan, N. V. Karamyan, H. A. Panosyan, and M. H. Injikyan, *Khim. Geterotsikl. Soedin.*, 2004, 541 [*Chem. Heterocycl. Compd.*, 2004 (Engl. Transl.)].
16. J. Lehmann and A. Gossen, *Arch. Pharm.*, 1988, **321**, 443.

Received March 12, 2004;
in revised form June 15, 2005