New aspects of the aldol condensation of acetylpyridines with aromatic aldehydes

S. Z. Vatsadze, V. N. Nuriev, I. F. Leshcheva, and N. V. Zyk*

Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax: +7 (095) 939 0290. E-mail: nvn@org.chem.msu.ru

Aldol condensation of acetylpyridines with aromatic aldehydes was studied. A series of new products of cascade reactions were isolated and characterized.

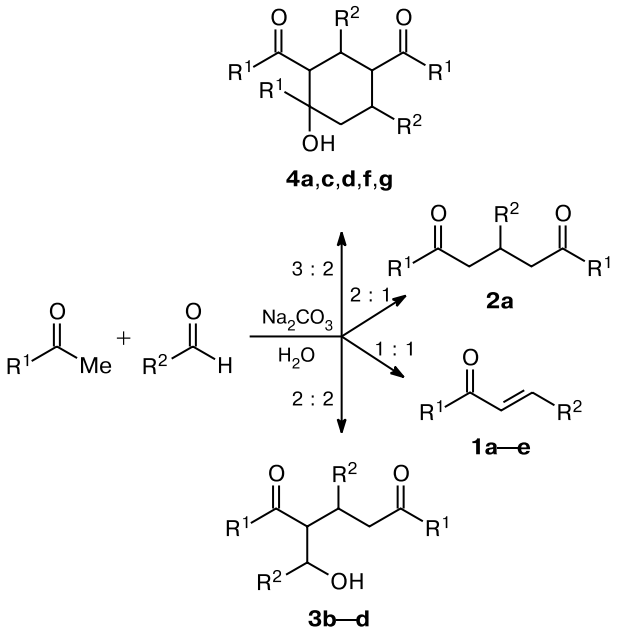
Key words: aldol condensation, pyridinecarbaldehydes, acetylpyridines, diastereospecificity, chalcones, organic ligands.

1,3-Diarylpropenones, or chalcones, are key intermediates in organic synthesis and are widely used in heterocyclization reactions.[1,2] With the aim of preparing new heterocyclic compounds containing one or several pyridine fragments, which are promising ligands for supramolecular chemistry and crystal engineering,[3,4] we developed procedures for the synthesis of 1,3-dipyridylpropenones. The main approach to the synthesis of α,β-unsaturated ketones was based on aldol condensation.[5,6] It is known[7—10] that the reactions of acetylpyridines with pyridinecarbaldehydes as well as with analogous compounds often afford by-products of the aldol synthesis, because the chalcone analog that formed can be involved in the Michael reaction. In addition to the nature of substrates, the reaction pathway and the character of the reaction products depend substantially on the polarity of the solvent, the base strength, the reaction temperature, and the order of addition of the reagents.[9]

Study of condensation of 3-acetylpyridine with nicotinaldehyde demonstrated that an increase in the base strength (the use of K_2CO_3 instead of Na_2CO_3) and a decrease in the polarity of the medium (the use of 60% aqueous EtOH instead of water) lead to a decrease in the ratio of enone **1a** to diketone **2a** (Scheme 1, Table 1).

When reproducing known procedures for the synthesis of 1,3-bis(4-pyridyl)propenone (**1b**) or isomeric enones **1c**,**d**,[5,6,8,9,11—14] we found that the reaction gave hydroxy diketone **3b** as the major product under virtually all conditions. Propenone **1b** was prepared by the Wittig reaction of 4-pyridinecarbaldehyde with (4-pyridyl)carbonylmethylidenetriphenylphosphorane (**5**).[15] The formation of **1b** was detected by TLC based on comparison with isomeric compound **1a**. Product **1b** was also identified in the mixture with the starting compounds (Scheme 2) by ^{1}H NMR spectroscopy. The assignment of the signals in the spectrum was made based on the data for analogs.[14,16,17]

Scheme 1



	R^1	R^2		R^1	R^2
a	3-Py	3-Py	**e**	Ph	4-Py
b	4-Py	4-Py	**f**	4-Py	Ph
c	3-Py	4-Py	**g**	4-Py	2-Thienyl
d	4-Py	3-Py			

The structure of diketone **3b** was established by IR and ^{1}H NMR spectroscopy (the assignment of the signals was made by the ^{1}H—^{1}H double resonance method), mass spectrometry, and elemental analysis (Tables 2 and 3). For isomers **1c**,**d**, it was also demonstrated that enones were prepared as minor reaction products, whereas diketones **3c**,**d** were isolated in higher yields. In addition, the reactions afforded isomeric products **4c**,**d**. According to the mass-spectrometric data, these possess the same

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 874—878, April, 2004.

1066-5285/04/5304-0911

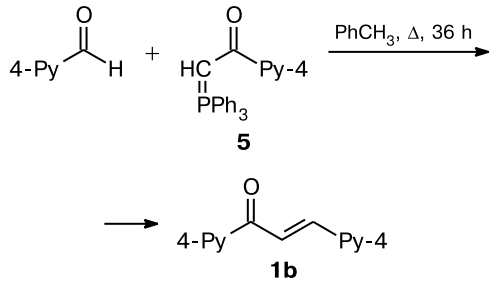
Table 1. Yields of aldol condensation products (water, Na_2CO_3)[a]

Major (side) product	R^1	R^2	Yield[b] (%) of major (side) product
1a (**2a**)	3-Py	3-Py	68 (<10)
1b	4-Py	4-Py	<10 [c]
1e	Ph	4-Py	81
2a (**1a**)[d]	3-Py	3-Py	43 (21)
3b	4-Py	4-Py	95
3c (**1c**, **4c**)	3-Py	4-Py	55 (<5,[e] 28)
4a[f]	3-Py	3-Py	62
4d (**1d**, **3d**)	4-Py	3-Py	46 (<5,[e] 12)
4f	4-Py	Ph	78
4g	4-Py	2-Thienyl	74

[a] Except for **1b**, which was synthesized by the Wittig reaction.
[b] The yields are given for individual compounds prepared under optimum conditions, unless otherwise indicated.
[c] According to the ^{1}H NMR spectroscopic data.
[d] EtOH—H_2O, K_2CO_3.
[e] The product was identified by TLC based on comparison with **1a**.
[f] KOH.

scheme of molecular ion fragmentation. The cyclic structure of the saturated core of compound **4c** and its analogs **4d**—**f** has a substantial effect on the chemical shifts of the geminal protons H(5) and H(6) ($\delta \approx 2$ and 3.2, respectively; $J_{gem} \approx 12$—13 Hz; Table 4). This difference is apparently associated with the influence of the O atom of the hydroxy group and the rigid geometry of the structure. The model with the given arrangement of the substituents is also evidenced by the presence of the W spin coupling

Scheme 2

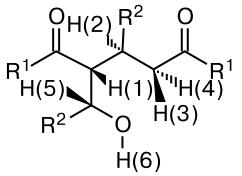


constant (~2.4 Hz) between the hydroxy H(7) proton and the H(5) proton.[18,19] It should be emphasized that all reaction products belong to the same type of diastereomers, *i.e.*, the reaction proceeds diastereospecifically. Analysis of the reaction mixtures by ^{1}H NMR spectroscopy demonstrated that before isolation the percentage of the minor diastereomer is no higher than 5% with respect to the major diastereomer. Since the ratio between the reaction products **3c** and **4c** differs substantially from the **3d** : **4d** ratio, we studied the influence of the nature of the aryl substituent in the carbonyl and methylene components on the character of the compounds formed. In the case of the less reactive methylene component of acetophenone and pyridine-4-carbaldehyde, the reactions afforded enone **1e** as the only product, whereas the reactions of 4-acetylpyridine with benzaldehyde and thiophene-2-carbaldehyde gave rise to **4f**,**g**, which are structural analogs of compound **4c**, as the major products. The results of our study led to the conclusion that the methylene component makes the major contribution to the side

Table 2. Physicochemical characteristics and results of elemental analysis for the compounds synthesized

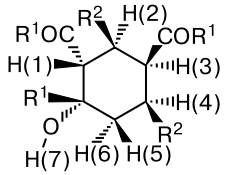
Compound	M.p./°C	Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}	MS, m/z (I_{rel} (%))
		C	H	N			
1e	71 (72 [8])	—	—	—	—	—	—
3b	158	70.85 / 71.22	5.34 / 5.06	11.78 / 12.78	$C_{26}H_{22}N_4O_3$	3400, 1690	438 $[M]^{+\bullet}$ (2), 106 $[PyCO]^{+\bullet}$ (100)
3c	151 (decomp.)	70.90 / 71.22	5.52 / 5.06	12.22 / 12.78	$C_{26}H_{22}N_4O_3$	3380, 1690	438 $[M]^{+\bullet}$ (6), 106 $[PyCO]^{+\bullet}$ (100)
3d	153 (decomp.)	70.66 / 71.22	5.12 / 5.06	11.84 / 12.78	$C_{26}H_{22}N_4O_3$	3350, 1680	438 $[M]^{+\bullet}$ (5), 106 $[PyCO]^{+\bullet}$ (100)
4a	186	72.60 / 73.18	5.45 / 5.02	13.12 / 12.93	$C_{33}H_{27}N_5O_3$	3400, 1705	541 $[M]^{+\bullet}$ (7), 106 $[PyCO]^{+\bullet}$ (100)
4c	179	72.82 / 73.18	4.81 / 5.02	12.42 / 12.93	$C_{33}H_{27}N_5O_3$	3350, 1700	541 $[M]^{+\bullet}$ (7), 106 $[PyCO]^{+\bullet}$ (100)
4d	184	72.68 / 73.18	4.90 / 5.02	12.58 / 12.93	$C_{33}H_{27}N_5O_3$	3320, 1700	541 $[M]^{+\bullet}$ (7), 106 $[PyCO]^{+\bullet}$ (100)
4f	167	78.20 / 77.90	5.66 / 5.42	8.12 / 7.79	$C_{35}H_{29}N_3O_3$	3400, 1680	539 $[M]^{+\bullet}$ (7), 208 $[PyCOCH{=}CHPy]^{+\bullet}$ (100)
4g	189	66.98 / 67.49	5.22 / 4.57	8.24 / 7.62	$C_{31}H_{25}N_3O_3S_2$	3390, 1695	551 $[M]^{+\bullet}$ (7), 137 $[COCH{=}CHTh]^{+\bullet}$ (100)

Table 3. ^{1}H NMR spectra ($CDCl_3$) of 2-hetaryl(hydroxy)methyl-1,3,5-trihetarylpentane-1,5-diones **3b—d**



Compound	δ (*J*/Hz)						
	H(1) (t)	H(2) (td)	H(3) (dd)	H(4) (dd)	H(5) (d)	H(6) (s)	H (arom.)
3b	3.75 ($J_{1,5}$ = $J_{1,2}$ = 10.0)	4.08 ($J_{2,3}$ = $J_{2,1}$ = 10.0, $J_{2,4}$ = 3.9)	1.95 ($J_{3,4}$ = 13.7, $J_{3,2}$ = 10.0)	2.18 ($J_{4,3}$ = 13.7, $J_{4,2}$ = 3.9)	5.58 ($J_{5,1}$ = 10.0)	6.99	8.56—6.95 (16 H)
3c	3.80 ($J_{1,5}$ = $J_{1,2}$ = 10.3)	4.02 ($J_{2,3}$ = $J_{2,1}$ = 10.3, $J_{2,4}$ = 3.8)	2.05 ($J_{3,4}$ = 13.6, $J_{3,2}$ = 10.3)	2.15 ($J_{4,3}$ = 13.6, $J_{4,2}$ = 3.8)	5.61 ($J_{5,1}$ = 10.3)	6.95	8.90—7.08 (16 H)
3d	3.73 ($J_{1,5}$ = $J_{1,2}$ = 11.0)	4.04 ($J_{2,3}$ = $J_{2,1}$ = 11.0, $J_{2,4}$ = 3.7)	1.88 ($J_{3,4}$ = 13.3, $J_{3,2}$ = 11.0)	2.24 ($J_{4,3}$ = 13.3, $J_{4,2}$ = 3.7)	5.65 ($J_{5,1}$ = 11.0)	7.05	8.82—7.00 (16 H)

Table 4. ^{1}H NMR spectra (DMSO-d_6) of 2,4-dihetaroyl-1,3,5-trihetaryl-substituted cyclohexanols **4a**,**c**,**d**,**f**,**g**



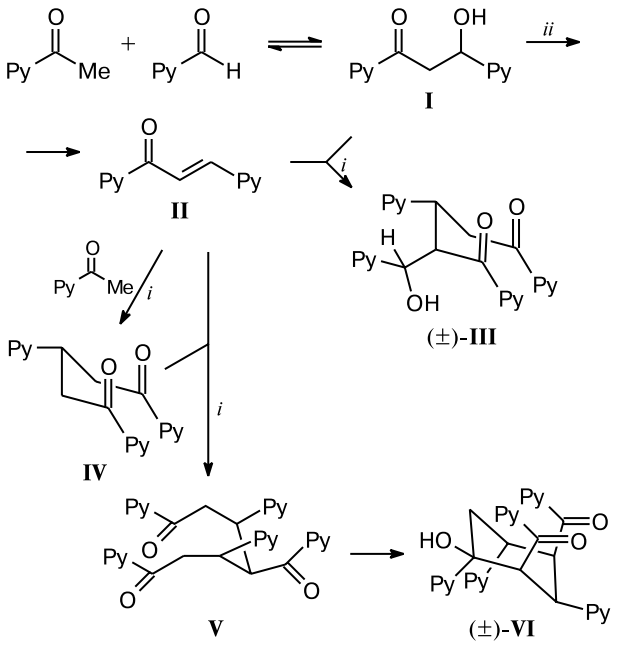
Compound	δ (*J*/Hz)							
	H(1) (d)	H(2)	H(3) (t)	H(4)	H(5)	H(6)	H(7)* (d)	H (arom.)
4a	5.10 ($J_{1,2}$ = 11.9)	4.45 (dd, $J_{2,1}$ = 11.9, $J_{2,3}$ = 4.8)	4.82 ($J_{3,4}$ = $J_{3,2}$ = 4.8)	4.18 (ddd, $J_{4,3}$ = 4.8, $J_{4,5}$ = 12.2, $J_{4,6}$ = 3.6)	3.42 (td, $J_{5,6}$ = $J_{5,4}$ = 12.2, $J_{5,7}$ = 2.4)	1.82 (dd, $J_{6,5}$ = 12.2, $J_{6,4}$ = 3.6)	5.40 ($J_{7,5}$ = 2.4)	9.02—6.99 (20 H)
4c	5.08 ($J_{1,2}$ = 12.6)	4.52 (dd, $J_{2,1}$ = 12.6, $J_{2,3}$ = 4.5)	4.89 ($J_{3,4}$ = $J_{3,2}$ = 4.5)	4.18 (ddd, $J_{4,3}$ = 4.5, $J_{4,5}$ = 12.5, $J_{4,6}$ = 3.4)	3.32 (t, $J_{5,6}$ = $J_{5,4}$ = 12.5, $J_{5,7}$ = 2.3)	1.85 (ddd, $J_{6,5}$ = 12.5, $J_{6,4}$ = 3.4)	5.12 ($J_{7,5}$ = 2.3)	9.06—7.12 (20 H)
4d	5.18 ($J_{1,2}$ = 12.0)	4.45 (dd, $J_{2,1}$ = 12.0, $J_{2,3}$ = 4.6)	4.82 ($J_{3,4}$ = $J_{3,2}$ = 4.6)	4.18 (ddd, $J_{4,3}$ = 4.6, $J_{4,5}$ = 12.5, $J_{4,6}$ = 3.4)	3.42 (t, $J_{5,6}$ = $J_{5,4}$ = 12.5, $J_{5,7}$ = 2.4)	1.82 (dd, $J_{6,5}$ = 12.5, $J_{6,4}$ = 3.4)	5.40 ($J_{7,5}$ = 2.4)	8.72—6.95 (20 H)
4f	5.51 ($J_{1,2}$ = 12.9)	4.15—4.11 (m)	4.30 ($J_{3,4}$ = $J_{3,2}$ = 4.5)	4.15—4.11 (m)	3.20 (t, $J_{5,6}$ = $J_{5,4}$ = 13.0, $J_{5,7}$ = 2.3)	2.09 (dd, $J_{6,5}$ = 13.0, $J_{6,4}$ = 3.4)	5.00 ($J_{7,5}$ = 2.3)	8.60—6.80 (22 H)
4g	5.52 ($J_{1,2}$ = 12.8)	4.42 (dd, $J_{2,1}$ = 12.8, $J_{2,3}$ = 4.2)	4.48 ($J_{3,4}$ = $J_{3,2}$ = 4.2)	4.35 (ddd, $J_{4,3}$ = 4.2, $J_{4,5}$ = 12.5, $J_{4,6}$ = 3.5)	3.00 (t, $J_{5,6}$ = $J_{5,4}$ = 12.5, $J_{5,7}$ = 2.2)	2.14 (dd, $J_{6,5}$ = 12.5, $J_{6,4}$ = 3.5)	4.98 ($J_{7,5}$ = 2.2)	8.55—6.40 (18 H)

* The chemical shift δ changes upon the addition of D_2O.

reactions giving rise to acyclic and cyclic products of types **2**—**4**. This component enhances the reactivity of ketone and its intermediates as donors and also indirectly influences the activity of the resulting chalcone analog as an acceptor in the Michael reaction.

Based on the above results, we proposed a scheme of formation of the products of the cascade synthesis (Scheme 3).

Scheme 3

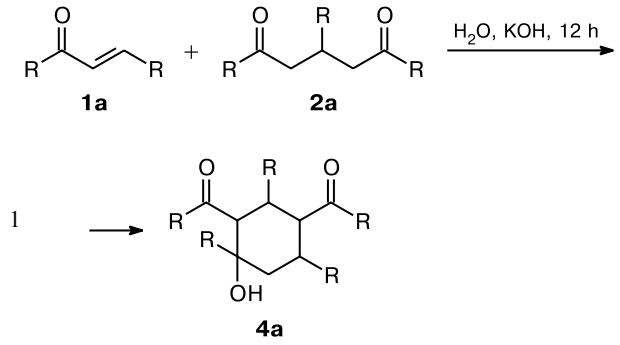


i. Michael addition; *ii*. Elimination.

The first step of the reaction involves the reversible formation of aldol **I** followed by its transformation into the *E* isomer of enone **II**. In the case of high reactivity of chalcone as the acceptor as well as high reactivity of aldol and aryl methyl ketone as donors, the Michael reaction affords *nonsym*-hydroxymethyl-1,5-diketone **III** or *sym*-1,5-diketone **IV**. Substrate **IV** also contains the active methylene component and is involved in the Michael addition with chalcone to give intermediate **V**. *sym*-1,5,7-Triketone **V** is very labile. It is known[18—20] that such compounds readily undergo the Baylis—Hillman transformation accompanied by intramolecular aldol condensation to form cyclic product **VI**. The chemical nature of the methylene and carbonyl components influences primarily the rate of formation and reactivity of intermediates. It should be noted that product **III** is formed only if both reagents are rather reactive and it is not involved in the competitive Michael addition only due to very poor solubility.

To confirm the above facts, we carried out the independent synthesis of compound **4a** (Scheme 4). The latter was not generated in the reaction of the corresponding aldehyde with ketone, but it was synthesized in good yield by the reaction of enone **1a** with *sym*-1,5-diketone **2a**. The compounds synthesized hold promise as synthetic intermediates as well as for purposes of coordination chemistry.

Scheme 4



R = 3-Py

Experimental

The ^{1}H NMR spectra were recorded at 30 °C on a Varian VXR-400 instrument operating at 400 MHz with the use of $CDCl_3$ and DMSO-d_6 as the solvents. The ^{1}H—^{1}H spin coupling constants are given. The IR spectra were measured on a UR-20 spectrometer in Nujol mulls. The mass spectra were obtained on an HP-5890 mass spectrometer with direct inlet of the sample; the temperature of the ion source was 150 °C; the energy of ionizing electrons was 70 eV; the accelerating voltage was 3 kV; the range of 1 was 40—550 amu. The melting points were determined on an ElectroThermal-9100 instrument in open capillary tubes; the uncorrected melting points are given. Acetylpyridines, pyridinecarbaldehydes, and thiophene-2-carbaldehyde (Acros) were used without additional purification. The course of the reactions and the purity of the reaction products were monitored by TLC on a fixed layer of silica gel (Silufol plates). Preparative separation of the reaction mixtures was carried out by column chromatography on Acros silica gel (SiO_2 35—60 μm).

(2*E*)-1,3-Bis(4-pyridyl)propenone (1b). A suspension of (4-pyridyl)carbonylmethylidenetriphenylphosphorane (**5**) (2 g, 5.2 mmol) and pyridine-4-carbaldehyde (0.6 g, 5.5 mmol) in toluene (50 mL) was heated under argon. The reaction mixture was allowed to cool and then concentrated. The residue was extracted with CH_2Cl_2 (3×20 mL). The extract was washed with water (2×5 mL), CH_2Cl_2 was removed, and the residue was washed on a filter with small portions of Et_2O. The mixture was analyzed without additional purification. ^{1}H NMR ($CDCl_3$), δ: 9.05 (d, H(2), H(6), PyC(O), ^3J = 6.8 Hz); 8.75 (d, H(2), H(6), PyCH=CH, ^3J = 6.8 Hz); 7.96 (d, PyCH=C<u>H</u>C(O)Py, ^3J = 15.3 Hz); 7.72 (d, H(3), H(5), PyC(O), ^3J = 6.8 Hz); 7.55 (d, PyC<u>H</u>=CH, ^3J = 15.3 Hz); 7.32 (d, H(3), H(5), PyCH=CH, ^3J = 6.8 Hz).

Condensation of aromatic aldehydes with acetylpyridines (general procedure). An aqueous solution of a base (a 10% Na_2CO_3

solution; in the case of compound **4a**, a 1 *M* KOH solution) was added to a solution of an aldehyde (50 mmol) and a ketone (50 mmol) in water (100 mL). The mixture was stirred at ~20 °C for 4—12 h. Insoluble reaction products were filtered off and washed with water. The precipitates were dried *in vacuo* using a water-aspirator pump. Compounds **1a**,**e**, **3b**, and **4c**,**d**,**f**,**g** were isolated. The mother liquor was extracted with CH_2Cl_2 (3×50 mL), the solvent was evaporated, and the residue was subjected to chromatographic separation on a column with SiO_2 using a 90 : 10 $CHCl_3$—MeOH mixture as the eluent to prepare compounds **2a**, **3c**,**d**, and **4a**. The melting points and data from IR and ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis of compounds **3b—d** and **4a**,**c**,**d**,**f** are given in Tables 2—4.

(2*E*)-1,3-Bis(3-pyridyl)propenone (1a) was synthesized according to the general procedure in 68% yield, m.p. 128 °C (from ethyl acetate) (*cf.* lit. data[11]: m.p. 130 °C). ^{1}H NMR ($CDCl_3$), δ: 9.23 (d, 1 H, C(O)Py<u>H</u>(2), ^4J = 1.8 Hz); 8.86 (d, 1 H, <u>H</u>(2)PyCH=CH, ^4J = 1.8 Hz); 8.82 (dd, 1 H, <u>H</u>(6)PyC(O), ^3J = 4.9 Hz, ^4J = 1.8 Hz); 8.65 (dd, 1 H, <u>H</u>(6)PyCH=CH, ^4J = 4.9 Hz, ^4J = 1.8 Hz); 8.30 (dt, 1 H, <u>H</u>(4)PyC(O), ^3J = 8.0 Hz, ^4J = 1.8 Hz); 7.96 (dt, 1 H, <u>H</u>(4)PyCH=CH, ^3J = 8.0 Hz, ^4J = 1.8 Hz); 7.82 (d, 1 H, PyCH=C<u>H</u>C(O)Py, ^3J = 15.5 Hz); 7.55 (d, 1 H, PyC<u>H</u>=CHC(O)Py, ^3J = 15.5 Hz); 7.47 (dd, 1 H, <u>H</u>(5)PyC(O), ^3J = 8.0 Hz, ^3J = 4.9 Hz); 7.38 (dd, 1 H, <u>H</u>(5)PyCH=CH, ^3J = 8.0 Hz, ^3J = 4.9 Hz). **1,3,5-Tris(3-pyridyl)pentane-1,5-dione (2a)** was obtained from the mother liquor in 10% yield, m.p. 134 °C (from EtOH) (*cf.* lit. data[11]: m.p. 168 °C). Compounds **1a** and **2a** were isolated using a procedure published earlier[7] (in the presence of potassium carbonate; in a 40 : 60 aqueous-ethanolic solution) in 21 and 43% yields, respectively.

This study was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-32401).

References

1. S. M. Desenko and V. D. Orlov, *Azageterotsikly na osnove aromaticheskikh nepredel´nykh ketonov* [*Azaheterocycles Based on Aromatic Unsaturated Ketones*], Folio, Kharkov, 1998, 148 pp. (in Russian).
2. L. Aeppli, K. Bernauer, F. Schneider, and K. Strub, *Helv. Chim. Acta*, 1980, **63**, 630.
3. S. Z. Vatsadze, V. N. Nuriev, A. V. Chernikov, and N. V. Zyk, *Izv. Akad. Nauk, Ser. Khim.*, 2002, **51**, 1804 [*Russ. Chim. Bull., Int. Ed.*, 2002, **51**, 1957].
4. M. H. Kingele and S. Brooker, *Coord. Chem. Rev.*, 2003, **241**, 119.
5. J. Thesing and A. Muller, *Chem. Ber*, 1957, **90**, 711.
6. A. P. Terent´ev, R. A. Gracheva, N. N. Preobrazhenskaya, and L. M. Volkova, *Zh. Obshch. Khim.*, 1962, **33**, 4006 [*J. Gen. Chem. USSR*, 1962, **33** (Engl. Transl.)].
7. S. V. Tsukerman, Ch. K. Shon, and V. F. Lavrushin, *Zh. Obshch. Khim.*, 1963, **34**, 832 [*J. Gen. Chem. USSR*, 1963, **34** (Engl. Transl.)].
8. C. S. Marvel, L. E. Coleman, and G. P. Scott, *J. Org. Chem.*, 1955, **20**, 1785.
9. N. Wachter-Jursak, C. Radu, and K. Redin, *Tetrahedron Lett.*, 1998, **39**, 3903.
10. U. Kube and U. Holzgrabe, *Monatsh. Chem.*, 2001, **132**, 407.
11. H. S. Prakash-Rao, B. Bharathi, and K. Jeyalakshmi, *Ind. J. Chem., Sect. B*, 1997, **36B**, 557.
12. E. Krasnec, J. Durinda, and L. Szucs, *Chem. Zvesti*, 1961, 558.
13. J. Durinda, J. Kolena, L. Szucs, and J. Heger, *Cesk. Pharm.*, 1967, **16**, 14.
14. Jpn Pat. 80,65,295; *Chem. Abstrs*, 1980, **93**, 248281b.
15. B. Portevin, C. Tordjman, P. Pastoureau, J. Bonnet, and G. Nanteuil, *J. Med. Chem.*, 2000, **43**, 4582.
16. T. Liptaj, V. Mlynaric, M. Remko, J. Durinda, and J. Heger, *Collect. Czech. Chem. Commun.*, 1961, **46**, 1486.
17. B. Z. Jovanovic, M. Music-Vukovic, A. D. Markinovic, and J. Csanadi, *J. Mol. Struct.*, 1999, **482—483**, 371.
18. F. Dinon, E. Richards, and J. Murphy, *Tetrahedron Lett.*, 1999, **40**, 3279.
19. M. M. Al-Arab and B. S. Ghanem, *Tetrahedron*, 1989, **45**, 6545.
20. M. M. Al-Arab, B. S. Ghanem, and M. M. Olmstead, *Synthesis*, 1992, 1003.

Received September 19, 2003;
in revised form April 7, 2004