Synthesis of 6-acylpyrido[2,3-*d*]pyrimidine derivatives from 5-acetyl-4-aminopyrimidine hydrochlorides

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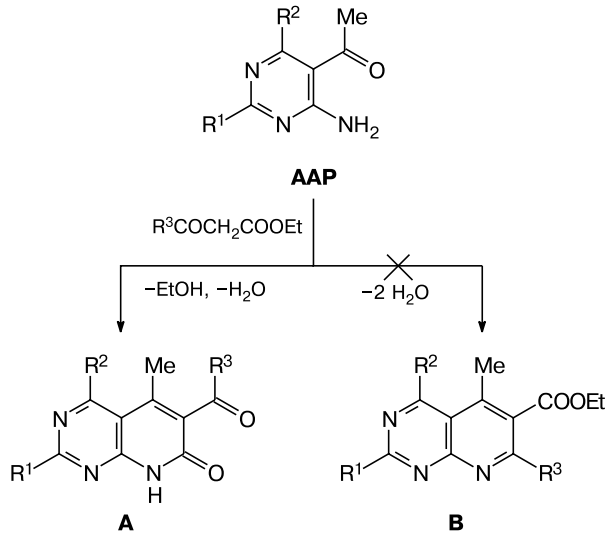
Reaction of 2,6-disubstituted 5-acetyl-4-aminopyrimidine hydrochlorides with acetylacetone or benzoylacetone afforded new substituted 6-acylpyrido[2,3-*d*]pyrimidines. The reaction of these hydrochlorides with ethyl acetoacetate also proceeds according to the classical version of the Friedländer condensation to form the corresponding pyrido[2,3-*d*]pyrimidine-6-carboxylic acid esters.

Key words: 2,6-disubstituted 5-acetyl-4-aminopyrimidine hydrochlorides, acetylacetone, benzoylacetone, ethyl acetoacetate, the Friedländer reaction, 6-acylpyrido[2,3-*d*]pyrimidines, ethyl pyrido[2,3-*d*]pyrimidine-6-carboxylates.

Earlier, in a series of papers,[1—5] we proposed various pathways for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives from 2,6-disubstituted 5-acetyl-4-aminopyrimidines (AAP), easily obtained from acetylacetone or benzoylacetone and *N*-cyanoamidines in the presence of Ni acetate.[1,3,6] In particular,[4] it was found that the heating (180—190 °C) of AAP with excess acetoacetic or benzoylacetic ester in the absence of a catalyst leads to the corresponding 6-acylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (structure **A**), *i.e.*, the heterocyclization proceeds with elimination of EtOH from β-ketoester, rather than follows the classical version of the Friedländer condensation, which should lead to pyrido[2,3-*d*]pyrimidine-6-carboxylic acid esters (structure **B**).

Scheme 1



6-Acylpyrido[2,3-*d*]pyrimidines, obviously, can be transformed to the corresponding azomethines, oximes, and hydrazones, as well as they can be used in other schemes for the modification of pyrido[2,3-*d*]pyrimidine derivatives. In continuation of the preceding research, it was logically to try β-diketones in the reactions with AAP to obtain 6-acylpyrido[2,3-*d*]pyrimidines. However, the reflux of AAP with acetylacetone in the absence of catalysts leaves the starting compounds unchanged. It is pertinent to mention the data in Ref. 7 which reported unsuccessful efforts to obtain the condensation products of acetylacetone with 4-amino-2-methoxy-5-formylpyrimidine both in the presence of bases and under acid-catalyzed conditions. It should be also taken into account that the use of bases as the catalysts in the transformations of compounds of the AAP type is not advisable, since the latter can undergo the Friedländer self-condensation under such conditions.[3]

For the problem formulated to be solved, a version of the Friedländer reaction (the Kempter modification, for a review see Ref. 8), based on the use of AAP in form of hydrochloride, turned out to be suitable. In fact, the solvent-free heating of hydrochlorides **1a,b** with excess acetylacetone or benzoylacetone to 140—150 °C afforded the corresponding 6-acylpyrido[2,3-*d*]pyrimidines **2a,b** (Scheme 2). It is noteworthy that, in case of unsymmetrical diketone, benzoylacetone, the condensation proceeds selectively with participation of the acetyl fragment to form 6-benzoylpyridopyrimidine **2c** only.

Usually (see, for example, Ref. 9). the Friedländer condensation is considered as the two-step process,

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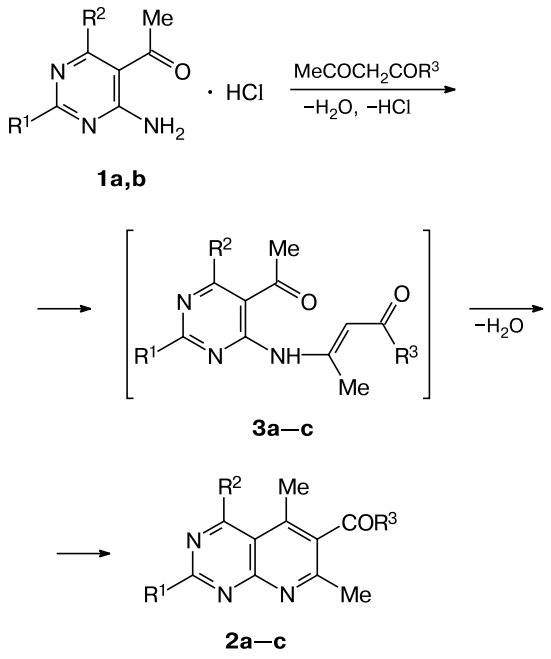
Scheme 2



Compound	R^1	R^2	Compound	R^3
1a, 2a	Ph	Me	**2a**	Me
1b, 2b	4-ClC_6H_4	Me	**2b**	Me
2c	Ph	Me	**2c**	Ph

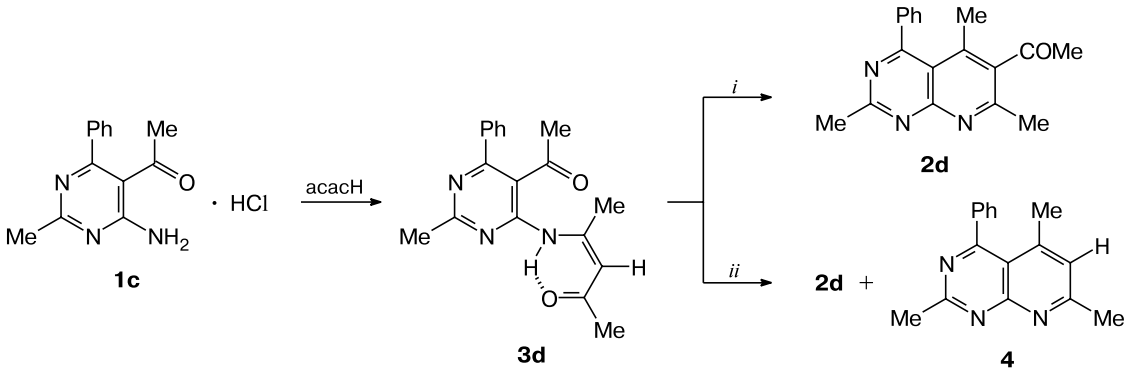
including formation of enamines of the type **3** (see Scheme 2) and their cyclization. It is interesting that hydrochloride **1c** upon reflux in excess acetylacetone gives the enamine **3d** (Scheme 3), whereas the corresponding pyrido[2,3-*d*]pyrimidine is not formed under these conditions. Apparently, the electrophilicity of the carbonyl group of the acetyl fragment in this case is weakened by the influence of the phenyl group in the adjacent position of the pyrimidine ring, that is why no pyridine ring closure takes place. Nevertheless, enamine **3d** can be converted to 6-acetylpyrido[2,3-*d*]pyrimidine **2d** upon reflux in benzene in the presence of catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

If enamine **3d** is treated with MeONa in MeOH even under mild conditions (~20 °C), the cyclization to a considerable extent is accompanied by deacetylation to form pyrido[2,3-*d*]pyrimidine **4** (according to the NMR spectra, compounds **2d** and **4** were obtained in the ratio ~1 : 6).

However, it should be noted that enamines **3a—c** are presented as the small admixtures in the reaction mixtures, obtained by the reaction of diketones with salts **1a,b**. The main products, pyrido[2,3-*d*]pyrimidines **2a—c**, can be easily enough purified from these admixtures by column chromatography, the intermediate enamine **3a** being successfully isolated in pure form in 8% yield when compound **2a** has been synthesized.

The synthesized crystalline compounds **2a—d**, **3d**, and **4** are readily soluble in organic solvents, excluding light petroleum. Their structures were confirmed by spectroscopy methods. In the mass spectra of pyrido[2,3-*d*]pyrimidines **2a—d** and **4**, intensive peaks of the molecular ions are observed (Table 1). The ^1H NMR spectra of compounds **2a—b**,**d** in $CDCl_3$, containing acetyl group, are characterized by the presence of singlets in the region 2.53—2.62 ppm, the spectrum of heterocycle **2c** contains sets of signals from the two phenyl groups (COPh and 2-Ph), while in the spectrum of compound **4**, a characteristic singlet at 7.12 ppm (H(6)) is observed (Table 2). An absorption of the carbonyl group of the acetyl fragment with ν 1708 cm^{-1} (compounds **2a,b,d**) or the benzoyl fragment with ν 1672 cm^{-1} (compound **2c**) is characteristic of the IR spectra of the pyridopyrimidines in $CHCl_3$ (see Table 2). In contrast to pyridopyrimidines **2**, a very weak peak of the molecular ion is observed in the mass spectrum of enamine **3d**, while the ion $[M - COMe]^+$ is the most intensive. In ^1H NMR spectrum of this compound in $CDCl_3$, characteristic singlets are presented at 5.4 ppm (CH=) and 12.9 ppm (NH), while the IR spectra in $CHCl_3$ show the presence of two carbonyl groups (absorption bands with ν 1684 and

Scheme 3



i. DBU, C_6H_6, Δ. *ii*. MeONa, MeOH, 20 °C.

Table 1. Yield, melting points, elemental analysis data, and mass spectra of compounds **2a—d**, **4**, and **5a,b**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	MS, m/z (I_{rel} (%))
2a	55	210—211	73.97 74.20	6.15 5.88	14.13 14.42	$C_{18}H_{17}N_3O$	291 $[M]^+$ (49), 276 $[M - Me]^+$(100), 207 [M – MeCN – COMe]$^+$ (77), 166 [M – 2 MeCN – COMe]$^+$ (34)
2b*	37	164—165	66.54 66.36	5.18 4.95	12.74 12.90	$C_{18}H_{16}ClN_3O$	325 $[M]^+$ (63), 310 $[M - Me]^+$ (100), 241 [M – MeCN – COMe]$^+$ (93), 200 [M – 2 MeCN – COMe]$^+$ (43)
2c	22	200—201	77.87 78.16	5.36 5.42	11.54 11.89	$C_{23}H_{19}N_3O$	353 $[M]^+$ (100), 352 $[M - H]^+$ (83), 337 $[M - H - Me]^+$ (27), 311 [M – H – MeCN]$^+$ (19), 276 $[M - Ph]^+$ (19), 207 [M – MeCN – COPh]$^+$ (18), 166 [M – 2 MeCN – COPh]$^+$ (16), 105 $[COPh]^+$ (34)
2d	53	128—129	73.85 74.20	6.18 5.88	13.92 14.42	$C_{18}H_{17}N_3O$	291 $[M]^+$ (100), 276 $[M - Me]^+$ (94), 248 [M – COMe]$^+$ (60), 207 [M – MeCN – COMe]$^+$ (26), 166 [M – 2 MeCN – COMe]$^+$ (33)
4	48	147—148	76.73 77.08	5.92 6.06	16.85 16.86	$C_{16}H_{15}N_3$	249 $[M]^+$ (44), 248 $[M - H]^+$ (100), 234 $[M - Me]^+$ (10), 233 $[M - H - Me]^+$(15)
5a	33	144—145	70.93 71.01	6.21 5.96	12.78 13.08	$C_{19}H_{19}N_3O_2$	321 $[M]^+$ (100), 306 $[M - Me]^+$ (39), 276 [M – OEt]$^+$ (37)
5b	27	91—92	70.62 71.01	6.09 5.96	12.59 13.08	$C_{19}H_{19}N_3O_2$	321 $[M]^+$ (74), 320 $[M - H]^+$ (52), 292 [M – Et]$^+$ (25), 276 [M – OEt]$^+$ (32), 274 [M – H – EtOH]$^+$ (100), 248 [M – Et – CO_2]$^+$(39)

* Found/calculated (%): Cl, 10.83/10.88.

Table 2. ^{1}H NMR spectra in $CDCl_3$ and IR spectra in $CHCl_3$ of compounds **2a—d**, **4**, and **5a,b**

Compound	^{1}H NMR, δ (*J*/Hz) 2-Me (s, 3 H)	4-Me (s, 3 H)	5-Me (s, 3 H)	7-Me (s, 3 H)	COMe (s, 3 H)	CO_2Et	Ar	IR, ν/cm^{-1}
2a	—	3.12	2.69	2.74	2.61	—	7.52 (m, 3 H); 8.71 (m, 2 H)	1708 (CO), 1584, 1556
2b	—	3.14	2.69	2.77	2.62	—	7.48 (d, 2 H, *J* = 7.5); 8.67 (d, 2 H, *J* = 7.5)	1708 (CO), 1580, 1560
2c	—	3.18	2.58	2.69	—	—	7.45—7.60 (m, 5 H); 7.68 (t, 1 H, *J* = 7.8); 7.85 (d, 2 H, *J* = 7.8); 8.76 (m, 2 H)	1672 (CO), 1600, 1584, 1556
2d	2.93	—	1.95	2.70	2.53	—	7.40—7.60 (m, 5 H)	1708 (CO), 1580, 1548
4*	2.93	—	2.03	2.74	—	—	7.40—7.60 (m, 5 H)	1600, 1556
5a	—	3.14	2.74	2.82	—	1.45 (t, 3 H, Me, *J* = 6.8); 4.50 (q, 2 H, CH_2, *J* = 6.8)	7.51 (m, 3 H); 8.72 (m, 2 H)	1724 (CO), 1588, 1556
5b	2.94	—	2.02	2.75	—	1.38 (t, 3 H, Me, *J* = 6.8); 4.42 (q, 2 H, CH_2, *J* = 6.8)	7.40—7.60 (m, 5 H)	1724 (CO), 1588, 1552

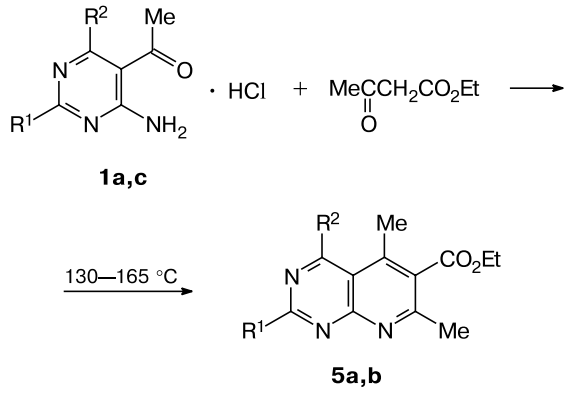
* 7.12 (s, 1 H, H(6)).

1640 cm^{-1}), one of which is involved into the intramolecular hydrogen bonding.

As it was mentioned above, the reaction of AAP with ketoesters does not follow the classical version of the Friedländer condensation. That is why it would have been interesting to study the reaction of acetoacetic ester with hydrochlorides of AAP. It turned out that the heating of hydrochloride **1a** with excess acetoacetic ester to 130—135 °C afforded pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ester **5a** in 33% isolated yield (Scheme 4). Ester **5b**,

similar to compound **5a**, was obtained from salt **1c**, however, the more drastic conditions were required (the reaction was carried out at the temperature of 160—165 °C).

Scheme 4



R^1 = Ph, R^2 = Me (**1a**, **5a**); R^1= Me, R^2 = Ph (**1c**, **5b**)

Esters **5a,b** are readily soluble in organic solvents. Their structures were confirmed by spectroscopy methods. Their mass spectra contain intensive peaks of the molecular ions (see Table 1), in the ^{1}H NMR spectra, signals of the ethyl group from ethoxycarbonyl fragment are observed, while in the IR spectrum there is an absorption with ν 1724 cm^{-1} characteristic of the fragment.

In conclusion, it was found that the use of AAP hydrochlorides instead of free bases in the transformations with β-diketones allows one to accomplish the Friedländer reaction with the construction of pyrido[2,3-*d*]pyrimidine system and, in case of ketoesters, also gives a possibility to conduct the Friedländer condensation in its classical version.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer, IR spectra were recorded on a Specord-M80 spectrometer, mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV; the ionizing chamber temperature, 250 °C; direct inlet of a substance). 2,6-Disubstituted 5-acetyl-4-aminopyrimidines were synthesized according to the known procedures.[1,3,6] Their hydrochlorides were obtained by treatment with concentrated HCl in MeOH. After MeOH was evaporated *in vacuo*, benzene was added to the residue, this was refluxed with a Dean—Stark trap, and salts **1a—c** were filtered off.*

* ^{1}H NMR spectrum of hydrochloride **1a** (DMSO-d_6), δ: 2.59 (s, 3 H, Me); 2.64 (s, 3 H, Me); 7.61 (t, 2 H, Ph, J = 7.8 Hz); 7.68 (t, 1 H, Ph, J = 7.8 Hz); 8.31 (d, 2 H, Ph, J = 7.8 Hz); 8.71 (br.s, 2 H, NH_2); signals of the salt's NH and H_2O in DMSO-d_6 are broadened to a large extent due to the exchange and, therefore, are not visible. For a comparison, the spectrum of the starting base is given (DMSO-d_6), δ: 2.50 (s, 3 H, Me); 2.55 (s, 3 H, Me); 7.38 (br.s, 2 H, NH_2); 7.49 (m, 3 H, Ph); 8.33 (m, 2 H, Ph).

6-Acyl-2-aryl-4,5,7-trimethylpyrido[2,3-*d*]pyrimidines (2a—c) (general procedure). A mixture of hydrochloride **1a** or **1b** (1 mmol) and acetylacetone (120 mmol) was refluxed for 2—3 h or a mixture of hydrochloride **1a** (1 mmol) and benzoylacetone (25 mmol) was heated for 4 h at 145—150 °C. The residue was subjected to column chromatography on SiO_2 (eluent: C_6H_6, then, C_6H_6—$CHCl_3$ 1 : 1, and $CHCl_3$), the fraction compositions were monitored by TLC (in the preparation of compounds **2a,b**, with prior evaporation of excess acetylacetone). The solvent was evaporated *in vacuo* from the latter fractions, the residue was recrystallized from light petroleum — benzene, 4 : 1 (in case of **2a,b**) and from MeCN (in case of **2c**) to obtain pyridopyrimidines **2a—c** (see Tables 1 and 2).

In the synthesis of compounds **2a**, after evaporation of the solvent from the medium fractions and crystallization of the residue from light petroleum, 5-acetyl-6-methyl-4-(2-oxopent-3-en-4-yl)amino-2-phenylpyrimidine (**3a**) was isolated, the yield was 8%, m.p. 110—111 °C. Found (%): C, 69.96; H, 6.35; N, 13.19. $C_{18}H_{19}N_3O_2$. Calculated (%): C, 69.88; H, 6.19; N, 13.58. MS, m/z (I_{rel} (%)): 309 $[M]^+$ (2), 266 $[M - MeCO]^+$ (100), 249 $[M - COCH_2 - H_2O]^+$ (82). IR ($CHCl_3$), ν/cm^{-1}: 1696 (CO); 1636 (CO); 1544. ^{1}H NMR ($CDCl_3$), δ: 2.14 (s, 3 H, COMe); 2.52 (s, 3 H, COMe); 2.68 (s, 3 H, Me); 2.70 (s, 3 H, Me); 5.43 (s, 1 H, CH=); 7.49 (m, 3 H, Ph); 8.48 (m, 2 H, Ph); 12.89 (br.s, 1 H, NH).

5-Acetyl-2-methyl-4-(2-oxopent-3-en-4-yl)amino-6-phenylpyrimidine (3d). A mixture of hydrochloride **1c** (0.264 g, 1 mmol) and acetylacetone (12 mL, 116 mmol) was refluxed for 2 h, acetylacetone was evaporated *in vacuo*, the residue was subjected to column chromatography on SiO_2 (eluent: C_6H_6, then, C_6H_6—$CHCl_3$, 4 : 1). After the solvent was evaporated from the corresponding fraction, the residue was recrystallized from light petroleum (3 mL) to obtain enamine **3d** (0.124 g, 40%), m.p. 111—112 °C. Found (%): C, 69.74; H, 6.43; N, 13.22. $C_{18}H_{19}N_3O_2$. Calculated (%): C, 69.88; H, 6.19; N, 13.58. MS, m/z (I_{rel} (%)): 309 $[M]^+$ (1), 266 $[M - MeCO]^+$ (100), 183 (24). IR ($CHCl_3$), ν/cm^{-1}: 1684 (CO); 1640 (CO); 1600, 1584, 1544. ^{1}H NMR ($CDCl_3$), δ: 1.98 (s, 3 H, COMe); 2.17 (s, 3 H, COMe); 2.58 (s, 3 H, Me); 2.68 (s, 3 H, Me); 5.43 (s, 1 H, CH=); 7.50 (m, 3 H, Ph); 7.62 (m, 2 H, Ph); 12.88 (br.s, 1 H, NH).

6-Acetyl-2,5,7-trimethyl-4-phenylpyrido[2,3-*d*]pyrimidine (2d). 1,8-Diazabicyclo[5.4.0]undecene (3 drops) was added to enamine **3** (0.155 g, 0.5 mmol) in benzene (10 mL), the mixture was refluxed for 1 h, then, benzene was evaporated *in vacuo* and the residue was subjected to column chromatography on SiO_2 (eluent: $CHCl_3$). The solvent was evaporated, the residue was recrystallized from light petroleum to obtain pyridopyrimidine **2d** (0.077 g, 53%) (see Tables 1 and 2).

2,5,7-Trimethyl-4-phenylpyrido[2,3-*d*]pyrimidine (4). A mixture of enamine **3** (0.155 g, 0.5 mmol) and MeONa (0.5 mmol) in MeOH (10 mL) was stirred for 30 min. The solvent was evaporated *in vacuo*, the residue was subjected to column chromatography on SiO_2 (eluent: C_6H_6—$CHCl_3$, 1 : 1). The solvent was evaporated *in vacuo* from the corresponding fractions (TLC monitoring) and the residue was recrystallized from light petroleum to obtain pyridopyrimidine **4** (0.059 g, 48%) (see Tables 1 and 2).

Ethyl 4,5,7-trimethyl-2-phenyl- and 2,5,7-trimethyl-4-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylates (5a,b). A mixture of hydrochloride **1a** or **1c** (1 mmol) and ethyl acetoacetate (120 mmol) was heated for 2—3 h to 130—135 °C and

165—170 °C, respectively, the excess ethyl acetoacetate was evaporated *in vacuo*, and the residue was subjected to column chromatography on SiO_2 (eluent: C_6H_6, then, C_6H_6—$CHCl_3$, 2 : 1). After the solvent was evaporated from the corresponding fractions (TLC monitoring), the oily residue was recrystallized from light petroleum to obtain esters **5a,b** (Tables 1 and 2).

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References

1. A. V. Komkov, B. I. Ugrak, V. S. Bogdanov, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1469 [*Russ. Chem. Bull.*, 1994, **43**, 1392 (Engl.Transl.)].
2. A. V. Komkov, A. M. Sakharov, V. S. Bogdanov, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1324 [*Russ. Chem. Bull.*, 1995, **44**, 1278 (Engl.Transl.)].
3. A. V. Komkov and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1726 [*Russ. Chem. Bull.*, *Int. Ed.,* 2002, **51**, 1875].
4. A. V. Komkov, I. P. Yakovlev, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 770 [*Russ. Chem. Bull.*, *Int. Ed.*, 2005, **54**, 784].
5. A. V. Komkov, M. A. Prezent, A. V. Ignatenko, I. P. Yakovlev, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 2006 [*Russ. Chem. Bull.*, *Int. Ed.,* 2006, **55**, 2085].
6. V. A. Dorokhov, M. F. Gordeev, A. V. Komkov, and V. S. Bogdanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 145 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 130 (Engl.Transl.)].
7. F. Perandones and J. L. Soto, *J. Heterocycl. Chem.*, 1998, **35**, 413.
8. C.-C. Cheng and S.-J. Yan, *Organic Reactions*, Ed. W. G. Dauben, John Willey and Sons, New York, 1982, **28**, p. 42.
9. S. Atechian, N. Nock, R. D. Norcross, H. Ratni, A. W. Thomas, J. Verron and R. Masciadri, *Tetrahedron*, 2007, **63**, 2811.

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