4H-3,1-BENZOXAZINES FROM *o*-AMINOACYLBENZENES

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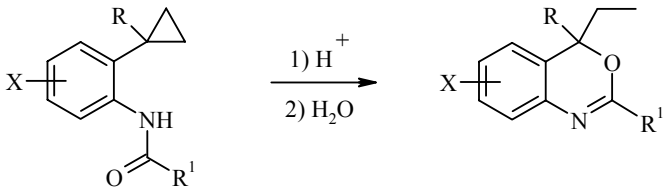
A new efficient method has been proposed for the synthesis of 4H-3,1-benzoxazines from 2-aminoacylbenzenes. This reaction sequence may be used either for 2-aminoaryl alkyl ketones or 2-aminobenzophenones.

Keywords: 2-aminoacylbenzenes, α-(2-N-acylaminoaryl)alkanols, 2-N-acylaminoaryl alkyl ketones, 2-N-acylaminobenzhydrols, 2-N-aminobenzophenones, 4H-3,1-benzoxazines, intramolecular heterocyclization.

4H-3,1-Benzoxazines are important heterocyclic compounds, which may provide new generation drugs [1]. Quite a few approaches have been developed for the synthesis of 4H-3,1-benzoxazines, providing compounds for biological investigation. However, in the case of the reported syntheses for 4H-3,1-benzoxazines, the range of substituents in the heterocyclic system is rather limited. For example, when derivatives of *o*-aminobenzyl halides [2] or *o*-aminobenzyl alcohols are used in the synthesis of 4H-3,1-benzoxazines [3-6], variation of the substituents is practical only in the step involving acylation at the amino group of these amines. As a consequence, only 3,1-benzoxazines with different substituents at $C_{(2)}$ were obtained. The very recently discovered rearrangement of 2-acylaminophenylcyclopropanes opens broader possibilities for the synthesis of substituted 4H-3,1-benzoxazines [7].



X = Hal, Alk, Ac; R = H, Me; R^1 = Alk, Ar, Het

However, in this case, even with broad possibilities for varying the substituents both in the fused benzene ring and at $C_{(2)}$ in the 3,1-benzoxazine system, variation of substituents at $C_{(4)}$ of the heterocycle using this scheme is limited only to the most simple alkyl fragments.

In previous work [7], we have already noted that, in principle, we might expect the formation of 4H-3,1-benzoxazine products if there is a fragment in the starting aromatic substrate undergoing intramolecular acid-catalyzed heterocyclization, from which a benzylic carbenium site may be generated, while an NH-C(R)=O

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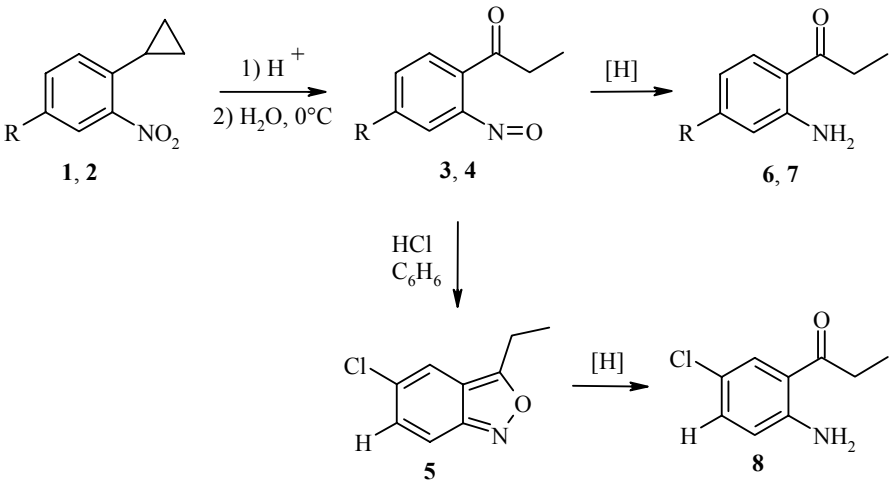
moiety is located in the *ortho* position to this fragment, permitting formation of a benzoxazine ring. In the present work, we have shown that substrates meeting these requirements may readily be synthesized from *o*-aminoacylbenzenes.

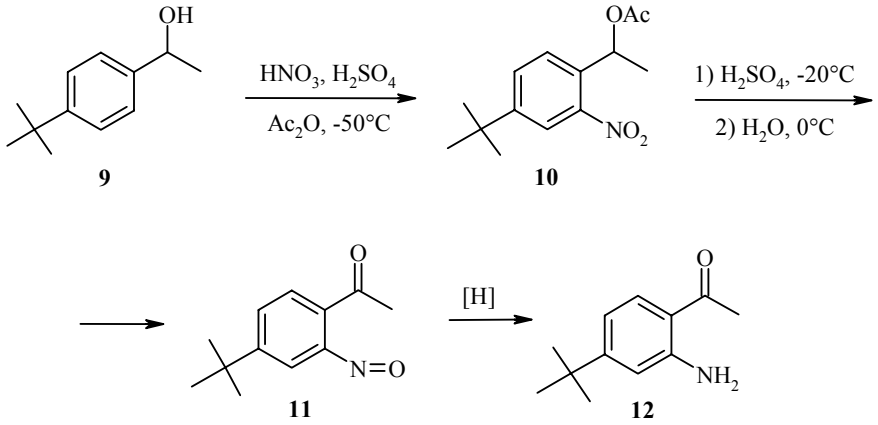
We should stress that the synthesis of 2-aminoacylbenzenes by nitration of aromatic ketones and subsequent reduction of the nitro group in the nitration products is not always feasible. However, studies have recently appeared showing that this problem may be circumvented, sometimes by well-known reactions, and the desired 2-aminoacylbenzenes may be obtained in high yield. For example, the reported acid-catalyzed rearrangement of variously substituted 2-nitrophenylcyclopropanes **1** and **2** gives 2-nitrosopropiophenones **3** and **4,** which may be transformed to yield a broad range of 2-aminopropiophenones **6-8** [8-10].



1, **2** **3**, **4** **6**, **7** **5** **8**

1, **3**, **6**, R = H; **2**, **4**, **7** R = Br

1-(4-*tert*-Butyl-2-nitrophenyl)ethyl acetate (**10**), which is the product of the nitration of 1-(4-*tert*-butyl-phenyl)ethanol (**9**), undergoes a similar rearrangement to give 4-*tert*-butyl-2-nitrosoaceto-phenone (**11**) [11]. We are the first to report the synthesis of 2-amino-4-*tert*-butylacetophenone (**12**) by the reduction of **11**.

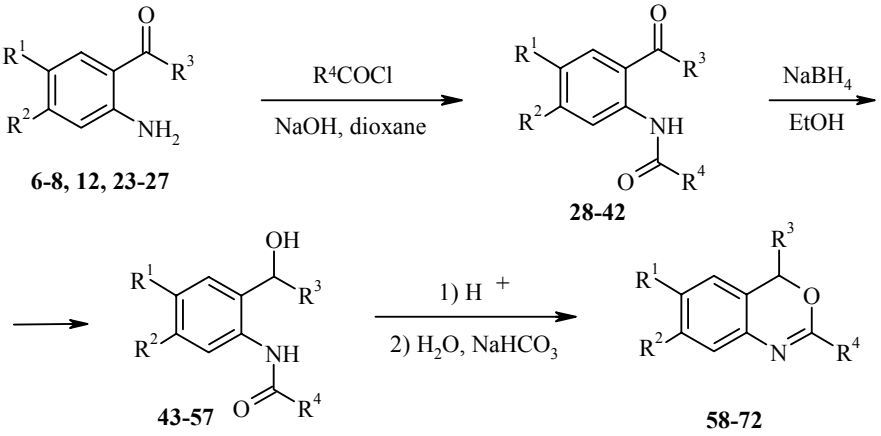


9 **10** **11** **12**

Alkyl aryl ketones or diaryl ketones **13-17** containing alkoxy groups at both $C_{(3)}$ and $C_{(4)}$ in one of the benzene rings may serve as substrates giving *o*-aminoacylbenzenes **23-27** through direct nitration and subsequent reduction.

As shown in this work and in previous studies [12, 13], the nature of substituent R^3 in the acyl fragment has hardly any effect on the orientation of the entering nitro group and the yields of the nitro compound products in the nitration of these acylbenzenes under the conditions employed. However, in some cases, the nitration of such acylbenzenes may be accompanied by nitrodeacylation (*ipso* substitution of the acyl fragment) [14].

We then found that the consecutive acylation of the resultant 2-aminoacylbenzenes at the amino group, reduction of the acyl fragment directly attached to the aromatic system, and acid-catalyzed cyclization of the corresponding amidoalcohols may yield variously substituted 4H-3,1-benzoxazines.



6-8, 12, 23-27 **28-42** **43-57** **58-72**

28, **29**, **31**, **43**, **44**, **46**, **58**, **59**, **61** R^1 = H; **30**, **45**, **60** R^1 = Cl; **32**, **47**, **62** $R^1 = R^2$ = OMe;
3-42, **48-57**, **63-72** $R^1+R^2 = OCH_2CH_2O$; **28**, **30**, **43**, **45, 58**, **60** R^2 = H;
29, **44**, **59** R^2 = Br; **31**, **46**, **61** R^2 = *t*-Bu; **28**–**30**, **33**–**36**, **43**–**45**, **48**–**51**, **58**–**60**, **63**–**66** R^3 = Et;
31, **46**, **61** R^3 = Me; **32**, **39**, **40**, **47**, **54**, **55**, **62**, **69**, **70** R^3 = *o*-ClC_6H_4; **37**, **38**, **52**, **53**, **67**, **68** R^3 = Ph;
41, **42**, **56**, **57**, **71**, **72** R^3 = *p*-BrC_6H_4; **28**, **42**, **43**, **57**, **58, 72** R^4 = *o*-BrC_6H_4;
29, **44**, **59** R^4 = *m*-ClC_6H_4; **30**, **45**, **60** R^4 = *o*-ClC_6H_4; **31**, **35**, **41**, **46**, **50**, **56**, **61**, **65**, **71** R^4 = 2-thienyl;
32, 47, 62 R^4 = *m*-BrC_6H_4; **33**, **48, 63** R^4 = *o*-FC_6H_4; **34**, **49**, **64** R^4 = *p*-MeC_6H_4;
36, **37**, **51**, **52**, **66**, **67** R^4 = 2-furyl; **38**, **40**, **53**, **55**, **68**, **70** R^4 = *m*-IC_6H_4; **39**, **54**, **69** R^4 = *m*-$MeOC_6H_4$

Acylation of **6-8, 12,** and **23-27** by acid chlorides proceeded with high yield and was virtually independent of the substituents both in the starting amines and in the acid fragments (Table 1). In contrast, the nature of the substituents in the acyl fragment of **28-42** affected the rate of their reduction by sodium borohydride. Greater reaction time and a larger reagent mole ratio were required for the complete reduction of some amidobenzophenones such as **32, 39,** and **40**. However, the amide carbonyl group in all cases was not affected.

Intramolecular acid-catalyzed cyclization of acylaminocarbinols **47-49, 53-55,** and **57** to give the corresponding 4H-3,1-benzoxazines was carried out using concentrated sulfuric and trifluoroacetic acids. High yields of 3,1-benzoxazines are obtained by the action of concentrated sulfuric acid only in the cyclization of acylaminocarbinols lacking acidophobic substituents such as a furan or thiophene fragment. The cyclization of furan- and thiophene-containing substrates by the action of concentrated sulfuric acid is much more difficult*.

* Similar difficulties in the cyclization of thienyl- and furyl-containing substrates to give 4H-3,1-benzoxazines by the action of a strong protic acid, namely, perchloric acid, were seen by Gromachevskaya [5].

TABLE 1. Characteristics of *o*-Acylanilides **28-42**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*[2]	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
28*[3]	$C_{16}H_{14}BrNO_2$	57.72 / 57.85	4.32 / 4.23	4.26 / 4.22	101-102	1.15 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$,); 3.10 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); .23 (1H, t, *J* = 7.6); 7.40-7.75 (5H, m); 8.10 (1H, d, *J* = 7.7); 8.65 (1H, d, *J* = 7.7, ArH); 12.85 (1H, s, NHCO)	86
29	$C_{16}H_{13}BrClNO_2$	52.01 / 52.41	3.31 / 3.57	3.54 / 3.82	130-131	1.20 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$,); 3.06 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 7.29 (1H, dd, *J* = 8.4, *J* = 2.0); 7.48 (1H, t, *J* = 8.1); 7.54 (1H, dd, *J* = 8.1, *J* = 2.2); 7.83 (1H, d, *J* = 8.4); 7.92 (1H, d, *J* = 8.1); 8.04 (1H, d, *J* = 2.0); 9.19 (1H, d, *J* = 2.0, ArH); 12.76 (1H, s, NHCO)	90
30	$C_{16}H_{13}Cl_2NO_2$	59.22 / 59.65	3.88 / 4.07	4.01 / 4.35	122-123	1.20 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$,); 3.15 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 7.45 (2H, m); 7.48 (1H, d, *J* = 7.7); 7.54 (1H, d, *J* = 7.7); 7.60 (1H, d, *J* = 8.6); 7.90 (1H, d, *J* = 2.6); 8.95 (1H, d, *J* = 8.6, ArH); 12.70 (1H, s, NHCO)	87
31	$C_{17}H_{19}NO_2S$	67.42 / 67.74	6.04 / 6.35	4.38 / 4.65	143-144	1.38 (9H, s, *t*-Bu); 2.66 (3H, s, As); 7.19 (2H, m); 7.75 (2H, m); 7.96 (1H, d, *J* = 8.3); 8.84 (1H, d, *J* = 1.9, thienyl, ArH); 12.52 (1H, s, NHCO)	92
32	$C_{22}H_{17}BrClNO_4$	55.22 / 55.66	3.41 / 3.61	2.72 / 2.95	155-156	3.60 (3H, s, CH_3O); 3.94 (3H, s, CH_3O); 6.84 (1H, s); 7.46 (1H, t, *J* = 7.8); 7.51-7.60 (4H, m); 7.84 (1H, d, *J* = 7.9); 7.90 (1H, d, *J* = 7.9); 8.01 (1H, s); 8.22 (1H, s, ArH); 12.08 (1H, s, NHCO)	82
33	$C_{18}H_{16}FNO_4$	65.21 / 65.65	4.71 / 4.90	4.02 / 4.25	170-171	1.08 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$,); 3.04 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 4.35 (4H, m, OCH_2CH_2O); 7.36-7.44 (2H, m); 7.61-7.68 (2H, m); 7.88 (1H, t, *J* = 7.6); 8.25 (1H, s, ArH); 12.25 (1H, s, NHCO)	88
34	$C_{19}H_{19}NO_4$	69.86 / 70.14	5.61 / 5.89	4.03 / 4.31	194-195	1.24 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$,); 2.43 (3H, s, $Ar\underline{CH_3}$); 2.98 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 4.30 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 7.30 (2H, dd, *J* = 7.7, *J* = 2.3); 7.46 (1H, s); 7.96 (2H, dd, *J* = 7.7, *J* = 2.1); 8.58 (1H, s, ArH); 12.30 (1H, s, NHCO)	76
35	$C_{16}H_{15}NO_4S$	60.22 / 60.55	4.51 / 4.76	4.19 / 4.41	168-169	1.15 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$,); 3.05 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 4.29 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 7.25 (1H, dd, *J* = 5.6, *J* = 3.6), 7.58 (1H, s); 7.75 (1H, d, *J* = 3.6); 7.85 (1H, d, *J* = 5.6); 8.16 (1H, s, thienyl, ArH); 12.55 (1H, s, NHCO)	76

TABLE 1. (continued)

1	2	3	4	5	6	7	8
							82
36	$C_{16}H_{15}NO_5$	63.36 / 63.78	4.83 / 5.02	4.31 / 4.65	207-208	1.08 (3H, t, J = 7.2, $CH_2\underline{CH_3}$,); 3.09 (2H, q, J = 7.2, $\underline{CH_2}CH_3$); 4.28 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 6.74 (1H, dd, J = 3.6, J = 1.7); 7.26 (1H, d, J = 1.7); 7.66 (1H, s); 8.05 (1H, d, J = 3.6); 8.26 (1H, s, furyl, ArH); 12.56 (1H, s, NHCO)	
37	$C_{20}H_{15}NO_5$	68.41 / 68.76	4.01 / 4.33	3.82 / 4.01	215-216	4.28 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 6.70 (1H, dd, J = 3.6, J = 1.7); 6.99 (1H, s); 7.20 (1H, d, J = 1.7); 7.50-7.70 (5H, m); 7.90 (1H, s); 8.00 (1H, d, J = 3.6, furyl, ArH); 11.49 (1H, s, NHCO)	81
38	$C_{22}H_{16}INO_4$	54.12 / 54.45	3.11 / 3.32	2.61 / 2.89	188-189	4.28 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 6.98 (1H, s); 7.28 (1H, m); 7.46 (2H, m); 7.51 (1H, m); 7.58 (1H, t, J = 8.0); 7.65 (2H, m); 7.70 (1H, d, J = 8.0); 7.87-7.98 (2H, m, ArH); 10.83 (1H, s, NHCO)	68
39	$C_{23}H_{18}ClNO_5$	64.88 / 65.18	3.96 / 4.28	3.03 / 3.30	212-214	3.85 (3H, s, CH_3O); 4.25 (2H, m, OCH_2CH_2O); 4.39 (2H, m, OCH_2CH_2O); 6.78 (1H, s); 7.40-7.70 (8H, m); 8.30 (1H, s, ArH); 12.20 (1H, s, NHCO)	85
40	$C_{22}H_{15}ClINO_4$	50.11 / 50.84	2.73 / 2.91	2.51 / 2.70	219-220	4.25 (2H, m, OCH_2CH_2O); 4.40 (2H, m, OCH_2CH_2O); 6.78 (1H, s); 7.40 (1H, t, J = 7.9); 7.48-7.62 (4H, m); 7.93 (1H, d, J = 7.9); 8.01 (1H, d, J = 7.9); 8.12 (1H, s); 8.24 (1H, s, ArH); 11.98 (1H, s, NHCO)	80
41	$C_{20}H_{14}BrNO_4S$	53.81 / 54.07	2.95 / 3.18	2.91 / 3.15	205-207	4.28 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 7.05 (1H, s); 7.22 (1H, dd, J = 4.8, J = 4.0); 7.45-7.73 (4H, m); 7.72 (1H, d, J = 4.0); 7.87 (1H, d, J = 4.8); 8.14 (1H, s, ArH, thienyl); 11.86 (1H, s, NHCO)	73
42	$C_{22}H_{15}Br_2NO_4$	50.54 / 51.09	2.61 / 2.92	2.41 / 2.71	168-170	4.26 (2H, m, OCH_2CH_2O); 4.38 (2H, m, OCH_2CH_2O); 6.95 (1H, s); 7.20 (2H, m); 7.36 (2H, m); 7.52-7.78 (5H, m, ArH); 10.72 (1H, s, NHCO)	89

* Recrystallization: **28-31, 35, 36** from ethanol, **32-34, 37-42** from 2:1 ethanol-chloroform

*[2] Spectra taken in DMSO-d_6 (for **28, 31-33, 35-40, 42**) or $CDCl_3$ for **29, 30, 34**.

*[3] The coupling constants for the signals of the protons of analogs **39, 30, 33-36** correspond to the coupling constants of **28**.

TABLE 2. Characteristics of *o*-Acylaminobenzyl Alcohols **43-57**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	^{1}H NMR spectrum, d, ppm. (*J*,Hz)*[2]	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
43	$C_{16}H_{16}BrNO_2$	57.20 / 57.50	4.99 / 4.83	4.20 / 4.19	98-99	0.90 (3H, m, $CH_2\underline{CH_3}$,); 1.85 (2H, m, $\underline{CH_2}CH_3$); 3.10 (1H, s, OH); 4.68 (1H, m, $\underline{CH}$OH); 7.08 (2H, m); 7.25-7.39 (3H, m); 7.48 (1H, dd, *J* = 8.2, *J* = 1.6); 7.60 (1H, d, *J* = 8.1); 8.24 (1H, d, *J* = 8.1, ArH); 9.50 (1H, s, NHCO)	76
44	$C_{16}H_{15}BrClNO_2$	52.06 / 52.13	4.25 / 4.10	3.80 / 3.80	133-134	0.95 (3H, m, $CH_2\underline{CH_3}$,); 1.75-1.95 (2H, 2m, $\underline{CH_2}CH_3$); 3.40 (1H, s, OH); 4.68 (1H, m, $\underline{CH}$OH); 6.88 (1H, d, *J* = 8.3); 7.12 (1H, dd, *J* = 8.3, *J* = 2.0); 7.37 (1H, t, *J* = 8.0); 7.48 (1H, dd, *J* = 8.0, *J* = 1.9); 7.68 (1H, dd, *J* = 8.0, *J* = 1.9); 7.85 (1H, d, *J* = 2.0); 8.62 (1H, s, ArH); 10.35 (1H, s, NHCO)	79
45	$C_{16}H_{15}Cl_2NO_2$	59.25 / 59.28	4.57 / 4.66	4.10 / 4.32	110-111	0.80 (3H, m, $CH_2\underline{CH_3}$,); 1.85 (2H, m, $\underline{CH_2}CH_3$); 3.40 (1H, s, OH); 4.68 (1H, m, $\underline{CH}$OH); 7.06 (1H, d, *J* = 7.7); 7.22-7.45 (4H, m); 7.57 (1H, dd, *J* = 8.6, *J* = 2.6); 8.40 (1H, d, *J* = 8.6, ArH); 9.60 (1H, s, NHCO)	80
46	$C_{17}H_{21}NO_2S$	67.10 / 67.29	7.15 / 6.98	4.54 / 4.62	140-141	1.33 (9H,s, *t*-Bu); 1.64 (3H, d, *J* = 6.9, $\underline{CH_3}$CHOH); 3.15 (1H, s, OH); 5.05 (1H, q, *J* = 6.9, $\underline{CH}$OH); 7.05 (3H, m); 7.50 (1H, d, *J* = 4.5); 7.59 (1H, d, *J* = 3.2); 8.42 (1H, d, *J* = 1.9, thienyl, ArH); 10.10 (1H, s, NHCO)	95
47	$C_{22}H_{19}BrClNO_4$	55.12 / 55.42	3.81 / 4.02	2.69 / 2.94	176-177	3.72 (6H, 2s, CH_3O); 6.06 (1H,s, $\underline{CH}$OH); 6.22 (1H, s, OH); 7.02 (1H, s); 7.08 (1H, s); 7.20-7.34 (4H, m); 7.46 (1H, t, *J* = 7.8); 7.76 (1H, d, *J* = 7.8); 7.82 (1H, d, *J* = 7.9); 7.95 (1H,s, ArH); 9.98 (1H, s, NHCO)	54
48	$C_{18}H_{18}FNO_4$	64.91 / 65.25	5.24 / 5.48	4.11 / 4.23	132-133	0.81 (3H, m, $CH_2\underline{CH_3}$,); 1.62 (2H, m, $\underline{CH_2}CH_3$); 4.22 (4H, m, OCH_2CH_2O); 4.55 (1H, m, $\underline{CH}$OH); 5.60 (1H, s, OH); 6.80 (1H, s); 7.30-7.40 (3H, m); 7.59 (1H, m); 7.78 (1H, t, *J* = 7.5, ArH); 10.12 (1H, s, NHCO)	59
49	$C_{19}H_{21}NO_4$	69.32 / 69.71	6.34 / 6.47	4.11 / 4.28	162-163	0.80 (3H, m, $CH_2\underline{CH_3}$,); 1.65 (2H, m, $\underline{CH_2}CH_3$); 2.38 (3H, s, Ar$\underline{CH_3}$); 4.22 (4H, m, OCH_2CH_2O); 4.59 (1H, m, $\underline{CH}$OH); 5.83 (1H, s, OH); 6.78 (1H, s); 7.32 (2H, d, *J* = 7.7); 7.48 (1H, s); 7.80 (2H, d, *J* = 7.7, ArH); 10.23 (1H, s, NHCO)	66

TABLE 2. (continued)

1	2	3	4	5	6	7	8
					140-142	0.80 (3H, m, $CH_2\underline{CH_3}$,); 1.12 (2H, m, $\underline{CH_2}CH_3$); 4.23 (4H, m, OCH_2CH_2O);	68
50	$C_{16}H_{17}NO_4S$	60.18 60.17	5.43 5.37	4.58 4.39		4.60 (1H, m, <u>CH</u>OH); 5.75 (1H, s, OH); 6.79 (1H, s); 7.20 (1H, dd, *J* = 4.2, *J* = 3.9); 7.34 (1H, s); 7.71 (1H, d, *J* = 3.9); 7.83 (1H, d, *J* = 4.2, thienyl, ArH); 10.23 (1H, s, NHCO)	
51	$C_{16}H_{17}NO_5$	63.10 63.36	5.42 5.65	4.21 4.62	135-136	0.80 (3H, m, $CH_2\underline{CH_3}$,); 1.62 (2H, m, $\underline{CH_2}CH_3$); 4.23 (4H, m, OCH_2CH_2O); 4.52 (1H, m, <u>CH</u>OH); 5.96 (1H, s, OH); 6.69 (1H, dd, *J* = 3.2, *J* = 1.7); 6.76 (1H, s); 7.19 (1H, d, *J* = 1.7); 7.51 (1H, s); 7.92 (1H, d, *J* = 3.2, furyl, ArH); 10.37 (1H, s, NHCO)	72
52	$C_{20}H_{17}NO_5$	66.40 68.37	4.76 4.88	3.81 3.99	120-121	3.55 (1H, s, OH); 4.19 (4H, m, OCH_2CH_2O); 5.85 (1H, m, <u>CH</u>OH); 6.46 (1H, dd, *J* = 3.5, *J* = 2.0); 6.57 (1H, s); 7.06 (1H, d, *J* = 2.0); 7.19-7.36 (5H, m); 7.43 (1H, d, *J* = 3.5); 7.67 (1H, s, furyl, ArH); 9.30 (1H, s, NHCO)	63
53	$C_{22}H_{18}INO_4$	53.94 54.23	3.55 3.72	2.64 2.87	147-148	3.49 (1H, s, OH); 4.22 (4H, m, OCH_2CH_2O); 5.85 (1H, s, <u>CH</u>OH); 6.62 (1H, s); 7.08 (1H, t, *J* = 8.0); 7.25-7.35 (5H, m); 7.56 (1H, d, *J* = 8.0); 7.75-7.80 (2H, m); 7.94 (1H,s, ArH); 9.13 (1H, s, NHCO)	69
54	$C_{23}H_{20}ClNO_5$	64.61 64.87	4.52 4.73	3.01 3.29	147-148	3.82 (3H, s, CH_3O); 4.22 (4H, m, OCH_2CH_2O); 5.35 (1H, s, OH); 6.15 (1H,s, <u>CH</u>OH); 6.52 (1H, s); 7.14 (1H, m); 7.23-7.47 (8H, m, ArH); 9.95 (1H, s, NHCO)	73
55	$C_{22}H_{17}ClINO_4$	50.34 50.65	3.11 3.28	2.42 2.68	176-177	3.64 (1H,s, OH); 4.22 (4H, m, OCH_2CH_2O); 6.14 (1H,s, <u>CH</u>OH); 6.46 (1H, s); 7.17 (1H, t, *J* = 8.0); 7.23-7.38 (3H, m); 7.48-7.55 (2H, m); 7.76 (1H, d, *J* = 7.8); 7.84 (1H, d, *J* = 7.8); 8.16 (1H, s, ArH); 9.05 (1H, s, NHCO)	65
56	$C_{20}H_{16}BrNO_4S$	53.52 53.82	3.31 3.61	2.81 3.14	146-147	4.24 (4H, m, OCH_2CH_2O); 5.82 (1H,s, <u>CH</u>OH); 6.41 (1H, s, OH); 6.82 (1H, s); 7.16-7.30 (4H, m); 7.44 (2H, d, *J* = 7.3); 7.67 (1H, d, *J* = 4.3); 7.81 (1H, d, *J* = 4.8, thienyl, ArH); 9.90 (1H, s, NHCO)	74
57	$C_{22}H_{17}Br_2NO_4$	50.88 50.89	3.21 3.30	2.90 2.70	160-161	4.24 (4H, m, OCH_2CH_2O); 5.91 (1H,s, <u>CH</u>OH); 6.00 (1H, s, OH); 6.79 (1H, s); 7.18 (1H, s); 7.20-7.50 (7H, m); 7.69 (1H, d, *J* = 8.1, ArH); 9.68 (1H, s, NHCO)	59

* Products **43-54, 56,** and **57** were recrystallized from ethanol, product **55** was recrystallized from 2-propanol.

*[2] Spectra were taken in $CDCl_3$ (**43-46, 52, 53, 55**) and DMSO-d_6 (**47-51, 54, 56, 57**).

TABLE 3. Characteristics of 4H-3,1-Benzoxazines **58-72**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (for ethanol)*	^{1}H NMR spektrum ($CDCl_3$), δ, ppm. (*J*, Hz)	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
58	$C_{16}H_{14}BrNO$	60.49 / 60.78	4.32 / 4.46	4.27 / 4.43	—	1.08 (3H, m, $CH_2\underline{CH_3}$); 2.07 (2H, m, $\underline{CH_2}CH_3$); 5.49 (1H, m, H-4 benzoxazine); 7.03 (1H, t, *J* = 7.3); 7.19-7.41 (5H, m); 7.60-7.73 (2H, m, ArH)	91
59[*2]	$C_{16}H_{13}BrClNO$	54.81	3.74	3.99	—	1.06 (3H, m, $CH_2\underline{CH_3}$); 1.95 (2H, m, $\underline{CH_2}CH_3$); 5.29 (1H, m, H-4 benzoxazine); 6.86 (1H, d, *J* = 9.0); 7.32 (1H, dd, *J* = 9.0, *J* = 1.8); 7.36 (1H, t, *J* = 8.9); 7.42-7.49 (2H, m); 8.01 (1H, d, *J* = 9.0, *J* = 1.6); 8.11 (1H, s, ArH)	65
60[*2]	$C_{16}H_{13}Cl_2NO$	62.76	4.28	4.57	—	1.10 (3H, m, $CH_2\underline{CH_3}$); 2.11 (2H, m, $\underline{CH_2}CH_3$); 5.45 (1H, m, H-4 benzoxazine); 7.03 (1H, d, *J* = 1.4); 7.23 (1H, d, *J* = 7.9); 7.26-7.42 (3H, m); 7.47 (1H, d, *J* = 7.9); 7.76 (1H, dd, *J* = 7.3, *J* = 1.4, ArH)	53
61[*2]	$C_{17}H_{19}NOS$	71.54	6.71	4.91	—	1.35 (9H, s, *t*-Bu); 1.66 (3H, d, *J* = 6.8, CH_3); 5.53 (1H, q, *J* = 6.8, H-4 benzoxazine); 6.97 (1H, d, *J* = 8.8); 7.10 (1H, dd, *J* = 5.4, *J* = 4.9); 7.21 (1H, dd, *J* = 8.8, *J* = 2.2); 7.32 (1H, d, *J* = 2.2); 7.47 (1H, d, *J* = 5.4); 7.74 (1H, d, *J* = 4.9, thienyl, ArH)	71
62	$C_{22}H_{17}BrClNO_3$	57.33 / 56.78	3.61 / 3.83	3.33 / 5.91	115-116	3.78 (3H, s, CH_3O); 3.95 (3H, s, CH_3O); 6.40 (1H, s, H-4 benzoxazine); 6.90 (1H, s); 6.96 (1H, s); 7.09 (1H, d, *J* = 8.0); 7.15-7.29 (3H, m); 7.46 (1H, d, *J* = 7.9); 7.56 (1H, d, *J* = 7.9); 7.97 (1H, d, *J* = 7.7); 8.24 (1H, s, ArH)	52
63[*2]	$C_{18}H_{16}FNO_3$	69.00	5.15	4.47	—	1.10 (3H, m, $CH_2\underline{CH_3}$,); 1.96 (2H, m, $\underline{CH_2}CH_3$); 4.28 (4H, m, OCH_2CH_2O); 5.32 (1H, m, H-4 benzoxazine); 6.55 (1H, s); 6.84 (1H, s); 7.15-7.30 (2H, m); 7.42 (1H, dd, *J* = 8.4, *J* = 1.4); 7.96 (1H, dd, *J* = 8.4, *J* = 1.6, ArH)	74
64	$C_{19}H_{19}NO_3$	73.51 / 73.77	5.96 / 6.19	4.21 / 4.53	81-82	1.09 (3H, m, $CH_2\underline{CH_3}$,); 1.90 (2H, m, $\underline{CH_2}CH_3$); 2.42 (3H, s, $Ar\underline{CH_3}$); 4.24 (4H, m, OCH_2CH_2O); 5.26 (1H, m, H-4 benzoxazine); 6.54 (1H, s); 6.86 (1H, s); 7.23 (2H, d, *J* = 7.7); 8.04 (2H, d, *J* = 7.7, ArH)	83
65	C16H15NO3S	63.41 / 63.77	4.73 / 5.02	4.31 / 4.65	—	1.05 (3H, m, CH2CH3,); 1.90 (2H, m, CH2CH3); 4.25 (4H, m, OCH2CH2O); 5.20 (1H, m, H-4 benzoxazine); 6.50 (1H, s); 6.80 (1H, s); 7.10 (1H, dd, *J* = 5.3, *J* = 4.0); 7.45 (1H, d, *J* = 5.3); 7.70 (1H, d, *J* = 4.0, thienyl, ArH)	72

TABLE 3. (continued)

1	2	3	4	5	6	7	8
66	$C_{16}H_{15}NO_4$	67.04 / 67.36	5.16 / 5.30	4.67 / 4.91	—	1.00 (3H, m, $CH_2\underline{CH_3}$,); 1.84 (2H, m, $\underline{CH_2}CH_3$); 4.25 (4H, m, OCH_2CH_2O); 5.17 (1H, m, H-4 benzoxazine); 6.47 (2H, m); 6.86 (1H, s); 6.98 (1H, d, *J* = 3.5); 7.54 (1H, d, *J* = 1.8, furyl, ArH)	56
67	$C_{20}H_{15}NO_4$	72.36 / 72.06	4.40 / 4.54	3.71 / 4.20	174-175	4.20 (4H, m, OCH_2CH_2O); 6.25 (1H, s, H-4 benzoxazine); 6.29 (1H, s); 6.45 (1H, m); 6.96 (2H, m); 7.33-7.38 (5H, m); 7.54 (1H, d, *J* = 1.8, furyl, ArH)	72
68	$C_{22}H_{16}INO_3$	56.03 / 56.31	3.17 / 3.44	2.42 / 2.98	154-155	4.24 (4H, m, OCH_2CH_2O); 6.31 (2H, m, H-4 benzoxazine, ArH); 6.91 (1H, s); 7.11 (1H, t, *J* = 7.5); 7.37 (5H, m); 7.76 (1H, d, *J* = 7.6); 8.03 (1H, d, *J* = 7.6); 8.42 (1H, s, ArH)	80
69	$C_{23}H_{18}ClNO_4$	67.41 / 67.73	4.17 / 4.45	3.33 / 3.43	182-183	3.84 (3H, s, CH_3O); 4.22 (4H, m, OCH_2CH_2O); 6.36 (1H, s, H-4 benzoxazine); 6.78 (1H, s); 6.92-6.99 (2H, m); 7.18-7.28 (4H, m); 7.43 (1H, dd, *J* = 8.0, *J* = 1.2); 7.58-7.65 (2H, m, ArH)	81
70	$C_{22}H_{15}ClINO_3$	52.60 / 52.46	3.17 / 3.00	2.56 / 2.78	200-201	4.26 (4H, m, OCH_2CH_2O); 6.37 (1H, s, H-4 benzoxazine); 6.83 (1H, s); 6.95 (1H, s); 7.13 (1H, t, *J* = 8.4); 7.24 (1H, d, *J* = 7.7); 7.29-7.39 (2H, m); 7.48 (1H, d, *J* = 8.2); 7.78 (1H, d, *J* = 8.4); 8.04 (1H, d, *J* = 8.4); 8.44 (1H, s, ArH)	74
71	$C_{20}H_{14}BrNO_3S$	56.22 / 56.09	3.41 / 3.29	2.91 / 3.27	—	4.25 (4H, m, OCH_2CH_2O); 6.23 (1H, s, H-4 benzoxazine); 6.31 (1H, s); 6.88 (1H, s); 7.04 (1H, dd, *J* = 5.5, *J* = 4.0); 7.23 (2H, d, *J* = 8.6); 7.43 (1H, d, *J* = 5.5); 7.49 (2H, d, *J* = 8.6); 7.63 (1H, d, *J* = 4.0, thienyl, ArH)	70
72	$C_{22}H_{15}Br_2NO_3$	52.34 / 52.72	2.83 / 3.02	2.61 / 2.79	63-64	4.25 (4H, m, OCH_2CH_2O); 6.26 (1H, s, H-4 benzoxazine); 6.63 (1H, s); 7.06-7.12 (3H, m); 7.22-7.32 (3H, m); 7.39 (2H, d, *J* = 8.0); 7.58 (1H, d, *J* = 7.7, ArH)	73

* Products **58-61, 63, 65, 66,** and **71** are viscous oils.

*[2] Elemental analysis was not performed for **59-61, 63.** Mass spectrum, *m/z* ($I_{rel,}$ %): Compound **59** – 351 $[M]^+$ (21.9), 322 (100), 210 (4.7), 160 (8.1), 139 (16.1), 111 (18.6), 75 (20.5), 50 (3.8); compound **60** – 305 $[M]^+$ (20.9), 276 (100), 186 (5.2), 166 (4.4), 139 (19.4), 111 (19.1), 102 (3.7), 75 (18.1), 51 (4.1), 29 (32); compound **61** – 285 $[M]^+$ (48.2), 270 (100), 255 (6.3), 242 (6.4), 199 (10.8), 174 (4.4), 158 (5.2), 144 (8.2), 118 (31.3), 111 (74.6), 91 (15.4), 77 (10.1), 57 (21.6), 39 (44.4); compound **63** – 313 $[M]^+$ (16.3), 190 (100), 175 (14.0), 134 (28.8), 123 (72.5), 95 (28.8), 91 (7.5), 75 (22.5), 65 (5.2), 39 (4.3), 28 (5.2).

We later found that acylaminocarbinols **43-46, 50-52,** and **56** (Table 2) can be smoothly converted to the corresponding 4H-3,1-benzoxazines by the action of trifluoroacetic acid, which is weaker than sulfuric acid. Complete conversion in this case requires only a slightly longer reaction time and moderate heating (see Experimental). A clear advantage of trifluoroacetic acid as the cyclizing agent is that the action of this acid on acylaminocarbinols with acidophobic substituents leads to the corresponding 4H-3,1-benzoxazines in high yield (Table 3).

The composition and structure of newly synthesized acylaminoketones **28-42**, acylamino-carbinols **43-57**, and 4H-3,1-benzoxazines were supported by physicochemical methods and elemental analysis (Tables 1-3). Thus, *o*-aminoacylbenzenes may be used in the synthesis of variously substituted 4H-3,1-benzoxazines.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian VXR-400 spectrometer at 400 MHz for solutions in $CDCl_3$ with $CDCl_3$ as the internal standard and a Bruker AM-300 spectrometer at 300 MHz for solutions in DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Finnigan SSQ-7000 GC/MS with a 30-m capillary column packed with DB-1 using helium as the gas carrier and temperature programming from 50 to 300°C (10 deg/min). The purity of the products was checked by thin-layer chromatography on plates with grade-II activity alumina using 1:1:3 ether–chloroform–hexane as the eluent.

2-Aminopropiophenone (6) was obtained in 96% yield; mp 45-46 (from ethanol) as described in our previous work [8].

2-Amino-4-bromopropiophenone (7) was obtained in 72% yield; mp 85-87°C (from ethanol) as described in our earlier work [9].

2-Amino-5-chloropropiophenone (8) was obtained in 92% yield; mp 80°C (from ethanol) as described in our previous work [10].

2-Amino-4-*tert*-butylacetophenone (12) was obtained in 74% yield by the reduction of nitroso derivative **11** according to our previous procedure [8], mp 96-97°C (from ethanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.30 (9H, s, *t*-Bu); 2.55 (3H, s, Ac); 6.26 (2H, br. s, NH_2); 6.65 (1H, d, *J* = 2.0, H-3); 6.73 (1H, dd, *J* = 9.7, *J* = 2.0, H-5); 7.65 (1H, d, *J* = 9.7, H-6). Found, %: C 75.16; H 8.78; N 7.16. $C_{12}H_{17}NO$. Calculated, %: C 75.35; H 8.96; N 7.32.

2-Aminoacylbenzenes 23-27 were obtained by the reduction of nitroso compounds **18-22** as described in our earlier work [12].

2-Amino-4,5-dimethoxy-2'-chlorobenzophenone (23) was obtained in 54% yield; mp 51-52°C (from 2:1 ethanol-chloroform). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.60 (1H, s, CH_3O); 3.88 (1H, s, CH_3O); 6.19 (1H, s, ArH); 6.54 (2H, br. s, NH_2); 6.58 (1H, s); 7.32-7.44 (4H, m, ArH). Found, %: C 61.42; H, 4.71; N 4.51. $C_{15}H_{14}ClNO_3$. Calculated, %: C 61.76; H 4.84; N 4.80.

2-Amino-4,5-ethylenedioxypropiophenone (24) was obtained in 73% yield; mp 92°C (from ethanol) [12]. **2-Amino-4,5-ethylenedioxybenzophenone (25)** was obtained in 69% yield; mp 135°C (from ethanol) [12]. **2-Amino-4,5-ethylenedioxy-2'-chlorobenzophenone (26)** was obtained in 58% yield, mp 161°C (from ethanol).

2-Amino-4,5-ethylenedioxy-4'-bromobenzophenone (27 was obtained in 71% yield; mp 151-152°C (from 2:1 ethanol–chloroform). ^{1}H NMR spectrum, δ, ppm (DMSO-d_6): 4.18 (2H, m, OCH_2CH_2O); 4.30 (2H, m, OCH_2CH_2O); 5.95 (2H, s, NH_2); 6.22 (1H, s); 6.93 (1H, s); 7.50-7.52 (4H, m, ArH). Found, %: C 52.90; H 3.49; N 4.19. $C_{15}H_{12}BrNO_3$. Calculated, %: C 53.91; H 3.62; N 4.19.

***o*-Acylanilides 28-42 (General Method)**. A sample of 0.01 mol acid chloride and 0.01 mol 3 N aq. NaOH were added together to a stirred solution of 0.01 mol corresponding *o*-aminoacylbenzene (**6-8, 12, 23-27**) in 30 ml dioxane, stirred for 30 min, and poured into 300 ml water. The precipitate formed was filtered off, washed with water, and recrystallized from a suitable solvent.

***o*-Acylaminobenzyl Alcohols 43-57 (General Method)**. A sample of 20 mmol (10 mmol for **28-31**) corresponding amidoacylbenzene **28-42** was added with stirring to a solution of 10 mmol $NaBH_4$ in 20 ml ethanol over 30 min. The reaction mixture was heated to 40-50°C and stirred for 30-120 min until the reaction was complete as indicated by thin-layer chromatography. Then, 10% hydrochloric acid was slowly added until the mixture was slightly acidic. The aqueous ethanolic solution was poured into 150 ml water. The precipitated reduction product was filtered off and recrystallized from a suitable solvent.

Cyclization of *o*-Acylamidobenzyl Alcohols 47-49, 53-55, and 57 to give 4H-3,1-Benzoxazines 62-64, 68-70, and 72 by the Action of Sulfuric Acid (General Method). A. A sample of 1 mmol amido alcohol **47-49, 53-55,** or **57** was added to a 10-fold excess of concentrated sulfuric acid (d = 1.84) (relative to the mass of the starting carbinol) cooled to from 0 to -5°C and the mixture was stirred until a uniform solution was obtained (from 30 to 60 min). The sulfuric acid solution of the cyclization product was poured into a mixture of 20 ml water and 20 ml ice. The reaction mixture was neutralized by adding sodium bicarbonate and extracted with chloroform. The extract was washed with water and dried over magnesium sulfate. After evaporation of the solvent, the product was isolated by thick-layer chromatography on an alumina plate.

Cyclization of *o*-Acylaminobenzyl Alcohols 43-46, 50-52, and 56 to give 4H-3,1-Benzoxazines 58-61, 65-67, and 71 by the Action of Trifluoroacetic Acid (General Method). B. A sample of 1 mmol amido alcohol **43-46, 50-52,** or **56** was added in batches with stirring to a 10-fold amount of CF_3CO_2H (d 1.48) (relative to the mass of the starting alcohol) and heated at 40°C for 1 h. After cooling to room temperature, the reaction mixture was poured into a mixture of 20 ml water and 20 ml ice and neutralized by adding sodium bicarbonate. The mixture was extracted with chloroform. The extract was washed with water and dried over $MgSO_4$. The solvent was evaporated and the residue was subjected to thick-layer chromatography on an alumina plate.

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REFERENCES

1. H. Kuch, K. Schmitt, G. Seidl., and J. Hoffman, West Ger. Pat. 1670772 (1978); *Ref. Zh. Khim.*, 3O158 (1979).
2. S. Gabriel and T. Posner, *Ber.*, **27**, 3509 (1894).
3. O. Widmann, *Ber.*, **16**, 2576 (1883).
4. A. G. Bayer, West Ger. Pat. Application 3806490 (1989); *Ref. Zh. Khim.*, 10O403P (1990).
5. E. V. Gromachevskaya, T. P. Kosulina, A. L. Chekhun, and V. G. Kulnevich, *Khim. Geterotsikl. Soedin.*, 542 (1993) [*Chem. Heterocycl. Comp.*, **29**, 465 (1993)].
6. E. V. Gromachevskaya, V. G. Kulnevich, D. P. Elchinov, T. P. Kosulina, and A. L. Chekhun, *Khim. Geterotsikl. Soedin.*, 547 (1993) [*Chem. Heterocycl. Comp.*, **29**, 469 (1993)].
7. S. S. Mochalov, R. A. Gazzaeva, A. N. Fedotov, Yu. S. Shabarov, and N. S. Zefirov, *Khim. Geterotsikl. Soedin.*, 922 (2003) [*Chem. Heterocycl. Comp.*, **39**, 794 (2003)].
8. A. N. Fedotov, S. S. Mochalov, and Yu. S. Shabarov, *Zh. Prikl. Khim.*, **50**, 1860 (1977).
9. Yu. S. Shabarov and S. S. Mochalov, *Zh. Org. Khim.*, **8**, 293 (1972).
10. Yu. S. Shabarov and S. S. Mochalov, *Khim. Geterotsikl. Soedin.*, 1334 (1973) [*Chem. Heterocycl. Comp.*, **9**, 1207 (1973)].
11. R. A. Gazzaeva, A. N. Fedotov, A. N. Fedotov, E. V. Trofimova, O. A. Popova, S. S. Mochalov, and N. S. Zefirov, *Zh. Org. Khim.*, **42**, 94 (2006).

12. S. S. Mochalov, D. V. Kosynkin, I. D. Yudin, V. I. Atanov, Yu. S. Shabarov, and N. S. Zefirov, *Khim. Geterotsikl. Soedin.*, 601 (1994) [*Chem. Heterocycl. Comp.*, **30**, 527 (1994)].
13. V. K. Daukšas and E. V. Udrėnaitė, *Khim. Geterotsikl. Soedin.*, 1155 (1975) [*Chem. Heterocycl. Comp.*, **11**, 1003 (1975)].
14. V. K. Daukšas, and E. B. Udrėnaitė, *Nauchn. Trudy Vuzov LitSSR, Khim. Khim. Tekhnol.*, **16**, 191 (1974).