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SYNTHESIS OF HETEROCYCLES FROM THE PRODUCTS OF ANIONIC ARYLATION OF UNSATURATED COMPOUNDS. 7*. PRODUCTS OF HALOARYLATION OF ACRYLIC ACID AND ITS ESTERS IN THE SYNTHESIS OF BENZO[*b*]THIOPHENE DERIVATIVES

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3-Chloro-2-chlorocarbonylbenzo[b]thiophenes were obtained on oxidation of Meerwein reaction products, viz. 3-aryl-2-halopropionic acids and their esters, with thionyl chloride in the presence of N-benzyl-N-methylmorpholinium chloride. Disubstituted thioureas were synthesized by the reaction of these compounds with ammonium thiocyanate and aromatic amines, and were cyclized by interaction with iodoacetic acid with the formation of 4-thiazolidinone derivatives. The same cyclization in the presence of aromatic aldehydes leads to the formation of the corresponding 5-arylidene-substituted 4-thiazolidinones.

Keywords: 3-aryl-2-halopropionic acids, benzo[*b*]thiophene, thiazolidinones, oxidation with thionyl chloride, Meerwein reaction.

One of the most convenient methods of synthesizing benzo[*b*]thiophenes is the oxidation of cinnamic acid and its derivatives [2-7] or 3-arylpropionic acids [2,6-9] with thionyl chloride. The synthetic possibilities of this method depend mainly on the availability of the initial acids. Cinnamic acids substituted in the aromatic ring or their esters may be obtained by the Meerwein reaction [10,11].

In the present work, continuing investigations on the products of interaction of unsaturated compounds with arenediazonium salts [1,12-15], the possibility of synthesizing benzo[*b*]thiophene derivatives using the products of haloarylation of acrylic acid has been studied.

We have established that the products of bromoarylation of acrylic acids **1a-e** react with thionyl chloride in the presence of pyridine with the formation of substituted 3-chloro-2-chlorocarbonylbenzo[*b*]thiophenes **2a-e** (method A).

Acids **1a-e** were obtained by the interaction of arenediazonium bromides with acrylic acid catalyzed by copper salts [16,17]. 3-Aryl-2-chloropropionic acids, obtained by the chloroarylation of acrylic acid, interact with thionyl chloride analogously.

Products of the haloarylation of acrylic acid esters **3**, **4** are more accessible from a preparative point of view [10,14,18].

* For Part 6 see [1].

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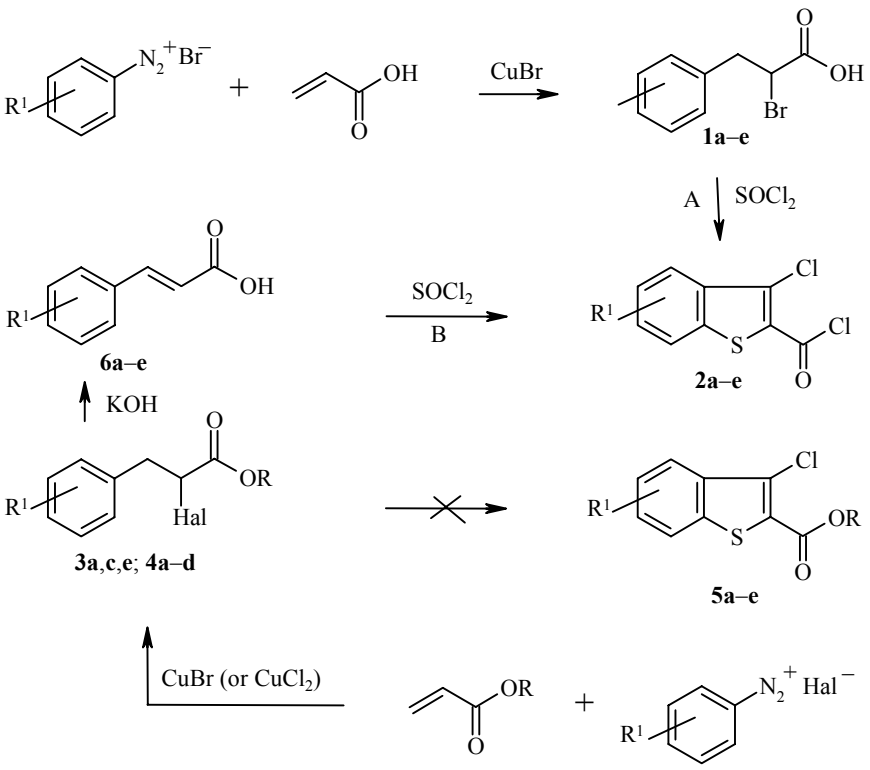
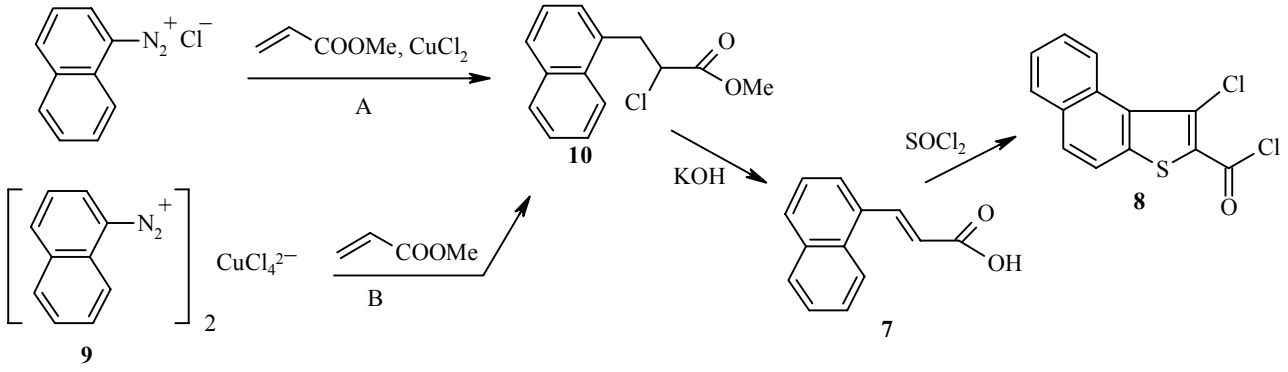


1, **3**, **4**, **6 a** R^1 = H, **b** R^1 = 2-Cl, **c** R^1 = 4-Me, **d** R^1 = 4-Cl, **e** R^1 = 4-NO_2; **3** Hal = Cl, R = Me; **4** Hal = Br, R = Et; **2**, **5 a** R^1 = H, **b** R^1 = 4-Cl, **c** R^1 = 6-Me, **d** R^1 = 6-Cl, **e** R^1 = 6-NO_2

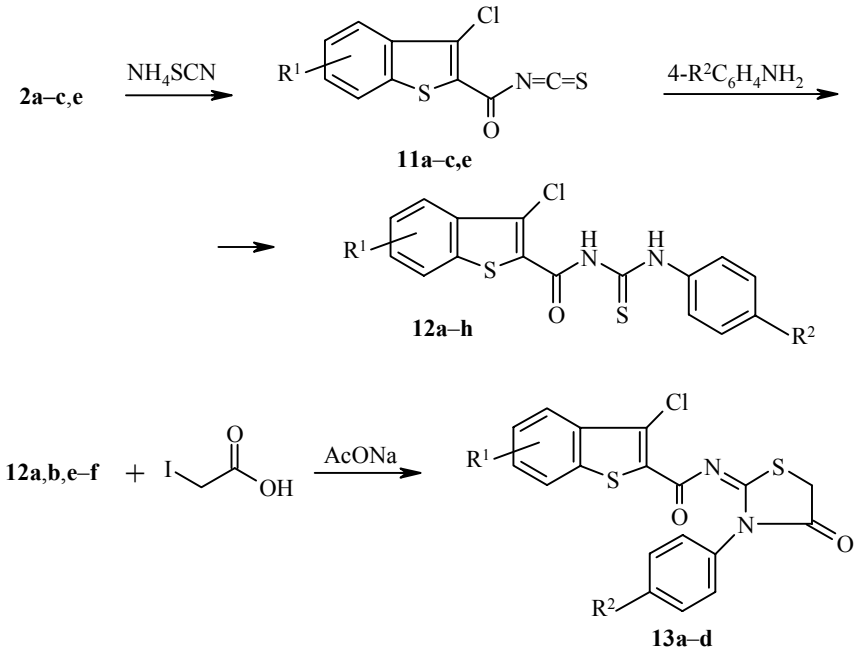
We attempted to obtain benzo[*b*]thiophene derivatives by the oxidation of esters **3**, **4** with thionyl chloride. However compounds **5a-e** were formed in low yield or were not isolated at all. It is possible to obtain acid chlorides **2a-e** from esters **3**, **4** through cinnamic acids **6a-e** (method B). Dehydrohalogenation and saponification of esters **3**, **4** takes place smoothly and in high yield on treatment with alkali.

3-Chloro-2-chlorocarbonylnaphtho[2,1-*b*]thiophene **8** was obtained from acid **7** by an analogous scheme (method A). A modified Meerwein reaction (method B) proved to be more efficient in this case using the new arylating reagent, 1-naphthalenediazonium tetrachlorocuprate(II) **9**, proposed in [19]. This enabled the yield of 2-chloro-3-(1-naphthyl)propionic acid methyl ester **10** to be increased from 42 to 69%.

The use of equimolar amounts of triethylbenzylammonium chloride in place of pyridine in oxidations with thionyl chloride increases the yield of acid chlorides **2** [5]. We used N-benzyl-N-methylmorpholinium chloride in these reactions.

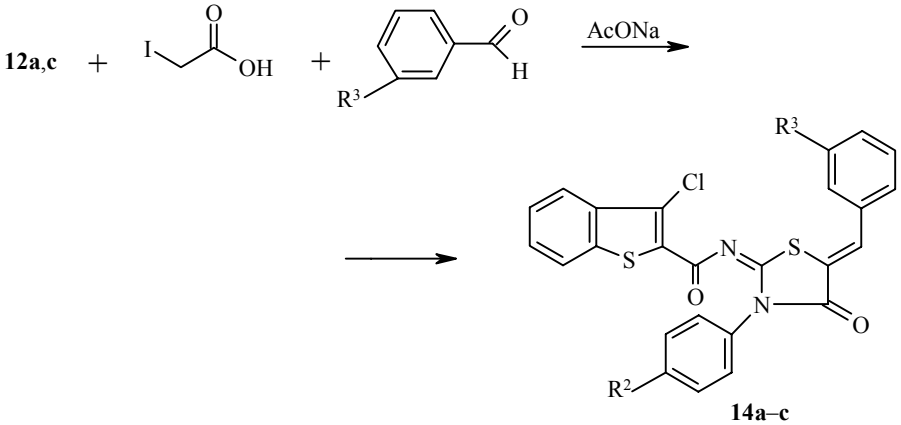


We used acid chlorides **2a,c-e** for the synthesis of more complex heterocyclic systems. The interaction of these compounds with ammonium thiocyanate gave substituted 3-chloro-2-isothiocyanatocarbonylbenzo-[*b*]thiophenes **11a,c-e**, which were reacted without isolation with aromatic amines. N,N'-disubstituted thioureas **12a-h** (Table 1) were synthesized in this way. The latter react with iodoacetic acid in the presence of sodium acetate with closure of the 4-thiazolidinone ring (compounds **13a-d**, Table 1).



12 a–d R^1 = H; **a** R^2 = H, **b** R^2 = Me; **c** R^2 = Cl; **d** R^2 = COOH; **e** R^1 = 6-Me, R^2 = H; **f** R^1 = 6-Me, R^2 = Me; **g** R^1 = 4-Cl, R^2 = H; **h** R^1 = 6-NO_2, R^2 = H; **13 a** R^1 = R^2 = H; **b** R^1 = H, R^2 = Me; **c** R^1 = 6-Me, R^2 = H; **d** R^1 = 6-Me, R^2 = Me

It was shown using the examples of thioureas **12a-e** that cyclization with simultaneous condensation at the methylene group of the thiazolidinone ring was possible. On interacting these compounds with iodoacetic acid and benzaldehyde or 3-nitrobenzaldehyde the 5-arylidene-substituted 4-thiazolidinones **14a-c** were formed (Table 1).



14 a R^2 = H, R^3 = NO_2; **b** R^2 = Cl, R^3 = H; **c** R^2 = Cl, R^3 = NO_2

TABLE 1. Characteristics of Compounds **12-14**

Compound	Empirical formula	Found, % / Calculated, %			T., °C*	Yield, %
		C	H	N		
12a	$C_{16}H_{11}ClN_2OS_2$	55.23 / 55.40	3.18 / 3.20	7.95 / 8.08	156-157	85
12b	$C_{17}H_{13}ClN_2OS_2$	56.69 / 56.58	3.65 / 3.63	7.58 / 7.76	158.5-159	74
12c	$C_{16}H_{10}Cl_2N_2OS_2$	50.23 / 50.40	2.57 / 2.64	7.23 / 7.35	180-181.5	80
12d	$C_{17}H_{11}ClN_2O_3S_2$	52.16 / 52.24	2.75 / 2.84	7.14 / 7.17	218-220	75
12e	$C_{17}H_{13}ClN_2OS_2$	56.40 / 56.58	3.52 / 3.63	7.69 / 7.76	162-163	65
12f	$C_{18}H_{15}ClN_2OS_2$	57.38 / 57.67	3.95 / 4.03	7.53 / 7.47	177-178	83
12g	$C_{16}H_{10}Cl_2N_2OS_2$	50.51 / 50.40	2.60 / 2.64	7.33 / 7.35	175-176	84
12h	$C_{16}H_{10}ClN_3O_3S_2$	48.93 / 49.04	2.48 / 2.57	10.61 / 10.72	178-179	56
13a	$C_{18}H_{11}ClN_2O_2S_2$	55.71 / 55.88	2.82 / 2.87	7.14 / 7.24	240-241	85
13b	$C_{19}H_{13}ClN_2O_2S_2$	57.07 / 56.92	3.20 / 3.27	6.82 / 6.99	230-232	63
13c	$C_{19}H_{13}ClN_2O_2S_2$	56.85 / 56.92	3.30 / 3.27	6.86 / 6.99	223	40
13d	$C_{20}H_{15}ClN_2O_2S_2$	57.63 / 57.89	3.62 / 3.64	6.52 / 6.75	219-220	38
14a	$C_{25}H_{14}ClN_3O_4S_2$	57.48 / 57.75	2.70 / 2.71	8.02 / 8.08	297-298	41
14b	$C_{25}H_{14}Cl_2N_2O_2S_2$	58.83 / 58.94	2.69 / 2.77	5.44 / 5.50	>300	50
14c	$C_{25}H_{13}Cl_2N_3O_4S_2$	54.22 / 54.16	2.28 / 2.36	7.40 / 7.58	290-291	53

* Mp are given for compounds **12a-h**, decomposition points are given for compounds **13**, **14**.

3-Aryl-2-bromo(chloro)propionic acids and their esters may be used in addition to cinnamic and hydrocinnamic acid derivatives for the synthesis of substituted 3-chloro-2-chlorocarbonylbenzo[*b*]thiophene. The starting materials are readily obtained by the haloarylation of acrylic acids or acrylates. Combination of the haloarylation reaction with subsequent oxidation of the obtained products with thionyl chloride enables derivatives of benzo[*b*]thiophene to be obtained with various substituents in the benzene ring.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian VXR-300 (300 MHz) instrument in DMSO-d_6, internal standard was HMDS. The mass spectra were taken on a Finnigan MAT INKOS-50 chromato-mass spectrometer, ionization energy was 70 eV.

Acids **1a-e** were obtained by procedures close to those described in [16,17], their constants coincided with the data of [16,17,20].

Procedures for the synthesis of esters **3**, **4** are described in [15]. The constants of compounds **3**, **4a,c** agreed with the data of [10,11,14,15].

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm*									
	Benzo[*b*]thiophene fragment					$R^2C_6H_4$, $R^3C_6H_4$	R^2 (3H, s)	NHC=S (1H, s)	NHC=O (1H, s)	CH_2 (2H, s) or CH= (1H, s)
	4-H	5-H	6-H	7-H	R^1 (3H, s)					
12a	7.97 (1H, m)	7.65 (2H, m)		8.17 (1H, m)		7.29 (1H, t); 7.44 (2H, t); 7.71 (2H, d)		11.28	12.06	
12b	7.97 (1H, m)	7.65 (2H, m)		8.18 (1H, m)		7.23 (2H, d); 7.58 (2H, d)	2.33	11.25	12.00	
12c	7.98 (1H, m)	7.66 (2H, m)		8.18 (1H, m)		7.49 (2H, d); 7.73 (2H, d)		11.40	12.02	
12f	7.85 (1H, d)	7.46 (1H, d)		7.95 (1H, s)	2.50	7.23 (2H, d); 7.57 (2H, d)	2.32	11.08	11.99	
12g		7.60 (2H, m)		8.17 (1H, d)		7.29 (1H, t); 7.44 (2H, t); 7.70 (2H, d)		11.68	12.04	
13a	7.90 (1H, d)	7.56 (5H, m)*[2]		8.01 (1H, d)		7.44 (2H, d)				4.22
13b	7.91 (1H, d)	7.57 (2H, m)		8.02 (1H, d)		7.30 (2H, d); 7.38 (2H, d)	2.42			4.20
13d	7.77 (1H, d)	7.34 (1H)		7.78 (1H, s)	2.42	7.30 (2H, d); 7.38 (2H, d)	2.42			4.19
14a	8.01 (1H, d)	7.50-7.65 (7H, m)*[2]		8.16 (1H, d)		3-$O_2NC_6H_4$: 7.91 (2H, m); 8.34 (1H, d); 8.57 (1H, s)				8.12
14b	7.93 (1H, d)	7.50-7.67 (9H, m)*[2]		7.96 (1H, d)		7.78 (2H, d, C_6H_5)				8.03
14c	7.87-8.00 (3H, m)*[2]	7.50-7.67 (6H, m)*[2]		8.19 (1H, d)		3-$O_2NC_6H_4$; 8.35 (1H, d), 8.61 (1H, s)				8.15

* In the case of narrow multiplets the centers are indicated.

*[2] Partial overlap of signals of the benzene ring protons.

2-Bromo-3-(2-chlorophenyl)propionic Acid Ethyl Ester (4b) was obtained in 48% yield; bp 140-142°C (2 mm Hg), mp 41-43°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 1.22 (3H, t, CH_3); 4.18 (2H, dq, OCH_2); 3.35 (1H, dd, CH_2); 3.52 (1H, dd, CH_2); 4.61 (1H, t, CH); 7.25-7.43 (4H, m, C_6H_4). Found, %: Cl + Br 39.45. $C_{11}H_{12}BrClO_2$. Calculated, %: Cl + Br 39.56.

2-Bromo-3-(4-chlorophenyl)propionic Acid Ethyl Ester (4d) was synthesized in 60% yield; bp 142-143°C (2 mm Hg), n_D^{20} 1.5391. Found, %: Cl + Br 39.50. $C_{11}H_{12}BrClO_2$. Calculated, %: Cl + Br 39.56.

3-(2-Chlorophenyl)acrylic Acid (6b). Sodium hydroxide (13 g) was dissolved with heating in ethanol (70 ml), ester **4b** (16 g, 55 mmol) was added, and the mixture boiled for 2.5 h. The reaction mixture was poured into hot water (200 ml). Acid **6b** was isolated by acidification with HCl.

Compounds 6a,c-e were obtained analogously. The constants of acids **6a-e** corresponded with the data of [21].

3-Chloro-2-chlorocarbonyl-R^1-benzo[*b*]thiophenes (2a-e). A. A mixture of acid **1a-e** (7.5 mmol), N-benzyl-N-methylmorpholinium chloride (1.7 g, 7.5 mmol), and $SOCl_2$ (2 ml) was heated to 140°C and further $SOCl_2$ (3 ml) poured in at this temperature. The mixture was heated for 2.5 h, and the product extracted with boiling heptane. Yields (%) were **2a** 58, **2b** 30, **2c** 55, **2d** 52, and **2e** 32.

B. Acid **6a-e** (140 mmol), N-benzyl-N-methylmorpholinium chloride (20.4 g, 90 mmol), and $SOCl_2$ (15 ml) were heated to 140°C. Then $SOCl_2$ (35 ml) was added to the reaction mixture dropwise so that the temperature did not exceed 135-140°C. Heating was continued for a further 3 h, and acid chlorides **2a-e** extracted with boiling heptane. Yields (%) were **2a** 76, **2b** 55, **2c** 64, **2d** 62, and **2e** 58.

The melting points and spectral characteristics of compounds **2a-e** corresponded with those given in studies [2-5].

2-Chloro-3-(1-naphthyl)propionic Acid Methyl Ester (10). A. A solution of 1-naphthalenediazonium chloride, obtained by the diazotization of 1-naphthylamine (14.3 g, 100 mmol), was added dropwise with stirring to a mixture of methyl acrylate (9 ml, 100 mmol), $CuCl_2 \cdot 2H_2O$ (4 g), and acetone (100 ml). The reaction mixture was heated gently until evolution of nitrogen started. The reaction proceeded at room temperature until the end of gas evolution. Water (100 ml) was poured in, the mixture extracted with ether, and the extract dried over $MgSO_4$. The solvent was evaporated, and 1-chloronaphthalene and ester **10** [19] were obtained by distillation in vacuum, yield 42%; bp 167-169°C (2 mm Hg), mp 48-49°C (ethanol).

B. Methyl acrylate (9 ml, 100 mmol), HCl (2 ml), acetone (100 ml), and water (100 ml) were mixed and at 30°C naphthalenediazonium tetrachlorocuprate(II) **9** (5.16 g, 10 mmol), obtained by the procedure of [19], was added with stirring. After the beginning of nitrogen evolution the temperature of the mixture was brought to 20-22°C, and further diazonium salt **9** (20.63 g, 40 mmol) was added in portions during 1 h. Treatment of the reaction mixture and isolation of the products was carried out analogously to method A. The yield of compound **10** was 69%.

3-(1-Naphthyl)acrylic Acid (7). Compound **10** (15.6 g, 63 mmol) was added to a hot solution of KOH (14 g) in ethanol (80 ml). The reaction mixture was boiled for 3 h, then poured into 10% HCl (300 ml). The precipitate was filtered off, and recrystallized from ethanol. Yield 12 g (96%); mp 210-211°C (mp 211-212°C [21]).

3-Chloro-2-chlorocarbonylnaphtho[2,1-*b*]thiophene (8). A mixture of acid **7** (12.9 g, 65 mmol), N-benzyl-N-methylmorpholinium chloride (14.8 g), and thionyl chloride (13 ml) was heated to 140°C and thionyl chloride (25 ml) was added dropwise at this temperature. Reaction was conducted for a further 2 h at 140°C. Compound **8** was extracted with boiling heptane. Yield 8.4 g (46%); mp 147-148°C (mp 147-149°C [22]).

1-(3-Chlorobenzo[*b*]thien-2-ylcarbonyl)-3-phenylthiourea (12a). Acid chloride **2a** (2.31 g, 10 mmol), dissolved in the minimum amount of anhydrous acetone, was added to a solution of ammonium thiocyanate (0.91 g, 12 mmol) in acetone (15 ml). The reaction mixture was heated, aniline (0.93 g, 10 mmol) was added, and the mixture boiled for 2-3 min. After cooling, the mixture was poured into water, the solid was filtered off, and recrystallized from DMF.

Compounds 12b-h were obtained analogously (**12d** was crystallized from DMSO).

2-(3-Chlorobenzo[*b*]thien-2-ylcarbonylimino)-3-phenylthiazolidin-4-one (13a). A mixture of thiourea **12a** (1.9 g, 5.5 mmol), monoiodoacetic acid (1 g, 5.5 mmol), and anhydrous sodium acetate (0.9 g, 11 mmol), in glacial acetic acid (30 ml) was boiled for 4 h. The mixture was cooled, the solid separated, washed with water, and with alcohol, and recrystallized from DMF.

Compounds 13b-d were obtained analogously.

2-(3-Chlorobenzo[*b*]thien-2-ylcarbonylimino)-5-(3-nitrobenzylidene)-3-phenylthiazolidin-4-one (14a). A mixture of thiourea **12a** (1.04 g, 3 mmol), monoiodoacetic acid (0.56 g, 3 mmol), 3-nitrobenzaldehyde (0.45 g, 3 mmol), and anhydrous sodium acetate (0.5 g, 6 mmol) in glacial acetic acid (25 ml) was boiled for 3.5 h. The solid was filtered off, washed with water, and with alcohol, and recrystallized from DMF. Yield 0.6 g (38%). Mass spectrum, *m/z* (*I*, %): 519 $[M]^+$ (20), 386 (62), 352 (10), 236 (10), 195 (100), 167 (22), 123 (11), 77 (12).

Compounds 14b,c were obtained analogously.

Mass spectra, *m/z* (*I*, %): **14b**, 508 $[M]^+$ (8), 195 (100), 167 (30), 134 (75), 132 (22), 123 (23), 90 (15), 89 (15); **14c**, 553 $[M]^+$ (3), 195 (100), 179 (13), 167 (30), 132 (30), 123 (20), 89 (30).

The ^{1}H NMR spectra of compounds **12-14** are given in Table 2.

REFERENCES

1. M. D. Obushak, V. V. Karpjak, and M. I. Ganushchak, *Heteroatom Chem.*, **10**, 517 (1999).
2. S. Nakagawa, J. Okumura, F. Sakai, H. Hoshi, and T. Naito, *Tetrahedron Lett.*, 3719 (1970).
3. W. B. Wright and H. J. Brabander, *J. Heterocycl. Chem.*, **8**, 711 (1971).
4. W. Ried, G. Oremek, and B. Ocakcioglu, *Liebigs Ann. Chem.*, 1424 (1980).
5. T. N. Sidorenko, G. A. Terent'eva, V. S. Raida, O. S. Andrienko, Yu. V. Savinykh, and V. S. Aksenov, *Khim. Geterotsikl. Soedin.*, 1618 (1982).
6. T. Higa and A. J. Krubsack, *J. Org. Chem.*, **40**, 3037 (1975).
7. T. Higa and A. J. Krubsack, *J. Org. Chem.*, **41**, 3399 (1976).
8. A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 5149 (1968).
9. A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 4515 (1973).
10. A. V. Dombrovskii, in *Reactions and Methods of Investigation of Organic Compounds* [in Russian], Vol. 11, Goskhimizdat, Moscow (1962), p. 285.
11. C. S. Rondestvedt, in *Organic Reactions*, Vol. 11, Wiley, New York (1960), p.189.
12. N. D. Obushak, V. S. Matiichuk, and R. L. Martyak, *Khim. Geterotsikl. Soedin.*, 986 (2001).
13. N. D. Obushak, V. S. Matiichuk, R. L. Martyak, and N. I. Ganushchak, *Khim. Geterotsikl. Soedin.*, 97 (1999).
14. N. D. Obushak, V. S. Matiichuk, N. I. Ganushchak, and Yu. E. Burlak, *Khim. Geterotsikl. Soedin.*, 555 (1998).
15. N. D. Obushak, V. S. Matiichuk, and N. I. Ganushchak, *Zh. Org. Khim.*, **34**, 266 (1998).
16. G. H. Cleland, *J. Org. Chem.*, **26**, 3362 (1961).
17. G. H. Cleland, *J. Org. Chem.*, **34**, 744 (1969).
18. C. S. Rondestvedt, in *Organic Reactions*, Vol. 24, John Wiley, New York, London (1976), p. 225.
19. N. D. Obushak, N. I. Ganushchak, and M. B. Lyakhovich, *Zh. Org. Khim.*, **27**, 1757 (1991).
20. Beilstein, Edit. 1, Vol. 9, p. 201.
21. I. M. Heilbron and G. M. Bunbury (editors), *Dictionary of Organic Compounds*, 2nd Edit., Oxford Univ. Press, New York (1949).
22. T. N. Sidorenko, G. A. Terent'eva, O. S. Andrienko, Yu. V. Savinykh, and V. S. Aksenov, *Khim. Geterotsikl. Soedin.*, 192 (1983).