Chemistry of Heterocyclic Compounds, Vol. 40, No. 1, 2004

1,1-DICHLORO-2,2,2-TRIHALOETHYL ISOCYANATES AND N-(1-CHLORO-2,2,2-TRIHALOETHYLIDENE)URETHANES IN THE SYNTHESIS OF 4-TRIHALOMETHYL-2H-1,3-BENZOXAZIN-2-ONES

M. V. Vovk, A. V. Bol'but, P. S. Lebed', and V. I. Boiko

4-Trihalomethyl-2H-1,3-benzoxazin-2-ones have been synthesized by the reaction of 1,1-dichloro-2,2,2-trihaloethyl isocyanates or N-(1-chloro-2,2,2-trihaloethylidene)urethanes with 3-dialkylamino-(alkoxy)phenols. The character of the products from the addition of nucleophiles has been shown to depend on the nature of the nucleophile and the trihalomethyl group.

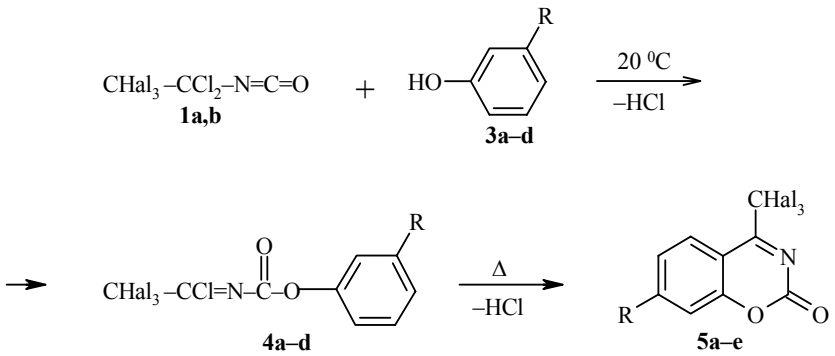
Keywords: N-alkylideneurethanes, *m*-dialkylamino(alkoxy)phenols, isocyanates, 4-trihalomethyl-2H-1,3-benzoxazin-2-ones.

In previous papers [1-3] we have shown the possibility of using thermal cyclocondensation of derivatives of 1-chloro-2-trifluoromethylalkyl isocyanates and N-alkylidene-O-arylurethanes to prepare trifluoromethyl-containing 3,4- and 2,3-dihydro-1,3-benzoxazines. With the objective of synthesizing non-hydrogenated analogs of known heterocyclic systems we have studied the reaction of 1,1-dichloro-2,2,2-trihalomethyl isocyanates **1a,b**, and the N-(1-chloro-2,2,2-trihaloethylidene)urethanes **2a-d** made from them, with phenols **3a-d** activated by dialkylamino or alkoxy groups.

It was found that interaction of the isocyanates **1a,b** with the *m*-dialkylaminophenols **3a,b** in benzene in the presence of an organic base led to the formation of the N-alkylideneurethanes **4a-c**, the structures of which were confirmed by the absence in the IR spectra of the reaction mixtures of the absorption band of the N=C=O groups in the 2260-2270 cm^{-1} region and the appearance of the absorption band of the C=O group in the 1760-1770 cm^{-1} region. According to the ^{19}F NMR spectrum, measured for compound **4b**, the N-alkylideneurethanes **4a-c** even at 20-25°C began to be converted slowly into 4-trihalomethyl-2H-1,3-benzoxazin-2-ones **5a-c** by intramolecular electrophilic attack of the imidoyl carbon at position 6 of the benzene ring, activated by the dialkylamino group. This process was completed by boiling the reaction mixture for 0.5 h. In the case of 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates the analogous reaction occurred only on heating in toluene for 10 h [2].

The decrease in the nucleophilicity of the phenoxy nucleus in N-alkylideneurethanes **4d,e** which resulted from replacing the dialkylamino groups by poorer donating alkoxy group led to considerably slower cyclization. The required compounds **5d,e** were isolated in yields of 41 and 9% respectively only after prolonged boiling of the reaction mixture in xylene.

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02094, Ukraine; e-mail: hetfos@ukrpack.net, mvovk@i.com.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 107-112, January, 2004. Original article submitted February 21, 2001.



1a Hal = F, **b** Cl, **3a** R = Me_2N, **b** Et_2N, **c** MeO, **d** EtO,
4, 5 a R = Me_2N, Hal = Cl, **b** R = Et_2N, Hal = F, **c** R = Et_2N, Hal = Cl,
d R = MeO, Hal = F, **e** R = EtO, Hal = Cl

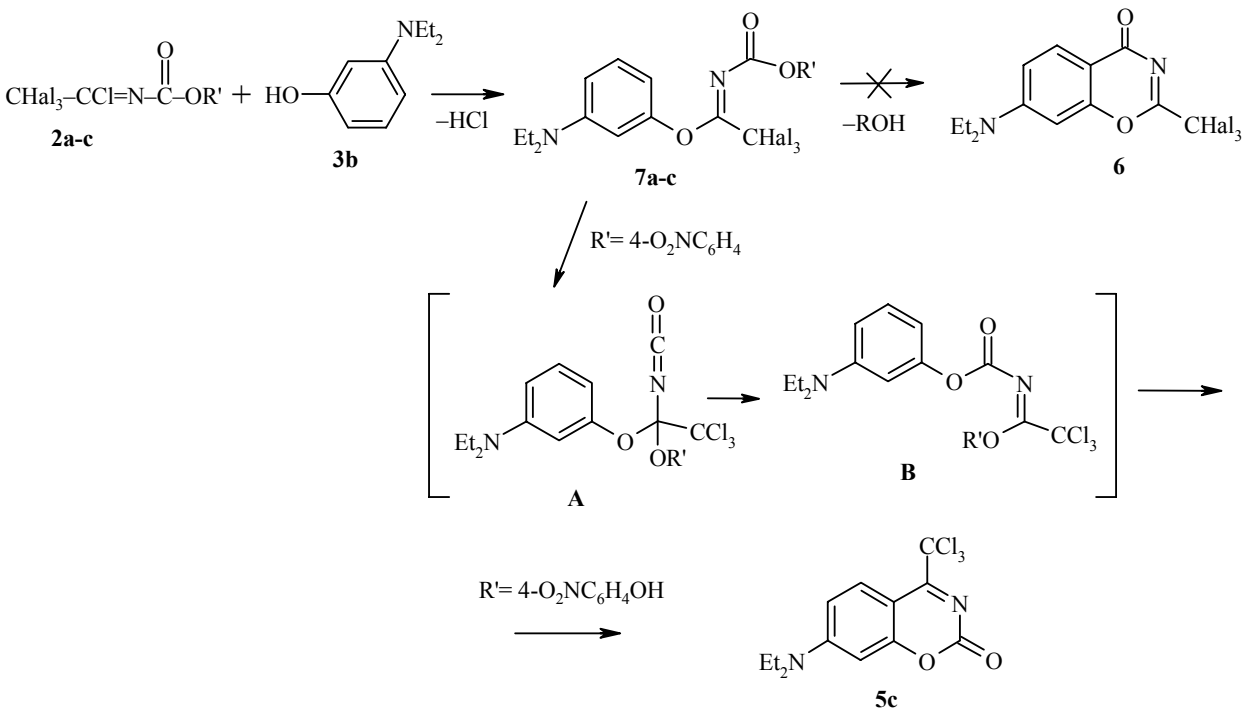
In the IR spectra of the 1,3-benzoxazinones **5** the absorption bands of the exocyclic C=O groups appear at 1735-1760 and the endocyclic C=N bond at 1630-1635 cm^{-1}. In the ^1H NMR spectra there are doublets for proton $C_{(8)}H$ (6.44-6.83) and proton $C_{(5)}H$ (7.65-8.17 ppm), and also a doublet of doublets for $C_{(6)}H$ (6.65-6.91 ppm) which confirms annelation at position 6 of the benzene ring. In the ^{19}F NMR spectra of compounds **5a,b,d** there are singlets for the CF_3 group in the range 67.2-68.0 ppm, typical for this group attached to sp^2-carbon atoms [4]. The cyclic structure of **5** was also confirmed by measuring the ^{13}C NMR spectrum for compound **5c**: 12.32 (CH_3), 45.04 (CH_2), 94.87 (CCl_3), 95.96 ($C_{(8)}$), 99.64 ($C_{(5a)}$), 109.10 ($C_{(6)}$), 129.53 ($C_{(5)}$), 151.71 ($C_{(8a)}$), 153.98 ($C_{(4)}$), 161.41 ($C_{(7)}$), 169.59 (C=O).

To obtain the isomeric with **5** 2-trihalomethyl-4H-1,3-benzoxazin-4-ones of type **6** we investigated the reaction of N-(1-chloro-2,2,2-trihalo)ethylidene-O-methylurethanes **2a,b** [5] with the phenol **3b**. The reason for choosing this solution was the results obtained previously for the cyclization of compounds **2a,b** with arylamines [6]. However, as we had established, the products of substitution of the chlorine atom **7a,b** did not undergo electrophilic attack at the *o*-position of the phenoxy substituent by the methoxycarbnyl group even on prolonged heating in mesitylene. Therefore N-alkylidene-O-(4-nitrophenyl)urethane **2c** was chosen to increase the electrophilicity of the carbonyl group in reaction with the phenol **3b**. We observed the unexpected conversion of the imidate **7c** in a yield of 51% not into a structure of type **6**, but into compound **5c** (the reaction occurs over a day at room temperature but in just 0.5 h in boiling dioxane). We suggest that in this case a mild transphenoxylation occurs into the heterodiene system of bonds, which most probably occurs by an anionic mechanism [7] through the stage of the 1,1-diphenoxyalkyl isocyanate **A**, Cyclization of the intermediate rearrangement product **B** is evidently facilitated by the ability of the 4-nitrophenoxy group as a leaving group (Scheme 1).

Reaction of alcohols with the benzoxazin-2-ones **5b,c** gave stable 2,3-dihydro-4-alkoxy derivatives **10a-c** which confirmed the ability of trihalomethyl group no matter what the halogen, to retain exocyclic alkoxy substituents.

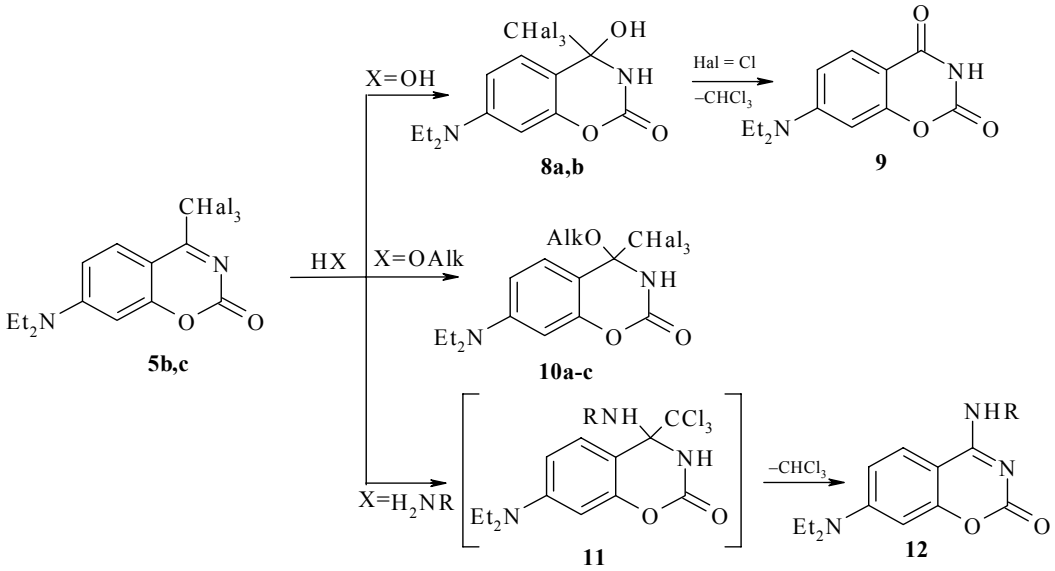
The increased electrophilicity of compound **5b**, caused by the presence of the CF_3 group, led to its reaction with ammonia occurring at both electrophilic centers with opening of the oxazine ring, as a result of which we were unable to isolate individual products of the reaction. At the same time the reaction of cyclohexylamine with compound **5c**, which contains a CCl_3 group, leaves the cyclic system unaffected. The initially formed 4-amino-3,4-dihydro derivative **11**, like its hydroxy analog **8b**, loses a molecule of chloroform and is converted into compound **12** which, according to its ^1H NMR spectrum in $CDCl_3$, exists as the 4-amino derivative **12**.

Scheme 1



2, **7 a** Hal = F, R'= Me, **b** Hal = Cl, R' = Me,
c Hal = Cl, R' = 4-$O_2NC_6H_4$

4-Trihalomethyl-2H-1,3-benzoxazin-2-ones of type **5** are little studied [8,9] benzannelated systems with two electrophilic centers – the carbon atoms of the C=O and C=N groups. The reactions of benzoxazinones **5** with some nucleophilic reagents might be used as a suitable variant for the synthesis of new dihydro derivatives. In particular, mild hydrolysis of compound **5b**, which contains a CF_3 group, occurs by addition of water to the C=N group with the formation of the stable product **8a**, whereas the CCl_3 group does not stabilize its analog **8b**, which undergoes haloform elimination to give the 2,4-dioxo derivative **9.**



8 a Hal = F, **b** Hal = Cl; **10 a** Hal = F, Alk = Me, **b** Hal = Cl, Alk = Me, **c** Hal = Cl, Alk = *i*-Pr; **12** R = *cyclo*-C_6H_{11}

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
5a	$C_{11}H_9Cl_3N_2O_2$	43.31 / 42.96	2.69 / 2.95	9.27 / 9.11	187-188	52
5b	$C_{13}H_{13}F_3N_2O_2$	54.21 / 54.55	4.39 / 4.58	10.07 / 9.79	155-156	44
5c	$C_{13}H_{13}Cl_3N_2O_2$	46.90 / 46.52	4.24 / 3.90	8.03 / 8.35	185-186	56 (A), 51 (B)
5d	$C_{10}H_6F_3NO_3$	48.61 / 48.99	2.32 / 2.47	5.50 / 5.71	97-98	41
5e	$C_{11}H_8Cl_3NO_3$	43.11 / 42.82	2.69 / 2.61	4.17 / 4.54	125-126	9
8a	$C_{13}H_{15}F_3N_2O_3$	51.44 / 51.32	5.18 / 4.97	9.52 / 9.21	134-135	95
9	$C_{12}H_{14}N_2O_3$	61.48 / 61.53	5.92 / 6.02	12.17 / 11.96	206-207	94
10a	$C_{14}H_{17}F_3N_2O_3$	53.06 / 52.83	5.27 / 5.38	8.62 / 8.80	119-120	73
10b	$C_{14}H_{27}Cl_3N_2O_3$	46.08 / 45.76	4.41 / 4.66	7.53 / 7.62	180-181	71
10c	$C_{16}H_{12}Cl_3N_2O_3$	48.86 / 48.56	5.11 / 5.35	6.72 / 7.08	168-169	70
12	$C_{18}H_{25}N_3O_2$	68.71 / 68.54	8.27 / 7.99	13.03 / 13.32	211-212	75

EXPERIMENTAL

IR spectra of KBr disks or solutions in chloroform or dioxane were recorded on a UR-20 apparatus. ^1H and ^{19}F NMR spectra of $CDCl_3$ solutions with TMS (^1H) or CCl_3F (^{19}F) internal standards were recorded on Varian-Gemini machine (300 and 188 MHz respectively). The characteristics of compounds **5a-e**, **8a**, **9**, **10a-c**, and **12** are cited in Table 1. Compounds **5a,b,d** were recrystallized from a benzene–dioxane mixture, **5c,e, 8a, 9, 12** from dioxane, **10a,b** from methanol, and **10c** from 2-propanol.

N-(1,2,2,2-Tetrachloro)ethylidene-O-(4-nitrophenyl)urethane (2c). Triethylamine (0.505 g, 5 mmol) in benzene (5 ml) was added dropwise to a mixture of isocyanate **1b** (1.22 g, 5 mmol) and 4-nitrophenol (0.696 g, 5 mmol) and the mixture was stirred for 2h. The precipitate of triethylammonium chloride was filtered off, the filtrate was evaporated and the residue recrystallized from a 6:1 mixture of hexane and benzene. Yield 89%; mp 91-92°C. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 1700 (C=N), 1780 (C=O). ^1H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 6.55 (2H, d, *J* = 9.3, 2,6-H); 7.62 (2H, d, *J* = 9.3, 3,5-H). Found, %: Cl 40.76; N 7.82. $C_9H_4Cl_4N_2O_4$. Calculated, %: Cl 40.99; N 8.10

N-[1-(3-Diethylaminophenoxy)-2,2,2-trihalomethylethylidene]-O-methylurethanes (7a,b). A mixture of phenol **3a** (0.826 g, 5 mmol) and triethylamine (0.505 g, 5 mmol) was added dropwise to a solution of N-alkylidenurethane **2a,b** (5 mmol) in benzene (15 ml) and the mixture stirred for 2 h. The precipitate of triethylammonium chloride was filtered off, the filtrate was evaporated and the oily precipitate was purified by freezing out from a 1:10 mixture of diethyl ether and hexane at -18°C.

Compound 7a. Yield 85%. IR spectra (CH_2Cl_2), ν, cm^{-1}: 1695 (C=N), 1765 (C=O). ^1H NMR spectrum (C_6D_6): δ, ppm (*J*, Hz): 0.74 (6H, t, *J* = 7.2, $2CH_3$); 2.76 (4H, q, *J* = 7.2, $2CH_2$); 3.16 (3H, s, OCH_3); 6.26 (1H, dd, $J_{1,2}$ = 8.7, $J_{1,3}$ = 2.1, 4-H); 6.34 (1H, dd, $J_{1,2}$ = 7.8, J_{13} = 1.7, 6-H); 6.38 (1H, t, *J* = 2.1, 2-H); 6.92 (1H, t, *J* = 8.7, 5-H). ^{19}F NMR spectrum (C_6D_6), δ, ppm: 71.3. Found, %: F 17.83, N 8.67. $C_{14}H_{17}F_3N_2O_3$. Calculated, %: F 17.91; N 8.80.

Compound 7b. Yield 53%. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 1690 (C=N), 1770 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.17 (6H, t, J = 7.2, $2CH_3$); 3.34 (4H, q, J = 7.2, $2CH_2$); 3.37 (3H, s, OCH_3); 6.39 (1H, t, J = 2.1, 2-H); 6.42 (1H, dd, $J_{1,2}$ = 8.3, $J_{1,3}$ = 2.0, 4-H); 6.54 (1H, dd, $J_{1,2}$ = 8.4, $J_{1,3}$ = 2.1, 6-H); 7.18 (1H, t, J = 8.3, 5-H). Found, %: Cl 29.07; N 7.71. $C_{14}H_{17}Cl_3N_2O_3$. Calculated, %: Cl 28.93; N 7.62.

4-Trihalo-2H-1,3-benzoxazin-2-ones (5a-e). A. A mixture of phenol **3a-c** (5 mmol) and triethylamine (0.505 g, 5mmol) was added to a solution of isocyanate **1a,b** (5 mmol) in benzene (10 ml) and the mixture was stirred for 3 h at room temperature. The precipitate of triethylammonium chloride was separated to give benzene solutions of the N-alkylideneurethanes **4a-e.** In the case of **4a-c** the solution was boiled for 0.5 h. For compounds **4d,e** the benzene was evaporated and xylene (15 ml) was added to the residue and boiled for 8 h (compound **4d**) and for 30 h (compound **4e**). After removal of the solvent, diethyl ether (20 ml) was added to the residue and the solid substance was filtered off after 24 h.

B. A mixture of phenol **3b** (0.826 g, 5 mmol) and triethylamine (0.505 g, 5 mmol) in dioxane (10 ml) was added to a solution of N-alkylideneurethane **2c** (1.73 g, 5 mmol) in dioxane (15 ml) and the mixture was stirred for 2h. The precipitate of triethylammonium chloride was filtered off, and the filtrate was kept for 24 h or boiled for 0.5 h. The solvent was removed and diethyl ether (20 ml) was added to the residue which was kept for 24 h and the solid product formed was filtered off.

4-Hydroxy-4-trifluoromethyl-2,3-dihydro-4H-1,3-benzoxazin-2-one (8a) and 2,3-Dihydro-4H-1,3-benzoxazin-2,4-dione (9). Water (0.1 ml) was added to a solution of compound **5b,c** (3 mmol) in DMSO (3 ml) and the solution was kept at room temperature for 24 h. The mixture was then diluted with water (10 ml) and the precipitate formed was filtered off and recrystallized.

4-Alkoxy-4-trichloromethyl-2,3-dihydro-4H-1,3-benzoxazin-2-ones (10a-c). Compounds **5a,b** were dissolved in methanol or 2-propanol (5 ml), 3 drops of triethylamine were added, and the mixture was kept for 48 h. The precipitate was filtered off and recrystallized.

4-Cyclohexylamino-2H-1,3-benzoxazin-2-one (12). Cyclohexylamine (0.198 g, 2 mmol) was added to a solution of compound **5c** (0,671 g, 2 mmol) in dioxane (10 ml) and the mixture was kept for 48 h. The precipitate was filtered off and recrystallized.

REFERENCES

1. M. V. Vovk, A. A. Pokholenko, and A. V. Bol'but, *Zhur. Org. Khim.,* **32**, 476 (1996).
2. M. V. Vovk and A. V. Bol'but, *Zhur. Org. Khim.,* **34**, 628 (1998).
3. M. V. Vovk and A. V. Bol'but, *Ukr. Khim. Zhur.,* **64**, 46 (1998).
4. M. V. Vovk and V. I. Dorokhov, *Izv. Vuzov. Khim. i Khim. Tekhnol.,* **39**, 15 (1996).
5. L. I. Samarai, V. I. Boiko, and M. N. Gertsyuk, *Zhur. Org. Khim.,* **26**, 745 (1990).
6. V. I. Boiko, V. M. Vovk, and L. I. Samarai, *Ukr. Khim. Zhur.,* **61**, 48 (1995).
7. A. G. Catchpole and E. D. Hughes, *J. Chem. Soc.,* 4 (1948).
8. J. Petridou-Fischer and E. P. Papadopoulos, *J. Heterocycl. Chem.,* **20**, 1159 (1983).
9. A. Kamal and P. B. Satur, *Synth. Commun.,* **12**, 157 (1982).