Russian Journal of Organic Chemistry, Vol. 38, No. 1, 2002, pp. 66–69. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 1, 2002, pp. 75–78.

Synthesis of Methyl *p*-Alkoxyphenylcarbamates and Some Their Reactions

A. V. Velikorodov, O. V. Bakova, and V. B. Mochalin

Astrakhan State Pedagogical University, ul. Tatishcheva 20A, Astrakhan, 414056 Russia
e-mail: avelikorodov@mail.ru

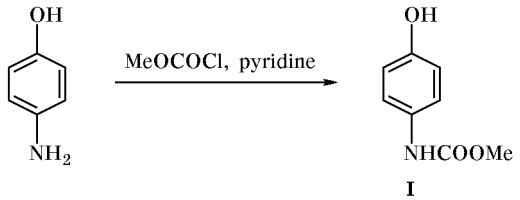
Received March 13, 2001

Abstract—Alkylation of methyl *p*-hydroxyphenylcarbamate with allyl bromide and 1,4-dibromobutane leads to formation of the corresponding methyl *p*-alkoxyphenylcarbamates. Reactions of methyl *p*-allyloxyphenylcarbamate with benzaldehyde, *p*-methoxybenzaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde oximes in boiling ethanol in the presence of *N*-chlorobenzenesulfonamide sodium salt yields 3-aryl-5-(*p*-methoxycarbonylaminophenoxymethyl)-4,5-dihydroisoxazoles. Methyl *p*-(4-bromobutoxy)phenylcarbamate reacts with morpholine in benzene to give methyl *p*-(4-morpholinobutoxy)phenylcarbamate.

Hydroxy and alkoxy derivatives of arylcarbamates attract considerable interest as intermediate products in the synthesis of new polyfunctional compounds. Some hydroxy- and alkoxyarylcarbamates exhibit important therapic properties [1–3]. We previously found [4] that acylation of *p*-aminophenol with methyl chloroformate in aqueous alkali leads to formation of methyl *p*-hydroxyphenylcarbamate (**I**) and methyl *p*-methoxycarbonyloxyphenylcarbamate. This result may be explained by the ability of phenolic hydroxy group to undergo ionization in the presence of bases, which considerably enhances its nucleophilicity.

In continuation of these studies and with the goal of obtaining new polyfunctional arylcarbamates, in the present work we examined the possibility for synthesizing methyl *p*-hydroxyphenylcarbamate (**I**) by acylation of *p*-aminophenol with methyl chloroformate in pyridine. We also studied alkylation of **I** with allyl bromide (**IIa**) and 1,4-dibromobutane (**IIb**) and some chemical transformations of the resulting alkoxy derivatives.

We have found that the use of anhydrous pyridine as a medium for acylation of *p*-aminophenol with methyl chloroformate allows us to considerably



I

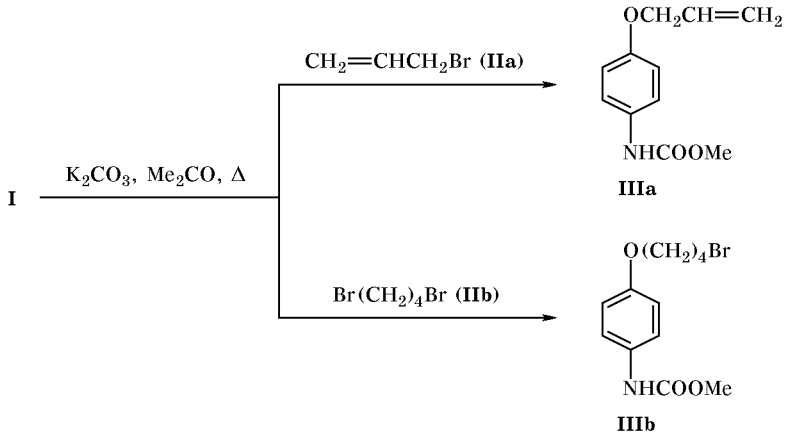
reduce the contribution of the O-acylation process; in addition, the yield of product **I** increases, and its purity is improved. The structure of compound **I** was confirmed by the IR data. Its IR spectrum contained only one carbonyl band at 1710 cm^{-1}, which is typical of stretching vibrations of carbamate C=O group. Methyl *p*-methoxycarbonyloxyphenylcarbamate [4] gives two absorption bands in the carbonyl region, at 1710 and 1780 cm^{-1}, the latter belonging to the carbonate C=O group.

The alkylation of **I** with allyl bromide (**IIa**) and 1,4-dibromobutane (**IIb**) was performed in acetone in the presence of potassium carbonate, following the procedure reported in [5]. A mixture of equimolar amounts of the reactants was heated for 6 h at 70°C. The products were expected *O*-alkyl derivatives **IIIa** and **IIIb** (Scheme 1). Their structure was confirmed by the IR spectra and subsequent chemical transformations. Compounds **IIIa** and **IIIb** are of interest as intermediate products in the synthesis of new heterocyclic carbamates.

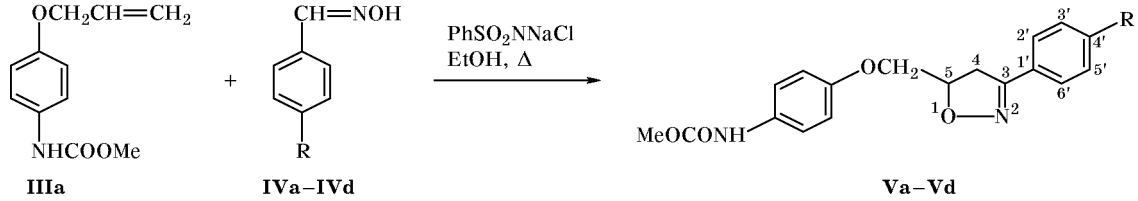
We previously reported on the reaction of allyl phenylcarbamate with some benzaldehyde oximes in the presence of *N*-chlorobenzenesulfonamide sodium salt. This reaction is characterized by high regioselectivity, and it yields 3-aryl-5-(phenylcarbamoyloxymethyl)-4,5-dihydroisoxazoles [6]. With a view to estimate applicability limits of the above reaction as a method of synthesis of 3,5-disubstituted 4,5-dihydroisoxazoles, allyloxyphenylcarbamate **IIIa** was brought into reactions with substituted benzaldehyde

1070-4280/02/3801-0066 $27.00 © 2002 MAIK "Nauka / Interperiodica"

Scheme 1.



Scheme 2.

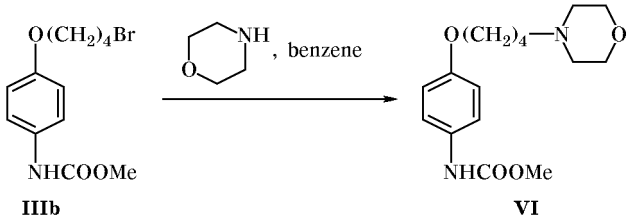


IV, **V**, R = H (**a**), 4-OMe (**b**), 4-NO_2 (**c**), 4-Cl (**d**).

oximes **IVa**–**IVd** in the presence of *N*-chlorobenzenesulfonamide sodium salt (Scheme 2). The IR and ^{1}H NMR spectra of the products indicate that 1,3-dipolar cycloaddition of substituted benzonitrile oxides, generated *in situ* from benzaldehyde oximes, to dipolarophile **IIIa**, as well as to allyl phenylcarbamate, occurs regioselectively with formation of the corresponding 3,5-disubstituted 4,5-dihydroisoxazoles **Va**–**Vd**. Their yields, melting points, IR and ^{1}H NMR spectral parameters, and elemental analyses are given in table. Compounds **Va**–**Vd** show in the mass spectra molecular ion peaks whose relative intensity ranges from 10 to 21%. The mass spectra contain abundant ion peaks with *m*/*z* 294 (**Va**), 324 (**Vb**), 339 (**Vc**), and 328.5 (**Vd**), indicating that fragmentation of the molecular ions begins with elimination of methanol. The presence of ion peaks with *m*/*z* 117 (**Va**), 147 (**Vb**), 162 (**Vc**), and 151.5 (**Vd**) suggests formation of 2-arylazirines during the fragmentation process [6, 7]. This is consistent with the assumed structures of compounds **Va**–**Vd**.

We also examined the reaction of carbamate **IIIb** with excess morpholine in dry benzene. The reaction was carried out at room temperature by keeping the reactants for 24 h. As expected, the product was methyl *p*-(4-morpholinobutoxy)phenylcarbamate (**VI**) (Scheme 3) which was converted into the corresponding hydrochloride by treatment with a solution of HCl in diethyl ether [8].

Scheme 3.



EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 MHz) in acetone-d_6 using TMS as internal reference. The mass spectra (70 eV) were obtained on a Kratos MS-30 instrument. The IR spectra (4000–400 cm^{-1}) were measured on an IKS-29 spectrophotometer in mineral oil. The purity of the products was checked by TLC on Silufol UV-254 plates.

Methyl *p*-hydroxyphenylcarbamate (I). To a solution of 14.55 g (0.1 mol) of *p*-aminophenol hydro-

Yields, melting points, IR and ^{1}H NMR spectra, and elemental analyses of 3,5-disubstituted 4,5-dihydroisoxazoles **Va**–**Vd**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
Va	85	167	3375 (NH); 1705 (C=O); 1605, 1555, 1515 (C=C, C=C$_{arom}$)	8.50 br.s (1H, NH), 7.75 d (2H, H$_{arom}$, 8.6), 7.52–7.42 m (5H, H$_{arom}$), 6.92 d (2H, H$_{arom}$, 8.6), 5.12 m (1H, 5-H), 4.15 d (2H, OCH$_2$, 4.7), 3.68 s (3H, OMe), 3.61 d.d (1H, 4-H, 10.4, 26.3), 3.42 d.d (1H, 4-H, 8.5, 26.3)
Vb	89	163	3420 (NH); 1745 (C=O); 1625, 1610, 1545, 1530 (C=C, C=C$_{arom}$)	8.49 br.s (1H, NH), 7.68 d (2H, 2′-H, 6′-H, 7.9), 7.45 d (2H, H$_{arom}$, 8.6), 7.02 d (2H, 3′-H, 5′-H, 7.9), 6.92 d (2H, H$_{arom}$, 8.6), 5.05 m (1H, 5-H), 4.13 d (2H, OCH$_2$, 4.4), 3.85 s (3H, OMe), 3.65 s (3H, OMe), 3.57 d.d (1H, 4-H, 9.7, 26.3), 3.35 d.d (1H, 4-H, 7.9, 26.3)
Vc	62	233	3340 (NH); 1735 (C=O); 1610, 1585, 1540, 1520 (C=C, C=C$_{arom}$)	8.50 br.s (1H, NH), 8.32 d (2N, 3′-H, 5′-H, 8.6), 8.03 d (2H, 2′-H, 6′-H, 8.6), 7.45 d (2H, H$_{arom}$, 8.6), 6.92 d (2H, H$_{arom}$, 8.6), 5.22 m (1H, 5-H), 4.05 d (2H, OCH$_2$, 4.4), 3.71 d.d (1H, 4-H, 9.7, 26.3), 3.67 s (3H, OMe), 3.52 d.d (1H, 4-H, 7.9, 26.3)
Vd	84	178	3335 (NH); 1740 (C=O); 1620, 1560, 1530 (C=C, C=C$_{arom}$)	8.49 br.s (1H, NH), 7.75 d (2H, 3′-H, 5′-H, 8.6), 7.45 t (4H, H$_{arom}$, 8.6), 6.92 d (2H, H$_{arom}$, 8.6), 5.12 m (1H, 5-H), 4.16 d (2H, OCH$_2$, 4.4), 3.68 s (3H, OMe), 3.62 d.d (1H, 4-H, 9.7, 26.3), 3.41 d.d (1H, 4-H, 7.9, 26.3)

Comp. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
Va	65.92	5.79	8.38	$C_{18}H_{18}N_2O_4$	66.26	5.52	8.59
Vb	63.68	5.34	8.01	$C_{19}H_{20}N_2O_5$	64.05	5.62	7.87
Vc	57.91	4.75	11.08	$C_{18}H_{17}N_3O_6$	58.22	4.58	11.32
Vd	60.26	4.33	7.29	$C_{18}H_{17}ClN_2O_4$	59.92	4.72	7.77

chloride in 46 ml of anhydrous pyridine we added dropwise over a period of 1.5 h (while stirring and cooling) 7.7 ml (0.1 mol) of methyl chloroformate. The mixture was stirred for 0.5 h on cooling, kept for 13 h at room temperature, poured onto ice, and carefully acidified with concentrated hydrochloric acid (using Congo Red paper). The solution was treated with ethyl acetate (4 × 50 ml), and the extract was washed with 100 ml of a saturated aqueous solution of sodium chloride and with water (2 × 50 ml), and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue crystallized. Recrystallization from chloroform gave 10.7 g (64%) of compound **I** as colorless crystals with mp 116°C. IR spectrum, ν, cm^{-1}: 3450–3250 (NH, OH); 1710 (C=O); 1615, 1570, 1540, 1515 (C=C$_{arom}$). Found, %: C 57.81; H 5.02; N 8.11. $C_8H_9NO_3$. Calculated, %: C 57.49; H 5.39; N 8.38.

Methyl *p*-allyloxyphenylcarbamate (IIIa). A mixture of 3.34 g (0.02 mol) of carbamate **I**, 2.42 g (0.02 mol) of freshly distilled allyl bromide (**IIa**), 2.8 g (0.02 mol) of potassium carbonate, and 3 ml of acetone was heated for 6 h at 70°C. It was then cooled, diluted with 25 ml of water, and extracted with diethyl ether (3 × 25 ml). The extract was washed with a 10% aqueous solution of sodium hydroxide (100 ml) and with water (50 ml) and dried over potassium carbonate. The solvent was removed, and the residue crystallized. Recrystallization from hexane gave 3.69 g (89%) of compound **IIIa** as colorless crystals with mp 72–73°C. IR spectrum, ν, cm^{-1}: 3360 (NH); 1710 (C=O); 1615, 1565, 1525 (C=C,

C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 8.48 br.s (1H, NH), 7.45 d (2H, H_{arom}, *J* = 8.6 Hz), 6.90 d (2H, H_{arom}, *J* = 8.6 Hz), 6.05 m (1H, 5-H), 5.41 d (1H, 4-H, *J* = 17 Hz), 5.22 d (1H, 4-H, *J* = 11 Hz), 4.55 d (2H, OCH_2, *J* = 4.3 Hz), 3.68 s (3H, OMe). Found, %: C 64.11; H 6.13; N 6.42. $C_{11}H_{13}NO_3$. Calculated, %: C 63.77; H 6.28; N 6.76.

Methyl *p*-(4-bromobutoxy)phenylcarbamate (IIIb) was synthesized in a similar way from 0.84 g (5.03 mmol) of carbamate **I**, 0.6 ml (4.97 mmol) of freshly distilled 1,4-dibromobutane (**IIb**), 0.69 g (5 mmol) of potassium carbonate, and 3 ml of acetone. Yellow crystals, yield 1.2 g (81%), mp 105°C (from diethyl ether). IR spectrum, ν, cm^{-1}: 3355 (NH); 1710 (C=O), 1620, 1555, 1530 (C=C_{arom}); 665 (C–Br). Found, %: C 47.56; H 5.03; N 5.01. $C_{12}H_{16}BrNO_3$. Calculated, %: C 47.68; H 5.30; N 4.64.

3-Aryl-5-(*p*-methoxycarbonylaminophenoxymethyl)-4,5-dihydroisoxazoles Va–Vd. A mixture of 1.35 mmol of carbamate **IIIa**, 1.35 mmol of benzaldehyde oxime **IVa–IVd**, and 1.35 mmol of *N*-chlorobenzenesulfonamide sodium salt trihydrate in 25 ml of anhydrous ethanol was refluxed for 6 h. The products were isolated by the procedure reported in [6] and were purified by recrystallization from chloroform.

Methyl *p*-(4-morpholinobutoxy)phenylcarbamate (VI). Freshly distilled morpholine, 0.26 ml (3 mmol), was added to a solution of 0.3 g (1 mmol) of carbamate **IIIb** in 12 ml of dry benzene, and the mixture was kept for 24 h at room temperature. The precipitate of morpholine hydrochloride was filtered off, and the solvent and excess amine were removed under reduced pressure. The residue was recrystallized from benzene–hexane (1 : 1). Yield 0.2 g (64%), colorless crystals, mp 91–92°C. IR spectrum, ν, cm^{-1}: 3355 (NH); 1710 (C=O); 1605, 1539 (C=C_{arom}). Found, %: C 61.96; H 7.84; N 9.21. $C_{16}H_{24}N_2O_4$. Calculated, %: C 62.34; H 7.79; N 9.09.

Compound **VI** was converted into the corresponding hydrochloride by treatment of a solution of 0.4 g (1.3 mmol) of free base **VI** in 7 ml of dry benzene with a solution of HCl in diethyl ether. Yield 0.43 g (95%), mp 153°C. Found, %: C 56.03; H 7.11; N 8.02. $C_{16}H_{25}ClN_2O_4$. Calculated, %: C 55.73; H 7.26; N 8.13.

REFERENCES

1. Maksimova, T.N., Shtonda, N.P., Velikorodov, A.V., and Khabarova, O.V., *Izv. Vyssh. Uchebn. Zaved., Ser. Khim. Khim. Tekhnol.*, 1987, vol. 30, no. 2, pp. 132–133.
2. Gregani, F., Durindai, J., and Chalikov, S.Ch., *Farm. Obz.*, 1990, vol. 59, no. 7, pp. 297–300.
3. Czech. Patent no. 276205, 1992; *Ref. Zh., Khim.*, 1994, no. 4O15P.
4. Yukinori, N., Yoshimoto, A., Takaniso, M., Nobumasa, I., Yoshikazu, F.M., Hiroyuki, I., and Massakazu, M., *Nippon Kagaku Kaishi*, 1993, no. 6, pp. 719–727.
5. *Weygand–Hilgetag organisch-chemische Experimentierkunst*, Hilgetag, G. and Martini, A., Eds., Leipzig: Johann Ambrosius Barth, 1964, 3rd ed.
6. Velikorodov, A.V. and Mochalin, V.B., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 1, pp. 83–86.
7. Barnet, K., *Angew. Chem.*, 1985, vol. 97, no. 3, pp. 231–232.
8. Grinev, A.N., Panishcheva, E.K., Cherkasova, A.A., Stolyarchuk, A.A., Ivanova, N.I., Lysaya, T.I., and Storozhuk, B.G., *Khim.-Farm. Zh.*, 1983, vol. 17, no. 8, pp. 940–946.