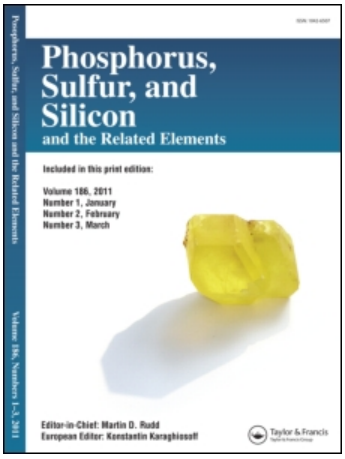

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Roman Mazurkiewicz[ab]; Anna W. Pierwocha[a]; Anna Brachaczek[a]; Iwona Mitrus[a]
[a] Institute of Organic Chemistry and Technology, The Silesian University of Technology, Gliwice, Poland [b] Department of Textile Engineering and Environmental Sciences, Technical University of Lodz, Bielsko-Biala, Poland

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HYDRO-DE-PHOSPHONIATION OF 4-SUBSTITUTED-4-TRIPHENYLPHOSPHONIO-5(4*H*)-OXAZOLONES WITH ALCOHOLS

ROMAN MAZURKIEWICZ[ab*], ANNA W PIERWOCHA[a*], ANNA BRACHACZEK[a*] and IWONA MITRUS[a*]

[a]*Institute of Organic Chemistry and Technology, The Silesian University of Technology, Krzywoustego 4, 44–100 Gliwice, Poland, and* [b]*Department of Textile Engineering and Environmental Sciences, Technical University of Lodz, Bielsko-Biala Campus, 43–300 Bielsko-Biala, Poland*

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4-Substituted-4-triphenylphosphonio-5(4*H*)-oxazolones with a bulky alkyl substituent at the position 4 treated with MeOH in the presence of DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) at room temperature give corresponding N-acyl-α-amino acid esters. In the case of a smaller substituent at the position 4 (Me, $MeOCH_2$), the triphenylphosphonium group was competitively displaced by the methoxy group. The latter reaction can be avoided by carrying out hydro-de-phosphoniation in CH_2Cl_2 in the presence of only 150% excess of *i*-PrOH at 50°C in the absence of DBU. Possible mechanisms of hydro-de-phosphoniation are discussed.

Keywords: : 4-Triphenylphosphonio-5(4*H*)-oxazolones; hydro-de-phosphoniation; DBU-MeOH system; *i*-PrOH; functionalization of glycine; mechanism

INTRODUCTION

Recently, we described a method for the hydro-de-phosphoniation of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones **2** by reduction of the P^+-C bond with a solution of HI in CH_2Cl_2[1]. The reported reaction, together with the previously described synthesis of 4-triphenylphosphoranylidene-5(4*H*)-oxazolones **1**[2] and the effective methods of their 4-C alkylation to the phosphonium salts **2**[3], offers a new way for the functionalization of the glycine α-position with alkylating agents. It should be stressed, that

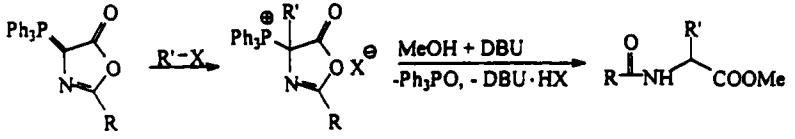
* Correspondence Author: e-mail: romanm@zeus.polsl.gliwice.pl

the practical applicability of the functionalization of glycine by direct base-catalyzed alkylation of 5(4*H*)-oxazolones is limited due to the competitive dimerization of 5(4*H*)-oxazolones in the presence of bases[4].

In the present paper we report an alternative, complementary, more convenient method for hydro-de-phosphoniation of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones **2** with MeOH-DBU system or with *i*-PrOH in the absence of DBU.

RESULTS AND DISCUSSION

Recently, we described a wide variety of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones[1,3] **2**, which can be synthesized by the alkylation of easily accessible 4-triphenylphposhoranylidene-5(4*H*)-oxazolones[2] **1** with alkyl halides (Scheme 1). Studying the reactivity of phosphonium salts **2** towards methanol we stated, that in some cases (R′ = Me or $MeOCH_2$) the oxazolone ring opens easily under the influence of methanol at room temperature to give methyl N-acyl-α-alkyl-α-tripenylphosphonioglycinates **3**, (Scheme 2) whereas some other phosphonium salts (e.g. R′ = $PhCH_2$) are stable in methanol solution even at the temperature raised up to 80°C[5]. When, however, phosphonium salts **2** were treated with methanol in the presence of DBU at 20°C for 1 hour the reaction direction changed completely. In most cases phosphonium salts **2** underwent hydro-de-phosphoniation to the corresponding N-acyl-α-amino acid methyl esters **4**, usually in a moderate to good yield (Scheme 1, Table I).



1 X = I or Br 2 4

SCHEME 1

Hydro-de-phosphoniation of phosphonium salts under the influence of aqueous sodium hydroxide or alcohols in the presence of sodium alkoxides is a known reaction[6,7], however, up to now, according to the best of our knowledge, alcohol-DBU systems were not used in these reactions.

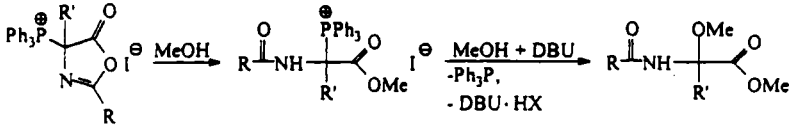
TABLE I Hydro-de-phosphoniation of 4-subtituted 4-triphenylphosphonio-5(4*H*)-oxazolone halides

Substrate				*Product*		*Solv.*	*Base*	*R'OH*	*Yield* [a] *[%]*	*M.p. [°C]*	*IR [cm^{-1}]*	*Elemental analyses (calcd./found) [%]*		
No.	*R*	*R'*	*X*	*No.*	*R"*							*C*	*H*	*N*
2c	*t*-Bu	$CH_2CH{=}CH_2$	I	**4a**	$CH_2CH{=}CH_2$	–	DBU	MeOH	85	oil	3440w, 1740s, 1665s, 1505m, 1205m	61.68/61.30	9.34/9.17	6.54/6.86
2d	*t*-Bu	CH_2Ph	Br	**4b**	CH_2Ph	–	DBU	MeOH	70[b]	90–92	3442w, 1740s, 1668s, 1510m, 1210m			
2e	*t*-Bu	CH_2Bt[c]	I	**4c**	CH_2Bt[c]	–	DBU	MeOH	66[b]	114.5–116	3445w, 1750s, 1669s, 1501m, 1200m			
2f	*t*-Bu	CH_2COOEt	I	**4d**	CH_2COOMe	–	DBU	MeOH	78	oil	3453w, 1739s, 1667s, 1504m, 1212m	53.87/53.27	7.81/7.93	5.71/5.56

Substrate				*Product*		*Solv.*	*Base*	*R'OH*	*Yield*[a] *[%]*	*M.p. [°C]*	*IR [cm^{-1}]*	*Elemental analyses (calcd./found) [%]*		
No.	*R*	*R'*	*X*	*No.*	*R''*							*C*	*H*	*N*
2g	*t*-Bu	$CH_2C{\equiv}N$	I	**4e**	$CH_2C{\equiv}N$	–	DBU	MeOH	50	91–92.5	3436w, 1750s, 1672s, 1502m, 1220m	56.59/56.29	7.60/7.83	13.20/13.15
2a	Ph	Me	I	**4f**	Me	CH_2Cl_2	–	*i*-PrOH	55	83.5–84.5	3440w, 1730s, 1663s, 1517m, 1215m	66.38/66.47	7.23/7.38	5.96/6.18
2b	*t*-Bu	Me	I	**4g**	Me	CH_2Cl_2	–	*i*-PrOH	57	79.5–81	3420w, 1724s, 1661s, 1518m, 1215m	61.37/61.02	9.83/9.82	6.51/6.43

a. Yield not optimized;
b. Identical with the compound described in our previous paper[11];
c. Bt = benzotriazol-1-yl group.

In the case of those 4-alkyl-4-triphenylphosphonio-5-(4*H*)-oxazolones, which open the oxazolone ring easily under the influence of MeOH (**2a-c**), the reaction with the MeOH-DBU system leads to the displacement of the triphenylphosphonium group by the methoxy group (Scheme 2):



2a: R = Ph, R' = Me
2b: R = *t*-Bu, R' = Me
2c: R = Ph, R' = CH_2OMe

3

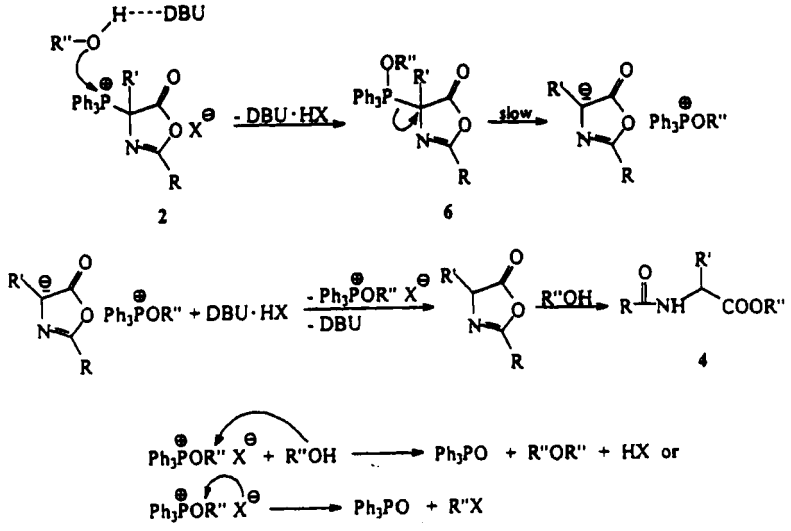
5a-c

SCHEME 2

Evidently, the triphenylphosphonium group in N-acyl-α-methyl-α-triphenylphosphonio glycinates **3** undergo displacement by the methoxy group more easily than hydro-de-phosphoniation. Nevertheless, we demonstrated, that even this kind of 4-alkyl-4-triphenylphosphonio-5-(4*H*)-oxazolones can be successfully hydrode-phosphoniated by heating the solution of a phosphonium salt **2** in CH_2Cl_2 with an excess of only 150% of isopropyl alcohol in the absence of DBU in a sealed glass tube at 50°C for 6–12 hours (Table I).

Similar hydro-de-phosphoniation of the phosphonium salt **2a** or **2b** was recently carried out with L-menthol or di-O-isopropylidene-β-D-glucofuranose by Mitrus[8]. In the case of phosphonium salt **2a** the corresponding iodo-derivative of di-O-isopropylidene-β-D-glucofuranose was isolated from the reaction mixture in 64% yield, besides the expected hydro-de-phosphoniation product (71%).

The mechanism of the hydro-de-phosphoniation of *p*-nitrobenzyltriphenyl phosphonium salts with sodium ethoxide was extensively studied by Grayson and Keough[6]. A possible mechanism of the hydro-de-phosphoniation of 4-triphenyl phosphonio-5(4*H*)-oxazolones, similar to that proposed by Grayson and Keough, involving a pentacovalent methoxyphosphorane **6** as the intermediate, can be formulated as follows:



SCHEME 3

As it follows from our results, the DBU assistance accelerates the investigated reaction considerably, however, hydro-de-phosphoniation can go also in the absence of DBU.

According to Grayson and Keough[6] the nucleophilic attack of the alkoxide anion on the alkoxy group of the alkoxyphosphonium salt results in the splitting off of the alkoxyphosphonium salt into triphenyphosphonium oxide and the corresponding ether. The aforementioned isolation of the corresponding iodo-derivative of di-O-isopropylidene-β-D-glucofuranose as a by-product indicates that alkoxyphosphonium salt may also be split off in result of the attack of the iodide anion on the α-carbon of the alkoxy group.

CONCLUDING REMARKS

The reported reaction offers an alternative, convenient way for the hydro-de-phosphoniation of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones, which is complementary to the previously described method for the hydro-de-phosphoniation of these compounds with hydrogen iodide[1]. Hydro-de-phosphoniation of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones is a crucial step of a new proposed way for the functionalization of the glycine α-position with alkylating agents[1,3].

TABLE II ^{1}H and ^{13}C NMR spectral data of the obtained new α-amino acid derivatives

Reaction product				*^{1}H NMR (CDCl$_3$/TMS δ (ppm)*	*^{13}C NMR (CDCl$_3$/TMS δ (ppm))*				
No.	*R*	*R'*	*R"*		$\overset{Q}{C}NH$	$\overset{Q}{C}O$	NHCH	$\overset{Q}{C}OMe$	*other carbons*
4a	*t*-Bu	$CH_2CH{=}CH_2$	Me	6.17 (d, 1H, NH, J_1 = 6.0 Hz); 5.70–5.60 (m, 1H, CH=); 5.18–5.06 (m, 2H, $=CH_2$); 4.65 (ddd, 1H, NHCH, J_1 = 6.6 Hz, J_2 = 6.6 Hz, J_3 = 5.8 Hz); 3.76 (s, 3H, OMe); 2.67–2.45 (m, 2H, CH_2); 1.21 (s, 9H, *t*-Bu)	178.0	172.5	51.3	52.4	132.3 *C*H-CH_2; 119.2 CH-*C*H_2; 38.7 *C*Me_3; 36.4 *C*H_2CH; 27.4 *CMe*$_3$
4d	*t*-Bu	CH_2COOMe	Me	6.72 (d, 1H, NH, J_1 = 7.2 Hz); 4.84 (ddd, 1H, CH, J_1 = 8.1 Hz, J_2= 4.4 Hz, J_3 = 4.4 Hz); 3.76 (s, 3H, OMe); 3.70 (s, 3H, OMe); 3.03 (dd, 1H,CH_2[a], J_2= 4.4 Hz, J_4 = 17.0 Hz); 2.84 (dd, 1H, CH_2[a], J_3 = 4.6 Hz, J_4 = 17.0 Hz); 1.22 (s, 9H, CMe_3)	178.3	171.7[b]	48.5	52.0[b]	171.5[b] CH_2C=O; 52.8[b] CH_2COOMe; 38.7 *C*Me_3; 35.9 CH_2; 27.4 C*Me*$_3$
4e	*t*-Bu	$CH_2C{\equiv}N$	Me	6.65 (d, 1H, NH, J_1 = 5.5 Hz); 4.69 (ddd, 1H, CH, J_1 = 6.3 Hz, J_2= 5.5 Hz, J_3 = 4.6 Hz); 3.86 (s, 3H, OMe); 3.12 (dd, 1H, CH_2, J_2 = 5.5 Hz, J_4 =17.0 Hz); 2.97 (dd, 1H, CH_2,[a] J_3 = 4.6 Hz, J_4 = 17.0 Hz); 1.25 (s, 9H, CMe_3)	178.8	169.6	49.0	53.3	116.1 CN; 38.9 *C*Me_3; 27.3 C*Me*$_3$; 21.1 CH_2
4f	Ph	Me	*i*-Pr	7.84–7.78 (m, 2H, Ph); 7.54–7.32 (m, 3H, Ph); 6.87 (d, 1H, NH, J_1 = 6.0 Hz); 5.09 (qq, 1H, *CH*Me_2, J_2 = 6.3 Hz, J_3 = 6.3 Hz); 4.74 (dq, 1H, *CH*NH, J_1 = 7.1 Hz, J_4 = 7.1 Hz); 1.50 (d, 1H, Me, J_4 = 7.2 Hz); 1.29 (d, 1H, CH*Me*$_2^c$, J_2 = 6.3 Hz); 1.28 (d, 1H, CH*Me*$_2^c$, J_3 = 6.3 Hz)	172.8	166.8	48.7	–	134.1, 131.6, 128.6, 127.0 Ph 69.3 *C*HMe$_2$; 21.73 CH*Me*$_2^c$; 21.67 CH*Me*$_2^c$; 18.7 Me

Reaction product				*^{1}H NMR (CDCl$_3$/TMS δ (ppm)*	*^{13}C NMR (CDCl$_3$/TMS δ (ppm))*				
No.	*R*	*R′*	*R″*		$\overset{\text{Q}}{\text{CNH}}$	$\overset{\text{Q}}{\text{CO}}$	NHCH	$\overset{\text{Q}}{\text{COMe}}$	*other carbons*
4g	*t*-Bu	Me	*i*-Pr	6.22 (s, br, 1H, NH); 5.05 (qq, 1H, C*H*Me$_2$, J_1 = 6.3 Hz, J_2 = 6.3 Hz); 4.50 (dq, 1H, C*H*NH, J_3 = 7.2 Hz, J_4 = 7.2 Hz); 1.37 (d, 1H, Me, J_3 = 7.2 Hz); 1.27 (d, 1H, CH*Me$_2$*[c], J_1 = 6.3 Hz); 1.25 (d, 1H, CH*Me$_2$*[c], J_2 = 6.3 Hz);1.22 (s, 9H, CMe$_3$)	176.9	171.9	47.1	–	67.9 *C*HMe$_2$; 37.5 *C*Me$_3$; 26.4 C*Me$_3$*; 20.66 CH*Me$_2$*[c]; 20.59 CH*Me$_2$*[c]; 17.4 Me
5a	Ph	Me	Me	7.75–7.20 (m, 6H, Ph and NH); 3.78 (s, 3H, COOMe); 3.24 (s, 3H, OMe); 1.78 (s, 3H, Me)	171.3	166.9	84.2	53.0	133.6, 132.1, 128.6, 127.2 Ph 58.1 OMe
5b	*t*-Bu	Me	Me	6.59 (s, 1H, NH); 3.83 (s, 3H, COOMe); 3.24 (s, 3H, OMe); 1.75 (s, 3H, Me); 1.23 (s, 9H, *t*-Bu)	177.8	171.3	84.8	53.1	51.5 OMe; 39.2 *C*Me$_3$; 23.2 C*Me$_3$*
5c	Ph	CH_2OMe	Me	7.83–7.60 (m, 6H, Ph and NH); 4.23 (d, 1H, CH_2,[a] J = 9.6 Hz); 3.89 (s, 3H, COMe); 3.85 (d, 1H, CH_2[a], J = 9.6 Hz); 3.41 (s, 3H, CH_2O*Me*); 3.36 (s, 3H, COOMe)					

a. One of the diastereotopic protons of the CH_2group;
b. Reverse assignment also possible;
c. One of the diastereotopic Me groups.

EXPERIMENTAL

General

M.p.'s, determined in capillary tubes, are uncorrected. IR spectra were recorded on a Zeiss Specord M 80 spectrophotometer; the measurements were carried out in CH_2Cl_2 (0.2 *M*) using cells of 0.075 mm. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian UNITY INOVA-300 spectrometer at operating frequencies of 300 and 75.5 MHz, respectively, in the FT mode using *TMS* as an internal standard.

Starting materials

4-Alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones **2** were synthesized as previously described[1,3]. Commercial grade acetonitrile and CH_2Cl_2 were distilled and dried over molecular sieves 4A.

Reaction of 4-alkyl-4-triphenylphosphonio-5(4H)-oxazolone halides 2 with MeOH/DBU (General procedure)

To a stirred solution of DBU (0.36 ml, 0.37 g, 2.4 mmol) in MeOH (5.3 ml, 4.19 g, 131 mmol) 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolone halide (2 mmol) was added at 0°C. After 5 minutes the reaction mixture was allowed to warm up to room temperature, and the reaction was continued for 1 h. The excess of MeOH was then removed under reduced pressure and the product was isolated from the residue by column chromatography on silica gel (Kieselgel 60 Merck, 0.063–0.200 mm, 25 ml) eluting with a mixture of benzene and ethyl acetate (5:1, *v/v*) to give a crude hydro-de-phosphoniation product, which was then recrystallized from a mixture of benzene and hexane (Table I and II).

In the case of 4-methyl- and 4-methoxymethyl-4-triphenylphosphonio-5(4*H*)-oxazolones **2a-c**, the following N-acyl-α-alkyl-α-methoxy-α-amino acid methyl esters **5** were isolated as the only reaction products:

5a: 0.380 g, 80%, m.p. 136–137°C. IR (cm^{-1}): 3420m, 1740s, 1680vs, 1510s, 1145s. Anal: Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90; Found: C, 60.53; H; 6.40; N, 5.99.

5b: 0.191 g, 44%, m.p. 80–82°C. IR (cm^{-1}): 3430m, 1752s, 1735s, 1685vs, 1515s, 1130s. Anal: Calcd. for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45; Found: C, 55.09; H; 8.98; N, 6.55.

5c: 0.166 g, 31%, m.p. 117–118.5°C. IR (cm^{-1}): 3420m, 1755s, 1740s, 1680vs, 1521s, 1125s. Anal: Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24; Found: C, 58.80; H; 6.31; N, 5.16. ^1H and ^{13}C NMR spectral data of these compounds were gathered in Table II.

Reaction of 4-alkyl-4-triphenylphosphonio-5(4H)-oxazolone iodides 2 with i-PrOH

A mixture of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolone iodide (1.5 mmol), *i*-PrOH (0.29 ml, 0.225 g, 3.75 mmol) and CH_2Cl_2 (3.6 ml) was sealed in a glass tube and heated at 50°C for 6 h (**2a**, R = Ph, R′ = Me) or 12 h (**2b**, R = *t*-Bu, R′ = Me). The excess of *i*-PrOH was then removed under reduced pressure and the obtained hydro-de-phosphoniation product was isolated and purified as described above (Table I and II).

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