N-TRICHLOROACETOXYPHTHALIMIDE AS A NEW REAGENT FOR THE SYNTHESIS OF THE N-HYDROXYPHTHALIMIDE ESTERS OF N-PROTECTED AMINO ACIDS

A. V. Il'ina, Yu. A. Davidovich, and S. V. Rogozhin

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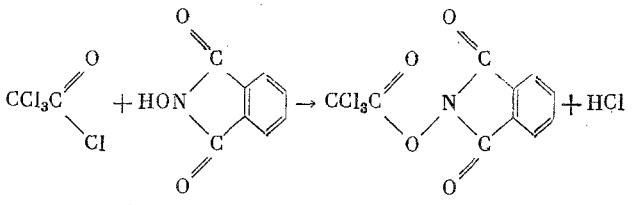
The N-hydroxyphthalimide esters of N-protected amino acids are used as intermediates in the synthesis of biologically active peptides [1, 2]. These compounds are characterized by a high reactivity in aminolysis reactions, which permits effecting the synthesis of peptides under mild conditions, quickly, and in good yield [3]. In addition, they are easily crystallized, while the formed hydroxyphthalimide is easily separated from the peptide product by washing with aqueous $NaHCO_3$ solution. The N-hydroxyphthalimide esters are most frequently obtained by condensing the appropriate carboxyl component (N-protected amino acid) with N-hydroxyphthalimide in the presence of dicyclohexylcarbodiimide [4]. However, this method is long and tedious, and requires using the expensive and difficultly available dicyclohexylcarbodiimide. Besides this, the latter can be used directly for peptide formation, which eliminates the sense of using it to obtain carboxy-activated intermediate derivatives, and it is characterized by a noticeable toxicity, which causes the experimenters to become allergic in a number of cases. In addition, information exists in the literature on the preparation of N-hydroxyphthalimide esters by reacting N-protected amino acids with either N-acetoxyphthalimide [5] or N-trifluoroacetoxyphthalimide [6]. However, N-acetoxyphthalimide has a low reactivity in the transesterification reaction with a modified carboxyl component, which does not permit obtaining the N-hydroxyphthalimide esters in high yield, while N-trifluoroacetoxyphthalimide is an unstable and difficultly available compound, which practically cannot be stored. In view of this, both of these reagents are not used in peptide synthesis practice.

We proposed a method for obtaining N-trichloroacetoxyphthalimide, a new efficient reagent for the synthesis of the N-hydroxyphthalimide esters of N-protected amino acids, which consists in treating N-hydroxyphthalimide with trichloroacetyl chloride by the following scheme.



The reaction was run in an inert organic solvent using either an equimolar ratio of the indicated reagents or an excess of CCl_3COCl in the reaction mixture. To complete the reaction and reach a high yield of N-trichloroacetoxyphthalimide it is preferable that the mole ratio of CCl_3COCl and N-hydroxyphthalimide be at least 3:1. As the solvents, suitable for running the reaction, mention can be made of various aprotic solvents that are satisfactory solvents for the starting N-hydroxyphthalimide, such as ethyl acetate, CH_2Cl_2, and THF. The reaction was run in the range from ~20°C to the boiling point of the corresponding solvent, and preferably at 50-70°C. N-trichloroacetoxyphthalimide is a crystalline solid that is stable when stored under atmospheric conditions (mp 199-200°C), is readily soluble in most of the organic solvents that are used in peptide synthesis, and has a high reactivity in the transesterification reaction with N-protected amino acid derivatives, which proceeds in the presence of an organic base.

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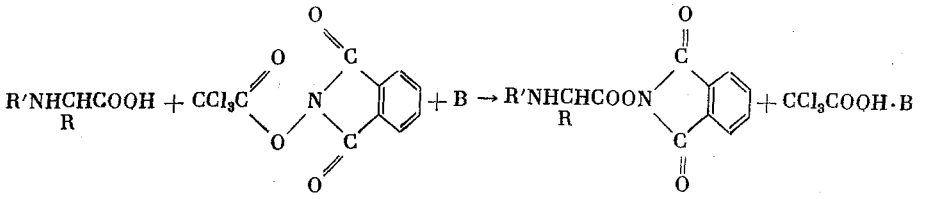
TABLE 1

Compound	Yield, %	Mp, °C	$[\alpha]_D^{22}$, deg (C 1)	Literature reference
BocGlyONPht	85	191–192	–	–
ZGlyONPht	100	128–129 *	–	[4]
BocAlaONPht	96	72–73	−66,2 †	–
BocProNPht	90	69–70	−83 †	–
ZProONPht	98	101–102 *	−82,5 ‡	[4]
BocLeuONPht	99	–	−27 ‡	–
BocIleONPht	100	–	−29 †	–
BocTyr(OBzl)ONPht	98	62–63	−27 †	–
ZPheONPht	98	118–119 *	−46,3 *, ‡	[4]
BocTyr(OBoc)ONPht	99	76–77	−29,7 †	–
BocLys(Z)ONPht	96	130–131	−23 †	–

*cf. [4].
†In ethyl acetate
‡In AcOH.



R' = $COOCH_2Ph$(Z) or $COOC(Me)_3$(Base); R = amino acid moiety; B = base: pyridine, N-methylmorpholine, triethylamine.

The use of N-trichloroacetoxyphthalimide assures obtaining the N-hydroxyphthalimide esters of various substituted acids in 85-100% yield if the reaction is run in an organic solvent (DMF, DMSO, THF, MeCN, dioxane, CH_2Cl_2, ethyl acetate) for 2-12 h at ~20°C, and an equimolar ratio of the reactants is used (Table 1).

EXPERIMENTAL

N-Hydroxyphthalimide was obtained as described in [7], and the solvents were purified as described in [8]. We used N-protected L-amino acids that were purchased from the Reanal Company. The melting point was determined on a Kofler stand, and the specific optical activity of the obtained compounds was measured on an AI-EPO photoelectronic polarimeter using a cell with a length of 0.2 dm. The IR spectra were taken on an IRS Hitachi 260-10 instrument.

N-Trichloroacetoxyphthalimide. To a suspension of 10 g (61 mmoles) of N-hydroxyphthalimide in 100 ml of EtOAc at 22-23°C was added 33 g (183 mmoles) of CCl_3COCl. The reaction mass was stirred for 3-4 h at 70-72°C. The precipitate obtained on cooling to 22-23°C was filtered, washed in succession with 2 × 20 ml of EtOAc and 2 × 20 ml of ether, and dried in vacuo. The yield of product was 17 g (90%, mp 199-200°C). The product was chromatographically homogeneous, R_f 0.7 in the system: $CHCl_3$:MeOH:benzene (85:10:5), and R_f 0.75 in the system: benzene:acetone:AcOH (80:40:1). Infrared spectrum (ν, cm^{-1}): 1835, 1820, 1790, 1795, 1720. Found: C 38.15; H 1.26; Cl 34.87; N 5.16%. $C_{10}H_4NCl_3O_4$. Calculated: C 38.98; H 1.30; Cl 34.52; N 4.54%.

Typical Method for Synthesis of N-Hydroxyphthalimide Esters of N-Protected Amino Acids. To a stirred solution of 10 mmoles of the N-protected amino acid and 10 mmoles of pyridine in 10 ml of a polar solvent (MeCN, DMF, THF, CH_2Cl_2, EtOAc) was added 10 mmoles of N-trichloroacetoxyphthalimide. The reaction mass was kept for 2-12 h at 22-23°C. Then it was concentrated in vacuo and the residue was diluted with 50 ml of EtOAc and washed in succession with 3 × 10 ml of water and 3 × 10 ml of 5% $NaHCO_3$ solution. The extract was dried over anhydrous Na_2SO_4. The excess solvent was vacuum-distilled. The residue was recrystallized from a suitable solvent. The yield of the products was 85-100%; see Table 1.

CONCLUSIONS

A method was proposed for the preparation of N-trichloroacetoxyphthalimide, a new efficient reagent for the synthesis of the N-hydroxyphthalimide esters of N-protected amino acids, which consists in treating N-hydroxyphthalimide with CCl_3COCl.

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REACTION OF η^5-INDENYLTRICARBONYLRHENIUM WITH UROTROPIN IN ETHANOL, LEADING TO RUPTURE OF C—C AND O—H BONDS IN ETHANOL

N. E. Kolobova, V. I. Zdanovich, I. A. Lobanova, V. G. Andrianov, Yu. T. Struchkov, and P. V. Petrovskii

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The refluxing of η^5-indenyltricarbonylrhenium η^5-$C_9H_7Re(CO)_3$ with PPh_3 in toluene leads to the formation of η^5-$C_9H_7Re(CO)_2PPh_3$ [1]. It was shown by us that the reaction with triisopropyl phosphite proceeds similarly. However, in contrast to this, when η^5-$C_9H_7Re(CO)_3$ is reacted with urotropin in ethanol the CO group is not replaced by urotropin, like in the case of η^5-cyclopentadienyltricarbonylrhenium [2], and instead rupture of the metal—π-ligand bond is observed and a crystalline compound with empirical formula $C_{18}H_{28}N_4O_9Re_2$ (I) is formed. The structure of complex (I) was established by the RSA method and some of its physicochemical properties were studied.

EXPERIMENTAL

The compounds were synthesized in an argon atmosphere. The toluene was made absolute by distillation over sodium. The urotropin was recrystallized from abs. EtOH. The η^5-indenyltricarbonylrhenium was synthesized as described in [3]. Silica gel L 100/160 μm was used for the chromatography. The IR spectra were taken on a UR-20 instrument, and the PMR spectra on a Bruker WP-200 SY instrument (200.13 MHz) from HMDS as the internal standard.

Reaction of η^5-$C_9H_7Re(CO)_3$ with Urotropin in Ethanol. A mixture of 0.64 g (1.66 mmoles) of η^5-$C_9H_7Re(CO)_3$ and 0.25 g (1.78 mmoles) of $(CH_2)_6N_4$ in 65 ml of abs. EtOH was refluxed for 6 h, the solvent was removed in vacuo, and the residue was recrystallized from an ethanol—petroleum ether mixture. We isolated 0.59 g (87%) of (I), mp 140°C (decompn.). Found: C 26.89; H 3.55; N 6.91; Re 45.48%. $C_{18}H_{28}N_4O_9Re_2$. Calculated: C 26.47; H 3.46; N 6.86; Re 45.59%.

The (I) crystals are monoclinic, and at 20°C: a = 11.155(2), b = 18.939(4), c = 12.008-(3) Å, β = 92.72(2)°, V = 2534.0 Å^3, d_{calc} = 2.141 g/cm^3, Z = 4, space group $P2_1/c$. The intensities of the 1722 independent reflections were measured on an automatic Hilger—Watts diffractometer (λMoK_α, graphite monochromator, $\theta/2\theta$ scanning, $2 \leqslant 2\theta \leqslant 50°$); due to the indistinct shape of the crystal it proved impossible to take into account the quite strong absorption $\mu(\lambda Mo)$ = 101.5 cm^{-1}. The structure was deciphered by the heavy atom method, which

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow.

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