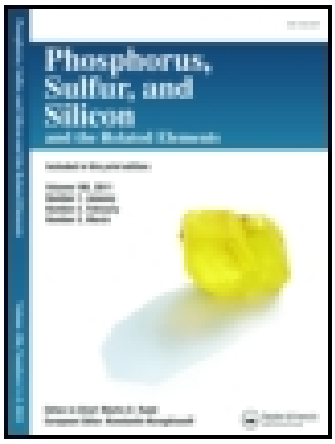

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Synthesis and Chemical Constitution of Diphenoxyphosphoryl Derivatives and Phosphonium Salts as Coupling Reagents for Peptide Segment Condensation

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SYNTHESIS AND CHEMICAL CONSTITUTION OF DIPHENOXYPHOSPHORYL DERIVATIVES AND PHOSPHONIUM SALTS AS COUPLING REAGENTS FOR PEPTIDE SEGMENT CONDENSATION

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(Received October 9, 2001)

The reactions of diphenoxyphosphoryl chloride ($(PhO)_2P(O)Cl$) and different chlorophosphonium salts ($[R_3PCl]X$, $R = (CH_3)_2N$, pyrrolidine, $X = PF_6^-$, BF_4^-), respectively, with 7-aza-1-hydroxybenzotriazole (HOAt), 1-hydroxybenzotriazole (HOBt), hydroximinomalonitrile (HOxDCO), and ethyl hydroximinocyanoacetate (HOxO) are described. The structures of the new compounds, which are useful coupling reagents for epimerization-free peptide segment condensation, are discussed on the basis of their ^1H, ^{13}C, ^{31}P NMR, and IR spectra. The reactions of $(PhO)_2P(O)Cl$ lead to mixtures of O- *and* N-*phosphorylated isomers of varying ratios. Contrary, reactions of chlorophosphonium salts yield exclusively one isomer.*

Keywords: Ambidence; coupling reagents; diphenoxyphosphoryl derivatives; oximes; phosphonium salts

INTRODUCTION

An effective formation of a peptide bond not only depends on reaction rate and yield but also on the maintenance of the configurational integrity of the carboxylic component. Besides carbodiimides, the most widely used coupling reagents are phosphonium and uronium salts, such as benzotriazole-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) or *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU). These compounds

Dedicated to Professor Alfred Kolbe on the occassion of his 70th birthday.

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combine the functions of activating agents with epimerization suppressing additives and were successfully introduced in peptide synthesis by Castro et al.[1]

Recently we reported on analogous additive releasing reagents based on phosphonium and uronium salts, sulfonates, and phosphates.[2] Comparing these coupling reagents with the same additive residue the diphenylphosphates have been found to be more effective than the corresponding onium salts and sulfonates using dichloromethane and acetonitrile as solvents. In this article we report on the reactions of diphenoxyphosphoryl chloride, tris(dimethylamino)chlorophosphonium hexafluorophosphate (CloP), tris(dimethylamino)chlorophosphonium tetrafluoroborate (TCloP), and tripyrrolidino-chlorophosphonium hexafluorophosphate (PyCloP) with 7-aza-1-hydroxybenzotriazole (HOAt), 1-hydroxybenzotriazole (HOBt), hydroxyiminomalonitrile (HOxDCO), and ethyl hydroximinocyanoacetate (HOxO). For these hydroxyimino species ambident behavior is known. With electrophiles[3,4] or transition metal ions[5] they react via oxygen or nitrogen (nitroso or triazole N) and thus different isomers can be expected.

The syntheses of related diphenoxyphosphoryl compounds (i.e., 1,4-epoxy-5-norbonene-2,3-dicarboximido diphenylphosphate (ENDPP), norbon-5-ene-2,3-dicarboximido diphenylphosphate (NDPP) and *N*-succinimidyl diphenylphosphate (SDPP)) are already described.[6–8]

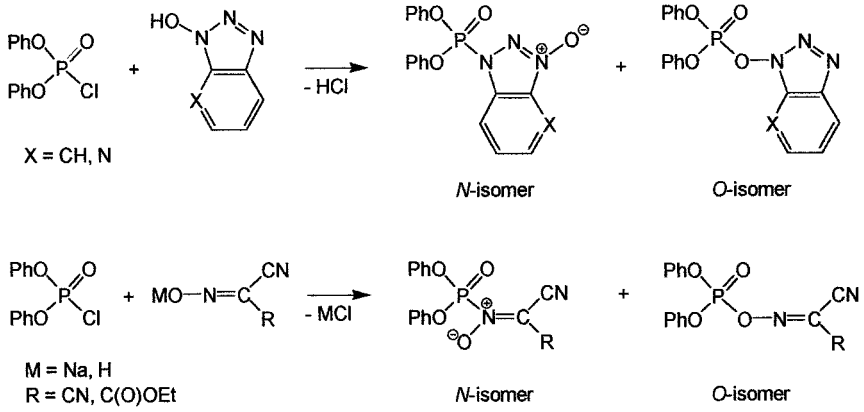
The synthesis of BOP was improved by different research groups.[9–11] Phosphonium salts derived from HOAt such as 7-azabenzotriazole-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (AOP) and 7-azabenzotriazole-1-yl-oxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) also have been prepared and generally are more efficient than BOP and benzotriazole-1-yl-oxytris(pyrrolidino) phosphonium hexafluorophosphate (PyBOP).[12,13]

RESULTS AND DISCUSSION

Structural moieties and abbreviations of the diphenoxyphosphoryl derivatives and phosphonium salts are listed in Tables I and II, respectively. Experimental data are summarized in Tables III and IV.

Diphenoxyphosphoryl Derivatives

The diphenoxyphosphoryl derivatives were synthesized according to Scheme 1. Anhydrous conditions are necessary for the synthesis and handling of the corresponding additives.



SCHEME 1 Reaction scheme for the diphenoxyphosphoryl derivatives.

Recently we reported the effect of usually applied HOBt-hydrate (water content >10%) instead of "anhydrous" HOBt (water content <5%) in the synthesis of *N*1-(diphenoxyphosphoryl)-benzo-[2,3-d][1,2,3]-triazole-3-oxide (*N*-phosphorylated isomer of BDPP concerning the *O*-isomer 1-hydroxybenzotriazole-diphenylphosphate (see below).[14] In the presence of water 1-hydroxy-benzotriazolium diphenylphosphate arises forming hydrogen bridged co-crystals of HOBt and diphenylphosphate which is inactive in peptide synthesis.

The ^{31}P NMR chemical shifts of the diphenoxyphosphoryl derivatives reveal interesting structural aspects concerning the bond of the additive to the phosphorus atom. Generally, we observe the formation of mixtures with changing ratios of isomeric components in dependence on the additive. In the literature the ^{31}P-NMR resonances for $(PhO)_2P(O)X$ with X = ONH_4, OPh and NCS are found at −9.8, −17.3, and −29.3 ppm respectively. Hence we would assign a signal at about −25 ppm in our derivatives as due to the N-phosphorylated compounds.[15]

TABLE I Structural Moieties and Abbreviations for the Diphenoxyphosphoryl Derivatives $(PhO)_2P(O)Y$

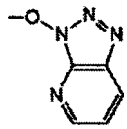
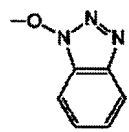
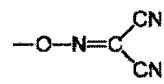
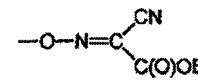
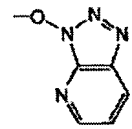
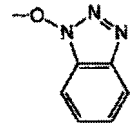
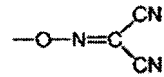
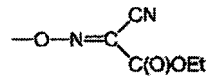
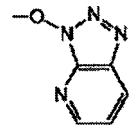
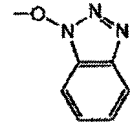
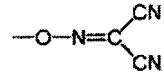
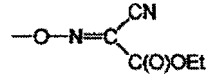
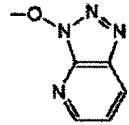
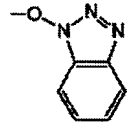
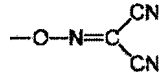
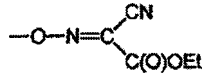
Abbreviation	ADPP	BDPP	DCODPP	ODPP
Y				

TABLE II Structural Moieties and Abbreviations for the Phosphonium Salts $[R_3PY]^+X^-$

R	X^-	Y	Abbreviation
$(CH_3)_2N$—	PF_6^-	Cl	CloP
$(CH_3)_2N$—	PF_6^-		AOP
$(CH_3)_2N$—	PF_6^-		BOP
$(CH_3)_2N$—	PF_6^-		DCOOP
$(CH_3)_2N$—	PF_6^-		OOP
$(CH_3)_2N$—	BF_4^-	Cl	TCloP
$(CH_3)_2N$—	BF_4^-		TAOP
$(CH_3)_2N$—	BF_4^-		TBOP
$(CH_3)_2N$—	BF_4^-		TDCOOP
$(CH_3)_2N$—	BF_4^-		TOOP
	PF_6^-	Cl	PyCloP

(Continued on next page)

TABLE II Structural Moieties and Abbreviations for the Phosphonium Salts $[R_3PY]^+X^-$ *(Continued)*

R	X^-	Y	Abbreviation
	PF_6^-		PyAOP
	PF_6^-		PyBOP
	PF_6^-		PyDCOOP
	PF_6^-		PyOOP

Based on crystallographic investigations of HBTU and *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU),[3,4] we conclude that the phosphorylation preferably yields the *N*-isomers. Indeed, the ^{31}P NMR spectra reveal a majority of the *N*-phosphorylated isomers *N*1-(diphenoxyphosphoryl)-pyrido-[2,3-d][1,2,3]-triazole-3-oxid (ADPP), *N*1-(diphenoxyphosphoryl)-benzo-[2,3-d][1,2,3]-triazole-3-oxid (BDPP), and *N*-(diphenoxyphosphoryl)-oximinomalonitrile (DCODPP) corresponding to the type $(PhO)_2P(O)\text{—}N(O)CR_2$ (cf. Table III). In the case of BDPP only the *N*-isomer is formed.

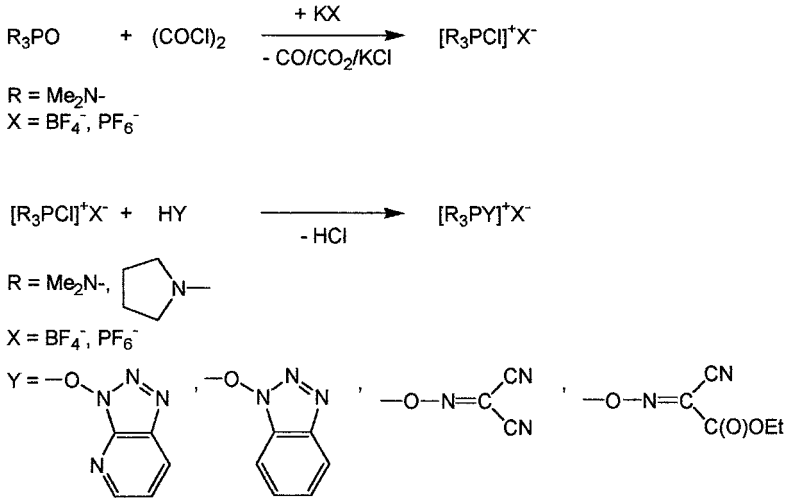
Surprisingly, the reaction of HOxO with diphenoxyphosphoryl chloride gives almost 95% of the *O*-phosphorylated isomer ethyl iminocyanoacetate *O*-diphenylphosphate (ODPP) and only 5% of the *N*-isomer ethyl oximinonitrilocyanoacetate *N*-diphenylphosphate.

It is worth mentioning that all products work as peptide coupling reagents independently of the formed isomer and the isomeric ratio.[2,16]

Phosphonium Salts

The synthesis of the phosphonium salts was performed according to Scheme 2. For the synthesis of the chlorophosphonium salts CloP and TcloP a new one-pot procedure was developed.

In contrast to the reactions of diphenoxyphosphoryl chloride with the discussed additives the reactions of the phosphonium salts yield only



SCHEME 2 Reaction scheme for the phosphonium salts.

products with ^{31}P NMR chemical shifts of the phosphonium cations in the range of 43–49 ppm. The ^{31}P NMR spectrum of BOP shows a resonance at 43.7 ppm (dichloromethane),[9] however, the chemical constitution of the compound was not discussed. Generally, the ^{31}P NMR chemical shifts available for tris(dimethylamino)phosphonium cations with a P—O bond are observed below 40 ppm and in case of an additional P—N bond the resonance occurs above 40 ppm.[17] This indicates that a P—N bond exists for all tris(dimethylamino)phosphonium additives presented here (cf. Table IV) in agreement with the constitution of the uronium salts determined by x-ray crystallography.[3,4] The ^{13}C NMR chemical shifts of the oxime substituents of OOP, TOOP, and PyOOP as well as of DCOOP, TDCOOP, and PyDCOOP, respectively, are almost similar, which hints at a unique substitution mode of these compounds.

EXPERIMENTAL

Materials, Equipment, and Methods

All solvents are commercially available. They were dried according to appropriate standard procedures.[18] Diphenylchlorophosphate (Janssen Chimica), triethylamine (TEA, Merck), hexamethylphosphoric triamide (HMPT, Fluka), dimethylformamide (DMF, Fluka), and oxalylchloride (Merck) were used as received. PyCloP (Fluka) and the additives HOAt (PerSeptive Biosystems) and HOBt (Fluka and Janssen Chimica) also

TABLE III Selected Analytical Data of the Diphenoxyphosphoryl Derivatives

			NMR data (ppm)				
Compound	M_w (g/mol)	Yield (%)	δ ^{31}P	δ ^{13}C (main product)		δ ^{1}H	
ADPP[a]	368.29	83	−24.9			8.73	1H, m, Ar—*H*
			N-isomer			8.42	1H, m, Ar—*H*
			(−13.0, 30%)			7.49	4H, m, Ar—*H*
			O-isomer			7.33	1H, m, Ar—*H*
						7.24	4H, m, Ar—*H*
						7.14	2H, m, Ar—*H*
BDPP	367.30	63	−24.9	151.6	1C, d, Ar—*C*	7.34	1H, m, Ar—*H*
			N-isomer	149.8	2C, d, Ar—*C*	7.30	2H, m, Ar—*H*
				142.9	1C, s, Ar—*C*	7.27	4H, m, Ar—*H*
				137.6	1C, s, Ar—*C*	7.24	1H, m, Ar—*H*
				129.8	4C, m, Ar—*C*	7.20	4H, m, Ar—*H*
				127.0	1C, Ar—*C*	7.16	2H, m, Ar—*H*
				125.9	2C, Ar—*C*		
				119.9	4C, Ar—*C*		
				115.5	1C, s, Ar—*C*		
				111.9	1C, s, Ar—*C*		
DCODPP	327.08	58	−25.0	149.4	2C, t, Ar—*C*	7.35	4H, m, Ar—*H*
			N-isomer	130.0	4C, m, Ar—*C*	7.26	4H, m, Ar—*H*
			(−10.8, 5.1%)	126.5	2C, m, Ar—*C*	7.17	2H, m, Ar—*H*
			O-isomer	119.8	4C, m, Ar—*C*		
				108.9	1C, d, N=*C*$(CN)_2$		
				105.6	2C, s, *C*N		
ODPP	374.29	96	−13.2	155.8	1C, s, *C*=O	7.35	4H, m, Ar—*H*
			O-isomer	149.7	2C, d, Ar—*C*	7.26	4H, m, Ar—*H*
			(−25.0, 4.7%)	134.4	1C, d, N=*C*R_2	7.21	2H, m, Ar—*H*
			N-isomer	129.9	4C, m, Ar—*C*	4.40	2H, q, C*H*$_2$
				126.1	2C, Ar—*C*	1.34	3H, t, C*H*$_3$
				119.9	4C, m, Ar—*C*		
				106.1	1C, s, *C*N		
				64.4	1C, *C*H_2		
				13.6	1C, *C*H_3		

[a]Melting point: 186°C (decomposition). A ^{13}C NMR spectrum was not recorded due to low solubility of ADPP in $CDCl_3$.

TABLE IV Selected Experimental Data of the Phosphonium Salts

Compound	M_w (g/mol)	m.p. (°C)	Yield (%)	NMR data (ppm/Hz) δ ^{31}P (^{1}J ^{31}P–^{19}F)	δ ^{13}C	δ ^{1}H
CloP[a]	343.62	340	72	60.2 (s), −138.4 (sept., J 708)	37.3 (6C, d, *C*H$_3$)	2.98 (18H, d, CH$_3$)
AOP[b]	443.27	168–170	62	49.6 (s), −138.5 (sept., J 710)	152.8 (1C, s, Ar–*C*), 139.4 (1C, s, Ar–*C*), 134.0 (1C, s, Ar–*C*), 129.6 (1C, Ar–*C*), 121.8 (1C, Ar–*C*), 36.7 (6C, m, *C*H$_3$)	8.66 (1H, m, Ar–*H*), 8.31 (1H, m, Ar–*H*), 7.47 (1H, m, Ar–*H*), 2.68 (18H, d, CH$_3$)
DCOOP[a]	402.22	169–171	85	48.7 (s), −138.4 (sept., J 708)	109.2 (1C, N=*C*R$_2$), 105.9 (2C, *C*N), 37.4 (6C, *C*H$_3$)	3.02 (18H, d, CH$_3$)
OOP[c]	449.27	131–133	84	43.0 (s), −143.8 (sept., J 711)	155.5 (1C, *C*=O), 136.1 (1C, N=*C*R$_2$), 106.0 (1C, *C*N), 65.0 (1C, *C*H$_2$), 37.2 (6C, *C*H$_3$), 13.8 (1C, *C*H$_3$)	4.46 (2H, q, CH$_2$), 2.89 (18H, d, CH$_3$), 1.40 (3H, t, CH$_3$)
TCloP[a]	285.46	320	59	60.1 (s)	37.3 (6C, d, *C*H$_3$)	2.97 (18H, d, CH$_3$)
TAOP[c]	385.11	185	84	44.6 (s)	153.3 (1C, Ar–*C*), 148.5 (1C, Ar–*C*), 130.1 (1C, Ar–*C*), 128.2 (1C, Ar–*C*), 122.2 (1C, Ar–*C*), 37.4 (6C, d, *C*H$_3$)	8.81 (1H, d, Ar–*H*), 8.45 (1H, q, Ar–*H*), 7.57 (1H, q, Ar–*H*), 2.87 (18H, d, CH$_3$)
TBOP[c]	384.12	161	60	44.4 (s)	142.8 (1C, Ar–*C*), 130.9 (1C, Ar–*C*), 126.2 (1C, Ar–*C*), 120.8 (1C, Ar–*C*),	8.07 (1H, d, Ar–*H*), 7.72 (1H, t, Ar–*H*), 7.52 (1H, t, Ar–*H*), 7.27 (1H, Ar–*H*),

					113.8 (1C, Ar—*C*), 107.6 (1C, Ar—*C*), 37.4 (6C, *C*H_3)	2.81 (18H, d, C*H*$_3$)
TDCOOP[d]	344.06	148	60	48.2 (s)	110.8 (1C, N=*C*R_2), 107.1 (2C, *C*N), 36.0 (6C, *C*H_3)	2.73 (18H, m, C*H*$_3$)
TOOP[c]	391.11	101–102	75	43.0 (s)	155.6 (1C, *C*=O), 136.1 (1C, N=*C*R_2), 106.1 (1C, *C*N), 64.7 (1C, *C*H_2), 37.1 (6C, *C*H_3), 13.7 (1C, *C*H_3)	4.42 (2H, q, C*H*$_2$), 2.86 (18H, d, C*H*$_3$), 1.36 (3H, t, C*H*$_3$)
PyDCOOP[a]	480.33	150–152	75	36.1 (s), −138.4 (sept., J 708)	109.2 (1C, N=*C*R_2), 106.0 (2C, *C*N), 48.73 (6C, N—*C*H_2), 26.8 (6C, N—*C*H_2—*C*H_2)	3.54 (12H, m, N—C*H*$_2$), 2.05 (12H, m, N—CH_2—C*H*$_2$)
PyOOP[c]	527.39	162–167	67	31.0 (s), −143.8 (sept., J 712)	155.6 (1C, *C*=O), 135.4 (1C, N=*C*R_2), 106.0 (1C, *C*N), 65.0 (1C, *C*H_2), 48.7 (6C, N—*C*H_2), 26.8 (6C, N—CH_2—*C*H_2), 13.8 (1C, *C*H_3)	4.48 (2H, q, C*H*$_2$), 3.38 (12H, m, N—C*H*$_2$), 2.03 (12H, m, N—CH_2—C*H*$_2$), 1.40 (3H, t, C*H*$_3$)

[a]Solvent for NMR spectra: acetone-d_6.
[b]Solvent for NMR spectra: $CDCl_3/CD_3CN$, 1:1.
[c]Solvent for NMR spectra: $CDCl_3$.
[d]Solvent for NMR spectra: $CDCl_3$/acetone-d_6, 1:1.

are available commercially. HOxDCO and HOxO were prepared as described previously.[19,20] In the case of HOxDCO only the Na- or K-salt (NaOxDCO or KOxDCO) is stable. Furthermore, the additive releasing reagents BOP, PyAOP, and PyBOP are commercial products.

IR spectra were recorded on a Mattson 5000 FTIR spectrometer. NMR measurements were performed on Varian Gemini 200 (200 MHz, ^{31}P), Varian Gemini 2000 (400 MHz, ^{1}H, ^{13}C), and Varian Unity 500 (500 MHz, ^{1}H, ^{13}C), spectrometers. *Ortho*-phosphorous acid (85%) and tetramethylsilane were used as standards for ^{31}P, ^{13}C, and ^{1}H NMR respectively.

The *N*/*O*-phosphorylated isomer ratios were calculated from the ratios of the heights of the corresponding peaks.

Synthesis of the Diphenylphosphoryl Derivatives

To a solution of 0.01 mmol (2.69 g) diphenylchlorophosphate and 0.01 mmol of the corresponding additive (HOAt: 1.36 g, HOBt: 1.35 g, HOxO: 1.42 g) in anhydrous THF (50 ml) 0.01 mmol TEA (1.01 g) was added under argon atmosphere. Instead of the additive and TEA, for the synthesis of DCODPP 0.01 mmol (1.17 g) NaDCOxO was used. After stirring for 3 h the reaction mixture was filtered off and the solvent was removed under reduced pressure. The resulting yellow oils were washed with dichloromethane (10 ml) and *n*-pentane (10 ml).

Synthesis of CloP and TCloP

0.05 mmol (9.25 g) potassium hexafluorophosphate or 0.05 mmol (6.3 g) potassium tetrafluoroborate, respectively, were dispersed in acetonitrile (250 ml) by vigorous stirring. 0.05 mmol (4.3 ml) oxalylchloride and 0.03 mmol (2.5 ml) DMF were added under argon atmosphere. The DMF exhibits a catalytic function.[21] To this mixture 0.05 mmol (8.75 ml) HMPT was slowly added at 0°C. After keeping the mixture at 0°C for 5 min the cooling bath was removed. The end of the reaction was indicated by ceasing of the gas evolution (after ca. 4 h). The potassium chloride was filtered off and the filtrate was graduated (up to ca. 50 ml) under reduced pressure. The chlorophosphonium salt was precipitated by addition of diethylether (500 ml) and purified by recrystallization from acetone (30 ml)/diethylether (250 ml).

Synthesis of the Final Coupling Reagents (Phosphonium Salts)

1 mmol of the chlorophosphonium salt (CloP: 0.343 g, TCloP: 0.285 g, PyCloP: 0.211 g), 1 mmol of the additive (HOAt: 0.136 g, HOBt: 0.135 g,

HOxO: 0.142 g), and 1 mmol TEA (0.101 g) were dissolved in acetone (10 ml) and stirred for 1 h [the additive HDCOxO and TEA were substituted by 1 mmol NaDCOxO (0.117 g) for the syntheses of DCOOP, TDCOOP, and PyDCOOP]. The solution was filtered off and the solvent was removed under reduced pressure. The crude product was purified by precipitating from acetone (5 ml) by addition of diethylether (50 ml) yielding white solids.

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