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THE USE OF DIACETOXYPHENYLIODINE FOR THE DIRECT OXIDATIVE CONVERSION OF S-PROTECTED L-CYSTEINE COMPOUNDS TO L-CYSTINE DERIVATIVES

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Summary: Diacetoxyphenyliodine was used for the direct oxidative conversion of S-Trt, S-Dpm and S-Acm-L-cysteine derivatives to optically pure L-cystine compounds.

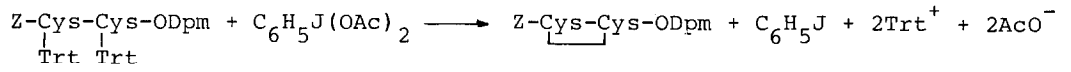
The cysteine S-protecting groups triphenylmethyl (trityl, Trt)[1], diphenylmethyl (Dpm)[2,3] and acetamidomethyl (Acm)[4] have been shown to be very useful in the synthesis of cystine peptides[5,6]. Recently, the application of the S-Trt group has been expanded since Kamber et al[7] have prepared cystine peptides from S-trityl cysteine peptides by direct oxidation with iodine.

We are now reporting the use of diacetoxyphenyliodine[8] as a new method which can be successfully applied to convert in high yields S-Trt, S-Dpm and S-Acm-L-cysteine derivatives (1) to optically pure L-cystine compounds (2). The general procedure is described below and some results are summarized in the Table. Using diacetoxyphenyliodine the reaction can take place in the presence of acid sensitive amino- and carboxyl- protecting groups such as, e.g., the N-butyloxycarbonyl, or the -ODpm group[9]. The method cannot be applied in the presence of amide groups since it is known that pheynyliodine diesters oxidize amides, having unsubstituted the NH_2-group, to amines; however, it can be applied to peptides[10].

An interesting example of the application of the new method to a peptide is the preparation of N-benzyloxycarbonyl-cyclo-L-cystinyl diphenylmethyl ester[11] (4) from N-benzyloxycarbonyl-S-trityl-L-cysteinyl-S-trityl-L-cysteine diphenylmethyl ester (3)[11]

$$2\ \underset{\underset{Y}{|}}{\text{X-Cys-OH}} + C_6H_5J(OAc)_2 \longrightarrow \underset{\underset{\text{X-Cys-OH}}{|}}{\text{X-Cys-OH}} + C_6H_5J + 2Y^+ + 2AcO^-$$

1 2



3 4

X: Z = $C_6H_5CH_2OCO$, Boc = $(CH_3)_3COCO$

Y: Trt = $(C_6H_5)_3C$, Dpm = $(C_6H_5)_2CH$, Acm = $CH_3CONHCH_2$

To our opinion, the new method will prove to be very useful in the case of the S-Dpm group, which can now be removed under conditions much more mild than those previousely reported (e.g., by trifluoroacetic acid in the presence of phenol, by thiocyanogen, or sulfenyl-thiocyanates)[2,3]. This is especially important since S-Dpm-L-cysteine and various of its derivatives can be easily obtained pure in high yield[2] and are also more resistant to acidic reagents than the corresponding S-Trt derivatives. Even the N-benzyloxycarbonyl group can be used under certain conditions[5,12,13] in the presence of the S-Dpm group.

Work is in progress to test the applicability of the new method to different peptides and other cysteine S-protecting groups in the presence of various amino- and carboxyl-protecting groups. The above results seem also to indicate the possibility of selective removal of S-trityl in the presence of S-acetamidomethyl groups[14].

Conversion of S-Trt, S-Dpm or S-Acm-L-cysteines (1) to L-Cystines (2); General Procedure

To a solution of starting material (2 mmol) in dichloromethane (10ml) diacetoxyphenyliodine (0.71 g, 2.2 mmol) is added and the mixture is stirred at room temperature (see the Table). The solution is then diluted with the same solvent and extracted 4 times with water to remove most of the acetic acid formed during the reaction. The organic layer is dried over sodium sulphate, concentrated to dryness and the residue dissoved in ethyl acetate. The cystine derivative is precipitated either as the free acid or in the form of the corresponding salt after the addition of the appropriate amine (2.2 mmol) as shown in the Table.

N-Benzyloxycarbonyl-cyclo-L-cystinyl Diphenylmethyl Ester (4):

A solution of diacetoxyphenyliodine (0.65 g, 2 mmol) in chloroform (100ml) is added dropwise within 45 min and under stirring at room temperature to a solution of N-benzyloxycarbonyl-S-trityl-L-cysteinyl-S-trityl-L-cysteine diphenylmethyl ester[11] (2.02 g, 2 mmol) in chloroform (100 ml). After stirring for 30 more min, the mixture is extracted with water, the organic layer is dried and evaporated to dryness. The residue is triturated with ether, filtered off and recrystallized from methanol.

Starting material	Product	Reaction time	Yield (%)	m.p[b] (°C)	Specific rotation[c] $[\alpha]_D^{25}$		
					$CHCl_3$	DMF	MeOH
Z-Cys(Trt)-OH[15]	Z-Cys(Z-Cys)-OH[d]	5min	97[e]	189-190[d]		-51.5[d]	
Z-Cys(Dpm)-OH[15]	Z-Cys(Z-Cys)-OH[d]	10min	92[e]	189-190[d]		-51.5[d]	
Boc-Cys(Trt)-OH[5,17]	Boc-Cys(Boc-Cys)-OH[f]	90min	70[e]	143-145[g]			-136°[g]
Boc-Cys(Dpm)-OH[19]	Boc-Cys(Boc-Cys)-OH[f]	90min	70[e]	143-145[g]			-136°[g]
Z-Cys(Acm)-OH[4]	Z-Cys(Z-Cys)-OH[d]	180min	85[e]	189-190[d]		-51.5[d]	
Z-Cys(Trt)-Cys(Trt)-ODpm[11]	Z-Cys-Cys-ODpm[h]	75min	65[i]	156-158	+7.6°		

[a] Compounds were compared with authentic samples by mixed melting point determination and by TLC on silica gel G(Fluka) containing 13% calcium sulphate, in the solvent systems given below.

[b] M.p's. were determined in capillary tubes and are uncorrected.

[c] Specific rotations were measured at 1% concentration (unless otherwise stated) with a Perkin-Elmer 141 automatic polarimeter (1-dm cell).

[d] Isolated as dicyclohexylammonium salt[16]; R_F 0.8 in butan-1-ol/acetic acid/water (100: 10: 30, v/v). Lit[16], m.p. 190-191°, $[\alpha]_D^{20-26}$ -51.8°

[e] Prepared by the general procedure.

[f] For the purification a sample of the crude mixture was dissolved in $CHCl_3$ and applied to a column of silica gel. $CHCl_3$ was first used for elution which was changed to $CHCl_3$ containing 5% (v/v) CH_3OH. The fractions containing pure material (TLC) were combined and evaporated.
Rf. 0.7 in butan-1-ol/acetic acid/water (100: 10: 30, v/v).

[g] Lit.[18], m.p. 145-146°, $[\alpha]_D^{19}$ -138° (C 2.5 in methanol)

[h] Prepared as described in the experimental.

[i] Lit.[11], m.p 157-158°, $[\alpha]_D^{20}$ +7.8°

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