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2-Phenyl Isopropyl and t-Butyl Trichloroacetimidates: Useful Reagents for Ester Preparation of N-Protected Amino acids under Neutral Conditions.

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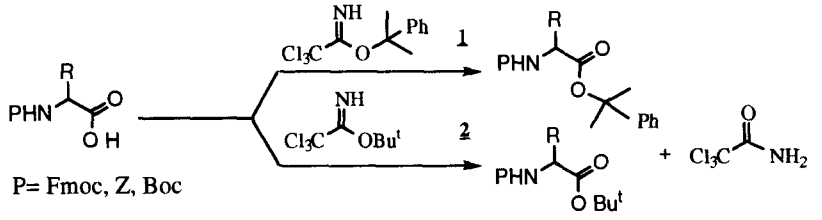
Abstract : *2-Phenylisopropyl and t-butyl trichloroacetamidates 1 and 2 are useful reagents for the esterification of N-protected aminoacids under mild neutral conditions. In the case of hydroxyl-containing amino acids, dialkylation occurs but no selectivity could be obtained.*

Alkyl trichloroacetimidates have been reported in a number of cases of O-alkylation of acids or alcohols[1-7]. These reagents have proven particularly useful in the glycoside synthesis area[8] where they have been used as donors for building the glycosidic bond. Benzyl-type and allyl trichloroacetimidates have been employed for ether as well as for ester synthesis and 2-phenylisopropyl trichloroacetamidate has been used for esterification of N-protected aminoacids[4].

An acid catalyst (BF_3-Et_2O[1-3] or methanesulfonic acid[2]) was required in all the examples using allyl and benzyl-type trichloroacetimidates, whereas, in contrast, no catalyst was necessary for the esterification of N-protected aminoacids with 2-phenylisopropyltrichloroacetamidate **1**[4]. This observation led us to reinvestigate the need for acid catalysis in the reaction of N-protected aminoacids with t-butyl trichloroacetamidate **2**. We describe here the esterification of N-protected aminoacids with **2**. We also provide further examples illustrating the use of **1** for the alkylation of N-protected aminoacids.



Scheme 1

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Esterification with 2-Phenylisopropyl trichloroacetamidate 1

A typical illustrative procedure is as follows: Fmoc, Z or Boc protected amino acids in solution in dichloromethane(6mL/mmole) were reacted overnight with **1** (2 equiv.) prepared as previously described[4]. The white precipitate of trichloroacetamide was filtered off and the filtrate was concentrated in vacuo. The ester was isolated by flash column chromatography. Yields of esters were good even in case of dipeptides (entries 5, 6) or amino acids bearing sensitive fonctionnalities (Met, Trp, Tyr) (entries 1, 2, 4) and no acid catalysis was required. However, no selectivity was achieved as it can be seen from the cases of Z-Ser-OH and Fmoc-Tyr-OH (entries 3, 4) which both yielded esters (respectively 67% and 43%) along with some dialkylated products (respectively 14% and 23%).

The influence of the solvent was also studied as it has been stated that a non polar solvent was best for the reaction. Treatment of Fmoc-Met-OH, used as a test substrate with **1** (2 equiv.), yielded the corresponding ester in good yield (toluene: 95%, acetonitrile: 93%).

Table 1: Alkylation with 2-Phenyl Isopropyl Trichloroacetimidate **1**

Entry	Substrate	Yield(%)(a)
1	Fmoc-Met-OH	98
2	Z-D-Trp-OH	80
3	Z-Ser-OH	67+14(b)
4	Fmoc-Tyr-OH	43+23(b)
5	Boc-Nle-D-Trp-OH	78
6	Fmoc-Lys(Boc)-Pro-OH	87

a)Yield in pure isolated compounds after column chromatography, b)Yield in dialkylated compounds.

Esterification with t-butyl trichloroacetamidate 2

We then turned to the esterification with t-butyl trichloroacetamidate **2**. Fmoc, Z or Boc protected amino acids in solution in dichloromethane(10mL/mmole)[9] were reacted with **2** (1.5-4 equiv.)[10] either overnight at room temperature or 2-5h at reflux. Once again, no chemoselectivity was observed : both the carboxylic function and alcohol side chain of N-protected Ser, Thr and Tyr were alkylated yielding a mixture of t-butyl esters and di-t-butyl derivatives. The results shown in Table 2 clearly demonstrate that there is no need for an acid catalyst for esterification to proceed. However, it seems that alkylation of the alcohol side chain of the tyrosine derivative requires some acid catalyst, probably achieved by the α-carboxylic group as the reaction of Fmoc-Tyr-OBu^t with **2** (6 equiv.) does not yield any t-butyl ether even after 72h. The same holds true for Z-Ser-OBu^t which did not produce any ether when treated with **1** (2 equiv.) for 24h. Furthermore, it should be pointed out that complete dialkylation of Fmoc-Tyr-OH could not be achieved even with 6 equivalents of reagent **2**.

Table 2: Alkylation with t-butyl trichloroacetimidate **2**

Substrate	Reaction conditions	Reagent (equiv.)	Yield(%) (b)
Fmoc-Met-OH	room temp.	1.5	78
"	reflux	1.5	95
Fmoc-Pro-OH	room temp.	1.5	73
Fmoc-Asp(OBu^t)-OH	"	3	77
Z-Glu-OBzl	"	2	66
Z-D-Trp-OH	"(a)	1.5	71
"	reflux	2	90
Fmoc-Ser-OH	room temp.(a)	1.5	56+9(c)
"	reflux	4	54+42(c)
Z-Ser-OH	room temp.(a)	2	62+10(c)
"	"	4	49+36(c)
"	reflux	4	60+36(c)
Z-Thr-OH	room temp.	2	76+10(c)
"	reflux	4	77+22(c)
Boc-Tyr-OH	room temp.	2	53+17(c)
Fmoc-Tyr-OH	"	4	40+32(c, d)

a) solvent:THF/CH_2Cl_2, b) Yield in pure isolated compounds after column chromatography, c) Yield of dialkylated compound, d) the monoalkylated compound was not easily separated from the trichloroacetamide.

Solvent effect on alkylation with t-butyl trichloroacetimidate 2

The solvent effect on the chemoselectivity of the alkylation reaction by **2** of Fmoc-Tyr-OH on one hand and of Fmoc-Ser-OH on the other hand, has been studied. Acetonitrile, diethyl ether, toluene, THF and ethyl acetate have been used. The reaction was run with 4 equivalents of **2** at room temperature for 24 h.

No starting material was left after that time, except for toluene and THF. Thus, in THF, the reaction did not proceed at all and in toluene was incomplete for the alkylation of Fmoc-Tyr-OH. In acetonitrile, the reaction mixture contained several side products. The results in Table 3 show that diethyl ether and ethyl acetate were good solvents.

The alkylation of Fmoc-Tyr-OH in diethyl ether and ethyl acetate yielded quite different ratios of mono and di t-butyl compounds.

For the alkylation of Fmoc-Ser-OH, similar results were obtained in diethyl ether, toluene and THF, the reaction yielding a 1/1 mixture of mono t-butyl ester and dialkylated products. However, in ethyl acetate, the t-butyl ester was the major product (66%) as in the case of Fmoc-Tyr-OH. Surprisingly, the reaction was effective in THF and complete in toluene, in this case. No clearcut trend could be seen from these various experiments. In all cases, the carboxylic acid was first alkylated as no Fmoc-Ser(Bu^t)-OH resulting from monoalkylation of the side chain was isolated.

Table 3. Solvent Effect on Alkylation with **2**[11]

	Fmoc-Tyr-OBu^t(%)	Fmoc-Tyr(Bu^t)-OBu^t(%)	Fmoc-Ser-OBu^t(%)	Fmoc-Ser(Bu^t)-OBu^t(%)
Diethyl ether	40	57	47	53
AcOEt	64	36	66	34
Toluene	16[a]	36[a]	47	53
THF	0[b]	0[b]	56	44

a) the reaction was incomplete, b) no reaction

Although some published procedures [12,13] allow the esterification of N-protected hydroxy aminoacids, they are not suitable for N-Fmoc-derivatives; the use of **2** provides in a single step the t-butyl N-protected amino esters .

In conclusion, it should be pointed out that the reported method allowed the esterification without acid catalysis of N-protected aminoacids yielding 2-phenyl isopropyl and t-butyl esters. It is important to mention that no reaction took place when benzyl or allyl trichloroacetimidates were used under the same conditions.

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9. A mixture of CH_2Cl_2/THF(4/1, v/v) was used to achieve dissolution of Z-Ser-OH, Fmoc-Ser-OH and Z-D-Trp-OH.
10. A 1M solution of commercially available t-butyl trichloroacetimidate(Aldrich, Senn Chemicals, Lancaster, NovaBiochem) in cyclohexane was prepared and stored at -20°C for an extended period of time.
11. Reaction mixtures were analyzed by RP-HPLC. % of each compound was calculated from the area of the corresponding peak of the chromatogram recorded at 270nm.
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