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Simple and mild esterification of *N*-protected amino acids with nearly equimolar amounts of alcohols using 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline

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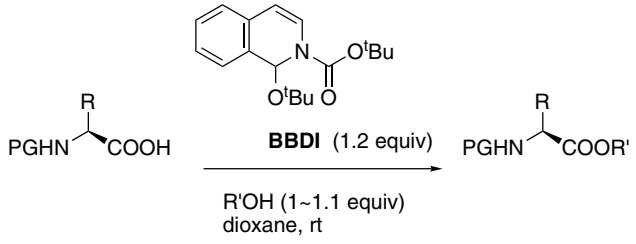
Abstract—A very mild, one-step esterification using nearly equimolar amounts of *N*-protected amino acids and alcohols, in conjunction with 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as a novel condensing reagent is described.

The synthesis of carboxylic esters is one of the most fundamental and pivotal protocols for producing natural and synthetically useful compounds in organic chemistry. To date, a variety of esterification conditions have been developed.[1] Among them, coupling reactions between activated derivatives of carboxylic acids and alcohols have been employed.[2] However, most procedures require either the presence of strong acids,[3] bases,[4] or other catalysts or heating. In some cases, a reagent-derived byproduct such as urea makes product purification difficult. Accordingly, the further development of simple methods for esterification under mild condition would be desirable. These procedures are of considerable interest, especially as relate to the manipulation of peptides or complicated biologically active compounds such as macrolides. Following our interest in the use of 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as a novel butoxycarbonylation reagent in the organic synthesis,[5] we describe herein a simple and mild esterification that uses nearly equimolar amounts of *N*-protected amino acids and alcohols and BBDI as a novel condensing reagent without the need for any additives (Scheme 1).



Scheme 1.

Recently, Zacharie et al. reported[6a] a simple one-step conversion of carboxylic acids to esters using 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) as a new condensing reagent.[6] However, this procedure requires a large excess of alcohol, because EEDQ in the presence of carboxylic acids liberates ethanol, which reacts with carboxylic anhydride to produce the corresponding ethyl ester as a byproduct. With this drawback in mind, we considered the possibility of reacting BBDI with carboxylic acids to afford the corresponding mixed anhydrides **A** which, represents a promising active intermediate for esterification, because the *tert*-butanol liberated from the BBDI would not attack the carboxylic anhydride owing to steric hindrance (Scheme 2).

In practice, it is found that the method allows the preparation of *N*-protected amino acid esters in a single-step reaction.[7,8] Thus, the *N*-protected amino acid is treated with BBDI (1.2 equiv) in dioxane for 30 min, followed

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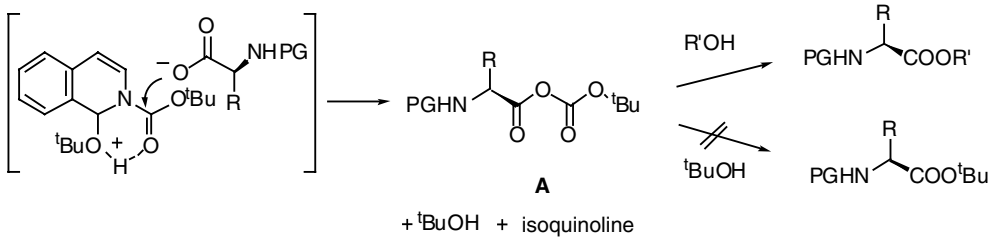


Scheme 2.

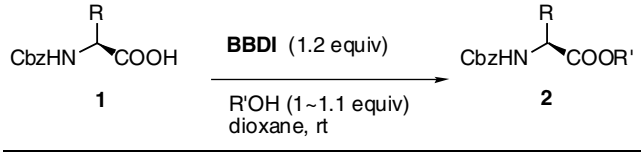
by the addition of alcohol (1–1.1 equiv) at room temperature. This procedure allows the esterification to proceed in a single operation. The reaction mixture was concentrated, ethyl acetate added and the organic solvent washed with diluted HCl and brine. The reagent-derived byproducts are easily removed by a simple aqueous workup. Our results using *N*-Cbz amino acids are shown in Table 1. It is possible that the prepared alkyl (allyl, benzyl, *p*-methoxyphenyl, 2-trimethylsilylethyl) esters are selectively cleaved (entries 4–13).[9] The reaction is not fast and requires from 5 to 20 h for completion in most cases except for entries 13 and 14. Extended reaction times were needed for both the use of *N*-Cbz-valine (R = isopropyl) (entry 13) and a secondary alcohol (entry 14). Accordingly, the rate of the reaction is dependent on the bulkiness of reactants. However, in all cases examined, the yields were high, and no *tert*-butyl esters were found in the reaction mixture.[10] On the other hand, similar esterification of *N*-Cbz-alanine with benzyl alcohol (1 equiv) using EEDQ gave **2f** (42%) accompanied by the corresponding ethyl ester (57%). Thus, BBDI appears to be superior to EEDQ as a reagent.[12] Unfortunately, the esterification of *N*-Cbz-serine and -threonine containing a hydroxy group with an equimolar amount of allyl alcohol resulted in very low yields (6% and a trace) of the desired esters **2o** and **2p** accompanied by a mixture of unknown compounds. However, when allyl alcohol was used as a solvent, the yields were improved to 56% and 51%, respectively (entries 15,16).

The method is also compatible with the commonly used *N*-protecting groups and no deprotection was noted even with both the acid-labile *N*-Boc-protected and the base-labile *N*-Fmoc-protected amino acids, as shown from the results reported in Table 2.

The data collected show that no significant racemization of the chiral center on the α-carbon atom occurred during the synthesis.[13]

In conclusion, a simple and mild esterification of *N*-protected amino acids using BBDI as a novel condensing reagent in a one-pot method was developed. This protocol has several advantages including the use of nearly equimolar amounts of alcohols, no requirement for additives, and no racemization occurs.[15] The scope and limitations of BBDI as dehydrating reagent are currently under investigation.[16]

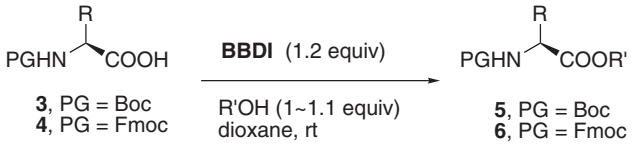
Table 1. Esterification of *N*-Cbz-protected amino acids **1** with BBDI



Entry	1	R′	Product	Yield (%)[c]
1	Cbz-Ala	CH_3[a]	**2a**[d]	86
2	Cbz-Ala	C_2H_5[b]	**2b**[d]	95
3	Cbz-Ala	C_6H_5[a]	**2c**[e]	90
4	Cbz-Ala	Allyl[a]	**2d**[e]	85
5	Cbz-Ala	*p*-MeOPh[b]	**2e**[e]	90
6	Cbz-Ala	$C_6H_5CH_2$[b]	**2f**[d]	88
7	Cbz-Ala	2-$TMSCH_2CH_2$[a]	**2g**[d]	90
8	Cbz-Phe	Allyl[a]	**2h**[e]	91
9	Cbz-Phe	$C_6H_5CH_2$[b]	**2i**[e]	82
10	Cbz-Met	Allyl[a]	**2j**[e]	89
11	Cbz-Met	$C_6H_5CH_2$[b]	**2k**[e]	92
12	Cbz-Pro	Allyl[a]	**2l**[d]	84
13	Cbz-Val	Allyl[a]	**2m**[f]	81
14	Cbz-Phe	$(CH_3)_2CH$[a]	**2n**[g]	84
15	Cbz-Ser	Allyl[a]	**2o**[d]	6 (56)[h]
16	Cbz-Thr	Allyl[a]	**2p**[d]	Trace (51)[h]

[a] 1.1 equiv.
[b] 1 equiv.
[c] Isolated yield.
[d] Reaction time: 20 h.
[e] Reaction time: 5 h.
[f] Reaction time: 72 h.
[g] Reaction time: 24 h.
[h] Allyl alcohol was used as a solvent in place of dioxane.

Table 2. Esterification of *N*-Boc- and *N*-Fmoc-protected amino acids **3** and **4** with BBDI



Entry	*N*-PG-AA	R′[a]	Product	Yield (%)[b]
1	Boc-Ala	*p*-MeOPh	**5a**[c]	95
2	Boc-Ala	$C_6H_5CH_2$	**5b**[d]	91
3	Boc-Ala	Allyl	**5c**[c]	83
4	Boc-Phe	Allyl	**5d**[d]	85
5	Boc-Phe	$C_6H_5CH_2$	**5e**[d]	96
6	Boc-*S*-Bzl-Cys	Allyl	**5f**[c]	88
7	Fmoc-Ala	Allyl	**6a**[d]	85
8	Fmoc-Phe	Allyl	**6b**[d]	90

[a] 1.1 equiv was used except for entry 1 (1 equiv).
[b] Isolated yield.
[c] Reaction time: 5 h.
[d] Reaction time: 24 h.

Acknowledgements

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10. Typical procedure: The procedure for the preparation of (*S*-*N*-benzyloxycarbonyl)alanine allyl ester **2d**, is representative of all cases. BBDI (1.2 mmol) was added to a solution of (*S*)-*N*-benzyloxycarbonyl)phenylalanine (1 mmol) in dioxane (5 mL) with stirring at room temperature. The reaction mixture was stirred for 30 min. To the reaction mixture was added allyl alcohol (1.1 mmol). The reaction mixture was stirred for 5 h and then concentrated. After the addition of ethyl acetate, the organic phase was washed twice with 5% HCl and brine. The organic layers were dried ($MgSO_4$) and the solvent evaporated to give the crude compound, which was purified by chromatography on a short column to yield **2h** (296 mg, 91%), colorless liquid; IR (KBr): 1714, 1728, 3340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.04–3.19 (2H, m), 4.59 (2H, d, $J = 5.8$ Hz), 4.60–4.71 (1H, m), 5.08 (2H, s), 5.21–5.35 (3H, m), 5.77–5.91 (1H, m), 7.07–7.19 (2H, m), 7.24–7.38 (8H, m); $[\alpha]_D^{21}$ −14.8 (*c* 1.3, MeOH) [lit.[11] $[\alpha]_D^{25}$ −15.6 (*c* 2.03, MeOH)]; MS (EI) *m*/*z* 339 (M^+); HRMS *m*/*z* Calcd for $C_{20}H_{21}NO_4$ (M^+) 339.1471. Found: 339.1458.
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12. The reaction of *N*-Cbz-alanine (1 mmol) with allyl alcohol (1 mmol) using 1-isopropoxy-2-ethoxycarbonyl-1,2-dihydroisoquinoline (1.2 mmol) provided *N*-Cbz amino allyl ester (47%) together with *N*-Cbz amino isopropyl ester (12%) and *N*-Cbz amino ethyl ester (30%) as byproducts.
13. The specific optical rotations of samples of (**2a**)$[\alpha]_D^{23}$ −33.0 (*c* 1.2, CH_3OH), lit.[14] $[\alpha]_D^{25}$ −32.7 (*c* 1.3, CH_3OH), **2b** $[\alpha]_D^{27}$ −32.6 (*c* 1.5, CH_3OH), lit.[14] $[\alpha]_D^{23}$ −32.2 (*c* 1.0, CH_3OH) were in good agreement with literature values. In fact, the enantiomeric purities of **2a**, **2b** and **2h** were >99% ee, as determined by chiral HPLC analysis (Chiralcel OD column, 95:5 hexane/2-propanol, 1.0 mL/min) for **2a,b** and (Chiralcel OJ column) for **2h**.
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16. Results including esterification of other carboxylic acids will be published in due course.