

Chemoselective alkoxy-carbonylation reagent having trifluoromethylsulfonyl-4-trifluoromethylanilide as a leaving group †

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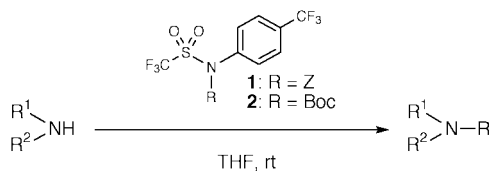
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N-Benzyloxy- and *N*-*tert*-butoxycarbonyltrifluoromethylsulfonyl-4-trifluoromethylanilides were prepared and were found to be chemoselective and shelf-storable alkoxy-carbonylation reagents.

Selective alkoxy-carbonylation of amines according to their chemical types is an important synthetic operation. Selective reagents have been developed by devising a leaving group such as chloride,¹ imidazolide,² imide,³ oxime,⁴ enolate,⁵ and so on.⁶ Although some of the reagents are now commercially available, continuing efforts have been made to develop an ideally selective reagent.⁷ It is reasonably assumed that a reagent having a bulky leaving group may satisfy such a requirement. However, bulkiness retards the reaction as well. We designed a new alkoxy-carbonylation reagent of amines employing trifluoromethylsulfonyl-4-trifluoromethylanilide as a leaving group. Since the trifluoromethylsulfonyl and 4-trifluoromethylphenyl groups are powerful electron-withdrawing ones,⁸ the sulfonamide of 4-trifluoromethylaniline is expected to behave as a bulky and excellent leaving group. Calculation of *Z*-anilide **1** (Scheme 1)



by MOPAC (PM3, precise mode) indicated that the 4-trifluoromethylphenyl group is placed almost perpendicular to the plane of O=C–N.⁹ Therefore, sufficient steric bulkiness is provided around the carbonyl group. We describe herein that **1** and Boc-anilide **2** are chemoselective and rapid alkoxy-carbonylation reagents of amines.

Attempted benzyloxycarbonylation of *N*-trifluoromethylsulfonyl-4-trifluoromethylaniline¹⁰ under the standard acylation conditions,¹¹ ZCl and triethylamine–DMAP in chloroform at rt for 12 h, however, gave an *N*-benzylation product in 84% yield without formation of the expected *Z*-anilide **1**.¹² Fortunately, this problem was solved by treating the sodium salt of sulfonamide with ZCl in THF at 0 °C for 24 h. After column chromatography, **1** was obtained as shelf-storable needles of mp 105–107 °C in 76% yield together with *N*-benzylsulfonylanilide in 24% yield.¹³ Boc-anilide **2** was also prepared under the same conditions for **1** using (Boc)₂O in 95% conversion yield as shelf-storable needles of mp 65–67 °C.

Benzyloxycarbonylation of several types of amines with **1** was examined in THF at rt.¹⁴ The reaction was monitored by

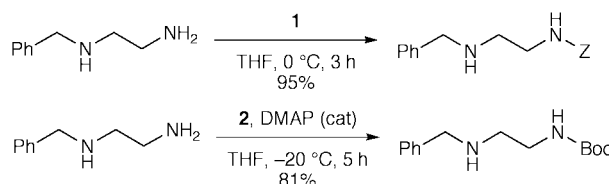


Fig. 1 Selective benzyloxy- and *tert*-butoxycarbonylation.

TLC. A typical primary amine, 2-phenylethylamine, was converted into the *Z*-derivative in 95% yield within 5 min by treating with 1.2 equiv. of **1** (Table 1). An α -branched primary amine, 1-phenethylamine, was converted into the *Z*-derivative in 99% yield in 15 min. It took 24 h for the conversion of *tert*-butylamine into the *Z*-derivative in 88% yield. A secondary amine, benzylmethylamine, was converted into the *Z*-derivative in 99% yield in 5 min. Aniline was benzyloxycarbonylated in 97% yield in 3 h. *N*-Methylaniline, however, was slowly converted to the *Z*-derivative in 89% yield in 24 h. These differences in the reaction time apparently indicate the high chemoselectivity of **1**, which distinguishes steric and electronic characters of amines. Thus, primary amine-selective monobenzyloxycarbonylation of a diamine, *N*-(2-aminoethyl)benzylamine, was realized by treating with 1.0 equiv. of **1** at 0 °C for 3 h in THF to afford the mono-*Z*-derivative¹⁵ in 95% yield (Fig. 1). The leaving group of **1**, trifluoromethylsulfonyl-4-trifluoromethylanilide, was recovered quantitatively for recycling simply by extracting with aq. sodium bicarbonate. After washing, concentration gave the benzyloxycarbonylated product, which was purified by recrystallization or column chromatography.

The *Z*-anilide **1** was also a good benzyloxycarbonylation reagent for α -amino acids. Treatment with 1.1 equiv. of **1** in a 1:1 mixture of aq. dioxane in the presence of 1.5 equiv. of triethylamine at rt for 0.2–24 h gave *Z*-amino acids in high yields without racemization as shown in Table 2.

Under the same conditions using **2**, 2-phenylethyl, 1-phenylethyl, and benzylmethylamines were converted to the Boc-derivatives in 99, 90, and 90% yields for 0.1, 1, and 1 h, respectively (Table 1).¹⁶ Aniline and *tert*-butylamine were not converted to the Boc-derivatives at rt for 24 h; instead they were recovered unchanged. However, upon addition of 0.1 equiv. of DMAP these amines were converted to the Boc-amines in high yields. Proline and phenylalanine were converted into Boc-amino acids in 97 and 59% yields for 24 h (Table 2). These impressive differences in reactivity are attributable to the efficient bulkiness around the carbonyl group of **2** by the *tert*-butoxy and sulfonylanilide groups, indicating that reactivity of **2** is sensitive to the steric and electronic characters of the amines. Chemoselective *tert*-butoxycarbonylation was also possible in the presence of cat. DMAP (Fig. 1).

In conclusion, the anilides **1** and **2** were shown to be chemoselective and shelf-storable crystalline alkoxy-carbonylation reagents. Since ZCl is an irritant, unstable liquid, and (Boc)₂O is a solid of low melting point, **1** and **2** are good alternatives.

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† Experimental details for the preparation and reactions of **1** and **2** are available as supplementary data. For direct electronic access see <http://www.rsc.org/suppdata/p1/1999/2233>, otherwise available from BLDSC (SUPPL. NO. 57604, pp. 2) or the RSC Library. See Instructions for Authors available via the RSC web page (<http://www.rsc.org/authors>).

Table 1 Synthesis of Z- and Boc-amines with **1** or **2**

Amine	Z-Amine with 1		Boc-Amine with 2		Boc-Amine with 2 and DMAP	
	t/h	Yield/%	t/h	Yield/%	t/h	Yield/%
	0.1	95	0.1	99		
	0.3	99	1	90		
t-Bu-NH ₂	24	82	24	0	19	87
	0.1	99	1	90		
Ph-NH ₂	3	97	24	31	6	93
	24	89	24	0	168	99

Table 2 Synthesis of Z- and Boc-AA in aq. dioxane at room temp.

1 or 2	AA	t/h	Yield/%
1	Ala	24	99
	Phe	0.2	93
	Tyr	3	83
	Gln	1	98
	Trp	3	84
	Pro	3	93
2	Phe	24	59
	Pro	24	96

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