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Tetrahedron Letters 47 (2006) 3051–3053

Tetrahedron Letters

Convenient removal of *N*-*tert*-butyl from amides with scandium triflate

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Received 1 December 2005; revised 23 February 2006; accepted 1 March 2006

Abstract—Scandium triflate has been used as a convenient and efficient catalyst for removal of *N*-*tert*-butyl from amide groups. A variety of *N*-*tert*-butyl aryl and alkyl amides under these conditions gave the corresponding primary amide in high yields. With the use of microwave heating the deprotection reaction could be completed within 1 h.

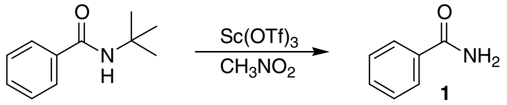
1. Introduction

Acid labile protecting groups are important in organic synthesis.[1,2] Among them, the *tert*-butyl group is commonly used for protection of a large variety of functional groups, for example, acids,[3] alcohols,[4,5] phenols,[6,5] and sulfonamides.[7] On the other hand, the *tert*-butyl group is very rarely used for the protection of amides[8–10] probably due to the conditions required for its removal. Most of the known methodologies require harsh conditions such as sulfuric acid, trifluoroacetic acid, or hydrobromic acid.[8–10] A mild and efficient removal would be attractive and likely to increase the use of *tert*-butyl as a protecting group for amides. Additionally, a convenient removal of *N*-*tert*-butyl groups from amides could be used as an alternative two-step procedure to obtain primary amides from acid chlorides via the *N*-*tert*-butyl amide.

Scandium triflate is an effective Lewis acid that, unlike traditional Lewis acids, is water stable.[11,12] Due to its unique water stability scandium triflate could, in an environmentally friendly manner, be recovered and reused for several reaction cycles.[13] We wanted to explore the possibility of using scandium triflate as a mild reagent for the removal of *N*-*tert*-butyl groups from primary amides, in combination with both conventional and microwave heating.

Initially, *N*-*tert*-butyl-benzamide was treated with 20 mol % of scandium triflate in nitromethane at 50 °C (Scheme 1). A substantial amount of benzamide **1** was formed, although the reaction was incomplete after 24 h. We therefore applied 1 equiv of scandium triflate and increased the temperature to 100 °C. This resulted in full conversion after 4 h, and benzamide could be isolated in 96% yield. To further decrease the time of the reaction, microwave heating was applied. At 170 °C the reaction was completed in 1 h and delivered an equally high yield of the deprotected compound.

To examine the scope and limitations of the deprotection procedure, a series of electron-rich and electron-poor aromatic amides, as well as aliphatic substrates, were selected for evaluation. The preparative results are shown in Table 1. All of the *N*-*tert*-butyl aryl amides provided excellent yields with both thermal and microwave heating. All the aliphatic substrates gave full conversion and with *N*-*tert*-butyl-3-phenyl-propionamide (entry 8) a good yield was obtained. However in the cases of entries 9 and 10, a lower yield was obtained. In the case of 3-(thiophen-2-yl)-propionamide **9** the low yield was caused by formation of degradation products and for pentanamide **10** the volatile nature of the



Scheme 1.

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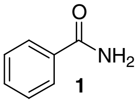
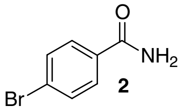
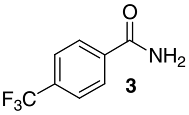
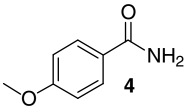
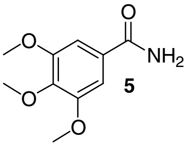
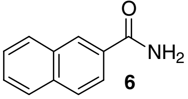
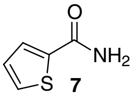
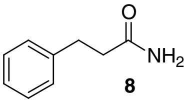
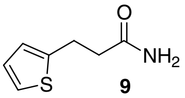
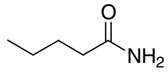
doi:10.1016/j.tetlet.2006.03.010

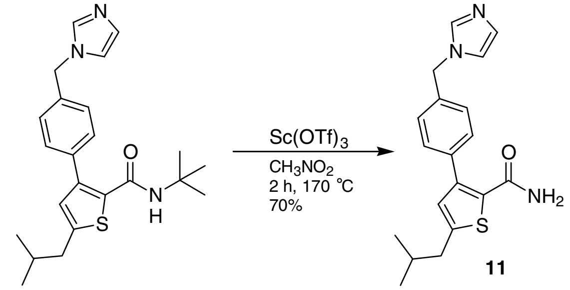
Table 1. Deprotection of *tert*-butyl amides with scandium triflate[a]

Entry	Product	Thermal heating yield (%)	Microwave heating yield (%)
1	 **1**	96	94
2	 **2**	94	98
3	 **3**		99
4	 **4**	93	99
5	 **5**	95	96
6	 **6**		96
7	 **7**	86	99
8	 **8**		90
9	 **9**		64
10	 **10**		68

[a] 0.5 mmol *tert*-butyl amide, 0.5 mmol scandium triflate, 2.0 mL nitromethane, microwave heating: 170 °C, 1 h or 100 °C.

product lowered the isolated yield during isolation of the product. No carboxylic side product (derived from cleavage of the amide bond) was detected in any of the reactions, which can be a major concern when aqueous acids are used for the deprotection of amides.[10]

To verify the deprotection method on a more complex molecule, an intermediate in an ongoing medicinal chemistry program[14,15] was used as a test molecule (Scheme 2). The *tert*-butyl protected compound was dissolved in nitromethane and 1 equiv of scandium triflate was added. The reaction was heated to 170 °C with microwave irradiation. The reaction required double the time (2 h) for completion but gave a good yield of the deprotected compound **11** (70%).



Scheme 2.

In summary, a high-yielding method for removal of *N*-*tert*-butyl protecting groups from amides has been developed. The use of scandium triflate provides, to the best of our knowledge, the first fast and more generally applicable route for deprotection of *N*-*tert*-butyl amides.

2. General procedure

A process vial (5 mL) was charged with a *tert*-butyl amide[16] (0.5 mmol), scandium triflate (0.5 mmol), and nitromethane (2.0 mL). The vessel was exposed to microwave heating[17] for 1 h at 170 °C (or 4 h at 100 °C with a heat block). The reaction tube was thereafter cooled to room temperature and the solvent was removed under vacuum. The residue was dissolved in dichloromethane, washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified on a silica gel column (acetone/petroleum ether) to give the pure compounds **1**–**11**.[18]

Acknowledgments

We gratefully acknowledge financial support from the Swedish foundation for Strategic Research (SSF). We thank Biotage AB for providing the microwave synthesizer.

Supplementary data

NMR-data of compound **11** and its corresponding starting material are provided in the supplementary data file. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.010.

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16. The starting materials were all commercialy available except for *tert*-butyl-2-thiophenepropionamide, which was synthesized from the corresponding acid chloride, *tert*-butyl-4-trifluoromethylbenzylamide: Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750–5753, and the *tert*-butyl protected compound **11** (see Supplementary data).
17. The microwave heating was performed in a single mode cavity, Smith Synthesizer (Biotage AB, Uppsala, Sweden), producing controlled irradiation at 2450 MHz.
18. All the deprotected products were compared with commercial material except for compound **11** (see Supplementary data).