Solvent-free Cleavage of *tert*-Butyl Esters under Microwave Conditions

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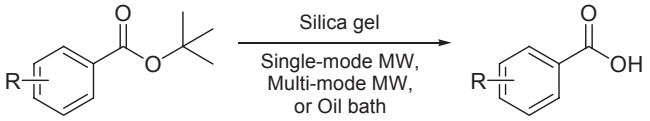
Protection and deprotection of carboxylic acid with sterically bulky alkyl groups are essential steps in synthetic organic chemistry.[1] Among them, *tert*-butyl is the most commonly used to protect the carboxylic acid group because the resulting *tert*-butyl esters are highly stable under neutral and basic conditions, and can be easily prepared from a variety of free carboxylic acids. The *tert*-butyl group could be removed usually by using strong acids such as CF_3COOH,[2] HNO_3,[3] and H_2SO_4[4]. However, major drawbacks of these strong acid conditions are formation of unwanted side products and decomposition of acid labile substrates. On the other hand, the use of Lewis acids such as MgI_2,[5] and $ZnBr_2$[6] have a merit of mild reaction condition but need to long reaction time, higher reaction temperature, and involve toxic metals which are detrimental to the environment. In 2001, *Jackson* reported an interesting method using silica gel as an efficient reagent for the cleavage of *tert*-butyl esters. Unfortunately this method also required long reaction time at high reaction temperature as exemplified by cleavage of *tert*-butyl from the *tert*-butyl 4-methoxybenzoate took 7 h at reflux.[7]

In recent years, microwave (MW) irradiation technique has been attracted much attention as a powerful method for the various organic transformations.[8] Microwave heating has advantages of short reaction time, high chemical yield, clean reaction with easy work up, and solvent-free reaction condition.[9] Although various kinds of reactions have been conducted under microwave irradiations, to our best knowledge, only one example of deprotection of *tert*-butyl esters by using *p*-toluenesulfonic acid monohydrate under microwave condition has been published.[10]

In this paper, we describe the simple and effective method for the cleavage of *tert*-butyl esters by combination of silica gel (230-400 mesh, standard grade for flash column chromatography) and two different type of microwave irradiation (CEM Discover microwave as a single-mode microwave unit and CEM MARS5 microwave as a multi-mode microwave unit) in solvent-free conditions (Scheme 1).

The reactions were carried out by simple mixing *tert*-butyl esters with silica gel followed by irradiation with a temperature controlled single-mode or multi-mode microwave reactor. For comparisons, the same reaction has been carried out under conventional heating condition. After screening the reaction temperature, we found that irradiation of *tert*-butyl benzoate doped into silica gel at 120 °C for 3.5 min using single-mode MW showed complete cleavage of the *tert*-butyl group resulted in benzoic acid in > 99% yield (Entry 1, Table 1). Utilization of multi-mode MW required slightly longer reaction time, thus, the reaction was completed in 5 min irradiation. In contrast, when the same reaction was conducted under conventional thermal condition at 120 °C, it took 3 h reaction time to obtain benzoic aid in 90% yield. Various *tert*-butyl esters have been investigated, and the results are summarized in Table 1. As shown in Table 1, all of the *tert*-butyl esters examined can be cleavage effectively under MW condition with strikingly shorted reaction time (3-5 min) compare to that required under conventional heating condition. Moreover, the MW irradiation increased chemical yield. It has been also found that single-mode MW irradiation is slightly more effective than the multi-mode MW irradiation, which could ascribe to the focused irradiation increasing local micro-heating. The electron density in aromatic ring did not much affect the efficiency of the present method.



Scheme 1. Solvent-free cleavage of tert-butyl group under microwave irradiations

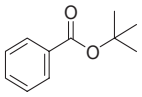
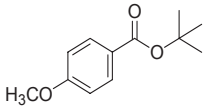
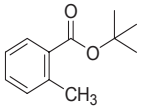
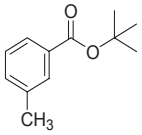
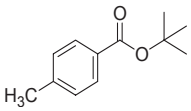
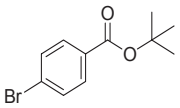
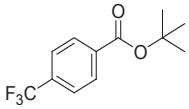
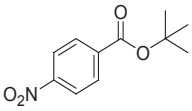
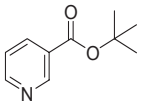
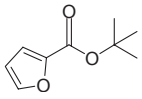
In conclusion, we have developed a simple and effective method for the cleavage of *tert*-butyl esters using silica gel in solvent-free condition under microwave irradiation. This method is remarkable for high chemical yield and the operational simplicity of the procedure is also attractive.

Experimental Section

Microwave irradiation was carried out with CEM Discover microwave at 30 watts as a single-mode microwave unit and CEM MARS5 microwave, at 600 watts as a multi-mode microwave unit. ^{1}H NMR spectra were obtained on a BRUKER 300 in DMSO-d_6 with TMS as an internal standard.

General procedure for the cleavage of *tert*-butyl esters: *tert*-Butyl ester (10 mmol) doped on a silica gel (2.5 g) was mixed thoroughly on a vortex mixer. The reaction mixture was subjected to single-mode microwave at 30 watts for 3.0-3.5 min. or multi-mode microwave at 600 watts for 4.5-5.0 min. or conventional heating use of oil bath at 120 ℃ for 180 min. Upon completion of the reaction, the reaction mixture was diluted with 10% methanol in dichloromethane, and the reaction mixture was filtered through a pad of Celite®. Finally, the filtrate was evaporated under reduced pressure to afford the product.

Table 1. Cleavage of *tert*-butyl esters with silica gel in solvent-free conditions

Entry	Ester	Single-mode MW (30 W)			Multi-mode MW (600 W)			Conventional heating (oil bath)		
		Time (min.)	Temp. (℃)	Yield (%)[a]	Time (min.)	Temp. (℃)	Yield (%)[a]	Time (min.)	Temp. (℃)	Yield (%)[a]
1		3.5	120	99	5.0	120	99	180	120	90
2		3.5	120	99	5.0	120	98	180	120	92
3		3.5	120	99	4.5	120	99	180	120	92
4		3.5	120	98	5.0	120	98	180	120	89
5		3.0	120	99	5.0	120	99	180	120	88
6		3.0	120	99	5.0	120	99	180	120	91
7		3.5	120	97	5.0	120	95	180	120	82
8		3.5	120	97	5.0	120	94	180	120	84
9		3.5	120	95	5.0	120	91	180	120	78
10		3.5	120	99	5.0	120	99	180	120	90

[a]Isolated yield.

Benzoic acid (Entry 1): δ 7.48 (t, J = 7.56 Hz, 2H, 2×CH), 7.61 (t, J = 7.43 Hz, 1H, CH), 8.11 (d, J = 7.12 Hz, 2H, 2×CH).

4-Methoxybenzoic acid (Entry 2): δ 3.86 (s, 3H, OCH_3), 6.92 (d, J = 8.86 Hz, 2H, 2×CH), 8.03 (d, J = 8.85 Hz, 2H, 2×CH).

2-Methylbenzoic acid (Entry 3): δ 2.67 (s, 3H, CH_3), 7.26-7.31 (m, 2H, 2×CH), 7.46 (t, J = 7.46 Hz, 1H, CH), 8.08 (d, J = 8.42 Hz, 1H, CH).

3-Methylbenzoic acid (Entry 4): δ 2.42 (s, 3H, CH_3), 7.39 (t, J = 15.60 Hz, 1H, CH), 7.39 (d, J = 15.70 Hz, 1H, CH), 7.93 (d, J = 7.10 Hz, 1H, CH), 7.94 (s, 1H, CH).

4-Methylbenzoic acid (Entry 5): δ 2.44 (s, 3H), 7.28 (d, J = 8.07 Hz, 2H, 2×CH), 8.01 (d, J = 8.19 Hz, 2H, 2×CH).

4-Bromobenzoic acid (Entry 6): δ 7.57 (d, J = 8.39 Hz, 2H, 2×CH), 7.92 (d, J = 8.40 Hz, 2H, 2×CH).

4-Trifluoromethylbenzoic acid (Entry 7): δ 7.70 (d, J = 8.18 Hz, 2H, 2×CH), 8.18 (d, J = 8.12 Hz, 2H, 2×CH).

4-Nitrobenzoic acid (Entry 8): δ 8.15 (d, J = 11.13 Hz, 2H, 2×CH), 8.32 (d, J = 11.14 Hz, 2H, 2×CH).

Nicotinic acid (Entry 9): δ 7.55 (d, J = 4.83 Hz, 1H, CH), 8.28 (t, J = 1.95 Hz, 1H, CH), 8.79 (d, J = 1.68 Hz, 1H, CH), 9.07 (s, 1H, CH).

2-Furoic acid (Entry 10): δ 6.64 (dd, J = 1.53 Hz & 1.74 Hz, 1H, CH), 7.20 (d, J = 3.47 Hz, 1H, CH), 7.90 (s, 1H, CH).

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