Amino Acids (2009) 36:493–499
DOI 10.1007/s00726-008-0109-7

ORIGINAL ARTICLE

Novel deprotection method of Fmoc group under neutral hydrogenation conditions

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Received: 17 March 2008 / Accepted: 7 May 2008 / Published online: 27 May 2008

Abstract Novel deprotection method of the Fmoc (9-flurorenylmethoxycarbonyl) protective group under Pd/C-catalyzed hydrogenation conditions at room temperature was developed. The addition of CH_3CN accelerated the deprotection of the Fmoc group, and also the application of H_2 pressure (3 atm) shows notable rate enhancement.

Keywords Pd/C · Hydrogenation · Fmoc · Deprotection

Introduction

The Fmoc (9-fluorenylmethoxycarbonyl) group is widely used to protect the amine functionalities in organic, especially, peptides syntheses (Wuts and Greene 2007; Pearson and Roush 1999; Kocieński 2005) and has a major advantage in that it tolerates the acidic conditions under which the Cbz (benzyloxycarbonyl) and Boc (*tert*-butoxycarbonyl) groups can be removed (Wuts and Greene 2007; Pearson and Roush 1999; Kocieński 2005). Only a limited example of Lewis acid catalyzed cleavage of Fmoc group was reported (Leggio et al. 2000). In addition, the Fmoc protective group survives under various conditions such as oxidation and reduction during the course of multi-step synthesis or total synthesis of natural products (Nicolaou et al. 1990). On the other hand, it is easily and nonhydrolytically cleaved under basic conditions by the addition of simple amines such as piperidine or morpholine and the protected amines are liberated as its free base (Carpino and Han 1970, 1972, 1983; Atherton et al. 1981; Ueki and Amemiya 1987; Schmidt et al. 1990). However, highly reactive dibenzofulvene, which is formed by a deprotection of Fmoc group under basic conditions, induces the diverse side-reactions (polymerization, addition of amines, and so on), causing difficulty in purifying the liberated amines (Carpino et al. 1978, 1983; Ueki et al. 1993). Although there are a few reports that describe the progress of deprotection of Fmoc-protected amino acids under acidic hydrogenation conditions (Atherton et al. 1979; Martinez et al. 1979), Fmoc groups are generally recognized as a stable protective group under the hydrogenation conditions (Carpino and Han 1970, 1972, 1986; Kelly et al. 1986; Pearson and Roush 1999; Kocieński 2005; Wuts and Greene 2007).

We have recently developed the Pd/C-catalyzed monoalkylation method of primary amines using nitriles as an alkylating agent under hydrogenation conditions (Sajiki et al. 2004). During the course of the study, we found that the monoalkylation reaction of Fmoc-lysine did not proceed at all but the deprotection of the Fmoc protective group quantitatively occurred and the corresponding free lysine was obtained together with 9-methylfluorene (Fig. 1).

In this article, we report that the Fmoc group can be deprotected under neutral hydrogenation conditions. The cleavage of Fmoc group was accelerated by the addition of 2–5 equiv of CH_3CN at ordinary pressure or simple application of H_2 pressure (3 atm) without any additives. Furthermore, we discuss the reaction mechanism of the acceleration effect by the addition of CH_3CN.

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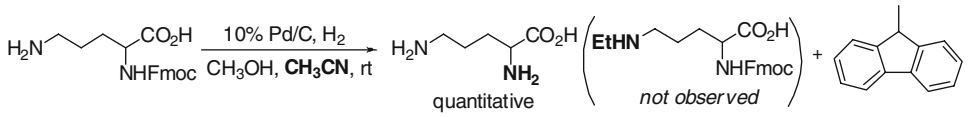


Fig. 1 Pd/C-catalyzed monoalkylation method of primary amines using nitriles as an alkylating agent under hydrogenation conditions

Materials and methods

General

Ten percent Pd/C was purchased from N. E. Chemcat Corporation. MeOH (HPLC grade) was purchased from Wako Pure Chemical Industries, Ltd. and used without purification. MeCN were purchased from commercial sources and used without further purification. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM), or Kanto Chemical Co., Inc. 60°N (63–210 μm spherical, neutral). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL AL 400 spectrometer or JEOL EX 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are expressed in ppm and are internally referenced (0.00 ppm for TMS in $CDCl_3$ and 2.49 ppm for DMSO-d_6 for ^{1}H NMR; 77.0 ppm for $CDCl_3$ and 39.5 ppm for DMSO-d_6 for ^{13}C NMR). EI and FAB mass spectra were taken on a JEOL JMS-SX102A instrument.

Material

All starting Fmoc protected amino acids and amines except *N*-Fmoc-phenylalanine methyl ester (Table 2, entry 2) and *N*-Fmoc-heptylamine (Table 2, entry 9) were purchased from commercial sources and used without further purification. All deprotected products except for heptylamine · HCl (Theodorou et al. 2005; Table 2, entry 9) were commercially available and the ^{1}H NMR spectra of these products were identical with those from commercial sources.

Synthesis of *N*-Fmoc-phenylalanine methyl ester (Dzubeck and Schneider 2000; Table 2, entry 2, substrate)

Phenylalanine methyl ester hydrochloride (216 mg, 1.00 mmol) was suspended in 10% solution of $NaHCO_3$ in H_2O (3 mL) and treated with a solution of Fmoc-chloride (257 mg, 1.00 mmol) in dioxane (5 mL). The mixture was stirred at 0°C for 3 h and at room temperature for 21 h. The reaction mixture was extracted with diethyl ether (50 mL × 2) and water (50 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane → *n*-hexane/AcOEt = 7/1) to give *N*-Fmoc-phenylalanine methyl ester (339 mg, 84%) as a colorless solid. ^{1}H NMR (DMSO) δ 7.87 (4H, d, J = 7.4 Hz), 7.63 (2H, d, J = 7.4 Hz), 7.40 (2H, d, J = 7.4 Hz), 7.33–7.15 (6H, m), 4.08–3.97 (4H, m), 3.43 (3H, s), 3.04 (1H, dd, J = 13.8 Hz, 5.1 Hz), 2.89 (1H, dd, J = 13.8 Hz, 10.4 Hz). MS (EI) m/z 401 (M^+, 1%), 178 (100%), 165 (9%), 91 (9%), 44 (7%) HRMS (EI) Calcd for $C_{22}H_{27}NO_2$ (M^+) 401.16271. Found 401.16349.

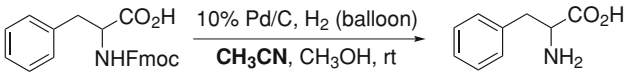
N-Fmoc-heptylamine (Table 2, entry 9, substrate)

Heptylamine (148 μL, 1.00 mmol) was suspended in 10% solution of $NaHCO_3$ in H_2O (3 mL) and treated with a solution of Fmoc-chloride (257 mg, 1.00 mmol) in dioxane (5 mL). The mixture was stirred at 0°C for 3 h and at room temperature for 21 h. The reaction mixture was extracted with diethyl ether (50 mL × 2) and water (50 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane → *n*-hexane/AcOEt = 5/1) to give *N*-Fmoc-heptylamine (303 mg, 90%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, d, J = 7.2 Hz), 7.59 (2H, d, J = 7.2 Hz), 7.40 (2H, t, J = 7.2 Hz), 7.31 (2H, t, J = 7.2 Hz), 4.72 (1H, s), 4.40 (2H, d, J = 6.8 Hz), 4.22 (1H, t, J = 6.8 Hz), 3.19 (2H, q, J = 6.8 Hz), 1.30 (8H, m), 0.89 (3H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 156.4, 144.0, 141.3, 127.6, 127.0, 125.0, 119.9, 66.5, 47.3, 41.1, 31.7, 29.9, 26.7, 22.6, 14.1; MS (EI) m/z 337 (M^+, 2%), 178 (100%), 165 (9%) HRMS (EI) Calcd for $C_{22}H_{27}NO_2$ (M^+) 337.20418. Found 337.20506.

The reaction of Fmoc-lysine under the mono-alkylation conditions (Fig. 1)

N-Fmoc lysine (59.1 mg, 0.1 mmol), 10% Pd/C (5.9 mg, 10 wt % of *N*-Fmoc lysine), and acetonitrile [26 μL, 0.5 mmol (5 equiv)] in MeOH (2.0 mL) was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (50 mL × 2) and water (50 mL). The aqueous layer was washed with ethyl acetate (30 mL) and concentrated under reduced pressure to give lysine (36.5 mg, quantitative). 9-Methylfluorene was obtained by concentration of ethereal layer without further purification (30.8 mg, 68%; low yield of 9-methylfluorene comes from sublimation). ^{1}H NMR (DMSO-d_6) δ 7.84(2H, d, J = 6.8 Hz), 7.57 (2H, d,

Table 1 Addition effect of CH_3CN



Entry	CH_3CN (equiv)	Time (h)	Yield[a] (%)
1	None	24	100
2	1	24	92
3	2	17	100
4	5	13	96
5	77 (solvent)	24	88

The reaction was carried out with the substrate (0.25 mmol) using 10% Pd/C (N. E. Chemcat Corp. 10 wt % of substrate), and CH_3CN in CH_3OH (1 mL) under ordinary H_2 pressure at room temperature

[a] Isolated yield

$J = 6.6$ Hz), 7.33 (4H, m), 3.93 (1H, q, $J = 7.4$ Hz), 1.44 (3H, d, $J = 7.4$ Hz).

Addition effect of CH_3CN (Table 1, Entries 2–5)

N-Fmoc-phenylalanine (96.9 mg, 0.25 mmol), 10% Pd/C (9.7 mg, 10 wt % of *N*-Fmoc-phenylalanine), and acetonitrile [Table 1, entry 2: 13 μL, 0.25 mmol (1 equiv); entry 3: 26 μL, 0.50 mmol (2 equiv); entry 4: 65 μL, 1.25 mmol (5 equiv); entry 5: 1 mL, 77 mmol (as a solvent)] in MeOH [1.0 mL (Entries 2–4), 0 mL (entry 5)] was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for the given time in Table 1. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (50 mL × 2) and water (50 mL). The aqueous layer was washed with ethyl acetate (30 mL) and concentrated under reduced pressure to give phenylalanine (entry 2: 38.0 mg, 92%; entry 3: 41.3 mg, 100%; entry 4: 39.6 mg, 96%; entry 5: 36.3 mg, 88%).

Deprotection of Fmoc compounds in the presence of CH_3CN

Table 2, Entries 1, 3–8, and 10

Fmoc compound (0.25 mmol), 10% Pd/C (10 wt % of substrate), and CH_3CN (65.0 μL, 1.25 mmol) in MeOH (1.0 mL) was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for the given time. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (50 mL × 2) and water (50 mL). The aqueous layer was washed with ethyl acetate (30 mL) and concentrated under reduced pressure to give the corresponding amino acid or amine [entry 1: 39.6 mg, 96%; entry 3: 23.6 mg, 90%; entry 4: 22.3 mg, 100%; entry 5: 33.0 mg, 100%; entry 6: 36.5 mg, 100%; entry 7: 36.8 mg, 100%; entry 8: 28.8 mg, 100%; entry 10: (middle): 15.0 mg, 80%].

Table 2, Entries 2 and 9

Fmoc compound (0.25 mmol), 10% Pd/C (10 wt % of substrate), and CH_3CN (65.0 μL, 1.25 mmol) in MeOH (1.0 mL) was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for 12 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and cooled to 0°C. About 2 M HCl solution in Et_2O (2 mL, 4 mmol) was added to the filtrate and the mixture was stirred for 1 h. The filtrate was concentrated under reduced pressure. Et_2O (20 mL) was added and the colorless precipitate was collected on a Büchner funnel, and dried under reduced pressure to give the corresponding amine · HCl salt (entry 2: 42.4 mg, 79%; entry 9: 35.8 mg, 94%).

The deprotection of various Fmoc-amino acids under 3 atm of H_2 pressure (Table 3)

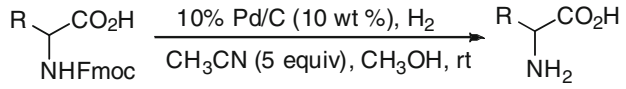
Fmoc compound (0.25 mmol), 10% Pd/C (10 wt % of substrate) in MeOH (2.0 mL) was vigorously stirred at room temperature (ca. 20°C) under 3 atm of hydrogen pressure in a sealed tube for the given time. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (50 mL × 2) and water (50 mL). The aqueous layer was washed with ethyl acetate (30 mL) and concentrated under reduced pressure to give the corresponding amino acid (entry 1: 37.5 mg, 91%; entry 2: 26.0 mg, 99%; entry 3: 22.3 mg, 100%; entry 4: 21.9 mg, 76%; entry 5: 36.5 mg, 100%; entry 6: 27.9 mg, 76%; entry 7: 28.8 mg, 100%).

The reaction mechanism

For top of the Fig. 2

A suspension of 10% Pd/C (10 wt % of *N*-Fmoc-phenylalanine) and CH_3CN (65.0 μL, 1.25 mmol) in MeOH (1.0 mL) was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was vigorously stirred with *N*-Fmoc-phenylalanine (96.9 mg, 0.25 mmol) at room temperature (ca. 20°C) under Ar atmosphere (balloon) for 36 h. The reaction mixture was extracted with diethyl ether (50 mL × 2) and water (50 mL). The organic layer was washed with brine

Table 2 Deprotection of the Fmoc amino acids in the presence of CH_3CN



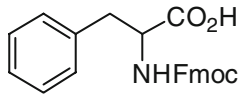
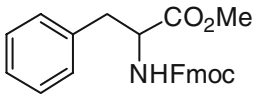
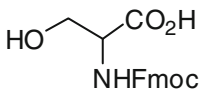
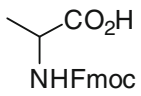
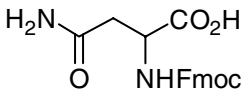
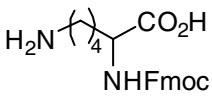
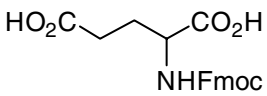
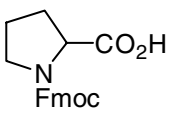
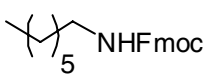
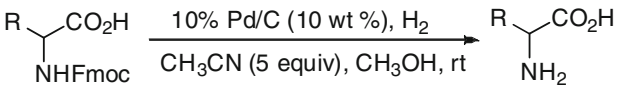
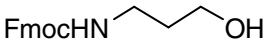
Entry	Substrate	Time (h)	Yield (%)[a]
1		13	96
2		12	79[b,c]
3		12	90
4		12	100
5		13	100
6		12	100
7		12	100
8		12	100
9		12	94[b]

Table 2 continued



Entry	Substrate	Time (h)	Yield (%)[a]
10		12	80[d]

The reaction was carried out using 10% Pd/C (N. E. Chemcat Corp. 10 wt % of substrate), and CH_3CN (5 equiv) in CH_3OH (1 mL) under ordinary H_2 pressure at room temperature

[a] Isolated yield

[b] The product was isolated as an HCl salt

[c] The rather lower yield was due to the undesirable and minor nucleophilic addition of the resulting free amine to the methyl ester

[d] The slightly lower yield was due to the loss caused by evaporation

(100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to recover the starting material, *N*-Fmoc-phenylalanine (96.9 mg, 100%).

For middle of the Fig. 2

A suspension of *N*-Fmoc-phenylalanine (96.9 mg, 0.25 mmol), 10% Pd/C (9.7 mg, 10 wt % of *N*-Fmoc-phenylalanine), 2 M $EtNH_2$ solution in MeOH (0.6 mL, 1.25 mol), and MeOH (1.0 mL) was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (50 mL × 2) and water (50 mL). The aqueous layer was washed with ethyl acetate (30 mL) and concentrated under reduced pressure to give phenylalanine (41.3 mg, 100%).

For bottom of the Fig. 2

N-Fmoc-phenylalanine (96.9 mg, 0.25 mmol), 10% Pd/C (9.7 mg, 10 wt % of *N*-Fmoc-phenylalanine), and 2 M $EtNH_2$ solution in MeOH (9 μL, 2 equiv vs. Pd metal) in MeOH (1.0 mL) was vigorously stirred at room temperature (ca. 20°C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (50 mL × 2) and water (50 mL). The aqueous layer was washed with ethyl acetate (30 mL) and concentrated under reduced pressure to give phenylalanine (33.8 mg, 82%).

Results and discussion

We first investigated the optimal reaction conditions, especially related to the addition effect of CH_3CN (Table 1).

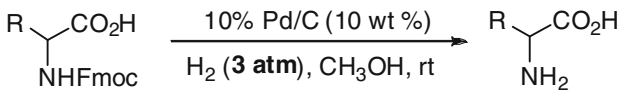
The deprotection of Fmoc group of Fmoc-phenylalanine was amazingly completed in CH_3OH at room temperature under H_2 atmosphere for 24 h. Furthermore, the dose-dependent acceleration effect of the deprotection was observed up to the addition of 5 equiv of CH_3CN and the reaction was completed within 13 h (Table 1, entry 4). The further increase amounts of CH_3CN may not have significant dose-dependency and the use of CH_3CN as a solvent (77 equiv) caused depression of the reaction efficiency and the longer reaction time was required for the completion of the deprotection (24 h was not enough) (Table 1, entry 5).

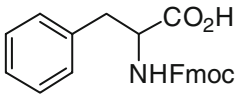
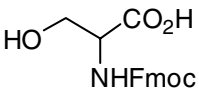
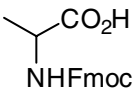
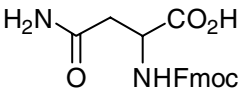
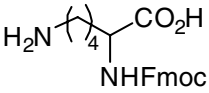
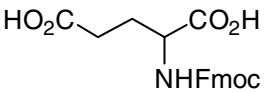
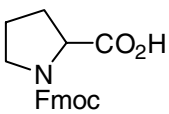
The present method assisted by the addition of CH_3CN under hydrogenation conditions was applied to the deprotection of various Fmoc-amino acids (Table 2). All evaluated *N*-Fmoc-protected compounds including Fmoc-amino acid derivatives were smoothly deprotected to the corresponding free amines in high yields at ambient temperature and pressure within 12–13 h by the addition of CH_3CN (5 equiv).

During the optimization of the reaction conditions, we have also found that the application of H_2 pressure was effective for the deprotection of the Fmoc group without CH_3CN. A variety of Fmoc-amino acids could be deprotected within 6–20 h at room temperature under 3 atm of H_2 pressure in MeOH as a solvent even in the absence of CH_3CN (Table 3, entry 1) (Ho and Ngu 1994).

It is not obvious yet why Fmoc-protected amine derivatives are labile under the hydrogenation conditions although they possess a homobenzylic carbamate moiety, not a benzylic carbamate. There is a possibility for the mechanism of the accelerating effect on the Fmoc-deprotection by the addition of CH_3CN that CH_3CN might act as a source of a quite small amount of a base (ethylamine or diethylamine) generated from the partial hydrogenation of CH_3CN in situ (Rylander 1985; Schmidt et al. 1990; Nishimura 2001) and accelerate the cleavage concertedly with hydrogenation. To clarify the role of CH_3CN, 5 equiv of CH_3CN was pre-stirred with 10% Pd/C in CH_3OH under H_2 atmosphere without a substrate. After 24 h, the H_2 replaced with Ar gas, and then Fmoc-phenylalanine was added to the reaction mixture. No cleavage of the Fmoc protective group was observed even after 36 h stirring at room temperature (Fig. 2, top). On the other hand, treatment of Fmoc-phenylalanine with 5 equiv (vs. Fmoc-phenylalanine) of $EtNH_2$ in CH_3OH at room temperature for 24 h led to a quantitative cleavage of the Fmoc group despite the lack of Pd/C catalyst and H_2 gas (Fig. 2, middle). Furthermore, we attempted the addition of catalytic amount of $EtNH_2$ (2 equiv vs. Pd metal) instead of CH_3CN to the 10% Pd/C-catalyzed hydrogenation conditions of Fmoc-phenylalanine. The deprotection of the Fmoc group was incomplete even after 24 h (Fig. 2, bottom). The addition of the catalytic amount of $EtNH_2$ induced rather suppressive effect because the Pd/C-catalyzed deprotection

Table 3 The deprotection of various Fmoc-amino acids under 3 atm of H_2 pressure



Entry	Substrate	Time (h)	Yield (%)[a]
1		6	91
2		6	99
3		18	100
4		6	76
5		6	100
6		24	76
7		18	100

The reaction was carried out using 10% Pd/C (N. E. Chemcat Corp. 10 wt % of substrate) in CH_3OH (2 mL) under 3 atm of H_2 pressure in a sealed tube at room temperature

[a] Isolated yield

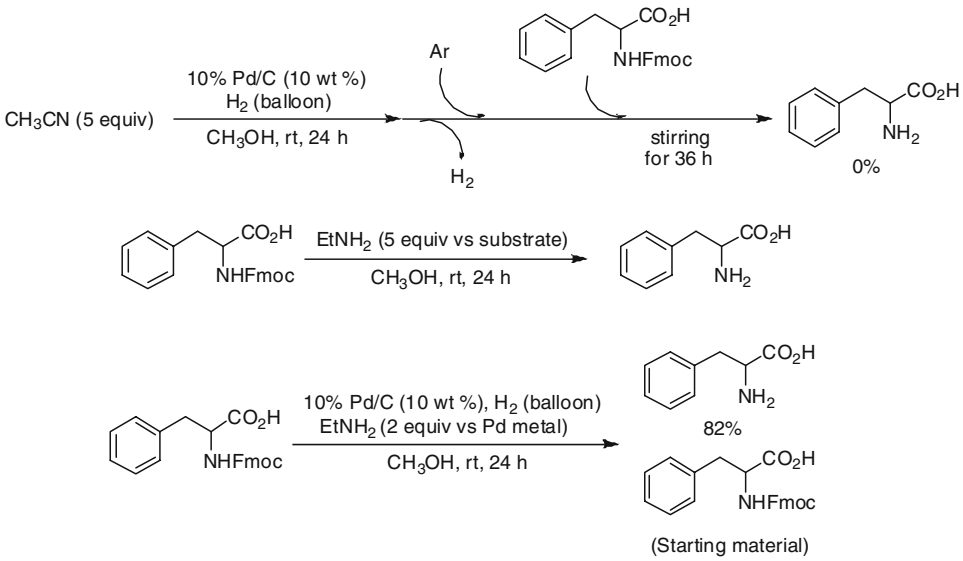


Fig. 2 Deprotection of Fmoc group of phenylalanine under various conditions

of Fmoc-phenylalanine was completed in 24 h without any additives (compare with Table 1, entry 1). These results obviously indicate the accelerating effect of the Pd/C-catalyzed cleavage of the Fmoc protective group by CH_3CN under H_2 atmosphere is not caused by the amine-based manner.

Conclusions

In conclusion, we have found a novel deprotection method of the Fmoc protective group under nearly neutral hydrogenation conditions (1 atm) at room temperature accelerated by the addition of CH_3CN. The present method is applicable to the deprotection of diverse Fmoc-protected compounds such as amino acids and aminoalcohols. Furthermore, the application of 3 atm of H_2 gas under absolutely neutral reaction conditions also smoothly completed the Fmoc cleavage at room temperature in the absence of CH_3CN. Although the mechanism of the acceleration effect by CH_3CN is not clear yet, we expect CH_3CN can activate the Pd directly by weak coordination as a ligand.

Acknowledgment We thank N. E. Chemcat Corporation for a gift of 10% Pd/C.

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