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Microwave assisted Wolff rearrangement: A facile method for the synthesis of Fmoc-β-amino acids

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Summary

The Wolff rearrangement of α-diazoketones, derived from Fmoc-α-amino acids, under no base conditions on exposure to microwave irradiation for 40 to 60 sec to Fmoc-β-amino acids with retention of configuration in good yield (91–95%) is described.

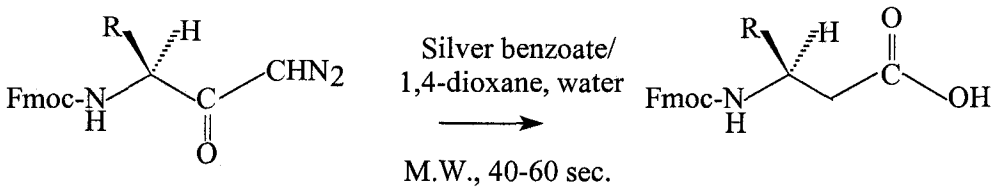
Introduction

The β-peptides, oligomers of β-amino acids, have particular appeal in understanding of protein structure and stabilization [1]. They are chemically stable, resistant to α-peptidases [2] and mimic the activities of peptide toxins and antibiotics [3]. In view of these recent findings, there is a need to develop a facile way for the synthesis of the monomers. The Wolff rearrangement of α-diazoketones derived from *N*-urethane protected α-amino acids is a key step in the convenient approach to optically pure β-amino acids through an Arndt-Eistert homologation [4] because, the rearrangement proceeds with retention of configuration at the chiral centre next to the carbonyl group. It can be accomplished thermally [4], photochemically [4] or by ultrasonication [5].

The rearrangement of Boc-/Z-protected amino-diazoketones when carried out using silver oxide/ $Na_2CO_3/Na_2S_2O_3 \cdot 5H_2O$ by refluxing at 80 °C for 1–3 h afforded the corresponding β-amino acids in about 75% yield [6]. Leggio *et al.* [7], synthesized Fmoc-β-amino acids in about 50–90% yield by refluxing the α-diazoketone at 70 °C in the presence of C_6H_5COOAg for about 1–3 h. The ultrasound promoted rearrangement of α-diazoketones at r.t. in presence of C_6H_5COOAg took place in about 30 min to give Fmoc-β-amino acids in about 70–82% yield [5]. On the other hand, the Ag^+ catalyzed decomposition of α-diazoketones by employing about 3 equiv. of a tertiary base was also utilized [8]. Under these conditions, the reactions have to be carried out for about 3–12 h and resulted in lower yields of Fmoc-β-amino acids when compared to Boc-/Z-β-amino acids [9–11]. The present communication deals with the decomposition of *N*-Fmoc-α-aminodiazoketones under microwave irradiation [12].

Materials and methods

Melting points were determined using capillary method and are uncorrected. IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). HPLC analysis was carried out with a Waters LC-3000 system using a C18 Bondapack (3.9 × 300 mm, 10μ) and chiralcel OD (4.6 × 250 mm, 10μ) columns with a linear gradient of water (0.1% TFA) and acetonitrile (0.1% TFA), with acetonitrile from 20 to 90% over 25 min. ^1H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Specific rotations were recorded on Rudolf Research Autopol IV automatic polarimeter. All the reactions were performed in a LG domestic microwave oven (2450 MHz) operating at 60% power.



1a-k **2a-k**

Compound	R	Compound	R
2a	H	**2g**	C_6H_5
2b	CH_3	**2h**	CH_2COO^tBu
2c	$CH(CH_3)_2$	**2i**	$CH_2CH_2COO^tBu$
2d	$CH_2CH(CH_3)_2$	**2j**	CH_2O^tBu
2e	$CH(CH_3)CH_2CH_3$	**2k**	$(CH_2)_4NHBoc$
2f	$CH_2C_6H_5$		

Scheme 1.

Table 1. Charactaristic data for the β-amino acids prepared

Sl. No.	Compound **2**	Time (sec)	m.p. (°C)	Yield (%)	$[\alpha]_D^{25}$ (c = 1, $CHCl_3$)	^{1}H NMR (δ, $CDCl_3$)
1	a	50	148	91	–	2.75 (2H, t), 3.4 (2H, m), 4.22 (1H, t), 4.6 (2H, d), 5.55 (1H, br), 7.25–7.85 (8H, m)
2	b	40	98	92	–21.0	1.12 (3H, d), 2.3 (1H, d), 2.45 (1H, d), 3.86 (1H, m), 4.1–4.35 (3H, m), 5.98 (1H, br), 7.25–7.85 (8H, m)
3	c	40	152	95	–36.2	0.94 (6H, d), 1.9 (1H, m), 2.47 (2H, d), 3.85 (1H, m), 4.17–4.33 (3H, m), 6.43 (1H, br), 7.27–7.8 (8H, m)
4	d	45	101	94	–12.0	0.8 (6H, d), 1.15 (2H, m), 1.45 (1H,m), 2.35 (2H, m), 3.8 (1H, m), 4.25–4.4 (3H, m), 6.75–7.8 (9H, m)
5	e	50	98	95	–16.8	0.8 (6H, m), 1.35 (2H, m), 1.5 (1H, m), 2.3 (2H, m), 4.2–4.4 (3H, m), 6.8 –7.85 (9H, m)
6	f	40	112	95	–26.0	2.55 (2H, m), 2.9 (2H, d), 4.1–4.35 (4H, m), 6.52 (1H, br), 7.16–7.85 (13H, m)
7	g	60	97	92	–22.0	2.5 (2H, d), 4.2–4.35 (4H, d), 5.9 (1H, br), 7.25–7.85 (13H, m)
8	g[a]	60	98	91	+21.8	2.45 (2H, d), 4.23 (2H, m), 4.35 (2H, d), 5.85 (1H, br), 7.25–7.85 (13H, m)
9	h	50	82	92	+0.3[b]	1.45 (9H, s), 2.65 (4H, m), 4.15–4.45 (4H, m), 6.45 (1H, br), 7.25–7.8 (8H, m)
10	i	40	58	91	–11.4	1.45 (9H, s), 2.45 (4H, m), 3.85–4.5 (4H, m), 5.7 (1H, d), 7.25–7.9 (8H, m)
11	j	40	96	92	+15.7	1.2 (9H, s), 2.5–2.65 (2H, d), 3.45–3.5 (2H, m), 4.15 (1H, m), 4.2–4.4 (3H, m), 6.35 (1H, br), 7.3–7.8 (H, m)
12	k	40	98	93	–8.3	1.45 (9H, s), 2.05 (8H, m), 2.45 (2H, d), 3.8 (1H, m), 4.15–4.35 (3H, m), 5.65 (1H, br), 7.25–7.8 (9H, m)

[a] D-Phg.
[b] (c = 1.9, MeOH).

General procedure for the synthesis of Fmoc-β-amino acids

A mixture of Fmoc-α-aminodiazoketone (10 mmol), 1,4-dioxane (7 ml), water (3 ml) and silver benzoate (0.15 mmol) in a beaker was exposed to microwave irradiation until the reaction was completed and filtered. Aqueous 10% sodium carbonate (50 ml) was added to the solution, stirred for few minutes, washed with ether (2 × 50 ml), acidified to pH 2 using 2 N HCl

solution and extracted with ethyl acetate (3 × 50 ml). The organic layer was washed with water, dried over anhydrous sodium sulphate, evaporated, precipitated and recrystalized to give the title compound.

Results and discussion

It is now found that the Wolff rearrangement of **1a–k** [13–15] can be accelerated under microwave irradiation. It was carried out by exposing the mixture of **1** and $C_6H_5COO^-Ag^+$ in 1,4-dioxane-water (7:3) to microwaves in an unmodified domestic microwave oven (Scheme 1). The decomposition of **1**, as monitored by TLC (chloroform:methanol:acetic acid, 40:2:1) and I.R., was complete in about 40–60 sec. The extraction of the β-amino acid into an aqueous sodium carbonate solution, acidification and routine work-up lead to the isolation of **2a–k** as crystalline solids in about 91–95% (Table 1). All the**2a–k**, prepared by this method, have been characterized by ^{1}H NMR. The reaction, as monitored by HPLC analysis of Fmoc-β-HVal-OH (R_t for L isomer 15.42 min and for racemic mixture (prepared specifically for analysis) 15.36 min and 16.12 min), is found to be completely free from racemization. Thus, a base-free Ag^+ catalyzed Wolff rearrangement of Fmoc-β-amino acids can be accomplished under microwave irradiation efficiently. The reaction is fast and the work-up is simple. It proceeds with good yield and without racemization. Furthermore, the decomposition of α-aminoacyldiazoketone using 1,4-dioxane-methanol mixture resulted in the concomitant formation of the methyl ester of the corresponding β-amino acid [16].

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