Solvent-Free, Efficient Synthesis of 2,5-Piperazinediones from Boc-Protected Dipeptide Esters under Microwave Irradiation

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Abstract: Microwave irradiation allows the efficient, solvent-free transformation of *N*-Boc dipeptide esters into 2,5-piperazinediones. The microwave-assisted conditions were found to be much better than traditional heating in terms of reaction time, yield and stereocenter integrity.

Key words: microwave irradiation, diketopiperazines, dipeptides, cyclizations, heterocycles

Many natural products with the 2,5-piperazinedione scaffold (DKPs) have been isolated, encompassing a wide range of biological activities.[1] Unnatural DKPs are also very common in medicinal chemistry and show a broad spectrum of interesting pharmacological properties.[2] Molecular recognition is another field of interest, since receptors based on DKP backbones interact with peptidic substrates with high specificity.[3] Finally, DKPs are very versatile synthetic intermediates.[4,5]

Due to their importance, the development of improved routes to DKPs continues to be of interest.[6] Diketopiperazines can be considered as 'head-to-tail' cyclic dipeptides. As such, their simplest preparations are those that take advantage of the chirality and commercial availability of amino acids, and normally involve the synthesis of a suitable linear dipeptide followed by N-deprotection and cyclization, which is normally effected under basic[7] or acidic[8] conditions. Ideally, the choice of N-protecting group should be such that deprotection takes place under the same conditions as cyclization, leading to a one-step preparation of the target DKP. We reasoned that, because *N*-Boc deprotection has been achieved under microwave conditions, albeit not from dipeptides,[9] and cyclization of dipeptide esters can be carried out under thermal conditions, normally in refluxing toluene or xylene for 24 hours,[10] the one-pot deprotection/cyclization of *N*-Boc dipeptide esters would be an excellent candidate for microwave optimization.

Table 1 displays the comparison between the results obtained in the preparation of several DKPs from the corresponding ethyl *N*-aminoacyl glycinates using conventional and microwave heating.[11,12] The reactions were carried out in 2–8 minutes under microwave irradiation, compared to 2–4.5 hours at 200 °C for the conventional heating reactions, and yields were also normally higher for the microwave assisted reactions, with the additional advantage of not requiring an inert atmosphere.[13] We employed a domestic microwave oven set at 600 W, with the reaction vessels introduced in an alumina heat sink. In our initial experiments we irradiated the reactions in one-minute pulses to prevent excessive heating (entry 1), however, under these conditions some N-substituted dipeptides reacted slowly or not at all (e.g. entry 7). In these cases, we found that addition of 10% silica gel to the reaction mixture enabled the transformation in five one-minute pulses, normally with improved yields with regard to the thermal reaction. The precaution of irradiating in short pulses was subsequently proved unnecessary, since irradiations of up to five consecutive minutes at 600 W were tolerated without decomposition (e.g. entry 3), making unnecessary the addition of silica gel. The microwave reactions could be scaled-up with only slight yield loss; for instance, the reaction in entry 12 was performed in 83% yield starting from 6 g of dipeptide.

Stereochemical integrity is also a very important aspect of the preparation of DKPs. A derivative of cyclo-(Gly-L-Ala) obtained under thermal conditions has been previously shown to be enantiomerically pure by proton NMR in the presence of $Eu(hfc)_3$.[14] Regarding valine derivatives, we have found that samples of compound **3e** prepared using three procedures, namely thermal and microwave cyclization of a *N*-Boc dipeptide ester and hydrogenolysis/cyclization of a *N*-Cbz dipeptide ester, which is known to be safe in terms of stereochemical integrity,[10] were identical in all respects, including optical rotation. Furthermore, none of these samples showed splitting of any ^{1}H NMR resonances upon addition of $Eu(hfc)_3$, under conditions developed on a reference racemic sample of **3e** prepared from (±)-Val. However, the reaction in entry 5, involving (*S*,*S*)-Ile, which is known to undergo a particularly easy epimerization,[15] led to a 1:1 mixture of diastereomers under thermal conditions. In this case, the microwave conditions afforded a (*S*,*S*/*R*,*S*) 9:1 mixture of diastereomers, showing an advantage in terms of stereochemical integrity.

In conclusion, we have developed an experimentally simple and environmentally benign procedure for the preparation of 2,5-piperazinediones from *N*-Boc-protected dipeptide esters. Because DKP ring formation is

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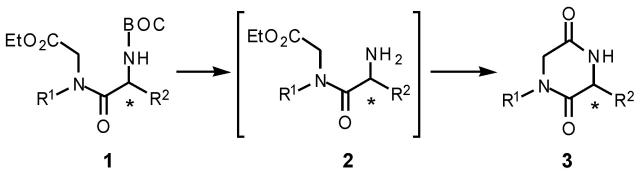
Table 1 Comparison of the Results Obtained in the Synthesis of 2,5-Piperazinediones from *N*-Boc Dipeptide Esters under Conventional Thermal and Microwave-Assisted Conditions



1 **2** **3**

Entry	Compound	R^1	R^2	Conf. at *	Heating (200 °C)		Microwave (600 W)	
					Time (h)	Yield (%)	Time (min)	Yield (%)
1	**3a**	H	Me	*S*	2	84	5[a]	65
2	**3a**	H	Me	*S*			6[b]	98
3	**3b**	H	*i*-Pr	*S*	3.5	56	5[c]	87
4	**3c**	H	Bn	*S*	4.5	72	2[c]	82
5	**3d**	H	(*S*)-*s*-Bu	*S*	4.5	81 (1:1 diast. mixture)	5[c]	92 (9:1 diast. mixture)
6	**3e**	3-Indolylmethyl	*i*-Pr	*S*	2	85	3[c]	90
7	**3f**	Bn	H	–	2	81	5[a]	0
8	**3f**	Bn	H	–			5[d]	64
9	**3f**	Bn	H	–			3[c]	84
10	**3g**	$Ph(CH_2)_2$	*i*-Pr	*S*	2	81	5[d]	65
11	**3g**	$Ph(CH_2)_2$	*i*-Pr	*S*			3[c]	90
12	**3h**	Me	H	–	3 (220 °C)	84	8[b]	95
13	**3i**	(4-MeO)Bn	H	–	–	–	3[c]	72
14	**3j**	$(3,4\text{-MeO})_2Bn$	H	–	2	79	5[d]	99
15	**3k**	$Ph(CH_2)_2$	H	–	2	80	5[d]	99

[a] Cycles of 1-min irradiation followed by 1-min cooling periods.
[b] Two irradiations, with intermediate 2-min cooling periods.
[c] Irradiation without intermediate cooling periods.
[d] The starting dipeptide was mixed with 10% silica gel prior to irradiation using conditions c.

sequence-dependent, being particularly favored for Pro or Gly residues but more difficult when hindered amino acids like Phe, Trp, Tyr, Val, Ile, etc. are involved, future work will be focused on the study of these cases, with special attention to stereochemical issues.

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(13) **Representative Procedure.**
A glass vial containing *N*′-Boc-Val-(*N*-3-indolylmethyl)-Gly-OEt (170 mg, 0.39 mmol) was submerged in alumina, contained in a beaker, and irradiated for 5 min at 600 W in a domestic microwave oven. Recrystallization from acetone gave diketopiperazine **3e** (91 mg, 90%) as a white solid; mp 228–229 °C; $[\alpha]_D^{23}$ 6.0 (*c* 0.4 g/100 mL in MeOH). IR (KBr): 3403, 3559, 1682, 1647, 742 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H, NH_{indole}), 7.71 (d, 1 H, *J* = 7.5 Hz, H-4′), 7.37 (d, 1 H, *J* = 8.0 Hz, H-7′), 7.20–7.09 (m, 3 H, H-2′,5′,6′), 6.15 (br s, 1 H, H-4), 4.90 and 4.71 (AB system, 2 H, *J* = 14.5 Hz, N-CH_2), 3.92–3.89 (m, 1 H, H-3), 3.85 (s, 2 H, H-6), 2.51–2.41 [m, 1 H, C*H*$(CH_3)_2$], 1.00 and 0.82 [2 d, 3 H, *J* = 7.0 Hz, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.3, 165.2, 136.2, 127.7, 124.7, 122.8, 120.3, 119.2, 111.4, 110.1, 61.0, 48.3, 40.8, 33.0, 19.0, 16.1 ppm. Anal. Calcd for $C_{16}H_{19}N_3O_2$ (M = 285): C, 67.36; H, 6.66; N, 14.73. Found: C, 66.92; H, 6.33; N, 14.53.
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