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Microwave accelerated efficient synthesis of *N*-fluorenylmethoxycarbonyl/*t*-butoxycarbonyl/benzyloxycarbonyl-5-oxazolidinones

Subramanyam J. Tantry, Kantharaju and Vommina V. Suresh Babu*

Department of Chemistry, Central College Campus, Bangalore University, Bangalore 560 001, India

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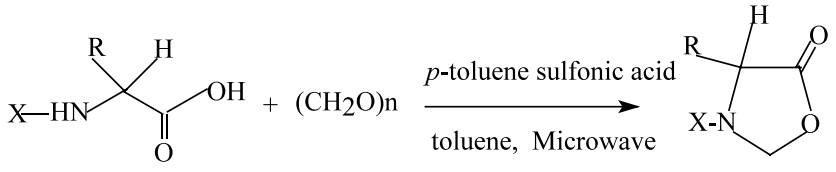
Abstract—The synthesis of *N*-protected 5-oxazolidinones using amino acids, paraformaldehyde and *p*-toluene sulfonic acid in a minimum amount of toluene accelerated by microwave irradiation for 3 min in high yield is described.

The *N*-(fluorenylmethoxycarbonyl)-5-oxazolidinones and *N*-(benzyloxycarbonyl)-5-oxazolidinones are not only intermediates in the synthesis of Fmoc/Z-*N*-methyl-amino acids[1,2] but are also utilized for the direct preparation of dipeptides containing *N*-methylamino acids.[3] They have also been used for the synthesis of differentially protected *meso*-2,6-diaminopimalic acid.[4] Recently, Johannesson et al. employed oxazolidinones as the key intermediates for the synthesis of angiotensin II analogues with full agonistic activity at the AT-receptor.[5,6]

The synthesis of 5-oxazolidinones is generally carried out by refluxing the mixture of *N*-protected amino acid, paraformaldehyde, and *p*-toluene sulfonic acid in toluene or benzene for several hours, until the solution becomes homogeneous with azeotropic removal of water using a Dean Stark apparatus, which is cumbersome and time consuming. In recent years, the utility of microwave irradiated organic synthesis has been explored due to its simplicity and to achieve rapid chemical modifications with cleaner products and high yield.[7] Although Reddy et al. demonstrated the use of microwave irradiation for the synthesis of oxazolidinones, their protocol using K_{10} clay has limited applicability for the synthesis of acetyl, benzoyl, and tosyl protected oxazolidinones[8] only and, in the case of Boc and Z-amino acids, it led to an intractable mixture of products. This communication deals with microwave assisted synthesis of *N*-Fmoc-/Boc-/Z-5-oxazolidinones.

In the present studies, the synthesis of **2a**–**n** using **1a**–**n**, paraformaldehyde and *p*-toluene sulfonic acid in a minimum amount of toluene has been accomplished utilizing microwave irradiation (Scheme 1). The reaction was carried out by exposing a slurry of the reactants in a beaker to microwaves in an unmodified domestic microwave oven operated at 2450 MHz frequency at 80% power.[9] 5-Oxazolidinone formation, as monitored by TLC (ethyl acetate:hexane, 35:65), was found to be complete in 3 min. A simple work-up gave **2a**–**n**, in good to excellent yields (Table 1).



1a-n **2a-n**

Scheme 1.

* Corresponding author.

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Table 1. Physical constants of 5-oxazolidinones[a]

Sample no.	5-oxazolidinones (**2**)		Time (min)	IR (cm^{-1})	Melting point (°C)		Yield (%)
	X	R			Rep.[1,2]	Obs.	
a	Fmoc	CH_3	3	1801, 1705	142–144	142–44	96
b	Fmoc	$CH(CH_3)_2$	3	1801,1705	72–74	72	96
c	Fmoc	$CH_2C_6H_5$	3	1799, 1715	Oil	105–108	93
d	Fmoc	$CH_2CH(CH_3)_2$	3	1799, 1711	–	61–63	91
e	Fmoc	CH_2SCH_3	3	1800, 1710	74–76	74–76	95
f	Fmoc	$(CH_2)_4N$(Pth)	4	1800, 1775, 1700	150–52	150–152	88
g	Fmoc	CH_2COOH	6	3200, 1800, 1714	–	175–177	85
h	Fmoc	CH_2CH_2COOH	5	3200, 1722, 1712	–	Foam	90
i	Z	H	3	1801, 1715	85	83–84	90
j	Z	$CH_2CH(CH_3)_2$	3	1798, 1713	63	63–64	98
k	Z	$CH_2C_6H_5$	3	1799, 1714	83	81–83	82
l	Z	$(CH_2)_3COOH$	6	3200, 1800, 1720	Oil	Oil	82
m	Boc	$CH_2C_6H_5$	3	1802, 1709	–	74–76	81
n	Boc	$CH_2CH(CH_3)_2$	3	1802, 1702	–	Gum	87

[a] All the compounds were satisfactorily characterized by ^1H NMR spectroscopy

All the compounds **2a**–**n**, were characterized by IR (lack of peaks at around 3440 and 1510 cm^{-1} due to –OH and –NH of the carbamates and the presence of sharp and strong absorptions at around 1798–1802 cm^{-1} due to the C=O moiety) and ^1H NMR spectroscopy. Also, the compounds were found to have optical rotations similar to the values reported in the literature. Further, some of the 5-oxazolidinones created were converted into the corresponding *N*-methyl-amino acids which are being used in the solid phase synthesis of cyclosporine.

Unlike the protocol involving the use of K_{10} clay for the synthesis of oxazolidinones under microwave irradiation,[8] it has been demonstrated that the synthesis of oxazolidinones containing both Z-/Boc- as well as the Fmoc group can be accomplished. In conclusion, the synthesis of *N*-Fmoc-/Boc-/Z-5-oxazolidinones has been accomplished by utilizing microwave irradiation for 3 min in good to excellent yields with high purity. In the traditional approach, for the synthesis of 5 mmole of a 5-oxazolidinone, 100 mL of toluene has to be used, azeotropic distillation of water has to be carried out and removal of large quantities of toluene under vacuum has to be performed, all of those are tedious and time consuming especially if multiple gram quantities of oxazolidinones have to be prepared. On the other hand, the present approach is not only simple and efficient but can also be carried out easily because it circumvents the removal of water by azeotropic distillation. Thus, it can be conveniently scaled up for the preparation of 5-oxazolidinones in large quantities.

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9. General procedure for the synthesis of *N*-Fmoc-5-oxazolidinone: A slurry of Fmoc-amino acid (10 mmol), paraformaldehyde (2 g) and *p*-toluene sulfonic acid (100 mg), in toluene (8 mL), in a beaker was subjected to microwave irradiation (domestic microwave oven operated at 2450 MHz). After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (25 mL), washed with water (10 mL×2), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was crystallized using dichloromethane:hexane (1:3).