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A Novel, Simple and Rapid Protocol For N-Protected-oxazolidine-5-ones

G. Vidyasagar Reddy $^{\rm a}$, G. Venkat Rao $^{\rm a}$ & D. S. Iyengar $^{\rm a}$ Indian Institute of Chemical Technology , Hyderabad, 500 007, India

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A NOVEL, SIMPLE AND RAPID PROTOCOL FOR N-PROTECTED-OXAZOLIDINE-5-ONES.

G. Vidyasagar Reddy*, G. Venkat Rao and D. S. Iyengar*

Indian Institute of Chemical Technology, Hyderabad - 500 007, India

Abstract: A simple and efficient method for the preparation of N-protected oxazolidine-5-ones using microwave irradiation is described.

N-Protected oxazolidine-5-ones derived from amino acids are versatile synthons used in the synthesis of several bioactive molecules and their key intermediates¹. In view of this, variety of methodologies have been developed for their preparation²⁻⁵. In general, the most common method used involves the treatment of N-Protected α-amino acids with paraformaldehyde in presence of catalytic PTSA². In addition to this, few other methods have been reported, which invloves the reaction of N-protected α-amino acids with paraformaldehyde / CH₂Cl₂ / MgSO₄³, 37% CH₂O / PTSA / THF⁴, paraformaldehyde / PTSA / Silicagel / DCM or BF₃. Et₂O⁵.

^{*} To whom correspondence should be addressed. IICT Communication No. 4217

In recent years microwave irradiation has become an important technique to accelarate the reactions. In connection with our ongoing programme in the area of oxazolidinone chemistry, 6-10 we became interested to use microwave irradiation in the preparation of N-protected oxazolidinones. Here in, we wish to disclose the results obtained in the present study with a variety of N-protected-\(\alpha\)-amino acids.

In a preliminary experiment, microwave irradiation of N-Ts-alanine and paraformaldehyde for 2 min. gave the corresponding N-Ts-oxazolidinone in an excellent yield (96%). Encouraged by this result a variety of N-protected-α-amino acids were subjected to the same reaction conditions to give corresponding N-protected oxazolidinones in excellent yields. (Scheme-1, Table-1). However, to our surprise N-Boc and N-Cbz amino acids under these reaction conditions led to a intractable mixture of products. This might be due to the cleavage of Boc and Cbz groups under these reaction conditions. All the compounds obtained were fully characterised by 'H-NMR, IR, mass spectral data.

Scheme-1

PG-N-OH
$$(CH_2O)_n / Clay$$
 PG-N-O

NW. 2 min.

PG = Ts, CH, C-, PhC-

EXPERIMENTAL SECTION

General Procedure: To a solution of N-protected-α-amino acid (4 mmol) in dichloromethelene (10 ml) was added paraformaldehyde (20 mmol) and

K₁₀ clay (5 g), then solvent was removed on rotaryevaporator to leave fine dry clay powder. This was transferred to a 20 ml test tube and kept in microoven (600 W, operating at a frequence of 2450 MHz) for 2 min., then brought to room temperature. Ethyl acetate (10 ml) was added and stirred for 10 min. Filtration through a silicagel pad gave clear solution, which was concentrated under reduced pressure to give pure N-protected-oxazolidinone.

Table-1

Preparation of N-protected-oxazolidinones under microwave irradition.

Entry	PG	R	*Yield (%)
	(=\)		
1.	н,с-⟨;;	CH ₃	96
2.	"	(CH ₃) ₂ CH	91
3.	II .	(CH ₃) ₂ CHCH ₃	94
4.	"	PhCH,	95
5.	II .	CH,CH,CH(CH,)	93
6.	11	BnOC ₆ H ₄ CH,	95
7.	O H₃C−C−-	CH ₃	92
8.	11	(CH ₃) ₂ CH	90
9.	**	(CH ₃), CHCH ₂	93
10.	11	PhCH ₂	91
11.	O PhC	(CH ₃) ₂ CH	93
12.	11	$(CH_3)_2$ CHCH ₂	92
13.	H	PhCH ₂	94
14.	II .	CH ₃ CH ₂ CH(CH ₃)	91

a: Isolated yield

In conclusion, we report a novel and rapid method for the preparation of N-protected-oxazolidinones under microwave irradiation conditions.

SPECTROSCOPIC DATA (1H NMR, 200 MHz, CDCl,

Compound 1: Colourless solid, M.P. 137°C.

¹H NMR : δ 1.45 (d, 3H, J = 6.5 Hz, C \underline{H}_3 CH), 2.45 (s, 3H, C \underline{H}_3 -Ar), 4.70 (q, 1H, J = 6.8 Hz, C \underline{H} CH₃), 5.10 (d, 1H, J = 8.6 Hz, NC \underline{H}_2 O), 5.60 (d, 1H, J = 8.6 Hz NC \underline{H}_2 O), 7.35 (d, 2H, J = 9.0 Hz, Ar), 7.70 (d, 2H, J = 9.0 Hz, Ar).

 $e/z : 283 (M^+).$

Compound 2: Colourless solid, M.P. 75°C.

¹H NMR: δ 1.05 (d, 3H, J = 6.8 Hz, CH₃CH), 1.15 (d, 3H, J = 6.8 Hz, CH₃CH), 2.00-2.20 (m, 1H, CH(CH₃)₂, 2.45 (s, 3H, CH₃-Ar), 4.35 (d, 1H, J = 6 Hz, CHCH), 5.05 (d, 1H, J = 6.2 Hz, NCH₂O), 5.50 (d, 1H, J = 6.2, NCH₂O), 7.35 (d, 2H, J = 9.0 Hz, Ar), 7.70 (d, 2H, J = 9.0 Hz, Ar) e/z: 297 (M⁺).

Compound 3: Colourless solid, M.P. 87°C.

¹H NMR: δ 0.90 (d, 3H, J = 8.8 Hz, CH₃CH), 1.05 (d, 3H, J = 8.8 Hz, CH₃CH), 1.30-1.60 (m, 2H, CH₂CH), 1.85-2.10 (m, 1H, CH(CH₃)₂), 2.45 (s, 3H, CH₃-Ar), 4.60 (dd, 1H, J = 12.0, 4.5 Hz, CHCH₂), 5.05 (d, 1H, J = 8.8 Hz, NCH₂O), 5.60 (d, 1H, J = 8.8 Hz, NCH₂O), 7.35 (d, 2H, 9.0 Hz, Ar), 7.70 (d, 2H, J = 9.0 Hz, Ar).

 $m/z : 297 (M^+).$

Compound 4: Colourless solid, M.P. 139°C.

¹H NMR: δ 2.45 (s, 3H, C \underline{H}_3 -Ar), 3.10 (d, 2H, J = 6.4 Hz, C \underline{H}_2 Ph), 4.45 (d, 1H, J = 8.5 Hz, NCH₂O), 4.85 (t, 1H, J = 6.3 Hz, C \underline{H} CH₂), 5.40 (d, 1H, J = 8.5 Hz, NC \underline{H}_2 O), 7.10-7.35 (m, 7H, Ar), 7.65 (d, 2H, J = 9.0 Hz, Ar). e/z: 255 (M⁺).

Compound 5: Colourless solid, M.P. 85°C.

¹H NMR : δ 0.90 (t, 3H, J = 8.2 Hz, CH₃CH₂), 1.05 (d, 3H, J = 6.75 Hz,

 $C\underline{H}_3CH$), 1.10-1.30 (m, 1H, $C\underline{H}CH_3$), 1.60-1.90 (m, 2H, $C\underline{H}_2$ - CH_3), 2.45 (s, 3H, $C\underline{H}_3$ -Ar), 4.35 (d, 1H, J = 6.8 Hz, $C\underline{H}CH_3$), 5.10 (d, 1H, J = 8.6 Hz, NCH₂O), 5.50 (d, 1H, J = 8.6 Hz), 7.30 (d, 2H, J = 9.0 Hz, Ar), 7.65 (d, 2H, J = 9.0 Hz, Ar).

e/z: 331 (M^+).

Compound 6: Colourless solid, M.P. 137°C.

¹H NMR : δ 2.40 (s, 3H, $C\underline{H}_3$ - C_6H_4), 3.12-3.38 (m, 2H, $C\underline{H}_2$ -Ar), 4.15-4.42 (m, 1H, $C\underline{H}N$), 4.50 (s, 2H, $PhC\underline{H}_2O$), 5.05 (d, 1H, J = 8.8 Hz, $NC\underline{H}_2O$), 5.50 (d, 1H, J = 8.8 Hz, $NC\underline{H}_2O$), 6.80-7.55 (m, 13H, Ar). FABM : 422 [M⁺ +H].

Compound 7: Colourless syrup.

¹H NMR: (Two rotamers) δ 1.40-1.50 (2d, 3H, J = 7.8 Hz, CH_2CH_3), 2.10-2.20 (2s, 3H, CH_3CO), 4.70-4.58, 5.00-5.15 (2m, 1H, H-4), 5.25, 5.40, 5.50, 5.65 (4d, 2H, J = 6.1 Hz, H-2).

 $m/z : 143 (M^+).$

Compound 8: Colourless syrup.

¹H NMR: (Two rotamers) δ 0.90 (d, 3H, J = 6.8 Hz, CH₃CH), 1.00 (d, 3H, J = 6.8 Hz, CH₃CH), 1.40-1.70 (m, 1H, CH(CH₃)₂), 2.00 (s, 3H, CH₃CO), 4.60-4.75 (m, 1H, H-4), 5.10, 5.25, 5.35, 5.50 (4d, 2H, J = 6.2 Hz, H-2).

m/z: 171 (M^+).

Compound 9: Colourless syrup.

¹H NMR: (Two rotamers) δ 0.80-1.00 (d, 6H, J = 6.8 Hz, $(C\underline{H}_3)_2$ CH), 1.95-2.10 (m, 2H, $C\underline{H}_2$), 2.05 (s, 3H, $C\underline{H}_3$ CO), 2.15-2.40 (m, 1H, $C\underline{H}(CH_3)_2$), 4.45-4.60, 4.90-5.00 (2m, 1H, H-4), 5.00, 5.15, 5.30, 5.40 (4d, 2H, J = 6.1 Hz, H-2).

m/z: 185 (M+).

Compound 10: Colourless syrup.

¹H NMR: (Two rotamers) δ 1.60, 1.90 (2s, 3H, CH₃CO), 2.90-3.30 (m, 2H, CH₂Ph), 4.00, 5.00, 4.60, 5.60 (4d, 2H, J = 6.1 Hz, H-2), 4.70-4.85, 5.10, 5.25 (2m, 1H, H-4), 7.00-7.30 (m, 5H, Ph).

m/z: 219 (M^+) .

Compound 11: Colourless solid, M.P. 97°C.

¹H NMR : δ 1.00-1.10 (m, 6H, $(C\underline{H}_3)_2$ CH), 1.50-1.70 (m, 1H, $C\underline{H}(CH_3)_2$, 4.65-4.90 (m, 1H, $C\underline{H}$), 5.35-5.50 (m, 2H, CH_2), 7.50 (m, 3H, Ar), 8.1 (d, 2H, Ar).

e/z: 265 (M^+) .

Compound 12: Colourless solid, M.P. 72°C.

¹H NMR : δ 0.90-1.00 (d, 6H, J = 6.8 Hz (C \underline{H}_3)₂CH), 1.90-2.10 (m, 2H, CH₂), 2.20-2.40 (m, 1H, C \underline{H} (CH₃)₂), 4.70-4.90 (m, 1H, C \underline{H} -N), 5.30-5.55 (m, 2H, O-C \underline{H}_3 N), 7.40-7.45 (m, 3H, Ar), 8.10 (d, 2H, Ar).

e/z: 279 (M^+).

Compound 13: Colourless solid, M.P. 110°C.

¹H NMR : δ 2.90-3.20 (m, 2H, $C\underline{H}_2$ Ph), 4.80-5.10 (m, 1H, $C\underline{H}_-$), 5.30-5.50 (m, 2H, $C\underline{H}_2$ -N), 7.20-7.50 (m, 8H, Ar), 8.10 (d, 2H, Ar).

e/z: 302 (M^+).

Compound 14: Colourless solid, M.P. 53°C.

¹H NMR : δ 0.8-1.10 (m, 8H, CH_3CH_2 & CH_3), 1.5-1.7 (m, 1H, $C\underline{H}CH_3$), 4.60-4.85 (m, 1H, $C\underline{H}N$), 5.30-5.50 (m, 2H, $O-C\underline{H}_2N$), 7.50 (m, 3H, Ar), 8.10 (d, 2H, Ar).

e/z: 279 (M+).

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