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

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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 intermediates[1]. In view of this, variety of methodologies have been developed for their preparation[2-5]. In general, the most common method used involves the treatment of N-Protected α-amino acids with paraformaldehyde in presence of catalytic PTSA[2]. In addition to this, few other methods have been reported, which invloves the reaction of N-protected α-amino acids with paraformaldehyde / CH_2Cl_2 / $MgSO_4$[3], 37% CH_2O / PTSA / THF[4], paraformaldehyde / PTSA / Silicagel / DCM or BF_3. Et_2O[5].

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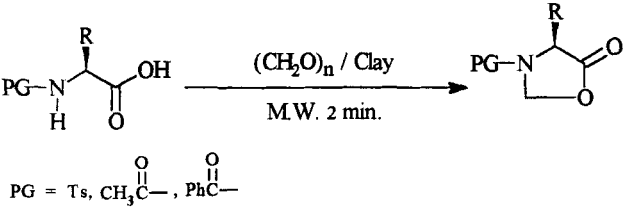
In recent years microwave irradiation has become an important technique to accelarate the reactions. In connection with our ongoing programme in the area of oxazolidinone chemistry,[6-10] we became interested to use microwave irradiation in the preparation of N-protected oxazolidinones. Here in, we wish to disclose the results obtained in the present study with a variety of N-protected-α-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 ^{1}H-NMR, IR, mass spectral data.

Scheme-1



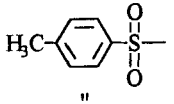
EXPERIMENTAL SECTION

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

K_{10} 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 micro-oven (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	[a]Yield (%)
1.		CH_3	96
2.	"	$(CH_3)_2CH$	91
3.	"	$(CH_3)_2$ $CHCH_2$	94
4.	"	$PhCH_2$	95
5.	"	$CH_3CH_2CH(CH_3)$	93
6.	"	$BnOC_6H_4CH_2$	95
7.		CH_3	92
8.	"	$(CH_3)_2CH$	90
9.	"	$(CH_3)_2$ $CHCH_2$	93
10.	"	$PhCH_2$	91
11.		$(CH_3)_2CH$	93
12.	"	$(CH_3)_2$ $CHCH_2$	92
13.	"	$PhCH_2$	94
14.	"	$CH_3CH_2CH(CH_3)$	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 (^{1}H NMR, 200 MHz, $CDCl_3$

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

^{1}H NMR : δ 1.45 (d, 3H, J = 6.5 Hz, $C\underline{H}_3CH$), 2.45 (s, 3H, $C\underline{H}_3$-Ar), 4.70 (q, 1H, J = 6.8 Hz, $C\underline{H}CH_3$), 5.10 (d, 1H, J = 8.6 Hz, $NC\underline{H}_2O$), 5.60 (d, 1H, J = 8.6 Hz $NC\underline{H}_2O$), 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.

^{1}H NMR : δ 1.05 (d, 3H, J = 6.8 Hz, $C\underline{H}_3CH$), 1.15 (d, 3H, J = 6.8 Hz, $C\underline{H}_3CH$), 2.00-2.20 (m, 1H, $C\underline{H}(CH_3)_2$, 2.45 (s, 3H, CH_3-Ar), 4.35 (d, 1H, J = 6 Hz, $C\underline{H}CH$), 5.05 (d, 1H, J = 6.2 Hz, $NC\underline{H}_2O$), 5.50 (d, 1H, J = 6.2, $NC\underline{H}_2O$), 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.

^{1}H NMR : δ 0.90 (d, 3H, J = 8.8 Hz, $C\underline{H}_3CH$), 1.05 (d, 3H, J = 8.8 Hz, $C\underline{H}_3CH$), 1.30-1.60 (m, 2H, $C\underline{H}_2CH$), 1.85-2.10 (m, 1H, $C\underline{H}(CH_3)_2$), 2.45 (s, 3H, CH_3-Ar), 4.60 (dd, 1H, J = 12.0, 4.5 Hz, $C\underline{H}CH_2$), 5.05 (d, 1H, J = 8.8 Hz, NCH_2O), 5.60 (d, 1H, J = 8.8 Hz, NCH_2O), 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.

^{1}H NMR : δ 2.45 (s, 3H, $C\underline{H}_3$-Ar), 3.10 (d, 2H, J = 6.4 Hz, $C\underline{H}_2Ph$), 4.45 (d, 1H, J = 8.5 Hz, NCH_2O), 4.85 (t, 1H, J = 6.3 Hz, $C\underline{H}CH_2$), 5.40 (d, 1H, J = 8.5 Hz, $NC\underline{H}_2O$), 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.

^{1}H NMR : δ 0.90 (t, 3H, J = 8.2 Hz, $C\underline{H}_3CH_2$), 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, NCH_2O), 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, $CH_2C\underline{H}_3$), 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, $C\underline{H}_3CH$), 1.00 (d, 3H, J = 6.8 Hz, $C\underline{H}_3CH$), 1.40-1.70 (m, 1H, $C\underline{H}(CH_3)_2$), 2.00 (s, 3H, $C\underline{H}_3CO$), 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, $(C\underline{H}_3)_2CH$), 1.95-2.10 (m, 2H, $C\underline{H}_2$), 2.05 (s, 3H, $C\underline{H}_3CO$), 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.

^{1}H NMR : (Two rotamers) δ 1.60, 1.90 (2s, 3H, C$\underline{H}_3$CO), 2.90-3.30 (m, 2H, C$\underline{H}_2$Ph), 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.

^{1}H 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.

^{1}H NMR : δ 0.90-1.00 (d, 6H, J = 6.8 Hz (C$\underline{H}_3$)$_2$CH), 1.90-2.10 (m, 2H, CH$_2$), 2.20-2.40 (m, 1H, C$\underline{H}$(CH$_3$)$_2$), 4.70-4.90 (m, 1H, C$\underline{H}$-N), 5.30-5.55 (m, 2H, O-C$\underline{H}_2$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.

^{1}H 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.

^{1}H NMR : δ 0.8-1.10 (m, 8H, CH$_3$CH$_2$ & 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$\underline{H}_2$N), 7.50 (m, 3H, Ar), 8.10 (d, 2H, Ar).

e/z : 279 (M^+).

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