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ALUMINA SUPPORTED SYNTHESIS OF β-LACTAMS USING MICROWAVE

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Abstract : N(4-hydroxycyclohexyl)-3-mercapto/cyano-4-arylazetidine-2-one were synthesised from N-(4-hydroxycyclohexyl)-arylaldimine by reacting with ethyl α-mercapto/α-cyanoacetate on basic alumina under microwaves, wherein not only the reaction time has been brought down from hours to minutes in comparison to conventional heating but also with improved yield.

Owing to high efficacy and extremely safe toxicological profile, β-lactam a class of compound is a drug of choice for the microbial infectious diseases in the current therapeutic index.[1-4] Tremendous efforts are on for the synthesis and structural modification of β-lactam, various substituted monocyclic β-lactams serve as important starting materials for the preparation of a wide variety of natural products[5] and biologically active compounds.[6] Besides this, the unique feature of these strained molecules is their usefulness as a powerful building blocks for

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the synthesis of a variety of organic compounds[7-8] having different functionalities such as α-amino acids, β-amino acids, α-hydroxy-β-amino acids, amino sugars and other heterocycles.

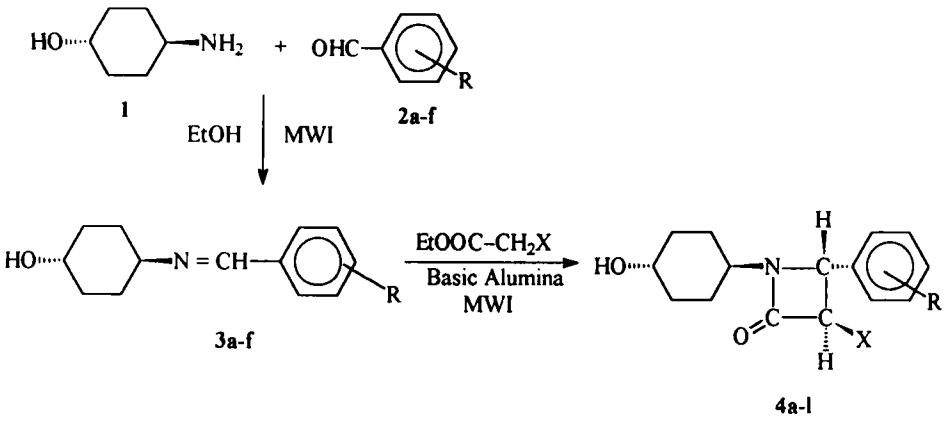
In recent years, among the several methods developed for the synthesis of the β-lactam ring, the ester-imine condesation route has been recognized to be one of the most useful.[9] The condensation of imines with ester enolates to form β-lactam is an important route to this structural class which has been extended beyond the original Giliman-Specter version.[10]

β-Lactam's synthesis have been widely reported through conventional heating, however, alternative strategies that are more ecofriendly than traditional one are being sought, due to the increasing concern about the impact of chemicals on the environment.

In recent past MORE (Microwave Induced Organic Reaction Enhancement) technique has gained considerable importance in synthetic chemistry as a practically convenient, safe and rapid methodology[11-12], but these procedures[13] are practically limited because of low boiling solvents. Usage of reagents supported on inorganic solid materials in the absence of solvent (solvent free conditions)[14-15] not only circumvent these problems but also leads to shorter reaction time[16] with improved yield. Further, the usage of basic alumina as the inorganic solid support, also eliminates the need for the external base.

Keeping in view the biological and synthetic importance of the β-lactams and the potential of solvent free microwave chemistry, it was thought worthwhile to prepare the title compounds via an ester-imine based synthesis using solvent free microwave technique.

The *trans*-4-aminocyclohexanol (**1**), prepared from the literature method[17] was condensed with different aromatic aldehyde (**2a-f**) to give the respective schiff base (**3a-f**). These schiff-base, with ethyl α-mercapto/α-cyano acetate, in presence of base, afforded the required



		R			R
	4a	H		4g	H
	4b	4OH		4h	4OH
X = SH	4c	$4OCH_3$	X = CN	4i	$4OCH_3$
	4d	2OH		4j	2OH
	4e	$3NO_2$		4k	$3NO_2$
	4f	4Cl		4l	4Cl

Scheme-1

3-mercapto/cyano β-lactams respectively (**4a-l**). Both the schiff base and the β-lactam were synthesised using conventional as well as microwave heating in solution phase, with MORE technique showing a clear advantage over the former one. Further the β-lactams were also synthesised in solvent free, microwave irradiated conditions.

In I.R. a band at 1720 cm^{-1} characteristic of β-lactam confirmed the desired product's formation and the disappearance of the band at 1540 cm^{-1} and 1700 cm^{-1} corresponding to C=N of imines and C=O of esters confirmed the formation of β-lactam. The stereochemistry of the β-lactams was resolved through ^{1}H-NMR wherein the J value for the two doublet (1.8-2.5 Hz) corresponding to the H atom at C-3 and C-4, indicated the trans-product.

Experimental

Melting points were taken on Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on 1710 Perkin-Elmer FTIR using KBr discs. ^{1}H-NMR spectra were recorded on a FT NMR Hitachi R-600 spectrometer operating at 90 MHz using TMS as internal standard (δ in ppm). The purity of the compound were checked on silica gel coated Aluminium plates (Merck). Microwave irradiations were carried out in a Padmini Essentia domestic microwave oven, model Browine, at 2450 MHz.

General procedure for the preparation of Aldimines ***(3a-f)***

Method A (Conventional)

Trans-4-aminocyclohexanol (**1**) (0.01 mole) and arylaldehyde (**2a-f**) (0.01 mole) were taken in ethanol (15 ml) in a 100 ml round bottom flask fitted with a reflux condenser. The flask was subjucted to reflux in water bath for 6-8 hours. The reaction mixture was cooled and the solid separated was filtered off, washed with water and recrystallized from ethanol.

Method B (MORE)

Trans-4-aminocyclohexanol (**1**) (0.01 mole) and arylaldehyde (**2a-f**) (0.01 mol) were taken in chlorobenzene (15 ml) in a 250 ml Erlenmyer flask. The flask capped with a glass funnel, was subjected to microwave irradiation for 2-3 minutes. Later the reaction was worked up as indicated in method A.

General procedure for the preparation of N(4-hydroxycyclohexyl)-3-mercapto cyano-4-arylazetidine-2-one ***(4a-l)***

Method A (Conventional)

To a solution of aldimines (**3a-f**) (0.01 mole) and K_2CO_3 (0.02 mole) in ethanol (15 ml), added dropwise ethyl-α-mercapto/ α-cyanoacetate (0.01 mole) with constant stirring. After refluxing for 5-6 hours, the inorganic salt was filtered off and the reaction mixture was

poured in water. The solid obtained was filtered, washed with water and recrystallized from ethanol-acetone mixture.

Method B (Solution phase - MORE)

To a solution of aldimine (**3a-f**) (0.01 mole) in ethanol (15 ml), taken in an Erlenmyer flask (500 ml) fitted with trap, added K_2CO_3 (0.02 mole) and ethyl-α-mercapto/α-cyanoacetate (0.01 mole). The reaction mixture was subjected to microwave irradiation for 2-3 minutes with an interval after every 20-30 seconds. The reaction mixture was worked up as indicated in method A for β-lactams.

Method C (Solid phase - MORE)

To a solution of aldimine (**3a-f**) (0.01 mole) in acetone, added ethyl-α-mercapto/α-cyanoacetate (0.01 mole) followed by basic alumina (20 gm) with constant stirring. The reaction mixture taken in a beaker, was throughly mixed and the adsorbed material was dried in air. The adsorbed reactant in the beaker was placed in an alumina bath[18] and subjected to microwave irradiation for 1-2 minutes. On completion of the reaction as followed by TLC examination, the mixture was cooled to room temperature and the product was extracted into acetone (3 x 15 ml). Recovering of solvent under reduced pressure yielded the product, which was purified by recrystallization from the mixture of ethanol-acetone.

Table 1

Compound No.	Reaction Period A (h) / B (sec)	Yield (%) A / B
3a	7.0/150	65/86
3b	6.5/140	65/88
3c	7.0/140	70/89
3d	8.0/150	68/90
3e	6.0/130	70/90
3f	7.5/170	70/92

The physical, spectral and analytical data of all the compounds are as follows :

3a : m.p. : 101-103°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.20 (complex multiplet, 8H, C_6H_8), 2.45-2.85 (m, 1H, CHOH), 3.50-3.75 (m, 1H, CHN), 7.10-7.80 (m, 5H, Ar-H), 8.50 (s, 1H, N=CH); IR (KBr) : 3400 (OH), 1510 (C=N); Anals. Calcd. for $C_{13}H_{17}NO$: C 76.84; H 8.37; N 6.89. Found : C 76.82; H 8.34; N 6.91.

3b : m.p. : > 203°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.20 (complex multiplet, 8H, C_6H_8), 2.48-2.80 (m, 1H, CHOH), 3.50-3.76 (m, 1H, CHN), 4.40 (s, 1H, OH), 6.60 (s, 1H, ArOH), 7.00-7.40 (m, 4H, Ar-H), 8.50 (s, 1H, N=CH); IR (KBr) : 3460 (OH), 1525

(C=N); Anals. Calcd. for $C_{13}H_{17}NO_2$: C 71.23; H 7.76; N 6.39. Found : C 71.25; H 7.79; N 6.36.

3c : m.p. : 106-108°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.00 (complex multiplet, 8H, C_6H_8), 2.48-2.85 (m, 1H, CHOH), 3.40-3.75 (m, 1H, CHN), 3.90 (s, 3H, OCH_3), 7.20-7.60 (m, 4H, Ar-H), 8.30 (s, 1H, N=CH); IR (KBr) : 3500 (OH), 1575 (C=N); Anals. Calcd. for $C_{14}H_{19}NO_2$: C 72.10; H 8.15; N 6.00. Found : C 72.12; H 8.12; N 6.04.

3d : m.p. : 161-163°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.10 (complex multiplet, 8H, C_6H_8), 2.45-2.80 (m, 1H, CHOH), 3.45-3.75 (m, 1H, CHN), 4.60 (s, 1H, CHOH), 6.50 (s, 1H, ArOH), 7.20-7.60 (m, 4H, Ar-H), 8.60 (s, 1H, N=CH); IR (KBr) : 3455 (OH), 1520 (C=N); Anals. Calcd. for $C_{13}H_{17}NO_2$: C 71.23; H 7.76; N 6.39. Found : C 71.26; H 7.78; N 6.37.

3e : m.p. : 66-68°C; ^{1}H-NMR : δ = 1.00-2.20 (complex multiplet, 8H, C_6H_8), 2.40-2.83 (m, 1H, CHOH), 3.40-3.74 (m, 1H, CHN), 7.00-7.50 (m, 4H, Ar-H), 8.5 (s, 1H, N=CH); IR (KBr) : 3410 (OH), 1525 (C=N), 1390 & 1490 (NO_2); Anals. Calcd. for $C_{13}H_{16}NO_3$: C 62.90; H 6.45; N 11.29. Found : C 62.88; H 6.48; N 11.26.

3f : m.p. : 113-115°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.88-2.10 (complex multiplet, 8H, C_6H_8), 2.48-2.86 (m, 1H, CHOH), 3.50-3.77 (m, 1H, CHN), 7.30-7.60 (m, 4H, Ar-H), 8.70 (s, 1H, N=CH); IR

(KBr) : 3450 (OH), 1535 (C=N); Anals. Calcd. for $C_{13}H_{16}NOCl$: C 65.68; H 6.73; N 5.89. Found: C 65.66; H 6.72; N 5.87.

4a : m.p. : 74-76°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.20 (complex multiplet, 8H, C_6H_8), 2.46-2.86 (m, 1H, CHOH), 3.60-3.80 (m, 1H, CHN), 4.30 (d, 1H, J = 2.3 Hz, 4-CH), 5.20 (1, 1H, J = 2.3 Hz, 3-CH), 7.10-7.80 (m, 5H, Ar-H), 11.2 (d, 1H, SH); IR (KBr) : 3410 (OH), 1730 (C=N); Anals. Calcd. for $C_{15}H_{19}NO_2S$: C 64.95; H 6.55; N 5.05. Found : C 64.98; H 6.53; N 5.04.

4b : m.p. : 78-80°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.20 (complex multiplet, 8H, C_6H_8), 2.50-2.85 (m, 1H, CHOH), 3.56-3.75 (m, 1H, CHN), 4.50 (s, 1H, OH), 4.7 (d, 1H, J = 2.4 Hz, 4-CH), 5.1 (q, 1H, J = 2.4 Hz, 3-CH), 7.00-7.60 (m, 4H, Ar-H), 11.50 (d, 1H, SH); IR (KBr) : 3440 (OH), 1729 (C=O); Anals. Calcd. for $C_{15}H_{19}NO_3S$: C 65.50; H 6.53; N 4.78. Found: C 65.53; H 6.51; N 4.76.

4c : m.p. : 70-72°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.00 (complex multiplet, 8H, C_6H_8), 2.48-2.83 (m, 1H, CHOH), 3.50-3.73 (m, 1H, CHN), 3.80 (s, 3H, OCH_3), 4.40 (d, 1H, J = 2.2 Hz, 4-CH), 5.00 (q, 1H, J = 2.2 Hz, 3-CH), 7.10-7.70 (m, 4H, Ar-H), 11.3 (d, 1H, SH); IR (KBr) : 3475 (OH), 1730 (C=O); Anals. Calcd. for $C_{16}H_{21}NO_3S$: C 62.51; H 6.89; N 4.55. Found : C 62.53; H 6.88; N 4.56.

Table 2

Compound No.	Reaction Period A (h) / B (sec) / C (sec)	Yield (%) A / B / C
4a	6.0/180/100	60/82/93
4b	5.5/180/80	65/84/95
4c	5.5/150/80	63/85/94
4d	6.0/150/90	65/80/95
4e	5.0/120/80	68/85/96
4f	5.0/150/90	65/80/92
4g	5.5/120/80	68/85/95
4h	5.0/150/80	60/82/90
4i	6.0/180/90	55/80/90
4j	5.5/150/70	58/79/90
4k	6.0/140/60	60/85/96
4l	6.0/150/70	65/86/97

4d : m.p. : 68-70°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.10 (complex multiplet, 8H, C_6H_8), 2.45-2.80 (m, 1H, CHOH), 3.50-3.74 (m, 1H, CHN), 4.60 (s, 1H, OH), 4.75 (d, 1H, J = 2.3 Hz, 4-CH), 5.10 (q, 1H, J = 2.3 Hz, 3-CH), 7.20-7.70 (m, 4H, Ar-H), 11.8 (d, 1H, SH); IR (KBr) : 3450 (OH), 1731 (C=O); Anals. Calcd. for

$C_{15}H_{19}NO_3S$: C 65.50; H 6.53; N 4.78. Found: C 65.53; H 6.52; N 4.76.

4e : m.p. : 72-74°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.00 (complex multiplet, 8H, C_6H_8), 2.45-2.87 (m, 1H, CHOH), 3.50-3.73 (m, 1H, CHN), 4.80 (d, 1H, J = 2.1 Hz, 4-CH), 5.20 (q, 1H, J = 2.1 Hz, 3-CH), 7.00-7.50 (m, 4H, Ar-H), 11.3 (d, 1H, 5H); IR (KBr) : 3410 (OH), 1732 (C=O); Anals. Calcd. for $C_{15}H_{18}N_2O_4S$: C 55.89; H 5.63; N 8.69. Found: C 55.86; H 5.62; N 8.69.

4f : m.p. : 76-78°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.88-2.10 (complex multiplet, 8H, C_6H_8), 2.48-2.86 (m, 1H, CHOH), 3.50-3.77 (m, 1H, CHN), 4.60 (d, 1H, J = 2.3 Hz, 4-CH), 5.0 (q, 1H, J = 2.3 Hz, 3-CH), 7.30-7.70 (m, 4H, Ar-H), 11.2 (d, 1H, 5H); IR (KBr) : 3450 (OH), 1728 (C=O); Anals. Calcd. for $C_{15}H_{18}NO_2SCl$: C 57.78; H 5.82; N 4.49. Found: C 57.77; H 5.80; N 4.50.

4g : m.p. : 68-70°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.00 (complex multiplet, 8H, C_6H_8), 2.45-2.86 (m, 1H, CHOH), 3.60-3.80 (m, 1H, CHN), 4.40 (d, 1H, J = 2.0 Hz, 4-CH), 5.50 (q, 1H, J = 2.0 Hz, 3-CH), 7.00-7.80 (m, 5H, Ar-H); IR (KBr) : 3400 (OH), 1729 (C=O); Anals. Calcd. for $C_{16}H_{18}N_2O_2$: C 71.09; H 6.71; N 10.36. Found: C 71.10; H 6.70; N 10.38.

4h : m.p. : 85-87°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.20 (complex multiplet, 8H, C_6H_8), 2.45-2.80 (m, 1H, CHOH), 3.55-3.75 (m,

1H, CHN), 4.40 (s, 1H, OH), 4.60 (d, 1H, J = 2.4 Hz, 4-CH), 5.60 (q, 1H, J = 2.4 Hz, 3-CH), 7.0-7.6 (m, 4H, Ar-H); IR (KBr) : 3430 (OH), 1726 (C=O); Anals. Calcd. for $C_{16}H_{18}N_2O_3$: C 67.12; H 6.34; N 9.78. Found: C 67.15; H 6.35; N 9.80.

4i : m.p. : 78-78°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.10 (complex multiplet, 8H, C_6H_8), 2.50-2.85 (m, 1H, CHOH), 3.50-3.75 (m, 1H, CHN), 3.90 (s, 3H, $-OCH_3$), 4.50 (d, 1H, J = 2.3 Hz, 4-CH), 5.40 (q, 1H, J = 2.3 Hz, 3-CH), 7.10-7.60 (m, 4H, Ar-H); IR (KBr) : 3470 (OH), 1728 (C=O); Anals. Calcd. for $C_{17}H_{20}N_2O_3$: C 71.31; H 7.04; N 9.78. Found : C 71.34; H 7.05; N 9.80.

4j : m.p. : 79-80°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.00 (complex multiplet, 8H, C_6H_8), 2.45-2.80 (m, 1H, CHOH), 3.50-3.75 (m, 1H, CHN), 4.70 (s, 1H, OH), 4.80 (d, 1H, J = 2.1 Hz, 4-CH), 5.6 (q, 1H, J = 2.1 Hz, 3-CH), 7.20-7.70 (m, 4H, Ar-H); IR (KBr) : 3440 (OH), 1730 (C=O); Anals. Calcd. for $C_{16}H_{18}N_2O_3$: C 67.12; H 6.34; N 9.78. Found: C 67.13; H 6.34; N 9.80.

4k : m.p. : 72-80°C; ^{1}H-NMR ($CDCl_3$) : δ = 1.00-2.10 (complex multiplet, 8H, C_6H_8), 2.45-2.85 (m, 1H, CHOH), 3.50-3.75 (m, 1H, CHN), 4.80 (d, 1H, J = 2.0 Hz, 4-CH), 5.70 (q, 1H, J = 2.0 Hz, 3-CH), 7.00-7.60 (m, 4H, Ar-H); IR (KBr) : 3415 (OH), 1730 (C=O); Anals. Calcd. for $C_{16}H_{17}N_3O_4$: C 60.94; H 5.43; N 13.33. Found: C 60.96; H 5.45; N 13.30.

4l : m.p. : 65-67°C; ^{1}H-NMR ($CDCl_3$) : δ = 0.90-2.10 (complex multiplet, 8H, C_6H_8), 2.50-2.85 (m, 1H, CHOH), 3.50-3.75 (m, 1H, CHN), 4.70 (d, 1H, J = 2.1 Hz, 4-CH), 5.50 (q, 1H, J = 2.1 Hz, 3-CH), 7.30-7.80 (m, 4H, Ar-H); IR (KBr) : 3455 (OH), 1726 (C=O); Anals. Calcd. for $C_{16}H_{17}N_2O_2Cl$: C 62.40; H 5.62; N 9.19. Found: C 62.38; H 5.61; N 9.21.

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