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SYNTHESIS OF AZETIDIN-2-ONES FROM IMINES AND ACIDS USING TRICHLOROACETONITRILE-TRIPHENYLPHOSPHINE REAGENT

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Abstract: A one step synthesis of azetidin-2-ones (**3a-j**) has been described by the reaction of imines (**1**) with acids (**2**) in presence of trichloroacetonitrile, triphenylphosphine and triethylamine.

Among the several methods for the synthesis of β-lactams, the cycloaddition reaction of ketenes with imines (Staudinger reaction) for the construction of β-lactam ring has found wide acceptance.[1] This is mainly because of its simplicity, predictability of stereochemical outcome and proven utility of this method for the synthesis of a large number of monocyclic, bicyclic, tricyclic and spirocyclic β-lactams.[2]

The ketenes are usually generated from acid halides (preformed or generated *in situ*) in the presence of tertiary amines. Alternatively acid activating

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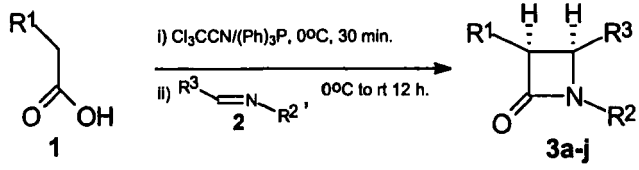
reagents, like ethyl chloroformates,[3] trifluoroacetic anhydride,[4] p-toluene-sulfonylchloride,[5] phosphorus derived reagents,[6] Mukaiyama reagent,[7] cyanuric chloride,[8] and several others[1] have been used. We now wish to report an application of trichloroacetonitrile-triphenylphosphine as a mild reagent for *in situ* generation of acid chlorides in the synthesis of azetidin-2-ones (β-lactams) *via* ketene-imine cycloaddition reaction.

In situ generated acid chloride from acid (**1**), by the reaction of trichloroacetonitrile and triphenylphosphine,[9] was reacted with imine (**2**) at 0°C to give β-lactam (**3**) in good yields (Scheme 1). The cycloaddition reaction was found to be stereoselective and only *cis*-β-lactam formation was observed.

Scheme 1



To explore the generality of this method, several substituted β-lactams (**3a-j**) were synthesized in good yields (Table-1). This method can also be used for the synthesis of β-lactams derived from acids, which are sensitive to mineral acids or thionyl chloride (see entry 10).

Experimental

All ^{1}H NMR Spectra were recorded in $CDCl_3$ on a Brucker AC 200 and Brucker MSL 300 spectrometers and chemical shifts were reported in ppm downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin-

Table 1 : Synthesis of β-lactams (**3a-j**) from acids (**1**) and imines (**2**).

Entry No.	R^1	R^2	R^3	Product	Yield (%)[a]	M.p. (°C)[b]
1	PhO	Ph	PMP	**3a**	61	150-151 (149-150)[10]
2	PhO	PMP	Ph	**3b**	59	185-186
3	PhO	PMP	PMP	**3c**	56	166-167
4	MeO	PMP	Ph	**3d**	65	159-161
5	PhO	PMP	Styryl	**3e**	62	178-180
6	PhO	Ph	Styryl	**3f**	65	193-194 (193-195)[11]
7	PhO	m-Tolyl	Styryl	**3g**	71	161-162
8	PhthN	PMP	Styryl	**3h**	61	191-193 (192-194)[6e]
9	MeO	PMP	Styryl	**3i**	62	139-141
10		Styryl	PMP	**3j**	70[c]	232-233[d]

[a] Isolated yield of pure products. [b] The figures in parenthesis refers to the literature melting points. [c] Isolated yield of diastereomeric mixture (7:3). [d] M.p. of major diastereomer obtained in 45% yield by single crystallization from acetone-pet. ether (3:7).

Elmer Infracord spectrophotometer Model 599-B using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. Methylene chloride was distilled over P_2O_5 under argon. Silica gel (SD's 60-120 mesh) was used for column chromatography.

A general procedure for the preparation of β-lactams (3a-j). To a solution of acid **1** (1 mmol) and trichloroacetonitrile (2 mmol) in dry CH_2Cl_2 (5 ml), a

solution of triphenylphosphine (2 mmol) in dry CH_2Cl_2 (3ml) was added at 0°C and stirred for 30 min. This mixture was then slowly added to a solution of imine **2** (0.5 mmol) and triethylamine (6 mmol) in CH_2Cl_2 (20 ml) at 0°C over a period of 15 min. The reaction mixture was allowed to warm-up to room temperature and stirred further for 12 h. It was washed successively with water (20 ml) satd. $NaHCO_3$ (20 ml) and brine (10 ml). The organic layer was dried (Na_2SO_4), concentrated and the product was purified by crystallization from methanol or column chromatography to give pure β-lactams (**3a-j**) in 56 to 71% yields.

4-*p*-Anisyl-3-phenoxy-1-phenylazetidin-2-one (3a). IR : 1739 cm^{-1}; ^1H NMR : δ 3.75 (s, 3H), 5.35 (d, J = 5.4 Hz, 1H), 5.50 (d, J = 5.4 Hz, 1H), 6.75-7.50 (m, 14H). Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.49; H, 5.54; N, 4.05. Found C, 76.31; H, 5.18; N,3.85.

1-*p*-Anisyl-3-phenoxy-4-phenylazetidin-2-one (3b). IR : 1753 cm^{-1}; ^1H NMR : δ 3.75 (s, 3H), 5.40 (d, J = 5.4 Hz, 1H), 5.60 (d, J = 5.4 Hz, 1H), 6.70-7.50 (m, 14H). Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.49; H, 5.54; N, 4.05. Found C, 76.23; H, 5.21; N, 3.93.

1,4-Bis(*p*-anisyl)-3-phenoxyazetidin-2-one (3c). IR : 1739 cm^{-1}; ^1H NMR : δ 3.85 (s, 6H), 5.40 (d, J = 5.4 Hz, 1H), 5.60 (d, J = 5.4 Hz, 1H), 6.80-7.50 (m, 13H). Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.57; H, 5.64; N, 3.73. Found C, 73.20; H, 4.81; N,3.56.

1-*p*-Anisyl-3-methoxy-4-phenylazetidin-2-one (3d). IR : 1741 cm^{-1}; ^1H NMR : δ 3.15 (s, 3H), 3.70 (s, 3H), 4.75 (d, J = 5.5 Hz, 1H), 5.15 (d, J = 5.5 Hz, 1H), 6.70-7.50 (m, 9H). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.01; N, 4.94. Found C, 71.96; H, 6.04; N, 4.75.

1-*p*-Anisyl-3-phenoxy-4-styrylazetidin-2-one (3e). IR : 1751 cm^{-1}; ^1H NMR : δ 3.75 (s, 3H), 5.00 (dd, J = 4.4 & 8.1 Hz, 1H), 5.50 (d, J = 4.4 Hz, 1H), 6.30 (dd, J

= 8.1 & 15.7 Hz, 1H), 6.75-7.50 (m, 15H). Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.59; H, 5.70; N, 3.77. Found C, 77.38; H, 5.42; N, 3.80.

3-Phenoxy-1-phenyl-4-styrylazetidin-2-one (3f). IR : 1739 cm^{-1}; ^1H NMR : δ 5.60 (dd, J = 5.4 & 8.1 Hz, 1H), 6.15 (d, J = 5.4 Hz, 1H), 6.50 (dd, J = 8.1 & 15.0 Hz, 1H), 6.70 (d, J = 15 Hz, 1H), 6.75-7.80 (m, 15H). Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.90; H, 5.61; N, 4.10. Found C, 80.51; H, 5.45; N, 3.87.

3-Phenoxy-4-styryl-1-*m*-tolylazetidin-2-one (3g). IR : 1755 cm^{-1}; ^1H NMR : δ 2.35 (s, 3H), 5.00 (dd, J = 5.2 & 8.1 Hz, 1H), 5.50 (d, J = 5.2 Hz, 1H), 6.20 (dd, J = 8.1 & 15.7 Hz, 1H), 6.75-7.50 (m, 15H). Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.09; H, 5.96; N, 3.94. Found C, 81.00; H, 6.34; N, 3.77.

1-*p*-Anisyl-3-phthalimido-4-styrylazetidin-2-one (3h). IR : 1743, 1728 cm^{-1}; ^1H NMR : δ 3.75 (s, 3H), 5.00 (dd, J = 5.8 & 8.8 Hz, 1H), 5.67 (d, J = 5.8 Hz, 1H), 6.31 (dd, J = 8.8 & 16.1 Hz, 1H), 6.79 (d, J = 16.1 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.25-7.35 (m, 3H), 7.46 (d, J = 8.8 Hz, 2H), 7.71-7.85 (m, 4H).

1-*p*-Anisyl-3-methoxy-4-styrylazetidin-2-one (3i). IR : 1745 cm^{-1}; ^1H NMR : δ 3.50 (s, 3H), 3.70 (s, 3H), 4.70-4.85 (m, 2H), 6.30 (dd, J = 7 & 15 Hz, 1H), 6.75-7.00 (m, 3H), 7.20-7.50 (m, 7H). Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.52. Found C, 73.38; H, 5.98; N, 4.35.

1-*p*-Anisyl-4-styryl-3-[3′,7′,7′-trimethyl-3′-methoxy]bicyclo(4.1.0)hept-4′-yl-oxy]azetidin-2-one (3j-major). IR : 1740 cm^{-1}; ^1H NMR : δ 0.71 (s, 3H), 0.87 (s, 3H), 1.02 (m, 1H), 1.27 (s, 3H), 1.55-2.15 (m, 6H), 3.27 (s, 3H), 3.75 (s, 3H), 4.70 (dd, J = 4.8 & 9.5 Hz, 1H), 5.42 (d, J = 4.8 Hz, 1H), 6.37 (dd, J = 8.5 & 14.4 Hz, 1H), 6.85 (m, 3H), 7.15-7.55 (m, 7H); $[\alpha]_D^{25}$: -3.3 (c 1.2, CH_2Cl_2).

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