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SYNTHESIS OF SUBSTITUTED N-PHENYL β- LACTAMS USING GRIGNARD REAGENT

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Abstract:
β-Lactam, a four-membered cyclic lactam (azetidin-2-one) skeleton has been recognized a useful building block for the synthesis of a large number of organic molecules by exploiting the strain energy associated with it. It has been extensively used as a template to build the heterocyclic structure fused to the four member rings. It has been considered as a versatile nucleus which posses almost all types of biological activities mainly antibiotics, antimicrobial and antifungal activity.

Key words: Azetidin-2-one, Ethylmagnesium bromide, Tetrahydrofuran

Introduction:

β-Lactams (azetidin-2-ones) are four-membered cyclic amides, first synthesized by Staudinger in1907[1]. With the discovery of penicillin[II-III] in 1928 by Sir Alexander Fleming and its structural confirmation by X-ray crystallography[IV] the scientific community recognized the potent biological activity of compounds containing the β-lactam subunit and their extensive use worldwide continued to be a front line of action against infectious pathogens[V-VII]. β-Lactams were found in other crucial applications to human,e. g. inhibitors of serine protease[VIII-IX] and acyl coenzyme a cholesterol transferases (ACAT)[X-XIV]. These types of molecules were used as starting materials for the preparation of various heterocycles of biological significance.[XV-XVII]. For example, substituted hydroxy β-lactams were used in the semi-synthesis of Taxol and Taxotere[XVIII-XIX]. A number of important strategies are available for the synthesis of the 2-azetidinone core ring present in all *β*-lactams (Staudinger cycloaddition reaction[XX-XXI], ester enolate-imine condensation[XXII-XXIII], hydroxamate approach[XXIV], alkene-isocyanate method[XXV] and the alkyne-nitrone reaction (Kinugasa reaction) [XXVI]. Due to their medicinal activity and potential use as synthetic starting materials, synthesis and biological studies of β-lactams has been intensely investigated for more than 70 years. Considerable work has been performed by chemists and biologist to continue updating their findings about β-lactam synthesis, based on either new or established methods, or on the modifications of pre-existing groups linked to this ring system.

Experimental Section:

The melting points were taken in open glass capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer IRTM spectrometer model BX-II in KBr pellets, whereas ^{1}H NMR spectra were recorded on Bruker 300-MHz instrument with TMS as internal standard. ^{13}C NMR were recorded on the same instrument at 75.47 MHz in Chloroform-d and DMSO-d6. All chemical shifts are reported in δ downfield from tetramethylsilane.

General Procedure for the Preparation of l-Arylazetidin-2-ones (Scheme-1):

A solution of ethylmagnesium bromide (3mol l^{-1}) in ether (20 ml) was added to a solution of the appropriate ethyl-β-anilinopropionate (0.04 mol) in dry tetrahydrofuran (250 ml) at room temperature. For (2h), ethyl magnesium bromide was added while the mixture was cooled in ice. The mixture was stirred for 14 h, evaporated, and the residue diluted with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with benzene as eluant.

1-Phenyl-2-azetidinone(2a): M.P.: 78-79°C; IR1735(C=O)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.10 (t, *J* = 6.7 Hz, 2H), 3.50(t, *J* = 6.7 Hz, 2H), 7.26-7.50 (m, 5H, phenyl); Anal. Data for C_9H_9NO(147.17): Calcd C 73.45, H 6.16, N 9.52; Found C 73.50, H 6.20, N 9.55.

1-(4-Methoxyphenyl)-2-azetidinone(2b): M.P.: 97-98°C, IR1760(C=O)cm^{-1}; ^{1}HNMR($CDCl_3$): δ 2.98 (t, *J* = 6.9, 2H), 3.50 (t, *J* = 6.9, 2H); Anal. Data for $C_{10}H_{11}NO_2$(177.20): Calcd C 67.78, H 6.26, N 7.90; Found C 67.60, H 6.24, N 7.95.

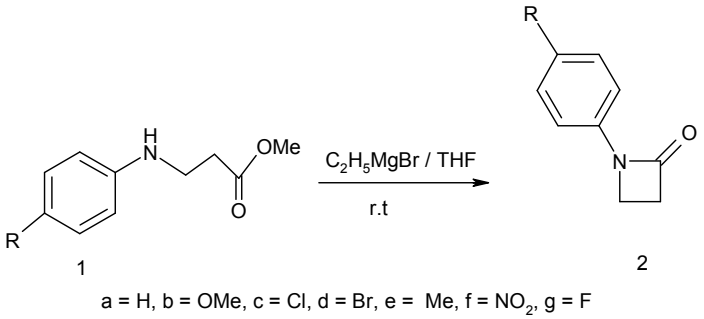
1-(4-Chlorophenyl)-2-azetidinone(2c): M.P.:124-125°C; IR1735(C=O)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.12 (t, *J* = 6.6, 2H), 3.60 (t, *J* = 6.6, 2H); Anal. Data for C_9H_8ClNO(181.62): C 59.52, H 4.44, N 7.71; Found C 59.55, H 4.46, N 7.80.

1-(4-Bromophenyl)-2-azetidinone(2d): M.P.:125-126°C, IR1765(C=O)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 2.93 (t, *J* = 6.8 Hz, 2H), 3.50(t, *J* = 6.8 Hz, 2H), 8.20-8.12 (m, 4H, phenyl); Anal. Data for C_9H_8BrNO (226.07): Calcd C 47.82, H 3.57, N 6.20; Found C 47.90, H 3.58, N 6.25.

1-(4-Methylphenyl)-2-azetidinone(2e): M.P.: 87-88°C; IR1750(C=O) cm^{-1}; ^{1}H NMR($CDCl_3$): δ 2.35(s, 3H), 3.10(t, *J* = 6.7 Hz, 2H), 3.52(t, *J* = 6.7 Hz, 2H), 6.85 - 8.35(m, 4H, phenyl); Anal. Data for $C_{10}H_{11}NO$(161.20): Calcd C 74.51, H 6.88, N 8.69; Found C 74.50, H 6.80, N 8.65.

1-(4-Nitrophenyl)-2-azetidinone(2f): M.P.:160-161°C; IR1750(C=O)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.08(t, *J* = 6.8 Hz, 2H), 3.50(t, *J* = 6.8 Hz, 2H), 6.86 - 8.30(m, 4H, phenyl); Anal. Data for $C_9H_8N_2O_3$(192.17): Calcd C 56.25, H 4.20, N 14.58; Found C 56.50, H 4.30, N 14.85.

1-(4-Fluorophenyl)-2-azetidinone(2g): M.P.: 82-84°C; IR1760(C=O)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.10 (t, *J* = 6.5 Hz, 2H), 3.50(t, *J* = 6.5 Hz, 2H), 7.26-7.30 (m, 4H, phenyl); Anal. Data for C_9H_8FNO(165.16):Calcd C 65.45, H 4.88, N 8.48; Found C 65.50, H 4.90, N 8.55.



Scheme-1

Result and discussion:

The l-arylazetidin-2-ones (2a-g) were prepared by cyclisation of the ethyl p-anilinopropionatesn(la-g), obtained by Michael addition of ethyl acrylate to the corresponding aniline derivatives with ethylmagnesium bromide. The reaction sequence leading to the formation of desired l-arylazetidin-2-ones is outlined in Scheme-1. Incorporation of an amide linkage into a four membered ring results in angle strain and some degree of inhibition of amide resonance, rendering β-lactams more susceptible than normal amides to nucleophilic attack at the carbonyl group. Not surprisingly, β-lactams undergo N(1)-C(2) cleavage on treatment with a variety of nucleophiles and this ability of a β-lactam to act as an acylating agent is generally considered to be, at least in part, responsible for the antibacterial properties of penicillins and cephalosporins.

Conclusion:

This literature reveals the various diverse biological activities such as anti-microbial, anti-bacterial, anticancer, anti-convulsant, antitubercular and anti-inflammatory properties of 2-azetidinone derivatives. A variety of drugs in market today possess the β-lactam moiety and many ongoing research is focused on developing newer antibiotics in which azetidinones play a crucial role. Hence it can be concluded that derivatives of 2-azetidinones have a great potential as bioactive molecules.

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