

4,4'-bis-[4-(substituted-phenyl)-1-azetidiny-2-one]-biphenyl Via an Improved Procedure Using Zn-Cu Couple in Sonic Reformatsky Reaction

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Abstract: Considerable interest has been focused on azetidinone (β -lactam) compounds for their broad spectrum antimicrobial activity. Therefore, a new series of bis-azetidinone compounds (5a-l) have been synthesized via the reaction of new Schiff bases (3a-l) with ethylbromoacetate and Zn-Cu couple in THF under nitrogen pressure with ultrasonic agitation. The structure of isolated products was confirmed spectroscopically. On the other hand, the prepared compounds were tested in vitro for their antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: Reformatsky Reaction, Beta Lactam, Azetidinone, Zn-Cu Coupling, Schiff Base

1. Introduction

β -lactams or azetidin-2-ones are one of the most successful groups of antibiotics including penicillin, cephalosporins, carbapenem and carbecephan (Kamath & Ojima, 2012), which are classified depending on their core-ring structures (Dalhoff et al., 2006), and they continue as first-line drugs, for treatment of bacterial infections. This class of antibiotics have long been studied in bacterial infections combating. In spite of new diseases and occurring resistance, β -lactam antibiotics remain for many years to play a prominent role in our therapeutic-arsenal (Barlam et al., 2016; Meredith, et al., 2015).

Numerous methods for construction of β -lactam rings have been reported (Li et al., 2007; Huang, et al., 2009; Brandi et al., 2008; Kingston, 2009). β -Lactams are prepared via a Reformatsky like reaction. This is a reaction in which an α -bromoester reacts with zinc to form an organozinc intermediate before combining with an imine to form a closed β -lactam and/or an open β -aminoester (Mukerjee et al., 1978). The reaction is carried out in a variety of solvents such as benzene (Gilman & Speeter, 1943), Diethyl ether (Park et al., 2001), Dichloromethane (Li & Chan, 1999), Tetrahydrofuran (Storz et al., 1999), Dioxan (Srirajan et al, 1996), using different catalysts such as RhCl(PPh₃)₃ (Kim et al., 2014), Cs₂CO₃ (Lu & Li, 2006) and PPh₃ (Zhu et al., 2014). In some cases, ultrasonic irradiation can be utilized as alternative energy source for organic reactions ordinarily accomplished by heating (Hussain, 2003; Mohamed, 2016).

A Reformatsky reaction with Zn-Cu couple affords easy access to the synthesis of 3-hydroxyalkanoic ester from aldehydes or ketones (Santaniello & Manzocchi, 1977; Tsukamoto & Kitazume, 1992). We

have now investigated the applicability of the Zn-Cu couple to the Reformatsky-like reaction for entertain hopes, wider spectrum of activity.

It has been noted that the Zn-Cu couple is relatively insensitive towards poisoning by impurities in the solvents or starting materials; when solvents of normal reagent-grade purity were used without previous purification the reaction had to be initiated.

2. Materials and Methods

Melting points were determined using Gallenkamp melting point apparatus and uncorrected. IR spectra were recorded on a Thermo Nicolet AVATAR 330 FT-IR spectrophotometer using a Mikro ATR module which allows the detection of bands directly on the substance without KBr tablets, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ data were acquired with the aid of Bruker DPX 300NRR spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C . All chemical shifts are given in ppm relative to the residual deuterated solvent signal (CDCl_3 or DMSO-D_6). The sonicator was Ultramet sonic cleaner Beuhlex Ltd. (220-240 V 50Hz). TLC were carried out using pre-coated whatman plates. Reactions were performed under a nitrogen atmosphere.

2.1 General Procedure for the Synthesis of N^4, N^4 - bis (substituted – benzylidene) – biphenyl – 4, 4' -diamines (3a-l)

These compounds were prepared by mixing two equivalents of benzaldehyde or substituted benzaldehyde in 20 ml ethyl alcohol with one equivalent of 4,4'-diaminobiphenyl in 30 ml ethyl alcohol at room temperature. The reaction immediately gave quantitative yield of the product. The solvent was decanted and ethyl alcohol (50 ml) was added. The mixture was sonicated for 30 seconds, the solvent was decanted and washed with diethyl ether then dried at 35 °C. The product N^4, N^4 -bis (substituted-benzylidene)-biphenyl-4,4'-diamine was obtained; color and melting point recorded in Table 1.

Table 1: Physical properties of bis-benzylidenes

Prod. (3)	X	Color and shape	(m.p.) °C
a	H	bright golden crystals	222-223
b	2-Br	fine yellow crystals	177-178
c	2-Cl	chalky yellow crystals	180-181
d	2-F	yellow powder	154-156
e	4-F	bright golden crystals	235-236
f	4-OCH ₃	bright yellow powder	246-248
g	2-NO ₂	chalky yellow powder	204 dec.
h	3-NO ₂	orange powder	224 dec.
i	4-NO ₂	deep yellow powder	236-238
j	2-OH	golden powder	208-209
k	3-OH	yellow powder	235 dec.
l	2,4-diOH	yellow powder	230-231

2.2 Preparation of Zn-Cu Couple (LeGoff, 1964)

The procedure was modified by using Ultrasonic waves instead of stirring. A mixture of zinc dust (0.75 g) and copper (II) acetate hydrate [Cu(OAc)₂.H₂O, 0.075 g] in acetic acid (3 ml) was partially submerged in a sonic bath at room temperature for eight minutes. The acetic acid was decanted and the Zn-Cu couple was washed with diethyl ether (3 x 10 ml) then with THF (5 ml).

2.3 General Procedure for the Synthesis of 4,4'-bis [4 - (substituted – phenyl) –1–azetidiny]– biphenyl (5a-l)

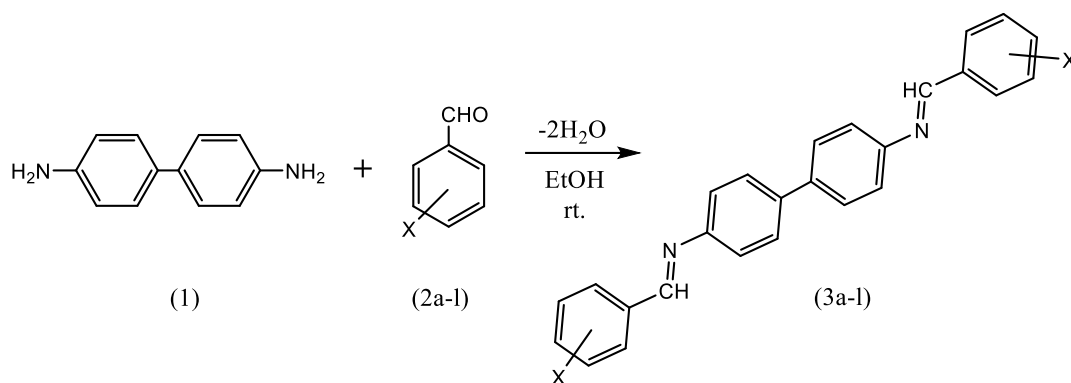
A solution of freshly prepared Zn-Cu couple, in THF (5 ml) was added dropwise to a solution of the Schiff base (0.0025 moles) and ethyl bromo-acetate (0.006 moles) in THF (50 ml). The mixture was partially submerged in the sonic bath at room temperature and under nitrogen atmosphere. The progress of the reaction was monitored with TLC. The solution was acidified with 10 % hydrochloric acid (10 ml) and the mixture was sonicated for another 5 minutes. The mixture was dried (MgSO₄), filtered and the solvent was evaporated in vacuo to yield a crud product which was washed with water and diethyl ether, to give the desired bis-azetidinone compounds, as shown in Table 2.

Table 2: Physical properties of β -lactams

Prod. (5)	X	Reaction time (hr.)	Yield (%)	(m.p.) °C
a	H	1:15	89	152-154
b	2-Br	2:30	80	170-173
c	2-Cl	1:20	85	80-82
d	4-F	3:00	88	325-327
e	2-F	1:15	82	232-234
f	4-OCH ₃	6:00	88	332-335
g	2-NO ₂	3:00	81	127-130
h	3-NO ₂	2:15	86	328-330
i	4-NO ₂	3:15	90	210-212
j	2-OH	2:00	75	142-144
k	3-OH	1:00	80	283-285
l	2,4-diOH	1:45	85	330-332

3. Results and Discussion

Synthesis of a series of new Schiff bases (3a-l) is the first stage of the investigation. This is done by reacting benzaldehyde or substituted benzaldehydes with 4,4'-diaminobiphenyl in ethanol, Scheme 1.



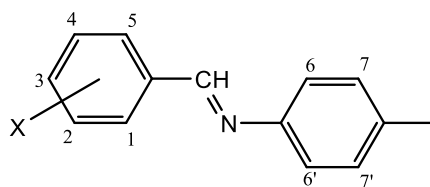
X(a-l)= H, 2-Br, 2-Cl, 2-F, 4-F, 4-OCH₃, 2-NO₂, 3-NO₂, 4-NO₂, 2-OH, 3-OH, 2,4-di-OH

Scheme 1

We employed IR, ¹H-NMR and ¹³C-NMR spectra for the identification of the prepared imines (3a-l). The IR spectra of imines showed an absorption at 1590-1627 cm⁻¹ which indicates the presence of C=N and absence of absorption at 3400-3500 cm⁻¹ and 1700 cm⁻¹ which indicates the disappearance of N-H (for diamine) and C=O (for aldehyde) respectively. In the ¹H-NMR spectra, the amine and aldehyde proton signals disappeared at δ 3-6 and δ 9-10 respectively, and a new signal appeared at δ 8.47-8.05 related to imine proton. The three protons of OCH₃ group have a signal at δ 3.84 in compound 3f. Chemical shift of protons absorption of imines are listed in Table 3.

Table 3: The ¹H-NMR data for some prepared bis-benzylidenes; Solvent DMSO

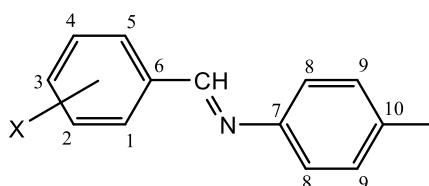
Comp. (3)	δ OH ppm (s, 1H)	δ HC=N ppm (s, 1H)	δ CH _{aromatic} ppm
a		8.7	7.96 (d, 1H _{1,5}), 7.76, 7.36 (dd, 4H), 7.57 (m, 3H _{2,3,4})
b		8.93	8.27 (dd, 1H ₄), 7.79, 7.38 (dd, 4H), 7.64 (d, 1H ₅), 7.45 (d, 1H ₂), 7.29 (d, 1H ₃)
f		8.70	7.89 (dd, 2H _{1,5}), 7.27 (m, 6H)
h		8.92	8.78 (d, 1H ₁), 8.39 (m, 2H _{3,5}), 7.88 (d, 1H ₄), 7.85, 7.45 (dd, 4H), 7.84, 7.56 (dd, 4H)
j	13.1	9.05	7.68 (d, 1H ₅), 7.4 (t, 1H ₃), 7.00 (m, 2H _{2,4})
l	12.85 10.10	8.48	7.4 (m, 7H)



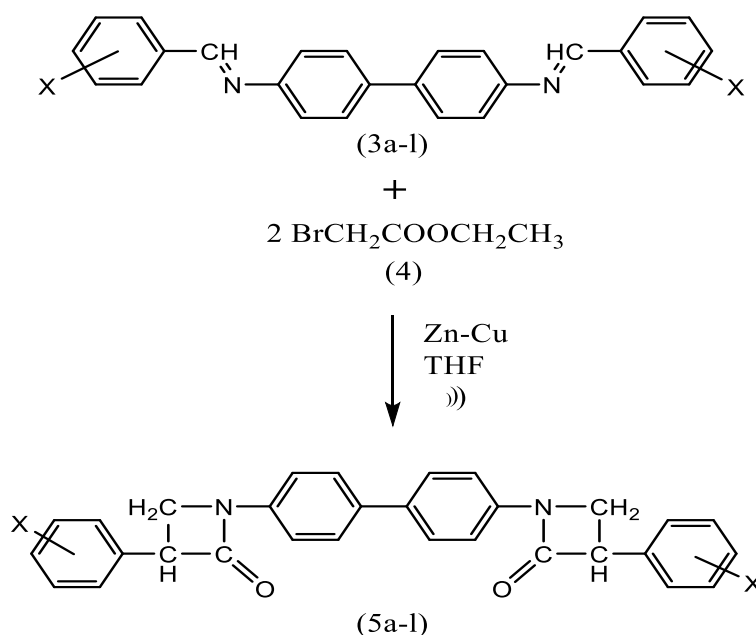
The ¹³C-NMR spectra of compounds (3a, l) in Table 4, show a signal for carbon of N=C at 160.13-161.42 ppm. The aromatic carbons appear in the aromatic region 114.2-148.67 ppm.

Table 4: Chemical shift of ^{13}C -NMR spectra for some prepared bis-benzylidenes; Solvent: DMSO

Com p.	CH imine	CH (aromatic)									
		CH ₁	CH ₂	CH ₃	CH ₄	CH ₅	CH ₆	CH ₇	CH ₈	CH ₉	CH ₁₀
3a	160.1 3	131.2 5	127.1 5	128.6 6	132.0 8	148.6 7	121.4 8	128.5 9	136.1 0		
3l	161.4 2	162.2 8	114.2 0	163.0 3	126.4 0	134.2 5	138.7 0	148.3 5	121.3 9	126.9 5	14 5.4 4



The new bis-1-azetidiny-2-one compounds (5a-1) are prepared by condensation of two equivalents of ethylbromoacetate with one equivalent of each of the prepared Schiff bases (3a-1) in the presence of Zn-Cu couple. The reactions have been done in the presence of sonic waves under nitrogen atmosphere in hydrous THF (Scheme 2). The results are listed in Table 2.



Scheme 2

The structures bis-1-azetidiny-2-one compounds have been confirmed by physico-chemical methods. IR, ^1H -NMR and ^{13}C -NMR confirming the accuracy of results of bis-1-azetidiny-2-one compound (5a-1), it was noted that the absorption of C=O group for azetidiny-2-one ring at $1726\text{--}1765\text{ cm}^{-1}$, on the other hand a clear difference was observed in the ^1H -NMR spectra of compounds (5a-1) Table 5. A singlet carried out signal at $8.47\text{--}8.05\text{ ppm}$ for protons in imine groups and a signal of ethyl group of esters disappeared at 4 and 1.3 ppm. While three new signals are observed as doublet-doublet at 4.35--

4.2 ppm for the proton of CH of β -lactam ring and two signals as doublet-doublet at 4.2-2.88 ppm and 3.33-2.44 ppm for two protons of CH_2 of β -lactam ring. This behavior results from the cis and trans interaction.

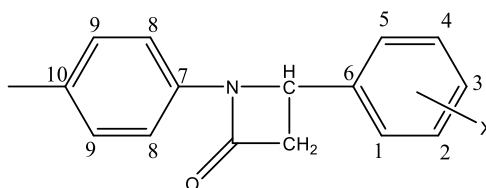
These $^1\text{H-NMR}$ results are in agreement with chemical shifts, which were determined with help of full spectral analysis and no β -amino ester or β -amino acids (Pavia et al., 2008) were formed for series of aldimines (3a-1). The $^{13}\text{C-NMR}$ spectra of compounds (5a,g,j) in Table 6, show three signals for lactam carbons at ~ 190 ppm for the carbonyl carbon, 65-43 ppm for the CH carbon and at ~ 38 ppm for the CH_2 carbon of the β -lactam, and the disappearance of the signal at 161-147 ppm which belongs to the carbon of imine groups.

Table 5: The $^1\text{H-NMR}$ for some prepared bis- β -lactam; Solvent: DMSO

Comp.	δ CH ar ppm	δ CH ppm (dd,1H)	δ HCH _{cis} ppm (dd,1H)	δ HCH _{trans} ppm (dd,1H)
5a	7.80-7.10 (m, 8H)	4.20	4.10	3.90
5g	8.20-7.10 (m, 8H)	4.20	3.30	2.90
5j	8.30-7.20 (m, 8H)	4.30	3.65	2.90

Table 6: The $^{13}\text{C-NMR}$ data for some prepared bis- β -lactams; Solvent: DMSO

Co mp.	C=O carbon yl	CH (aromatic)										CH ₂ , CH β -lactam
		CH ₁	CH ₂	CH ₃	CH ₄	CH ₅	CH ₆	CH ₇	CH ₈	CH ₉	CH ₁₀	
5a	193.7	136.5	127.1	129.1	122.2	128.8	126.6	132.1	114.1	128.3	129.9	60.8, 38
5g	190.4	157.0	121.0	122.4	131.1	128.3	134.3	147.0	114.7	124.7	130.0	60.9, 37
5j	193.9	160.9	117.6	123.6	122.0	127.7	128.9	137.3	120.4	123.6	131.0	60.7, 40



The general accepted mechanism for the organometallic reaction is believed to be an initial single electron transfer (SET) from the metal to the carbon halogen bond that will lead to a freely diffusing radical intermediates; sonication can clearly keep the surface clean in the heterogeneous reaction. The

effect of sonication on reaction has not been completely understood; it is believed to be related to high temperature (up to 5000 K) and pressure (up to 1000 bas) resulting from acoustic cavitation (Han & Boudjouk, 1982). Antimicrobial evaluation of all synthesized p-phenylene-bis [4-substituted benzo-azetidinone-2-one] compounds were studied against *Staphylococcus aureus* and *Escherichia coli*, it shows that all bis-azetidinones exhibit antimicrobial activities in Table 7.

Table 7: Results of *S-aureus* and *E-coli* sensitivity against bis β -lactams

Compound	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l
E-coli G (-)	+	+	+	+	+++	+	++	+++	++++	++	-	+
S-aureus G (+)	+	++	+	+	+++	+	++	++	++++	++	+	+

Key to symbols: Highly active ++++ (inhibition zone ≥ 33 mm); Active +++ (inhibition zone 26-33 mm); Moderately active ++ (inhibition zone 19-26 mm); Slightly active + (inhibition zone 12-19 mm); Inactive – (inhibition zone < 12 mm).

4. Conclusion

In conclusion, we have reported an efficient, easy and fast approach to bis-azetidinone through a valuable-protocol, which avoids the presence of by-products. The desired products synthesized by Reformatsky reaction from Schiff base using Zn-Cu couple and Sonication in order to reduce the reaction time and increasing the yield of the products.

References

- Barlam, T. F., Cosgrove, S. E., Abbo, L. M., MacDougall, C., Schuetz, A. N., Septimus, E. J., ... & Hamilton, C. W. (2016). Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clinical Infectious Diseases*, 62(10), e51-e77.
- Brandi, A., Cicchi, S., & Cordero, F. M. (2008). Novel syntheses of azetidines and azetidinones. *Chemical Reviews*, 108(9), 3988-4035.
- Dalhoff, A., Janjic, N., & Echols, R. (2006). Redefining penems. *Biochemical pharmacology*, 71(7), 1085-1095.
- Gilman, H., & Speeter, M. (1943). The Reformatsky reaction with benzalaniline. *Journal of the American Chemical Society*, 65(11), 2255-2256.
- Han, B. H., & Boudjouk, P. (1982). Organic sonochemistry. Sonic acceleration of the Reformatsky reaction. *The Journal of Organic Chemistry*, 47(25), 5030-5032.
- Huang, X. L., Chen, X. Y., & Ye, S. (2009). Enantioselective synthesis of aza- β -lactams via NHC-catalyzed [2+ 2] cycloaddition of ketenes with diazenedicarboxylates. *The Journal of organic chemistry*, 74(19), 7585-7587.
- Hussain, F.H.S. (2003). Synthesis of Some New p-Phenylene-Bis [4-Substitutedbenzo-azetidine-2-one] Via the Ultrasonic Promoted Reaction. *ZANCO*, 15(2), 5-7.
- Kamath, A., & Ojima, I. (2012). Advances in the chemistry of β -lactam and its medicinal applications. *Tetrahedron*, 68(52), 10640.
- Kim, I., Roh, S. W., Lee, D. G., & Lee, C. (2014). Rhodium-catalyzed oxygenative [2+ 2] cycloaddition of terminal alkynes and imines for the synthesis of β -lactams. *Organic Letters*, 16(9), 2482-2485.
- Kingston, D. G. (2009). Tubulin-interactive natural products as anticancer agents. *Journal of Natural Products*, 72(3), 507-515.

- LeGoff, E. (1964). Cyclopropanes from an easily prepared, highly active Zinc—Copper couple, dibromomethane, and olefins. *The Journal of Organic Chemistry*, 29(7), 2048-2050.
- Li, B., Wang, Y., Du, D. M., & Xu, J. (2007). Notable and obvious ketene substituent-dependent effect of temperature on the stereoselectivity in the Staudinger reaction. *The Journal of Organic Chemistry*, 72(3), 990-997.
- Li, C.J., Chan, T.H. (1999). Organic syntheses using indium-mediated and catalyzed reactions in aqueous media. *Tetrahedron*, 55(37), 11149-11176.
- Lu, H., & Li, C. (2006). General and Highly Efficient Synthesis of 2-Alkylideneazetidines and β -Lactams Via Copper-Catalyzed Intramolecular N-Vinylation. *Organic Letters*, 8(23), 5365-5367.
- Meredith, H. R., Srimani, J. K., Lee, A. J., Lopatkin, A. J., & You, L. (2015). Collective antibiotic tolerance: mechanisms, dynamics and intervention. *Nature Chemical Biology*, 11(3), 182.
- Mohamed, M. A. (2016). Sonochemistry (Applications of Ultrasound in Chemical Synthesis and Reactions): A Review Part I. *Journal of Pharmaceutical Sciences*, 53, 108-122.
- Mukerjee, A. K., & Singh, A. K. (1978). β -Lactams: retrospect and prospect. *Tetrahedron*, 34(12), 1731-1767.
- Park, S. H., Lee, S. Y., & Bose, A. K. (2001). An Efficient and Eco-friendly Approach to 15 N-Unsubstituted β -Lactams: 15 N-Labeled Synthons for Taxol and Its Analogs. *Bull. Korean Chem. Soc.*, 22(5), 493-498
- Pavia, D. L., Lampman, G. M., Kriz, G. S., & Vyvyan, J. A. (2008). *Introduction to Spectroscopy*. Cengage Learning. 4th ed. Washington.
- Santaniello, E., & Manzocchi, A. (1977). Use of the Zn-Cu couple in the Reformatsky reaction. *Synthesis*, 1977(10), 698-699.
- Srirajan, V., Deshmukh, A. R. A. S., & Bhawal, B. M. (1996). An efficient synthesis of cis-3-hydroxy-4-phenyl- β -lactams: Precursor for taxol side chain. *Tetrahedron*, 52(15), 5585-5590.
- Storz, T., Bernet, B., & Vasella, A. (1999). β -Lactams from D- Erythrose- Derived Imines: A Convenient Synthesis of 2, 3- Diamino- 2, 3- dideoxy- D- mannonic- Acid Derivatives. *Helvetica Chimica Acta*, 82(12), 2380-2412.
- Tsukamoto, T., & Kitazume, T. (1992). Reformatsky Reaction of Ethyl 4-Chloro-4, 4-difluorocrotonate Preparation of α -Substituted 4, 4-Difluoro-3-butenates. *Synlett*, 1992(12), 977-979.
- Zhu, L., Xiong, Y., & Li, C. (2014). Synthesis of α -methylene- β -lactams via PPh₃-catalyzed umpolung cyclization of propiolamides. *The Journal of Organic Chemistry*, 80(1), 628-633.