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SYNTHESIS OF 2-AMINO-3-PHENYLPROPAN-1-OL COMPOUNDS FROM BAYLIS-HILLMAN DERIVATIVES, CARBON NANOTUBE, KINETIC, LIFETIME AND BIOLOGICAL STUDIES

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ABSTRACT

We have successfully synthesized a novel class 2-amino-3-phenylpropane-1-ol by carbon nanotube method reaction for the first time. We have also carried out the iron acidic acid reduction reaction on Baylis-Hillman adducts to synthesize an array of novel 2-amino-3-phenylpropane-1-ol from nitroolefin derivatives reaction with good yields. Amine compounds carried out kinetic and Biological Studies.

Keywords: Baylis-Hillman adducts, Carbon nanotube, Iron acidic acid, (*E*)-2-nitro-3-phenylprop-2- en-1-ol, 2-amino-3-phenylpropane-1-ol.

INTRODUCTION

The Baylis-Hillman reaction, in the current day version, is an atom-economic carbon-carbon bond-forming reaction between the α-position of the activated alkenes and carbon electrophiles under the influence of a catalyst or catalytic system given that diverse classes of densely functionalized molecules, which are usually referred to as the Baylis-Hillman adducts
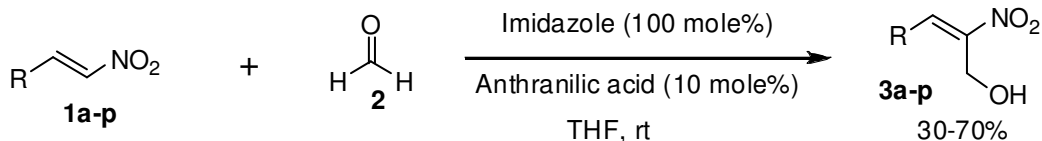(Scheme-1).[1-6]

Most of the Baylis-Hillman reactions are catalyzed by organic compounds like tertiary amines and alkyl(aryl) phosphines, and thus these reactions are referred to as the "organocatalysis reactions". The Baylis-Hillman reaction is a three-component carbon-carbon bond-forming reaction [activated alkenes (alkynes), electrophiles, and catalysts] as long as a molecule with diverse functionalities. This reaction creates a chiral center in the case of a prochiral electrophile thus contribution challenges and opportunities for increasing its asymmetric version. Since the Baylis-Hillman adducts are compactly functionalized molecules and due to the closeness of functional groups, these adducts are extremely useful as synthons in a number of synthetic processes and also in the synthesis of interesting natural and unnatural products of medicinal applications.

If the substrate contains both the activated alkene and electrophile components in appropriate positions, there is the option of developing an intramolecular version of this reaction leading to the synthesis of carbocyclic or heterocyclic compounds, and thus this reaction offers challenges to design and synthesize of various substrates that can be transferred into diverse classes of carbocyclic and heterocyclic compounds. Many variations of parameters present in this reaction, in fact, generate wide spectra of mechanistic pathways, thereby making understanding the mechanism of this reaction an intellectual challenge.

The Baylis-Hillman adducts have been successfully utilized as synthons in several named reactions such as Heck reaction, Diels-Alder reaction, Aldol condensation, Claisen rearrangement, Friedel-Crafts reation[7-10] etc. The FriedelCraftsreaction is one of the most widely used reactions in organic chemistry whose applications in academic as well as industrial fields have been well documented.[11-17]

EXPERIMENTAL

To execute our idea we premeditated to synthesize various Baylis-Hillman adducts (**3a**) by the treatment of (*E*)-(2-nitrovinyl)arenes (**1**) with paraformaldehyde (2) using imidazole and anthranilic acid as a catalytic system according to Scheme1. The compound **3a** was characterized by IR, 1H & 13C NMR spectroscopy, mass spectrometry and elemental analysis (Scheme-1).


R = Ph, 2-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-Et-C$_6$H$_4$, 4-i-*Pr*-C$_6$H$_4$, 2-MeO-C$_4$H$_4$,
4-MeO-C$_6$H$_4$, 3,4-(MeO)$_2$-C$_6$H$_3$, 3,4-(OCH$_2$O)-C$_6$H$_3$, 4-F-C$_6$H$_4$, 2-Cl-C$_6$H$_4$,
3-Cl-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 2-furyl, 2-thienyl, 1-naphthyl

Scheme-1

The 1H NMR spectrum of compound **3a** showed a singlet for hydroxyl proton at δ 2.61 and doublet was observed for O-CH2 protons at δ 4.71. The aromatic protons appeared as multiplet in the region of δ 7.48-7.58. The olefinic proton observed as a singlet at δ 8.22.

To implement our idea, first we have chosen the (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**3a**) derived from nitrostyrene and formaldehyde as starting material for reduction reaction. The best results were obtained when the addition of a catalytic amount of Fe and acidic acid solution (excess) (**4**) at reflux temperature successfully led to the most wanted product 2-amino-3-phenylpropane-1-ol. (**5**) in 82% yield after column chromatography purification. The compound **5a** was characterized by IR, ^{1}H, ^{13}C NMR, mass and elemental analyses (Scheme-2).
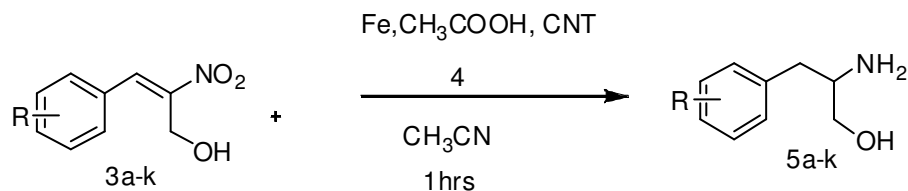
R = 2-Me, 4-Me, 4-Et, 4-*i*-Pr, 4-OMe, 3,4-di-OMe,
3,4-OCH$_2$O-, 4-F, 2-Cl, 3-Cl, 4-Cl

Scheme-2

Confident by this result, we utilized a variety of (*E*)-2-nitro-3-arylprop-2-en-1-ols(**3b-k**) as starting materials for the synthesis of (*E*)-2-nitro-1,3-diarylprop-1-enes. Treatment of the compounds with Fe and acidic acid successfully led to the desired chiral amine compounds (**5b-k**) in 74-80% yields. The ^{1}H NMR spectrum of compound **5a** showed a doublet of the doublet doublet for O-CH$_2$ protons at δ 3.15. The CH-CH$_2$ protons appear as a multiplet at δ 2.73-3.06 and CH$_2$CH- proton appears as a multiplet at δ 2.83-3.21. The aromatic protons appeared as multiplet in the region of δ 7.25-7.48 and the OH proton appeared as a singlet at δ 3.59. The NH$_2$ appear as a singlet at δ 5.23 which confirms the *E*-geometry.

Typical experimental procedure for the synthesis of (*E*)-(2-nitroprop-1-ene-1,3-diyl)dibenzene (5a)
To a stirred solution of (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**5a**) (0.48g, 2 mmol) in acidic acid (10 ml), and Iron powder (Excesses) (0.5 ml) was added at reflux temperature. The reaction mixture was stirred at reflux temperature for about 1 h. After the completion of reaction (confirmed by TLC analysis), the mixture was poured into water and the aqueous layer was extracted with ethyl acetate (3 x 10ml). The

combined organic layer was washed with brine (20ml), and dried over anhydrous Na_2SO_4. The crude product thus obtained was purified by column chromatography (2%, EtOAc / hexanes) to provide the desired compound **5a** in 82% (0.23 g) yield, as a yellow oil.

IR (KBr): 2346, 1353, 764 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz): δ 2.73-3.06 (m, 1H), 3.15. (dd, 2H), 2.83-3.21 (m, 2H), 3.59 (bs, 1H), 5.23 (bs, 2H), 7.25-7.48 (m, 5H) ^{13}CNMR ($CDCl_3$, 75 MHz) : δ 35.29, 47.03, 65.69, 128.98, 129.17, 129.72, 130.47, 143.76.

MS (m/z): 151 (M^++1).

Elemental Analysis for $C_9H_{13}NO$

Calculated: C, 71.49; H, 8.67; N, 9.26.

Found: C, 71.47; H, 8.68; N, 9.25

RESULTS AND DISCUSSION

Lifetime Measurement of nitro compounds

Time connected Single Photon Counting (TCSPC) measurement of fluorescence lifetime has simplified the use of the time domain method. This fitting evidently shows that the compound is well fitted with tri exponential and bi exponential fitting.[22] The emission spectra and decay time measurements for the 5a compound allowed the identification of the highest triplet state shown in Fig.-1. 5a having high lifetime value compared to another mononuclear compound. The order of the lifetime is increased.
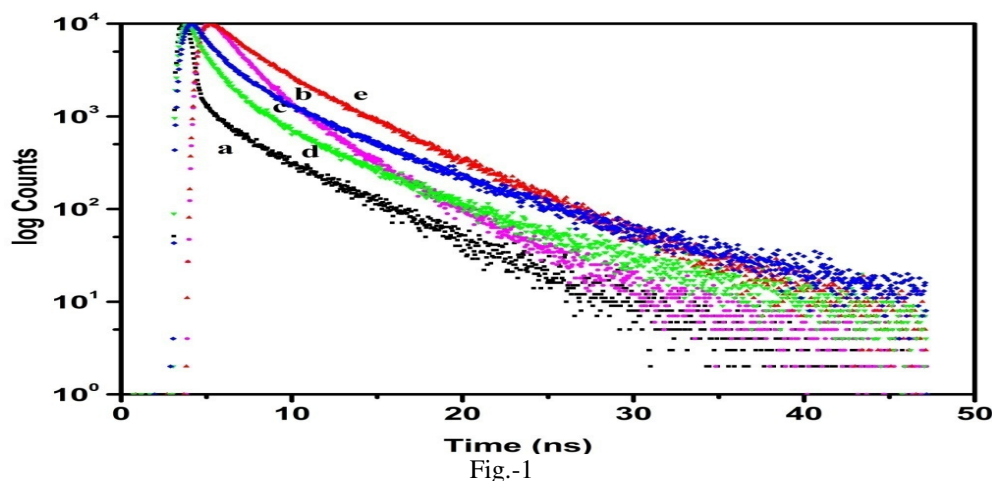

Fig.-1

Table-1: Lifetime measurement value of nitro compound

Compound	τ_1/ns	α_1 (%)	τ_2/ns	α_2 (%)	τ_3/ns	α_3 (%)	χ^2
5a	0.952	22.86	1.500	32.11	6.750	45.03	1.079
5c	0.322	14.03	1.370	41.69	5.450	44.29	1.105
5d	1.640	28.41	5.080	71.59	-----	-------	1.144
5e	1.330	50.82	-------	------	3.910	49.18	1.114
5h	0.132	55.83	2.750	11.06	5.350	33.11	1.176

Kinetic studies of Hydroxy amino compound

The catalytic activity of the Hydroxy amino compound was determined spectrophotometrically by monitoring the increase in the characteristic absorbance of the amine anion at420 nm over the time in dimethylformamide at 25 °C.For this purpose, 10^{-3} mol dm^{-3} solutions of the amino compound were treated with 100 equivalents of 4-nitrophenyl in the presence of air.The course of the reaction was followed at 420 nm for nearly 45 min at regular time intervals. The slope was determined by the method of initial rates by monitoring the growth of the 420 nm band of the product 4-nitro anion. A linear relationship between all the compound shows a first-order dependence on the compound concentration for the systems.Plots of log (Aα/Aα-At) versus time for hydrolysis of amine activity of the compound are obtained and shown in Fig.-2.
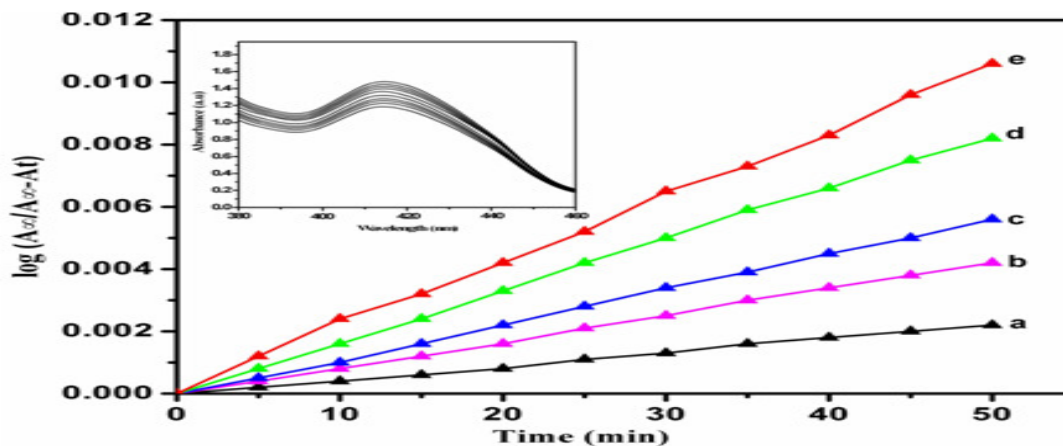
177

Fig.-2

Microorganisms
The test bacterial strains *Escherichia coli*, *Klebsiella sp, Candida albicans,Salmonella typhi*, and *Staphylococcus aureus* were obtained from the Department of Microbiology, SRM University, Chennai, Tamil Nadu was isolated clinically. The test organisms were sub-cultured at 37° C and maintained on nutrient agar media.

Anti-Microbial activity, Disc Diffusion Method
The bacterial inoculum was uniformly spread using sterile glass rod on a sterile Petri dish containing Nutrient Agar. Five concentrations of 25, 50, 75, 100 and 125 µM of pure substances were prepared in DMSO. The test substances of 50 µL were added to each of the 5 wells (7 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24 h at 36 °C ± 1 °C, under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in mm. Tests were performed in duplicate, whose minimum inhibitory concentration (MIC) values are provided in centimeters (CM) in diameter.

Antimicrobial activity of synthesized compound against five tested microorganisms has been studied. As per the recorded data all the mono nuclear compounds showed different effects against the different organisms showing highest activity against *Klebsiella sp* and at the concentration of 125 µM. Compound **5a** has the highest antimicrobial activity against all the organisms, MIC of Nutrient agar plates photos are given as Figures-3 and 4. In contrast, **5h** showed the lowest activity. This difference might be due to the different structure of chemical compounds and activity of side chains i.e. the difference in the binding site of the amine with the molecules data are given in the Tables-1 to 5.

Table-2: Antibacterial Activity of the Test Compound 5a

	25µM	50 µM	75 µM	100 µM	125 µM
E. coli	0.00 ± 0.00	00.00 ± 0.00	0.67 ± 0.58	0.90 ± 0.00	1367 ± 0.58
S. typhi	00.00 ± 0.00	0.70 ± 1.00	1.443 ± 0.057	1.67 ± 0.58	1.97 ± 0.58
C.albicans	0.00 ± 0.00	0.00 ± 0.00	00.00 ± 0.00	0.67 ± 0.115	0.93 ± 0.057
S. aureus	00.00 ± 00	0.00 ± 0.00	0.60 ± 0.16	1.00 ± 0.10	1.67 ± 0.58
Klebsiella	0.67 ± 0.58	0.7 ± 0.05	1.47 ± 0.05	1.7 ± 0.00	2.33 ± 0.15

Table-3: Antibacterial activity of the test compound 5c

	25µM	50 µM	75 µM	100 µM	125 µM
E. coli	0.60 ± 0.00	08.00 ± 0.05	1.3 ± 0.10	1.40 ± 0.05	1.6 ± 0.58
S. typhi	00.64 ± 0.11	1.2 ± 1.00	1.8 ± 0.057	2.00. ± 0.58	3.00 ± 0.58
C.albicans	0.00 ± 0.00	0.00 ± 0.00	00.80 ± 0.10	1.00 ± 0.115	1.10 ± 0.057
S. aureus	1.00 ± 0.00	1.40 ± 0.05	2.00 ± 0.152	3.20 ± 0.057	3.47 ± 0.58
Klebsiella	0.67 ± 0.11	1.2 ± 0.05	1.87 ± 0.152	2.0 ± 0.00	3.00 ± 0.115

178

Table-4: Antibacterial activity of the test compound 5d

	25µM	50 µM	75 µM	100 µM	125 µM
E. coli	0.80 ± 0.10	1.00 ± 0.58	1.2 ± 1.11	1.40 ± 0.00	1.8 ± 0.05
S. typhi	00.0 ± 0.0	00.0 ± 0.0	0.0 ± 0.00	0.70. ± 1.00	1.00 ± 0.10
C.albicans	0.00 ± 0.00	0.00 ± 0.00	00.00 ± 0.10	0.00 ± 0.00	0.00 ± 0.00
S. aureus	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Klebsiella	0.00 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.7 ± 0.11	0.7 ± 0.115

Table-5: Antibacterial activity of the test compound 5e

	25µM	50 µM	75 µM	100 µM	125 µM
E. coli	0.00 ± 0.00	0.60 ± 0.10	0.8 ± 0.05	1.20 ± 0.115	1.4 ± 0.58
S. typhi	00.64 ± 0.58	1.2 ± 0.58	1.4 ± 0.057	1.80. ± 0.11	2.00 ± 0.10
C.albicans	0.00 ± 0.00	1.00 ± 0.11	1.60 ± 0.15	1.80 ± 0.15	1.80 ± 0.057
S. aureus	0.60 ± 0.00	1.00 ± 0.05	1.60 ± 0.10	2.00 ± 0.057	3.00 ± 0.057
Klebsiella	0.00 ± 0.00	0.6 ± 0.05	0.8 ± 0.10	1.2 ± 0.00	1.40 ± 0.057

Table-6: Antibacterial activity of the test compound 5h

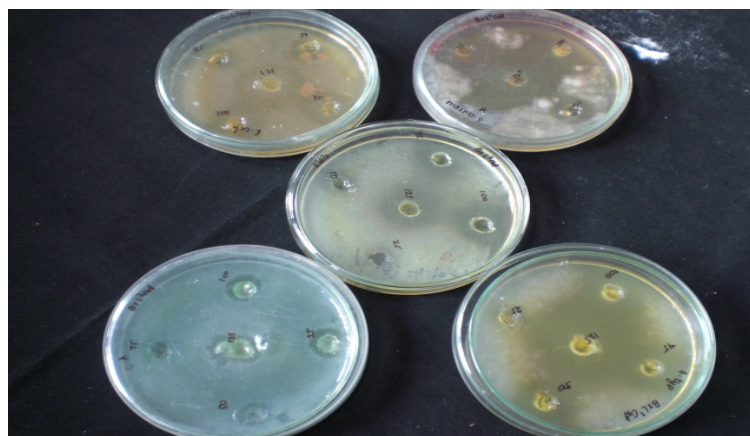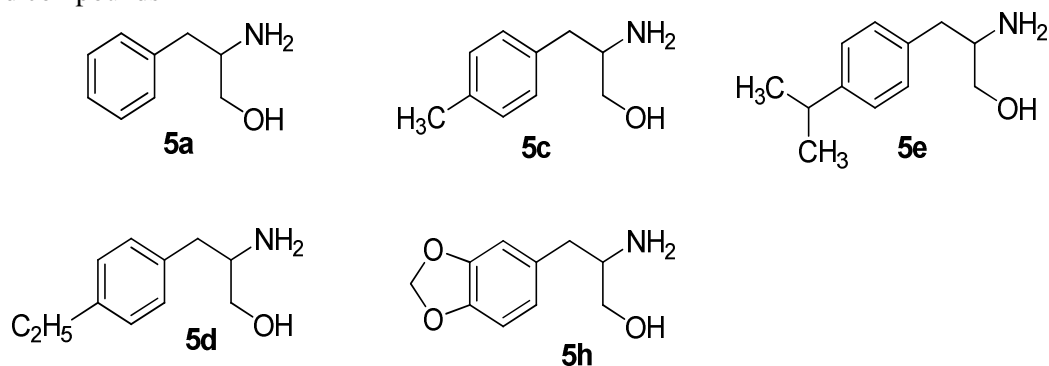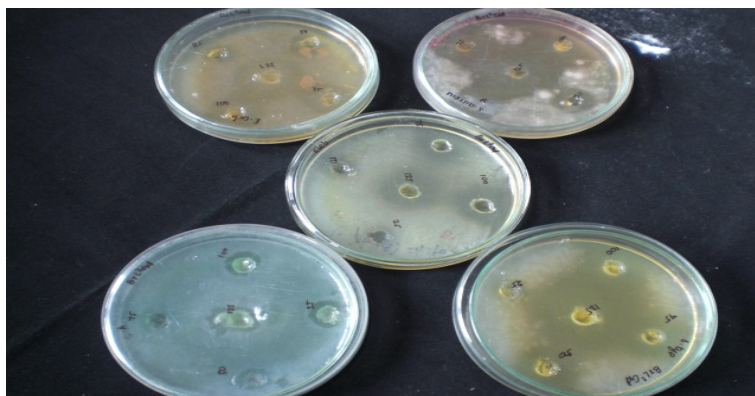|	25µM	50 µM	75 µM	100 µM	125 µM
E. coli	0.80 ± 0.00	1.2.00 ± 0.05	1.6 ± 0.10	1.80 ± 0.05	2.40 ± 0.58
S. typhi	1.04 ± 0.11	1.4 ± 0.10	1.6 ± 0.057	1.80. ± 0.10	2.40 ± 0.11
C.albicans	0.00 ± 0.00	0.60 ± 0.10	00.60 ± 0.10	0.60 ± 0.115	0.60 ± 0.05
S. aureus	1.00 ± 0.00	1.60 ± 0.1	1.80 ± 0.00	2.00 ± 0.00	3.00 ± 0.00
Klebsiella	3.00 ± 0.11	2.4 ± 0.05	3.0 ± 0.152	0.60 ± 0.00	2.40 ± 0.00

Tested compounds

Fig.-3: Tested compound 5a

Fig.-4: Tested compound 5e

CONCLUSION

In conclusion, simply synthesized a novel class 2-amino-3-phenylpropane-1-ol by carbon nanotube method reaction for the first time. We have also carried nitro alcohol to amine compounds from iron and acidic acid reduction reaction method. Baylis-Hillman adducts to synthesize from a nitroolefin derivatives reaction with good yields. This reaction carried out lifetime kinetic and Biological Studies.

ACKNOWLEDGEMENT

REFERENCES

1. V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev.*, **109**, 1, (2009).
2. V. Singh and S. Batra. *Tetrahedron.*, **64**, 4511, (2008).
3. D. Basavaiah, A.J. Rao and T. Satyanarayana, *Chem. Rev.*, **103**,811 (2003).
4. E. Ciganek, In *Organic Reactions*; L.A. Paquette, Ed; New York:Wiley., **51**, 201. (1997).
5. D. Basavaiah, P.D Rao, and R.S. Hyma, *Tetrahedron.*, **52**, 8001, (1996).
6. W. Guo, W. Wu, N. Fan, Z. Wu, and C. Xia, *Synth. Commun.*, **35**, 1239, (2005).
7. Z. Wu, G. Zhou, J. Zhou, and W. Guo, *Synth. Commun.*, **36**, 2491, (2006).
8. S. Karur, J. Hardin, and A. Headley and G. Li, *Tetrahedron Lett.*, **44**, 2991 (2003).
9. D. Basavaiah and A. J. Rao, *Tetrahedron Lett.*, **44**,4365 (2003).
10. J. Vesely, R. Rios and A. Cordova, *Tetrahedron Lett.*, **49**, 1137 (2008).
11. R. Sengodan, R. Ranjithkumar, K. Selvam and B. Chandarshekar, *Rasayan J. Chem.,* **11**, 68 (2017).
12. S. Purwantiningsih, A. Salsabila, I. Auliya and A. Budi, *Rasayan J. Chem.*, **10(3)**,175 (2017).
13. H. Cao, T. Viera, and H. Alper, *Org. Let.*, **13**, 11, (2011).
14. S. Hemalatha and M. Makeswari, *Rasayan J. Chem.*, **10(3)**,843 (2017).
15. Sunil Kumar and R. Bigan, *Rasayan J. Chem.*, **10(3)**,934 (2017).
16. V. Calo, A. Nacci, L. Lopez and A. Napola, *Tetrahedron Lett.*, **42**, 4701,(2001).
17. B.A. Kulkarni and A. Ganesan, *J.Com. Chem.*, **1**, 373 (1999).

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