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SYNTHESIS, CHARACTERIZATION AND ANTI BACTERIAL ACTIVITY OF NEW 2-PYRIDONES, AMINO NICOTINATES FROM AROMATIC ALDEHYDES

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ABSTRACT
Synthesis from aromatic aldehyde to new 2-pyridones as well as amino nicotinates by treating acetylated Baylis-Hillman esters and acetylated Baylis-Hillman nitriles with enamines via [3+3] annulation protocol and it yields well. It was characterized by spectroscopic techniques and screened their antibacterial activity. The compounds exhibit inhibitory effect on the growth of some bacteria of Gram positive and Gram negative are Bacillus substilis, Micrococcus luteus, salmonellatyphi, Escherichia coli by using standard drug Treptomycin and solvent DMSO. In this method provides highly efficient access to multi functionalized pyridine compounds, which are useful intermediates for further chemical manipulation leading to preparation of other functional group or pyridine fused heterocycles.

KEYWORDS: Aromatic aldehyde, Baylis-Hillman reaction, antibacterial activity.

1.0 INTRODUCTION[1,8]
Recently the Baylis-Hillman reaction, a reaction that results in the formation of carbon-carbon bond between the α-position of activated alkenes 2 and carbon electrophiles 1 containing electron-deficient sp^2 carbon atom under the influence of a suitable catalyst, particularly a tertiary amine, such as 1,4-diazabicyclo[2.2.2] octane(DABCO) 3 producing multifunctional molecules 4. Yet another importantatom economy reaction, added to the list of these useful carbon-carbon bond forming reactions. Moreover this Baylis-Hillman reaction has been now a day recognized as a useful and emerging reaction having enormous synthetic potential as a source for various stereoselective processes. By using Baylis-Hillman adducts several acyclic and cyclic compounds includingquinolines, indoles, pyrazoles, naphthalenes, indazoles, etc. were synthesized efficiently. Infectious diseases caused by bacteria have increased tremendously inrecent years. Though many significant advances have been made in antibacterial therapy, the widespread use and misuse of antibiotics have caused the emergence of bacterial resistance to antibiotics.

The pyridine ring system occurs in the structures of man y natural products,pharmaceutical and other commercial agrochemical chemicals compounds and other commerci al substances.

Similarly, 2,5- di- substituted pyridines which appear to be important in many biologically active compounds have also been reported.

2.0 MATERIALS AND METHODS
All chemicals were obtained from Aldrich and instruments were used are ^{1}HNMR spectrum was recorded on AVENCE 500 spectrometer, Mass spectra were recorded on thermo finnigan ESI ion trap mass spectrometer, IR spectrum was recorded on FITR spectrometer. IR spectrum was recorded on Perkin-Elmer FT-IR spectrometer and TLC.

3.0 Experimental section
3.1 General experimental Procedure for the Synthesis of Baylis-Hillman adducts (90a-j and 99a-g)
Aromatic aldehyde (10 mmol), activated olefin (20 mmol) and DABCO (30 mol% with respect to aldehyde) were mixed well and allowed to stir at room temperature until completed the reaction was monitored by the TLC. After completion, the reaction mixture was diluted with water (15 mL) and extracted with ether (3x20 mL). The combined organic layer were dried over sodium sulphate, filtered, concentrated under vacuum and purified by silica gel column chromatography using ethyl acetate:hexane (100% hexane followed by 1:9) as eluent to afford pure compounds. All the synthesized compounds are characterized by ^{1}H-NMR and mass

spectroscopic techniques and the data was matched with the reported data.

1. Synthesis of 2-(trifluoromethyl)phenyl)methyl) acrylonitrile

Yield (%): 89% , TLC[hexane: ethyl acetate (1:1)]: 0.64, ^{1}H NMR ($CDCl_3$, 300MHz): δ7.78 (d, 1H), 7.70 (d, 1H), 7.65 (t, 1H), 7.49 (t, 1H), 6.10 (s, 1H), 6.07 (s, 1H), 5.77 (s, 1H), 2.79 (s, 1H).ESI-MS: 250m/z.

2. Synthesis of 2-(hydroxy(2,5 dimethoxyphenyl) methyl)acrylonitrile.

Yield (%): 72 %, TLC [hexane: ethyl acetate (1:1)]: 0.46, ^{1}H NMR ($CDCl_3$, 300MHz): 6.92 (s, 1H), 6.85 (d, 2H), 6.02 (s, 2H), 5.47 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.23 (s, 1H). ESI-MS: 220 m/z.

3. Synthesis of 2-(2-bromophenyl)(hydroxy)methyl) acrylonitrile.

Yield (%): 85 %, TLC [hexane: ethyl acetate (1:1)]: 0.58, ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.61 (d, 1H), 7.56 (d, 1H), 7.40 (t, 1H), 7.22 (t, 1H), 6.07 (s, 2H), 5.73 (s, 1H), 3.02 (s, 1H). ESI-MS: 239*m/z*.

4. Synthesis of 2-((4-bromophenyl)(hydroxy)methyl) acrylonitrile.

Yield (%): 78%, TLC[hexne: ethyl acetate (1:1)]: 0.71, ^{1}H NMR ($CDCl_3$, 300MHz): 7.55-7.52 (d, 2H), 7.29-7.27 (d, 2H), 6.13 (s, 1H), 6.05 (s, 1H), 5.29 (s, 1H), 2.52 (s, 1H). ESI-MS: 239*m/z*.

3.2 General experimental Procedure for the Synthesis of Baylis-Hillman acetates (93a-j and100a-g).

To a well stirred solution of Baylis Hilmann adduct (10 mmol) in dichloromethane (20 mL) was added pyridine (11 mmol) and cooled to 0 ^{o}C. Then acetyl chloride (11 mmol) was added slowly at the same temperature under nitrogen atmosphere and allowed to stir at room temperature until the reaction completed. The reaction was monitored by the TLC. After completion, the reaction mixture was diluted with water (15 ml) and extracted with dichloromethane (2x20 mL). The combined organic layers were washed with saturated $CuSO_4$ solution until pyridine removed then separated the layers and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography using EtOAc:hexane(1:9) as eluent to afford pure compound. Thus synthesized Baylis-Hillman acetates were characterized by spectroscopic techniques and the data was good agreement with the reported data.

1. Synthesis of 2-(trifluoromethyl)phenyl)methyl)acrylonitrile

Yield: 88%, TLC [hexane:ethyl acetate(1:1)]: 0.34, ^{1}HNMR ($CDCl_3$, 300MHz): δ 7.80 (d, 1H), 7.71 (d, 1H), 7.66 (t, 1H), 7.51(t,1H), 6.75(s,1H) 6.12 (s, 1H), 5.59 (s, 1H), 2.17 (s, 3H). ESI-MS: 269m/z.

2. Synthesis of 2-cyano-1- (2,5-dimethoxyphenyl) allyl acetate.

Yield**:** 85%, TLC [hexane:ethyl acetate(1:1)]: 0.48,^{1}H NMR ($CDCl_3$,300MHz): δ 7.02 (d, 1H), 6.85 (d, 2H), 6.69 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.18 (s, 3H). ESI-MS: 262 *m/z.*

3. Synthesis of 1-(2-bromophenyl)-2-cyanoallyl acetate.

Yield: 93%, TLC [hexane:ethyl acetate(1:1)]: 0.67,^{1}H NMR ($CDCl_3$, 300MHz): δ 7.59 (d, 1H),7.57 (d, 1H), 7.41 (t, 1H), 7.25 (t, 1H), 6.69 (s, 1H), 6.13 (s, 1H), 6.11 (s, 1H), 2.19 (s, 3H). ESI-MS: 280m/z.

4. Synthesis of 1-(4-bromophenyl)-2-cyanoallyl acetate.

Yield: 90%, TLC[hexane:ethylacetate(1:1)]:0.51,^{1}H NMR ($CDCl_3$,300MHz): δ 7.65 (d, 2H), 7.20 (d, 2H), 6.25 (s, 1H), 6.09 (s, 1H), 6.01 (s, 1H), 2.74 (s, 3H), ESI-MS: 280 m/z.

3.3 General experimental Procedure for the Synthesis of Amino Nicotinate derivatives from Acetylated Baylis-Hillman Nitriles and Enamines

To a well-stirred solution of NaH (60% in paraffin oil; 240 mg, 6mmol) in anhyd THF (15 mL) was added the enamino ester 2a or2b (2 mmol) dissolved in anhyd THF (5 mL) at r.t. under N2 atmosphere and the mixture was stirred for 15 min at the same temperature. Then, an acetylated Baylis–Hillman nitrile 1a–g (2.2 mmol) dissolved in anhyd THF (5 mL) was added slowly and the mixturewas stirred at r.t. until the reaction was completed. After completion, the solvent was removed under reduced pressure and the residuewas diluted with ice-cold H_2O (15 mL) and extracted withEtOAc (3 × 30 mL). The combined organic layers were washedwith H_2O (10 mL), dried (Na2SO4), concentrated under reducedpressure and purified by silica gel column chromatography(EtOAc–hexane, 1:9 followed by 1:4) to afford pure compound3a–j.

I. Synthesis of methyl 6-amino-5-((2-trifluoromethyl) benzyl)-2-methylnicotinate.

Yield:55%, TLC[hexane:ethyl acetate(1:1)]: 0.64, Melting point: 299 ^{o}c, IR (KBr): 3439, 3332, 3149, 2953, 2231, 1704, 1658, 1562, 1256, 961cm1. ^{1}HNMR ($CDCl_3$, 300MHz): δ7.48(s,1H), 7.71(d,1H), 7.43(t,1H), 7.36(t,1H), 7.08(d,1H), 4.68(brs.2H), 4.01(S,2H), 3.83(s,3H), 2.70(s,3H). ESI-MS: 325m/z.

II. Synthesisofmethyl 6-amino-5-(2,5-dimethoxybenzyl)-2-methylnicotinate.

Yield:68%, TLC[hexane:ethyl acetate(1:1)]: 0.78, Melting point: 363^{0}c IR (KBr): 3424,3335,3148,2967,2835,1703,1667,1557,1267,1075c m–1.^{1}H NMR ($CDCl_3$, 300MHz): δ 7.95 (s, 1 H), 6.83 (d, 1 H), 6.73 (d, 1 H), 6.66 (s, 1H), 5.11(brs, 2H), 3.85 (s, 6 H), 3.76 (s, 2 H), 3.71(s,3H),2.66(s,3H). ESI-MS: 316m/z.

III. Synthesis of methyl 6-amino-5-(2-bromobenzyl)-2-methylnicotinate.

Yield: 65%, TLC[hexane: ethyl acetate(1:1)]: 0.69, Melting point: 344^{0}c, IR (KBr): 3432,3325,3151,2946,2835,1701,1653,1599,1251,660cm –1.^{1}HNMR($CDCl_3$,300MHz):7.84 (s, 1 H), 7.61 (d, 1 H), 7.23 (t, 1 H), 7.13 (t, 1 H),7.01(d,1H), 4.79 (brs, 1 H), 3.91 (s, 2 H), 3.83 (s, 3 H), 2.70 (s, 3 H). ESI-MS: 337m/z.

IV. Synthesis of methyl 6-amino-5-(-4-bromobenzyl)-2-methylnicotinate.

Yield: 70%, TLC[hexane: ethylacetate (1;1)]: 0.64, Melting point: 344^{0}c, IR(KBR): 3289,2922,2852,1722, 1606,1671,1567,1488,1299,593 cm-1. ^{1}H NMR ($CDCl_3$, 300MHz): 8.10 (s, 1 H), 7.41 (d, 2 H), 6.98 (d, 2 H), 4.82 (brs, 2 H), 3.96 (s, 2 H), 3.83 (s, 3 H), 2.72 (s, 3 H).ESI-MS: 337m/z.

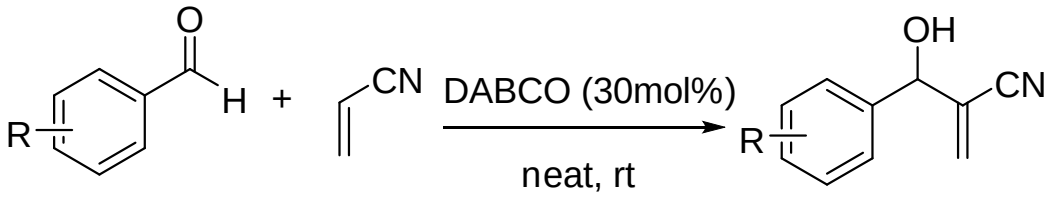
4.0 RESULTS AND DISCUSSION

In scheme-1 aromatic aldehyde, activated olefin and DABCO used in reactions were synthesized (fig-1). The reactions are monitor on TLC. All the synthesized compounds are characterized by ^{1}H-NMR and mass spectroscopic techniques and the data was matched with the reported data.

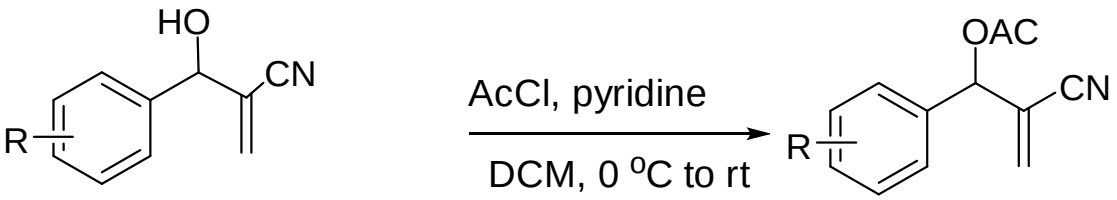
In scheme-2 the synthesis of baylis-hillman acetates, in this reaction baylis hilmann adduct and pyridine undergone in the presence of dichloromethane and acetyl chloride and reaction were synthesized the baylis-hillman acetates and characterized by spectral data and it matched with the reported data. The reactions are monitor on TLC.

In scheme-3 the synthesis of amino nicotinate derivatives from acetylated baylis-hillman nitriles and Enamines,in this reactions involved are baylis Hillman acetate nitrile, NaH and anhydrous THF and reactions were synthesized. The reactions were monitored on TLC. Thus synthesized compounds were characterized by spectral data and it matched with reported data.

STEP 1.



STEP 2.



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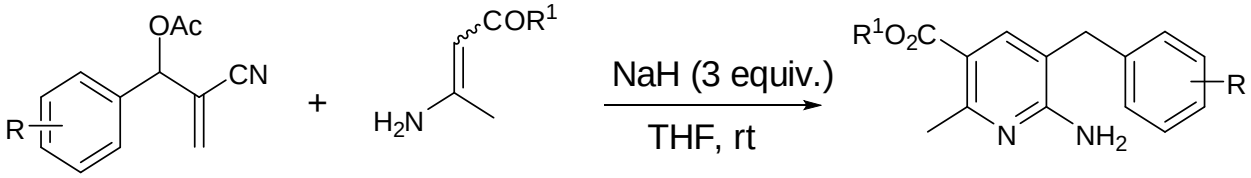

Fig 1: Steps involved in the synthesis of amino nicotinate derivatives.

4.1 Physical Characterization Data of Synthesised Compounds Chemistry

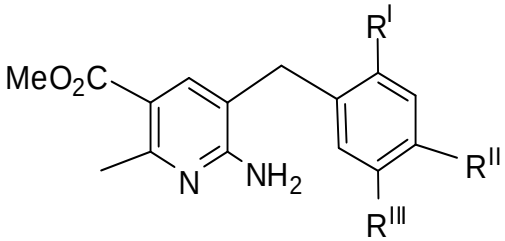

Fig.2: Skeletal structure of synthesized compounds.

Table 1: Physical characterization of synthesized compounds.

Compound No.	Molecular formula	RI	RII	RIII	Molecular weight	Percentage (%)	Melting point (^{o}c)	Rf value
IX	C16H15	F3	N2O2	CF3	324	55	299	0.64
X	C17H20	N2O4	OCH3	OCH3	316	68	363	0.78
XI	C15H15	Br	N2O2	Br	335	65	344	0.69
XII	C15H15	Br	N2O2	Br	335	70	344	0.64

4.2 Antibacterial activity

The test bacterial cultures were grown in nutrient broth (Nutrient agar) medium at 37^{0}C. 100 uL of each stock-culture were added to 3 mL of autoclaved nutrient broth cultures were kept at 36ºC ± 1ºC and the purity of cultures was checked after 8 h of incubation. The presence of definite zones around the cup of any size indicated antibacterial activity. The diameter of the zone of inhibition was measured and recorded.

4.2.1 ZONE OF INHIBITION (In mm)

Table 2: Data of Zone of inhibition indicates anti bacterial activity.

S .NO	COMPOUND	E .COLI	B.SUBTILIS	M.LUTEUS	S.TYPHI
1	IX	14	0	0	0
2	X	10	0	0	0
3	XI	14	13	0	0
4	XII	15	12	0	0

Standard: Streptomycin 24 18 31 29
Control: DMSO 0 0 0 0
Sample loaded: 100 µl.
Concentration of samples: 1 mg/ml.

5.0 CONCULSION

This method was straight forward and provides highly efficient for the synthesis of new 2-pyridones and amino nicotinates by treating baylis-hillman esters and acetylated baylis-hillman nitriles with enamines. These synthesized compounds shown antibacterial activity and it has been reported.

6.0 ACKNOWLEDGMENT

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