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ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 4: (3), 2014, 371-376

SYNTHESIS OF SUBSTITUTED 5-ACETYL-3-BENZOYLINDOLIZINE-1-CARBOXYLATE FROM SUBSTITUTED 2-ACETYL PYRIDINIUM BROMIDES.

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ABSTRACT
A series of substituted 5-acetyl-3-benzoylindolizine-1-carboxylates (**2a-p**) from subtitled 2-acetyl pyridinium bromides using 1,3-dipolar cycloaddition methods using TEA in THF with electron withdrawing Alkynes. The structures of newly synthesized compounds were characterized by analytical spectral data. The pyridinium bromides(**1a-d**) were synthesized neat at 120^0C using 2-acetyl pyridine and substituted phenacyl bromides.

Keywords
5-Acetyl Indolizine, Alkynes, TEA, THF, 2-acetylpyridine.

Introduction:
Certain Acyclic substrates bearing a 1,3-diene subunit and an allylic subunit undergo efficient stereoselective iron catalysed carbocyclisation to form five or six membered carbocycle and heterocycles[I,II,III]. The 1-azabicyclo[4,3,0]nonane (indolizine) framework occupies a special place in heterocyclic systems due to the presence of this structural assembly in a number of natural products of biological importance such as tubersonine, (-)-strychine[IV], (+)-vinblastine[V], (-)-monomorine[VI], (-)-gephyrotoxin[VII] etc. On the other hand, synthetic indolizine derivatives have been reported as calcium channel blockers[VIII], PLA_2 inhibitors[IX], histamine H_3-receptors antagonist[X] and 5-HT^3-receptors antagonists[XI]. Besides this, indolizines are also associated with pharmaceutical activites[XII] such as antiinflammatory, anti-tumor agents or even CNS activity.
The synthesis of biologically active indolizines[XIII] continues to attract the attention[XIV] of organic chemists. The indolizines are most commonly synthesized by sequential *N*-quarternization and intramolecular cyclocondensation reactions[XV] or the cycloaddition reaction[XVI] of *N*-acyl/alkyl pyridinium salts. Another stereoselective route is based on the iron-catalyzed cyclization of *N*-substituted pyrrolotrienes[XVII]. A similar strategy was reported for the

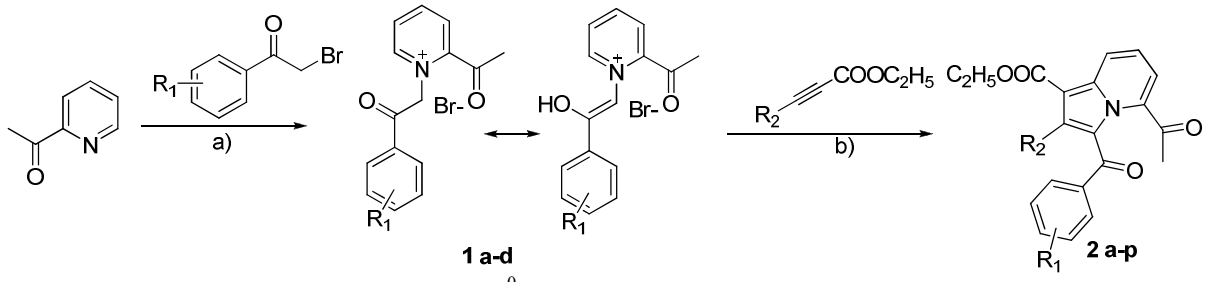
synthesis of indolizines via intramolecular 1,5-dipolar cyclization of 2-vinyl pyridinium ylide in the presence of tetrakis[pyrido]cobalt(II)-dichromate[XVIII]. A new pathway to chiral indolizines was accomplished from proline via the Pauson Khand reaction[XIX] involving an intramolecular cyclization reaction.

MATERIALS AND METHODS

All reactions were carried out in hot-air dried glass wares under nitrogen atmosphere using dry solvents.^{1}H-NMR (400 MHz) spectra were recorded at ambient temperature using $CDCl_3$, DMSO-D_6 as a solvent using Bruker-400 spectrometer. Chemical shift values are measured in δ ppm and were referenced with TMS. The peak multiplicities were given as followed; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. LC-MS analysis was performed on Agilent LC-1200 series coupled with 6140 single quad mass spectrometer with ESI +ve and –ve mode, MS range 100-2000. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

RESULTS AND DISCUSSION

N-Heterocyclic ylides **(1a-d)** were prepared by stirring substituted pyridines with substituted phenacyl bromides neat at 120^{0}C under nitrogen atmosphere at 30 mins. The solids were melt at above 75^{0}C. Reaction completion was monitored by TLC. After reaction completion cool to room temperature and diluted with hexane and stirred it at 10 mins. Solids were filtered and dried under vacuum and used as such. The ylides obtained were up to 90-95% yield. Anticipated indolizines have been prepared by the 1,3-dipolar cycloaddition reaction of N-haterocyclic ylides with electron deficient alkynes in the presence of anhydrous TEA in THF as a solvent. The completion of reaction was monitored by TLC. The solvent was removed by distillation under reduced pressure and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, brine and dried with anhydrous sodium sulphate, purified by column chromatography using 60-120 mesh silica gel and hexane-ethylacetate as a solvent



Scheme 1. a) Neat@120^{0}C 30 mins; b) TEA, THF, rt, 60-90 mins**.**

Table 1
Synthesis of pyridinium bromides (**1a-d**) and indolizine derivatives (**2a-p**).

Comp	R^1	Yield (%)	Comp	R^1	R^2	Yield (%)
1a	4-H	97.0	**2a**	4-H	H	65
1b	4-CH_3	93.3	**2b**	4-H	CH_3	62
1c	4-Cl	95.5	**2c**	4-H	C_2H_5	59
1d	4-Br	96.8	**2d**	4-H	$COOC_2H_5$	63
			2e	4-CH_3	H	61
			2f	4-CH_3	CH_3	58
			2g	4-CH_3	C_2H_5	55
			2h	4-CH_3	$COOC_2H_5$	76
			2i	4-Cl	H	71
			2j	4-Cl	CH_3	70
			2k	4-Cl	C_2H_5	63
			2l	4-Cl	$COOC_2H_5$	70
			2m	4-Br	H	69
			2n	4-Br	CH_3	63
			2o	4-Br	C_2H_5	64
			2p	4-Br	$COOC_2H_5$	66

All the compounds have been purified by column chromatography and recrystallized using appropriate solvents. The structures of all the synthesized compounds have been confirmed by various spectroscopic techniques such as LC-MS, ^{1}H-NMR, Elemental analysis.

Acknowledgement
We are thankful to the Principal, Sahyadri Science College, Shimoga, for providing laboratory facilities.

Conclusion
The research work is focused on the efficient synthesis of indolizines with organic base in THF. The reactions performed are eco-friendly as they are carried out at room temperature. The preparation of ylides (**1a-d**) are new method of preparation. The publication of these facts would be of significant use for the scientific community.

Experimentals
1. 2-Acetyl-1-(2-oxo-2-phenylethyl)pyridiniumbromide ***1a***
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 240.12; ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.04-9.03 (d, J=5.6 Hz, 1H), 8.69-8.63 (m, 2H), 8.48 (s, 1H), 8.39-8.37 (d, J=8.0 Hz, 1H), 8.26-8.22 (m, 1H), 7.89-7.86 (m, 2H), 7.60-7.58 (m, 3H), 2.15 (s, 3H).
2. *2-Acetyl-1-(2-oxo-2-p-tolylethyl)pyridiniumbromide* ***1b***
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 254.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ: 9.02-9.00 (d, J=5.6 Hz, 1H), 8.66-8.60 (m, 2H), 8.45 (s, 1H), 8.35-8.33 (d, J=8.0 Hz, 1H), 8.26-8.22 (m, 1H), 7.89-7.86 (m, 2H), 7.60-7.58 (m, 2H), 2.35 (s, 3H), 2.15 (s, 3H).
3. *2-Acetyl-1-(2-(4-chlorophenyl)-2-oxoethyl)pyridiniumbromide* ***1c***
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 274.12; ^{1}H NMR (400 MHz, DMSO-d_6): δ: 9.02-9.00 (d, J=6 Hz, 1H), 8.72 (s, 1H), 8.68-8.64 (m, 1H), 8.54 (s, 1H), 8.40-8.38 (d, J=8Hz, 1H), 8.27-8.23 (m, 1H), 7.90-7.87 (m, 2H), 7.71-7.68 (m, 2H), 2.15 (s, 3H).

4. *2-Acetyl-1-(2-(4-bromophenyl)-2-oxoethyl)pyridiniumbromide* ***1d***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 318.2; ^1H NMR (400 MHz, DMSO-d_6): δ: 9.01-8.99 (d, J=6 Hz, 1H), 8.72 (s, 1H), 8.68-8.64 (m, 1H), 8.56 (s, 1H), 8.40-8.38 (d, J=7.2 Hz, 1H), 8.28-8.24 (m, 1H), 7.92-7.88 (m, 2H), 7.70-7.65 (m, 2H), 2.16 (s, 3H).

5. *Ethyl-5-acetyl-3-benzoylindolizine-1-carboxylate* ***2a***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 336.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.53-8.51 (d, J=6.8 Hz, 1H), 7.81 (s, 1H), 7.75-7.71 (m, 2H), 7.61-7.59 (m, 3H), 7.45-7.41 (m, 2H), 4.37-4.33 (q, J=7.2Hz, 2H), 2.61 (s, 3H), 1.39-1.35 (t, J=7.2Hz, 3H); Elemental analysis calcd (%) for $C_{20}H_{17}NO_4$: C 71.63, H 5.11, N 4.18; Found: C 70.72, H 5.11, N 4.01.

6. *Ethyl-5-acetyl-3-benzoyl-2-methylindolizine-1-carboxylate* ***2b***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 350.2; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (d, J=7.2 Hz, 1H), 7.74-7.71 (m, 2H), 7.62-7.60 (m, 1H), 7.48-7.44 (m, 4H), 4.27-4.23 (q, J=7.2 Hz, 2H), 2.63 (s, 3H), 2.23 (s, 3H), 1.57-1.53 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 4.01; Found: C 71.25, H 5.44, N 3.51.

7. *Ethyl-5-acetyl-3-benzoyl-2-ethylindolizine-1-carboxylate* ***2c***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 364.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.59-8.57 (d, J=4Hz, 1H), 7.76-7.72 (m, 2H), 7.56-7.54 (m, 1H), 7.42-7.40 (m, 2H), 7.38-7.36 (m, 2H), 4.47-4.43 (q, J=7.2 Hz, 2H), 2.67-2.63 (q, J=7.2 Hz, 2H), 2.61 (s, 3H), 1.79-1.75 (t, J=7.2 Hz, 3H) , 1.06-1.01 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{22}H_{21}NO_4$: C 72.71, H 5.82, N 3.85; Found: C 71.44, H 5.49, N 3.68.

8. *Diethyl-5-acetyl-3-benzoylindolizine-1,2-dicarboxylate* ***2d***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 408.2; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (d, J=7.2Hz, 1H), 7.89-7.87 (m, 2H), 7.60-7.56 (m, 1H), 7.49-7.36 (m, 4H), 4.36-4.31 (q, J=7.2 Hz, 2H), 3.70-3.65 (q, J=7.2 Hz, 2H), 2.62 (s, 3H), 1.35-1.31 (t, J=7.2 Hz, 3H), 1.05-1.01 (t, J=7.2 Hz, 3H). Elemental analysis calcd (%) for $C_{23}H_{21}NO_6$: C 67.80, H 5.20, N 3.44; Found : C 66.78, H 5.16, N 3.05.

9. *Ethyl-5-acetyl-3-(4-methylbenzoyl)indolizine-1-carboxylate* ***2e***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 350.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.55-8.53 (d, J=7.2 Hz, 1H), 7.81 (s, 1H), 7.77-7.75 (d, J=8 Hz, 2H), 7.62-7.60 (m, 2H), 7.32-7.30 (m, 2H), 4.41 (q, J=7.2 Hz, 2H), 2.71 (s, 3H), 2.47(s, 3H), 1.42 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 4.01; Found: C 71.05, H 5.31, N 4.01.

10. *Ethyl-5-acetyl-2-methyl-3-(4-methylbenzoyl)indolizine-1-carboxylate* ***2f***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 364.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.87-8.55 (d, J=7.2 Hz, 1H), 7.70-7.78 (d, J=8.4 Hz, 2H), 7.47-7.45 (d, J=7.2 Hz, 1H), 7.33-7.29 (m, 3H), 4.44-4.40 (q, J=7.2 Hz, 2H) , 2.65 (s, 3H), 2.42 (s, 3H), 2.20 (s, 3H), 1.48-1.44 (t, J=7.2Hz, 3H); Elemental analysis calcd (%) for $C_{22}H_{21}NO_4$: C 72.71, H 5.82, N 3.85; Found: C 72.23, H 5.68, N 3.56.

11. *Ethyl-5-acetyl-2-ethyl-3-(4-methylbenzoyl)indolizine-1-carboxylate* ***2g***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 378.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.83-8.81 (d, J=7.2 Hz, 1H), 7.57-7.48 (m, 3H), 7.35-7.31 (m, 3H), 4.45-4.41 (q, J=7.2 Hz, 2H), 2.65 (s, 3H), 2.64-2.60 (q, J=7.2, 2H), 2.53 (s, 3H), 1.43-1.39 (t, J=7.2 Hz, 3H), 1.04-1.01 (t, J=8 Hz, 3H); Elemental analysis calcd (%) for $C_{23}H_{23}NO_4$: C 73.19, H 6.14, N 3.71; Found: C 72.92, H 5.82, N 3.48.

12. *Diethyl-5-acetyl-3-(4-methylbenzoyl)indolizine-1,2-dicarboxylate* ***2h***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 422.2; ^1H NMR (400 MHz, $CDCl_3$): δ 8.89-8.87 (d, J=7.2 Hz, 1H), 7.60-7.58 (d, J=8. Hz, 2H), 7.56-7.54 (d, J=7.2 Hz, 2H), 7.36-7.31 (m, 2H), 4.37-4.34 (q, J=7.0 Hz, 2H), 3.65-3.61 (q, J=7.2 Hz, 2H), 2.67 (s, 3H), 2.37(s, 3H), 1.39-1.35 (t, J=7.2 Hz,

3H), 1.06-1.02 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{24}H_{23}NO_6$: C 68.40, H 5.50, N 3.32; Found: C 68.24, H 5.32, N 3.19.

13. *Ethyl-5-acetyl-3-(4-chlorobenzoyl)indolizine-1-carboxylate* ***2i***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 370.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.85-8.83 (d, J=7.2 Hz, 1H), 7.79-7.77 (d, J=8.4 Hz, 2H), 7.61 (s, 1H), 7.61-7.59 (d, J=7.2 Hz, 2H), 7.41-7.36 (m, 2H), 4.44-4.40 (q, J=7.2 Hz, 2H), 2.65 (s, 3H), 1.44-1.40 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{20}H_{16}ClNO_4$: C 64.96, H 4.36, N 3.79; Found: C 64.62, H 4.21, N 3.63.

14. *Ethyl-5-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate* ***2j***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 384.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.86-8.84 (d, J=7.2 Hz, 1H), 7.65-7.63 (d, J=8.4Hz, 2H), 7.49-7.46 (d, J=8.4 Hz, 2H), 7.37-7.31 (m, 2H), 4.45-4.41 (q, J=7.2 Hz, 2H) , 2.2.65 (s, 3H), 2.20 (s, 3H), 1.48-1.44 (t, J=7.2Hz, 3H); Elemental analysis calcd (%) for $C_{21}H_{18}ClNO_4$: C 65.71, H 4.73, N 3.65; Found: C 65.40, H 4.71, N 3.47.

15. *Ethyl-5-acetyl-3-(4-chlorobenzoyl)-2-ethylindolizine-1-carboxylate* ***2k***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 398.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.83-8.81 (d, J=8 Hz, 1H), 7.68-7.66 (d, J=8 Hz, 2H), 7.45-7.43 (d, J=8.4 Hz, 2H), 7.40-7.34 (m, 2H), 4.45-4.41 (q, J=7.2 Hz, 2H), 2.72-2.68 (q, J=7.2 Hz, 2H), 2.61 (s, 3H), 1.44-1.40 (t, J=7.2 Hz, 3H), 1.06-1.02 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{22}H_{20}ClNO_4$: C 66.42, H 5.07, N 3.52; Found: C 66.42, H 5.02, N 3.33.

16. *Diethyl-5-acetyl-3-(4-chlorobenzoyl)indolizine-1,2-dicarboxylate* ***2l***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 442.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.88-8.86 (d, J=7.6 Hz, 1H), 7.66-7.64 (d, J=8.4 Hz, 2H), 7.54-7.52 (d, J=7.2 Hz, 2H), 7.38-7.34 (m, 2H), 4.37-4.33 (q, J=7.2 Hz, 2H), 3.76-3.72 (q, J=7.2 Hz, 2H), 2.66 (s, 3H), 1.38-1.34 (t, J=7.2 Hz, 3H),1.09-1.05 (t, J=7.2Hz, 3H); Elemental analysis calcd (%) for $C_{23}H_{20}ClNO_6$: C 62.52, H 4.56, N 3.17; Found: C 61.99, H 4.49, N 3.11.

17. *Ethyl-5-acetyl-3-(4-bromobenzoyl)indolizine-1-carboxylate* ***2m***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 414.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.85-8.83 (d, J=8 Hz, 1H), 7.79-7.76 (d, J=8.4 Hz, 2H), 7.50-7.30 (m, 5H), 4.35-4.31 (q, J=7.2 Hz, 2H), 2.63 (s, 3H), 1.35-1.32 (t, J=7.2Hz, 3H); Elemental analysis calcd (%) for $C_{20}H_{16}BrNO_4$: C 57.99, H 3.89, N 3.38; Found: C 57.42, H 3.61, N 3.11.

18. *Ethyl-5-acetyl-3-(4-bromobenzoyl)-2-methylindolizine-1-carboxylate* ***2n***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 428.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.86-8.84 (d, J=7 Hz, 1H), 7.61-7.59 (d, J=8.0 Hz, 2H), 7.40-7.38(d, J=8 Hz, 2H), 7.30-7.25 (m, 2H), 4.44-4.40 (q, J=7.2 Hz, 2H), 2.64 (s, 3H), 2.21 (s, 3H), 1.44-1.40 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{21}H_{18}BrNO_4$: C 58.89, H 4.24, N 3.27; Found: C 58.21, H 4.11, N 3.19.

19. *Ethyl-5-acetyl-3-(4-bromobenzoyl)-2-ethylindolizine-1-****carboxylate 2o***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 442.2; ^1H NMR (400 MHz, $CDCl_3$): δ; 8.84-8.82 (d, J=7 Hz, 1H), 7.58-7.56 (m, 2H), 7.44-7.30 (m, 4H), 4.45-4.41 (q, J=7.2 Hz, 2H), 2.78-2.74 (q, J=7.2 Hz, 2H), 2.61 (s, 3H),1.46-1.42 (t, J=7.2 Hz, 3H), 1.04-1.00 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{22}H_{20}BrNO_4$: C 59.74, H 4.56, N 3.17; Found: C 60.52, H 4.52, N 3.04.

20. *Diethyl-5-acetyl-3-(4-bromobenzoyl)indolizine-1,2-dicarboxylate* ***2p***

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 486.2; ^1H NMR (400 MHz, $CDCl_3$): δ 8.58-8.56 (d, J=7 Hz, 1H), 7.78-7.76 (d, J=7.2 Hz, 2H), 7.66-7.64 (d, J=7.2 Hz, 2H), 7.60-7.58 (m, 1H),7.40-7.38 (m, 1H), 4.38-4.34 (q, J=7.2 Hz, 2H), 3.79-3.75 (q, J=7.2 Hz, 2H), 2.62 (s, 3H), 1.39-1.35 (t, J=7.2 Hz, 3H), 1.09-1.05 (t, J=7.2 Hz, 3H); Elemental analysis calcd (%) for $C_{23}H_{20}BrNO_6$: C 56.80, H 4.15, N 2.88; Found: C 56.4, H 4.09, N 2.75.

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Received on May 5, 2014.