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Efficient synthesis of indolizines and new imidazo[1,2-a]pyridines via the expected cyclization of aromatic cycloimmonium ylides with electron deficient alkynes and ethyl cyanoformate

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A B S T R A C T

Aromatic cycloimmonium ylides underwent smooth cyclization with electron deficient alkynes in presence of anhydrous K_2CO_3 in DMF solvent at room temperature to afford substituted indolizines. Ylides have also undergone expected cyclization with ethyl cyanoformate to produce imidazo[1,2-a]pyridines. The structures of these newly synthesized compounds have been confirmed by spectroscopic techniques and X-ray diffraction studies.

Keywords:

Indolizines

Cycloaddition

Imidazo[1,2-a]pyridines

Alkynes

Ethylcyanoformate.

Indolizines are aromatic organic compounds containing condensed five and six- membered rings with bridging nitrogen. They are isoelectronic with indole and represent a group of heterocyclic compounds structurally related to purines. Indolizine skeletons with different degrees of unsaturation are present in a wide variety of natural and unnatural azacyclic compounds. Most of the naturally occurring indolizines have been isolated from species of genus dendrobates (poison-arrow frogs); monomorium (ants); dendrobium (orchids); tylophora and the leguminosae family (plants). Indolizine alkaloids display broad spectrum of biological activities.[1]. Polyhydroxylated indolizine alkaloids are excellent inhibitors of biologically important path ways. These include the binding and processing of glycoproteins, potent glycosidase inhibitor activities, activity against AIDS and some carcinogenic cells as well as against other important pathologies.[2,3.] Indolizines are the simplest pyrroloazines, formally obtained by the condensation of a pyridine and a pyrrole ring, being isomeric to indole. This relatively simple indolizine skeleton offers the possibility of fine tuning certain properties by varying the number and type of substituents.[4,6.] Such an example is the synthesis of highly specific chemosensors obtained by linking 7-substituted indolizines to a cyclodextrine moiety.[9.] Several synthetic methods for obtaining indolizines are known, one of

the most versatile being *N*-ylide 1,3-dipolar cycloadditions.[7,8.] These have been successfully applied for the synthesis of a number of substituted indolizines and offer the advantages of a few reaction steps and simple work-up. Furthermore, the method has recently been reconsidered as a one-pot multicomponent process.[10,11.]

A careful look at the indolizine framework would logically suggest that one step or one-pot simultaneous tandem construction of the N-C bond and C-C bond on to six- membered nitrogen heterocycles (piperidine/pyridine), in an appropriately organized manner, using a suitable reagent would lead to the formation of the desired azabicyclo(4,3,0)nonane frame work.[12,13.]

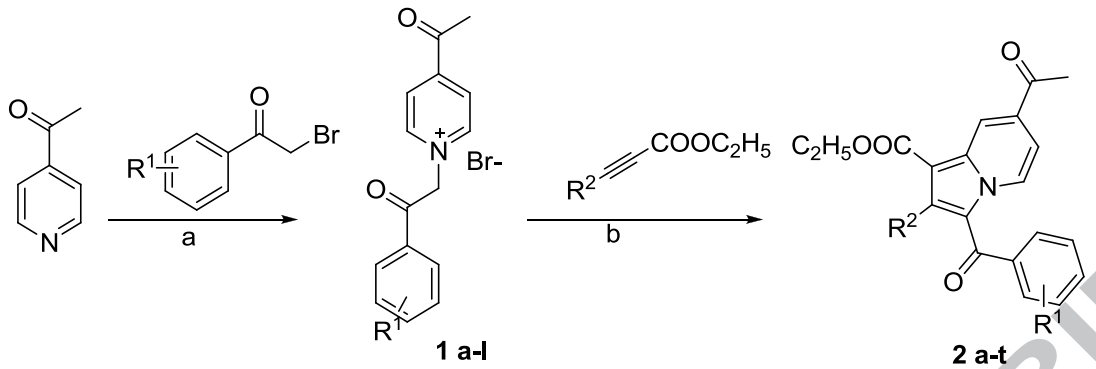
Typical molecular constructions of indolizines fall in to three classes.

a. Condensation reactions of a 2-alkylpyridine with acid anhydrides (Scholta reaction)[14] or α-haloketones (Tschitschibabin reaction).[15.]

b. Reaction of an α-unsubstituted pyridine with a three- carbon fragment such as an acyl or aryl substituted allyl halides or esters[16] and methyl propiolates.[17.]

c. Reaction of pyridinium N-methylides generated from pyridinium salts under K_2CO_3,[18], pyridine and carbenes[19] or N-trimethyl silyl methyl pyridinium triflates under fluoride ion.[20] with acetylenes or reaction of pyridinium N-methyllides with ethylene in the presence of an oxidant.[21.] The third route has been utilized for the synthesis of indolizines (Scheme 1) in the present investigation. Acetylenes bearing one electron withdrawing group and one electron donating group is an additional factor.

N-Heterocyclic ylides were prepared by stirring substituted pyridines with substituted phenacyl bromides separately in the presence of acetone at room temperature. The solids were filtered and dried under vacuum and used as such. The ylides obtained were up to 96-99% 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 K_2CO_3 and DMF as a solvent. The reaction time has been drastically reduced to just 30 minutes with constant stirring. 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) Acetone, rt; b) K_2CO_3, DMF, rt, 30 mins.

Table 1

Synthesis of pyridinium bromides (**1a-l**) and indolizine derivatives (**2a-t**).

Comp	R^1	Yield (%)	Comp	R^1	R^2	Yield (%)
1a	4-H	99.0	**2a**	2-Cl	H	70
1b	4-F	98.3	**2b**	2-Cl	CH_3	66
1c	4-Cl	98.5	**2c**	2-Cl	C_2H_5	60
1d	4-Br	98.8	**2d**	2-Cl	$COOC_2H_5$	63
1e	4-CN	99.1	**2e**	2-NO_2	H	65
1f	4-CH_3	98.18	**2f**	2-NO_2	CH_3	60
1g	2-Cl	97.4	**2g**	2-NO_2	C_2H_5	55
1h	2-NO_2	97.6	**2h**	2-NO_2	$COOC_2H_5$	64
1i	3-NO_2	96.8	**2i**	3-NO_2	H	77
1j	3-OCH_3	98.3	**2j**	3-NO_2	CH_3	71
1k	2,5-CF3	96.7	**2k**	3-NO_2	C_2H_5	64
1l	4-OCH_3	97.2	**2l**	3-NO_2	$COOC_2H_5$	70
			2m	3-OCH_3	H	69
			2n	3-OCH_3	CH_3	64
			2o	3-OCH_3	C_2H_5	60
			2p	3-OCH_3	$COOC_2H_5$	75
			2q	3,5-CF_3	H	70
			2r	3,5-CF_3	CH_3	70
			2s	3,5-CF_3	C_2H_5	66
			2t	3,5-CF_3	$COOC_2H_5$	61

In continuation of our research work, we tried to make use of N-pyridyl ylides for the construction of other heterocyclic moieties. We decided to test the 1,3-dipolar addition of aromatic cycloimmonium ylides to electron deficient nitriles.

In this regard, N-pyridyl ylides were treated with ethyl cyanoformate in the presence of triethylamine base using THF as a solvent with constant stirring at room temperature (Scheme 2 and 3). Interestingly, the expected formation of imidazo[1,2-a]pyridine was observed after stirring for 3-4 h. It was possible to isolate **twenty three** imidazo[1,2-a]pyridine derivatives and this would be a new method for the synthesis of imidazole ring fused with indolizine moiety. But the formation of imidazo[1,2-a]pyridines was not observed when N-pyridyl ylides were stirred with other nitriles such as cyanogen bromide, benzonitrile and benzoylcyanide possibly because of less positive charge on carbon of cyano group and stereochemistry. The formation of the imidazo[1,2-a]pyridine was confirmed by spectroscopic techniques. The position of nitrogen in imidazo[1,2-a]pyridine that is 1-position or 2- position was confirmed by single crystal X-ray diffraction studies of 4-methoxy imidazo[1,2-a]pyridine derivative. 3-Acetyl-pyridiniumbromides **4a-k** on addition to ethylcyanoformate produced ethyl-6-acetyl-3-(3-methoxybenzoyl)imidazo[1,2-a]pyridine-2-carboxylate **5a-k** and minor quantities-. (below 5%) of ethyl-8-acetyl-3-(3-methoxybenzoyl)imidazo[1,2-a]pyridine-2-carboxylates which are not isolated. Single crystal X-ray diffraction structure has been shown in Figure 1.

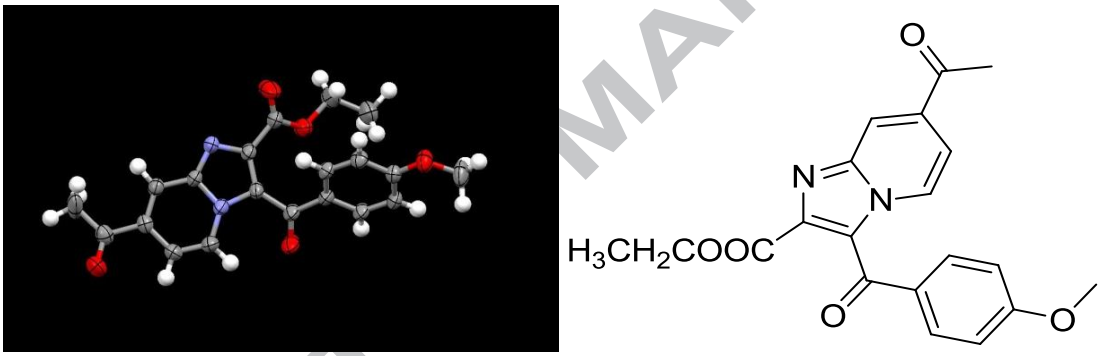
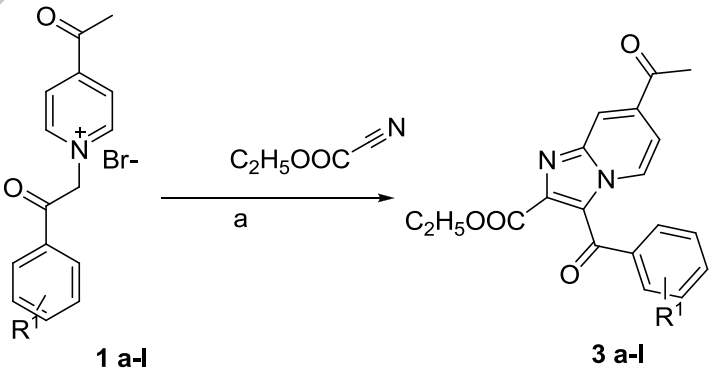


Fig 1 Single crystal X-ray crystallographic study of ethyl-7-acetyl-3-(4-methoxybenzoyl)imidazo[1,2-a]pyridine-2-carboxylate (**3l**).

All the imidazo[1,2-a]pyridines 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, IR, along with elemental analysis and x-ray studies.



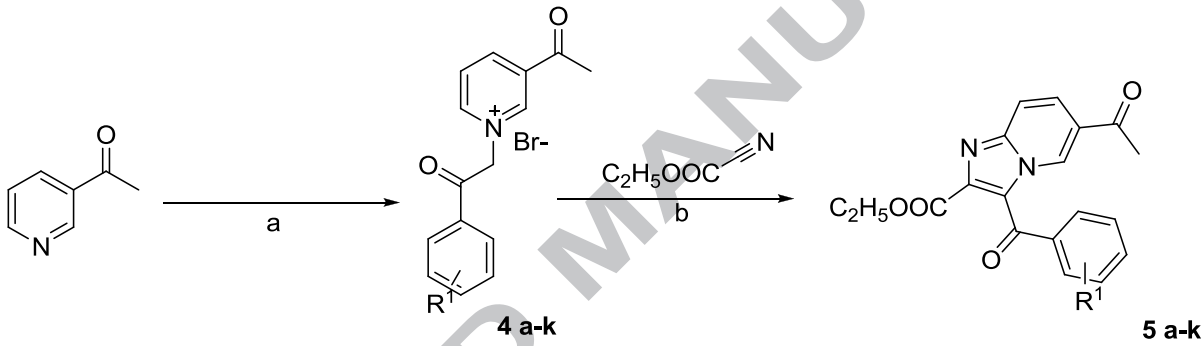
1 a-l **3 a-l**

Scheme 2. a) TEA, THF, rt, 2-5h.

Table 2

Synthesis of 7-acetyl- imidazo[1,2-a]pyridine derivatives (**3a-l**).

Comp	R^1	Yield (%)	Comp	R^1	Yield (%)
3a	4-H	64	**3g**	2-Cl	65
3b	4-F	60	**3h**	2-NO_2	69
3c	4-Cl	63	**3i**	3-NO_2	66
3d	4-Br	66	**3j**	3-OCH_3	60
3e	4-CN	67	**3k**	3,5-CF_3	65
3f	4-CH_3	69	**3l**	4-OCH_3	52



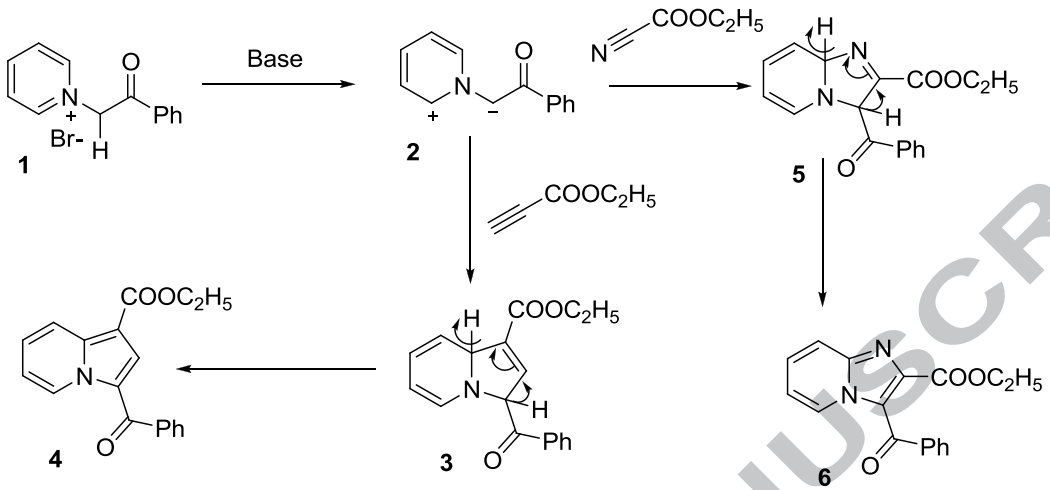
Scheme 3. a) Acetone, rt, b) TEA, THF, rt, 2-5h.

Table 3

Synthesis of pyridinium bromides (4a-k) and 6-acetyl- imidazo[1,2-a]pyridine derivatives (**5a-k**).

Comp	R^1	Yield(%)	Comp	R^1	Yield(%)
4a	4-H	99.2	**5a**	4-H	57
4b	4-Cl	98	**5b**	4-Cl	55
4c	4-Br	98.5	**5c**	4-Br	54
4d	4-CN	98.9	**5d**	4-CN	50
4e	4-CH_3	97.5	**5e**	4-CH_3	48
4f	2-Cl	97.3	**5f**	2-Cl	59
4g	2-NO_2	97.9	**5g**	2-NO_2	53
4h	3-NO_2	97.1	**5h**	3-NO_2	57
4i	4-OCH_3	98	**5i**	4-OCH_3	61
4j	4-F	97.6	**5j**	4-F	50
4k	3-OCH3	98.5	**5k**	3-OCH3	46

All the synthesized compounds have been purified by column chromatography and recrystallized with ethyl acetate. The structures have been confirmed by spectroscopic techniques like IR, ^{1}H-NMR, LC-MS, elemental analysis and x-ray studies.



Proposed mechanism for synthesis of substituted indolizines and substituted new imidazo[1,2-a]pyridines.

The research work is focused on the efficient synthesis of indolizines with drastically reduced time of reaction. It has also made an observation on new method of synthesis of imidazo[1,2-a]pyridines. The reactions performed are eco-friendly as they are carried out at room temperature. The publication of these facts would be of significant use for the scientific community.

Acknowledgement

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22. **Preparation of 4-acetyl-1-(2-oxo-2-p-tolylethyl)pyridiniumbromide 1f.** To a stirred solution of 4-acetylpyridine 1g (0.0082 mol) in dry acetone (5 mL), was added 1.75 g (0.0082 mol) of 4-methylphenacylbromide and stirred at room temperature for 5 h. Solids formed were separated out, filtered and dried under vacuum to afford 2.7 g (98.18 % yield) of 4-acetyl-1-(2-oxo-2-p-tolylethyl)pyridiniumbromide. Similarly, other compounds of the series **1a-l** were prepared.

Preparation of ethyl 7-acetyl-2-methyl-3-(3-nitrobenzoyl)indolizine-1-carboxylate 2j. To a stirred solution of 4-acetyl-1-(2-oxo-2-p-tolylethyl)pyridiniumbromide 0.5 g (0.0013 mol), in dry DMF, was added ethyl but-2-ynoate 0.169 g (0.00151 mol), K_2CO_3 0.416 g (0.0030 mol). It was stirred at room temperature for 30 min. Completion of reaction was monitored by TLC. After completion, reaction mass was evaporated under reduced pressure and diluted with ethyl acetate. Organic layer was washed with water, brine and dried with sodium sulphate. The crude compound was purified by column chromatography using a mixture of ethylacetate/hexane (1:5) to afford 0.38 g (71 % yield) of ethyl 7-acetyl-2-methyl-3-(3-nitrobenzoyl)indolizine-1-carboxylate. Similarly, other compounds of the series **2a-ar** were prepared.

Preparation of 3-acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridinium bromide 4d. To a stirred solution of 3-acetyl pyridine 1 g (0.0082 mol) in dry acetone (5 mL), was added 1.75 g (0.0082 mol) of 4-cyano phenacylbromide, stirred at room temperature for five hours. Solids were separated out, filtered and dried under vacuum to afford 2.82 g (98.9 % yield) of 3-acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridiniumbromide. Similarly, other compounds of the series **4a-k** were prepared.

Preparation of ethyl-7-acetyl-3-(4-methylbenzoyl)imidazo[1,2-a]pyridine-2-carboxylate 3l. A mixture of 4-acetyl-1-(2-(4-methoxyphenyl)-2-oxoethyl)pyridiniumbromide 0.5 g (0.0014 mol), in dry THF(5 mL) and ethylcyanoformate 0.156 g (0.0015 mol) was stirred in presence of triethylamine 0.322 g (0.0031 mol) for 5 hours at room temperature. Completion of reaction was monitored by TLC. The reaction mixture was evaporated under reduced pressure and diluted with ethyl acetate. Organic layer was washed with water, brine and dried with sodium sulphate. The crude compound was purified by column chromatography using a mixture of ethylacetate/hexane (1:3) to afford 0.273 g (52% yield) of ethyl-7-acetyl-3-(4-methoxybenzoyl)imidazo[1,2-a]pyridine-2-carboxylate. Similarly, other compounds of the series **3a-l** were prepared.

Preparation of ethyl 6-acetyl-3-(3-methoxybenzoyl)imidazo[1,2-a]pyridine-2-carboxylate 5k. To a stirred solution of 3-acetyl-1-(2-(3-methoxyphenyl)-2-oxoethyl)pyridiniumbromide 0.5 g (0.0014 mol), in dry THF(5 mL), was added ethylcyanoformate 0.156 g (0.0015 mol) and triethylamine 0.322 g (0.0031 mol). It was stirred it at room temperature for 5 hours. Completion of reaction was monitored by TLC. The reaction mass was evaporated under reduced pressure and diluted with ethyl acetate. Organic layer was washed with water, brine and dried with sodium sulphate. The crude compound was purified by column chromatography using a mixture of ethylacetate/hexane (1:3) to afford 0.243 g (46% yield) of ethyl-6-acetyl-3-(3-methoxybenzoyl)imidazo[1,2-a]pyridine-2-carboxylate Similarly, other compounds of the series **5a-k** were prepared

*Graphical Abstract (for review)

Efficient Synthesis of Indolizines and New Imidazo[1,2-a]pyridines via the Expected Cyclization of Aromatic Cycloimmonium Ylides with Electron Deficient Alkynes and Ethyl cyanoformate