Ammonium Acetate: An Efficient Reagent for the One-pot Synthesis of 5-Aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridines, 2,4-Diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones and α,α'-Bis(substituted benzylidene)cycloalkanones

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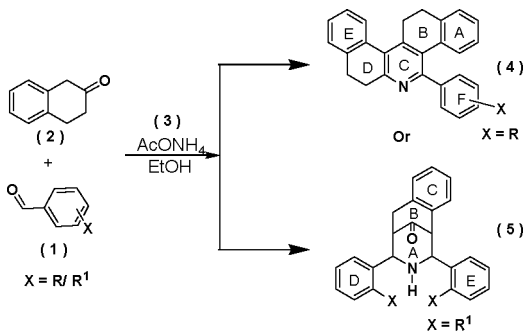
The condensation of cyclic ketone with aromatic aldehydes in the presence of ammonium acetate under ethanol media affords the corresponding 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine with excellent yield. This mild and efficient procedure with high yield is also applied to the synthesis of 2,4-diaryl-6,7-benzo-3-azabicyclo-[3.3.1]nonan-9-ones and α,α'-bis(substituted benzylidene)cycloalkanones.

Key Words: Cyclic ketone, Aromatic aldehyde, Ammonium acetate, Mannich reaction, Cross aldol condensation

Introduction

The Mannich reaction which involves the condensation of active methylene group of a ketone with aldehyde in the presence of ammonium acetate yields piperidone derivatives. In 1948, V. Balaiah *et al.*, reported that some piperidine derivatives could be obtained by Mannich reaction.[1] Furthermore, the present re-examination of the reaction with various cyclic ketones showed the formation of 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones (**5a**,**b**), α,α'-bis(substituted benzylidene) cycloalkanones (**8a-r**) and 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine derivatives (**4a-l**) which are interesting and unexpected. Phenanthridine derivatives are important core structures found in a variety of natural products and other biologically important molecules with a wide range of biological activities and applications, including antibacterial, antiprotozoal, and anti-cancer properties.[2,3] The Bischler-Napieralski cyclization has been used extensively to synthesize phenanthridine derivatives.[4,5] It is usually performed in the presence of P_4O_{10}, $POCl_3$, or PCl_5 at elevated temperature, thereby limiting the kind of functional groups those can be tolerated. Although several synthetic routes to substituted phenanthridines have been reported, most of them require multi-step synthesis, strict anhydrous conditions, poor yields or metal catalysts.[6-10] Thus, there is a need for more efficient, versatile and simpler synthetic methods of creating phenanthridines.

This study reports a new variant of the condensation reaction (Scheme 1). The one-pot reaction of 2-tetralone (**2**) with aromatic aldehydes (**1**) in the presence of ammonium acetate (**3**) in ethanol medium yields either an unexpected 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine (**4**) or an expected 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (**5**) in good quantities (Table 1).



R = 4-C_2H_5, 4-OC_2H_5, 4-OCH_2-CH=CH_2, 4-CH_3, 4-SCH_3, 4-F, 4-F, 4-CN, 4-OH, 3-F, 3-OH, 2-C_2H_5, 3,4-OCH_3
R^1 = 2-CH_3, 2-F

Scheme 1. General synthesis of 5-aryl-7,8,13,14-tetrahydrodibenzo-[*a*,*i*]phenanthridine (**4**) / 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones (**5**).

Table 1. The Reaction of 2-tetralone (**2**) with aromatic aldehydes (**1**) in presence of ammonium acetate (**3**).

Entry	Benzaldehyde (1)	Product	Yield (%)	Mp (°C)
1	4-ethoxy	**4a**	67	185 - 187
2	4-allyloxy	**4b**	95	158 - 160
3	4-cyano	**4c**	96	258 - 260
4	4-hydroxy	**4d**	53	268 - 270
5	4-fluoro	**4e**	64	192 - 194
6	4-ethyl	**4f**	80	164 - 166
7	4-methyl	**4g**	93	196 - 198
8	4-methylthio	**4h**	98	248 - 250
9	4-hydroxy	**4i**	65	66 - 68
10	3-fluoro	**4j**	67	154 - 156
11	2-ethyl	**4k**	88	154 - 156
12	3,4-dimethoxy	**4l**	89	190 - 192
13	2-fluoro	**5a**	96	184 - 186
14	2-methyl	**5b**	72	206 - 208

In our endeavour to extend the same reaction condition to 2-indanone (**6**) and 1-benzyl-4-piperidone (**7**) systems, we obtained α,α`-bis(substituted benzylidene)cycloalkanones instead of azabicyclo product (Mannich product). The mechanism of this reaction is that of cross aldol condensation. α,α`-bis(substituted benzylidene)cycloalkanone derivatives possess a broad spectrum of biological activities.[11,12] Recently our research group found the anti-cancer activity of its related analogues.[13] Thus, the synthesis of α,α'-bis(substituted benzylidene)cycloalkanones has attracted the attention of authors. Cross aldol condensation is classically carried out using acid or base.[14,15] However, this process suffers from reverse and side reactions resulting in low yields of the products. Subsequently improved methodologies have been reported where different complexes of metal(II) ions, such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II) were used as catalysts,[16] but yields have been less than 38%. Various other reagents[17-21] such as $(EtO)_4Si/CsF$ or KF, Cp_2ZrH_2-$NiCl_2$, Rh(III) porphyrin, Cp_2TiPh_2, BMPTO under microwave irradiation, $RuCl_3$, $TiCl_3OTf$, $FeCl_3$-[bmim][BF_4], SmI_3, KF-Al_2O_3 under ultrasound irradiation, TMSCl-NaI, H_2SO_4-SiO_2, Yb(OTf)$_3$, Et_2NTMS-LPDE, $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ under microwave irradiation[22] and LiOH[23] were used to catalyze the condensation reaction. In most cases, the yields were observed to be good at stringent reaction conditions, e.g., high temperature, sealed tube heating and longer reaction time. Further, the easy-evaporation of the solvents, such as THF, alcohol or MeCN, used in the traditional process proved difficult for reuse after the reaction. This might also cause heavy environment pollution in the event of large scale production. Since environment benign protocol is the hot topic of the current chemical Research and Development activities, it is appropriate that a commercially available and environmentally safe reaction process cherishes greater application value. In this context, there is still scope to develop a mild and more efficient method for the preparation of these compounds.

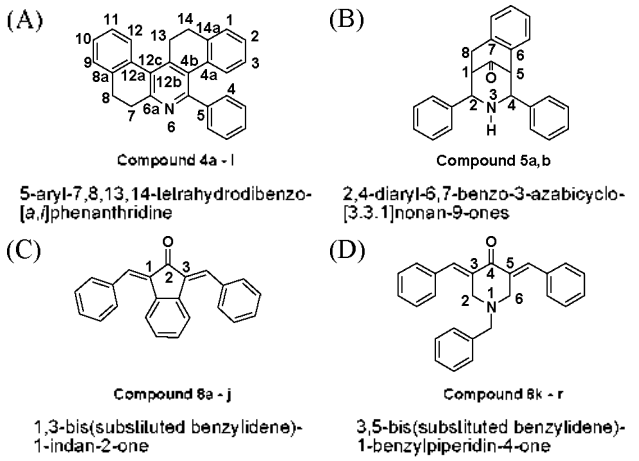
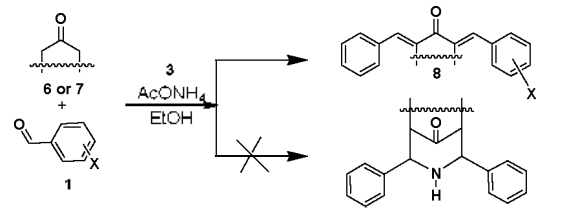


Figure 1. General structure of synthesized compounds.



Scheme 2. General synthesis of α,α`-bis(substituted benzylidene) cycloalkanoes.

Table 2. The reaction of 2-indanone (**6**) with aromatic aldehydes (**1**) in presence of ammonium acetate (**3**).

Entry	Benzaldehyde (**1**)	Product	Yield (%)	Mp (°C)
1	Benzaldehyde	**8a**	84	98 - 100
2	4-methoxy	**8b**	72	156 - 160
3	2-methoxy	**8c**	78	108 - 110
4	4-chloro	**8d**	83	182
5	2-chloro	**8e**	89	136
6	4-methyl	**8f**	89	78 - 80
7	2-methyl	**8g**	89	128 - 130
8	3-hydroxy	**8h**	85	200 - 202
9	4-ethoxy	**8i**	90	106 - 108
10	4-hydroxy3-methoxy	**8j**	78	128 - 130

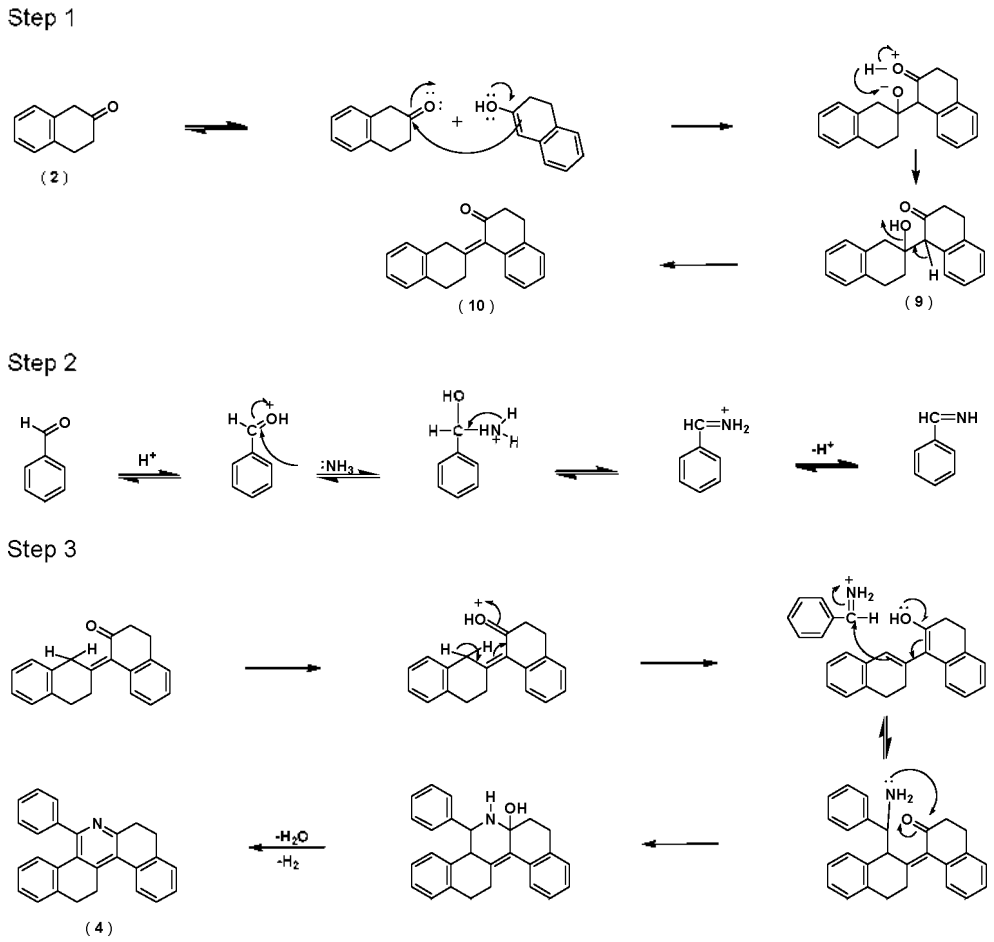
Results and Discussion

This study has a dual aim.

1. To know more about the unexpected 5-aryl-7,8,13,14-tetrahydrodibenzo[*a,i*]phenanthridines. Undoubtedly, the substituted aldehyde contributed to the geometric skeleton. The reaction of 2-tetralone (**2**) with aromatic aldehydes (**1**) and ammonium acetate (**3**), leads to expected 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones(**5**) and a new compound, which was identified as 5-aryl-7,8,13,14-tetrahydrodibenzo-[*a,i*]phenanthridines (**4**). We have proposed a mechanism to explain these results (Scheme 3). It is clear that two molecules of the starting ketone participate in the reaction. The first step involves the aldol condensation of the 2-tetralone (**2**) induced by traces of acid to form the hydroxy ketone (**9**). The last step of this condensation involves the elimination of a water mole-

Table 3. The reaction of 1-benzyl-4-piperidone (**7**) with aromatic aldehydes (**1**) in presence of ammonium acetate (**3**).

Entry	Benzaldehyde (**1**)	Product	Yield (%)	Mp (°C)
1	Benzaldehyde	**8k**	85	152-154
2	4-methoxy	**8l**	83	150-154
3	2-ethoxy	**8m**	81	110-114
4	4-allyloxy	**8n**	80	110-114
5	3-hydroxy	**8o**	91	114-116
6	2-fluoro	**8p**	83	180-184
7	3-fluoro	**8q**	90	136-140
8	4-fluoro	**8q**	94	146-150



Scheme 3. Mechanism of phenanthridine formation. Step 1. Formation of Binaphthalenone, Step 2. Formation of Aldimine ion, Step 3. Formation of Phenanthridine.

cule and affords binaphthalenone (**10**). The reaction of enone with aldimine ion followed by loss of H_2O, loss of H_2 and aromatization (cyclization) affords the 5-aryl-7,8,13,14-tetrahydrodibenzo[*a,j*]phenanthridines (**4**). A similar mechanism that involves an aldol condensation of cyclobutanone and subsequent reaction with one nitrile and two nitrile molecules,[24,25] has been reported. The nucleophilic substitution of the aldehyde group using ammonium acetate affords the phenanthridine skeletal. Thus, the reaction of 2-tetralone with ammonium acetate was investigated with various substituted aldehydes. The results show that the reaction is a regiospecific process.

2. Formation of 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1] nonan-9-ones (**5a,b**) and α,α'-bis(substituted benzylidene)cycloalkanones (**8a-j** and **8k-r**). The formation of 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one is already well documented.[1] As far as we know, this is the first report on the synthesis of α,α'-bis(substituted benzylidene)cycloalkanone (**8a-j** and **8k-r**) catalyzed directly by ammonium acetate. We have observed that ammonium acetate is very suitable to catalyse the cross-aldol condensation of aromatic aldehydes with selective ketones. The compounds 1-benzyl-4-piperidone and 2-indanone showed a similar activity towards the condensation with aromatic aldehydes in the presence of ammonium acetate (Scheme 2). No cross-aldol condensation was observed when 1-benzyl-4-piperidone (or) 2-indanone was treated with aromatic aldehyde in the absence of ammonium acetate, indicating the catalytic role of ammonium acetate. Ammonium acetate is an easily available, cheap and safe reagent. In the present conversion, ammonium acetate was observed to be remarkably efficient. It acts as a "dual activation agent" for the preparation of Mannich Product and cross-aldol product. Ammonium acetate is a well known base to effect the mannich type reaction. In the case of 2-tetralone, depending on the position of the substituent in benzaldehyde, it either gives Mannich product or phenanthridine skeleton.[26,27] Aldimine formation is not favoured in *ortho* substituted benzaldehydes. However, it is favoured in the case of parent, *para* and *meta* substituted benzaldehydes. In *ortho*-ethyl benzaldehyde, the aldimine formation is favoured since steric hindrance is over powered by the high electron releasing nature of ethyl group. In 2-tetralone, keto-enol equilibria involved the phenanthridine formation. But it was not observed in 2-indanone and 1-benzyl-4-piperidone. It could be due to differences in enolisation rates and basicity. In 2-indanone and 1-benzyl-4-piperidone, the basicity of ammonium acetate is enough to bring out cross-aldol condensation and NaOH, which is a well known catalyst for aldol condensation, is not required. Hence ammonium acetate is a versatile, efficient and powerful reagent for this

reaction. This protocol worked well with electron-withdrawing as well as electron-donating groups. It is important to note that the condensation proceeds smoothly with excellent yields upto 98%. All the reactions were free from by products.

Conclusion

In summary, we developed a highly convergent and rapid assembly of the phenanthridine skeleton through a simple condensation reaction. In all cases, the reactions afforded the products in good yields with excellent selectivity. The authors strongly believe that, this one-pot synthetic strategy will be a useful procedure for the synthesis of other phenanthridine derivatives. These novel heterocycles with two or more functionalities can be useful building blocks for further synthetic manipulations. α,α'-bis(substituted benzylidene)cycloalkanones resemeble curcumin analogue, since the authors tested them for anti-cancer activities and some of them are found to be of anti-cancer in nature. The highlight is that none of them are toxic.[13] The results show that this does not merely reveal the protocol but also provides a potential green alternative to traditional method and also for further drug development. Mild reaction condition, cost efficiency, simplicity in operations and separation, one-pot fashion are the significant features of this protocol.

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