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Three-component, one-pot synthesis of benzo[6,7]cyclohepta[1,2-*b*] pyridine derivatives under catalyst free conditions and evaluation of their anti-inflammatory activity

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ABSTRACT

An efficient three-component protocol is described for the synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives using β-chloroacroleins, 1,3-dicarbonyls and ammonium acetate under catalyst free conditions by using ethanol as reaction media. The mild reaction conditions, operational simplicity and high yields are the advantages of this protocol and the broad scope of this one-pot reaction makes this procedure promising for practical usages. All the final compounds were screened for anti-inflammatory activity. Among the compounds tested, the compounds **5a**, **5b**, **5c**, **5d**, **5f**, and **5k** exhibited significant inhibition of IL-1β and MCP-1 secretion as a measure of anti-inflammatory activity.

Benzocycloheptanone and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products and play a unique role in drug discovery program. They exhibit a wide range of biological activities such as cytotoxic, anticancer agents,[1–4] as high CB1 receptors,[5] and have very potent antagonistic activity.[5] In addition, these derivatives are widely used in diverse pharmaceutical applications, such as tricyclic antidepressants containing dibenzosuberone moieties mostly effecting the autonomic and central nervous systems and as traditional anti-depressants, like amitriptyline,[6] imipramine,[7] and noxiptiline[8] which continue to be used as first-line drugs in treating depressive disorders (Fig. 1). Pyridyl compounds are of interest to organic chemists in recent years owing to their wide spectrum of physiological activity.[9a–f] The condensed derivatives of pyridines play significant role in bioactive molecules, especially in the form of benzo[5,6]cyclohepta[1,2-*b*]pyridines which are structural analogs to benzosuberone. The benzo[5,6]cyclohepta [1,2-*b*]pyridine is an important core biologically active compound with diverse biological activities, such as antihistamine as well as antitumor and anti-inflammatory activities.[10a–j] It is a highly potent pharmacophore and widely used in drugmolecular design. Derivatives containing this group such as loratadine, desloratadine, rupatadine and lonafarnib could exhibit enhanced biological profile with fore mentioned biological activities. Because of the important aforementioned properties of benzocyclohepta[1,2-*b*] pyridines derivatives, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.

Due to enormous economic and ecological pressure,[11] multicomponent reaction (MCR) has gained importance and has been receiving considerable attention. Thereby MCR is becoming an attractive strategy for the schematic construction of useful novel and complex chemical compounds. The process efficiency concept is not only related to high chemical yield, but also to minimize the use of large amounts of harmful organic reagents, solvents, catalyst, and undesired chemical waste.[12] Developing a new MCR from easily available, effortless, and uncomplicated substrates is one of the most predominant research topics in organic chemistry. This novel schematic approach affords multiple molecules in a one-pot reaction and advances in a highly efficient and atom-economical manner to generate multiple and diverse new bonds, which saves time and energy by eluding multistep purifications of various intermediates.[13] Our recent studies have been focusing on the development of new synthetic pathways for the preparation of

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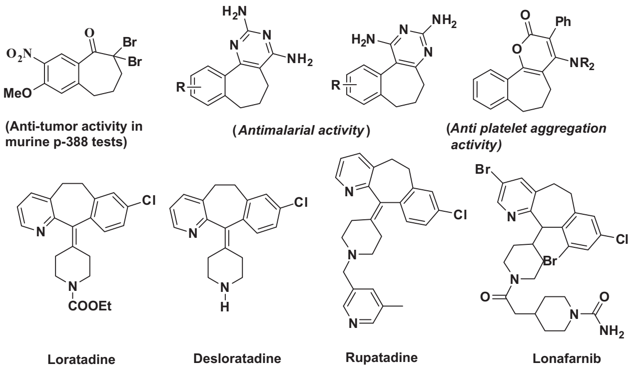
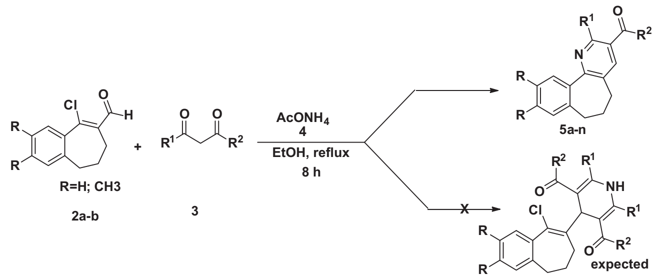


Figure 1. Representative examples of biologically active benzosuberones.



Scheme 1. Synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives. The reaction was performed with β-chloroacroleins (**2**) [0.42 mmol], 1,3-dicarbonyls (**3**) [0.42 mmol] and ammonium acetate (**4**) [0.84 mmol] in ethanol at reflux for 8 h. Yields are given after column chromatography.

cycle compounds, which was based on the use of cascade or one-pot reactions.[14]

In a recent articles Jagath Reddy et al.[15] and Thoraya et al.[16] found that, β-enaminone are key intermediate for the synthesis of these substituted pyridines by using acetic acid and Mont-morillonite K10 in 2-propanol and our literature survey revealed that the synthesis of these pyridines was not achieved using β-chloroacroleins and 1,3-dicarbonyls as starting materials. However, these methods suffer from low yields and exhibit limited substrate tolerance and reactivity. Keeping this in mind, we envisioned the catalyst-free three-component reaction of β-chloroacroleins, 1,3-dicarbonyls and ammonium acetate to give benzo[6,7]cyclohepta[1,2-*b*]pyridines using ethanol as reaction medium. To the best of our knowledge, there is no report concerning the catalyst-free three component synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridines. This process was established for the first time for the tandem construction of the benzocycloheptapyridines.

In continuation to our program toward the development of new protocols and their applications in the development of new synthetic pathways for the preparation of cycle compounds, we herein, report the synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridines from β-chloroacroleins and 1,3-dicarbonyls which was based on the use of cascade or one-pot reactions.[14]

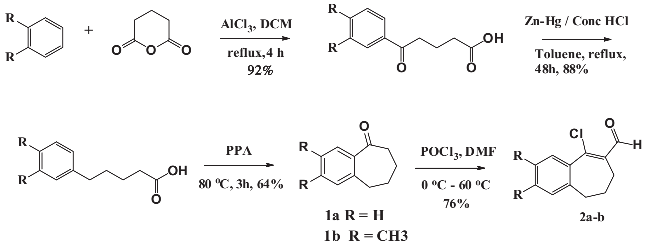
As part of our continuous research in the field of biologically active heterocyclic compounds. We examined the reaction between (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde, 1,3-dicarbonyls and ammonium acetate without using any catalyst. It is known that this reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with 2 equiv of a β-ketoester in the presence of ammonia source (Hantzsch dihydropyridine synthesis)[17a–c] and that this product might be useful in biological screening purpose. With this concept in mind, we began to investigate the reaction with (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde (β-chloroacroleins). An ethanol solution of (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde, 1,3-dicarbonyls with NH_4OAc as amine source was stirred at reflux for 8 h without using any catalyst. Surprisingly, the reaction proceeded smoothly in the absence of catalyst to offer an unexpected product benzo[6,7]cyclohepta[1,2-*b*]pyridine derivative which is confirmed by different spectroscopic data (Scheme 1).

The key intermediate (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde (**2a**–**b**) was synthesized using Vilsmeier Haack Arnold reaction[18] of substituted benzosuberones (**1a**–**b**) by treating with $POCl_3$, dimethylformamide in 84–87% yield. The structures of all the synthesized compounds were confirmed by spectral data (^1H NMR, ^{13}C NMR, FTIR and ESI-MS). In the ^1H NMR spectra, the presence of characteristic singlet at δ 10.33 ppm representing one proton provided evidence for the formation of carbaldehyde **2b**. The required starting compounds were synthesized from Fridel–Craft's acylation of aromatic hydrocarbons with glutaric anhydride furnishing aryl butyric acids which on Clemmenson reduction followed by cyclization with excess polyphosphoric acid gave substituted benzosuberones **2a**–**b** (Scheme 2).

Synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives (**5a**–**n**) was accomplished by Hantzsch type reaction via Michael addition which involves reaction of aldehydes **2**, 1,3-dicarbonyls (**3**) with NH_4OAc as amine source. Generally, such type reactions are carried in the presence of acidic catalysts. However, in the present study, more satisfactory results were obtained by carrying out the reaction without using any catalyst.

First, we selected 9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde, methylacetoacetate and ammonium acetate as substrates and examined the reaction with different solvents at reflux temperatures ranging from 8 to 12 h. The best results were obtained when ethanol was used as a solvent at reflux temperatures for 8 h. After preliminary experimentation, it was found that a mixture of 1 equiv of 9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde, methyl acetoacetate and 2 equiv of ammonium acetate in the presence of ethanol at reflux temperature for 8 h afforded methyl-2,9,10-trimethyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carboxylate **5a** (Table 3, entry **a**) in 85% yield. Subsequently, we investigated on the use of different solvents for the purpose. In aprotic solvents such as benzene and toluene, the reaction was very slow and resulted in lower product yield. Similar results were obtained in other solvents such as THF, acetonitrile. On the other hand, performing the reaction using protic solvents such as EtOH or MeOH; EtOH improved not only the rate of reaction but also the yield of product as compared to MeOH. Finally, EtOH proved promising as a solvent of choice for further reactions (Table 1, entry 1).

Various commercially available synthetic equivalents of ammonia were tested to access pyridine derivative **5a** (Table 2). Finally the ammonium acetate with 2 equiv was proved to be the best



Scheme 2. Synthesis of (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehydes.