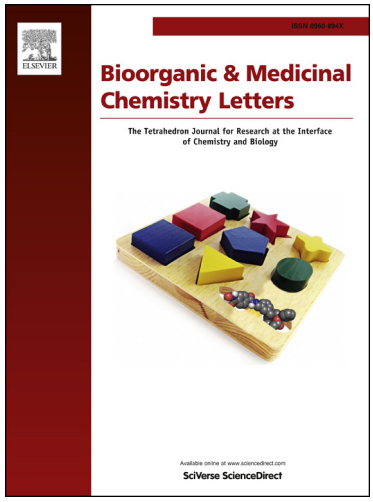

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PII: S0960-894X(15)30391-7
DOI: http://dx.doi.org/10.1016/j.bmcl.2015.12.078
Reference: BMCL 23439

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 21 October 2015
Revised Date: 17 December 2015
Accepted Date: 22 December 2015

Please cite this article as: Sajja, Y., Vulupala, H.R., Bantu, R., Nagarapu, L., Vasamsetti, S.B., Kotamraju, S., Nanubolu, J.B., 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, *Bioorganic & Medicinal Chemistry Letters* (2015), doi: http://dx.doi.org/10.1016/j.bmcl.2015.12.078

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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

Yasodakrishna Sajja[a], Hanmanth Reddy Vulupala[a], Rajashaker Bantu[a], Lingaiah Nagarapu[a*], Sathish Babu Vasamsetti[b], Srigiridhar Kotamraju[b], Jagadeesh Babu Nanubolu[c]

[a]*Organic Chemistry Division-II (CPC), CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad- 500007, India.*
[b] *Centre for Chemical Biology, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad-500007, India.*
[c]*Centre for X-ray Crystallography,, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad-500007, India*

Fax: + 91 40 27193382; Tel: +91 40 27191509; E-mail: lnagarapuiict@yahoo.com/nagarapu@iict.res.in

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
One-pot reaction,
Ammonium acetate,
Benzosuberone,
Catalyst free conditions,
Vilsmeier Haack Arnold reaction,
Anti-inflammatory activity.

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-1*β* and MCP-1secretion 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 (Fig1). 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 analogues 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 cycle compounds, which was based on the use of cascade or one-pot reactions.[14]

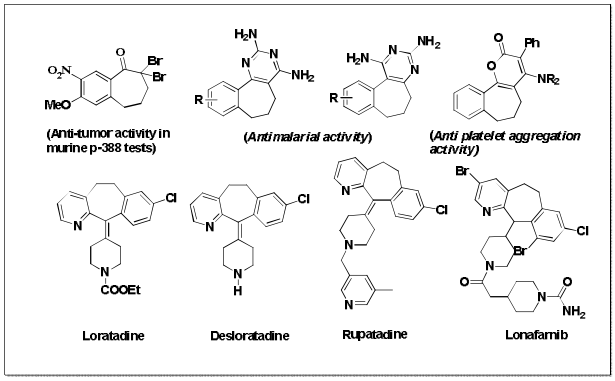
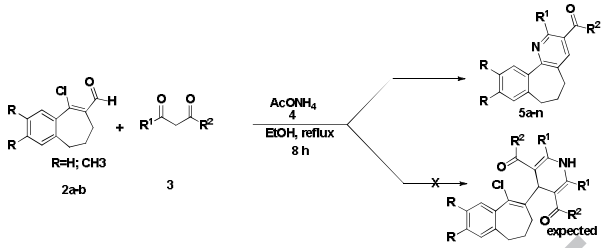


Figure 1: Representative examples of biologically active benzosuberones.

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 towards 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]

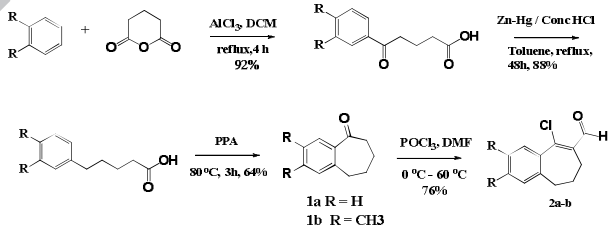
As part of our continuous research in the field of biologically active heterocyclic compounds. We examined the reaction between (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde ,1,3-dicarbonyls and ammonium acetate without using any catalyst. It is known that this reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents 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 8h 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 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.

Scheme 1: Synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives.

The key intermediate (Z)-9-chloro-6,7-dihydro-5H-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 (^{1}H NMR, ^{13}C NMR, FTIR and ESI-MS). In the ^{1}H 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).



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

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 8-12 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 equivalent of 9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde, methyl acetoacetate and 2 equivalents 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**).

Table 1: Optimization of the solvent.

Entry	Solvent	Time(hr)	Yield (%)[a]
1	Ethanol	8	85
2	Methanol	10	60
3	Benzene	15	20
4	Toluene	15	10
5	Tetrahydrofuran	15	Traces
6	Acetonitrile	20	10

[a]Isolated yield after column chromatography

Various commercially available synthetic equivalents of ammonia were tested to access pyridine derivative **5a** (Table 2**).** Finally the ammonium acetate with two equivalents was proved to be the best ammonia source for the preparation of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives.

Table 2: Screening of the ammonia source in the test reaction

Entry	Ammonia source	Amount(equiv.)	Acid cat.	Yield(%)[a]
1	NH_4OAc	1	NO	50
2	NH_4OAc	1.5	NO	60
3	NH_4OAc	2	NO	85
4	NH_4Cl	2	NO	traces
5	$(NH4)_2CO_3$	2	NO	traces
6	NH_4OAc	2	AcOH	40
7	NH_4OAc	2	HCl	-
8	NH_4OAc	2	H_2SO_4	-
9	NH_4OAc	2	MsOH	traces
10	NH_4OAc	2	CF_3SO_3H	traces

[a]Isolated yield after column chromatography

The formation of compound **5a** was evident from the ESI-MS spectrum with the appearance of $[M+H]^+$ peak at *m/z* 296, while the FT-IR spectrum revealed the presence of absorption band at 1721 cm^{-1} which attributed to the presence of ester group, which was obviously absent in **2b** and the presence of ring carbonyl group in **2b** was resonated at 1670 cm^{-1}. Further, in IR spectrum, a broad absorption band at 1543 cm^{-1} indicated the formation of pyridine ring in **5a**. Similarly, the ^1H NMR spectrum of **5a** exhibited singlet at δ 8.04 due to the presence of pyridine ring proton. Aromatic protons showed multiplet at δ 7.52-7.01 whereas ester protons appeared as singlet at δ 3.94. To provide further evidence for the proposed structure, ^{13}C NMR was recorded, which showed peaks at δ 52.0 due to ester carbon atoms which were absent in the starting material. Ester carbonyl carbon gave signals at δ 167.3, whereas methyl carbon attached to pyridine ring showed a signal at δ 24.6. The proposed structure was substantiated by its mass spectra, which exhibited molecular ion peak at *m/z* 296 $[M+H]^+$.

To further conform the structure of the product based on the X-ray diffraction data analysis (Crystal data for compound **5a**, AN30): $C_{19}H_{21}NO_2$, M = 295.37, colorless block, 0.36 x 0.32 x 0.24 mm^3, triclinic, space group P-1 (No. 2), a = 7.4807(8), b = 7.7633(9), c = 14.8941(17) Å, α = 77.051(2), β = 79.129(2), γ = 71.681(2)°, V = 793.70(15) $Å^3$, Z = 2, D_c = 1.236 g/cm^3, F_{000} = 316, CCD area detector, MoKα radiation,λ = 0.71073 Å, T = 293(2)K, $2\theta_{max}$ = 50.0º, 7659 reflections collected, 2790 unique (R_{int} = 0.0186), Final *GooF* = 1.027, *R1* = 0.0463, *wR2* = 0.1256, R indices based on 2141 reflections with I >2σ(*I*) (refinement on F^2), 203 parameters, μ = 0.080 mm^{-1}. CCDC 997653 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk.

X-ray diffraction data for the compound were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method.[19] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 2516 reflections for AN30 (**5a**). Integration and scaling of intensity data were accomplished using SAINT program.[19] The structures were solved by Direct Methods using SHELXS97[20] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[20] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H)$ = 1.2U_{eq} (C) or 1.5U_{eq} for methyl atoms. The structure is shown in Fig 2.

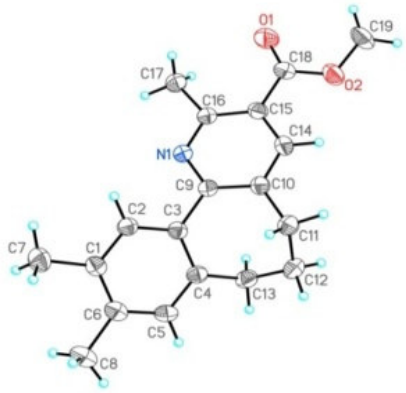
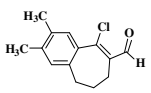
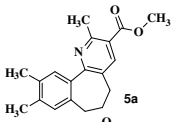
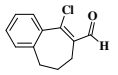
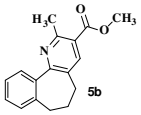
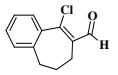
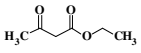
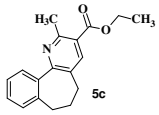
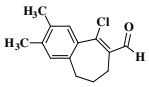
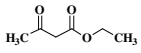
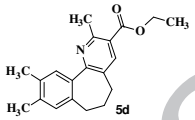
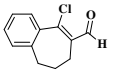
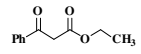
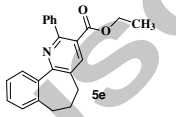
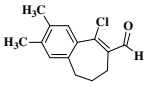
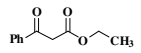
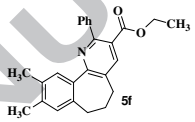
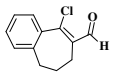
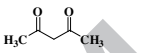
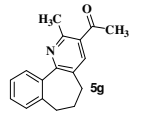
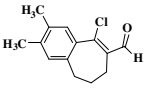
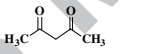
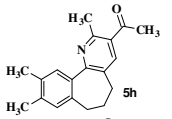
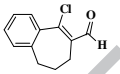
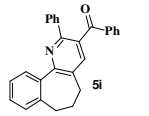
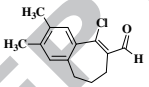
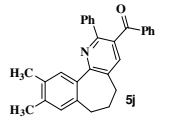
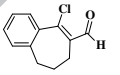
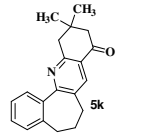
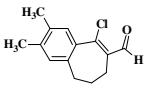
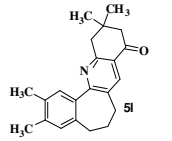
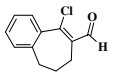
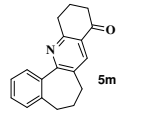
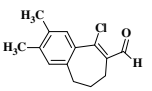


Figure 2: X-ray crystal structure of AN30 (**5a**)

Encouraged by this success, we attempted the reaction of substituted (*Z*)-9-chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehydes (*β*-chloroacroleins), with a range of other different substituted 1,3-dicarbonyls, and ammonium acetate with ethanol as a reaction medium under similar conditions furnishing the respective benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives **5a-5n** (Scheme 1) in excellent yields. The optimized results are listed in Table 3.

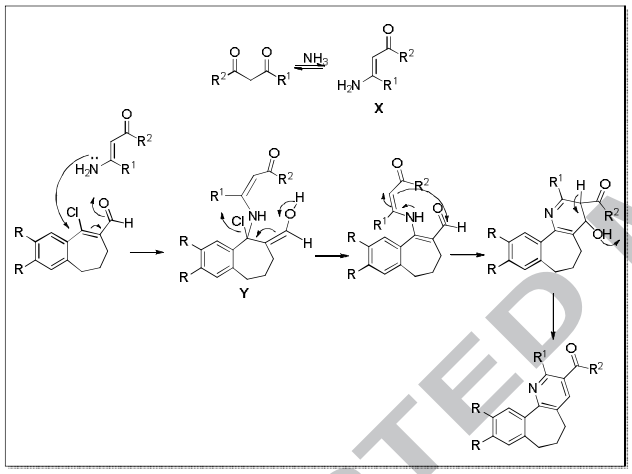
Table 3: Synthesis of benzo[6,7]cyclohepta[1,2-b]pyridine derivatives

Entry	Substrate	1,3-dicarbonyls	Product5(a-n)[a]	Yield (%)[b,c]
1	 2b		 5a	85
2	 2a		 5b	84
3	 2a		 5c	82
4	 2b		 5d	83
5	 2a		 5e	80
6	 2b		 5f	80
7	 2a		 5g	79
8	 2b		 5h	80
9	 2a		 5i	82
10	 2b		 5j	83
11	 2a		 5k	89
12	 2b		 5l	90
13	 2a		 5m	91
14	 2b		5n	92

[a]The products were characterized by 1H NMR, IR and Mass Spectroscopy; [b]Isolated yield after column chromatography;[c]All the reactions were performed for 8h.

In general, all the reactions were very clean, and *β*-chloroacroleins are vinyl chlorides, which were activated in the presence of an electron-withdrawing group which have been utilized extensively for the synthesis of various benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives in good to high yields (79-92%) (Scheme 1 and Table 3). Various 1,3-dicarbonyls containing acyclic and cyclic substituent's showed easy product formation in good to high yields. Results showed that the cyclic substituent groups like 5,5-dimethylcyclohexane-1,3-dione and cyclohexane-1,3-dione play a significant role in the reactivity of the substrate and high yields were obtained (Table 3: entry **k, l, m, n**; 89, 90, 91, 92 % yield).

On the basis of all our experimental results, we have proposed the plausible mechanism for the formation of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives (Scheme 3). The hypothesis supported the fact that the reaction was initiated by ammonium acetate, which reacted with 1,3-dicarbonyls for the formation of enamine (X). The enamine (X) undergoes Michael addition with *β*-chloroacroleins to give an intermediate (Y). Further, the mechanism follows dehydrohalogenation, intramolecular cyclization and aromatization giving rise to the formation of compounds **5(a-n)** (Scheme 3).



Scheme 3. Plausible mechanism for the synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives

All the synthesized compounds of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives (**5a-n**) were screened for anti-inflammatory activity in PMA (Phorbol 13-Myristate 12-acetate) stimulated THP-1 monocytes by measuring the levels of IL-1*β* and MCP-1 with reference to piroxicam and the results are summarized in the Table 4. Among the tested compounds **5a**, **5d** and **5f** inhibited both IL-1*β* and MCP-1 activities. Compound **5b**, **5c** and **5i** showed only IL-1*β* activity whereas compounds **5h** and **5k** showed only MCP-1 activity.

It was found that compounds **5a**, **5b**, **5c**, **5d** showed potent activity against IL-1*β* with IC_{50} 8.6, 8.2, 6.9, 6.5 *μ*M. Compounds **5d**, **5f**, **5k** showed potent activity against MCP-1 with IC_{50} 8.5, 8.5, 5.6 *μ*M. Under the same condition, piroxicam showed an IC_{50} of 18.1 *μ*M (IL-1*β*) Table 4. On the other hand, none of the compounds had any effect on cell viability even at 20 *μ*M concentration. This result clearly indicates that the anti-inflammatory activities of these compounds are not due to the induction of cytotoxicity in these cells. The structure activity relationship revealed that the activity is further enhanced in the presence of ester group on pyridine ring in combination with methyl group on C2 position. Further studies are underway to optimize the lead molecule.

Table-4: Inhibition efficacy of the synthesized compounds **5a-n** against inflammation for IL-1*β* and MCP-1.[a]

S.No	Compounds	IL-1β (IC_{50} μM)[b]	MCP-1 (IC_{50} μM)[b]	% cell viability[d]
1	**5a**	8.6 ± 0.9	16 ± 1.8	98.3±3.5
2	**5b**	8.2 ± 1.5	NA	97.2±1.3
3	**5c**	6.9 ± 1.7	NA	99.2±2.8
4	**5d**	6.5 ± 1.1	8.5 ± 2.1	95.9±3.1
5	**5e**	NA	NA	103.2±4.9
6	**5f**	18.2 ± 1.5	8.5 ± 0.8	97.6±2.7
7	**5g**	NA	NA	92.3±5.8
8	**5h**	NA	14.8 ± 1.5	97.6±3.6
9	**5i**	17.5 ± 0.7	NA	99.4±0.9
10	**5j**	NA	NA	101.3±2.3
11	**5k**	NA	5.6 ± 1.5	98.2±4.4
12	**5l**	NA	NA	105.2±3.8
13	**5m**	NA	NA	96.8±2.9
14	**5n**	NA	NA	97.1±4.0
	piroxicam[c]	18.1 ± 1.4	NT	98.1±2.2

[a] THP1 monocytes were pre-treated with 5, 10 and 20 μM concentrations of the above mentioned benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives (5 a-n) for 2 h followed by simulation with 100 nM of phorbol 13-myristate 12-acetate (PMA) to induce inflammation for a period of 48 h. At the end of the treatment, conditioned media was collected and levels of IL-1β and MCP-1 were measured by ELISA as described in the Materials and Methods.

[b] IC_{50} values are mean ± SD of three independent experiments, NA: indicates activity >20 μM.

[c] Piroxicam, a known anti-inflammatory agent is used as a positive control.

[d] THP-1 cell viability with synthesized compounds (20 μM).

In conclusion, we have demonstrated a highly efficient approach for the synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives by treatment of the corresponding 1,3-dicarbonyls with *β*-chloroacroleins and ammonium acetate by using ethanol as medium without addition of any catalyst. The synthetic approach demonstrated here is based on a simple one-pot procedure and allows for the syntheses of benzo[6,7]cyclohepta[1,2-*b*]pyridine is promisingly applicable for the syntheses of other pyridyl compounds. This method is simple, convenient and catalyst-free to produce the structural diversity in a one-pot process of various products (**5a**-**5n**). Among them six compounds (**5a**, **5b**, **5c**, **5d**, **5f**, and **5k**) showed impressive anti-inflammatory activities (IL-1*β* and MCP-1) at micro molar concentration which was found to be better than positive control i.e. piroxicam.

Acknowledgements

The authors are gratefully acknowledged to the **DST-SERB/EMEQ-078/2013** for the financial support. YK and HR thanks CSIR, New Delhi for research fellowships.

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Supplementary Information

Experimental section and Copies of the ^{1}H, $^{13}CNMR$ and ESI-MS spectra for some of the important compounds.

Graphical Abstract

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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Yasodakrishna Sajja[a], Hanmanth Reddy Vulupala[a], Rajashaker Bantu[a], Lingaiah Nagarapu[a*], Sathish Babu Vasamsetti[b], Srigiridhar Kotamraju[b], Jagadeesh Babu Nanubolu[c]

An efficient protocol has been developed for the synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives with *β*-chloroacroleins, 1,3-dicarbonyls and ammonium acetate without any catalyst as potent anti-inflammatory agents.