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Efficient, facile metal free protocols for the bromination of commercially important deactivated aminoanthracene9,10diones

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ABSTRACT

Highly efficient, mild synthetic protocols were developed for the oxidative bromination of deactivated aminoanthracene-9,10-diones by using H_2O_2-HBr and *m*-CPBA-HBr in methanolic medium. Both the protocols offer excellent bromine atom economy, good conversion (100%) along with high yield (82–93%) and high purity of desired product. The *N*-alkylated amines undergo *regio*-selective bromination to give selective *p*-bromo product. The commercial availability of all the starting materials, simple reaction procedure and ease of work up, and easily amenable for scale up demonstrated commercial feasibility of both the protocols.

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Brominated aminoanthracene-9,10-diones are found as important scaffolds in dyes industries since bromination enhances the brightness and the bleaching fastness of the dye. Consequently they serve as precursors for the syntheses of various disperse, vat, and acid dyes which are commercially exploited for various applications.[1–5] These brominated intermediates also serve as building blocks in the synthesis of synthetic polymer fibers,[6] chinnolines and isoindazole synthesis,[7] Hg^{2+} ion sensors,[8] pharmaceuticals[9,10] (synthesis of antitumor antibiotic dynemicins).[11] Similarly, the electron deficient 3-bromobenzanthrone has broad medicinal and synthetic applications in the synthesis of dG-C8 DNA adduct,[12] luminescent dyes for fluorescent probes,[13] violanthrene,[14] near infrared fluorescent dyes,[15] and perylene derivatives.[16] Although these brominated derivatives are versatile for various applications, it is difficult to carry out their bromination due to presence of electron withdrawing carbonyl groups which deactivated the ring towards electrophilic substitution.[17]

The classical methods for the bromination of aminoanthracene-9,10-diones involve the use of conc. H_2SO_4 (90–98%) and glacial acetic acid or mixture of these acids as a solvent.[18,19] The reaction require elevated temperatures (80–120 °C) and longer reaction time (10–20 h) for accomplishment. These all protocols inevitably use hazardous molecular bromine as brominating agent which is difficult to handle as well as afford only 50% bromine atom economy as the HBr generated during the course of reaction is not used for the further bromination[17–25] (Scheme 1).

In some of the cases, liquid bromine additions is performed at elevated temperature which is very hazardous operation in practice. Occasionally, molecular iodine, KI, Cu and $CuSO_4$ are also employed as catalyst to perform these transformations.[22–24] Many times the procedures are extremely tedious, complicated, and cumbersome as they involve frequent heating and cooling, multiple bromine addition steps and finally the reaction end up with mixture of mono and di-brominated products which in turn reduce the yield of desired product.[26,27] Thus, the excess use of hazardous chemicals, complicated operating procedures, lack of bromine atom economy, and product selectivity strongly demands the development of an improved protocol for bromination of these intermediates.

Recently the halogenation processes are profoundly modified to afford desired halogenated product in good yield, under mild conditions with improved selectivity. This resulted in development of various mild and efficient protocols for the halogenation reactions.[28–30] Of late the oxidative bromination has gained much attention due to its various advantages over conventional bromination protocols. The use of oxidizing agent along with bromine source resulted in formation of electrophilic bromonium ion which facilitates faster bromination of the substrate[31,32] additionally the reaction proceeds under mild conditions and product can be easily separated from reaction mass in high yield and purity. The most significant feature of this approach is attainment of 100% bromine atom economy as the use of oxidizing agent facilitates complete

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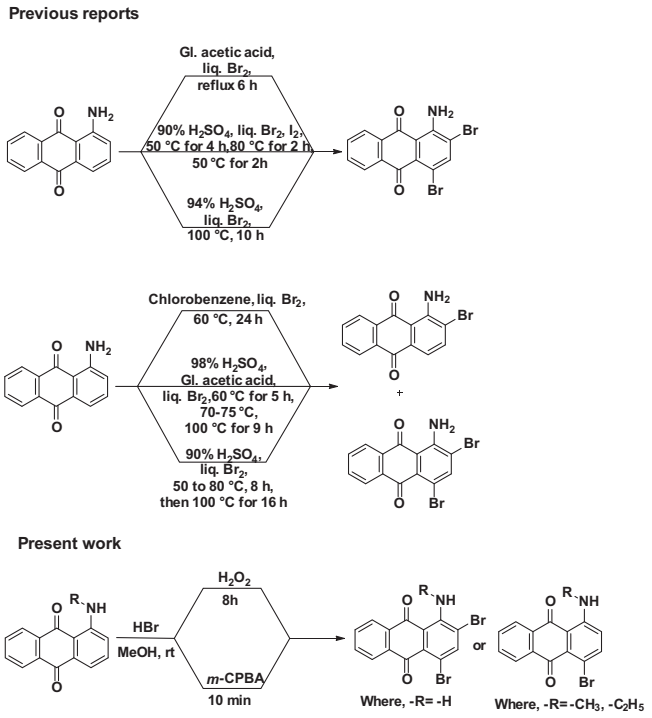


Scheme 1. Previous reports and present work.

consumption of bromine by oxidizing it to bromonium ion which lack in the traditional bromination protocols. Thus, the oxidative bromination serve as an efficient approach which overcomes the shortcomings of the conventional processes used for bromination of these intermediates.

Thus, in continuation of our previous work to develop efficient and selective oxidation protocols[32–38] herein we report two mild and easily amenable protocols viz. H_2O_2-HBr and *m*-CPBA-HBr for the oxidative bromination of deactivated aminoanthracene-9,10-diones in methanol at room temperature. The use of commercially available entities, such as H_2O_2, *m*-CPBA, HBr and methanol at ambient temperature with easy operational procedure enhances the commercial feasibility of both the protocols.

Results and discussion

The optimization of reaction parameters was carried out by taking 1-aminoanthracene-9,10-dione **1a** (1 equiv.) as key substrate, H_2O_2 (2 equiv.), and HBr (2 equiv.) (Table 1). The solvent screening study revealed that the bromination of **1a** efficiently proceeds in acetic acid and methanol under present conditions. Acetic acid gives 97% conversion for **2a** (Table 1, entry 2) whereas methanol gives 95% conversion for **2a** within 8 h at room temperature (Table 1, entry 9). The use of acetic acid was then ruled out as it gives a mixture of products during bromination of *N*-alkylated amine. In all other solvents, mixture of **2a** and **3a** was obtained (Table 1, entries 1, 3–7, 9–11). Unlike methanol, other alcohols failed to give high selectivity for **2a** under present conditions (Table 1, entries 10–16). In the case of ethanol only 23% selectivity was obtained for **2a** but the higher selectivity (77%) was observed for **3a** (Table 1, entry 10).

The H_2O_2 equivalents were varied to investigate its effect on the yield of **2a**. It was observed that, the yield of **2a** was increased with increasing the oxidant equivalents from 1.50 to 1.75 equivalents (Table 1, entries 17, 18) Further increase in the oxidant equivalents 2.15 did not show any significant influence on the yield of **2a** (Table 1, entry 19). The effect of other bromine sources such as KBr and NaBr was also investigated under present conditions (Table 1, entries 20, 21). In both the cases, traces of **2a** formation was observed after 24 h at room temperature.

After optimizing the solvent and oxidant equivalents we investigated the effect of other commonly used oxidizing agents on the bromination of **1a** (Table 2). To our surprise, *m*-CPBA showed exceptionally high reactivity towards oxidative bromination of **1a**. The oxidative bromination of **1a** with *m*-CPBA was completed within 10 min with 100% conversion at room temperature with 96% selectivity for **2a** (Table 2, entry 1). To the best of our knowledge, this is the fastest conversion obtained till date for the bromination of **1a**.

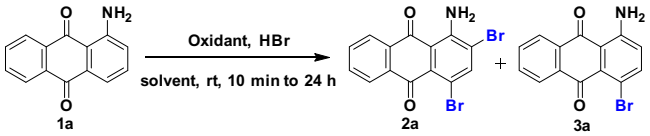
This encourages us to develop another protocol for the same transformation. Except these two oxidants, other oxidants failed to give any remarkable results under present conditions (Table 2, entries 2–9). Next to H_2O_2 and *m*-CPBA, Oxone was the only oxidant which gives high selectivity for **2a** but required 24 h (Table 2, entry 9). Thus, after extensive screening of the reaction parameters, the best results obtained for the oxidative bromination of **1a** are 2 equivalents of HBr, 2 equivalents of oxidant (H_2O_2 as well as *m*-CPBA) in methanol at room temperature.

Similar to H_2O_2-HBr, we also optimized conditions for *m*-CPBA–HBr system by taking **1a** as substrate. Except methanol, all other solvents failed to give high selectivity for **2a**. The oxidant equivalents study was also performed for 1, 1.5, 1.75 and 2.15 equivalents of *m*-CPBA which gives 34%, 56%, 70%, and 97% selectivity respectively for **2a** in 10 min. When the other bromine sources such as KBr and NaBr were used with *m*-CPBA, a mixture of **2a** and **3a** were obtained. The reaction performed with KBr resulted in formation of 54% of **2a** and 12% of **3a** whereas NaBr gave 50% of **2a** and 13% of **3a**.

With optimized conditions in hand, a series of substituted aminoanthracene-9,10-diones were executed by using both the methods and the results obtained were summarized in Table 3. All the reactions performed by using H_2O_2-HBr system required 8 h for completion, while that with *m-CPBA*-HBr completed within 10 min at room temperature to afford desired products in high yields. The aminoanthracene-9,10-diones bearing –Cl substituent **1b** and **1c** (at 1- and at 5-position respectively) gave respective brominated products in high yields at room temperature under both the methods (Table 3, entries 2, 3). The substrate **1e** which contains two amino functionalities; viz. unsubstituted and substituted (-NH_2 and –NHPh) afford selective di-bromination at ring bearing free amino group (Table 3, entry 5). Similarly, the substrate **1g** bearing –NH_2 and –OCH_3 groups gave selectively mono-bromination at position *ortho* with respect to –NH_2 group under both the methods (Table 3, entry 7). In order to check the selective mono bromination of the substrates such as **1a**, **1c**, **1d** and **1e**, which gave di brominated product we performed their reactions by taking 1 equivalent of HBr and 1 equivalent of H_2O_2 as well as *m*-CPBA. But, in all the cases a mixture of mono and di brominated products was obtained.

The *regio*-selective bromination of *N*-alkylated aminoanthracene-9,10-diones to *p*-bromo proceeds by using pyridine-bromine,[39] aluminum trichloride-liquid bromine-nitro benzene system,[40] liquid bromine with acetic acid[41] or mixture of acetic acid with propionic acid.[42] It was noticeable that the *N*-alkylated aminoanthracene-9,10-diones, **1i** and **1j** undergo *regio*-selective bromination under both the conditions at room temperature to give *p*-brominated product with excellent yields (Table 2, entries 9, 10). Even when 2 equivalents of HBr and 2 equivalents of H_2O_2 (as well as *m*-CPBA) were employed, only mono brominated product was obtained in both the methods. The substrate **1i** with H_2O_2-HBr system gives 86% yield within 8 h while with *m*-CPBA-HBr system afford 87% yield of **2i** within 10 min (Table 3, entry

Table 1
Optimisation of reaction parameters.[a]



Entry	Solvent	Oxidant equiv.	Time (h)	Conversion (%)[b]	
				2a	**3a**
Solvent study					
1	Toluene	2	24	57	43
2	Acetic acid	2	8	97	3
3	Ethyl acetate	2	24	62	38
4	Dichloromethane	2	24	59	41
5	Acetonitrile	2	24	64	36
6	DMF	2	24	32	18
7	DMSO	2	24	51	12
8	Water	2	24	13	–
9	Methanol	2	8	95	5
10	Ethanol	2	24	23	77
11	Glycerine	2	24	15	–
12	1-Propanol	2	24	–	Traces
13	2-Propanol	2	24	–	Traces
14	1-Butanol	2	24	–	Traces
15	2-Butanol	2	24	–	Traces
16	*tert.* Butanol	2	24	–	Traces
H_2O_2 equivalent study					
17	Methanol	1.50	24	53	17
18		1.75	24	74	11
19		2.15	8	96	4
Bromine source study					
20[c]	Methanol	2	24	Traces	–
21[d]		2	24	Traces	–

[a] Reaction conditions: **1a** (0.44 mmol, 1 equiv.), H_2O_2 (0.89 mmol, 2 equiv.), HBr (0.89 mmol, 2 equiv.), solvent 2 mL, temperature: room temperature.
[b] Conversion determined by HPLC by using area normalization method.
[c] KBr used as bromine source (2 equiv.).
[d] NaBr used as bromine source (2 equiv.).

Table 2
Effect of various oxidizing agents.[a]

Entry	Oxidant	Time	Conversion (%)[b]	
			2a	**3a**
1	*m*-CPBA	10 min	96	4
2	Performic acid	24 h	23	14
3	Peracetic acid	24 h	30	19
4	70% TBHP	24 h	19	58
5	Sodium percarbonate	24 h	38	32
6	Urea hydrogen peroxide	24 h	43	38
7	Sodium perborate	24 h	Traces	–
8	Potassium peroxydisulphate	24 h	Traces	–
9	Oxone	24 h	81	19

[a] Reaction conditions: **1a** (0.44 mmol, 1 equiv.), oxidant (0.89 mmol, 2 equiv.), HBr (0.89 mmol, 2 equiv.), methanol 2 mL, temperature: room temperature.
[b] Conversion determined by HPLC.

9). Similarly, the substrate **1j** gave 85% yield of **2j** with H_2O_2-HBr system within 8 h and 82% yield of with *m*-CPBA-HBr system within 10 min at room temperature (Table 3, entry 10). Thus, both the methods offer simple, convenient, and mild alternative for the preparation of *p*-bromo derivatives of *N*-alkylated aminoanthracene-9,10-diones.

The striking feature of the present work is bromination of electron deficient **1k** that requires sulphuryl chloride, liquid bromine and iodine as a catalyst with nitro benzene or acetic acid as solvent at 80–100 °C temperature.[22] Even in our previous work we performed same reaction at 55 °C temperature. Gratifyingly, the bromination of **1k** with both H_2O_2-HBr and *m*-CPBA-HBr proceed efficiently at room temperature without any catalyst or acid to afford industrially important 3-bromo-7H-benzo[*de*]anthracen-7-one **2k** in high yield, 91% and 89% respectively (Table 3, entry 11). The substrate **1l** gives 84% yield of **2l** in H_2O_2-HBr system

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Table 3
Substrate scope.[a]

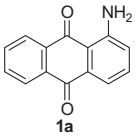
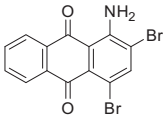
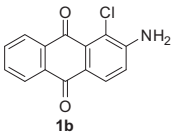
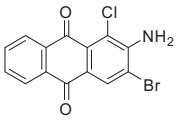
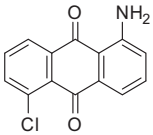
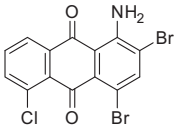
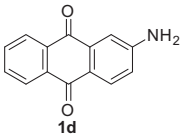
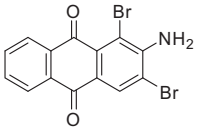
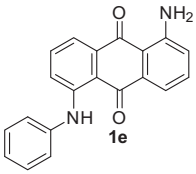
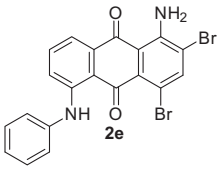
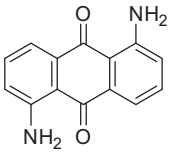
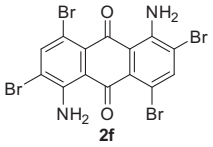
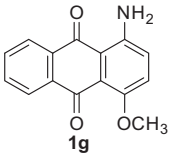
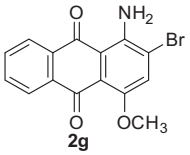
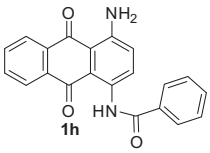
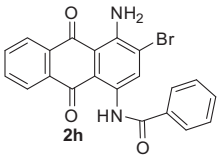
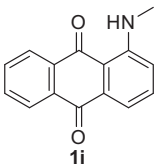
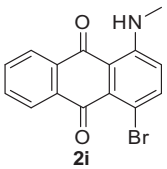
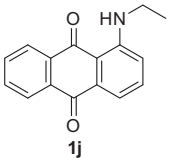
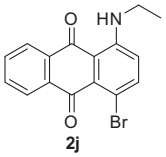
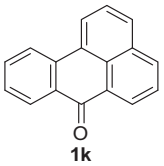
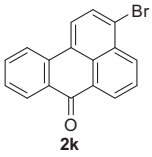
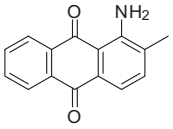
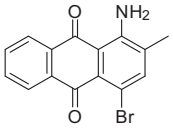
Entry	Substrate	Product	Yield[b] (%)	
			H_2O_2	*m*-CPBA
1.	 **1a**	 **2a**	91	92
2.	 **1b**	 **2b**	93	90
3.	 **1c**	 **2c**	90	89
4.	 **1d**	 **2d**	92	93
5.	 **1e**	 **2e**	86	91
6.	 **1f**	 **2f**	87	90
7.	 **1g**	 **2g**	87	89
8.	 **1h**	 **2h**	90	85
9.	 **1i**	 **2i**	86	87
10.	 **1j**	 **2j**	85	82

Table 3 (*continued*)

Entry	Substrate	Product	Yield[b] (%)	
			H_2O_2	*m*-CPBA
11.	 **1k**	 **2k**	91	89
12.	 **1l**	 **2l**	84	82

[a] Reaction conditions: **1** (1 equiv.), HBr [(1 equiv. for entries 2, 7–12), (2 equiv. for entries 1, 3–5), (4 equiv. for entry 6)], oxidants (H_2O_2 and *m*-CPBA): [(1 equiv. for entries 2, 7–12), (2 equiv. for entries 1, 3–5), (4 equiv. for entry 6)], methanol 2 mL, temperature: 30–32 °C (room temperature); Time: H_2O_2-HBr (8 h), *m*-CPBA-HBr (10 min).
[b] Yield: isolated yield.

whereas in *m*-CPBA-HBr system 82% yield was obtained (Table 3, entry 12).

The scope of present work was further explored for other aminoquinones bearing electron rich substituents such as 1-Amino-4-hydroxyanthracene-9,10-dione,1,4-diamine anthracene-9,10-diones but it failed to give brominated product. The protocol was also found unsuccessful for the bromination of electron deficient quinone such as 1-chloro anthracene-9,10-dione.

The mechanism of the reaction proceeds through formation of molecular bromine by oxidation of HBr with oxidant. The aminoanthracene-9,10-diones undergo electrophilic bromination with the molecular bromine to give desired brominated product. The HBr generated during this reaction gets re-oxidized by peroxide to molecular bromine that further utilized for the bromination.[43,44]

The gram scale study was done with 10 g of **1a** by using both the methods. The substrate **1a** on reaction with H_2O_2-HBr gave 93% yield and the *m*-CPBA-HBr method afford 91% yield of **2a** within 8 h and 10 min respectively. Similarly, scale up study for the bromination of **1k** was also investigated by using H_2O_2-HBr which gave 87% yield of **2k** within 8 h at room temperature. Thus, the scale up study confirms the viability of both protocols at gram level.

In summary, various deactivated aminoanthracene-9,10-diones are selectively brominated at room temperature by using H_2O_2-HBr and *m*-CPBA-HBr. Both the protocols overcome various short comings of traditional processes used for the bromination of these intermediates such as avoids multiple heating and cooling conditions, exposure to acidic solvents such as conc. sulphuric acid, glacial acetic acid, molecular bromine, sulphuryl chloride etc., and multiple bromine addition steps. High bromine atom economy was achieved and the desired products were obtained in high yields in shorter time with high purity. The *m*-CPBA-HBr system offer fastest route for bromination of these intermediates till date. Selective *p*-bromination was observed for *N*-alkylated amines. The use of commercially available entities and gram scale studies have made these approaches economically attractive and feasible at larger scale.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.05.078.

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General procedure for the bromination of 1-aminoanthracene-9,10-dione 1a by using H_2O_2-HBr: In 2 neck round bottom flask (10 mL) equipped with mercury sealed stirrer, 2 mL of methanol, 1-aminoanthracene-9,10-dione **1a** (1 equiv.) and HBr (2 equiv.) were added at room temperature. To this, H_2O_2 (2 equiv.) was added over 5 min. The reaction mass was stirred for 8 h. The progress of the reaction was monitored on TLC. The reaction was quenched by adding 2 mL saturated sodium thiosulphate ($Na_2S_2O_3$) solution and then 2 mL of 5% sodium bicarbonate ($NaHCO_3$) solution. 10 mL of water was added to the reaction mass and the solid obtained was filtered and washed with water. The crude product thus obtained was further purified using column chromatography with pet ether: ethyl acetate as an eluent to give purified 1-amino-2,4-dibromoaminoanthracene-9,10-dione **2a**.

*General procedure for the bromination of 1-aminoanthracene-9,10-dione **1a** by using m-CPBA-HBr:* The procedure used for bromination of 1-aminoanthracene-9,10-dione **1a** by using *m*-CPBA-HBr system is similar to that of H_2O_2-HBr system. The oxidant, *m*-CPBA was taken 2 equivalents and the reaction was stirred for 10 min at room temperature.

*Procedure for the scale up of bromination of 1-aminoanthracene-9,10-dione **1a** by using H_2O_2-HBr:* In 3 neck round bottom flask (250 mL) equipped with mercury sealed stirrer and water condenser, 50 mL of methanol, 10 g of 1-aminoanthracene-9,10-dione **1a** (0.044 mol, 1 equiv.) and HBr (0.089 mol, 2 equiv.) were added at room temperature. The reaction mass was stirred for 5 min. The oxidant, H_2O_2 (0.089 mol, 2 equiv.) was added slowly in 25–30 min (During scale up study it was observed that fast addition of the oxidant lead to exotherm and temperature increases up to 60–70 °C. This resulted in evolution of bromine gas from the reaction and consequently due to loss of bromine the reaction did not completed. On the other hand, slow addition of the oxidant with external cooling offered good yield of desired di-bromo product). The progress of the reaction was monitored on TLC. After completion, the reaction was quenched by adding 20 mL of saturated sodium thiosulphate solution and 20 mL of 5% sodium bicarbonate solution. The reaction mass was kept under stirring for 30 min. Finally, 100 mL of water was added and the solid obtained was filtered. The residue was washed with water till the filtrate exhibited neutral pH and dried in oven at 55–60 °C overnight. The product 1-amino-2,4-dibromoaminoanthracene-9,10-dione **2a** was obtained in 93% yield.

*Procedure for the scale up of bromination of 1-aminoanthracene-9,10-dione **1a** by using m-CPBA-HBr:* The procedure used for the scale-up study of bromination of 1-aminoanthracene-9,10-dione **1a** by using *m*-CPBA-HBr is similar to that of H_2O_2-HBr system. The oxidant, *m*-CPBA (0.089 mol, 2 equiv.) was added over 25–30 min. The reaction mass was kept for 10 min and the progress of the reaction was monitored on TLC. The product 1-amino-2,4-dibromoamino-anthracene-9,10-dione **2a** was obtained in 91% yield.

*Procedure for the scale up of bromination of 7H-benzo[de]anthracen-7-one **1k** by using H_2O_2-HBr:* The procedure used for the bromination of 7H-benzo[*de*] anthracen-7-one **1k** by using H_2O_2-HBr is similar to that 1-aminoanthracene-9,10-dione **1a**. The oxidant H_2O_2 (0.089 mol, 2 equiv.) was added over 25–30 min. The progress of the reaction was monitored on TLC. The product 3-bromo-7*H*-benzo[*de*]anthracen-7-one **2k** was obtained in 87% yield.

All the reactants and reagents were purchased from commercial suppliers and were used without further purification. All the experiments were performed by using 50% H_2O_2, 47% HBr, and 70% *m*-CPBA. All products were confirmed by melting point, proton nuclear magnetic resonance spectroscopic and mass spectrometry. The ^{1}H NMR (500 MHz) spectrums were recorded in DMSO-d_6 and $CDCl_3$) by using Bruker mercury plus and Agilent 500 MHz spectrometers and chemical shifts were expressed in δ ppm. The HPLC analysis was done using Jasco 2000 with acetonitrile: methanol (90:10) mobile phase (flow rate: 1 mL/min, detector: UV detector) and silica column C18 (HiQ Sil C18HS, size: 4.6 mm $\times$ 250 mm). Mass spectral data were obtained with a micromass-Q-Tof (YA105) spectrometers. All melting points were uncorrected and recorded from Sunder Industrial Products, Mumbai and are presented in degree celsius.