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COMMUNICATION

Synergic effect of nano-catalyst and continuous flow system: Dakin-West reaction catalyzed by Nafion-H@SPIONs in a microreactor

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The expansion of practical processes for the superferromagnetic nanocatalysts is a very attractive subject. In this work, we successfully developed a new and efficient procedure with combination of continuous flow technology with immobilizing of only 0.35 mol% of Nafion-H on silica-encapsulated superparamagnetic iron oxide nanoparticles (SPIONs) to maximize catalyst efficiency for the synthesis of β -acetamido ketones. The turnover frequency value varies in the range of 1336 to 1577 h⁻¹ compared to 256-515 h⁻¹ in the conventional stirred reactor. Moreover, the catalyst could be quickly recovered by external magnetic field and could be reused for several reaction cycles without any change in its catalytic activity.

Introduction

Nowadays sustainability is a fundamental concern in the development and progress of any chemical process. The green chemistry necessitates a movement from traditional concepts of process efficiency that concentrate largely on the yield of a product to one that assigns economic value to reducing waste and eliminating of toxic substances.¹ Upon tendency on the catalytic processes towards the development of eco-friendly chemical processes, hazardous chemical catalysts and leaching of them in the environmental has become a main concern in this area.² Therefore, many recent papers describing the utilizing of new catalysts pointed out that their use is ecologically friendly.³ Among them, Nafion-H as a perfluoro-resin with strongly sulfonic acid terminal groups, provides a green superacid which has been used widespread in organic synthesis.⁴ However, one of the major disadvantages of it as a catalyst is the low surface area especially when non-swelling solvents are applied.⁵ To improvement of this activity, a new generation of Nafion catalysts has been developed. One of the recent progresses in this field is immobilization of nanosized Nafion resin on a highly porous silica matrix.⁶ The results illustrate that the activity of these composites is much higher than of pure Nafion due to the better accessibility of the catalytically active acid sites.⁶

Therefore, extension of this investigation and presentation of a new derivative of this generation which could increase the efficiency of the catalyst is highly demanded.

Currently, a growing interest in various nanocatalysts employing the property of magnetic separation has been developed in a number of organic reactions.⁷ These magnetic nanoparticles (MNPs) that in some cases used as a support show excellent catalytic activity where magnetic separation behavior provides a very practical approach for removing of them from the reaction mixture.⁸ This can be considered as an environmentally benign that filtration steps were omitted in the reaction.⁹ Upon on this tremendously specification, various Lewis acids have been immobilized on them and their catalytic activity of these nanocatalysts studied in organic transformation so far.¹⁰

β -Acetamido ketones are vital intermediates in that their skeletons exist in a number of biologically or pharmacologically important compounds.¹¹ The Dakin-West reaction as the best known route for the synthesis of these compounds is carried out through the condensation of an aryl aldehyde, acetophenone and acetyl chloride in acetonitrile in the presence of different Lewis or Brønsted acids such as CoCl₂,¹² montmorillonite K-10 clay,¹³ silica sulphuric acid,¹⁴ heteropoly acids,¹⁵ Zr(HSO₄)₂,¹⁶ [Et₃N-SO₃H]Cl,¹⁷ Fe₃O₄ nanoparticles¹⁸ and [(PS)₂pi][OTf]₂.¹⁹ Although, these methods are valuable, however some of them suffer from some disadvantages such as long reaction times (in some cases more than 7h) or utilizing non-reusable catalysts. Therefore, the introduction of new and efficient methods for this multi-component reaction is still necessary. In this event, we felt that flow technology could considerably enhance rates due to improved heat and mass transfer.

Recently, micro-process technology allow a directed reactant flux through an immobilized catalyst, making them precise attractive process intensification tools by enhancing mass- and heat-transfer characteristics via low hold-up volumes and an excellent thermal transport capability and the ability to efficiently optimize reaction conditions by controlling of residence time.²⁰ Moreover, the results illustrated that at a very short residence time in the microreactor even in scaling up the obtained yields were much higher than operating in the conventional stirring.²¹

Undoubtedly, one of the significant parameter in the flow reaction design is the kind of the catalyst which it is not only efficient but also could not block the channels of the chambers during of the reaction.²² Therefore, it seems that combination of nanocatalysts especially nano-superferromagnetic nanocatalysts

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with continuous flow systems could prepare a new and practical manner for overcoming of the aforementioned problems.

These features encouraged us to explore an innovative method for the sustainable synthesis of β -acetamido ketones by immobilization of Nafion-H on SPIONs (Nafion-H@SPIONs) in a continuous flow system.

Result and Discussion

Nafion-H@SPIONs was characterized by means of fourier transform infrared spectroscopy (FT-IR), thermal gravimetric analysis (TG), vibrating sample magnetometry (VSM) and high resolution transmission electron microscopy (HR-TEM) and elemental analysis.

Figure 1 illustrates the FT-IR spectrums of SPIONs (a), and nanocatalyst Nafion-H@SPIONs (b) respectively.

The FT-IR spectrum of Nafion-H@SPIONs (Figure 1, b) showed absorption bands at 3400-3220 cm^{-1} (O-H stretching vibration), 1223 cm^{-1} (C-F) and 635-587 cm^{-1} (Fe-O) SPIONs.

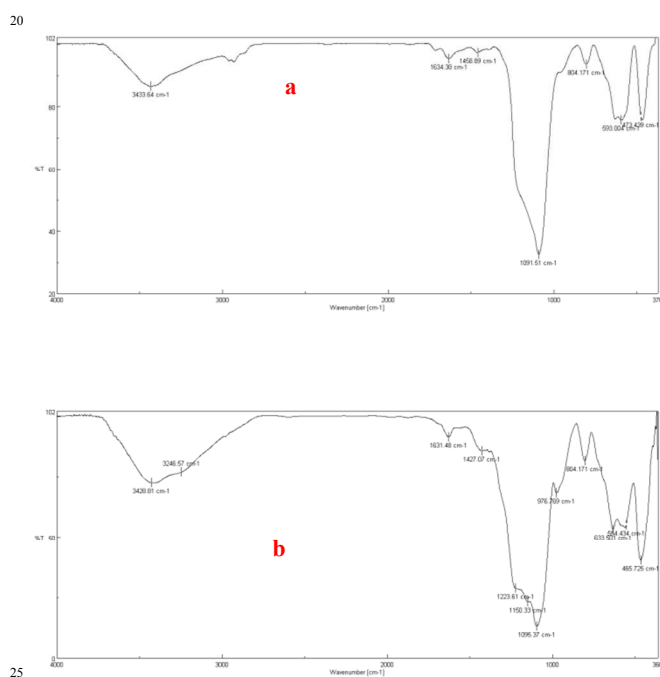


Fig. 1 Comparison of FT-IR spectrums of (a) SPIONs and (b) Nafion-H@SPIONs

The thermal stability of Nafion-H@SPIONs was also evaluated by TGA-DTG. According to this curve, two weight loss steps were observed. In the first step (around 100 $^{\circ}\text{C}$), the water molecules (4.59%) in the structure were omitted, while only 11.28% of the organic part were lost between 40-425 $^{\circ}\text{C}$ (Figure 2).

For the studying of morphology characteristics of Nafion-H@SPIONs, HR-TEM image was also investigated (Figure 3). HR-TEM images of Nafion-H@SPIONs revealed that it appears to have almost a spherical structure with the average size about 9-11 nm (Figure 3, b).

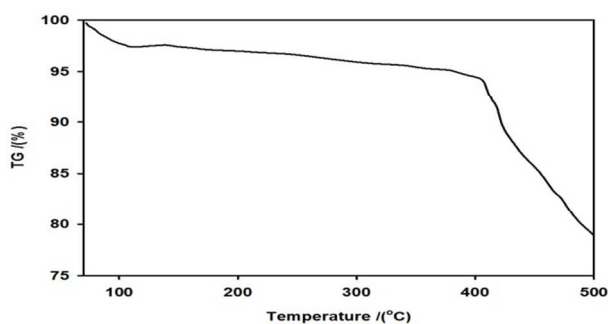


Fig. 2 TG-DTG analysis of Nafion-H@SPIONs

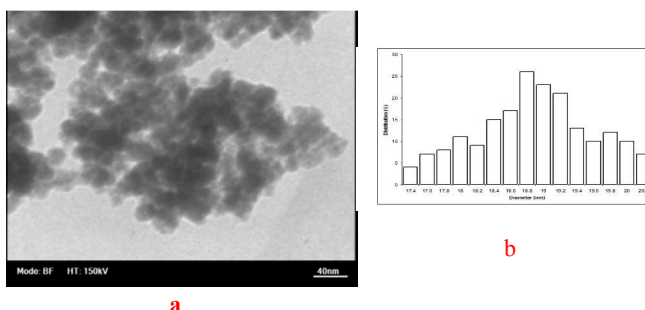


Fig. 3 (a) HR-TEM image of Nafion-H@SPIONs and (b) Nafion-H@SPIONs particle size distribution histogram

The dc magnetic characterization of Fe_3O_4 , the neat SPIONs nanoparticles and Nafion-H@SPIONs, were examined at room temperature in an external field range of ± 10 kOe. In this investigation, due to the functionalization of SPIONs by Nafion-H, M_s (saturation magnetization) is found to be 20.3 emu/g , which is considerably lower than that of the bulk magnetite (Figure 4).

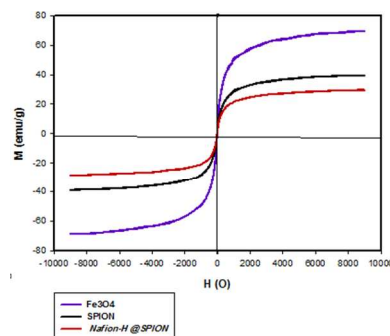
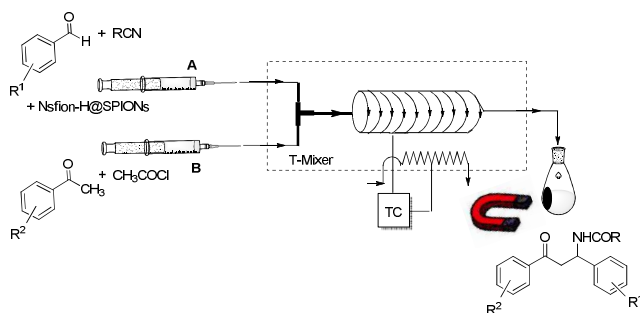


Fig. 4 The dc magnetic characterization of the nanoparticles

The schematic of the experimental setup is illustrated in Scheme 1. This procedure is very simple and no previous studies were available in the literature upon this protocol for this transformation. The microreactor system used in this study includes a T-shape micromixer and an in-house-made tubing glass reactor which can be implemented in any chemistry laboratory. The microtube reactor was fabricated in a glass column (internal diameter, 0.5 mm; internal volume, 0.6 mL; length, 200 cm), which was placed in a water bath.



Scheme 1 Microflow set-up for the preparation of β -acetamido ketones

Two syringes, fixed on a syringe pump, were used to introduce the reactants into the microreactor. Syringe **A**, consisted a sonicated mixture of an aldehyde (1 eq.), a nitrile (1.0 eq.) and Nafion-H@SPIONs (20 mg containing of 0.35 mol% Nafion-H) using THF as solvent with a concentration of 2 M and syringe **B**, involved a 2 M solution of an arylmethyl ketone (1.0 eq.) and acetyl chloride (1.0 eq.) in THF. A temperature controller (TC) was used for balancing and setting up heating. A round-bottom flask was connected to the flow reactor to collect the product. It should be noted that after the reaction was completed, the catalyst could be separated from the mixture by using a permanent magnet.

In an initial study with 3-nitrobenzaldehyde, acetyl chloride, acetonitrile and acetophenone as a template, revealed that the reaction temperature was a key factor for this transformation. It was found that at 40 °C with a residence time of 10 minutes the optimal isolated yield (90 %) was obtained exclusively (Table 1, entry 5).

We found that the catalyst could greatly act on this transformation.

Table 1 Optimization reaction of 3-nitrobenzaldehyde, acetophenone, acetyl chloride and acetonitrile in the presence of Nafion-H@SPIONs^a under the flow reaction^a

Entry	Nafion-H loaded (mol%)	T / °C	Residence Time/min	Yield (%) ^b
1	-	40	10	5
2	0.087	40	10	32
3	0.174	40	10	45
4	0.261	40	10	62
5	0.35	40	10	90
6	0.35 ^c	40	10	83
7	0.35	60	10	87
8	0.35	30	10	58
9	0.35	40	20	90
10	0.35	50	30	91
11	0.35 ^d	40	-	52

^a Reaction condition: 3-nitrobenzaldehyde (1.0 eq.), acetophenone (1.0 eq.), acetyl chloride (1.0 eq.), and acetonitrile (1.0 eq.) in the presence of 20 mg Nafion-H@SPIONs.

^b Isolated yield.

^c In 30 mg Nafion-H@SPIONs.

^d Under traditional conditions in a flask after 10 min.

Notably, lower yields were obtained when the same reaction carried out with utilizing of lower amount of the catalyst loading (Table 1, entries 2-4). On the other hand, in the absence of any catalyst the product was obtained very slightly (Table 1, entry 1). Moreover, temperature is also a key factor in this reaction. The improvement in the conversion (90%) was reached at 40 °C (Table 1, entry 5). Higher temperature made no obvious difference in the yield of the product (Table 1, entry 7) but using lower one (30 °C), sharply decreased the conversion to 58% yield (Table 1, entry 8). Further evaluations showed when the flow rate was decreased to 0.06 ml/min, the desired product increased to 90 % surprisingly (Table 1, entry 5). Further decrease (0.05 ml/min to 0.04 ml/min) makes no obvious difference in the yield of the product (Table 1, entries 9, 10).

In contrast to the traditional manner in a flask, it is interesting to note that the product of the model reaction was produced in a lesser amount, indicating a relatively slow conversion of it under the condition (Table 1, entry 11). Therefore, these achievements firmly approved that both the catalyst and continuous flow method have crucial impact on this transformation.

Table 2 The Dakin-West reaction catalyzed by Nafion-H@SPIONs in the microreactor

Entry	R ¹	R ²	R	Yield (%) ^{a,b}	TOF (h ⁻¹) ^b	Yield (%) ^{a,c}	TOF (h ⁻¹) ^c
1	H	H	CH ₃	92	1577	87 ^d	497
2	3-NO ₂	H	CH ₃	90	1542	90 ^e	256
3	4-NO ₂	H	CH ₃	87	1490	85 ^e	364
4	4-Cl	H	CH ₃	89	1526	84 ^f	410
5	4-CHO	H	CH ₃	80	1372	78 ^g	266
6	4-CH ₃ O	H	CH ₃	90	1542	90 ^d	515
7	2-HO	H	CH ₃	82	1404	75 ^h	284
8	H	4-Br	CH ₃	91	1562	87 ^d	497
9	4-Cl	4-Cl	CH ₃	88	1508	85 ^f	418
10	4-Cl	4-CH ₃ O	CH ₃	78	1336	75 ^g	256
11	4-CHO	4-Cl	CH ₃	89	1526	82 ^h	313
12	4-Cl	H	C ₆ H ₃	87	1490	83 ^d	475
13	4-Cl	H	4-ClC ₆ H ₃	90	1544	90 ^d	515

^a Isolated yield.

^b [mol product/ Nafion-H]/h under the flow reaction.

^c [mol product/ Nafion-H]/h under conventional stirred in a flask at 75 °C.

^d After 30 min.

^e After 40 min.

^f After 35 min.

^g After 50 min.

^h After 45 min.

We assume that one of the beneficial effect of continuous flow on this reaction may be attributed to a better dispersion of the nanocatalyst in an at least volume in comparison with magnetically stirred reaction, which it make the catalyst more effective in this transformation.

Next, upon the optimum conditions, a series of β -acetamido ketones were prepared with excellent turnover frequency ($>1300 \text{ h}^{-1}$) (Table 2) with representing a noteworthy acceleration compared to the corresponding batch experiments with lower one ($<512 \text{ h}^{-1}$).

This protocol also avoids the problems associated with handling, safety and pollution. Nafion-H@SPIONs can act as eco-friendly catalytic system for a variety of organic transformations, since it is non-volatile, non-explosive, easy to handle and thermally robust. The use of Nafion-H@SPIONs as a powerful nanocatalyst in combination with continuous flow system showed rate enhancements, high yields and short reactions times.

The recovered Nafion-H@SPIONs could also be reused straightforward by an applied magnetic field after the end of the reaction without any significant loss of its high catalytic performance (Figure 5).

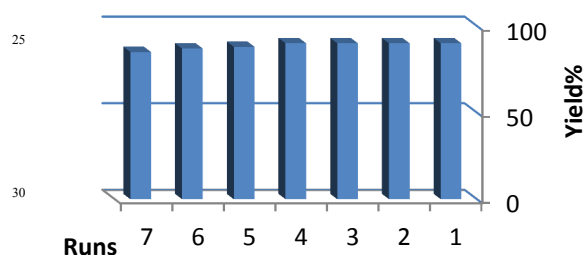


Fig. 5 Reusability of Nafion-H@SPIONs

The results illustrated the excellent stability of the catalyst under the reaction condition (Figure 6). The performance of the recovered catalyst during the synthesis of the template reaction was found to be satisfactory and no considerable variation in the yield.

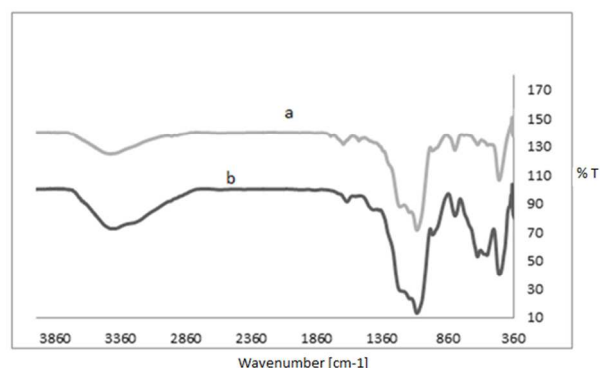
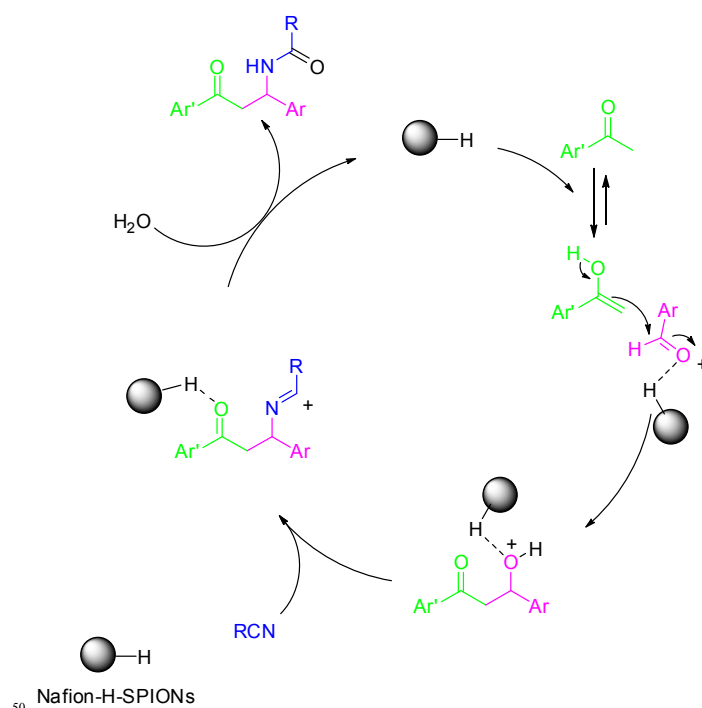


Fig. 6 FT-IR spectrums of (a) Nafion-H@SPIONs after 7 runs and (b) fresh Nafion-H@SPIONs

A plausible rationalization upon the literature^{11c} for the Dakin-

West reaction is shown in Scheme 2.



Scheme 2 Proposed mechanism

In summary, we have introduced the synthesis of a new and robust nanocatalyst which employed in the Dakin-West reaction, providing the corresponding products in very high to excellent yields. Moreover, for the first time, it was developed a simple system that allows combination of a superferromagnetic nanocatalyst and continuous flow technology as an expeditious process for the synthesis of β -acetamido ketones through a multicomponent reaction. The turnover frequency value is varied in the range of 1336 to 1577 h^{-1} in this investigation, while the value is only ca. 260 - 520 h^{-1} in a conventional stirred reactor. The catalyst loading is significantly lower than all cases that previously reported for the synthesis of β -acetamido ketones. Very high recyclability of the catalyst (more than seven runs) is other main characteristic of the process. Further investigations on the aspect of combination of nano-catalyst and micro-flow system are currently ongoing in our laboratory.

Experimental

All chemicals and Nafion-H (5% in ethanol) were purchased from Merck and DuPont companies, respectively. Fe_3O_4 nanocomposite and silica-coated magnetite nanoparticles (SPIONs) were synthesis according to the literature respectively.²⁹ All known organic products were identified by comparison of their physical and spectral data with those of authentic samples. Thin layer chromatography (TLC) was performed on UV-active aluminum-backed plates of silica gel (TLC Silica gel 60 F254). ^1H , and ^{13}C NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in CDCl_3 with chemical shift (δ) given in ppm. Coupling constants are

given in Hz. The FT-IR spectra were taken on a Nicolet-Impact 400D spectrophotometer in KBr pellets and reported in cm^{-1} . Melting points were determined using Stuart Scientific SMP2 apparatus and are uncorrected. The sonication was performed in a UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The TEM images were taken with a Philips CM30 unit operated at 150 kV. The magnetic measurements were performed with a vibrating sample magnetometer (VSM) at Meghnatis Daghigh Kavir Co. TGA curve was obtained with a heating rate of 10 $^{\circ}\text{C}/\text{min}$ on a TG 50 Mettler thermogravimetric analyzer from 30 $^{\circ}\text{C}$ to 600 $^{\circ}\text{C}$.

Preparation of Nafion-H@SPIONs

The catalyst was synthesized via impregnation method. To a mixture of SPIONs (80 mg) in absolute ethanol (10 ml) at 25 $^{\circ}\text{C}$, 0.4 ml Nafion-H (5% in ethanol) was added dropwise and sonicated for 15 minutes. The resulting mixture was stirred for 2h at 100 $^{\circ}\text{C}$ and subsequently calcinated at 120 $^{\circ}\text{C}$ for three hours.²⁹

General procedure for the Dakin-West reaction catalyzed by Nafion-H@SPIONs in microreactor system

A microreactor system containing a T-shaped micromixer, microtube reactor immersed in a water bath, and a syringing pump were used. The syringing pump was equipped with two syringes (1 ml). In a syringe, a sonicated solution of aldehyde (1.0 eq.), nitrile (1.0 eq.) and Nafion-H@SPIONs (20 mg containing of 0.35 mol% Nafion-H) using THF as solvent with a concentration of 2 M and in another, a 2 M solution of arylmethyl ketone (1.0 eq.) and acetyl chloride (1.0 eq.) in THF were charged. Next, the mixtures were fed into the system by syringe pump (flow rate: 0.06 ml/min) at 40 $^{\circ}\text{C}$. After the residence time was reached (10 min), the discharge was collected in a glass vessel equipped with an external permanent magnet. The collected catalyst by the magnet, washed two times with absolute ethanol (2 \times 1 ml), air-dried, and used directly for the next round. After separation of the catalyst from the resulting crude product, the volatile was removed in vacuum. The organic residue was washed with water (3 \times 5 ml), decanted and dried over anhydrous Na_2SO_4 . Purification by flash chromatography (silica gel, ethyl acetate/petroleum ether) afforded the corresponding products in 78-92% yields. Most of the products are known in the literature and were identified by comparison of their FT-IR and NMR with the literature data. As a sample, the characterization data for β -acetamido- β -(3-nitrophenyl) propiophenone is:

M.p.: 110-112 $^{\circ}\text{C}$. IR (KBr) ν_{max} = 3290, 1687, 1652 cm^{-1} ; ^1H -NMR (400MHz; CDCl_3) δ : 2.07 (s, 3H, CH_3), 3.50 (dd, J = 6.0 and 16.0 Hz, 1H, CH_2), 3.80 (dd, J = 5.2 and 16.0 Hz, 1H, CH_2), 5.70- 5.72 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H, NH), 7.45-7.61 (m, 5H, Ar-H), 7.73 (d, J = 8.0 Hz, 1H, Ar-H), 7.91 (d, J = 7.2 Hz, 1H, Ar-H), 8.10 (d, J = 8.0 Hz, 1H, Ar-H) 8.24 (s, 1H, Ar-H); ^{13}C -NMR (100 MHz, CDCl_3) δ : 198.08, 169.82, 148.40, 143.44, 136.16, 134.01, 132.96, 129.57, 128.88, 128.10, 126.37, 124.87, 122.41, 121.34, 49.06, 42.74, 23.42.

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