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Fe_3O_4 magnetic nanoparticles as efficient and recyclable catalyst for acetylation of Baylis-Hillman adducts under solvent-free conditions

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Abstract: Baylis-Hillman adducts were efficiently acetylated with acetic anhydride in the presence of nano-Fe_3O_4 at room temperature. In this protocol the use of nano catalyst provided a green, useful and rapid method to generate the product in short reaction times (5-15 min) and excellent yields (84-95%). This catalyst can be recovered and reused.

Keywords: Baylis-Hillman adduct, Fe_3O_4-nanoparticles, Acetylation, Solvent-free, Reusable catalyst.

Introduction

The acylation of alcohols and phenols is one of the most useful and versatile transformations in organic synthesis. Acylation using acid anhydride provides a cheap and efficient method for protecting OH groups during oxidation and coupling reactions [1,2]. Numerous homogenous catalytic systems are available for this transformation, but most of these methods exhibit disadvantages such as long reaction times, high loading of catalyst, non-recyclability of the catalyst, and high reaction temperature, waste generation, low yields, and harsh conditions, use of explosive and highly toxic or expensive catalysts [3-5]. *N,N,N',N'*-tetramethylenediamin (TMEDA) can be used as an organic base like amines and amidines. Kadam and et al. carried out acylation of alcohols, phenols and thiols by acetic anhydriede in the presence of TMEDA as catalyst [6].

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Dawson acid as heteropoly acid catalyst has been used for acetylation of alcohols, thiols, amines and phenols [7]. Various metal salts like $CoCl_2$ [8], $NiCl_2$ [9], $V(O)(OTf)_2$ [10] and $Mg(ClO_4)_2$ [11] as catalyst have also been used. Vanadyl derivatives, such as vanadyl sulfate have been employed for acylation of alcohols and phenols [12]. Heravi et al. performed the same reaction by using acetic anhydride and vanadyl sulfate under solvent-free conditions [13]. Dodecylbenzenesulfonic acid (DBSA) has also been used for the acylation reaction with ethyl formate at room temperature [14]. Cai et al. have used ruthenium (III) chloride and ionic liquids 1-butyl-3-methylimidiazolium hexafluorophosphate ([bmim][PF_6]) for acylation of alcohols, phenols, and thiols at room temperature [15]. Choudary et al. succeed to perform selective acylation of alcohols employing carboxylic acid with montmorillonites [16].

On the other hand, magnetic nanoparticles (MNPs) have also gained recognition as potential environmentally benign replacements of the conventional Lewis acid and base catalysts in various organic synthetic processes. MNPs as solid acid

catalysts have served as important functional materials in industrial processes [17-19] and their applications have expanded beyond materials science into the biomedical, chemical and electronics fields because of their high surface area volume ratios, conductivity, magnetic susceptibility and catalytic activity [20,21]. MNPs as heterogeneous catalyst, with unique properties and potential applications in various fields, have gained popularity in organic synthesis due to simple work-up procedures, environmentally benign nature, reusability, low cost, and ease of isolation [22, 23].

In adition, the Baylis-Hillman reaction is a powerful carbon-carbon bond-forming reaction between the α-position of the activated alkenes (alkynes) and carbon electrophiles under the influence of a catalyst or catalytic system providing diverse classes of densely functionalized molecules in organic synthesis, and has gained much attention because of its atom economy, selectivity, mild reaction conditions, and provides an unique class of attractive molecules which can be further manipulated to various carbocyclic and heterocyclic compounds [24,25].

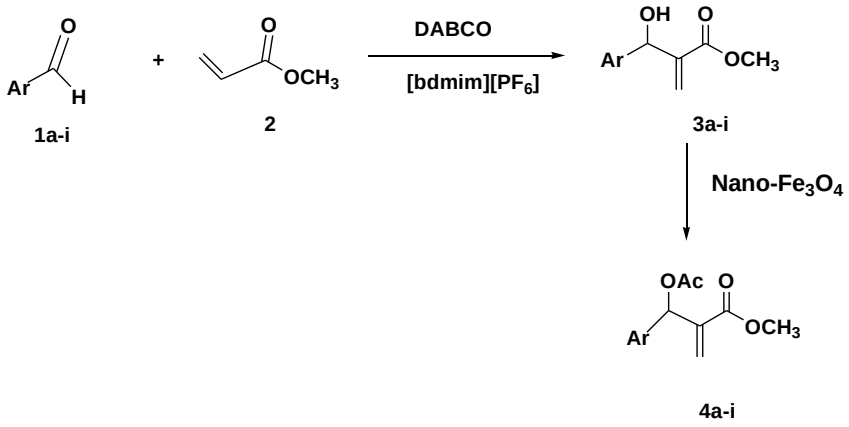
Results and Discussion

A variety of strategies have successfully demonstrated the application of Fe_3O_4 nanoparticles as catalysts [19]. At present study, in connection with our continued interests in benign protocols for the synthesis of biologically important products and development of environmentally friendly methodologies [26] we report here a practical and efficient method for acetylation of Baylis-Hillman adducts (Scheme **1**).

Reactionof 2, 4-dichloro-6-phenylpyrimidine-5-carbonitrile **1** with ethylthioglycolate**2** as shown in Scheme **1**.

Initially, the Baylis-Hillman adducts (**3)** were prepared by the reaction of aryl aldehyde (**1**) and methyl acrylate (**2**) in the presence of DBCO and ionic liquid [bdmim][PF_6] [24]. In the next step the reaction of adduct **3a** (1mmol) and acetic anhydride (2 mmol) as model reaction was carried out in the presence of Fe_3O_4 nanoparticles (20 mg) at room temperature under solvent-free conditions to furnish the desired acetylated product **4a** in 5 min and 94% yield (Table **1**, entry 1). To optimize the reaction conditions variety of solvents such as $CHCl_3$, dioxane, DMF, THF, CH_3CN, MeOH, EOH and sovent-free condition and different temperatures were examined which the solvent-free condition at room temperature gave the best result.

Under optimized reaction conditions several Baylis-Hillman adducts (**3a-h)** were acetylated successfully in short reaction times (5-15 min) and excellent yields (84-95%) . The resuls are presented in Table **1**. In this protocol the nanocatalyst was easily separated from the reaction mixtutre by applying an external magnet, washed by CH_2Cl_2, dried and reused in next run. After 5 consecutive runs the catalytic activity of the catalyst almost was remained unchanged. The structure of all the products was established by spectroscopic analysis.



Scheme 1: Acetylation of Baylis-Hillman adducts using Fe_3O_4 nanoparticles.

Finally, to show the efficiency of present method in acetylation of the Baylis-Hillman addacts, we have compared the present method with others such as DMAP/TEA, iodine and potassium-exchanged molecular sieves (13X/KCl) as catalyst (Table **2**). This study revealed that acetylation in the presence of nano-Fe_3O_4 catalyst produces better results.

Table 1. Acetylation of Baylis-Hillman adducts using nano-Fe_3O_4 catalyst at room temperature.

Entry	Ar	Tim (min)	Product	Yield (%)
1	3-$NO_2C_6H_4$	5	**4a**[a]	94
2	2-$NO_2C_6H_4$	7	**4b**[a]	90
3	4-$NO_2C_6H_4$	5	**4c**[a]	95
4	4-ClC_6H_4	8	**4d**[b]	91
5	2,4-$Cl_2C_6H_3$	10	**4e**[b]	92
6	2-ClC_6H_4	12	**4f**[b]	89
7	2-naphtyl	5	**4g**[b]	97
8	CH_3CH_2	15	**4h**[b]	84

[a]Identified by spectroscopic analyses (IR, ^{1}H NMR).
[b]Identified by comparison of IR and ^{1}H NMR spectra with those reported in the literature [27].

Table 2. Comparison of acetylation of Baylis-Hillman adducts using nano-Fe_3O_4 catalyst with other methods.

Entry	Ar	DMAP/TEA[a] Time (h)(Yield %)[c]	Iodine[b] Time (h)(Yield %)[c]	Nano-Fe_3O_4 Time (min)(Yield %)[c]
1	3-$NO_2C_6H_4$	19 (45)	4 (90)	5 (94)
2	2-$NO_2C_6H_4$	19 (40)	4 (85)	7 (90)
3	4-$NO_2C_6H_4$	17 (45)	2 (92)	5 (95)(180)[d](91)[d]
4	4-ClC_6H_4	36 (38)	18 (80)	8 (91)(120)[d](90)[d]
5	2,4-$Cl_2C_6H_3$	24 (42)	6 (92)	10 (92)
6	2-ClC_6H_4	29 (37)	15 (84)	12 (89)
7	2-naphtyl	18 (45)	8 (90)	5 (97)
8	CH_3CH_2	48 (40)	28 (87)	15 (84)

[a]Conditions: Ac_2O (0.21 mol), **3a-h** (0.1 mol). DMAP (4.1 mmol), triethylamine (0.15 mol) at room temperature.
[b]Conditions: Ac_2O (1.05 eq.), **3a-h** (1 eq.), Iodine (0.1 eq.) at room temperature.
[c]Isolated yield.
[d]In the presence of potassium-exchanged molecular sieves (13X/KCl) [27].

Experimental

General:

IR spectra were recorded on a Shimadzo FT-IR-8900 spectrometer. ^{1}H NMR spectra were recorded on a 400 MHz Bruker DRX-500 using $CDCl_3$ as the solvent and TMS as internal standard. All the chemicals were purchased from Merck and Fluka. The solvents used were dried and distilled according to standard procedures.

General procedure for Acetylation of Baylis-Hillman adducts using nano-Fe_3O_4 catalyst at room temperature:

The required Baylis-Hillman adducts **3** were prepared according to the procedures reported in Ref [24]. Then the synthesized adducts (1 mmol) were acetylated by acetic anhydride (2 mmol) in the presence of catalytic amount of nano-Fe_3O_4 (20 mg) under solvent-free conditions. After the completion of the reaction, which was monitored by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 and the catalyst was easily separated from the reaction mixture by an external magnet. The product obtained, was collected by filtration, washed with diethyl ether and recrystallized from appropriate solvent to furnish the desired pure product (**4a-h**). Some data of selected compounds are listed below and the structure of the products was established by IR and ^{1}H NMR spectroscopy.

Methyl 2-(acetoxy(3-nitrophenyl)methyl)acrylate (4a):

Yellow oil; yield: (94%); FT-IR (KBr)(ν_{max}, cm^{-1}): 3094 (Ar-H), 2955 (C-H aliph.), 2868 (O-CH_3), 1742 (C=O), 1637 (C=C), 1579, 1441 (C-C arom.), 1531, 1354 (NO_2), 1225, 1151 (C-O-C ester), 816, 770, 690 (olefinic C-H bend). ^{1}H NMR: δ= 8.25 (1H, s, ArH), 8.17 (1H, d, *J* = 8.0 Hz, ArH), 7.77 (1H, d, *J* = 7.6 Hz, ArH), 7.54 (1H, t, *J* = 8.0 Hz, ArH), 6.73 (1H, s, CH_2), 6.49 (1H, s, CH_2), 6.03 (1H, s, CH), 3.72 (3H, s, O-CH_3), 2.15 (3H, s, CH_3) ppm.

Methyl 2-(acetoxy(2-nitrophenyl)methyl)acrylate (4b):

Orange oil; yield: (90%); FT-IR (KBr)(ν_{max}, cm^{-1}): 3014 (C-H ArH), 2960 (C-H aliph.), 2864 (O-CH_3), 1747, 1707 (C=O), 1647 (C=C), 1580 (C-C arom.), 1528, 1358 (NO_2), 1443 (C-H bend), 1223, 1157 (C-O-C), 962 (olefinic C-H bend), 739 (arom. C-H bend). ^{1}H NMR: δ = 8.05 (1H, dd, *J* = 8.0, 0.8 Hz, ArH), 7.67 (1H, dt, *J* = 7.6, 0.8 Hz, ArH), 7.60 (1H, d, *J* = 6.8 Hz, ArH), 7.53 (1H, dt, *J* = 7.7, 1.4 Hz, ArH), 7.32 (1H, s, CH_2), 6.47 (1H, s, CH_2), 5.59 (1H, s, CH), 3.79 (3H, s, OCH_3), 2.16 (3H, s, CH_3) ppm.

Methyl 2-(acetoxy(4-nitrophenyl)methyl)acrylate (4c):

Yellow solid; yield: (95 %); mp 68-70 ^{o}C; FT-IR (KBr)(ν_{max}, cm^{-1}): 3026 (Ar-H), 2966, 2922 (C-H aliph.), 2852 (O-CH_3), 1745, 1711 (C=O), 1649 (C=C), 1607, 1578 (C-C arom.), 1518, 1350 (NO_2), 1444 (C-H bend), 1221, 1155 (C-O-C ester), 955 (olefinic C-H bend), 837 (arom. C-H bend). ^{1}H NMR: δ = 8.21 (2H, d, *J* = 8.80 Hz, ArH), 7.59 (2H, d, *J* = 8.80 Hz, ArH), 6.73 (1H, s, CH_2), 6.49 (1H, s, CH_2), 6.00 (1H, s, CH), 3.74 (3H, s, OCH_3), 2.16 (3H, s, CH_3) ppm.

Conclusion

In Summary, we have developed an efficient method for the acetylation of Baylis-Hillman adducts using Fe_3O_4 nanoparticles as catalyst at room temperature under solvent-free conditions. The reaction profile is clean, simple operation, short reaction time, excellent yields, easy separation of the products, and reusability of the catalyst are main advantages of present protocol.

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