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Development of Drug Intermediates *via* Alkylation Using $Fe(acac)_3$ as Transition Metal Catalyst

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ABSTRACT

The main challenges in the modern synthesis prompt the method development using iron catalyst. The alkylation of active methylene compounds in the presence of $Fe(acac)_3$ as transition metal catalyst were performed to afford the respective alkylated products. This method is very efficient for the synthesis 4-membered amide ring (β-lactam).

Keywords: Alkylation, $Fe(acac)_3$, benzylbromide; ethyl 2-cyano-3-phenylpropanoate.

INTRODUCTION

The carbon-carbon bond forming reaction, which provide important tools for constructing building blocks, is a basis not only of organic synthesis but also of future technologies[1]. A variety of transition metal (TM) catalyzed reactions have been developed for connecting unsaturated carbon centers such as *sp*-or sp^2 carbons and provided a variety of useful methods for synthesizing functional materials involving conjugated systems[2]. On the other hand, catalytic reactions forming carbon–carbon bonds at the *sp3*-carbons were much less developed[3]. The last three decades have witnessed increasing efforts to develop highly efficient and selective tools for the catalysed formation of carbon–carbon and carbon–heteroatom bonds one of the major challenges[4]. The alkylation of carbon nucleophiles such as stabilized carbon enolates and active methylene compounds such as malonates, cyanoesters, and malononitriles represent an important class of nucleophiles that can be used for synthesis of biologically active molecule[5] thus, considerably expanding the scope of the metal-assisted arylation reaction[6].

The History of iron began in 1891 when Mond[7] and Berthelot[8] discovered one species of iron: pentacarbonyl iron. In 1941, Kharasch[9] investigated the homocoupling of Grignard reagents by different metals and observed that iron was successful in catalyzing this reaction. The use of iron metal in organic synthesis has received considerable attention in recent times because of its great potential in a variety of organic transformations[10]. However, the use of Iron salt as important Lewis acid in organic transformation such as Kumada-like Coupling[11], Oxidative Coupling[12], Alkylation[13], Allylic Substitution[14], Aryl C-H Activation[15], N-Arylatation[16], C-N bond cleavage[17] and Cyclization of ene-dienes[18] etc. We have to demonstrated that substituted cyano ester is an important functionality in the field of agriculture and pharmaceutical industry[19]. It could serve as a source for amines, amide, ester, lactam and lactones.

In 1907, Staudinger[20] reported first synthesis of β-lactam ring. The β-lactams as a class acquired immense importance only after the discovery of penicillin by Fleming[21] in 1928 and its structural confirmation by X-ray crystallography[22] which unambiguously confirmed the presence of 4-membered amide ring (β-lactam).

The β-amino acids are basic key structure of peptides, peptidomimetics and other natural products[23]. In addition; they are essential chiral building blocks for the synthesis of pharmaceuticals. Furthermore, which is present in potentially biologically active molecules and interest as antibiotics[24]. Some β-amino acids show interesting pharmacological properties by themselves, but most are valuable intermediates for synthesis of novel molecules with biological and pharmacological activity. The β-amino acids are subdivided into β^2-, β^3- and $\beta^{2,3}$- amino acids depending on the position of the side chain at the 3-aminocarboxylic acid core[25]. Additionally, cyclic amino acids have the amino and ester moiety as substituent's or the amino group is integrated into the heterocyclic structure, such as β -proline[26].

We herein report the design and development of a transition metal $Fe(acac)_3$ as catalyst, for the alkylation of ethyl cyano acetate with benzyl bromide to afford alkyl cyano ester in good to excellent yields for the first time (Scheme 1).

EXPERIMENTAL SECTION

Materials and Methods

All reactions were carried out in dry solvents, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}, Merck). Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in 2, 4-dinitrophenylhydrazine/ anisaldehyde and charring on hot plate. All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and Mass. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 MHz spectrometer. IR spectra were obtained on a Shimadzu FTIR-8400 with samples loaded as thin films on KBr plate, neat or with CH_2Cl_2 as indicated. Mass spectra were recorded at an ionization potential of 70 eV; Melting points recorded are uncorrected. Column chromatography on silica gel (100-200 mesh) was performed with reagent grade ethyl acetate and hexane as an eluent.

Typical experimental procedure

A mixture of Ethyl cyano acetate (531mg, 4.7 mmol), $Fe(acac)_3$ (17 mg, 1 mol %) in DMSO (4 mL) was stirred at room temperature for 10 min and finally benzyl bromide (803mg, 4.7 mmol) was added and reaction stirred for 3.1h. Reaction monitored by TLC, and extracted with EtOAc (2 X 20mL). The organic layer was washed with brine solution (2 X 20mL) and dried with Na_2SO_4. Evaporation of solvent furnished the crude product.It was then purified by column chromatography over silica gel with 2% EtOAc in petroleum ether to give 3a(884mg, 89%) pure product.

2-Cyano-3-phenyl-propionic acid ethyl ester[1]: 89%; Colorless liquid; IR(KBr): 3032, 2984, 2933, 2249(C≡N), 1745(O-C=O), 1604, 1495, 1259, 1073, 847, 753, 694 cm^{-1}; ^{1}H-NMR(300MHz, $CDCl_3$): δ 7.37-7.26 (5H, m) [Ar-*H*]; 4.23 (2H, q, *J* = 7.2 Hz, $OC\mathit{H}_2CH_3$), 3.71 (1H, dd, *J* = 8.1, 5.7 Hz), 3.31-3.15 (2H, dABq, *J* = 14.1, 8.5 Hz, Ph-$C\mathit{H}_2$), 1.26 (3H, t, *J* = 7.2 Hz, $OCH_2C\mathit{H}_3$);^{13}C NMR (75MHz, $CDCl_3$):δ 165.85 (C, O-C=O), 135.10 (C), 128.76 (2 x CH), 128.69(2 x CH), 127.7 (CH), 115.9 (C, *C*≡N), 62.8 (CH_2, $OC\mathit{H}_2CH_3$), 39.6 2(CH), 35.57 (CH_2, $PhC\mathit{H}_2$),13.9 (CH_3, $OCH_2C\mathit{H}_3$); MS (m/z): Exact Mass: 203.09, mol.wt 203.24, m/z: 203.

Spectroscopic Data of new compounds

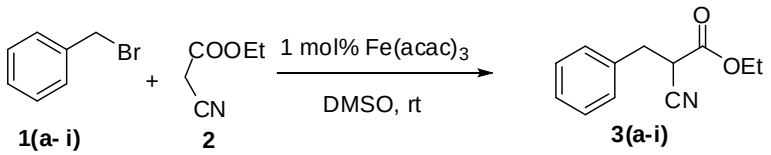
1) Ethyl 2-cyano-3-(3,5dimethylphenyl)propanoate(3c): 89%.Colorless oil IR(KBr): 2972, 2932, 2231 (C≡N), 1743 (O-C=O), 1591, 1018, 758, 692 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ 6.92 (1H, s) 6.87 (2H, s) [Ar-*H*]; 4.23 (2H, q, *J* = 6.7 Hz, $OC\mathit{H}_2CH_3$), 3.68 (1H, dd, *J* = 8.5, 5.7 Hz), 3.17 (2H, dABq, *J* = 13.9, 8.6 Hz, Ph$C\mathit{H}_2$), 2.29 (6H, s, Ph$C\mathit{H}_3$), 1.27 (3H, t, *J* =7.1 Hz, $OCH_2C\mathit{H}_3$);^{13}C NMR (75MHz, $CDCl_3$):δ 165.61 (C, O-C=O), 138.32 (2 x C), 135.12 (C), 129.30 (CH), 126.68 (2 x CH), 116.18 (C, *C*≡N), 62.79 (CH_2, $OC\mathit{H}_2CH_3$), 39.69 (CH), 35.63 (CH_2, $PhC\mathit{H}_2$), 21.15 (2 x CH_3), 13.88 (CH_3, $OCH_2C\mathit{H}_3$); MS (m/z): Exact Mass: 231.13, mol.wt: 231.29, m/z: 231.

2) Ethyl 3-(2-(benzyloxy)phenyl)-2-cyanopropanoate (3g): 90%, Colorless solid, m.p. 42°C; IR(KBr): 2984, 2930, 2234 (C≡N), 1738 (O-C=O), 1516, 1458,1372, 1265, 1109, 1082, 752, 733, 702 cm^{-1};^{1}H-NMR (300MHz, $CDCl_3$): δ 7.42 (5H, m), 7.30-723(2H, m)6.97-6.92 (2H, m) [Ar-*H*]; 5.12 (2H, s) 4.19 (2H, q, *J* = 7.1 Hz, $OC\mathit{H}_2CH_3$), 3.96 (1H, dd, *J* = 9.0, 6.2 Hz), 3.43(1H, dd, *J* = 13.4, 6.7 Hz), 3.13(1H, dd, *J* = 13.4, 6.7 Hz), 1.24 (3H, t, *J* =7.1 Hz, $OCH_2C\mathit{H}_3$);^{13}C NMR (75MHz, $CDCl_3$): δ 165.9 (C, O-C=O), 156.4(C), 136.6(C), 131.2, 129.2 (CH), 128.6 (2 x CH),128.0, 127.0 (2 x CH), 123.9, 121.0, 116.5, (C, *C*≡N),111.7, 69.9 (CH_2, $OC\mathit{H}_2CH_3$), 62.6, 39.6 (CH), 37.4 (CH_2, $PhC\mathit{H}_2$), 31.7, 13.9 (CH_3, $OCH_2C\mathit{H}_3$); MS (m/z): Exact Mass: 309.14, mol. wt: 309.36, m/z: 309.

RESULT AND DISCUSSION

As part of our ongoing research program herein, we wish to report on a new catalyst for alkylation. However, we are first time demonstrating that the use of $Fe(acac)_3$ for alkylation

of ethyl cyanoacetate 2 benzyl bromide 1a with furnished the 3a in 89 % yield in DMSO at ambient reaction condition.



Scheme 1

The formations of all products were confirmed unambiguously from their corresponding spectral analysis. ^{1}H NMR of the 3a shows characteristic signals at δ 3.31-3.15 (dABq) and 3.71(dd) due to methylene (CH_2) and methine (CH) protons respectively. Its ^{13}C NMR spectrum shows typical signals at δ 39.62, 35.57, 115.9 and 165.85 corresponding to the methine (CH), methylene (CH_2), *C*≡N and ester carbonyl carbon (CO_2Et) respectively. Its IR spectrum showed typical absorption band at 2234 cm^{-1} and 1738 cm^{-1} confirming the presence of cyanide and ester functionality.

While in DMF and DMSO catalyze the reaction to provided in good yields in 3.0-3.5h, the other solvents provided lower yields under similar reaction condition. We found that DMSO is having the yield of 3a 89 %, has been emerged as the most convenient solvent and DMF is also having the yield of 3a 87 %. It is interesting to note that (DMF and DMSO) are highly polar solvent and they have lack of the ability to form hydrogen bonding. But these solvents are still able to solvate cation by donating electron from oxygen. Therefore, we measured the ^{1}H-NMR spectrum of ethyl cyanoacetate in DMSO-D_6 as well as in $CDCl_3$ as solvent. In case of DMSO-D_6, singlet appearing at δ 3.99 while it was at δ 3.48 in $CDCl_3$. This difference in chemical shift of the singlet of ethyl cyanoacetate could be explain by presence of enolization in DMSO as solvent (Figure 1). As a result of investigation several solvents, DMSO was found to be the most effective solvent for promoting favorable reaction condition 3a was obtained in 89 % yield.

^{1}H-NMR of Ethyl Cyanoacetate (2) In $CDCl_3$ **^{1}H-NMR of Ethyl Cyanoacetate (2) In DMSO-D_6**

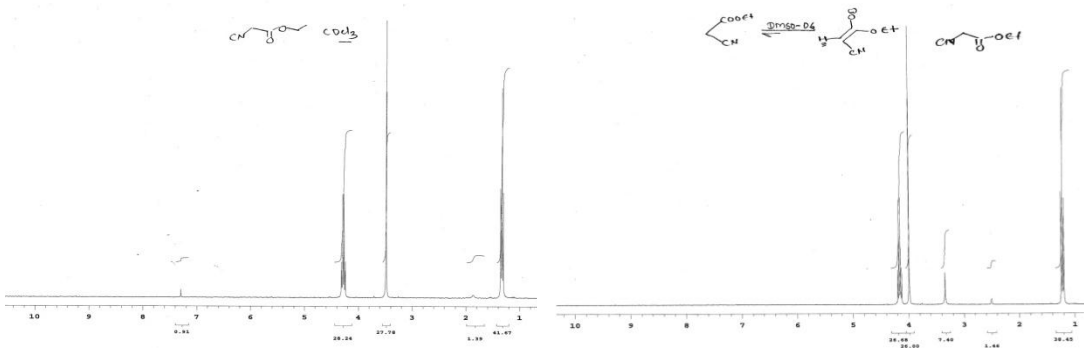
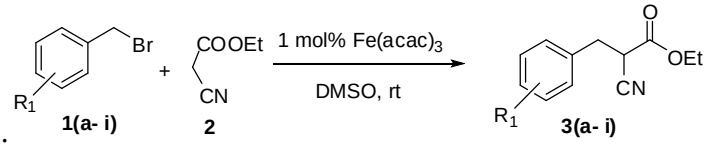


Figure 1

Encouraged by this result we examined that probe the scope of the benzyl bromide substrate are summarized in Table 1. Benzyl bromide bearing both electron withdrawing and electron donating underwent clean reactions, high yield and reasonably fast. The reaction conditions are mild enough to tolerate sensitive functionalities such as (OMe, Br, Cl, and NO_2) with desired products (3a-3i). A series of benzyl bromide (1a-1i) have been prepared from alcohol.[27] The substituent on benzyl bromidewith both electron withdrawing and electron donating but significant change was not observed in the yield. In this method we found that the yield of reaction depends on the stability of benzyl bromide towards the catalyst and exact reaction condition.



Scheme 2

Table 1: Alkylation of ethyl cyano acetate with substituted Benzyl bromide catalyzed by $Fe(acac)_3$ in DMSO

Entry.	R_1	Product	Time hr	Yield (%)[b]
1	H	3a	3.1	89
2	4-Me	3b	3.0	90
3	$3,5(Me)_2$	3c	4.0	89
4	4-Cl	3d	2.5	92
5	4-Br	3e	3.0	90
6	4-OMe	3f	3.2	86
7	2-OBn	3g	3.1	90
8	3-Cl	3h	3.0	91
9	$4-NO_2$	3i	3.5	89

[a]Reaction conditions i)Benzylbromide (4.7 mmol), ethyl cyanoacetate (4.7 mmol) and $Fe(acac)_3$ (1 mol%) DMSO 4mL, rt; [b]Isolated yield after chromatographic purification and characterized by spectral data (IR, ^1H, ^{13}C NMR and mass).

CONCLUSION

In summary, we have reported $Fe(acac)_3$ catalytic methodology for the alkylation of cyano esters to substituted benzyl bromide to provide good yield (86-92 %) with good selectivity and which is readily accessible from commercially available material. Advantages offered by this method include short reaction times and its potential in preparing other biologically active molecules containing nitrogen.

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