



NICKEL ACETYLACETONATE CATALYZED KNOEVENAGEL CONDENSATIONS AT ROOM TEMPERATURE

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Nickel acetylacetonate (Ni(acac)₂) as a catalyst was tested in Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate in DMSO to provide α -cyano ethyl cinnamate. The substituted benzaldehydes and 3-methylbutyraldehyde gave similar reaction and the corresponding products were obtained in good yields (78-92%) under clean and straightforward condition.

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Introduction

The Knoevenagel condensation is one of the most important C-C bond forming reaction, and the cyanoalkene reaction products have proved to be versatile intermediates in the organic synthesis.¹ These compounds are powerful electrophiles readily undergo Michael addition reactions and result in the synthesis of heterocyclic compounds.² They represent a significant functionality in organic transformations due to their easy conversion into elaborated functionalities of amines, amides, esters, lactams and lactones.³ Moreover, conjugated cyano alkenes are important compounds due to their biological properties.⁴

There are numerous known methods to access C=C bond formation, but these reactions are mainly catalyzed by amine-quaternary ammonium salt double activation catalysts⁵ and require harsh reaction conditions. The yields generally are limited. These methods particularly are unsuitable for atom economic synthesis.⁶ Development of new synthetic methodologies using transition metal Lewis acid catalyst has increased importance⁷ due to the numerous advantages like low cost, neutral condition, ambient temperature, high selectivity, and avoid of salt-type by-product formation. Transition metal catalysts mostly promote the activation of C-H functionalities due to their high ability to generate carbanion equivalent species.⁸

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 F₂₅₄, 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 a hot plate. All products were characterized by ¹H NMR, ¹³C NMR, IR, and mass spectrometry. ¹H NMR and ¹³C NMR spectra 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 CH₂Cl₂ 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.

Synthesis of 2-cyano-3-phenylacrylic acid ethyl ester (3a)

A mixture of ethyl cyanoacetate (531 mg, 4.7 mmol) Ni(acac)₂ (10 mg, 0.9 mol %) in DMSO (2 mL) were stirred at room temperature, aldehyde(benzaldehyde) (498 mg, 4.7 mmol), was added, the reaction mixture was further stirred for 1.0 h. The progress of the reaction was monitored by taking TLC. After completion of the reaction, the mixture was diluted with water. The reaction mixture was extracted with EtOAc (2 x 20 mL) and the organic layer was washed with brine and dried with Na₂SO₄. Evaporation of solvent furnished the crude product that was purified by column chromatography over silica gel using EtOAc in petroleum ether to give a pure solid product. Yield: 85 %, M.p.: 68 °C, IR: ν =1726 (C=O, ester) and 2225 (CN) cm⁻¹; ¹H NMR(CDCl₃, TMS): δ 1.43 (t, 3H, *J*= 7.2 Hz), 4.38 (q, 2H, *J*= 7.2 Hz), 7.53 (d, 2H, *J*= 7.8 Hz), 8.13 (d, 3H, *J*= 7.8 Hz), 8.26 (s, 1H)

The other compounds have been synthesized in an analogous way with using the solvent and reaction time given in Table 1.

Result and Discussion

The nickel acetylacetonate (Ni(acac)₂) is a crucial Lewis acid catalyst proved to be highly effective in a various organic reaction like Michael addition,⁹ Grignard reactions,¹⁰ alkylations, alkenylations,¹¹ aryl C-H activation coupling reactions,¹² N-arylations and C-N bond cleavage,¹³ cyanoesterification¹⁴ and homocoupling reactions.¹⁵

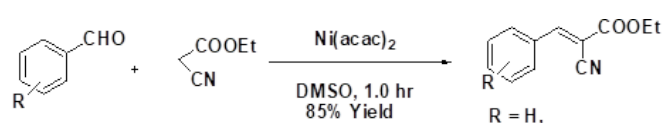
As part of our ongoing program, we inspired and encourage developing new methodologies for Knoevenagel condensation of ethyl cyanoacetate with aldehydes and

cyclic ketones. We are demonstrating first time using Ni(acac)₂ as a catalyst in Knoevenagel condensation reaction. The Knoevenagel condensation of benzaldehyde (**1a**) with ethyl cyanoacetate (**2**) furnished the **3a** in EtOH with good yield at ambient reaction condition in 1 h. For optimization of reaction condition, we screened the role of solvents and temperature. In EtOH at 25 °C, the **3a** was formed in 80 % yield in 8 h then reaction condition changed heating to reflux for 1 h resulted in 85% yield of **3a** on reflux condition. When the reaction was carried out in polar protic solvents like MeOH, the yield was decreased, i.e., 80 % while other polar solvents such as acetonitrile and acetone gave **3a** with good yield under the same conditions. Aprotic polar solvents like DMF gives 83 % and DMSO 85% were proved to be the best choice for these syntheses during short reaction time at room temperature.

The products were obtained in high yield with increasing temperature because of the endotherm character of the reaction. Due to enolization in DMSO as solvent¹⁶ polar aprotic solvents (DMF and DMSO) was selected and as a result of detailed studies, DMSO was found to be the most effective solvent for promoting favorable reaction conditions. in DMSO **3a** was formed with good yield in 1 h even at room temperature.

This result demonstrated that Ni(acac)₂ is an effective catalyst for Knoevenagel condensation reaction, therefore we have tested its activity in the reaction of benzaldehyde with other active methylene group-containing compounds. The analogous reaction with malononitrile proceeded very fast and gave a corresponding product with excellent yield (90 %), while with ethyl acetoacetate the corresponding product was formed in moderate yields (75 %). Diethyl malonate gave very low yield 20 % even under long reaction time (12 h). It is noted that according to previous reports the presence of cyano moiety is a critical condition to generate carbon nucleophile and promote insertion of the metal into the C-H bond and hydrogen shift by metals to oxo species.^{17,18}

After finding optimized solvent and reaction condition as shown in Scheme 1, we have studied the influence of the amount of catalyst in DMSO on the yield of **3a**.



It has been observed that the model reaction did not initiate at all without the catalyst for 12 h in DMSO. The amount of catalyst used for the reaction was varied between 0.5 and 10 mol %. Decreasing the amount of catalyst loading from 10 mol % to 1 mol %, the yield of **3a** is hardly changed. The reaction rate, however, decreased and with 0.5 mol % of catalyst was found the less yield (70 %). It shows that the minimum amount of catalyst to give good results is 0.9 mol %.

The usability of Ni(acac)₂ catalyst was examined in the reaction of variously substituted benzaldehydes, 3-methylbutyraldehyde and cyclic ketones (cyclohexanone or cyclopentanone) with ethyl cyanoacetate. All reactions were

performed in the presence of 0.9 mol% Ni(acac)₂ catalyst in DMSO as a solvent. The results are summarized in Table 1. There was no particular influence of the electron donating and withdrawing substituents on the yield of desirable products comparing with unsubstituted benzaldehyde.

Table 1. Synthesis of Knoevenagel condensation products in the presence of 0.9 mol % Ni(acac)₂ from oxo-compounds and ethyl cyanoacetate in DMSO at room temperature

Starting oxo compound	Reaction time, h	Yield, %
Benzaldehyde	1.0	85
2,5-Dimethylbenzaldehyde ^a	1.0	90
4-Methoxybenzaldehyde	1.0	87
3-Methoxybenzaldehyde	1.5	86
4-Chlorobenzaldehyde	1.3	92
4-Nitrobenzaldehyde	0.3	85
4-Bromobenzaldehyde	1.4	78
2-Nitrobenzaldehyde	0.3	80
2-Benzoyloxybenzaldehyde ^a	1.3	81
3-Methylbutyraldehyde	1.0	78
Cyclopentanone	1.0	78
Cyclohexanone	1.0	78

^anew product

Neither the acid sensitive alkoxy nor the halide substituent has any coupling or other by-reaction, but salicylaldehyde resulted in coumarin in 83 % yield under 3 h. Salicylaldehyde hydroxyl group was protected with benzyl group when the condensation reaction proceeded under the same conditions gave above giving 81 % yield. The aliphatic aldehyde, 4-methylbutyraldehyde gave the desired product with 78 % yield in 1 h, and cyclic ketones (cyclopentanone and cyclohexanone) provided 78% and 78% yields, under 1.0 h, respectively.

Conclusion

We could demonstrate that the formation of C=C bond can be catalyzed with Ni(acac)₂ in a reaction of CN-group containing active methylene reactants and aldehydes or ketones under neutral condition without formation of salt-like byproducts. The present methodology can be applied in the synthesis of β -lactam type drugs.

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