



ONE-POT MULTI-COMPONENT GRINDING SYNTHESIS OF CYANOACETYL HYDRAZENE LIGANDS

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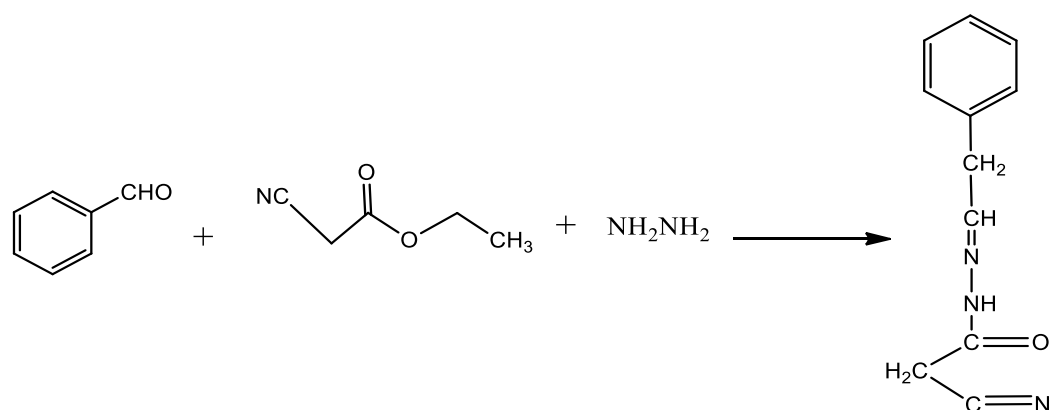
Abstract: - A rapid, improved and ecofriendly synthesis of cyanoacetyl hydrazene ligands is carried out via one-pot multicomponent reaction of ethyl cyano acetate (1 mmol) and hydrazine hydrate (1 mmol) and aromatic aldehyde (1 mmol) in pestle mortar at room temperature. The structures of the synthesized products were assigned on the basis of IR and NMR spectral data. The major advantageous features of this green protocol excellent yields, shorter reaction time, and easy work-up.

Keywords: Heterocycles, ecofriendly, one-pot, multi-component synthesis, cyanoacetyl hydrazene ligands.

Introduction

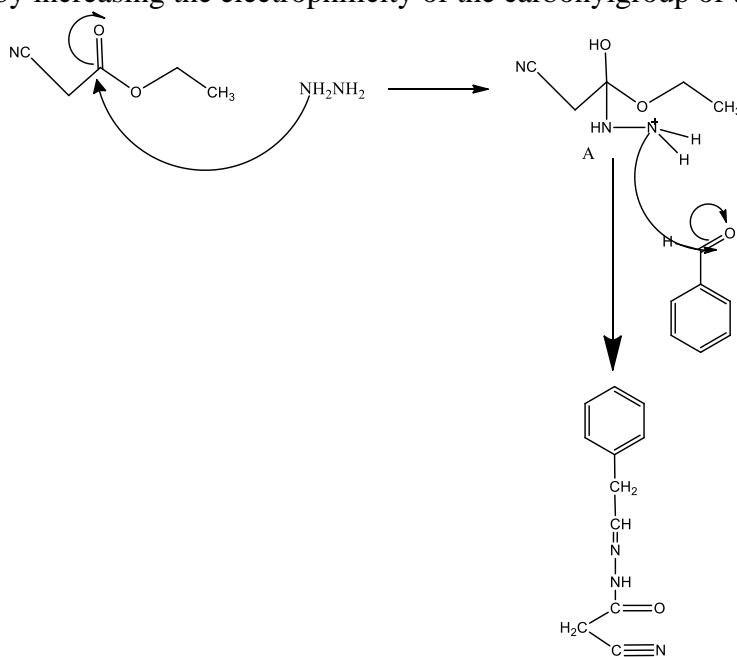
Cyanoacetic acid hydrazide is a convenient and versatile intermediate for the synthesis of heterocyclic compounds. The β -functional nitrileⁱ⁻ⁱⁱⁱ moiety of the molecule is important unit for addition followed by cycloaddition or cyclization with numerous reagents gives heterocyclic compounds with one or several hetero atoms that are interesting as herbicides,^{iv} pharmaceuticals,^{v,vi} dyes^{vii,viii} and antibacterial agents.^{ix} Their reactions with dinucleophiles usually result in the formation of polycyclic ring systems which may be the skeleton of important heterocyclic compounds. In various publications, novel synthesis of azoles,^{x,xi} azines^{xii} and azoloazines^{xiii} have been reported utilizing β -functional nitriles as starting components. Among the β -functional nitriles, cyanoacetic acid hydrazide and their analogues are especially important starting materials or intermediates for the synthesis of various nitrogen-containing heterocyclic compounds. Present research work deals with the effective use of cyanoacetic acid hydrazide in the synthesis of a variety of polyfunctional heterocyclic compounds with biological interest.

The literature survey reveals that hydrazone compounds exhibit significant biological importance. This compound when coordinated to metal centers enhances antibacterial and antifungal activity. Keeping this in mind in the present work synthesis of cyano acetyl hydrazone compounds have been carried out by multi-component grinding method, using pestle and mortar at room temperature. Our methodology confers advantages such as short reaction time (**Scheme-1**).



Scheme-1. Synthesis of cyanoacetyl hydrazene ligands

A proposed mechanism for the reaction is outlined in **Scheme 2**. Based on this mechanism, it is highly probable that the carbonyl groups of ethyl cyanoacetate are activated, which occurs when the carbonyl oxygen is coordinated. Therefore, it may be proposed that this facilitates the formation of intermediate [A] by increasing the electrophilicity of the carbonyl group of the aldehyde.



Scheme 2. Proposed molecular mechanism of cyanoacetyl hydrazene ligands.

Experimental

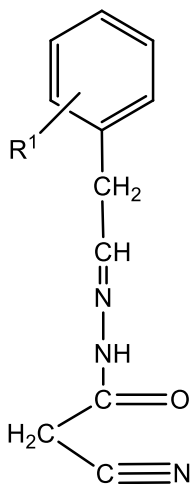
Materials and methods:

All materials were commercial reagent grade and purchased from Sigma Aldrich E-Mark/Rankem. All reactions were monitored by thin-layer chromatography (TLC) with E-merck silica gel 60 F254 pre-coated plates (0.25mm) and visualization was performed by UV and iodine chamber. Melting points were measured in open glass capillary and are uncorrected. FT-IR spectra of compounds were recorded using KBr pellets on Shimadzu IR Affinity-1, Fourier-Transform infrared spectrometer. NMR spectra were recorded with a Bruker AV III spectrometer at 400 MHz (^1H NMR) and 300 MHz (^{13}C NMR) using CDCl_3 as the solvent with tetramethylsilane (TMS) as internal standard. Elemental analysis was performed on Elementarvario MICRO cube analyser. All yields refer to isolated products.

Synthesis of cyanoacetyl hydrazene Ligands involving one-pot multi-component reaction using grinding method:

A mixture of ethyl cyano acetate (1 mmol), hydrazine hydrates (1 mmol) and aryl aldehyde (1 mmol) was subjected to grinding at room temperature for 10 min in pestle mortar. The progress of the reaction was monitored by TLC. The resultant solid was dissolved in acetone. The solid isolated was dried in air. The crystalline pure cyanoacetyl hydrazene ligands were obtained by further recrystallization from acetone.

Table 1: - Physical data of synthesized cyanoacetyl hydrazene ligands using with multi-component synthesis procedure



Entry	R ¹ (aldehyde)	Ethyl cyano acetate	Hydrazine hydrate	Product	Time (min)	Yield (%)	M.P.
1	H	Ethyl cyano acetate	NH ₂ NH ₂	4A	20	95	174 °C
2	Cinnamaldehyde	Ethyl cyano acetate	NH ₂ NH ₂	4B	15	94	200 °C
3	4-OH	Ethyl cyano acetate	NH ₂ NH ₂	4C	10	98	104 ⁰ C
4	4- NO ₂	Ethyl cyano acetate	NH ₂ NH ₂	4D	15	92	247 ⁰ C
5	2-OH	Ethyl cyano acetate	NH ₂ NH ₂	4E	12	90	240 ⁰ C
6	3- Cl	Ethyl cyano acetate	NH ₂ NH ₂	4F	10	94	104 ⁰ C
7	4- OCH ₃	Ethyl cyano acetate	NH ₂ NH ₂	4G	20	89	236 ⁰ C

8	4- Cl	Ethyl cyano acetate	NH ₂ NH ₂	4H	15	96	215 ⁰ C
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Spectral data of 2-cyno-N-(3-phenylallylidene) acetohydrazide (4A): solid powder, m.p. 174° C; **IR (KBr) cm⁻¹** 3192.32 (N-H), 2973.66 (C-H), 2264.04 (CN), 1694.22 (C=O), 1404.69 (C=C). **¹H NMR** (400 MHz, CDCl₃) ppm: 10.36 (s, 1H), 3.10 (s, 3H), 7.49–8.13 (m, 5H, Aromatic), 1.95 (m, 1H). **¹³C NMR** (300 MHz, CDCl₃) ppm: 166.76, 140.06, 134.94, 132.98, 130.48, 129.89, 129.05, 128.66, 127.69, 124.28, 27.96. Anal. Calcd. for: C₁₁H₁₁N₃O C, 65.66; H, 5.51; N, 20.88; O, 7.95. Found: C, 65.52; H, 5.46; N, 20.75; O, 7.89.

Spectral data of 2-cyno-N-(3-phenylallylidene) acetohydrazide (4B): solid powder, m.p. 200° C; **IR (KBr) cm⁻¹** 3424.69 (N-H), 2923.91 (C-H), 2219.74 (CN), (C=O), 1494.29 (C=C). **¹H NMR** (400 MHz, CDCl₃) ppm: 10.26 (s, 1H), 7.34–7.53 (m, 5H, Aromatic). 3.36 (s, 4H), 1.81 (m, 1H). **¹³C NMR** (300 MHz, CDCl₃) ppm: 177.66, 140.06, 134.94, 132.98, 130.48, 129.89, 129.05, 128.66, 127.69, 124.28, 22.28. **ESI MS (m/z):** 212.30. Anal. Calcd. for: C₁₂H₁₁N₃O C, 69.59; H, 5.20; N, 19.71; O, 7.50. Found: C, 69.49; H, 5.10; N, 19.61; O, 7.40.

Spectral data of 2-cyano-N'-(2-(4-hydroxyphenyl)ethylidene)acetohydrazide (4C): solid powder, m.p. 200° C; **IR (KBr) cm⁻¹** 3550.69 (O-H), 3424.69 (N-H), 2923.91 (C-H), 2219.74 (CN), (C=O), 1494.29 (C=C). **¹H NMR** (400 MHz, CDCl₃) ppm: 10.26 (s, 1H), 7.34–7.53 (m, 5H, Aromatic). 3.36 (s, 4H), 5.10 (s, 1H), 1.81 (m, 1H). **¹³C NMR** (300 MHz, CDCl₃) ppm: 177.66, 140.06, 134.94, 132.98, 130.48, 129.89, 129.05, 128.66, 127.69, 124.28, 22.28. **ESI MS (m/z):** 217.09. Anal. Calcd. for: C₁₁H₁₁N₃O₃ C, 60.82; H, 5.10; N, 19.34; O, 14.73. Found: C, 60.49; H, 5.09; N, 19.31; O, 14.63.

Spectral data of 2-cyano-N'-(2-(4-nitrophenyl)ethylidene)acetohydrazide (4D): solid powder, m.p. 200° C; **IR (KBr) cm⁻¹** 3400.69 (N-H), 2900.91 (C-H), 2225.74 (CN), 1494.29 (C=C). **¹H NMR** (400 MHz, CDCl₃) ppm: 10.29 (s, 1H), 7.35–7.53 (m, 5H, Aromatic). 3.36 (s, 4H), 1.70 (m, 1H). **¹³C NMR** (300 MHz, CDCl₃) ppm: 177.66, 140.06, 134.94, 132.98, 130.48, 129.89, 129.05, 128.66, 127.69, 124.28, 22.28. **ESI MS (m/z):** 246.080. Anal. Calcd. for: C₁₁H₁₀N₄O₃, C, 53.66; H, 4.09; N, 22.75; O, 19.49. Found: C, 53.49; H, 4.00; N, 22.65; O, 19.40.

Spectral data of 2-cyano-N-(2-hydroxybenzylidene)acetohydrazide (4E): solid powder, m.p. 240° C; **IR (KBr) cm⁻¹** 3221.30 (N-H), 3450.60 (OH), 2967.69 (C-H), 1677.79 (C=O), 1611.38 (C=C), 2256.80 (CN). **¹H NMR** (400 MHz, CDCl₃) ppm: 13.13 (s, 1H), 10.36 (s, 1H), 3.65 (s, 4H), 7.49–8.13 (m, 4H, Aromatic), 1.95 (m, 1H). **¹³C NMR** (300 MHz, CDCl₃) ppm:

170.46, 140.06, 134.94, 132.98, 130.48, 129.89, 129.05, 128.66, 127.69, 124.28, 29.89. Anal. Calcd. for: C₁₀H₉N₃O₂ C, 59.11; H, 4.46; N, 20.68; O, 15.75. Found: C, 59.00; H, 4.36; N, 20.55; O, 15.65. ESI MS (m/z): 203.25

Spectral data of N-(4-chlorobenzylidene)-2-cyanoacetohydrazide(4F): solid powder, m.p.104° C; **IR (KBr) cm⁻¹** 3442.80 (N-H), 2927.92 (C-H), 2256.23 (CN), 1675.17 (C=O), 1563.05 (C=C).**¹H NMR** (400 MHz, CDCl₃) ppm: 10.65 (s,1H), 2.90 (s,3H). 7.49–8.13 (m, 4H, Aromatic), 1.95(m 1H).**¹³C NMR** (300 MHz, CDCl₃) ppm: 170.46, 140.06, 134.94, 132.98, 130.48, 129.89, 129.05, 128.66, 127.69, 124.28, 24.28. Anal. Calcd. for: C₁₀H₈ClN₃OC, 54.15; H, 3.64; N, 18.96; Cl, 16.00, O, 7.22. Found: C, 54.05; H, 3.54; N, 18.86; O, 7.12. ESI MS (m/z):220.10

Spectral data of 2-cyano-N-(4-methoxybenzylidene) acetohydrazide (4G): solid powder, m.p.236° C; **IR (KBr) cm⁻¹** 3437.67 (N-H), 2960.55 (C-H), 2262.35 (CN), 1678.72, (C=O), 1413.89 (C=C).**¹H NMR** (400 MHz, CDCl₃) ppm: 10.53 (s1H), 3.67 (s 3H), 7.45–7.67 (m, 4H, Aromatic), 2.38(m 3H).**¹³C NMR** (300 MHz, CDCl₃) ppm: 170.46, 133.15, 130.05, 129.17, 128.79, 128.05, 125.63, 115.39, 35.90. Anal. Calcd. for: C₁₁H₁₁N₃O₂C, 60.82; H, 5.10; N, 19.34; O, 14.73. Found: C, 60.72; H, 5.00; N, 19.24; O, 14.63.

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