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RESEARCH ARTICLE

Four - Component Reaction Between Cyanoacetamide, Aryl Aldehydes and Ethyl Acetoacetate with Ammonium Acetate

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Abstract: A new and efficient one-pot synthesis of dihydropyridones derivatives by four-component reaction between cyanoacetamide, aryl aldehydes and ethyl acetoacetate with ammonium acetate using pyridine is described. The reaction was performed in ethanol under reflux conditions and afforded good yields of products.

Keywords: Multi-component reaction, Dihydropyridones derivatives, Ammonium acetate, Cyanoacetamide, Aryl aldehydes

Introduction

Substituted dihydropyridones derivatives are important intermediates in the pharmaceutical, dye and photo industries[1]. Pyridones are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products such as NAD nucleotides, pyridoxol (vitamin B_6) and pyridine alkaloids[2]. Due to their π-stacking ability, some pyridines are used in supramolecular chemistry[3]. Some examples are used as pharmaceuticals (as antimalarial, vasodilator, anesthetic, anticonvulsant and antiepileptic), dyes, additives (as antioxidant), agrochemicals (as fungicidal, pesticidal and herbicidal), veterinary (as anthelmintic, antibacterial and antiparasitic) and also in qualitative and quantitative analysis[4-7]. So far, the most common synthetic methods for the preparation of pyridine ring systems involve: transformation of another ring and cyclizations classified on the basis of the number of ring atoms in each of the components being cyclized: from six ring atoms by $N–C_\alpha$, $C_\alpha–C_\beta$, or $C_\beta–C_\gamma$ bond formation; by formation of two bonds, from [5+1], [4+2], or [3+3] atom fragments; by formation of three bonds, from [4+1+1], [3+2+1], or [2+2+2] atom fragments; and by formation of four bonds, from [3+1+1+1] or [2+2+1+1] atom fragments[8,9]. We have reported synthesis of 4-aryl-3-cyano-2,5-dihydro pyridin-2-one derivatives under solvent-free conditions[10].

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Islamic Azad University, Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H and ^{13}C NMR spectra were obtained on solution in $CDCl_3$ using TMS as internal standard. Column chromatography was performed with Merck silica gel 60, 230-400 mesh. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

In a typical experiment, a mixture of pyridine (10 mol%), aryl aldehydes **1** (1 mmol) and cyanoacetamide **2** (1 mmol) in ethanol (20 mL) was stirred at room temperature for 5 h and was added to it a solution of, ethyl acetoacetate(1 mmol) **3** and NH_4OAc(1 mmol) and was refluxed for 8 h. After completion of the reaction, as indicated by TLC, the product was extracted with ethyl acetate (10 mL). The combined organic extracts were concentrated in vacuum and the resulting product was purified by column chromatography on silica gel with ethyl acetate and n-hexane (1:1) as eluent to afford the pure product.

*Ethyl 5-cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine 3-carboxylate (**1A**)*

White powder, (59%), m.p. 143-145 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3411 (NH), 2234 (CN), 1709 (C=O), MS, *m/z* (%): 284 ($M^{+\cdot}$, 5). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85 %. Found: C, 67.43; H, 5.72; N, 9.75%. ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 0.80(3H, t, $^{3}J_{HH}$ = 7 H_Z, CH_3), 2.38 (3H, s, CH_3), 4.09 (2H, q, $^{3}J_{HH}$ = 7 H_Z, CH_2), 4.16 (H, d, $^{3}J_{HH}$ = 7.1H_Z, CH), 4.47 (H, d, $^{3}J_{HH}$ = 7.1H_Z, CH), 7.26-7.61 (5H, m, aromatic), 13.38(1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 14.50 and 19.27 ($2CH_3$), 41.66 and 41.97 (2CH), 61.23 (CH_2), 108.12 (CN), 114.62 and 146.48 (C=C), 128.25, 128.95, 129.45, 136.47 (aromatic), 163.71 and 165.91 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(4-chlorophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (**2A**)*

White powder, (58%), m.p. 162-164 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3403 (NH), 2273 (CN), 1706 (C=O), MS, *m/z* (%): 318 ($M^{+\cdot}$, 10). Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79%. Found: C, 60.20; H, 4.87; N, 8.63%. ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 1.21(3H, t, $^{3}J_{HH}$ = 7 H_Z, CH_3), 2.49 (3H, s, CH_3), 4.13 (2H, q, $^{3}J_{HH}$ = 7 H_Z, CH_2), 3.66 (H, d, $^{3}J_{HH}$ = 7.1H_Z, CH), 4.48 (H, d, $^{3}J_{HH}$ = 7.1H_Z, CH), 7.10 -7.38 (4H, m, aromatic), 12.74 (1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 14.30 and 18.51 ($2CH_3$), 40,99 and 41.83 (2CH), 60.31 (CH_2), 104.62 (CN), 116.05 and 148.30 (C=C), 129.17, 130.04, 132.99, 137.50 (aromatic), 163.28 and 166.10 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(4-bromophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (**3A**)*

White powder, (61%), m.p.175-177 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3414 (NH), 2210 (CN), 1697 (C=O), MS, *m/z* (%): 363 ($M^{+\cdot}$, 8).Anal. Calcd for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.16; N, 7.71%. Found: C, 52.60; H, 4.25; N, 7.61%. ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 1.22 (3H, t,

$^3J_{HH}$ = 7 H_Z, CH_3), 2.46 (3H, s, CH_3), 4.11 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 3.62 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 4.47 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 7.12 -7.49 (4H, m, aromatic), 7.84(1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 14.12 and 19.03 ($2CH_3$), 40,99 and 41.07 (2CH), 60.97 (CH_2), 107.38 (CN), 113.85 and 146.05 (C=C), 122.72, 129.35, 132.26, 134.93 (aromatic), 162.79 and 165.18 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (**4A**)*

White powder, (57%), m.p. 134-136 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3415 (NH), 2220 (CN), 1705 (C=O), MS, *m/z* (%): 314 ($M^{+\cdot}$, 12).Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91%. Found: C, 64.88; H, 5.70; N, 8.95 %. ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 1.24 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 2.44 (3H, s, CH_3), 3.80 (3H, s, O*C*H_3), 4.16 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.10 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 4.48 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 6.79-7.29 (4H, m, aromatic), 7.82 (1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 14.11 and 18.87 ($2CH_3$), 39.82 and 42.91 (2CH), 55.23 (O*C*H_3), 60.82 (CH_2), 107.61 (CN), 113.39 and 146.02 (C=C), 113.08, 114.13, 120.03, 130.07, 137.51 159.87 (aromatic), 163.20 and 165.02 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(2-nitrophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (**5A**)*

White powder, (54%), m.p. 166-168 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3400 (NH), 2250 (CN), 1704 (C=O), 1346 and 1523 (NO_2). ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 1.10 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 2.57 (3H, s, CH_3), 4.04 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 3.97 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 4.29 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 7.20 -7.98 (4H, m, aromatic), 8.03(1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 13.75 and 18.91($2CH_3$), 39.93 and 41.95 (2CH), 60.97 (CH_2), 106.66 (CN), 114.94 and 147.46 (C=C), 125.58, 128.30, 129.48, 132.90, 134.01, 148.89 (aromatic), 163.08 and 165.22 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(3-nitrophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (**6A**)*

White powder, (68%), m.p. 190-192 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3410 (NH), 2230 (CN), 1707 (C=O), 1319 and 1525 (NO_2).^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 1.09 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 2.35 (3H, s, CH_3), 4.01 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.31 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 4.47 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 7.46 -8.09 (4H, m, aromatic), 10.54 (1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 14.04 and 18.87 ($2CH_3$), 44.81 and 45.94 (2CH), 65.28 (CH_2), 110.05 (CN), 112.13 and 153.14 (C=C), 120.25, 127.97, 134.80, 139.28, 144.37, 153.49 (aromatic), 163.97 and 166.92 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(4-nitrophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (**7A**)*

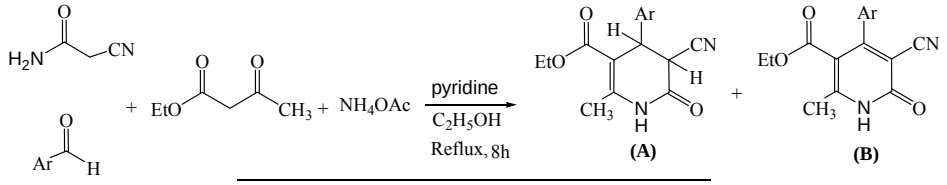
White powder, (63%), m.p. 183-185 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3407 (NH), 2255 (CN), 1715 (C=O), 1345 and 1515 (NO_2), MS, *m/z* (%): 329 ($M^{+\cdot}$, 10).Anal. Calcd for $C_{16}H_{13}N_3O_5$: C, 58.36; H, 4.59; N, 12.76%. Found: C, 58.50; H, 4.71; N, 12.53%. ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 1.06 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 2.31 (3H, s, CH_3), 3.98 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.13 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 4.18 (H, d, $^3J_{HH}$ = 7.1H_Z, CH), 7.31 -8.06 (4H, m, aromatic), 10.28 (1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 14.48 and 19.00 ($2CH_3$), 41.01and 41.71 (2CH), 61.01 (CH_2), 105.54 (CN), 114.59 and 144.77 (C=C), 124.42, 129.40, 148.12, 149.04 (aromatic), 162.34 and 165.70 (2C=O).

*Ethyl 5-cyano-2-methyl-6-oxo-4-(4-nitrophenyl)-1,6-dihydropyridine 3-carboxylate (**7B**)*

White powder, (37%), m.p. 198–200 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3395 (NH), 2225 (CN), 1721 (C=O), 1348 and 1593 (NO_2), MS, *m/z* (%): 327 ($M^{+\cdot}$, 3).Anal. Calcd for $C_{16}H_{13}N_3O_5$: C, 58.72; H, 4.00; N, 12.84%. Found: C, 58.55; H, 4.15; N, 12.99%. ^{1}H NMR (500.1 MH_Z, $CDCl_3$): δ = 0.88 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 2.66 (3H, s, CH_3), 3.96 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 7.25 -8.37 (4H, m, aromatic), 13.54 (1 H, broad s, NH). ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 13.96 and 18.87 ($2CH_3$), 62.46 (CH_2), 105.12 (CN), 114.18, 124.40, 129.01, 142.17, 149.04, 154.22, 159.33, 162.47 (aromatic and olefinic), 164.57 and 165.48 (2C=O).

Results and Discussion

Herein we report a new and efficient one-pot synthesis of polysubstituted dihydropyridones derivatives by four-component reaction between cyanoacetamide, aryl aldehydes and ethyl acetoacetate with ammonium acetate using pyridine. The reaction was performed in ethanol under reflux conditions and afforded good yields of products. (Scheme 1).



Entry	Ar	*yields (A-B)
1	C_6H_5	59 (Only A)
2	4-Cl C_6H_4	58 (Only A)
3	4-Br C_6H_4	61 (Only A)
4	3-MeO C_6H_4	57 (Only A)
5	2-$NO_2C_6H_4$	54 (Only A)
6	3-$NO_2C_6H_4$	68 (Only A)
7	4-$NO_2C_6H_4$	63/37

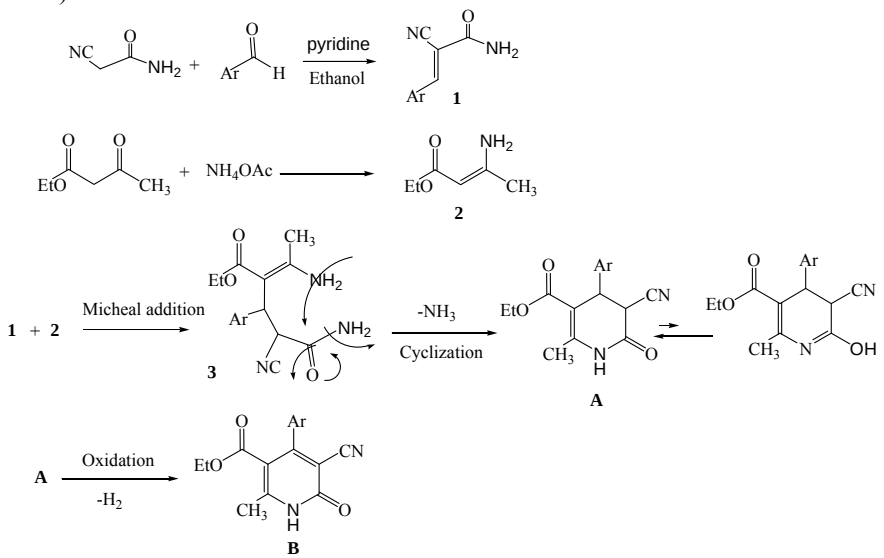
Isolated yields

Scheme 1. Four-component reaction between cyanoacetamide, aryl aldehydes and ethyl acetoacetate with ammonium acetate using pyridine

The reaction course without ammonium acetate in the absence of pyridine a complex mixture was obtained from which no product was isolated. The reaction course in the presence of ammonium acetate without pyridine afforded the product in lower yield and longer reaction time. Using pyridine afforded the product in higher yield and shorter reaction time. The structure of compounds **A** and **B** was deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra data. The mass spectrum of compound **7A** displayed the molecular ion peak at *m/z* = 329 as the base peak. The 500 MH_Z ^{1}H NMR spectrum of compound **7A** exhibited a D_2O-exchangable broad signal at 10.28 ppm for NH proton, and displays one sharp line (δ 2.31 ppm) for the methyl group. Ethyl protons were observed as a triplet ($^3J_{HH}$ = 7 H_Z) at 1.06 ppm and a quartet at 3.98 ppm. Two doublet were observed respectively at 4.13 and 4.18 ppm for methine protons. ($^3J_{HH}$ = 7.1 H_Z). Aromatic protons resonated between 7.31 and 8.06 ppm as multiplets. The ^{13}C NMR spectrum of compound **7A** showed 14 distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 3407 cm^{-1} for NH group. The carbonyl stretching

vibrations observed as strong absorption bonds at 1715 cm^{-1}. The nitrile stretching vibrations observed absorption bond at 2255 cm^{-1}. The nitro stretching vibrations observed absorption bonds at 1345 and 1515 cm^{-1}. The mass spectrum of compound **7B** displayed the molecular ion peak at m/z = 327 as the base peak. The 500 MH_Z ^1H NMR spectrum of compound **7B** exhibited a D_2O-exchangable broad signal at 13.54 ppm for NH proton, and displays one sharp line (δ 2.66 ppm) for the methyl group. Ethyl protons were observed as a triplet ($^3J_{HH}$ = 7 H_Z) at 0.88 ppm and a quartet at 3.96 ppm. Aromatic protons resonated between 7.25 and 8.37 ppm as multiplets. The ^{13}C NMR spectrum of compound **7B** showed 14 distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 3395 cm^{-1} for NH group. The carbonyl stretching vibrations observed as strong absorption bonds at 1721 cm^{-1}. The nitrile stretching vibrations observed absorption bond at 2225 cm^{-1}. The nitro stretching vibrations observed absorption bonds at 1348 and 1593 cm^{-1}. Although the mechanistic details of the above reaction are not known, a plausible mechanism may be advanced to rationalize product formation.

Resumably a intermediate **3** formed from michael addition of product **1** the addition of cyanoacetamide with aryl aldehydes using pyridine and product **2** the addition of ethyl acetoacetate with ammonium acetate which could undergo stepwise cyclization to produce **A** by elimination of NH_3. The amide tautomer is considerably more stable. Admittedly the exchangeable peak in the ^1H NMR spectrum is very high for a NH peak, and would appear to be more consistent with a OH peak. The **A** product is finally converted to **B** by oxidation (Scheme 2).



Scheme 2. Suggested mechanism for formation of compound **A** and **B**

Conclusion

Here we reported a four-component reaction between cyanoacetamide, aryl aldehydes and ethyl acetoacetate with ammonium acetate using pyridine. The reaction was performed in ethanol under reflux conditions and afforded good yields of products. The present method carries the advantage that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification.

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References

1. Misic-Vukovic M, Mijin D, Radojkovic-Velickovic M, Valentic N and Krstic V, *J Serb Chem Soc.,* 1998, **63**, 585.
2. Balasubramanian M, Keay J G, Katritzky A R, Rees C W and Scriven E V F, *Comprehensive Heterocyclic Chemistry II* Vol. 5, Pergamon Press, London, 1996, 245–300 Chapter 6.
3. Constable E C, Housecroft C E, Neuburger M, Phillips D, Raithby P R, Schofield E, Sparr E, Tocher D A, Zehnder M and Zimmermann Y, *J Chem Soc Dalton Trans.,* 2000, **13**, 2219-2228; DOI:10.1039/B000940G
4. Kim B Y, Ahn J B, Lee H W, Kang S K, Lee J H, Shin J S, Ahn S K, Hong C I and Yoon S S, *Eur J Med Chem.,* 2004, **39(5)**, 433-447; DOI :10.1016/j.ejmech.2004.03.001
5. Enyedy I J, Sakamuri S, Zaman W A, Johnson K M and Wang S, *Bioorg Med Chem Lett.,* 2003, **13(3)**, 513-517; DOI:10.1016/S0960-894X(02)00943-5
6. Pillai A D, Rathod P D, Franklin P X, Patel M, Nivsarkar M, Vasu K K, Padh H and Sudarsanam V, *Biochem Biophys Res Commun.,* 2003, **301(1)**, 183-186; DOI:10.1016/S0006-291X(02)02996-0
7. Klimešová V, Svoboda M, Waisser K, Pour M and Kaustová J, *II Farmaco*, 1999, **54(10)**, 666-672; DOI:10.1016/S0014-827X(99)00078-6
8. Jones G, Katritzky A R, Rees C W and Scriven E V F, Editors *Comprehensive Heterocyclic Chemistry II* Vol. 5, Pergamon Press, London 1996, 168–243 Chapter 5, and references cited therein.
9. Katritzky A R, Abdel-Fattah A A A, Tymoshenko D O and Essawy S A, *Synthesis,* 1999, **12**, 2114.
10. Rong L, Han H X, Jiang H, Zhang Q and Tu S, *Synth Commun.,* 2009, **39(6)**, 1027-1034; DOI:10.1080/00397910802463878