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Facile One-Pot Synthesis of Novel Hexahydro-2-quinolinecarboxylic Acids under Solvent-Free Reaction Conditions

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ABSTRACT

A simple and fastthree-component synthesis of new and biologically active hexahydro-2-quinolinecarboxylic acid scaffold 4 was carried out using cyclocondensation reaction of arylmethylidenepyruvic acids 1, 1,3-cyclohexandiones 2 and ammonium acetate 3 under solvent-free conditions and at room temperature. This protocol has the advantages of facility, easy work-up, high yields, short reaction time and environmentally friendly character.

Keywords: Arylmethylidene Pyruvic Acid; Hexahydro-2-quinolinecarboxylic Acids; Solvent-Free Conditions; One-Pot Three-Component Reaction

1. Introduction

Heterocyclic containing nitrogen atom in their skeleton, are abundant in nature and exhibit various important chemical and biological activities. Among them quinolones are of interest because they constitute an important class of natural and non-natural products, many of which have different biological activities such as antimalarial[1], antibacterial[2], antimicrobial[3], and antistaphylococcal activities[4]. Meanwhile, an important class of antibiotics possess 4-quinolone framework in their structure [5]. In addition, they can be used as useful drugs for the treatment of Alzheimer's disease [6]. Recently, Kumar *et al*. showed that some compounds with quinolone skeleton act as a lead in the antidiabetic discovery [7], with effects such as glycologenphosphorylase inhibitors [8-12], or as lipid lowering agent [13] and also for the treatment of metabolic disorder. Also, a number of quinolones are useful in industry as pigments [14].

There are several methods available for the synthesis of quinolinones, for example: 1) the reaction of aromatic aldehydes, dimedone and 3-amino-5-methylpyrazole*via* traditional heating in ethanol [15] or in water, 2) the reaction of Schiff base derivatives and dimedone in the presence of TEBAC as catalyst [16]; 3) the condensation reaction of Baylis-Hillman adductive products with cyclic enamine in *n*-buthanol at reflux conditions [17], and condensation of chalcones with dimedone and ammonium acetate in the presence of PTSA at reflux condition [7]. However, these methods are still not satisfactory in view of using catalyst, organic solvent waste, harsh reaction conditions, long reaction time and operational complexity. These facts and in continuation our previous studies on the development of new facile routes in heterocyclic synthesis [18-25] led us to explore other clean method for the synthesis of a new class of the important quinolinones derivatives.

The recent focus on the green chemical theme of eliminating the use of solvents also encouraged us to extent our studies to neat reaction conditions [26-34]. In this article, we report a very simple, efficient and clean synthetic route to 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid derivatives *via* three-component reaction of arylmethylidenepyruvic acids, 1,3-cyclohexandiones and ammonium acetate in solvent-free reaction condition. Moreover, the produced target compounds as heterocyclic*α*-amino carboxylic acids can be of interest for the synthesis of novel peptides containing a heterocyclic moiety in their skeleton, which could lead to some biologically active compounds. On the other hand, these compounds can be used as an efficient starting material for further multicomponent reactions, because of the possession of both amine and carboxylic acid functional groups.

In this reaction, arylmethylidenepyruvic acid plays an important role as an attractive starting material, for several reasons such as: 1) higher reactivity in comparison to

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usual *α*,*β*-unsaturated ketones; 2) containing active functional groups which can be used for further synthesis, and 3) easy preparation, *i.e*., they were synthesized according to the known procedure [35] by reaction of aromatic aldehydes and pyruvic acid in an aqueous MeOH solution of KOH.

2. Results and Discussion

When the reaction of arylmethylidenepyruvic acids 1, 1,3-cyclohexandiones 2 and ammonium acetate 3 was performed by abrasion in a mortar without using any solvent or catalyst at room temperature, high yields of 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid derivatives were obtained **(Scheme 1)**.

In order to apply this reaction to a library synthesis, various kinds of arylmethylidenepyruvic acids and 1,3-cyclohexandiones were subjected to give the corresponding 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acids 4, and representative examples are shown in **Table 1**.

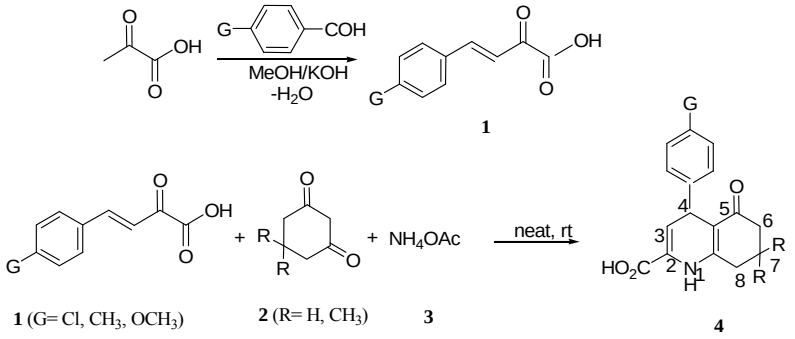
The structures of compounds 4a - 4f were deduced from their spectroscopic data, which displayed in each case, the molecular ion peak at the appropriate *m/z* values. All of the products exhibited a singlet in ^{1}H-NMR at about δ = 4.49 - 4.59 ppm for H-4 and also a distinguished peak at 36.2 - 36.8 ppm for C-4 in ^{13}C-NMR spectroscopy. Meanwhile, ^{1}H-NMR spectra of compounds 4d-f shows two doublets at 2.20 - 2.40 ppm with J = 16 Hz that is related to geminal coupling of H-6 protons. Selected spectroscopic data are reported.

Although we have not yet established the mechanism, a possible explanation is given in **Scheme 2**. Based on this mechanism, we suggest that, the formation of enamine intermediate 4 is occured in the first step by the reaction of 1,3-cyclohexandione 2 and ammonium acetate 3, and due to the *C*-nucleophilic character of the enamine intermediate 4, it is reasonable to assume that 5 can be formed *via* the initial Michael addition between arylmethylidenepyruvic acids 1 and enamine intermediate 4 to generate the Michael adduct 5, which isomerized under the reaction conditions to yield 6. Intramolecular cyclization of 6 gives 3 after dehydration of intermediate 7.

The products are unusual amino acids which could be used for the synthesis of novel peptides with heterocyclic skeleton.

3. Conclusion

In conclusion, we have found that the abrasion of arylmethylidenepyruvic acids, 1,3-cyclohexandiones and ammonium acetate leads to a facile synthesis of 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acids without the addition of any catalysts under solvent-free conditions at room temperature. Besides the simplicity of the method, our synthesized heterocyclic molecules have the potential to be biologically active or used as precursor to produce other biological active compounds. Further investigation about using of these products for the synthesis of novel peptides is going on our laboratory.

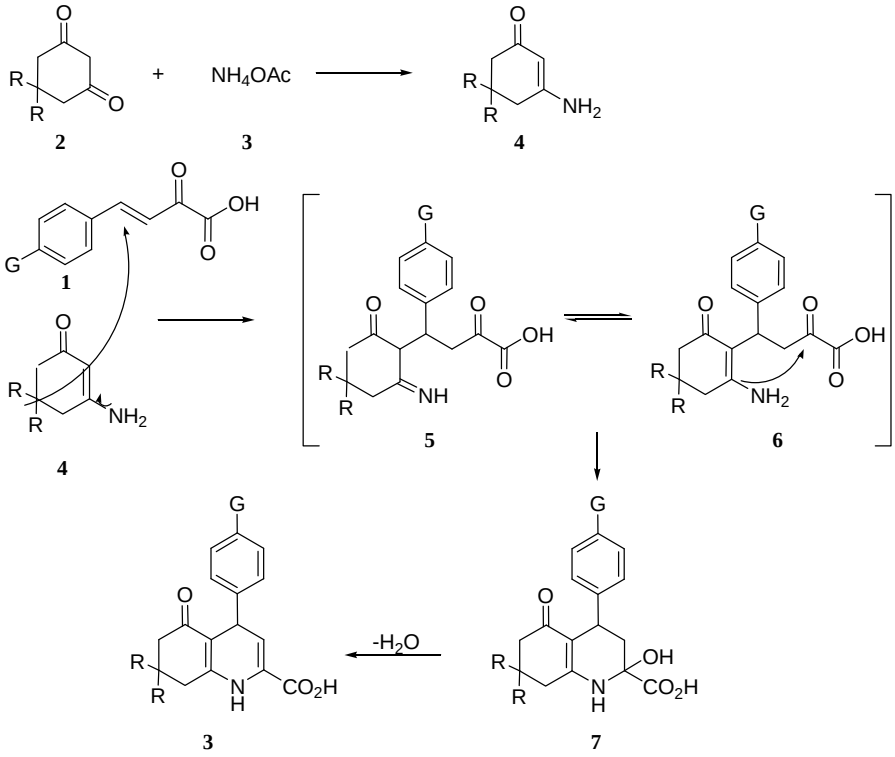


Scheme 1. Efficient synthesis of arylmethylidene pyruvic acid 1 and hexahydro-2-quinolinecarboxylic acid 4a - 4f.

Table 1. Synthesis of -oxo-4-phenyl-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acids 4a - 4f in solvent-free conditions.

Product	G	R	M.p. (˚C)	Yield[a] (%)
4a	Cl	H	213 - 215	95
4b	MeO	H	239 - 241	92
4c	Me	H	253 - 255	93
4d	Cl	Me	250 - 252	98
4e	MeO	Me	248 - 250	95
4f	Me	Me	259 - 261	94

[a]Yields refer to pure isolated products characterized by IR, ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometery.



Scheme 2. The proposed mechanism for the synthesis of 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acids in solvent-free conditions.

4. Experimental Section

Material and methods. Melting points were determined on an *Electrothermal* 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB *FT-IR* (FTLA 2000) spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a *BrukerDRX*-300 *AVANCE* at 300 and 75 MHz, respectively, using TMS as internal standard and DMSO(d_6) as solvent. Mass spectrawere obtained using a *GC-MS Hewlett Packard* (EI, 70 eV) instrument. The purity of prepared compounds was tested by the elemental analysis of C, H, and N elements using a Heraus CHN rapid analyzer.

General procedure for the preparation of compounds 4a - 4f: A mixture of the arylmethylidenepyruvic acids (1, 1 mmol), 1,3-cyclohexandiones (2, 1 mmol) and ammo- nium acetate 3 (0.144 mg, 2 mmol) was abrade in a mortar for 1.5 h. After completion the reaction which monitored by TLC (ethanol: ethyl acetate, 1:1) the reaction mixture was resolved in a required mixture of H_2O: EtOH (in a ratio of 1:1). After the evaporation of EtOH, the pH of solution was reached to 2.5 by adding concentrated solution of HCl, the precipitate was filtered and washed with water and $CHCl_3$ respectively to afford the pure products 4 in high yields(92% - 98%).

Selected data for compounds 4a - 4f:

5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (**4a**): Yield: 289 mg (95%). White powder. M.p. 213˚C - 215˚C. IR (KBr): 3326, 1690, 1654, 1567 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 1.84 (m, 2 H, H-7), 2.16 (m, 2 H, H-8), 2.43 (m, 1 H, H-6), 2.67 (m, 1 H, H-6′), 4.59 (d, J = 5.6 Hz, 1 H, H-4), 5.90 (d, J = 4.8 Hz, 1 H, H-3), 7.17 (d, J = 8.3 Hz, 2 H, H-Ar), 7.30 (d, J = 8.3 Hz, 2 H, H-Ar), 8.70 (s, 1 H, NH), 13.27 (brs, 1 H, COOH) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 20.8, 26.6, 36.4, 36.8, 105.6, 115.4, 127.1, 128.2, 129.1, 130.5, 145.8, 154.3, 163.6, 194.3 ppm. MS (EI 70 eV): *m/z* (%): 305 (M+2, 32), 303 (M$^+$, 55), 285 (32), 257 (100), 192 (85), 174 (61), 146 (93). Anal.Calcd.for $C_{16}H_{14}NO_3Cl$ (303.74): C, 63.27; H, 4.65; N, 4.61. Found: C, 63.20; H, 4.62; N, 4.57.

5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (**4b**): Yield: 275 mg (92%). White powder. M.p. 239˚C - 241˚C. IR (KBr): 3319, 1695, 1570, 1510 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 1.81 (m, 2 H, H-7), 2.17 (m, 2 H, H-8), 2.46 (m, 1 H, H-6), 2.63 (m, 1 H, H-6′), 3.68 (s, 3 H, OCH_3), 4.52 (d, J = 5.6 Hz, 1 H, H-4), 5.91 (dd, J = 5.7, 1.5 Hz, 1 H, H-3), 6.80 (d, J = 8.6 Hz, 2 H, H-Ar), 7.06 (d, J = 8.6 Hz, 2 H, H-Ar), 8.58 (s, 1 H, NH), 13.00 (brs, 1 H, COOH) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 20.9, 26.6, 35.9, 36.8, 55.0, 106.2, 113.6, 116.0, 126.8, 128.2, 139.3, 153.8, 157.5, 163.9, 194.3 ppm. MS (EI 70 eV): *m/z* (%): 299 (M$^+$, 19), 273 (100), 253 (79), 217 (87), 161 (60).

Anal.Calcd.for $C_{17}H_{17}NO_4$ (299.33): C, 68.22; H, 5.72; N, 4.68. Found: C, 68.18; H, 5.68; N, 4.71.

5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (**4c**): Yield: 263 mg (93%). White powder. M.p. 253˚C - 255˚C. IR (KBr): 3322, 1693, 1654, 1568 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.83 (m, 2 H, H-7), 2.15 (m, 2 H, H-8), 2.21 (s, 3 H, CH_3), 2.45 (m, 1 H, H-6), 2.66 (m, 1 H, H-6'), 4.53 (d, J = 5.6 Hz, 1 H, H-4), 5.90 (d, J = 4.9 Hz, 1 H, H-3), 7.03 (s, 4 H, H-Ar), 8.60 (s, 1 H, NH), 13.00 (brs, 1 H, COOH) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 20.6, 20.9, 26.6, 36.4, 36.8, 106.0, 116.2, 126.7, 127.2, 128.8, 134.9, 144.0, 153.9, 163.7, 194.3 ppm. MS (EI 70 eV): *m/z* (%): 283 (M^+, 90), 265 (22), 237 (100), 192 (88), 174 (67), 146 (93). Anal.Calcd.for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.02; N, 4.87.

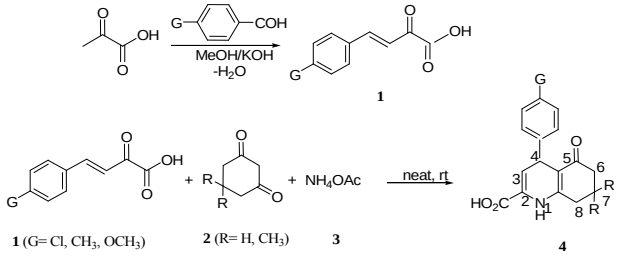
7,7-dimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (**4d**): Yield: 325 mg (98%). White powder. M.p. 250˚C - 252˚C. IR (KBr): 3375, 1701, 1663, 1564 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.91 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.96 (d, J = 16.1 Hz, 1 H, H-6), 2.13 (d, J = 16.1 Hz, 1 H, H-6´), 2.46 (m, 2 H, H-8), 4.57 (d, J = 5.5 Hz, 1 H, H-4), 5.88 (d, J = 5.5 Hz, 1 H, H-3), 7.17 (d, J = 8.3 Hz, 2 H, H-Ar), 7.30 (d, J = 8.3 Hz, 2 H, H-Ar), 8.64 (s, 1 H, NH), 13.28 (brs, 1 H, COOH) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 27.0, 29.0, 31.9, 36.7, 50.3, 104.7, 115.4, 127.2, 128.2, 129.2, 130.5, 146.0, 152.4, 163.7, 193.9 ppm. MS (EI 70 eV): *m/z* (%): 333 (M+2, 22), 331 (M^+, 60), 313 (13), 285 (100), 220 (95), 202 (47), 174 (94). Anal.Calcd.for $C_{18}H_{18}NO_3Cl$ (331.80): C, 65.16; H, 5.47; N, 4.22. Found: C, 65.19; H, 5.51; N, 4.26.

7,7-dimethyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (**4e**): Yield: 311 mg (95%). White powder. M.p. 248˚C - 250˚C. IR (KBr): 3369, 1701, 1661, 1565 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.92 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.96 (d, J = 16.1 Hz, 1 H, H-6), 2.12 (d, J = 16.1 Hz, 1 H, H-6´), 2.45 (m, 2 H, H-8), 3.68 (s, 3 H, OCH_3), 4.49 (d, J = 5.6 Hz, 1 H, H-4), 5.88 (d, J = 5.6 Hz, 1 H, H-3), 6.80 (d, J = 8.5 Hz, 2 H, H-Ar), 7.06 (d, J = 8.5 Hz, 2 H, H-Ar), 8.53 (s, 1 H, NH), 13.00 (brs, 1 H, COOH) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 26.9, 29.1, 31.9, 36.2, 50.4, 55.0, 105.2, 113.6, 116.3, 126.6, 128.3, 139.5, 152.0, 157.6, 163.8, 193.9 ppm. MS (EI 70 eV): *m/z* (%): 327 (M^+, 71), 309 (6), 281 (100), 220 (54), 202 (24), 174 (67). Anal.Calcd.for $C_{19}H_{21}NO_4$ (321.38): C, 69.71; H, 6.47; N, 4.36. Found: C, 69.68; H, 6.50; N, 4.32.

7,7-dimethyl-5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (**4f**): Yield: 292 mg (94%). White powder. M.p. 259˚C - 261˚C. IR (KBr): 3369, 1702, 1661, 1564 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.92 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.95 (d, J = 16.0 Hz, 1 H, H-6), 2.11 (d, J = 16.0 Hz, 1 H, H-6'), 2.21 (s, 3 H, CH_3), 2.45 (m, 2 H, H-8), 4.50 (d, J = 5.2 Hz, 1 H, H-4), 5.88 (d, J = 4.8 Hz, 1 H, H-3), 7.03 (s, 4 H, H-Ar), 8.51 (s, 1 H, NH), 12.95 (brs, 1 H, COOH) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 20.6, 26.9, 29.1, 31.9, 36.8, 50.3, 105.0, 116.2, 126.8, 127.3, 128.8, 135.0, 144.3, 152.1, 163.8, 193.8 ppm. MS (EI 70 eV): *m/z* (%): 311 (M^+, 67), 293 (7), 265 (100), 220 (76), 202 (30), 174 (71). Anal.Calcd.for $C_{19}H_{21}NO_3$ (311.38): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.34; H, 6.82; N, 4.56.

5. Graphical Abstract

Facile One-Pot Synthesis of Novel Hexahydro-2-quinolinecarboxylic Acids, under Solvent-Free Reaction conditions.



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