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Study on the use of commercial vegetable oils as green solvents in synthesis of 2-methyl-4(1*H*)-quinolin-4-ones

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Abstracts: Some substituted 2-methyl-4(1H)-quinolin-4-ones have been prepared from corresponding ethyl β-(substituted)anilinocrotonates. This research contributes to the synthetic method of quinoline-4(1H)-one ring by Conrad-Limpach method with the use of vegetable oils as high boiling-point solvents, which are friendly-environmental, and not expensive friendly-environmental. The structures of different substituted 4(1H)-quinolin-4-ones have been confirmed by using spectroscopic methods (IR, ^{1}H and ^{13}C NMR).

Keywords: Conrad-Limpach synthesis, 2-methyl-4(1H)-quinolin-4-ones, vegetable oils.

1. Introduction

Quinolones have been the subject of continuous academic interest and various structural modifications have resulted in second, third and fourth-generation quinolone antibiotics which are currently used in disease treatments [1], for example ciprofloxacin, is the most consumed antibacterial quinolone worldwide [2]. The bark of Cinchona plant containing quinine was utilized to treat palpitations, fevers and tertians for more than 200 years [3]. Continuous modifications in the basic structure of quinolones have increased their antibacterial spectrum and potency, making quinolones useful for the treatment of urinary, systemic and respiratory tract infections [4]. Insertion of some functional groups, such as formyl or chloride, could help us to bind other helpful molecular moieties into quinolone molecule. Substituted 2-methyl-4(1*H*)-quinolin-4-ones are needed precursors for our further researches, therefore, in this paper we reported the friendly-environmental large-scale synthesis of these quinolones from ethyl β-(substituted)anilinocrotonates using vegetable oils as high boiling-point solvents.

2. Experimental Section

Melting points were determined by open capillary method on STUART SMP3

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instrument (BIBBY STERILIN, UK) and are uncorrected. IR spectra (KBr disc) were recorded on an Impact 410 FT-IR Spectrometer (Nicolet, USA). ^{1}H and ^{13}C NMR spectra were recorded on Avance Spectrometer AV500 (Bruker, Germany) at 500 MHz and 125.8 MHz, respectively, using DMSO-d_6 as solvent and TMS as internal standard. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 $WF_{254}S$ (Merck, Germany). Ethyl substituted β-anilinocrotonates and substituted 2-methyl-4(1*H*)-quinolin-4-ones were synthesized below.

*2.1. Preparation of ethyl substituted β-anilinocrotonates **3a-h***

Respective substituted anilines **1a-h** (0.25 mol) and ethyl acetoacetate **1** (0.25 mol) were mixed, 5-10 drops of conc. Hydrochloric acid were added and the mixture was shaken well. It was left aside and within a few minutes, the mixture became turbid, indicating the liberation of water due to the condensation reaction. In case of solid aniline, absolute ethanol was used as solvent. At this stage, the mixture was kept inside a vacuum desiccator over conc. H_2SO_4 for 2–3 days. The β-anilinocrotonates **3a-h** formed as deep yellow or black oily liquids. They were separated and dried over anhydrous Na_2SO_4 and could be directly used for next reaction.

*2.2. Cyclization ethyl substituted β-anilinocrotonates to quinolones **4a-h***

Suitable commercial vegetable oil (50 mL, see Table 1) in round-bottom 250-mL flask was heated to 250–260°C with air condenser. To the heating oil 20 ml of ethyl β-anilinocrotonate **3c** was added dropwise through the condenser, while the reaction mixture was stirred continuously and the temparature was remained at about 250°C. After that, the mixture was heated further for 30 min and then cooled to room temperature. Petroleum ether (50 ml) was added while continuously stirring. The solids precipitated was filtered on Büchner funnel, washed by petrolium ether and recrystallized from 96% ethanol to afford quinolin-4-one **4c**. Other ethyl substituted β-anilinocrotonate **3a**-**h** were similarly converted to the corresponding quinolin-4-ones **4a**-**h**.

Yield, melting point, IR, ^{1}H NMR and ^{13}C NMR spectral data of these quinolin-4-ones as follows:

4a, **R=H:** Ivory white crystals. Yield 51%, m.p. 235–236°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3404, 3300, 3220, 3059, 1643, 1600, 1558, 1499; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.35 (s, 3H, 2-CH_3), 5.93 (s, 1H, H-3), 7.28 (t, *J*=7.5 Hz, 1H, H-5), 7.50 (d, *J*=8.0 Hz, 1H, H-6), 7.62 (m, 1H, H-7), 8.04 (d, *J*=8.0 Hz, 1H, H-8), 11.61 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 177.3 (C-4), 150.0 (C-2), 140.6 (C-8a), 132.0 (C-7), 125.6 (C-5), 124.9 (C-4a), 123.2 (C-6), 116.2 (C-8), 108.9 (C-3), 19.9 (2-CH_3).

4b, **6-CH_3:** Ivory white crystals. Yield 57%, m.p. 232–233°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3320, 3041, 1631, 1593, 1548, 1484; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.33 (s, 3H, 2-CH_3), 2.39 (s, 3H, 6-CH_3), 5.87 (s, 1H, H-3), 7.40 (d, 1H, *J*=8.5 Hz, H-8), 7.43 (s, =8.5 Hz, 1H, H-7), 11.48 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 176.5 (C-4), 149.1 (C-2), 138.1 (C-8a), 132.7 (C-7), 131.8 (C-6), 124.4 (C-5), 124.0 (C-4a), 117.6 (C-8), 108.1 (C-3), 20.7 (6-CH_3), 19.4 (2-CH_3).

4c, **R=7-CH_3:** Ivory white crystals. Yield 46%, m.p. 201–202°C (from 96%

ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3400, 3335, 3200, 3103, 1644, 1606, 1554, 1510; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.28 (s, 3H, 2-CH_3), 2.78 (s, 3H, 7-CH_3), 5.81 (s, 1H, H-3), 6.94 (d, 1H, *J*=7.0 Hz, H-6), 7.29 (d, *J*=8.5 Hz, 1H, H-8), 7.40 (d, *J*=6.0 Hz, 1H, H-5), 11.30 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 179.5 (C-4), 147.9 (C-2), 141.8 (C-8a), 139.1 (C-7), 130.5 (C-5), 125.1 (C-4a), 122.8 (C-6), 115.9 (C-8), 110.2 (C-3), 23.1 (7-CH_3), 18.9 (2-CH_3).

4d, **R=8-CH_3:** Ivory white crystals. Yield 72%, m.p. 168–169°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3384, 3076, 1630, 1607, 1565, 1550; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.52 (s, 3H, 2-CH_3), 2.41 (s, 3H, 8-CH_3), 5.95 (s, 1H, H-3), 7.18 (t, *J*=7.7 Hz, 1H, H-6), 7.45 (d, *J*=7.7 Hz, 1H, H-7), 7.93 (d, *J*=7.7 Hz, 1H, H-5), 10.43 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 177.6 (C-4), 150.6 (C-2), 139.3 (C-8a), 132.9 (C-7), 126.4 (C-8), 125.2 (C-4a), 123.2 (C-5), 122.9 (C-6), 109.2 (C-3), 20.3 (2-CH_3), 18.1 (8-CH_3).

4e, **R=6,8-di-CH_3:** Ivory white crystals. Yield 62%, m.p. 238–239°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3384, 3310, 3258, 3057, 1634, 1603, 1551, 1508; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.47 (s, 3H, 6-CH_3), 2.38 (s, 3H, 2-CH_3), 2.32 (s, 3H, 8-CH_3), 5.89 (s, 1H, H-3), 7.26 (s, 1H, H-7), 7.71 (s, 1H, H-5), 10.36 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 176.9 (C-4), 149.6 (C-2), 136.9 (C-8a), 133.8 (C-6), 131.4 (C-7), 125.8 (C-8), 124.7 (C-4a), 122.1 (C-5), 108.5 (C-3), 20.6 (6-CH_3), 19.7 (2-CH_3), 17.5 (8-CH_3).

4f, **R=6-C_2H_5:** Ivory white crystals. Yield 78%, m.p. 219–220°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3500, 3413, 3320, 3052, 1652, 1593, 1508, 1486; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 1.19 (t, 3H, 6-CH_2**CH_3**), 2.67 (q, 2H, 6-**CH_2**CH_3), 2.32 (s, 3H, 2-CH_3), 5.89 (s, 1H, H-3), 7,47–7.41 (m, 2H, H-7 & H-8), 7.86 (s, 1H, H-5), 11.57 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 176.8 (C-4), 149.3 (C-2), 138.4 (C-8a), 138.3 (C-7), 131.8 (C-6), 124.5 (C-5), 122.8 (C-4a), 117.8 (C-8), 108.2 (C-3), 27.8 (6-**CH_2**CH_3), 19.4 (6-CH_2**CH_3**), 15.6 (2-CH_3).

4g, **5-Cl-8-CH_3:** Pale yellow crystalls. Yield 23%, m.p. 237-238°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3500, 3455, 3335, 3200, 3050, 1633, 1566, 1509, 1490; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.35 (s, 3H, 2-CH_3), 2.45 (s, 3H, 5-CH_3), 5.90 (s, 1H, H-3), 7.12 (d, 1H, *J*=8.0 Hz, H-6), 7.35 (d, *J*=8.0 Hz, 1H, H-7), 10.12 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 176.3 (C-4), 148.8 (C-2), 141.1 (C-8a), 132.1 (C-7), 129.5 (C-5), 125.3 (C-4a), 124.9 (C-8), 120.6 (C-6), 111.0 (C-3), 19.3 (2-CH_3), 17.8 (8-CH_3).

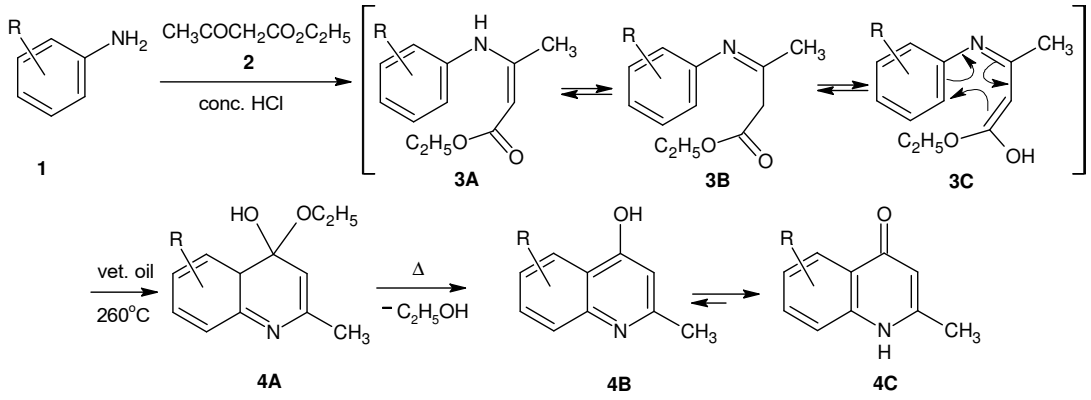
4h, **8-OCH_3:** Ivory white crystals. Yield 52%, m.p. 194–195°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3354, 3200, 3095, 1636, 1596, 1550, 1514; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 2.37 (s, 3H, 2-CH_3), 4.00 (s, 3H, 8-OCH_3), 5.92 (s, 1H, H-3), 7.21–7.20 (m, 2H, H-6 & H-7), 7.61 (dd, *J*=4.0, 5.0 Hz, 1H, H-6), 10.98 (s, 1H, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6), δ (ppm): 176.5 (C-4), 149.6 (C-2), 148.2 (C-8), 130.87 (C-8a), 125.5 (C-4a), 122.4 (C-6), 116.1 (C-5), 111.0 (C-7), 109.1 (C-3), 56.1 (8-OCH_3), 19.5 (2-CH_3).

3. Results and Discussion

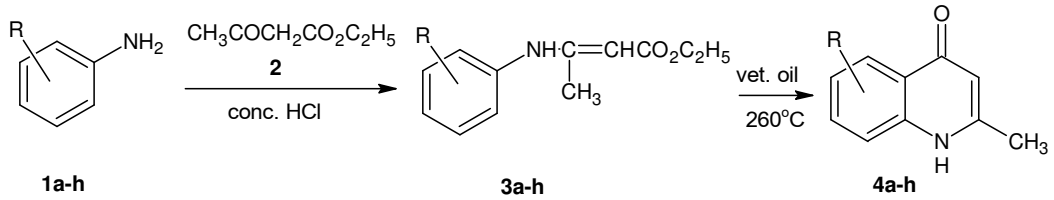
Our studies commenced with the design of suitable quinoline substrates which could be

easily converted into different functional groups, such as 3-formyl or 4-azido groups. Herein, we reported the synthesis of 2-methyl-4(1*H*)-quinolin-4-ones by cyclization of enamines **3a-h**, ethyl β-(substituted)anilinocrotonates. These enamines could be easily prepared by reaction of corresponding substituted anilines **1a-h** with ethyl acetoacetate in the presence of small amount of hydrochloric acid at room temperature.

This cyclization reaction, so-called the Conrad-Limpach synthesis, used to prepare quinolin-4-ones, is shown in Scheme 1. In this reaction, according to Brouet *et al.* [5], the ultimate substrate for the cyclization must be in the high-energy imine-enol tautomer (**3C**), and the cyclization into the hemiketal **4A** breaks the aromaticity of the phenyl ring, hence, solvents with very high boiling points are traditionally used for this reaction. Alternatively, a ketene-imine intermediate formed *via* direct elimination of EtOH from the imine ester **3B** is an alternative reaction pathway; the cyclization of this intermediate would also require the breaking of aromaticity and must use the same high boiling-point solvents [5]. In reality, the most widely referenced solvents are mineral oil (b.p. > 275°C), diphenyl ether (b.p. 259°C), and more recently, Dowtherm A, a mixture of biphenyl and diphenyl ether (b.p. 257°C) [5, 6]. It's known that two last solvents are very toxic.



Scheme 1. Mechanism of classical Conrad-Limpach reaction for synthesis of substituted quinolin-2-ones.



Scheme 2. Synthesis of substituted 2-methyl-4(1*H*)-quinolin-4-ones, where, R=H (**4a**), 6-CH_3 (**4b**), 7-CH_3 (**4c**), 8-CH_3 (**4d**), 6,8-diCH_3 (**4e**), 6-C_2H_5 (**4f**), 5-Cl-8-CH_3 (**4g**), 8-OCH_3 (**4h**).

For one of our further synthetic purposes, we required the synthesis of large quantities of the substituted 4-quinolones. Although the use of mentioned solvents (such as mineral oil, diphenyl ether or Dowtherm A) in classical Conrad-Limpach synthesis could give the high yields of quinolin-4-ones [7], but we did not apply these conditions in the synthesis of

required substituted 2-methylquinolin-4-ones in our lab due to its high toxicity. Based on the obtained results of Brouet *et al* and on the high temperature conditions of Conrad-Limpach synthesis, we found that the usual diphenyl ether or Dowtherm A could be replaced by the commercial vegetable oils (Scheme 2). These vegetable oils are cheaper than the above mentioned solvents and nontoxic. These oils could easily be removed from the product of the reaction by washing with petroleum ether, and does not have the unpleasant odor associated with the other solvents traditionally used. We have used the different commercial vegetable oils (Table 1) as solvent in cyclization of enamine **3c**, ethyl β-(*m*-methylanilino)crotonate, as model to obtain target 2,7-dimethyl-4(1*H*)-quinolin-4-one **4c**. Obtained results of this investigation are shown in Table 1.

Table 1 showed that Neptune's Sunflower oil with 25.12 g of saturated fat gave higher yield of 2,7-methyl-4(1*H*)-quinolin-4-one (**4c**). Perhaps, the higher content of saturated fat has helped this vegetable oil does not decompose at high temperature in this cyclization reaction (250–260°C) and remained its properties. Based on these obtained results, other 4(1*H*)-quinolin-4-ones have been synthesized by cyclization of corresponding ethyl β-(substituted anilino)crotonates. Synthesized 2-methyl-4(1*H*)-quinolin-4-ones have been confirmed their structure by spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) method and listed in Experimental Section.

Table 1. Investigation of some commercial vegetable oils used in synthesis of 2,7-dimethyl-4(1*H*)-quinolin-4-one (**4c**) at 260°C

Overall yield*, %	Neptune's Sunflower oil (25.12 g of sat. fat)	Canola oil (7 g of sat. fat)	Simply's Soybean oil (20 g of sat. fat)	Bizce's Sunflower oil (11 g of sat. fat)
Yield-1	45.78	25.63	43.42	40.78
Yield-2	48.72	26.05	41.05	38.58
Yield-3	43.58	27.75	42.72	39.76
Average yield	**46.03**	**26.48**	**42.40**	**37.75**

* Including enamine formation step and its cyclization one.

The identification signs to know the formation of these 2-methyl-4(1*H*)-quinolin-4-ones are the presence of absorption IR band in region at 1632–1666 cm^{-1} that belongs to C=O group in quinolin-4(1*H*)-one ring, resonance signal at δ=10.61–10.36 ppm in theirs ^{1}H NMR spectra that belong to NH group in this ring, and chemical shift at δ=177.6–176.3 ppm in theirs ^{1}H NMR spectra that belong to C=O carbonyl group on position 4. The appearance of two signals, δ_{NH} and $\delta_{C=O(carbonyl)}$ showed that the keto-enol tautomerism of tautomers **4B** and **4C** shifted toward **4C**, that means the compound exists in the form of quinoline-4-one instead of quinoline-4-ol. The methyl group on position 2 had chemical shift at 20.3–15.6 ppm. The position of resonance signal of carbon C-7 generally changed a little, $\delta_{C\text{-}7}$=132.9–132.1 ppm, except in the case of the following compounds: **4**c with methyl substituent in this position (with $\delta_{C\text{-}7}$=139.1 ppm), **4**h with 8-methoxy substituent (with $\delta_{C\text{-}7}$=111.0 ppm), **4f** with 6-ethyl group (with $\delta_{C\text{-}7}$=138.4 ppm), and compound **4e** with two methyl group on position 6 and 8 (with chemical shift $\delta_{C\text{-}7}$=131.4 ppm).

4. Conclusion

The Conrad-Limpach cyclization of ethyl β-(substituted)anilinocrotonates have been performed by using commercial vegetable oils as solvent. Some substituted 2-methyl-4(1*H*)-quinolin-4-ones have been synthesized and their structure were confirmed by IR and NMR

spectroscopic methods. This research contributes to the synthesis of some derivatives of quinoline-4(1*H*)-ones by using non-expensive, friendly-environmentally vegetable oils.

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Nghiên cứu sử dụng dầu thực vật làm dung môi xanh trong tổng hợp các 2-methyl-4(1*H*)-quinolin-4-on

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Tóm tắt: Một số 2-methyl-4(1*H*)-quinolin-4-on đã được điều chế bằng cách vòng hóa các ethyl β-anilinocrotonat thế tương ứng khi sử dụng dầu thực vật làm dung môi. Nghiên cứu này đóng góp vào phương pháp tổng hợp vòng quinolin-4(1*H*)-ones bằng phương pháp Conrad-Limpach với việc sử dụng dầu thực vật rẻ tiền và thân thiện môi trường để làm dung môi có điểm sôi cao cho phản ứng này. Cấu trúc của các vòng 4(1*H*)-quinolin-4-on thế khác nhau đã được xác nhận bằng các phương pháp phổ (IR, ^{1}H và ^{13}C NMR).

Từ khóa: Tổng hợp Conrad-Limpach, 2-methyl-4(1*H*)-quinolin-4-on, dầu thực vật.