

Synthesis of Some 3-Cyano-2-methylquinolin-4-ones

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The condensation of ethyl 2-cyano-3-ethoxycrotonate with various anilines gave the corresponding anilino crotonates which were cyclized in refluxing Dowtherm "A" to give the title quinolones.

[Keywords: Ethyl 3-anilino-2-cyanocrotonates; Ethyl 2-cyano-3-ethoxycrotonate; Gould-Jacobs reaction; Quinolines]

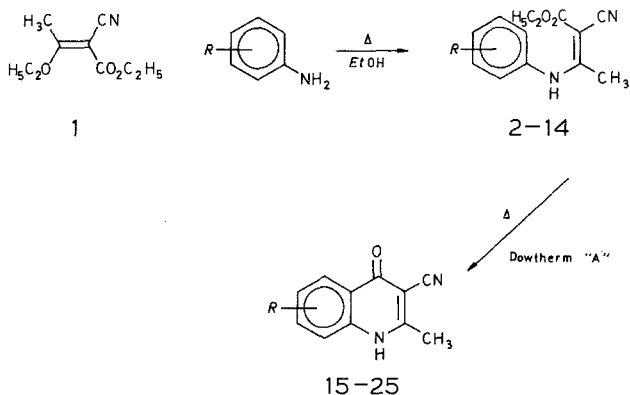
Synthese einiger 3-Cyano-2-methylchinolin-4-one

Die Titelverbindungen wurden mittels Kondensation von Ethyl 2-cyano-3-ethoxycrotonat mit verschiedenen Anilinen zu den entsprechenden Anilino crotonaten und deren Cyclisierung mit Duratherm „A“ am Rückfluß hergestellt.

Introduction

Various quinolin-4-ones which bear a carboxyl group in the 3 position have been shown to be good antibacterial agents and some of these such as nalidixic acid² and oxolinic acid³ are in clinical use. The synthesis of these quinolones use 3-ethoxyacrylates derived from malonic ester or other active methylene compounds in a *Gould-Jacobs* reaction⁴. The use of the corresponding crotonates in this reaction could lead to 2-methyl derivatives of quinolin-4-one which could also be of interest. Literature search revealed that ethyl 2-cyano-3-ethoxycrotonate (**1**) although reported some years ago⁵ has not been employed for such synthesis. In continuing our work on the use of *Gould-Jacobs* reaction⁶, we are extending the synthesis of quinolines using this crotonate as outlined in the scheme 1.

Scheme 1



Results and Discussion

1 was prepared from the reaction of triethyl orthoacetate and ethyl cyanoacetate in the presence of acetic anhydride⁵. The condensation of 1 with various anilines in refluxing ethanol gave the corresponding anilino crotonates (2—11, 13, and 14). The anilino crotonate (12) could only be obtained by condensation of *o*-nitroaniline and 1 at 180°. Some of these anilino crotonates (2, 5, 8, 11, and 14) are reported in the literature as by-products in the synthesis of cyclic amidines from ethyl 2-cyano-3-oxobutyrates⁷.

The anilino crotonates (2—14) on heating in Dowtherm "A" under reflux, in majority of the cases, cyclized to give the corresponding quinolin-4-ones (15—25) in good yields. The anilino crotonates (12 and 13), however, did not cyclize under these conditions.

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Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 MHz (*TMS* as internal standard). The infrared (IR) absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer. The samples were measured in potassium bromide disks. Melting points (m.p.) were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240 and are in full agreement with the calculated values.

Ethyl 3-N-anilino-2-cyanocrotonates (2—14)

General Method. Equimolar quantities of an aniline and ethyl 2-cyano-3-ethoxycrotonate (**1**) were heated under reflux in ethanol for a period of 3 to 4 h. On cooling the desired anilino-crotonate was filtered and purified by crystallization from aqueous ethanol.

Ethyl 3-N-anilino-2-cyanocrotonate (2): m.p. 113–115° (lit.⁷ m.p. 83–84°); yield 48%; IR (cm⁻¹): 3 200 (NH), 2 200 (C≡N), 1 660 (C=O); PMR δ (CCl₄): 1.35 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.25 (3 H, s, CH₃), 4.22 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.00–7.30 (5 H, m, H-2–H-6), 11.54 (1 H, br., NH).

Ethyl 2-cyano-3-N-o-toluidinocrotonate (3): C₁₄H₁₆N₂O₂; m.p. 109–112°; yield 57%; IR (cm⁻¹): 3 180 (NH), 2 200 (C≡N), 1 660 (C=O); PMR δ (CDCl₃): 1.31 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.15 (3 H, s, CH₃), 2.27 (3 H, s, CH₃), 4.23 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.00–7.35 (4 H, m, H-3 and H-5), 11.34 (1 H, br., NH).

Ethyl 2-cyano-3-N-m-toluidinocrotonate (4): C₁₄H₁₆N₂O₂; m.p. 72–73°; yield 50%; IR (cm⁻¹): 3 200 (NH), 2 200 (C≡N), 1 650 (C=O); PMR δ (CCl₄): 1.32 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.23 (3 H, s, CH₃), 2.37 (3 H, s, CH₃), 4.19 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 6.90–7.30 (4 H, m, H-2, H-4, H-5, and H-6), 11.48 (1 H, br., NH).

Ethyl 2-cyano-3-N-p-toluidinocrotonate (5): m.p. 104–106° (lit.⁷ m.p. 109–110°); yield 45%; IR (cm⁻¹): 3 200 (NH), 2 200 (C≡N), 1 670 (C=O); PMR δ (CDCl₃): 1.34 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.25 (3 H, s, CH₃), 2.40 (3 H, s, CH₃), 4.27 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.00 (2 H, d, *J* = 9.0 Hz, H-2 and H-6), 7.26 (2 H, d, *J* = 9.0 Hz, H-3 and H-5), 11.45 (1 H, br., NH).

Ethyl 3-N-o-chloroanilino-2-cyanocrotonate (6): C₁₃H₁₃ClN₂O₂; m.p. 135–137°; yield 29%; IR (cm⁻¹): 3 200 (NH), 2 210 (C≡N), 1 660 (C=O); PMR δ (CDCl₃): 1.35 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.23 (3 H, s, CH₃), 4.26 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.10–7.60 (5 H, m, H-2–H-6), 11.44 (1 H, br., NH).

Ethyl 3-N-m-chloroanilino-2-cyanocrotonate (7): C₁₃H₁₃ClN₂O₂; m.p. 140–143°; yield 53%; IR (cm⁻¹): 3 200 (NH), 2 200 (C≡N), 1 670 (C=O); PMR δ (CDCl₃): 1.41 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.28 (3 H, s, CH₃), 4.32 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.00–7.50 (4 H, m, H-2, H-4, H-5, and H-6), 11.63 (1 H, br., NH).

Ethyl 3-N-p-chloroanilino-2-cyanocrotonate (8): m.p. 142–144° (lit.⁷ m.p. 147–148°); yield 53%; IR (cm⁻¹): 3 220 (NH), 2 200 (C≡N), 1 670 (C=O); PMR δ (CDCl₃): 1.36 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.28 (3 H, s, CH₃), 4.28 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.09 (2 H, d, *J* = 9.0 Hz, H-2 and H-6), 7.41 (2 H, d, *J* = 9.0 Hz, H-3 and H-5), 11.52 (1 H, br., NH).

Ethyl 3-N-o-anisidino-2-cyanocrotonate (9): C₁₄H₁₆N₂O₃; m.p. 61–63°; yield 28%; IR (cm⁻¹): 3 200 (NH), 2 200 (C≡N), 1 665 (C=O); PMR δ (CDCl₃): 1.28 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.17 (3 H, s, CH₃), 3.81 (3 H, s, OCH₃), 4.20 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 6.80–7.30 (4 H, m, H-3, H-4, H-5, and H-6), 11.25 (1 H, br., NH).

Ethyl 3-N-m-anisidino-2-cyanocrotonate (10): C₁₄H₁₆N₂O₃; m.p. 96–97°; yield 51%; IR (cm⁻¹): 3 200 (NH), 2 200 (C≡N), 1 665 (C=O); PMR δ (CDCl₃): 1.34 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.29 (3 H, s, CH₃), 3.81 (3 H, s, OCH₃), 4.25 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 6.66–7.50 (4 H, m, H-2, H-4, H-5, and H-6), 11.50 (1 H, br., NH).

Ethyl 3-N-p-anisidino-2-cyanocrotonate (11): m.p. 118–119° (lit.⁷ m.p. 115–117°); yield 51%; IR (cm⁻¹): 3 210 (NH), 2 200 (C≡N), 1 655 (C=O); PMR δ (CDCl₃): 1.24 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.10 (3 H, s, CH₃), 3.72 (3 H, s, OCH₃), 4.12 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 6.73 (2 H, d, *J* = 9.0 Hz, H-3 and H-5), 6.96 (2 H, d, *J* = 9.0 Hz, H-2 and H-6), 11.37 (1 H, br., NH).

Ethyl 2-cyano-3-N-o-nitroanilinocrotonate (12): This was obtained by the condensation of *o*-nitroaniline with **1** under reduced pressure (10 mm) in the absence of ethanol and at a temperature of 180° (silicone bath). C₁₃H₁₃N₃O₄; m.p. 112–114°; yield 34%; IR (cm⁻¹): 3 100 (NH), 2 210 (C≡N), 1 660 (C=O), 1 520 and 1 330 (NO₂); PMR δ (CDCl₃): 1.35 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.34 (3 H, s, CH₃), 4.32 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.20–7.90 (3 H, m, H-4, H-5, and H-6), 8.12 (1 H, dd, *J* = 1.0 Hz and 9.0 Hz, H-3), 12.24 (1 H, br., NH).

Ethyl 2-cyano-3-N-m-nitroanilinocrotonate (13): C₁₃H₁₃N₃O₄; m.p. 138–140°; yield 27%; IR (cm⁻¹): 3 190 (NH), 2 210 (C≡N), 1 680 (C=O), 1 525 and 1 340 (NO₂); PMR δ (CDCl₃): 1.35 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.36 (3 H, s, CH₃), 4.28 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.50–8.30 (4 H, m, H-2, H-4, H-5, and H-6), 11.72 (1 H, br., NH).

Ethyl 2-cyano-3-N-p-nitroanilinocrotonate (14): m.p. 167–168° (lit.⁷ m.p. 170–175°); yield 25%; IR (cm⁻¹): 3 100 (NH), 2 215 (C≡N), 1 660 (C=O), 1 585 and 1 345 (NO₂); PMR δ (CDCl₃): 1.38 (3 H, t, *J* = 7.5 Hz, —O—CH₂—CH₃), 2.42 (3 H, s, CH₃), 4.27 (2 H, q, *J* = 7.5 Hz, —O—CH₂—CH₃), 7.28 (2 H, d, *J* = 9.0 Hz, H-2 and H-6), 8.28 (2 H, d, *J* = 9.0 Hz, H-3 and H-5), 11.88 (1 H, br., NH).

Quinolin-4-ones (15–25)

General method. To 5 ml of refluxing Dowtherm "A", 1 g of the anilincrotonate (**2–14**) was added in small portions and let heat under reflux for a period of 2 to 3 h. On cooling, the reaction mixture was precipitated with petroleum ether (b.p. 40–60°), filtered, washed with petroleum ether and crystallized from an appropriate solvent.

3-Cyano-2-methyl-1H-quinolin-4-one (15): m.p. > 300° (AcOH) (lit.⁷ m.p. 360–365° dec.); yield 87%; IR (cm⁻¹): 3 260, 3 220 (NH), 2 220 (C≡N), 1 628 (C=O); PMR δ (CF₃CO₂H): 3.12 (3 H, s, CH₃), 7.80–8.30 (3 H, m, H-6–H-8), 8.61 (1 H, dd, *J* = 1.5 and 8.0 Hz, H-5).

3-Cyano-2,8-dimethyl-1H-quinolin-4-one (16): C₁₂H₁₀N₂O; m.p. > 300° (DMSO–H₂O); yield 75%; IR (cm⁻¹): 3 260 (NH), 2 220 (C≡N), 1 610 (C=O); PMR δ (CF₃CO₂H): 2.88 (3 H, s, CH₃), 3.22 (3 H, s, CH₃), 7.95 (2 H, m, H-6 and H-7), 8.58 (1 H, dd, *J* = 1.5 and 9.0 Hz, H-5).

3-Cyano-2,7-dimethyl-1H-quinolin-4-one (17): C₁₂H₁₀N₂O; m.p. 260 (dec.) (DMSO–H₂O); yield 72%; IR (cm⁻¹): 3 270 (NH), 2 220 (C≡N), 1 640 (C=O).

3-Cyano-2,6-dimethyl-1H-quinolin-4-one (18): m.p. > 300° (DMSO–H₂O) (lit.⁷ m.p. 345–360° dec.); yield 38%; IR (cm⁻¹): 3 260 and 3 220 (NH), 2 220 (C≡N), 1 620 (C=O); PMR δ (CF₃CO₂H): 2.71 (3 H, s, CH₃), 3.12 (3 H, s, CH₃), 8.01 (2 H, s, H-7 and H-8), 8.39 (1 H, s, H-5).

8-Chloro-3-cyano-2-methyl-1H-quinolin-4-one (19): C₁₁H₇ClN₂O; m.p. 297° (dec.) (AcOH); yield 22%; IR (cm⁻¹): 3 230 (NH), 2 220 (C≡N), 1 610 (C=O); PMR δ (CF₃CO₂H): 3.10 (3 H, s, CH₃), 7.80 (1 H, d, *J* = 8.0 Hz, H-6), 8.15 (1 H, dd, *J* = 1.5 and 8.0 Hz, H-7), 8.48 (1 H, dd, *J* = 1.5 and 8.0 Hz, H-5).

7-Chloro-3-cyano-2-methyl-1H-quinolin-4-one (**20**): $C_{11}H_7ClN_2O$; m.p. $> 300^\circ$ (*DMSO-H₂O*); yield 56%; IR (cm^{-1}): 3 250, 3 200 (NH), 2 224 ($C\equiv N$), 1 630 ($C=O$); PMR δ (CF_3CO_2H): 3.09 (3 H, s, CH_3), 7.86 (1 H, dd, $J = 1.5$ and 9.0 Hz, H-6), 8.03 (1 H, d, $J = 1.5$ Hz, H-8), 8.56 (1 H, d, $J = 9.0$ Hz, H-5).

6-Chloro-3-cyano-2-methyl-1H-quinolin-4-one (**21**): m.p. $> 300^\circ$ (*DMSO*) (lit.⁷ m.p. $350-360^\circ$ dec.); yield 71%; IR (cm^{-1}): 3 250 and 3 200 (NH), 2 225 ($C\equiv N$), 1 630 ($C=O$); PMR δ (CF_3CO_2H): 3.08 (3 H, s, CH_3), 7.90-8.10 (2 H, m, H-7 and H-8), 8.51 (1 H, d, $J = 1.5$ Hz, H-5).

3-Cyano-8-methoxy-2-methyl-1H-quinolin-4-one (**22**): $C_{12}H_{10}N_2O_2$; m.p. $> 300^\circ$ (*AcOH*); yield 62%; IR (cm^{-1}): 3 200 (NH), 2 218 ($C\equiv N$), 1 620 ($C=O$); PMR δ (CF_3CO_2H): 3.19 (3 H, s, CH_3), 4.24 (3 H, s, OCH_3), 7.50-8.05 (2 H, m, H-6 and H-7), 8.17 (1 H, d, $J = 9.0$ Hz, H-5).

3-Cyano-7-methoxy-2-methyl-1H-quinolin-4-one (**23**): $C_{12}H_{10}N_2O_2$; m.p. $> 300^\circ$ (*DMSO*); yield 73%; IR (cm^{-1}): 3 230 (NH), 2 220 ($C\equiv N$), 1 630 ($C=O$); PMR δ (CF_3CO_2H): 3.10 (3 H, s, CH_3), 4.12 (3 H, s, OCH_3), 7.35 (1 H, d, $J = 1.5$ Hz, H-8), 7.50 (1 H, dd, $J = 1.5$ and 9.0 Hz, H-6), 8.48 (1 H, d, $J = 9.0$ Hz, H-5).

3-Cyano-6-methoxy-2-methyl-1H-quinolin-4-one (**24**): m.p. $> 300^\circ$ (*DMSO-H₂O*) (lit.⁷ m.p. $350-360^\circ$ dec.); yield 44%; IR (cm^{-1}): 3 250 and 3 210 (NH), 2 220 ($C\equiv N$), 1 615 ($C=O$); PMR δ (CF_3CO_2H): 3.08 (1 H, s, CH_3), 4.08 (3 H, s, OCH_3), 7.89 (3 H, m, H-5, H-7, and H-8).

3-Cyano-2-methyl-7-nitro-1H-quinolin-4-one (**25**): $C_{11}H_7N_3O_3$; m.p. $> 300^\circ$ (*DMSO-H₂O*); yield 32%; IR (cm^{-1}): 3 250 and 3 200 (NH), 2 224 ($C\equiv N$), 1 635 ($C=O$), 1 550 and 1 350 (NO_2); PMR δ (*DMSO-d₆*): 2.60 (3 H, s, CH_3), 7.90-8.25 (2 H, m, H-5 and H-6), 8.35 (1 H, d, $J = 1.5$ Hz, H-8).

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