FORMATION OF 2,5-DIHYDRO-3H-PYRAZOLO[4,3-c]QUINOLIN-3-ONES FROM ETHYL 3-ANILINO-2-(2-tert-BUTYL-2H-TETRAZOL-5-YL)ACRYLATES

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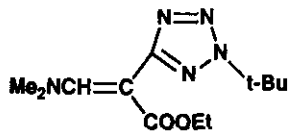
Abstract - Thermal cyclization of ethyl 2-(2-tert-butyl-2H-tetrazol-5-yl)-3-(4-chloroanilino)acrylate (5) did not afford the intended 4-quinolinone derivative (6), but yielded 2,5-dihydro-3H-pyrazolo[4,3-c]-quinolin-3-one (7). The reaction mechanism is thought to have been double cyclization of the nitrile imine intermediate (C).

We have previously described our work on the synthesis and the utility of ethyl 3-dimethylamino-2-(2-tert-butyl-2H-tetrazol-5-yl)acrylate (1),[1] a reagent for facile synthesis of antiallergic 2,3-(ring fused)-3,4-dihydro-5-(5-tetrazolyl)pyrimidin-4-ones (A) from amino-heterocycles such as 2-aminopyridine. Some series of 1,4-dihydro-3-(5-tetrazolyl)quinolin-4-one



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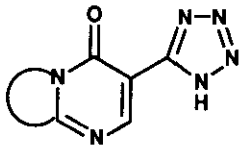
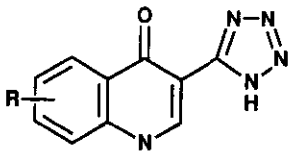


A

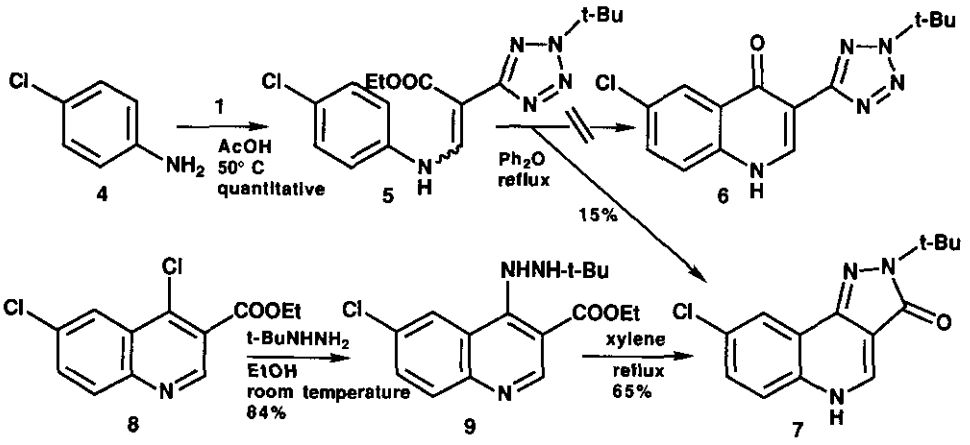


B

Scheme 1

derivatives (B) are reported to have interesting biological activities, such as antiallergic[2,3] or antihypertensive[4] actions (Scheme 1). Our attention has consequently been focused on the availability of **1**; whether the reaction products of **1** with aniline derivatives can thermally cyclize to afford the tetrazole substituted quinolone derivatives.

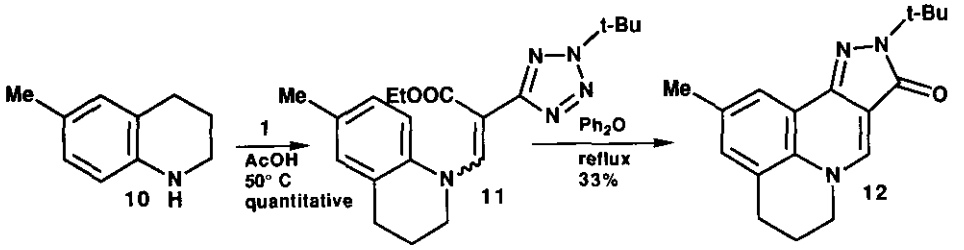
Reaction of 4-chloroaniline (**4**) with **1** in acetic acid afforded a mixture of E and Z forms of ethyl 2-(2-tert-butyl-2H-tetrazol-5-yl)-3-(4-chloroanilino)acrylate (**5**), which is confirmed by its ^{1}H-nmr spectra. When **5** was heated in diphenyl ether under the ring closure conditions of the Gould-Jacobs reaction,[5] yellow crystals were obtained in 15.3% yield. Its elemental analysis showed that not only the ring closure with release of ethanol, but also elimination of an equimolecular amount of nitrogen had occurred during the reaction. The chemical structure of the product was



Scheme 2

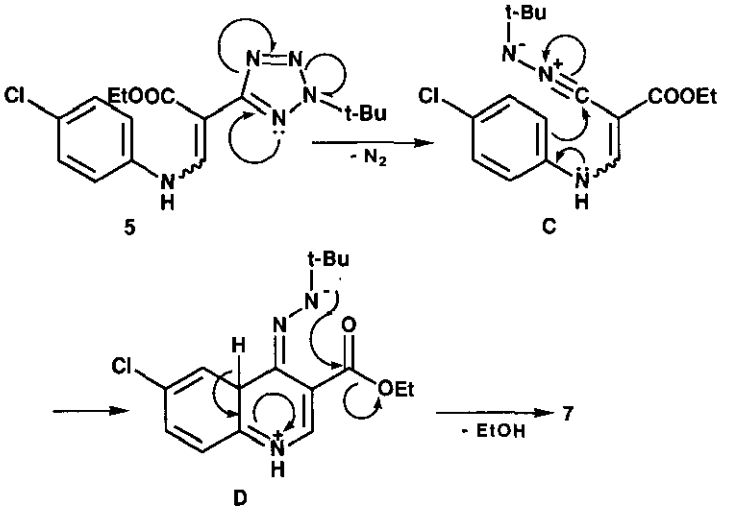
determined by X-ray analysis to be 2-tert-butyl-8-chloro-2,5-dihydro-3H-pyrazolo[4,3-c]quinolin-3-one (**7**), and this was confirmed by alternative synthesis of **7** starting from ethyl 4,6-dichloroquinoline-3-carboxylate (**8**)[6] according to the procedure of Yokoyama et al.[7] (Scheme 2). The raection of the secondary amine, 1,2,3,4-tetrahydro-6-methylquinoline (**10**),[8] with **1** similarly afforded a novel heterocyclic compound, 10-tert-butyl-

5,6,9,10-tetrahydro-2-methyl-4H-benzo[ij]pyrazolo[3,4-b]quinolizin-9-one (12) (Scheme 3).



Scheme 3

Scheme 4 shows the proposed reaction mechanism of the formation of 7. 2,5-Disubstituted tetrazole (5) decomposes thermally with the elimination of nitrogen to the nitrile imine (C) which forms the intermediate (D) under nucleophilic attack at the nitrilium carbon to form the quinoline ring followed by the second nucleophilic attack at the carbonyl carbon to form the pyrazole ring. This is one of the reactions of tetrazole derivatives that occur via nitrile imine,[9,10] and the above double cyclization is characteristic feature of this reaction.

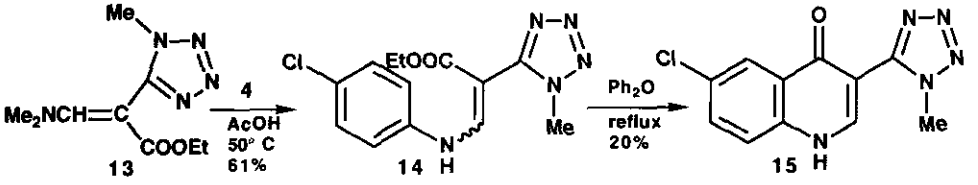


Scheme 4

Thus, the attempts to prepare the quinoline derivatives from 1 with anilines were unsuccessful, but a novel cyclization reaction via nitrile

imine was found.

In addition to the above reactions, the 1-substituted tetrazole derivative (13)[1] afforded the anticipated quinolone derivative (15), whose structure was ascertained by elemental analysis and from ^{1}H-nmr spectra (Scheme 5).



Scheme 5

EXPERIMENTAL

All melting points were determined on a Yanagimoto MP-1 melting point apparatus and are uncorrected. Ir spectra were obtained with a Hitachi 260-30 spectrophotometer. ^{1}H-Nmr spectra were measured on a Varian EM-360 spectrometer using tetramethylsilane as an internal standard.

Ethyl 2-(2-tert-Butyl-2H-tetrazol-5-yl)-3-(4-chloroanilino)acrylate (5) -- A mixture of ethyl 3-dimethylamino-2-(2-tert-butyl-2H-tetrazol-5-yl)-acrylate (1) (2.43 g, 9.1 mmol) and 4-chloroaniline (4) (1.15 g, 9.1 mmol) in AcOH (5 ml) was heated at 50°C for 2 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel (chloroform) to afford 5 as a pale brown oil (3.31 g, quantitatively). Ir(neat): 1700, 1670, 1640, 1600 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ: 1.39 and 1.43 (total 3H, each t, J=7 Hz, CH_3CH_2O), 1.80 and 1.83 (total 9H, each s, $(CH_3)_3C$), 4.40 and 4.43 (total 2H, each q, J=7 Hz, CH_3CH_2O), 7.00 - 7.56 (4H, m, Ar-H), 8.18 and 8.55 (total 1H, each d, J=13 and 14 Hz, NH-CH=), 12.16 (1H, m, NH-CH=).

Ethyl 2-(2-tert-Butyl-2H-tetrazol-5-yl)-3-(1,2,3,4-tetrahydro-6-methyl-quinolin-1-yl)acrylate (11) was quantitatively prepared as a pale yellow oil by an analogous procedure. Ir(neat): 1740, 1690, 1600 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, CH_3CH_2O), 1.60 - 1.95 (2H, m, $C_{3'}$-H_2),

1.81 (9H, s, $(CH_3)_3C$), 2.31 (3H, s, C_6,-CH_3), 2.66 (2H, t, J=6.5 Hz, C_4,-H_2), 3.03 (2H, t, J=6 Hz, C_2,-H_2), 4.23 (2H, q, J=7 Hz, CH_3CH_2O), 6.90 - 7.10 (3H, m, Ar-H), 8.39 (1H, s, N-CH=).

2-tert-Butyl-8-chloro-2,5-dihydro-3H-pyrazolo[4,3-c]quinolin-3-one (7) from (5) --- A solution of **5** (3.15 g) in diphenyl ether (5 ml) was added to refluxing diphenyl ether (7 ml), and the reflux was maintained for a further 15 min. After cooling to room temperature, hexane was added to the reaction mixture and the resulting precipitates were collected. Recrystallization from MeOH gave **5** (0.38 g, 15.3%) as yellow needles, mp over 300°C. Anal. Calcd for $C_{14}H_{14}N_3OCl$: C, 60.98; H, 5.12; N, 15.24. Found: C, 60.91; H, 5.14; N, 15.29. Ir(KBr): 1620 cm^{-1}. ^{1}H-Nmr(DMSO-d_6) δ: 1.63 (9H, s, $(CH_3)_3C$), 7.65 (2H, s, Ar-H), 8.00 (1H, s, Ar-H), 8.50 (1H, s, Ar-H).

10-tert-Butyl-5,6,9,10-tetrahydro-2-methyl-4H-benzo[ij]pyrazolo[3,4-b]-quinolizin-9-one (12) was prepared in 32.8% yield as brown prisms by an analogous procedure, mp 269 - 272°C. Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.97; H, 7.23; N, 14.09. Ir(KBr): 1625 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ: 1.70 (9H, s, $(CH_3)_3C$), 2.05 - 2.55 (2H, m, C_5-H_2), 2.45 (3H, s, C_2-CH_3), 3.02 (2H, t, J=6 Hz, C_4-H_2), 4.20 (2H, t, J=6 Hz, C_6-H_2), 7.14 (1H, br s, C_1 or C_3-H), 8.00 (1H, br s, C_1 or C_3-H), 8.15(1H, s, C_7-H).

Ethyl 4-(2-tert-Butylhydrazino)-6-chloroquinoline-3-carboxylate (9) --- Triethylamine (1.00 g, 10.0 mmol) was added to a suspension of tert-$BuNHNH_2$·HCl (0.75 g, 6.0 mmol) in EtOH (4 ml) followed by stirring at room temperature for 10 h. To the resultant solution was added ethyl 4,6-dichloroquinoline-3-carboxylate (**8**) (0.25 g, 1.0 mmol) and the stirring was continued for 24 h at the same temperature. The solvent was removed in vacuo and the residue was triturated with water and filtered. Recrystallization from MeOH gave **9** (0.27 g, 83.9%) as yellow plates, mp

153 - 155°C. Anal. Calcd for $C_{16}H_{20}N_3O_2Cl$: C, 59.32; H, 6.26; N, 13.06. Found: C, 59.73; H, 6.03; N, 13.16. Ir(KBr): 3200, 3150, 3100, 2980, 1660 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ: 1.22(9H, s, $(CH_3)_3C$), 1.42 (3H, t, J=7 Hz, CH_3CH_2O), 3.65 (1H, br s, NH), 4.39 (2H, q, J=7 Hz, CH_3CH_2O), 7.28 (1H, s, C_5-H), 7.57 (1H, dd, J=2 and 9 Hz, C_7-H), 7.84 (1H, d, J=9 Hz, C_8-H), 9.06 (1H, s, C_2-H).

(7) from (9) --- A solution of **9** (90 mg) in xylene (5 ml) was heated at reflux for 16 h. After cooling, the resulting precipitates were filtered to give **7** (48 mg, 65.4%) as a yellow powder, mp over 300°C, which was identified by comparing its ir and nmr spectra with those of **7** from **5**.

Ethyl 3-(4-Chloroanilino)-2-(1-methyl-1H-tetrazol-5-yl)acrylate (14) --- A solution of **4** (346 mg, 2.7 mmol) and ethyl 2-(1-methyl-1H-tetrazol-5-yl)-3-dimethylaminoacrylate (**13**) (610 mg, 2.7 mmol) in AcOH (3 ml) was heated at 50°C for 7 h. The solvent was removed in vacuo and the residue was washed with ether to give crude **14** (510 mg, 61.2%) as a colorless powder. ^{1}H-Nmr($CDCl_3$) δ: 1.29 and 1.36 (total 3H, each t, J=7 Hz, CH_3CH_2O), 3.97 and 4.07 (total 3H, each s, tetrazole-CH_3), 4.30 amd 4.33 (total 2H, each q, J=7 Hz, CH_3CH_2O), 7.00 - 7.46 (4H, m, Ar-H), 8.39 and 8.87 (total 1H, each d, J=14 Hz, NH-CH=).

6-Chloro-1,4-dihydro-3-(1-methyl-1H-tetrazol-5-yl)quinolin-4-one (15) --- To refluxing diphenyl ether (4 ml) was added **14** (1.20 g) and the reflux was then continued for 15 min. After cooling, the reaction mixture was left at room temperature overnight. The resulting precipitates were filtered and recrystallized from DMF to afford **14** (200 mg, 19.6%) as a colorless powder, mp over 300°C. Anal. Calcd for $C_{11}H_8N_5OCl$: C, 50.49; H, 3.08; N, 26.76. Found: C, 50.46; H, 3.27; N, 26.87. Ir(KBr): 1660, 1620, 1580 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ: 4.58 (3H, s, CH_3), 8.02 (2H, s, C_7 and C_8-H), 8.63 (1H, s, C_2-H), 9.36 (1H, s, C_5-H).

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