TRANSFORMATIONS OF 4-N-ARYLAMINO-4-(8-QUINOLINYL)-1-BUTENES AND 3-ARYL-2-(8-QUINOLINYL)-4-THIAZOLIDINONES

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Abstract: The chemistry of 4-N-arylamino-4-(8-quinolinyl)-1-butenes **1-5** and 3-aryl-2-(8-quinolinyl)-4-thiazolidinones **15** has been studied. N-Furoylation, N-allylation, mediated-acid intramolecular cychsation, amino-Claisen transposition and aldol reactions were used to prepare new C-8 substituted quinolines with biological potential.

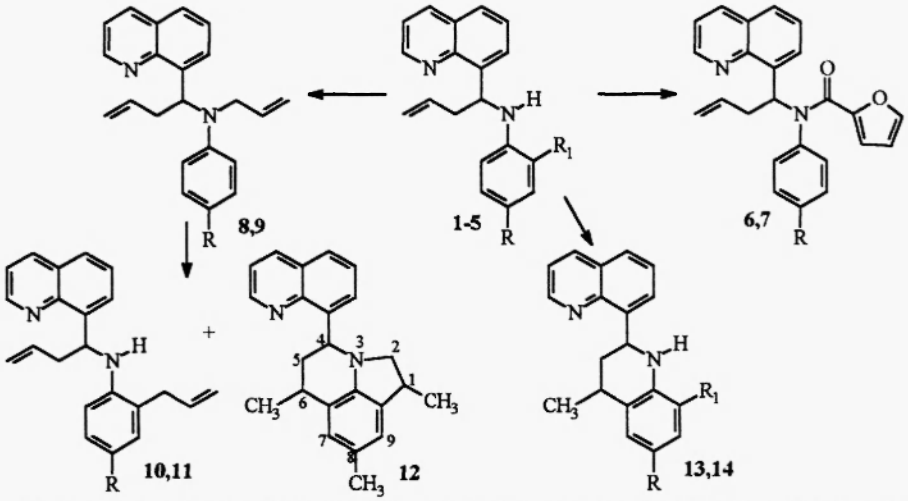
Introduction

Quinolines belong to an important group of natural products containing a heterocyclic ring. Moreover, a large number of quinoline derivatives are used in the pharmaceutical industry for a wide range of biological purposes like several parasitical drugs that are based on the 8-aminosubstituted quinoline nucleus[1-3]. Diverse biological activities have been associated with thiazolidinone derivatives[4-7]. We recently reported the synthesis of 4-N-arylamino-4-(8-quinolinyl)-1-butenes and 3-aryl-2-(8-quinolinyl)-4-thiazolidinones from quinoline-8-carbaldehyde, via formation of Schiff bases and further allylation or cyclocondensation of mercapto acids[8,9]. The biological significance of this class of compounds encouraged us to develop these C-8 substituted quinolines with possible biological activity. As part of our research program on the chemistry of homoallylamines and thiazolidinones with a quinoline ring, we wish to report here some transformations of 4-N-arylamino-4-(8-quinolinyl)-1-butenes and 3-aryl-2-(8-quinolinyl)-4-thiazolidinones.

Results and Discussion

Chemical transformations of 4-N-arylamino-4-(8-quinolinyl)-1-butenes **1-5** are shown in Scheme 1. Quinoline **3** was prepared from 8-[N-(p-ethoxyphenyl)formimidoyl]quinoline using an C-allylation reaction[9]. The treatment of aminobutenes **3,4** with α-furoyl chloride in the presence of Et_3N in dry benzene gave the respective quinoline amides **6** and **7** in 63-67% yields. The N-allylation of quinoline aminobutenes **1,2** was

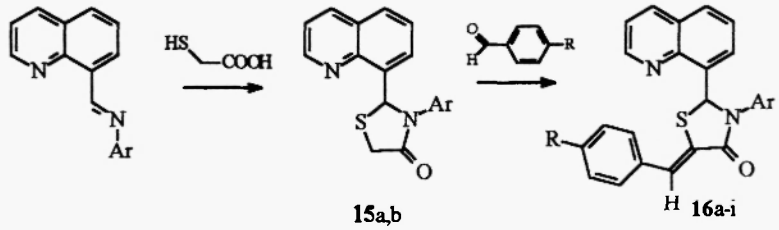
carried out with allyl bromide in the presence of K_2CO_3 in dry acetone affording the derivatives **8**[9] and **9**, which are used in the amino-Claisen rearrangement[10]. Under the conditions of this transformation (heating in BF_3OEt_2), the N-allylated derivative **9** gave a rearranged product **10** in 60% yield, meanwhile similar heating of product **8** afforded two different compounds: a rearranged product **11** (52%) and a quinoline **12** with the tricyclic lilolidine structure (42%). Intramolecular allyl cyclisation of the aminobutenes **3**,**5** was readily achieved heating these compounds in 82% H_2SO_4 producing the 4-methyl-2-(8-quinolinyl)-1,2,3,4-tetrahydroquinolines **13**,**14** in 35-76% yields. The final products were purified by column chromatography on alumina. The structural assignments proposed for the C-8 substituted quinolines **6-14** were consistent with their IR, ^{1}H- and ^{13}C-NMR spectra and were supported by the mass spectrometric data.



1, 8, 11 R= CH_3; **2, 9, 10** R=CH_3O; **3, 6, 13** R= CH_3CH_2O; **4, 7** R= Cl; **1-4, 6-13** R_1=H; **5, 14** R=R_1=CH_3

Scheme 1

Seeking substances with potential bioactivity among other series of C-8 substituted quinolines, we performed an aldol condensation reaction of 3-aryl-2-(8-quinolinyl)-4-thiazolidinones (Scheme 2).



15: a Ar = p-$CH_3C_6H_4$; b Ar = p-$CH_3OC_6H_4$; **16**a,c,e,g,i Ar = p-$CH_3C_6H_4$; **16**b,d,f,h Ar = p-$CH_3OC_6H_4$; **16**a,b R = H; **16**c,d R = Cl; **16**e,f R = CH_3O; **16**g,h R = $(CH_3)_2N$; **16**i R = OH

Scheme 2

The 5-arylidene thiazolidinone derivatives **16**a-i were synthesised from 3-(4-methylphenyl)- and 3-(4-methoxyphenyl)-2-(8-quinolinyl)-4-thiazolidinones (**15**a,b) that were obtained by a known procedure[9] and allowed to react with different aromatic aldehydes in the presence of sodium ethoxide to afford the final α,β-

cnones **16**, which showed in the IR spectra the characteristic C=O bands appearing in the region of 1676-1660 cm^{-1}. The ^1H NMR spectra of compounds **15**a.b displayed characteristic AB doublets at δ 3.77-4.06 ppm (5-CH_2). In the condensation products. this AB system was absent confirming that an aldol condensation had taken place.

Experimental

Melting points are uncorrected and were measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. Infrared spectra were recorded on a Perkin Elmer 599B-FT (compounds **6-14**) and on a Philips PU 9714 (compounds **15,16**) spectrometers as KBr pellets unless otherwise indicated. NMR spectra were determined on a Bruker AM-400 (compounds **6-14**) and on a Nicolet 300 MHz (compounds **15,16**) spectrometers in $CDCl_3$ with *TMS* as internal standard. Their mass spectra were obtained with a Shimadzu GS/MS QP 2000A spectrometer with 70 ev electron impact ionization. Elemental analyses were performed on a Leco CHN-600 analyzer. Column chromatography was performed with silica gel 60 (70-230 mesh) and aluminium oxide 90 active neutral (70-230 mesh). Elemental analyses were in satisfying agreement with the calculated data. Preparation of aminobutene **3** and N-furoylation or N-allylation of aminobutenes **1-5** were effectuated by the known procedures[9].

3: yield 65%; a pale yellow viscous oil; IR (KBr): ν = 3404, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-6.92 (6H, m, quinoline), 6.67-6.53 (4H, AA'BB'-system, Ar), 5.94-5.82 (1H, m, =CH), 5.20-5.08 (2H, m, $=CH_2$), 3.87 (2H, q, J = 6.9 Hz, OCH_2CH_3), 3.05 and 2.72 (1H, each, m, 3-CH_2, H_A and H_B), 2.05 (1H, dd, J = 7.0 Hz, 4-CH), 1.32 (3H, t, J = 6.9 Hz, OCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7-114.9 (quinoline and phenyl), 132.2 (=CH), 117.3 ($=CH_2$), 64.0 (OCH_2), 55.2 (4-CH), 41.7 (3-CH_2), 15.1 (CH_3) ppm; MS: *m/z* = 318 (M^+).

6: yield 63%; m.p. 89-90°C; IR (KBr): ν = 1635, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91-7.17 (7H, m, quinoline and α'-Fu), 6.53-6.49 (4H, AA'BB'-system, Ar), 5.99 (1H, s, β'-Fu), 5.97-5.90 (1H, m, =CH), 5.24 (1H, s, β-Fu), 5.14-4.96 (2H, m, $=CH_2$), 3.84 (2H, q, J = 6.9 Hz, OCH_2CH_3), 3.07 and 2.84 (1H, each, m, 3-CH_2, H_A and H_B), 1.85 (1H, dd, J = 6.9 Hz, 4-CH), 1.27 (3H, t, J = 6.9 Hz, OCH_2CH_3;); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9 (C=O), 158.3-121.3 (quinoline and phenyl), 143.7 (α'-Fu), 136.2 (α-Fu), 135.8 (=CH), 117.1 ($=CH_2$), 115.2 (β-Fu), 110.6 (β'-Fu), 63.4 (OCH_2), 40.9 (3-CH_2), 18.5 (4-CH), 14.6 (CH_3); MS: *m/z* = 412 (M^+).

7: yield 67%; a pale yellow viscous oil; IR (neat): ν = 1651, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92-7.18 (7H, m, quinoline and α'-Fu), 6.48-6.44 (4H, AA'BB'- system, Ar), 6.06 (1H, s, β'-Fu), 6.00-5.87 (1H, m, =CH), 5.62 (1H, s, β-Fu), 5.16-4.99 (2H, m, $=CH_2$), 3.09 and 2.89 (1H, each, m, 3-CH_2, H_A and H_B), 1.85 (1H, dd, 4-CH; J = 6.7 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (C=O), 155.3-119.4 (quinoline and

phenyl), 143.9 (α'-Fu), 135.6 (α-Fu), 135.4 (=CH), 117.3 (=CH_2), 115.9 (β-Fu), 110.7 (β'-Fu), 40.8 (3-CH_2), 18.5 (4-CH); MS: *m/z* = 402 (M^+ for ^{35}Cl).

9: yield 80%; a pale red oil; IR (neat): ν = 1599, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96-7.22 (6H, m, quinoline), 6.82-6.65 (4H, AA'BB'-system, Ar), 5.80-5.52 (2H, m, CH=), 5.05-4.88 (4H, m, CH_2=), 3.86 (2H, m, N-CH_2), 3.60 (3H, s, OCH_3), 2.78 (2H, m, CH_2-allyl), 1.79 (1H, dd, J = 6.6 Hz, N-CH-Qu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2-113.9 (quinoline and phenyl), 136.2, 136.1 (=CH), 116.2, 115.5 (=CH_2), 55.5 (OCH_3), 50.6 (N-CH_2), 36.9 (CH_2-allyl), 18.4 (N-CH-Qu); MS: *m/z* = 303 $(M-C_3H_5)^+$.

Amino-Claisen rearrangement of N-allyl substituted aminobutenes 8 and 9. General procedure.

The aminobutenes **8,9** (0.003 mol) was heated to reflux for 8-10 h in BF_3Et_2O (2.0 ml), cooled and poured into ice. The pH was brought to 8 with Na_2CO_3. The organic products were extracted with CH_2Cl_2 (3×10 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography (Al_2O_3, heptane/ethyl acetate, from 25:1 to 20:1) to afford the compounds **10-12**.

10: yield 60%; a viscous brownish liquid; IR (neat): ν = 3415 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96-6.23 (9H, m, quinoline and Ar), 5.94 and 5.71 (1H, each, m, -CH=), 5.11 and 4.83 (2H, each, m, CH_2=), 3.92-3.73 (2H, m, -CH_2-allyl), 3.57 (3H, s, OCH_3), 2.92-2.78 (2H, m, 3-CH_2), 1.94 (1H, d, J = 6.7 Hz, 4-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9-111.8 (quinoline and phenyl), 136.3 and 135.8 (=CH), 116.2 and 115.3 (=CH_2), 55.6 (OCH_3), 49.5 and 36.9 (-CH_2-allyl), 18.5 (4-CH) ppm; MS: *m/z* = 303 $(M-C_3H_5)^+$.

11: yield 52%; a viscous pale yellow liquid: IR (neat): ν = 3414 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 8.08-6.29 (9H, m, quinoline and Ar), 5.99 and 5.58 (1H, each, m, -CH=), 5.22 and 5.08 (2H, each, m, CH_2=), 3.39 (2H, m, -CH_2-allyl), 3.34 (2H, m, 3-CH_2), 2.77 (3H, s, CH_3), 2.18 (1H, d, J = 5.9 Hz, 4-CH); MS: *m/z* = 287 $(M-C_3H_5)^+$.

12: yield 42%; a viscous yellow liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 6.70-8.12 (8H, m, quinoline and Ar), 5.82-5.76 (1H, m, 4-H), 5.09 and 4.69 (1H, each, m, 2-CH_2, H_A and H_B), 3.41-3.56 (1H, m, 6-H), 2.82-2.78 (1H, m, 1-CH_3), 2.41 and 1.85 (1H, each, m, 5-CH_2, H_A and H_B), 2.16 (3H, s, 8-CH_3), 1.78 (3H, d, J = 4.2 Hz, 1-CH_3), 1.49 (3H, d, J = 6.8 Hz, 6-CH_3) ppm; MS: *m/z* = 328 (M^+).

Intramolecular acid cyclisation of quinoline aminobutenes 3 and 5. General procedure.

To a stirred and cooled (0 °C) solution of aminobutenes **3,5** (1.0 g) and chloroform (2.0 mL) was added dropwise during 5 min 4.0 mL of concentrated sulfuric acid. The reaction mixture was heated at 95 °C and vigorously stirred for three hours and monitored by TLC. The reaction mixture was neutralized with a concentrated solution of ammonium hydroxide (pH≈ 9-10) in the cold, extracted with dichloromethane (3x20 mL), and purified by column chromatography, to gave the corresponding tetrahydroquinolines **13** and **14**.

13: yield 35%; a red oil; IR (neat): ν = 3353 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 8.43-6.59 (9H, m, quinoline and Ar), 5.68 (1H, dd, J = 7.6 Hz, 2-H), 4.02 (2H, q, J= 6.8 Hz, OCH_2CH_3), 3.45-3.23 (1H, m, 4-H), 2.25

and 1.85 (1H, each, m, 3-CH_2, H_A and H_B), 2.00 (3H, d, J = 6.7 Hz, 4-CH_3), 1.43 (3H, t, J = 6.8 Hz, OCH_2CH_3) ppm; MS: *m/z* = 318 (M^+).

14: yield 76%; a orange crystals; m.p. 80-81°C; IR (KBr): ν = 3354 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.07-6.68 (8H, m, quinoline and Ar), 5.66 (1H, dd, J = 7.4 Hz, 2-H), 4.60 (1H, br.s, N-H), 3.37-3.28 (1H, m, 4-H), 2.43 and 1.98 (1H, each, m, 3-CH_2, H_A and H_B), 2.27, 2.08 (3H, each, s, 6/8-CH_3), 1.42 (3H, d, J = 6.7 Hz, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 141.5, 136.6, 132.5, 132.3, 128.7, 127.1, 126.7, 126.4, 126.0, 125.9, 125.8, 125.3, 122.0, 119.0, 50.6, 38.8, 31.4, 20.9, 18.6, 17.5 ppm; MS: *m/z* = 302 (M^+).

Preparation of 3-aryl-5-arylidene-2-(8-quinolinyl)-4-thiazolidinones 16a-i. General procedure.

Equimolar solutions of **15a** or **15b** (0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in dry benzene (25 ml) in the presence of sodium ethoxide, were refluxed for about 10-12 h. The reaction mixture was cooled and poured into ice cold water, acidified with glacial acetic acid and the benzene layer separated. The solution was dried ($CaCl_2$) and evaporated in vacuo. The crude product was crystallized from petroleum ether : diethyl ether (1:1) to give yellow crystals.

16a: yield 55%; m.p.153-4°C; IR (KBr): ν = 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.99-7.21 (16H, m, quinoline, phenyl and 2-CH), 7.08 (1H, d, =CH), 2.24 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C=O), 150.2-121.8 (quinoline and phenyl), 58.4 (2-CH), 22.1 (CH_3); MS: *m/z* = 408 (M^+).

16b: yield 70%; m.p. 170-2°C; IR (KBr): ν = 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.87-7.13 (16H, m, quinoline, phenyl and 2-CH), 6.70 (1H, d, =CH), 3.57 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3 (C=O), 158.3-114.8 (quinoline and phenyl), 58.4 (2-CH), 55.9 (OCH_3); MS: *m/z* = 424 (M^+).

16c: yield 51%; m.p. 150-1°C; IR (KBr): ν = 1676 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 8.85-7.13 (15H, m, quinoline, phenyl and 2-CH), 7.05 (1H, d, =CH), 2.23 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8 (C=O), 150.3-106.3 (quinoline and phenyl), 58.7 (2-CH), 21.3 (CH_3); MS: *m/z* = 442 (M^+ for ^{35}Cl).

16d: yield 66%; m.p. 163-5°C; IR (KBr): ν = 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.87-7.23 (15H, m, quinoline, phenyl and 2-CH), 6.71 (1H, d, =CH), 3.62 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C=O), 158.1-114.6 (quinoline and phenyl), 58.7 (2-CH), 55.7 (OCH_3); MS: *m/z* = 458 (M^+ for ^{35}Cl).

16e: yield 59%; m.p. 153°C; IR (KBr): ν = 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.91-6.99 (15H, m, quinoline, phenyl and 2-CH), 6.78 (1H, d, =CH), 3.72 (3H, s, OCH_3), 2.23 (3H, s, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3 (C=O), 159.8-109.3 (quinoline and phenyl), 58.5 (2-CH), 55.6 (OCH_3), 21.2 (CH_3); MS: *m/z* = 438 (M^+).

16f: yield 55%; m.p. 163°C; IR (KBr): ν = 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.01-6.86 (15H, m, quinoline, phenyl and 2-CH), 6.81 (1H, d, =CH), 3.79 (3H, s, OCH_3), 3.71 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (C=O), 160.1-109.0 (quinoline and phenyl), 58.9 (2-CH), 56.2 (OCH_3), 56.0 (OCH_3); MS: *m/z* = 454 (M^+).

16g: yield 70%; m.p. 175-6°C; IR (KBr): ν = 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.08-7.06 (15H, m, quinoline, phenyl and 2-CH), 6.67 (1H, d, =CH), 2.95 (6H, s, $N(CH_3)_2$), 2.24 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (C=O), 150.5-122.2 (quinoline and phenyl), 61.1 (2-CH), 34.2 ($N(CH_3)_2$), 21.4 (CH_3); MS: *m/z* = 451 (M^+).

16h: yield 72%; m.p. 170-1°C; IR (KBr): ν = 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.93-7.25 (15H, m, quinoline, phenyl and 2-CH), 6.74 (1H, d, =CH), 3.69 (3H, s, OCH_3), 2.98 (6H, s, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (C=O), 150.5-112.2 (quinoline and phenyl), 61.1 (2-CH), 55.8 (OCH_3), 34.2 ($N(CH_3)_2$); MS: *m/z* = 467 (M^+).

16i: yield 46%; m.p. 166°C; IR (KBr): ν = 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.05-7.01 (15H, m, quinoline, phenyl and 2-CH), 6.95 (1H, d, =CH), 2.26 (3H, s, CH_3); MS: *m/z* = 424 (M^+).

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