FUSED 1,2,4-TRIAZOLE HETEROCYCLES. II : REACTION OF 2-CHLORO-3-(1,3-DIOXOLAN-2-YL)QUINOLINES WITH 1,2,4-TRIAZOLE-5-THIOL

Ferenc Kóródi*, Zoltán Szabo and Zoltán Cziáky
Alkaloida Chemical Company Ltd., H-4440 Tiszavasvári, Hungary

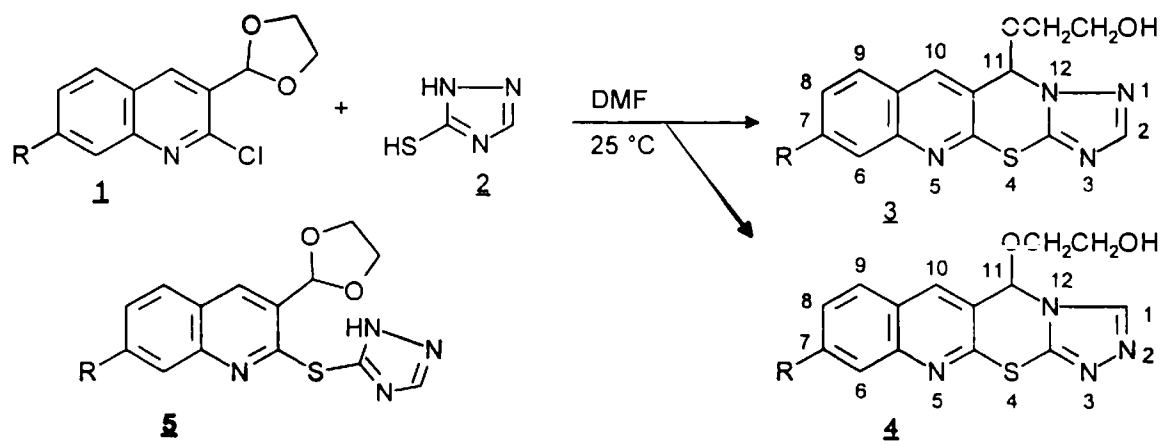
Abstract - Reaction of 2-chloro-3-(1,3-dioxolan-2-yl)quinolines 1 with 1,2,4-triazole-5-thiol 2 leads to the formation of a mixture of 11-(2-hydroxyethyl)oxy-11*H*-[1,2,4]triazolo[5′,1′:2,3][1,3]thiazino[6,5-*b*]quinolines 3 and 11-(2-hydroxyethyl)oxy-11*H*-[1,2,4]triazolo[3′,4′:2,3][1,3]thiazino[6,5-*b*]quinolines 4 . The structures of the separated regioisomers were determined by homonuclear NOE difference spectroscopy and the results were further confirmed by desulfurisation.

INTRODUCTION

It has recently been reported that 2-chloroquinoline-3-carbaldehydes or their diethyl acetal derivatives undergo cyclisation with 1,2,4-triazole-5-thiols leading to regioselective formation of 11*H*-[1,2,4]triazolo-[5′,1′:2,3][1,3]thiazino[6,5-*b*]quinoline derivatives. In continuation of our study on the synthesis of new heterocyclic ring systems (1-3) now we report the reaction of 2-chloro-3-(1,3-dioxolan-2-yl)quinolines 1 with 1,2,4-triazole-5-thiol 2 .

RESULTS AND DISCUSSION

When 2-chloro-3-(1,3-dioxolan-2-yl)quinolines 1 obtained from 2-chloroquinoline-3-carbaldehydes using the method described by Meth-Cohn and his coworkers (4) were treated with 1,2,4-triazole-5-thiol 2 in dimethylformamide at 25 °C, two products were obtained.



Scheme 1

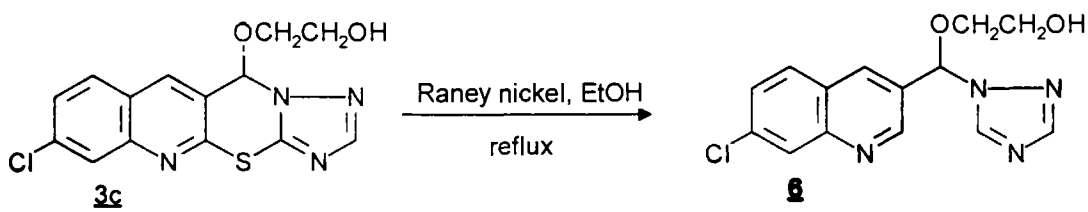
By analogy with the reaction of 2-chloroquinoline-3-carbaldehyde diethyl acetals with 1,2,4-triazole-5-thiol (1) it was assumed that the first step of the reaction is the formation of the intermediate 5. Cyclisation of this supposed intermediate may lead to the formation of two regioisomers (3 and 4) and this indeed was found to be the case as is shown below.

The two products formed were separated by column chromatography and subjected to analytical and spectroscopic investigations. Elemental analysis and mass spectral data showed that the two compounds had the same composition. Although these data were consistent with the supposed structures (3, 4) they could not differentiate between the regioisomers. The ^{1}H- and ^{13}C-nmr data of the isomeric pairs were found to have characteristic differences (5). Thus, for example, the triazole protons of the major products resonate at higher field (δ 8.34 - 8.36 ppm) than the corresponding protons of the minor products (δ 9.19 - 9.21 ppm). These data compared with literature data for disubstituted 1,2,4-triazoles (6) as well as thiazolo[1,2,4]triazole (7-10), [1,2,4]triazolo[1,3,5]triazine (11) and [1,2,4]triazolo[1,3]thiazine (12) regioisomers suggested that our major products should have [1,2,4]triazolo[5′,1′:2,3]- 3 , while the minor products had [1,2,4]triazolo[3′,4′:2,3][1,3]thiazino[6,5-*b*]quinoline 4 structures.

This assignation needed confirmation. NOE Difference spectroscopy was found to differentiate between 3 and 4. While irradiation of H-11 in the minor products caused a strong enhancement (13.4 - 17.1 %) of the triazole-H signal, this signal remained nearly unaffected (0.8 - 1.5 %) in the major products reflecting the larger distance between the H-11 and triazole proton (5).

These data clearly show that the major product of the reaction of 1 with 2 is a 11-(2-hydroxyethyl)oxy-11*H*-[1,2,4]triazolo[5′,1′:2,3][1,3]thiazino[6,5-*b*]quinoline 3 while the minor product is a 11-(2-hydroxyethyl)oxy-11*H*-[1,2,4]triazolo[3′,4′:2,3][1,3]thiazino[6,5-*b*]quinoline 4 derivative.

Furthermore one of the products, 3c , was subjected to desulfurisation with Raney nickel. The presence of two separated singlets (8.10 and 8.92 ppm) of triazole protons in the ^{1}H-nmr spectrum of the desulfurated product 6 indicates its triazol-1-yl structure and hence the structure of the starting compound 3c .



Scheme 2

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The nmr spectra were recorded on a Varian Gemini-200 instrument at 200MHz in DMSO-d_6 solution using TMS as internal standard and chemical shifts are expressed in ppm. The NOE experiments along with the total ^{1}H- and ^{13}C-nmr assignation of compounds 3, 4 have already been published (5). Mass spectra were scanned on a VG TRIO-2 spectrometer in EI mode at 70 eV.

Materials: 2-Chloro-3-(1,3-dioxolan-2-yl)quinolines (4) and 1,2,4-triazole-5-thiol (13) were prepared according to previously described procedures.

Preparation of 11-(2-hydroxyethyl)oxy-11H-[1,2,4]triazolo[5´ 1´:2,3][1,3]thiazino[6,5-b]quinolines 3 and 11-(2-hydroxyethyl)oxy-11H-[1,2,4]triazolo[3´,4´:2,3][1,3]thiazino[6,5-b]quinolines 4 : General procedure —
The corresponding 2-chloro-3-(1,3-dioxolan-2-yl)quinoline derivative 1 (10 mmol) was treated with 1,2,4-triazole-5-thiol 2 (1.21 g, 12 mmol) in dry dimethylformamide (10 ml) at 25°C until all the starting 2-chloroquinoline derivative 1 had been consumed (tlc). The reaction mixture was then poured into water (50 ml), the precipitated material was collected, washed with water and dried.
The isomers (3 and 4) were separated by column chromatography using silica gel packing and chloroform : ethanol (95 : 5, v/v) eluent. The first of the two products from the column was the 11-(2-hydroxyethyl)oxy-11*H*-[1,2,4]triazolo[5´,1´:2,3][1,3]thiazino[6,5-*b*]quinoline derivative 3 , the second crop was the 11-(2-hydroxyethyl)oxy-11*H*-[1,2,4]triazolo[3´,4´:2,3][1,3]thiazino[6,5-*b*]quinoline derivative 4 in every case.

Table 1: Preparation of Compounds 3 and 4.

R	Reaction Time (h)	Product	Yield[a] (%)	mp (°C)
H	31	3a	65	153-155 (EtOH)
		4a	12	193-195 (DMSO - EtOH = 1:2)
Me	36	3b	69	140-142 (EtOH)
		4b	8	163-164 (DMSO - EtOH = 1:2)
Cl	23	3c	63	169-171 ($CHCl_3$ - EtOH = 1:1)
		4c	16	205-207 (DMSO - EtOH = 1:2)

a) Yield of products separated by column chromatography

Table 2: Analytical and Mass Spectral Data of Compounds 3 and 4.

Compd.	Formula	Elemental Analysis (%) Calculated [Found] C	H	N	ms m/z (%)
3a	$C_{14}H_{12}N_4O_2S$	55.99 [55.91]	4.03 [4.01]	18.65 [18.68]	300 (M^+,14), 239 (100)
4a	$C_{14}H_{12}N_4O_2S$	55.99 [55.88]	4.03 [4.04]	18.65 [18.57]	300 (M^+,10), 239 (100)
3b	$C_{15}H_{14}N_4O_2S$	57.31 [57.15]	4.49 [4.48]	17.82 [17.71]	314 (M^+, 9), 253 (100)
4b	$C_{15}H_{14}N_4O_2S$	57.31 [57.29]	4.49 [4.47]	17.82 [17.79]	314 (M^+, 9), 253 (100)
3c	$C_{14}H_{11}N_4O_2SCl$	50.23 [50.40]	3.31 [3.28]	16.74 [16.85]	334 (M^+, 9), 273 (100)
4c	$C_{14}H_{11}N_4O_2SCl$	50.23 [50.02]	3.31 [3.36]	16.74 [16.70]	334 (M^+, 13), 273 (100)

Desulfurisation of compound 3c

Compound 3c (0.34 g, 1 mmol) and Raney nickel (4.0 g wet paste, washed with ethanol) were stirred at reflux temperature in ethanol (10 ml) under nitrogen for 1 h. The catalyst was separated by filtration and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel column using chloroform - ethanol (9 : 1, v/v) eluent to yield 3-(1-(1H-1,2,4-triazol-1-yl)-1-(2-hydroxyethyl)oxy)methyl-7-chloroquinoline 6 , 0.19 g (63 %), mp 111 -112 °C (ethanol); ^{1}H-nmr (DMSO-d_6): δ 3.45 - 3.78 (m, 4H), 4.85 (broad, 1H), 7.08 (s, 1H), 7.70 (dd, J_1=8.8 Hz, J_2=1.9 Hz, 1H), 8.10 (s, 1H), 8.13 (d, J=1.9 Hz, 1H), 8.15 (d, J=8.8 Hz, 1H), 8.50 (d, J=2.1 Hz, 1H), 8.92 (s, 1H), 8.98 (d, J=2.1 Hz, 1H); ms: m/z (%) 304 (M^+,8), 163 (100).

REFERENCES

1. F. Kóródi, Z. Cziáky and Z. Szabo, Heterocycles 34, 1711 (1992)
2. Z. Szabo and F. Kóródi, Synth. Commun. 20, 2473 (1990)
3. Z. Cziáky and F. Kóródi, Heterocycles 36, 2475 (1993)
4. O. Meth-Cohn, B. Narine, B. Tarnowski, R. Hayes, A. Keyzad, S. Rhouati and A. Robinson, J. Chem. Soc., Perkin Trans. I 1509 (1981)
5. Z. Szabó, F. Kóródi and Gy. Batta, Magn. Reson. Chem. 30, 1111 (1992)
6. W. Holzer, Tetrahedron 47, 5471 (1991)
7. K. T. Potts and S. Hussain, J. Org. Chem. 36, 10 (1971)
8. Y. Tamura, H. Hayashi, E. Saeki, J-H. Kim and M. Ikeda, J. Heterocycl. Chem. 11, 459 (1974)
9. R. Faure, J-P. Galy, E-J. Vincent, J. Elguero, J-P. Fayet, P. Mauret and M-C. Vertut, Bull. Soc. Chim. France, 288 (1977)
10. J. S. Bajwa and P. J. Sykes, J. Chem. Soc., Perkin Trans. I 2146 (1980)
11. G. Tenant and R. J. S. Vevers, J. Chem. Soc., Perkin Trans. I 421 (1976)
12. J. P. Clayton, P. J. O'Hanlon and T. J. King, J. Chem. Soc., Perkin Trans. I 1352 (1980)
13. H. Beyer and C. F. Kroger, Liebigs Ann. Chem. 637, 135 (1960)

Received October 10, 1994