THE CONDENSATION PRODUCTS OF 2-CHLORO-3-FORMYLQUINOLINES WITH o-AMINOTHIOPHENOL

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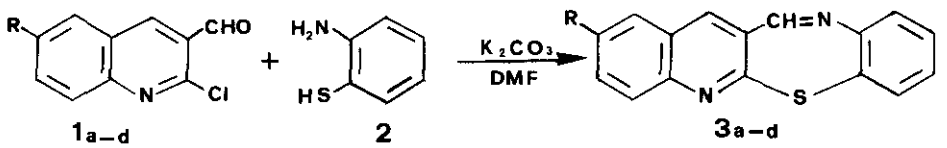
Abstract - 2-Chloro-3-formylquinolines 1a-d undergo cyclization with ortho-aminothiophenol (2) in DMF in the presence of potassium carbonate, at room temperature, to afford quino[2,3-b][1,5]benzothiazepines 3a-d. The benzothiazoline 5 or the benzothiazole 6 was instead obtained as the only isolable product when the above reaction was performed on 1b, in the absence of base, in DMF or in THF respectively. The reduction of 3a-c to 11,12-dihydroquino[2,3-b][1,5]benzothiazepines 4a-c is also reported.

As new examples of synthetic applications of 2-chloro-3-formylquinolines , several condensed heterocycles have been recently prepared[1]. In a previous paper[2] we described the one-pot synthesis of quino[2,3-b][1,5]benzoxazepines from some title aldehydes and o-aminophenol.

We wish now to report the results of the condensation of 2-chloroquinoline-3-carbaldehydes 1a-d with o-aminothiophenol (2). Treatment of 1a-d with 2 in N-N-dimethylformamide (DMF), in the presence of dry potassium carbonate, afforded quino[2,3-b][1,5]benzothiazepines 3a-d as the main products. In this case the reaction was carried out at room temperature and the intermediate imines could not be isolated[2]. Reduction of benzothiazepines 3a-c with lithium aluminum hydride in ether gave the corresponding 11,12-dihydro derivatives 4a-c in high yields.

The structural assignment of compounds 3a-d and 4a-c have been made on the basis of analytical and spectroscopic data.



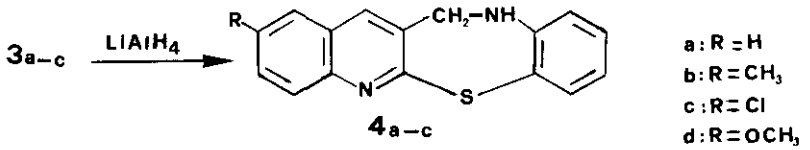


Table 1. Physical and analytical data of quino/2,3-b_7/1,5/benzothiazepines 3a-d and their 11,12-dihydro derivatives 4a-c

compound	yield % /a/	mp, °C crystallization solvent /b/	formula	analyses % calcd./found C	H	N
3a	79	195-196 D	$C_{16}H_{10}N_2S$	73.25 72.71	3.84 3.78	10.68 10.43
3b	65	200-201 D-H	$C_{17}H_{12}N_2S$	73.88 73.79	4.38 4.31	10.14 10.08
3c	81	265-265.5/c/ D	$C_{16}H_9ClN_2S$	64.75 64.74	3.06 2.98	9.44 9.36
3d	39	232-232.5 D	$C_{17}H_{12}N_2OS$	69.84 69.86	4.14 4.13	9.58 9.57
4a	83	219-220 D	$C_{16}H_{12}N_2S$	72.69 72.53	4.58 4.52	10.60 10.39
4b	90	195-196 D-H	$C_{17}H_{14}N_2S$	73.35 73.68	5.07 5.07	10.06 9.98
4c	80	194-195 D	$C_{16}H_{11}ClN_2S$	64.31 64.35	3.71 3.65	9.38 9.30

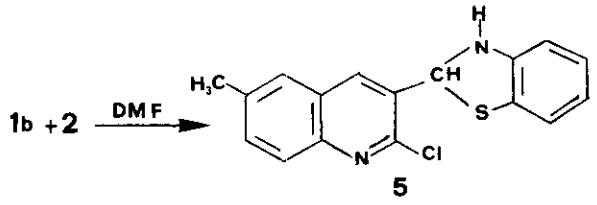
/a/ Yields from weights of homogeneous chromatographic fractions. /b/ D = dichloromethane; H = n-hexane. /c/ The melting, performed with a Kofler hot stage apparatus, occurs with decomposition.

Table 2. Selected spectral data for quino[2,3-b]/[1,5]benzothiazepines 3a-d and their 11,12-dihydro derivatives 4a-c

compound	^{1}H nmr (δ, ppm) /[a]/				ir (ν, cm^{-1})
	CH=N	13-H	CH_2-NH	2-R	
3a	8.90	8.10/[b]/			1630, 1055, 835
3b	8.90	8.03/[b]/		2.47 (CH_3)	1626, 1059, 839
3c	8.93	8.13/[b]/			1626, 1052, 838
3d	8.93	8.08/[b]/		3.92 (OCH_3)	1635, 1061, 839
4a		8.03/[b]/	4.77		3268, 1594, 1486
4b		7.81	4.77	2.49 (CH_3)	3285, 1596, 1484
4c		7.79	4.77		3357, 1588, 1478

/[a]/ All the reported signals appear as singlets; deuteriochloroform-methanol-d_4 solution for 4a. /[b]/ Superimposed on another aromatic.

A quite different reaction outcome was instead observed when the condensation of aldehyde 1b with 2 was performed in DMF in the absence of potassium carbonate. In fact, the benzothiazoline 5[3] was obtained by crystallization of the reaction residue and the thiazepine 3b was not detected.



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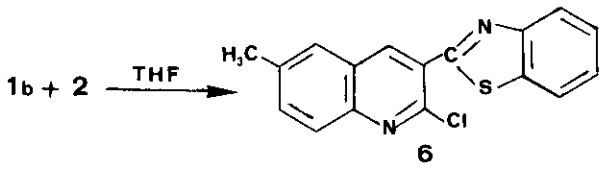
In agreement with the results of extensive investigations on the 2-arylbenzothiazoline 2-(benzylideneamino)thiophenol tautomerism and on related ring-chain isomerisms[4], we have not been able to isolate the iminic tautomer of 5.
In this connection the tetracyclic derivative 3 could derive from the base promoted formation of a Schiff base[4]. In order to check a possible thiazoline-imine equilibrium in presence of potassium carbonate, compound 5 was treated with the base under the conditions adopted for the cyclization of 1b to 3b. The starting material was the prevailing component of residue and the formation of thiazepine 3b, detected as traces by nmr and tlc, was not further confirmed. Thus, it seems reasonable to assume that the probable driving force for the reaction which leads to 3 is the

base catalyzed displacement of the chlorine in 1 by the sulfur atom of 2, although the initial formation of an imine cannot be ruled out. This hypothesis accounts for the great difference between the yields of 3c and 3d arising from the aldehydes which contain groups of opposite electronic effects at C-6. The halogen atom at C-2 of 1 should be made more labile when an electron withdrawing group is bonded to C-6, as in the case of 1c.

Finally, the benzothiazole 6 was the largely predominant product when the condensation of 1b with 2 was carried out in tetrahydrofuran (THF) in the absence of potassium carbonate.



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The auto-oxidation of thiazoline 5 by oxygen in THF may be postulated to rationalize the formation of 6. In accord, the nmr spectrum of the residue arising from the treatment of 1b with 2 in THF under nitrogen atmosphere showed the presence of 5 and 6 in a 2/1 ratio.

An overall analysis of our results indicates that the reaction conditions strongly influenced the condensation of 2-chloro-3-formylquinolines with o-aminothiophenol. Remarkable is the formation of 1,5-benzothiazepines and benzothiazoles in very mild conditions.

EXPERIMENTAL

Melting points were determined with a Büchi oil bath apparatus and are uncorrected. Ir spectra (KBr) were recorded with a Perkin-Elmer 983 spectrophotometer. The ^1H nmr spectra were measured with a Varian EM-390 (90 MHz) spectrometer, using deuteriochloroform as the solvent (tetramethylsilane as internal standard). Mass spectra were obtained using a Hewlett-Packard 5890A spectrometer at 70 eV, m/z (M^+) of all reported compounds were in satisfactory agreement with the assigned structures. Merck silica gel 60 (230-400 mesh) (1:50) was used for column chromatography. The drying agent was sodium sulphate. Dry tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were used.

General Procedure for the Synthesis of Quino[2,3-b][1,5]benzothiazepines 3a-d

A mixture of 2-chloroquinoline-3-carbaldehyde[5] 1a-d (0.5 mmol) and dry potassium carbonate (0.25 g) in DMF (1.5 ml) was stirred at room temperature for 5 min. A solution of o-aminothiophenol (2) (0.6 mmol) in 1.5 ml of DMF was then added and stirring was continued for 3 h. The mixture was partitioned between ethyl acetate

and water. The organic phases were dried and evaporated under reduced pressure to give a residue, which was chromatographed on a column of silica. Elution with dichloromethane-n-hexane (8:2 and 9:1) afforded pure title compounds 3a-d.

Reduction of Quino[2,3-b][7/1,5]benzothiazepines 3a-c

The reduction of benzothiazepines 3a-c with lithium aluminum hydride was performed as previously described[2], stirring for 1 h. After usual work up, the residue was chromatographed on a silica column, eluting with dichloromethane-n-hexane (7:3 and 9:1), to give pure 11,12-dihydroquino[2,3-b][7/1,5]benzothiazepines 4a-c.

Synthesis of 3-(Benzothiazolin-2-yl)-2-chloro-6-methylquinoline (5)

A solution of 1b (0.5 mmol) and 2 (0.6 mmol) in DMF (3 ml) was stirred at room temperature for 2 h. The mixture was partitioned between ethyl acetate and water and the organic phases were dried and evaporated. The residue[3] was crystallized from dichloromethane to give pure title compound 5 (0.071 g, 45%), mp 153.5-154.5 °C; ir: 3345, 819 cm^{-1}; nmr: δ 2.42 (3H, s, CH_3), 4.67 (1H, bs, NH), 6.57 (1H, s, CH-NH), 8.28 (1H, s, 4-H). Anal. Calcd. for $C_{17}H_{13}ClN_2S$: C, 65.27; H, 4.19; N, 8.96. Found: C, 65.21; H, 4.25; N, 8.77.

Synthesis of 3-(Benzothiazol-2-yl)-2-chloro-6-methylquinoline (6)

A solution of 1b (0.5 mmol) and 2 (0.6 mmol) in 2.5 ml of THF was stirred at room temperature for 3 h and evaporated under vacuum. The residue was chromatographed on a column of silica, eluting with dichloromethane-n-hexane (8:2 and 9:1) to give the title compound 6 (0.096 g, 62%), mp 176-176.5 °C (dichloromethane); ir: 1572, 1101, 817 cm^{-1}; nmr: δ 2.51 (3H, s, CH_3), 9.00 (1H, s, 4-H). Anal. Calcd. for $C_{17}H_{11}ClN_2S$: C, 65.69; H, 3.57; N, 9.01. Found: C, 65.40; H, 3.60; N, 8.91.

REFERENCES AND NOTE

1. R.P. Srivastava, Neelima, and A.P. Bhaduri, J. Heterocyclic Chem., 1987, 24, 219; ibid., Synthesis, 1987, 512.
2. G. Pagani Zecchini, I. Torrini, and M. Paglialunga Paradisi, Heterocycles, 1987, 26, 2443.
3. The yield of 5 (75%) was calculated by nmr analysis of the crude residue on the basis of the methyl signal.
4. F. Capitán, P. Espinosa, F. Molina, and L.F. Capitán-Vallvey, Rev. Roumaine Chim., 1987, 32, 151 and references cited therein.
5. O. Meth-Cohn, B. Narine, and B. Tarnowski, J. Chem. Soc., Perkin Trans. I, 1981, 1520.

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