A SIMPLE AND EFFICIENT ONE POT SYNTHESIS OF 4-OXO-SPIRO[THIAZOLIDINE-2,2'(1'*H*)-QUINOLINES] AND THEIR REACTIONS WITH DDQ

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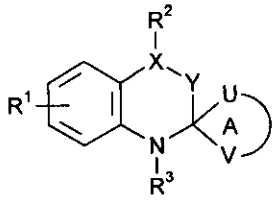
Abstract - The treatment of two equivalents of the anion of 3,4-dihydro-1*H*-quinoline-2-thione (**3**) with one equivalent of one of the *N*-substituted 2-bromoacetamides (**4a-d**) at room temperature afforded the title compounds in good yields (Scheme 1, Table 1). The reaction of the compounds (**6a-d**) with DDQ at room temperature and 90°C was studied. Mechanistic aspects of the processes are briefly discussed.

Dihydro- and tetrahydroquinoline derivatives are of considerable interest for many sectors of the chemical industry. Spirocyclic quinoline and dihydroquinoline compounds can have anticorrosive,[1] antiinflammatory,[2] antibacterial[3] or herbicidal[4] properties. In addition the use of special spirocyclic tetrahydroquinolines as dye stuff intermediates was reported recently.[5] In our search for compounds with potential fungicidal activity, we were interested in spirocyclic quinoline intermediates of the general formula (**1**).



1

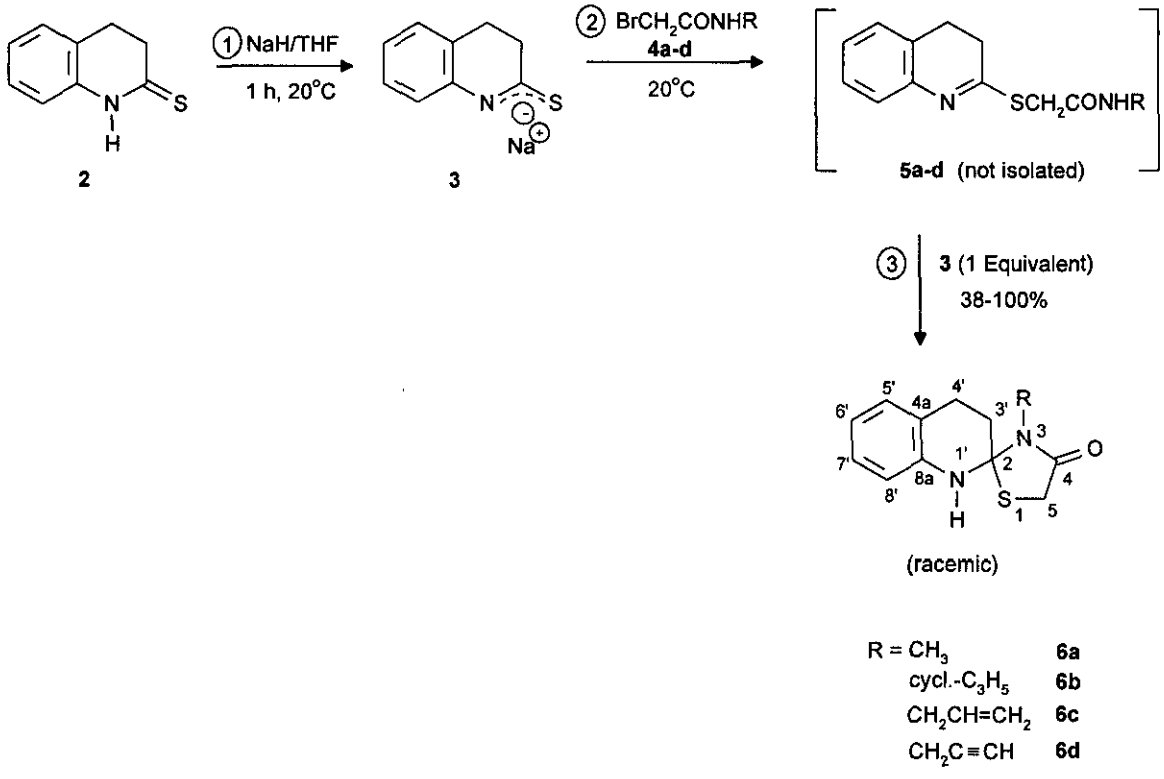
R^1-R^3 = any substituent
X-Y = $CHCH_2$, C=CH
U,V = O, S, NR^4 (R^4=H, Alkyl etc.)
A = 5- or 6-membered ring

To our knowledge compounds of this type are hitherto unknown. In this paper, we describe the synthesis of a series of these spirocyclic quinolines of type (**1**).

RESULTS AND DISCUSSIONS

In a first exploratory phase of our investigations on spirocyclic quinolines of the general formula (**1**), we chose 4-oxospiro[thiazolidine-2,2'(1'*H*)-quinolines] as target molecules, which should be available from simple starting materials. To prepare the model compounds (**6a-d**) (Scheme 1), we started from 3,4-dihydro-1*H*-quinoline-2-thione (**2**), which was synthesized by using a modified literature procedure.[6]

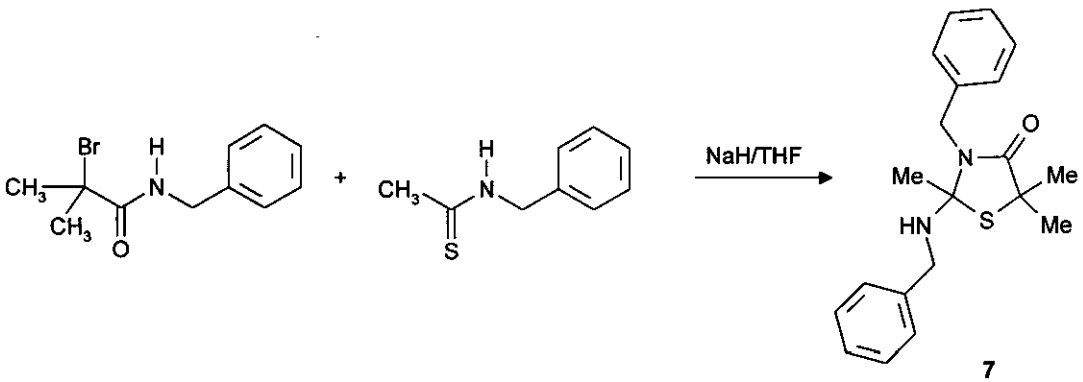
Scheme 1



2 **3**

For the synthesis of α-bromoacetamides (**4a-d**), the treatment of α-bromoacetyl chloride with the appropriate amine in the presence of a base (NEt_3 or the amine itself) in CH_2Cl_2 or THF at temperatures below -10°C turned out to be a satisfying approach to these compounds.[7] Using NaH as a base, the anion (**3**) was easily formed from **2**. The treatment of one equivalent of the anion (**3**) with one equivalent of one of the α-bromoacetamides (**4a-d**) gave the spirocyclic quinolines (**6a-d**) in only bad to moderate yields (<< 50%). Because we thought that the poor total yields are due to problems in the cyclization step ③ (Scheme 1), we tried to optimize this step. For this purpose, we first isolated the intermediate (**5b**) and then studied the cyclization of **5b** in the presence of several bases such as K_2CO_3, NMe_3, Hünig base and NaH in solvents such as THF or DMF. In all cases no cyclization occurred, and after workup, we obtained starting material or 3,4-dihydro-1*H*-quinoline-2-one together with small amounts of unidentified products. These results led us to the conclusion that the anion (**3**) might be the key reagent for a successful cyclization process. Indeed, all our attempts to cyclize **5b** in the presence of one equivalent of **3** lead to the spirocyclic quinoline (**6b**), which clearly proves that **3** plays the crucial role in the synthesis of this compound (Scheme 1). In the literature, we only found one example of a reaction of a comparable α-bromosubstituted amide with a thioamide under basic conditions, leading to 2-benzylamino-2,5,5-trimethylthiazolidin-4-one (**7**) (Scheme 2).[8]

Scheme 2



7

But in this paper no experimental details are given nor is the mechanism discussed. In our case, we think, there are two possibilities to explain the experimental results. The first possibility is, that the sodium salt of 3,4-dihydro-1*H*-quinoline-2-thione (**3**) has an optimal pK_a-value for deprotonating the amino hydrogen without affecting the S-methylene hydrogens and this, to our opinion may lead to a more selective

reaction process. Another possibility, which cannot be excluded with certainty, is, that the anion (**3**) first acts as a nucleophile and attacks the imino C-atom in **5a-d** and then, after deprotonation of the amino hydrogen, cyclization occurs under the loss of **3.** With our knowledge a first optimization of the yields of the synthesis of the spirocyclic quinolines (**6a-d**) could be achieved by simple use of two equivalents of **3** in the reactions with the α-bromoacetamides (**4a-d**). This approach normally gave the desired spirocyclic quinolines in good to excellent yields. (Table 1). The only exception was compound (**6b**), which was formed in a yield of *ca.* 40%. In this case, we think that the steric requirements of the cyclopropane ring were responsible for the lower yield.

Table 1 Preparation of 4-Oxospiro[thiazolidine-2,2'(1'*H*)-quinolines] from **2**[a,9]

R	Product	Yield [%]
CH_3	**6a**	79
cycl.-C_3H_5	**6b**	38
$CH_2CH{=}CH_2$	**6c**	100
$CH_2C{\equiv}CH$	**6d**	91

[a] *All reactions were carried out in absolute THF at room temperature.*[9]

The spiroquinolines (**6a-d**)[10] are stable crystalline products and can be stored at room temperature for a few months. The structure of compounds (**6a-d**) was mainly determined by nmr spectroscopic methods. The nmr spectroscopic differences between compounds (**5a-d**) and (**6a-d**) are obvious, because the compounds (**6a-d**) have an asymmetric C-atom (C-2) and therefore the ^{1}H nmr spectrum for example of **6a** shows an AB-system (^2J = 15.9 Hz) for the diastereotopic S-methylene hydrogens whereas the S-methylene hydrogens in **5a** appear as a singulett. In addition the ^{1}H nmr spectrum of **6a** in $CDCl_3$ after addition of (+)-(S)-2,2,2-Trifluoro-1-(anthr-9-yl)ethanol ((+)-TAE)[11] shows two separate singuletts for the N-CH_3 group with an integration ratio of 1:1, which clearly proves that **6a** is racemic. Also typical for the spiroheterocycles (**6a-d**) are the chemical shifts for the spiro C-2-atoms (δ = 83.9 - 85.3 ppm). In summary the nmr data of **6a-d** in addition with elemental analysis and ms data are well in accordance with the spirocyclic structure. To our opinion, testing the usefulness of these compounds in the synthesis

of other interesting quinoline compounds, seemed to be a challenging task. Our first investigations in this field concerned the behavior of compounds (**6a-d**) against oxidizing reagents. As a first oxidizing agent we chose DDQ and we report here on our results of the reaction of compounds (**6a-d**) with DDQ under various conditions.

The reaction of one equivalent of a compound (**6a-d**) with 1.5 equivalents of DDQ at 20° or 90°C in dioxane could be monitored by tlc (see experimental part) and gave in good yields the interesting dimeric quinoline compounds (**8a-c**)[12] (Table 2) and/or to a minor amount in 2-position *S*-substituted quinolines (**9a**, **9d** see Scheme 3). The structures of **8a-c** and **9a, d** were elucidated by ms, nmr (^{1}H, ^{13}C, HMBC[13]) and raman spectroscopic methods. The major problem we had, was to differentiate between the monomeric and the dimeric structure of the quinoline products. In the ^{1}H nmr spectra of **8a-c** there were no exchangeable protons in $CDCl_3$ as well as in DMSO-d_6. In the ir spectra of **8a-c** there again was no evidence for a SH fragment. The first direct proof for a S-S fragment in our molecules was the observation of a S-S stretching vibration in the raman spectrum at $\gamma \sim 500$ cm^{-1} (for example in **8a**: γ = 488 cm^{-1}).[14] Again in all the raman spectra taken, there was no evidence for an SH fragment. In addition we have taken FABms and FDms and in all cases observed the exact mass peaks of compounds (**8a-c**).

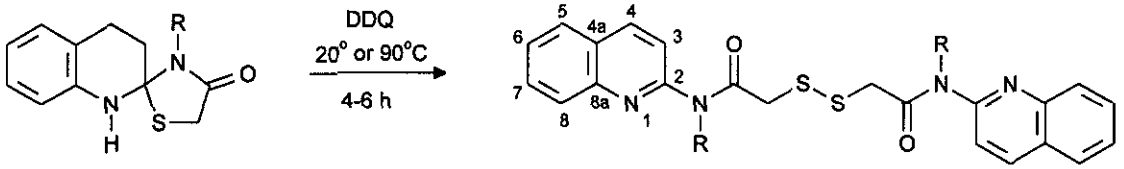
Table 2 Synthesis of Dimeric Quinolines (**8a-c**) from **6a-c**[15]

R	Reaction Conditions[a,b]		Product	Yield [%]
	t[h]	T[°C]		
CH_3	4	20	**8a**	66
	6	90	**8a**	78
cycl.-C_3H_5	4	20	**8b**	55
	6	90	**8b**	65
$CH_2CH{=}CH_2$	4	20	**8c**	53
	6	90	**8c**	57

[a] All reactions were carried out in absolute dioxane.

[b] Reaction conditions are not optimized.

Scheme 3

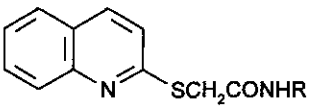


6a-d

53-78%

R = CH_3 **8a**
cycl.-C_3H_5 **8b**
$CH_2CH{=}CH_2$ **8c**

and / or

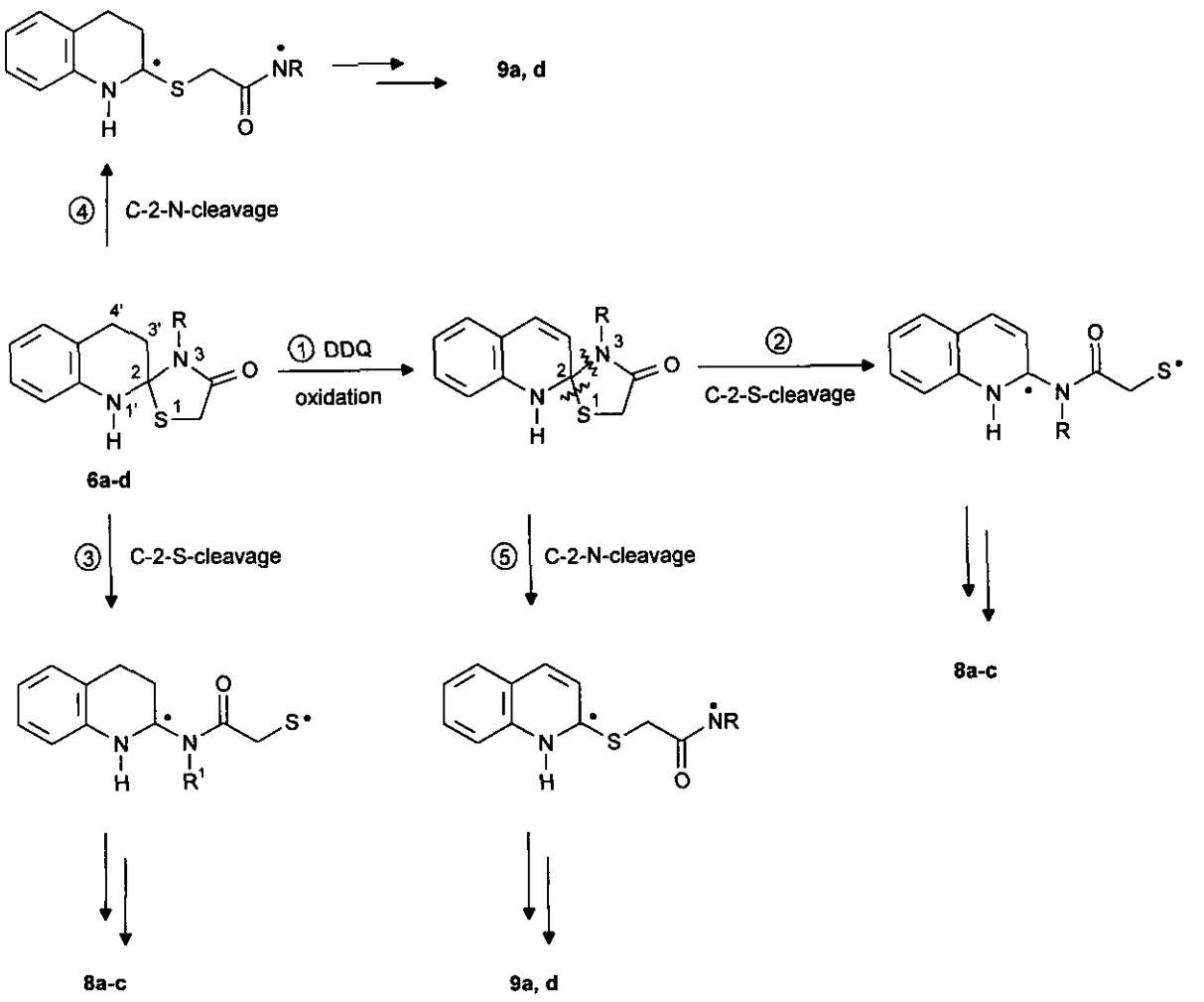


R = CH_3 **9a** only traces
$CH_2C{\equiv}CH$ **9d** 17-22%

This shows that the 5-membered thiazolidin-4-one ring is not stable under the reaction conditions. Even at room temperature cleavage of the thiazolidin-4-one ring was observed after 6 h. For the formation of the quinolines (**8a-c**) the crucial step must be the cleavage of the C-2-S-bond, whereas for the formation of quinoline (**9d**) the cleavage of the C-2-N-bond must be significant (Scheme 4).

From our experimental results, we cannot deduce the exact sequence of the single oxidation steps (Scheme 4), nor do we know which step is the first. The reaction of **6d** with DDQ demonstrates, that it is also possible to obtain C(2)-sulfenylated quinolines (**9d**). In this case, no dimeric quinoline (**8d**) could be isolated, but the yield of compound (**9d**) is not good (17-22%) and therefore the preparative usefulness is restricted in this case.

Scheme 4



CONCLUSION

We have shown, that the spiroquinolines (**6a-d**) could be easily synthesized in good yields in a one pot procedure starting from 3,4-dihydro-1*H*-quinoline-2-thione. In addition we were able to show, that the anion of 3,4-dihydro-1*H*-quinoline-2-thione (**3**) is necessary in the cyclization step ③ (Scheme 1). Furthermore the usefulness of the spiroquinolines (**6a-c**) in the synthesis of new dimeric quinoline compounds (**8a-c**) was demonstrated.

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9. **Typical experimental procedure**: To a solution of 3,4-dihydro-1*H*-quinoline-2-thione (3.26 g, 20 mmol) in THF (40 ml) was added NaH (0.92 g, 21 mmol) in small portions under an atmosphere of nitrogen. Stirring at 20°C continued for 20 min and then a solution of a *N*-substituted 2-bromoacetamide (**4a-d**) (10.5 mmol) in THF (20 ml) was added dropwise at 20°C. The reaction mixture was stirred at 20°C for 15 h, the solvent removed in vacuo, and the residue taken up in EtOAc and washed twice with water. The organic layer was dried (Na_2SO_4) and concentrated in

vacuo. The crude material was purified by flash chromatography (SiO_2, EtOAc/hexane 1:1-1:3 or EtOAc/cyclohexane 1:1).

10. Satisfactory analytical data were obtained for all new compounds. Selected data for compound (**6a**): ir (KBr, cm^{-1}) 3323, 2926, 1672, 1610, 1493, 1312, 1157, 1032, 741; ^1H nmr ($CDCl_3$) δ 2.04-2.14 (m, 1H, CH_2), 2.40-2.52 (m, 1H, CH_2), 2.84-2.94 (m, 1H, CH_2), 2.97 (s, 3H, CH_3), 3.15-3.29 (m, 1H, CH_2), 3.74 (m, 2H, SCH_2, (AB-system, ^2J=15.9 Hz)), 6.57 (d, J=7.9 Hz, 1H, arom. H), 6.79 (t, J=7.4 Hz, 1H, arom. H), 7.02-7.07 (m, 2H, aromatic H); ^{13}C nmr ($CDCl_3$) δ 24.39 (C-3'), 27.80 (N- CH_3), 32.05 (C-5), 34.33 (C-4') 84.01 (m, C-2), 115.55 (C-8'), 119.68 (C-6'), 120.12 (C-4'a), 127.24 (C-7'), 128.81 (C-5'), 140.99 (m, C-8'a), 169.76 (C-4); Elms, $^m/_z$ (rel. inten.) 234 (M^+, 100), 201 (38), 160 (40), 159 (92), 130 (46), 119 (34), 106 (22), 55 (28).
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12. Satisfactory analytical data were obtained for all new compounds. Selected data for compound (**8a**): mp 100-102°C; raman (powder, cm^{-1}) 3047, 1644, 1618, 1473, 1429, 1382, 778, 614, 564, 532, 488 (S-S!); ^1H nmr ($CDCl_3$) δ 3.47 (s, 6H, N-CH_3), 3.92 (s, 4H, SCH_2), 7.42 (d, J=8.0 Hz, 2H, arom. H), 7.53 (td, J=6.9, 0.9 Hz, 2H, arom. H), 7.72 (td, J=7.8, 0.9 Hz, 2H, arom. H), 7.81 (d, J=8.1 Hz, 2H, arom. H), 7.96 (d, J=8.3 Hz, 2H, arom. H), 8.17 (d, J=8.7 Hz, 2H, arom. H); ^{13}C nmr ($CDCl_3$) δ 35.52 (N-CH_3), 43.78 (SCH_2), 117.73 (C-3), 126.43 (C-4a), 126.59 (arom. C), 127.36 (arom. C), 128.59 (arom. C). 130.19 (arom. C), 138.57 (C-4), 146.54 (C-8a), 154.35 (C-2), 169.45 (Carbonyl-C); FDms, $^m/_z$ 462 (M^+).
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14. K. Nakanishi and P.H. Solomon, *Infrared Absorption Spectroscopy*, Holden Day Inc., San Francisco, 1977, p. 88.
15. **Typical experimental procedure**: A mixture of a 4-oxospiro[thiazolidin-2,2'(1'*H*)-quinoline] compound (**6a-c**) (10 mmol) and DDQ (2.27 g, 13 mmol) was stirred in dioxane (50 ml) at 20° or 90°C for 4-6 h (see Table 2). The dioxane was removed in vacuo and the residue taken up in EtOAc (insoluble parts are filtered off). The EtOAc layer was washed twice with sat. aq. Na_2CO_3 and then dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by flash chromatography (EtOAc/hexane 1:1-10:1).

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