An Easy and Efficient Synthesis of 4*H*-Thiazolo[5,4,3-*ij*]quinolin-4-ones and 5*H*-1,4-thiazino[2,3,4-*i,j*]quinolin-5-ones

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The title heterocycles have been synthesized by a Claisen-type self condensation of acetylbenzothiazolines and acetyldihydrobenzothiazines and subsequent cyclization.

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In a previous paper (1) we have reported on the organometallic promoted Claisen-type self-condensation of 4-acetyl-2,3-dihydrobenzo-1,4-thiazine, which provides 4-acetoacetyl-2,3-dihydrobenzo-1,4-thiazine in good yield.

The extension of this unprecedented reaction to acetylbenzothiazolines as well as to other acetylbenzothiazine derivatives has allowed us to achieve related self-condensed products and these have been employed to synthesize novel and, from the pharmaceutical viewpoint, potentially useful 4*H*-thiazolo[5,4,3-*ij*]quinolin-4-ones and 5*H*-1,4-thiazino[2,3,4-*ij*]quinolin-5-ones.

4*H*-2,3-Dihydrobenzo-1,4-thiazines **1** have been prepared from *o*-aminothiophenol and *vic*-dihaloalkanes in basic conditions (2) or by sodium borohydride reduction of the corresponding 2*H*-1,4-benzothiazines (3), whereas spiro-benzothiazolines **2** were synthesized from *o*-aminothiophenol and the appropriate cycloalkanones (4). Amines **1** and **2** were acetylated to **3** and **4** with acetyl chloride (2) in pyridine or with acetic anhydride (4).

The acetyl derivatives **3** and **4** reacted with *n*-butylmagnesium bromide in tetrahydrofurane furnishing β-ketoamides **5** and **6**, respectively and the free amines **1** and **2**.

The reaction has been easily carried out by dropping the organometallic reagent (1.1 moles/THF) to a solution of **3** (or **4**) (1 mole/THF) under nitrogen atmosphere at room temperature (≅ 20°). The reaction mixture was kept at this temperature until tlc showed complete disappearance of the starting material and then quenched by ammonium chloride (saturated solution). After isolation and purification good to high yields of **5** and **6** were obtained as indicated in Table 1.

We have some evidences to believe that a Claisen-type mechanism, very similar to that proposed for the condensation of esters (5), is here operating.

The procedure, by us discovered, to **5** and **6** is rather simple, convenient and requires very mild conditions, while an alternative route from acetoacetic ester and amines **1** and **2** respectively, in rather severe conditions (reflux in xylene for long time or neat reaction) according to the Knorr's (6) method, permitted to obtain only traces of the expected β-ketoamides **5** and **6**. Moreover, yet a low yield of **5** was observed by reacting **1** with diketene according to the procedure reported for the synthesis of carbostyrils (7).

β-Ketoamides **5** can be suitably alkylated in α position by alkyl halides and oxidized to the related 1,1-dioxides with *m*-chloroperbenzoic acid in dichloromethane.

Cyclization of **5** and **6**, performed in sulphuric acid, provided 5*H*-1,4-thiazino[2,3,4-*ij*]quinolin-5-ones **7** and 4*H*-thiazolo[5,4,3-*ij*]quinolin-4-ones **8**, respectively.

The cyclization of **5a** is illustrative: **5a** (2 mmoles) was dissolved in 5 ml of concentrated sulphuric acid at about 25° and the reaction mixture kept at this temperature for

Table 1

Self-condensation of 4-Acetyl-2,3-dihydrobenzo-1,4-thiazines and 3-Acethylbenzothiazolines with *n*-BuMgBr in THF at Room Temperature

Compound	Reactants Ratio	Reaction Time (hours)	Self-Condensed Product (c)	% Yield (a,b)
3a	1:1	1	**5a**	83
3b	"	15	**5b**	70
3c	"	20	**5c**	74
4a	"	3	**6a**	65
4b	"	4	**6b**	75
4c	"	4	**6c**	80

(a) Reactions were performed on a 2-3 mmole scale. (b) All yields are for isolated, pure materials obtained from column chromatography (silica gel, 50% ether-light petroleum). (c) Structures were established by elemental analyses and ir and nmr spectroscopy.

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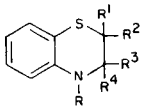
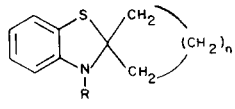
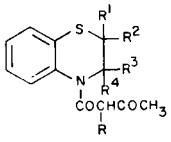
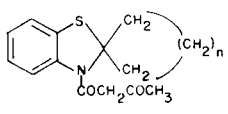




1a; R = R¹ = R² = R³ = R⁴ = H
1b; R = R¹ = R³ = H; R² and R⁴ = -(CH₂)₄-
1c; R = R³ = H; R¹ = R² = CH₃; R⁴ = Ph
3a; R = COCH₃; R¹ = R² = R³ = R⁴ = H
3b; R = COCH₃; R¹ = R³ = H; R² and R⁴ = -(CH₂)₄-
3c; R = COCH₃; R³ = H; R¹ = R² = CH₃; R⁴ = Ph

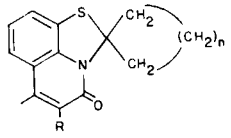
2a; n = 2; R = H
2b; n = 3; R = H
2c; n = 4; R = H
4a; n = 2; R = COCH₃
4b; n = 3; R = COCH₃
4c; n = 4; R = COCH₃



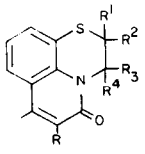


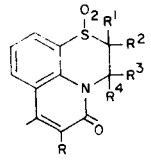
5a; R = R¹ = R² = R³ = R⁴ = H
5b; R = R¹ = R³ = H; R² and R⁴ = -(CH₂)₄-
5c; R = R³ = H; R¹ = R² = CH₃; R⁴ = Ph
5d; R = CH₃; R¹ = R² = R³ = R⁴ = H
5e; R = C₂H₅; R¹ = R² = R³ = R⁴ = H

6a; n = 2
6b; n = 3
6c; n = 4



8a; n = 2
8b; n = 3





7a; R = R¹ = R² = R³ = R⁴ = H
7b; R = R¹ = R³ = H; R² and R⁴ = -(CH₂)₄-
7c; R = R³ = H; R¹ = R² = CH₃; R⁴ = Ph
7d; R = CH₃; R¹ = R² = R³ = R⁴ = H
7e; R = C₂H₅; R¹ = R² = R³ = R⁴ = H

9a; R = R¹ = R² = R³ = R⁴ = H
9b; R = R³ = H; R¹ = R² = CH₃; R⁴ = Ph
9c; R = CH₃; R¹ = R² = R³ = R⁴ = H
9d; R = C₂H₅; R¹ = R² = R³ = R⁴ = H

1 hour and then quenched by pouring into cold water. The usual workup gave **7a** in excellent yield (see Table 2).

Oxidation of **7** with *m*-chloroperbenzoic acid in dichloromethane at room temperature (overnight) led to sulphones **9** in practically quantitative yields, while attempts to cyclize 1,1-dioxides of **5** with sulphuric acid failed because of the easy deacylation (2) to 4*H*-2,3-dihydrobenzo-1,4-thiazine 1,1-dioxides.

The procedure here reported for the above mentioned heterocycles seems to be applicable to other systems; therefore a variety of new and pharmaceutically useful heterocycles might be prepared in this way. Further work is in progress to this end.

Table 2

Cyclization of 4-Acetoacetyl-2,3-dihydrobenzo-1,4-thiazines and 3-Acetoacetylspiro-benzothiazolines in Concentrated Sulfuric Acid at Room Temperature

Compound	Reaction Time	Cyclization Product (a)	% Yields (b)
5a	1 hour	**7a**	95
5b	45′	**7b**	90
5c	45′	**7c**	95
5d	1 hour	**7d**	90
5e	1 hour	**7e**	95
6a	40′	**8a**	50
6b	40′	**8b**	73

(a) Structures were established by elemental analyses in ir and nmr spectroscopy. (b) Yields are for isolated, pure materials.

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