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Novel benzo[*e*][1,2]thiazine derivatives, synthesis and reactions

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ABSTRACT

New benzo[*e*][1,2]thiazine derivatives are described. The synthetic route to *N*-alkyl benzothiazinones, involving protection–deprotection steps is developed and their reactivity is investigated. Novel β-aminovinylketones, hydroxymethylene ketones and pyrazolobenzothiazines are obtained.

The derivatives of benzothiazine are biologically active compounds and this activity can vary greatly, depending on the substitution.[1,2] The significant group of medically applied drugs known as 'oxicams' are the 'second generation' nonsteroidal anti-inflammatory drugs (NSAIDs).[3] Most of these are benzo[*e*][1,2]thiazine-3-carboxamides. To date, the application of 'oxicams' is limited by the number of side effects, in particular stomach lining erosive activity potentially resulting in ulcer development.[4] Much research was carried out over the last 20 years, aimed towards improving anti-inflammatory drugs, and to avoid the side effects.[5,6]

In our previous work,[7] novel 2,1-benzothiazine chloroaldehydes were described and their chemistry was shown to be quite versatile. The current *Letter* illustrates the synthesis and properties of some new benzo[*e*][1,2]thiazine derivatives, which can be used as intermediates for the synthesis of more elaborate compounds with potential biological activity.

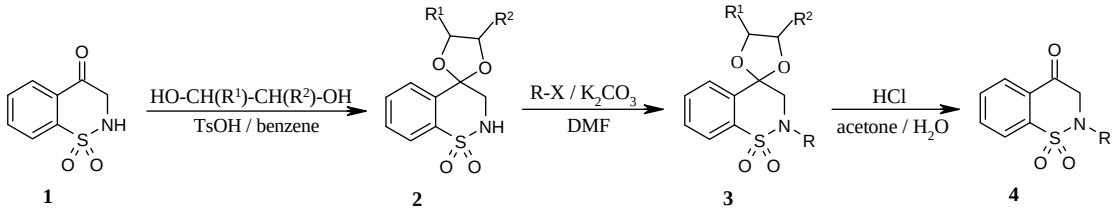
Due to limitations of the general methods for N-substituted benzo[*e*][1,2]thiazinone synthesis, only *N*-methyl derivatives have been described.[8,9] The synthetic route to *N*-alkyl benzo[*e*][1,2]thiazin-4-one 1,1-dioxides developed by our group allows for the introduction of a variety of substituents using different alkylating agents (Scheme 1). The synthesis of 2,3-dihydro-4*H*-benzo[*e*]-[1,2]thiazin-4-one 1,1-dioxide **1** had been previously described.[10] The reaction of **1** with 1,2-glycols catalysed by *p*-toluenesulfonic acid in benzene yields the corresponding protected product **2**, which is easily alkylated in DMF/K_2CO_3 to afford thiazines **3**. Finally, deprotection leads to *N*-alkyl compounds **4**.

Our next goal was to introduce a carbonyl group at the C-3 position of the benzothiazine ring. Such a transformation should lead to carbaldehydes, which have not been described to date, and could give access to a number of more complex compounds.

Direct acylation of the enolate, prepared from ketone **4** with formic acid methyl ester, was not successful. The Vilsmeier–Haack reaction and condensation with ethyl orthoformate were also ineffective. The corresponding pure dimethylaminomethylene-derivative **5** was isolated in almost quantitative yield, by reaction of **4** with dimethylformamide dimethyl acetal (DMFDA).

Enamines **5** are highly reactive compounds. We have found that the dimethylamino moiety is displaced easily by nucleophilic agents. Treatment of compounds **5** with sodium hydroxide leads to formation of the corresponding hydroxymethylene ketones **6**. The reaction of **5** with hydroxylamine and substituted hydrazines gives oximes **7** and hydrazones **8**, respectively, which are also accessible directly from hydroxymethylene ketones **6**.

Hydroxymethylene ketones **6** are enols of β-dicarbonyl compounds, the exocyclic carbon is reactive towards such nucleophiles as alcohols. Reflux in methanol, ethanol or isopropanol gives the corresponding enol ethers **9**. Heating hydrazones **8** in xylene with *p*-toluenesulfonic acid leads to intramolecular heterocyclisation to afford pyrazolothiazines **10**.



Scheme 1.

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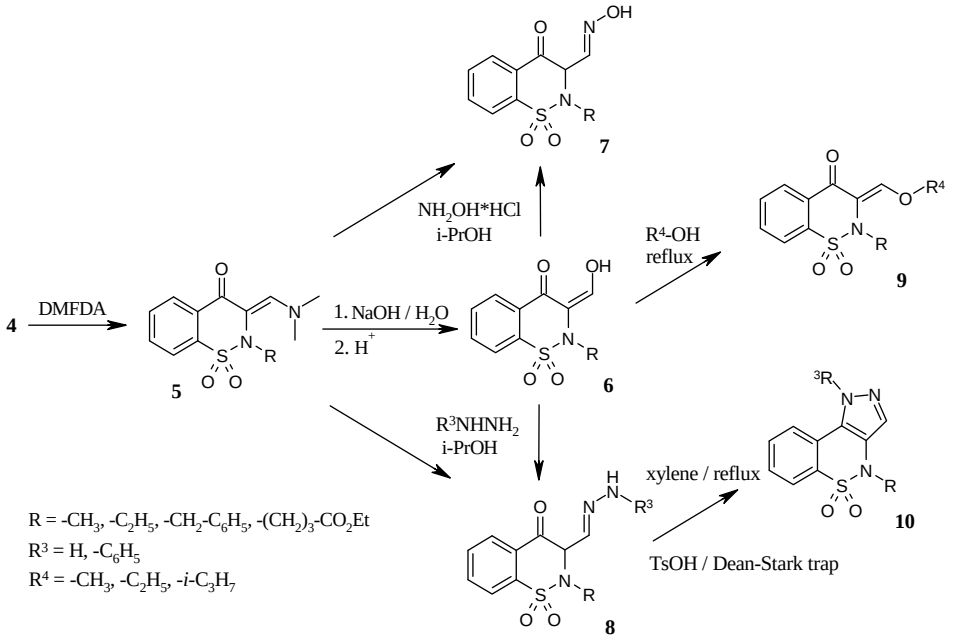
Table 1
Representative compounds obtained via Scheme 2

Product	Conditions	Elemental analyses C, H, N calcd/found	Yield (%)
5 (R = Me)	Dimethylformamide dimethyl acetal (10 equiv), reflux, 5 h	54.12, 5.30, 10.52/53.87, 5.2, 10.12	95
6 (R = Me)	Concentrated sodium (potassium) hydroxide solution, 75 °C, 3 h	50.20, 3.79, 5.85/50.01, 3.65, 5.43	99
7 (R = Me)	Hydroxylamine hydrochloride, ethanol, reflux, 3 h	47.24, 3.96, 11.02/47.02, 4.13, 11.17	83
8 (R = Me, R^3 = Ph)	Phenylhydrazine, ethanol, reflux, 3 h	58.35, 4.59, 12.76/58.58, 4.92, 13.05	89
9 (R = Me, R^4 = *i*-Pr)	Alcohol, reflux, 5 h	55.50, 5.37, 4.98/55.27, 5.68, 5.17	99
10 (R = Et, R^3 = Ph)	Xylene, *p*-toluenesulfonic acid, reflux, Dean–Stark trap, 10 h	62.75, 4.65, 12.91/62.43, 4.12, 12.57	78



Scheme 2.

The structures of all the above-mentioned products (Table 1) were established from their NMR spectra, elemental analyses and mass spectra.

In summary, we have described novel benzo[*e*][1,2]thiazine derivatives, in particular β-aminovinylketones **5** and β-hydroxymethylene ketones **6**, which were obtained in high yields (>95%) via convenient protocols.

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