Simple and Efficient Methoxylation of 1,3-Dihydrothiazine Derivatives

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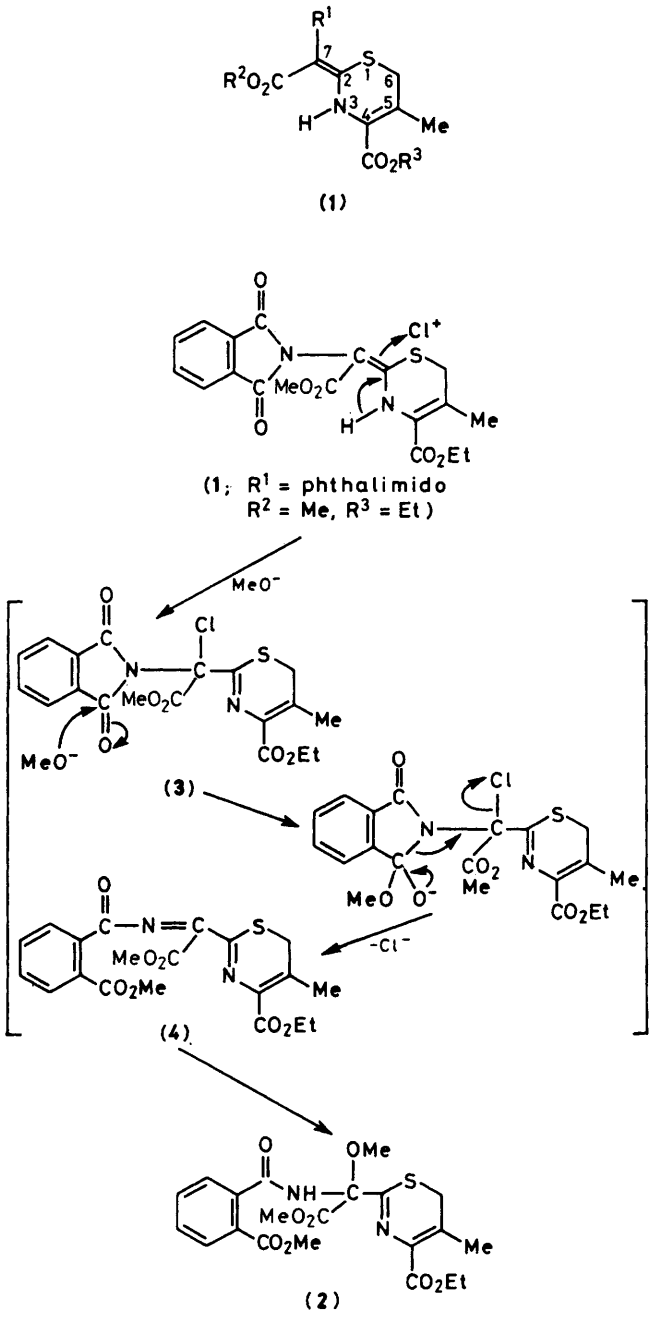
The methoxylation of dihydrothiazine derivatives has been carried out using t-butyl hypochlorite and lithium methoxide; a possible mechanism involving an acylimine intermediate is proposed.

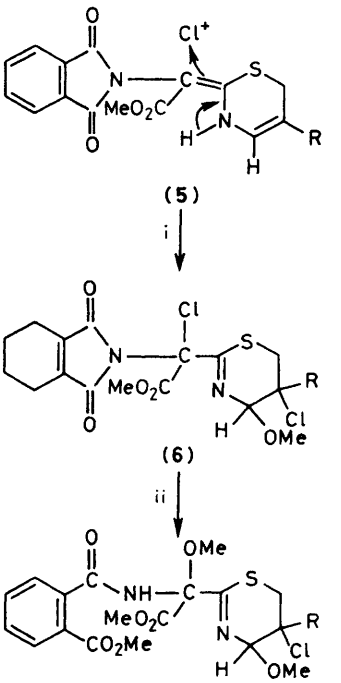
The substituted 2,3-dihydro-6*H*-1,3-thiazines (**1**) have been obtained by Eggers *et al.*[1] either *via* a [3 + 3] cyclocondensation of thioamides with vinyl keto-esters or by the opening of the lactam ring of cephalosporins by alkoxides. Recently,



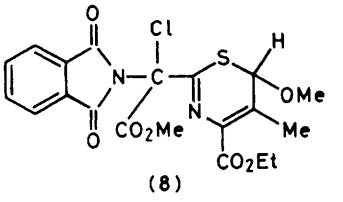
Scheme 1

Young *et al.* reported some interesting results concerning (a) the annelation of these dihydrothiazines using substituted acrylic acids to give 2*H*-pyrido[2,1-*b*]thiazin-6-ones[2] and (b) the photochemical rearrangement of the dihydrothiazines to give cyclopropathiazolines.[3] We report herein the methoxylation at C-7 of dihydrothiazine derivatives; the products are of considerable interest as potential precursors of cephamycins.[4]

After several exploratory tests, the best results were obtained by adding t-butyl hypochlorite to a solution of (**1**; R^1 = phthalimido, R^2 = Me, R^3 = Et) in tetrahydrofuran in the presence of a methanolic solution of lithium methoxide at −70 °C. Compound (**2**) was thus obtained in 70% yield.



Scheme 2. i, Bu^{t}OCl, THF, MeOH, −10 °C; ii, MeO$^-$Li$^+$, MeOH.



Methoxylation at the required position and migration of the double bond was accompanied by the opening of the phthalimido group to a 2-methoxycarbonylbenzamido group. This suggests a possible concerted mechanism as shown in Scheme 1. Electrophilic attack of Cl^+ on the exocyclic double bond followed by the action of MeO^- could afford the acylimine (**4**). Subsequent addition of methanol to the acylimine intermediate[5,6] would then yield the observed product (**2**).

Support for this mechanism was obtained using the analogue (**5**), which was prepared *via* a [4 + 2] cycloaddition reaction using a method[7] developed in our laboratory. When (**5**) was allowed to react with t-butyl hypochlorite in the absence of base the intermediate (**6**), an analogue of (**3**), was obtained. Addition of the elements of ClOMe across the endocyclic 4,5-double bond of the thiazine ring also occurred. Subsequent action of lithium methoxide on (**6**) gave the methoxylated product (**7**); this was accompanied by opening of the phthalimido group (Scheme 2). The stereochemistry of adducts (**6**) and (**7**) in the thiazine ring is not known at present.

Attempts to isolate intermediate (**3**) by carrying out the reaction in the absence of base at −70 °C were unsuccessful. However on warming to −20 °C, compound (**8**) was obtained in which substitution at C-6 by a methoxy group had occurred.

All compounds gave satisfactory microanalytical and spectroscopic (^{1}H and ^{13}C n.m.r., i.r., and mass spectral) data.

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