

Simple and Efficient Methoxylation of 1,3-Dihydrothiazine Derivatives

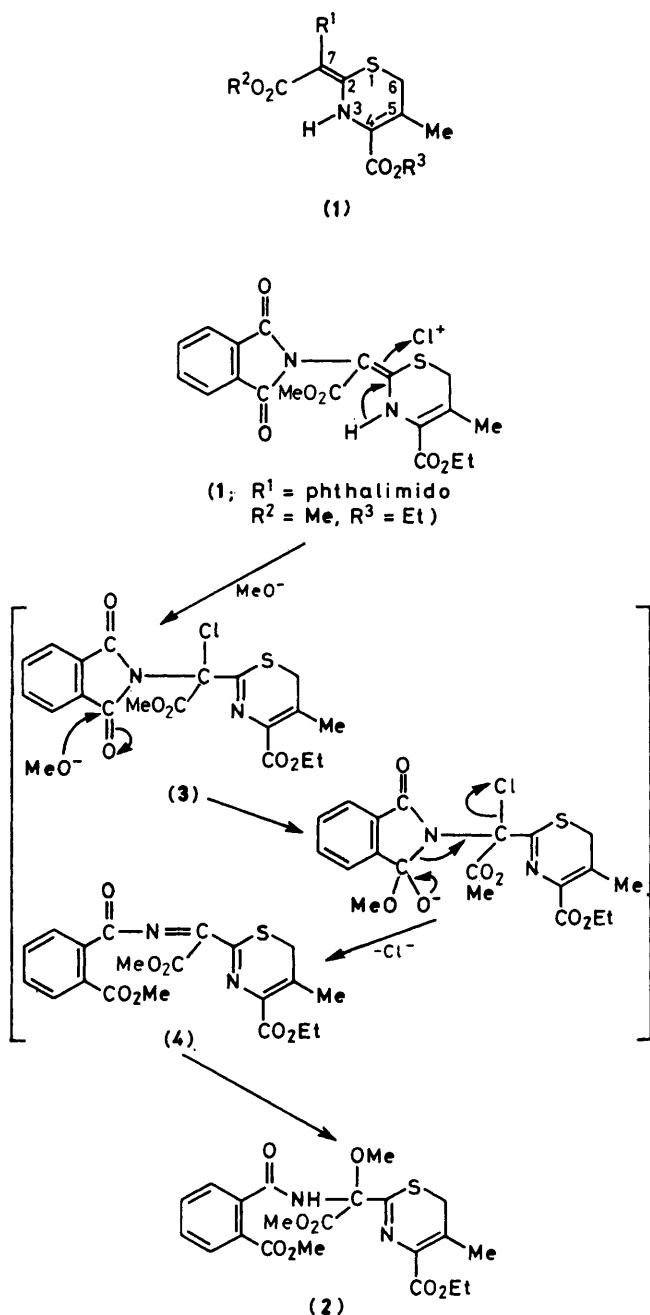
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The methoxylation of dihydrothiazine derivatives has been carried out using t-butyl hypochlorite and lithium methoxide; a possible mechanism involving an acylimine intermediate is proposed.

The substituted 2,3-dihydro-6*H*-1,3-thiazines (1) have been obtained by Eggers *et al.*¹ either *via* a [3 + 3] cyclocondensa-

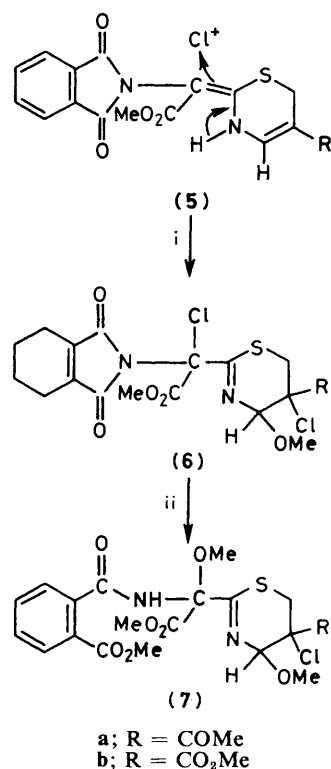
tion of thioamides with vinyl keto-esters or by the opening of the lactam ring of cephalosporins by alkoxides. Recently,



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-ones² 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^tOCl , 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-methoxycarbonylbenzamide 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 method⁷ 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 (^1H and ^{13}C n.m.r., i.r., and mass spectral) data.

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