IMPROVED METHOD FOR SYNTHESIS OF 7-AMINO-4-METHYLCOUMARIN

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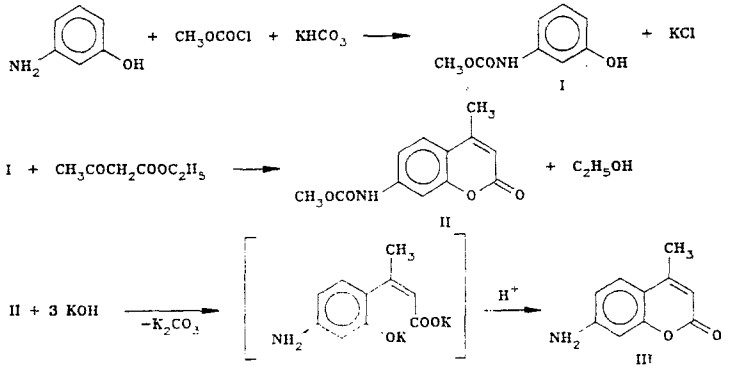
A new variant of the synthesis of 7-amino-4-methyl-coumarin from m-aminophenol via a three-step scheme is proposed. Acylation of m-aminophenyl with methoxycarbonyl chloride gave m-(N-methoxycarbonylamino)phenol, which was converted to 7-(N-methoxycarbonyl-amino)-4-methylcoumarin by condensation with acetoacetic ester in sulfuric acid. Heating of the coumarin with concentrated alkali leads to an intermediate, which, after acidification, is converted to 7-amino-4-methylcoumarin in high yield.

7-Amino-4-methylcoumarin (AMC) has intense fluorescence and, owing to this property, finds application in enzymology [1, 2]. 4-Methyl-7-coumaryl amides of amino acids and peptides are hydrolyzed by proteolytic enzymes with the formation of free AMC, the amount of which determined fluorometrically [1] or photometrically at 360 nm [2] makes it possible to form a judgment regarding the activity of the investigated enzyme.

Several methods for the synthesis of AMC are known [3]. The classical method of Pechmann and Schwarz [4], which is based on the condensation of m-aminophenol with acetoacetic ester by heating in alcohol in the presence of zinc chloride, makes it possible to obtain AMC in one step but in low yield (20-25%); the isolation of the AMC from the reaction mixture is hindered by the presence of side products [3]. Methods for the synthesis of AMC from N-substituted m-aminophenol via a three-step scheme have been studied [3]. It is apparent that the key feature of the three-step scheme is the correct selection of the protective grouping; it was established that protective groups of the urethane type have a favorable effect on the formation of the heterocyclic fragment of AMC [5]. However, in [1] in which an N-ethoxycarbonyl protective group was used the overall yield of AMC based on m-aminophenol proved to be low because of the low yields of intermediates in the steps involving blocking and unblocking of the amino group.

We have found that a methoxycarbonyl grouping, which, as one knows [6, p. 116], can be removed by alkaline hydrolysis, is considerably more suitable for the synthesis of AMC via a three-step scheme.



m-(N-Methoxycarbonyl(MOC)amino)phenol is formed in greater than 90% yield in the acylation of m-aminophenol with methoxycarbonyl chloride in ethyl acetate in the presence of aqueous potassium bicarbonate. The condensation of MOC-aminophenol with acetoacetic ester was carried out in concentrated H_2SO_4, and MOC-AMC was obtained in 87% yield. It is necessary to observe a number of conditions in the step involving the removal of the MOC group in order to obtain AMC of satisfactory quality in high yield. First of all, the unblocking reaction must

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be carried out as quickly as possible, since the resulting product with a free amino group is inclined to undergo oxidation and resinification. For the hydrolysis of the MOC group to occur at a high rate the alkali concentration should be high (we used 45% KOH solution), and the reaction must be carried out with heating (80-100°C) and vigorous stirring. In addition, one should take into account the fact that three equivalents of alkali are consumed per mole of MOC-AMC, since opening of the pyrone ring (see [3]) with the formation of a salt of cis-aminocoumaric acid occurs simultaneously with hydrolysis of the MOC group. After acidification, this acid undergoes spontaneous cyclization to AMC, but with an increase in the alkaline-treatment time the salt of cis-aminocoumaric acid is gradually converted to the trans isomer, which is not capable of forming a pyrone ring. In this connection, failure to observe the unblocking conditions, which slows down the process, inevitably leads to a decrease in the yield of AMC and to complications in its purification. After dissolving MOC-AMC in alkali with subsequent acidification and alkalization AMC was obtained in 83% yield. As a rule, the product isolated is chromatographically homogeneous and can be used to obtain 4-methyl-7-coumaryl amides of amino acids without additional purification.

Thus the use of an MOC-amino protective grouping makes it possible to substantially increase the overall yield of AMC based on m-aminophenol. The proposed method may evidently be of interest not only for the laboratory preparation of AMC but also for its industrial production.

EXPERIMENTAL

The IR spectra of KCl pellets of the compounds were recorded with a Pye-Unicam SP-1000 spectrometer (England). The compositions of the reaction mixtures and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in a benzene–acetone–acetic acid system (100:50:1). The melting points were determined in open capillaries and were not corrected. The results of elementary analysis for C, H, and N were in agreement with the calculated values.

m-(N-Methoxycarbonylamino)phenol (I, $C_8H_9NO_3$). An 18-ml (234 mmole) sample of methoxycarbonyl chloride was added dropwise in the course of 0.5 h with stirring and cooling (10-15°C) to a suspension of 22 g (202 mmole) of m-aminophenol and 25 g of $KHCO_3$ in 150 ml of ethyl acetate and 10 ml of water, after which the mixture was stirred for 1 h. Water (50 ml) was then added, and the mixture was stirred for another 3 h. The aqueous layer was separated, and the organic layer was washed successively with water, 1 M H_2SO_4, water, and saturated NaCl solution, dried with $MgSO_4$, and evaporated. The crystalline residue was recrystallized from benzene to give 31.5 g (94%) of I with mp 97-98°C and R_f 0.57. IR spectrum: 3480, 3380, 1705, 1620, 1570 cm^{-1}.

7-Methoxycarbonylamino-4-methylcoumarin (II, $C_{12}H_{11}NO_4$). A mixture of 23 g (137 mmole) of I and 25 ml of acetoacetic ester was added in portions with stirring to 60 ml of concentrated H_2SO_4, after which the mixture was stirred for 2 h and diluted with a mixture of water and ice (250-300 ml). The diluted mixture was stirred until crystallization ceased, and the precipitate was removed by filtration, washed with water, methanol, and ether and dried to give 23.0 g (87.5%) of II with mp 253-254°C and R_f 0.78. IR spectrum: 3380, 1745, 1705 cm^{-1}.

7-Amino-4-methylcoumarin (III). A suspension of 28 g (120 mmole) of II in 60 ml of 45% KOH solution was stirred at 80-90°C until a solution formed (15-20 min). The reaction mixture was cooled and diluted with water to 200 ml, and the solution, when necessary, was filtered and acidified cautiously with concentrated HCl to pH 5-6 with stirring and cooling. A solution of alkali was added to the resulting suspension to pH 8, and the mixture was stirred until crystallization ceased. The precipitate was removed by filtration, washed with water, methanol, and ether, and dried to give 17.4 g (83%) of III with mp 219-220°C and R_f 0.58 (mp 222-223°C [1]).

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