

ENZYMATIC CYCLIZATION INVOLVING INTRAMOLECULAR MICHAEL ADDITION BY
CATALASE : FORMATION OF 2-METHYLBENZIMIDAZOLES

Ahmed Kamal* and Riaz Hashim

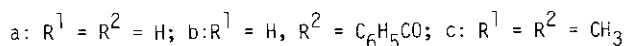
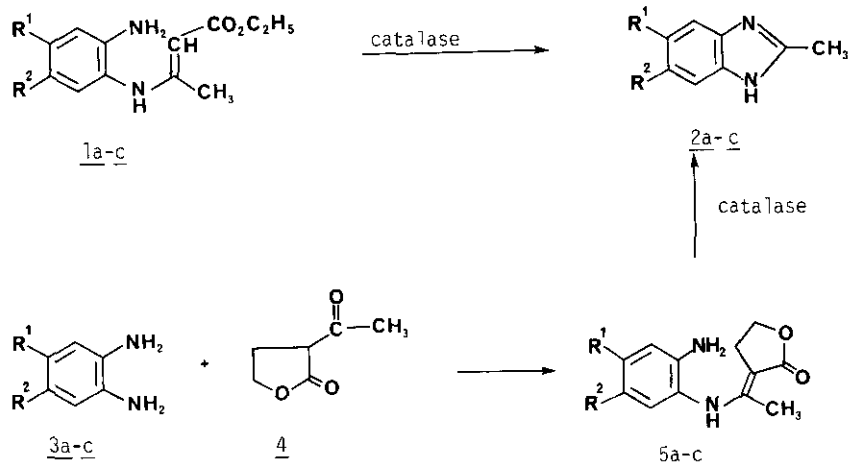
Division of Organic Chemistry, Indian Institute of Chemical Technology
Hyderabad-500 007, India

Abstract - Catalase-mediated intramolecular cyclization of ethyl β -2-aminoanilinoacrylates gives 2-methylbenzimidazoles in good yields

Our interest in the use of enzymes as biocatalysts for heterocyclic synthesis by intramolecular cyclizations exhibited interesting findings.^{1,2} Recently, we described³ the catalase-mediated cyclization of 1-allyl-3-(*o*-cyanophenyl)urea and *o*-cyanophenyl allylcarbamate. In the programme directed to explore the potential of enzymes in organic synthesis, various enzymes such as catalase, lipases and as well enzymes obtained from different sources such as liver microsomes and yeasts, were investigated for cyclization. Catalase has been widely used for the hydroperoxide-dependent *N*-dealkylation of a number of aromatic secondary and tertiary amines. Herein, we wish to report the novel use of catalase for the cyclization involving intramolecular Michael addition of ethyl β -2-aminoanilinoacrylates (1a-c) to 2-methylbenzimidazoles⁵ (2a-c). This strategy was further applied to the cyclization of adducts 5a-c obtained by the reaction of 1,2-phenylenediamines (3a-c) with 2-acetylbutyrolactone (4). It was interesting to observe that the adducts 5 on incubating with catalase also afforded 2-methylbenzimidazoles (2).

The starting materials 1a-c were prepared by the reaction of *o*-phenylenediamine with ethyl acetoacetate as described in the literature,⁵ while 5a-c were prepared by the reaction of 1,2-phenylenediamine with 2-acetylbutyrolactone at room temperature for 12 h.

In a typical reaction procedure, compound 1a (200 mg) was dissolved in ethanol (15 ml) and 0.1 M phosphate buffer (25 ml, pH 7.2), and to this was added catalase⁶ (0.6 ml). The reaction mixture was incubated at 20-25°C for 4 h with gentle shaking. The incubation mixture was then extracted thrice with chloroform (25 ml). The extract was dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The residue obtained was recrystallized from chloroform/hexane to give 105 mg (88% yield, mp 174-176°C) of 2-methylbenzimidazole(2a).



Similarly, other substituted 2-methylbenzimidazoles⁷ were prepared by the aforesaid method in yields ranging from 75% to 80%, whereas 2a-c were also prepared from 5a-c⁸ in 78% to 85% yields. In control reactions in the absence of catalase the cyclization did not take place and the starting material was recovered. It seems that catalase is just holding the substrate in a proper orientation and acting as a general base catalyst in these reactions.

Hence, the catalase-mediated cyclizations not only provide a new route for the synthesis of 2-methylbenzimidazoles but offer an approach for cyclizations involving intramolecular Michael addition at extremely mild conditions.

REFERENCES AND NOTES

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6. Catalase from beef liver as solution in glycerol, 30% (v/v), ethanol 10% (v/v); ca. 260000 U/ml; obtained from Boehringer Mannheim.
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8. Selected data - 5a: mp 133-134°C; ν (KBr): 3440, 3340, 3260, 1670 cm^{-1} ; $^1\text{H-NMR}$ δ (CDCl_3): 9.32 (1H, s, NH), 6.67-7.04 (4H, m, Ar-H), 4.32 (2H, t, $J=7$ Hz, OCH_2), 4.23 (2H, br s, NH_2), 2.86 (2H, t, $J=7$ Hz, CH_2), 1.80 (3H, s, CH_3); m/z 278.

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