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CATALASE-MEDIATED CYCLIZATION: SYNTHESIS OF 3-ALLYL-4-IMINO SUBSTITUTED 2(1H)-QUINAZOLINONES AND 1,3-BENZOXAZINE-2(3H)-ONES

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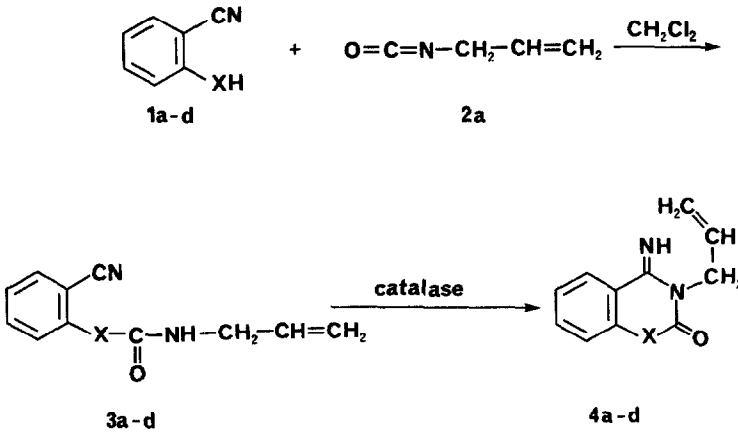
Abstract: The cyclization of N-allyl carbamoyl anthranilonitriles as well as O-allylcarbamoyl salicylonitrile to 2(1H)-quinazolinones and 1,3-benzoxazine-2(3H)-ones in quantitative yields by employing catalase has been described.

The application of enzymes[1] in the synthesis of organic compounds has increased tremendously in the last decade. In continuation of the earlier studies on the use of enzymes as biocatalysts[2,3], particularly in the cyclization reactions, various enzymes such as liver microsomes, yeasts, lipases, dehydrogenases and catalase were examined. Though all these enzymes gave the desired cyclizations, interestingly catalase-mediated reactions afforded quantitative cyclizations. Catalase[4] like peroxidases[5] and other hemeproteins[6] are well known to catalyze the hydroperoxide-dependent N-dealkylation of many aromatic secondary as well as tertiary amines. Herein we wish to report the novel use of catalase for the cyclization of N-allylcarbamoyl anthranilonitriles/ O-allylcarbamoyl salicylonitriles (**3a-d**) to 3-allyl-4-imino substituted 2(1H)-quinazolinones (**4a-c**) and 1,3-benzoxazine-2(3H)-one (**4d**). The utility of quinazolinones and 1,3-benzoxazinones has been well established[7,8] as biologically important class of heterocycles.



a, X = NH; b, X = NCH_3; c, X = NC_6H_5; d, X = O

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The starting materials **3a-d** were prepared by the reaction of anthranilo/salicyclo nitriles (**1a-d**) with allylisocyanate (**2**) in dry dichloromethane at room temperature for 3 h and recrystallized from methanol. To compound **3a**, 100 mg dissolved in ethanol (20 ml) and 0.1 M phosphate buffer (pH 7.2) was added catalase[9] (0.1 ml). The reaction mixture was incubated at 37°C for 6 h with shaking (200 rpm). The incubation mixture was then extracted thrice with chloroform (30 ml). The extract was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue obtained was recrystallized from methanol to give 95 mg (95% yield, m.p. 220-222, 99% purity by HPLC[10]) of 3-allyl-4-imino-2(1H)-quinazolinone (**4a**).

Similarly, N-methyl, N-phenyl anthranilonitrile adducts **3b-c** and salicylonitrile adduct **3d** were cyclized employing the above method to **4b-d** in good yields (75-93%). The products were characterized by analytical and spectroscopic data[11]. The possibility of compounds **4** to form the isomeric 4-allylamino heterocycles through Dimroth rearrangement has been ruled out by the unambiguous synthesis of 4-allylamino heterocycles[12], which were not identical to the ones obtained by the enzymatic method.

Although **3a-c** were further cyclized thermally, and also by using number of bases like ethanolic ammonia, triethylamine, pyridine to **4a-c** in 40-62% yields, the efforts to cyclize **3d** non-enzymatically resulted in the cleavage of O-carbamoyl linkage.

In summary, the present method employing catalase provides a new approach for the cyclization of 2-allylcarbamoyl benzonitriles, thus giving an access to biologically important heterocyclic compounds under extremely mild conditions. Further explorations of this new methodology are in progress.

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9. Catalase from beef liver as solution in glycerol, 30% (v/v), ethanol 10% (v/v), ca. 260000 U/ml; obtained from Boehringer Mannheim.
10. HPLC were obtained by using the 6A-Shimadzu instrument with a 254 nm variable-wavelength and chromatopac C-R4A integrator. All chromatography was performed at 25°C temperature on an Ultropac TSK-ODS column (250 x 4.6 mm). The mobile phase was 70% methanol in water with 1% AcOH (v/v) at 0.5 ml/min flow rate.
11. Selected data - **3a:** m.p. 173-174°C (88%), IR (KBr), $\nu_{(max)}$ 3270, 3230, 3210, 1640 cm^{-1}, NMR ($CDCl_3$) 3.8 (t,2H), 5.2 (t,2H), 5.6 (br s, 1H), 5.8 (m, 1H), 6.9-8.3 (m, 5H); **4a:** IR(KBr) $\nu_{(max)}$ 3240, 3030, 1690 cm^{-1}, NMR ($CDCl_3$) 3.9 (t,2H), 5.2 (2H), 5.9 (m, 1H), 6.9-8.4 (m,5H), 9.4 (br s,1H); **4d:** m.p. 87-90°C (75%), IR(KBr) $\nu_{(max)}$ 3330, 1715, 1610 cm^{-1}, NMR ($CDCl_3$) 3.8 (t,2H), 4.9 (br s, 1H), 5.2 (t,2H), 5.8 (m, 1H), 6.9-8.2 (m, 4H).
12. 4-Allylamino heterocycles were prepared by the reaction of respective 4-imino heterocycles[13] with allylchloride in presence of base.
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