A Novel Enzymatic Cyclization: Synthesis of Imidazo-fused Quinazolinones by Baker's Yeast

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Baker's yeast-mediated double cyclization of *N*-allylcarbamoylanthranilonitriles to 2-methylimidazo[1,2-*c*]quinazolin-5(3*H*)-ones is described.

Baker's yeast (*Saccharomyces cerevisiae*) has found widespread application in the synthesis of organic compounds.[1,2] However, its utility for cyclizations[3] has not been fully realized. Most of the enzymatic conversions take advantage of the oxidoreductases[4] found in this micro-organism. In continuation of our earlier studies on the use of enzymes as biocatalysts in organic synthesis,[5,6] we herein report the synthesis of biologically important heterocycles,[7] imidazo-fused quinazolinones formed by the double cyclization employing baker's yeast.

The precursors, *N*-allylcarbamoylanthranilonitriles (**3**), were prepared by the reaction of anthranilonitriles (**1**) with allyl isocyanate (**2**). In a typical reaction; to (**3a**) (100 mg) dissolved in ethanol (10 ml) and 0.1 M phosphate buffer (15 ml; pH 7.2) was added baker's yeast (Sigma, Type I; 350 mg). Incubation was carried out under aerobic conditions at 37 °C for 5 days with gentle shaking. The incubation mixture was extracted twice with chloroform (20 ml). The extract was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in chloroform–methanol (98:2) to give the imidazoquinazolinone (**5a**) (m.p. 185–187 °C).

The formation of (**5**) takes place *via* the intermediate (**4**) and has been substantiated by studying the time course of this reaction (Figure 1). The first cyclization of (**3**) gave rise to (**4**) which in turn produced (**5**) by the second cyclization. After one day of incubation (**5**) was formed in 20% yield with 75% of (**4**) and 3% of the starting compound (**3**). Compounds (**4**) and (**5**) were formed in equal amounts after ~60 h incubation. On the fifth day the conversion to (**5**) was 70%, while the amount of (**4**) was reduced to 20%. This remained constant even after 8 days of incubation.

A control incubation using a boiled yeast preparation afforded 97% recovery of the starting compound (**3**) and 2% of (**4**). Further, (**4**) was also cyclised on incubation with baker's yeast to give (**5**) in ~60% yield in 24 h. Any increase in the amount of baker's yeast employed had little effect on the rate and yield of these reactions. These results suggest that the conversion of (**3**) to (**4**) is relatively fast, and further transformation to (**5**) relatively slow.

This enzymatic cyclization method was extended to other *N*-alkyl and -aryl substituted anthranilonitriles which gave (**5b—d**) in 62—74% yields (Table 1). Analytical and spectroscopic data were satisfactory.†

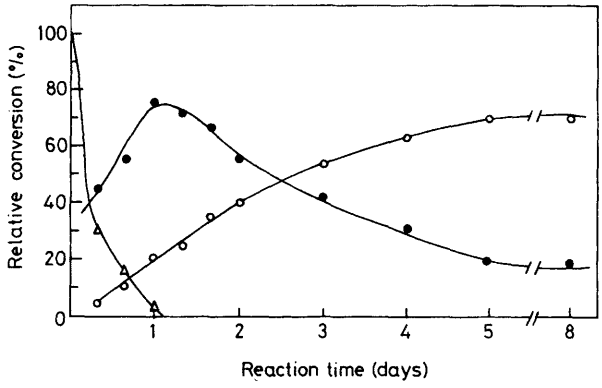


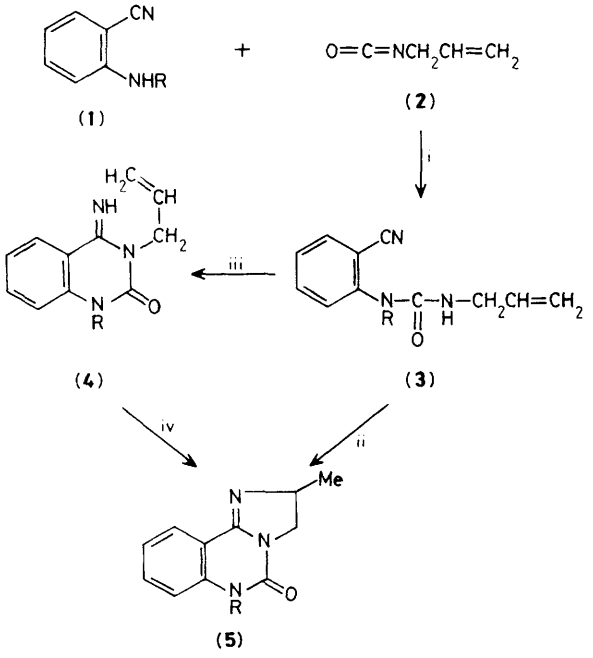
Figure 1. Time course of the incubation of (**3a**) with baker's yeast at 37 °C at the indicated times, showing relative concentration of (**3a**) (△), (**4a**) (●), and (**5a**) (○).

Table 1. Enzyme catalysed conversions of (**3**) to (**4**) and (**5**) after 5 days incubation.

		% Yield[a]	
(**3**)	R	(**4**)	(**5**)
(**3a**)	H	20	70
(**3b**)	Me	18	74
(**3c**)	Et	23	68
(**3d**)	Ph	27	62

[a] By h.p.l.c. employing TSK ODS-120A, 5 μm column (4.6 × 250 mm), water–methanol (30:70) with 2% AcOH (v/v) at 0.5 ml/min flow rate.

† *Selected spectral data* for (**3a**): m.p. 173—174 °C; i.r., ν_{max} (KBr) 3270, 3230, 3210, 1640 cm^{-1}; ^1H n.m.r. (80 MHz, $CDCl_3$), δ 6.9—8.3 (5H, m), 5.8 (1H, m), 5.6 (1H, br.s), 5.2 (2H, t), 3.8 (2H, t). (**4a**): m.p. 220—222 °C; i.r., $\nu_{max.}$ (KBr) 3240, 3030, 1690 cm^{-1}; ^1H n.m.r. (80 MHz, $CDCl_3$), δ 6.9—8.2 (4H, m), 5.8 (1H, m), 5.2 (2H, t), 4.9 (1H, br.s), 3.8 (2H, t). (**5a**): i.r., $\nu_{max.}$ ($CHCl_3$) 3400, 1665 cm^{-1}; ^1H n.m.r. (80 MHz, $CDCl_3$), δ 10.8 (1H, br.s), 7.0—8.1 (4H, m), 5.9 (1H, m), 5.2 (2H, t), 1.4 (3H, d).



Scheme 1. *Reagents*: i, dichloromethane, 25—28 °C, 3 h (85—96%); ii, baker's yeast, EtOH, phosphate buffer (pH 7.2), 37 °C, 5 days; iii, EtOH 75—78 °C, 8 h (60—67%); iv, baker's yeast, EtOH, phosphate buffer (pH 7.2), 4 days (65—78%).

There are few reports[8] on the cyclization of allyl-amidine-type compounds. Attempts to cyclize (**4**) to (**5**) by these methods and also by using *N*-iodosuccinimide as described in a recent report[9] did not yield the desired compounds (**5**). Compounds (**5a—d**) are chiral, but showed no optical rotation upon cyclization with baker's yeast either directly from (**3**) to (**5**) or from (**4**) to (**5**).

Therefore, this enzymatic cyclization process, even though it lacks stereoselectivity, provides a convenient method for the synthesis of heterocycles under extremely mild conditions. We are extending our studies, particularly in order to make the process enantioselective by employing isolated enzyme fractions.

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