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Baker's yeast (*Saccharomyces cerevisiae*) mediated transformations of *C*-aryl-*N*-phenylnitrones

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Abstract—*C*-Aryl-*N*-phenylnitrones are transformed to a mixture of azoxybenzene and aryl aldehydes when treated with a mixture of Baker's yeast and sucrose in pH = 6.0 phosphate buffer medium at 32 °C.

Baker's yeast (*Saccharomyces cerevisiae*) mediated enzymatic transformations of organic compounds are well known reactions in organic chemistry.[1–6] The most widely studied of these is the *Saccharomyces cerevisiae* promoted enzymatic reduction of the carbonyl compounds[1] like keto esters and ketones. Advantages in these reactions are the production of essentially enantiopure alcohols under mild and economical reaction conditions.

Reactions of nitrogen containing functional groups[2–6] are relatively less explored, and a survey in the current literature showed that selective and efficient reduction of nitro groups,[2] nitroso groups[4] and deoxygenation of *N*-oxides[6] have been achieved by these *Saccharomyces cerevisiae* mediated enzymatic processes. Further it was found that two types of reaction conditions have been employed in the reduction of nitrogen containing functionalities. The first type[2a–d,3b,5,6a] involved the reactions carried out at room temperature or 25–32 °C range and in the pH 5.5–6.0 buffered medium, with or without an added sugar such as glucose or sucrose. The second type of reaction conditions[2e,f,3a,6b] involved the reactions carried out at 70–80 °C or sometimes under reflux conditions and in the presence of a high concentration of sodium hydroxide in the medium with pH >12. Presumably different mechanisms are operating under these two different reaction conditions and the yeast is unlikely to be stable at high pH and temperature used in the type II conditions. Aromatic nitroso compounds[4] containing halogens and other labile substituents are known to reduce selectively to their corresponding amines under neutral conditions at 80 °C. On the other hand nitro aromatics[2e] could be efficiently reduced to amines only in the strongly basic conditions employing aqueous sodium hydroxide medium and at temperatures in the range of 70–80 °C. Aromatic and heteroaromatic *N*-oxides[6] have been deoxygenated using the same type II conditions.

Our interest[7] in the synthesis and chemistry of the nitrone functional group have revealed that there are no reports of any *Saccharomyces cerevisiae* promoted enzymatic transformations of the nitrone function. Nitrones are known for their properties as free radical scavengers as they can form stable free radicals in combining with hydroxyl and other radicals, and there are attempts to explore this radical trapping ability to develop nitrone based pharmaceuticals[8] as well. During these metabolic studies,[9] it has been reported that phenyl^{t}butylnitrone hydrolyzes to a mixture of benzaldehyde and ^{t}butylhydroxylamine when incubated with human epithelial fibroblasts cells and ^{t}butylhydroxyl amine further oxidizes to ^{t}butyl nitroxide as well.

We have under taken to study the possible enzymatic transformations of *C*-aryl-*N*-phenylnitrones, when treated with Baker's yeast–sucrose mixture in the pH = 6.0 phosphate buffer medium at room temperature. These nearly neutral conditions were chosen for the study, as nitrones are known[10] to hydrolyze to hydroxylamines and aldehydes in strongly acidic or basic conditions.

Keywords: Baker's yeast (*Saccharomyces cerevisiae*); *C*,*N*-Diarylnitrones; Azoxybenzene.
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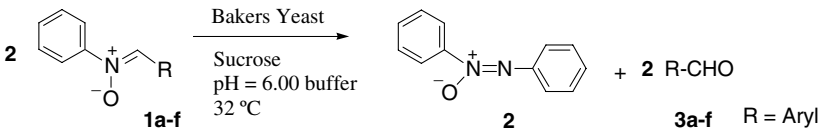

Figure 1.

Table 1.

Nitrone (**1**)	Reaction time (h)	Product yield	
		2	**3**
1a, R = C_6H_5–	40	92	76
1b, R = *p*-CH_3–C_6H_4–	40	85	80
1c, R = *p*-OCH_3–C_6H_4–	24	78	71
1d, R = *p*-NO_2–C_6H_4–	72	65	38[a]
1e, R = *o*-OH–C_6H_4–	40	88	70
1f, R = 2-Furanyl–	40	78	88

[a] 12% *p*-Amino benzaldehyde was also found as a product.

In this study we have found that *C*,*N*-diphenyl nitrone[11] (**1a**) converts into a mixture of azoxybenzene and benzaldehyde[12] in 92% and 76% yields, respectively, when incubated with Baker's yeast–sucrose mixture in a pH = 6.00 phosphate buffer medium for 40 h at 32 °C (Fig. 1).

In a control experiment with sucrose and pH = 6.00 phosphate buffer, in the absence of yeast, no hydrolysis or decomposition was observed and all the nitrone could be recovered unchanged after 72 h. In another experiment carried out without sucrose, only about 10% of the nitrone was converted into azoxybenzene and benzaldehyde and the remaining nitrone was recovered unchanged. In an attempt to identify the intermediates of this transformation, samples withdrawn after 6 and 24 h, were analyzed by NMR, after extraction into methylenechloride. These samples showed only partial conversions to the same products and unreacted nitrone, and the attempts to observe any intermediates were not successful.

Five other *C*-aryl-*N*-phenylnitrones[11] (**1b**–**f**) also reacted similarly to yield azoxybenzene (**2**) and the corresponding aldehydes (**3b**–**f**) as shown in Table 1. Results show that verity of *C*-aryl-*N*-phenylnitrones can undergo the *Saccharomyces cerevisiae* mediated hydrolytic process and electron withdrawing groups on the aryl ring appears to retard the reaction as shown in the case of *C*-*p*-nitrophenyl-*N*-phenylnitrone (**1d**) (Table 1).

In summary these results represent the first Baker's yeast mediated enzymatic transformation of the nitrone function and it appears to be an enzymatic hydrolysis followed by a reduction of the intermediate led to the formation of azoxybenzene.

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12. *Typical procedure: C*-aryl-*N*-phenylnitrone (0.635 mmol) was dissolved in 10 mL of 95% ethanol and sucrose (1.00 g) was added to this solution. Then 50 mL of pH = 6.00 phosphate buffer was added and swirled for 5 min to dissolve the sucrose in the medium. Baker's yeast (*Saccharomyces cerevisiae*) (250 mg) was then added and

further swirled for 2 min to yield a turbid solution, which was incubated in a warm water bath at 32 °C. Reaction was monitored by TLC (silica, solvent: ethylacetate:hexanes 1:9) and stopped after complete disappearance of the nitrone. After the reaction period, the solution was transferred to a separatory funnel and repeatedly extracted with methylene chloride (5×20 mL). Combined methylene chloride layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was chromatographed on silica, eluting with 10% ethylacetate in hexanes to isolate pure products. The products were identified by comparison of the ^{1}H and ^{13}C NMR of authentic samples of azoxybenzene and aldehydes.