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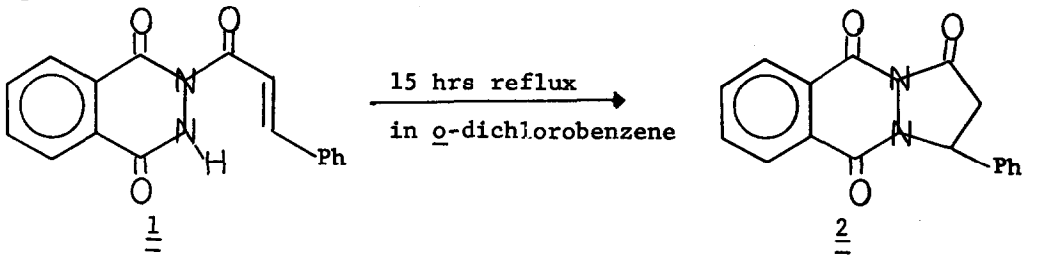
SYNTHESIS AND CYCLIZATION OF N-METHYL-O-CINNAMONYLHYDROXYLAMINE AND ITS BEARING ON BALDWIN'S RULES FOR RING CLOSURE

K.R. Fountain* and Greg Gerhardt
Northeast Missouri State University
Kirksville, Missouri 63501

Recently Baldwin [1] proposed a set of rules for predicting the facility of intramolecular cyclizations. Anselme [2] subsequently reported that under forcing conditions (15 hours reflux in o-dichlorobenzene) compound 1 undergoes ring closure which is contraindicated by Baldwin's rules for a five-membered transition state (5-endo-trig). The suggestion was made by Anselme that factors other than geometric and stereochemical considerations may play a role in determining whether cyclizations will occur when heteroatoms are involved. This paper reports the synthesis and cyclization of N-methyl-O-cinnamonylhydroxylamine (3) as a parallel to the cyclization of 1. This reaction occurs under much milder conditions than for 1 (refluxing bromobenzene). We suggest that electronic factors must be considered when 5-endo-trig cyclizations are examined. We synthesized 3 by the method of Carpino [3] except that in the synthesis of t-butyl-N-methyl-N-hydroxycarbamate the first extraction with ether, normally discarded, contained the product



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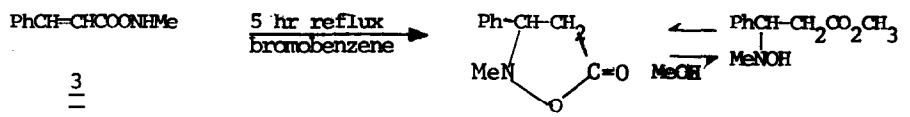

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desired. The hydrochloride salt was stable and gave correct (± 0.3) analytical results and the spectral data expected. Compound 3 resulting from the neutralization of this salt with $NaOCD_3$ in methanol-d_4 had a CH_3-N signal at δ 2.92 at pH=8-9 (Hydrion paper). The CH_3-N signal of N-methylhydroxylamine at δ 2.70 also appeared in this mixture (authentic sample confirms value). The CH_3N signals from both 3 and N-methylhydroxylamine were quite pH dependent, shifting to lower fields at lower pH. The CH_3N signal of 4 was also quite pH dependent, but at pH=8-9 absorbed at δ 2.80. The signal at δ 2.45 reported earlier by us [4] as due to N-CH_3 of 3 is clearly in error and probably belongs to N-CH_3 of 5 as reported by Stamm and Steudel. [5] These assignments allowed us to follow the cyclization of 3 in methanol-d_4.

When 3 was generated by neutralization to pH=8-9 in CD_3OD with CD_3ONa, we found that N-methylhydroxylamine, as well as methyl cinnamate (OCD_3), was present. The CH_3N signal at

2.80 due to 4 was well developed (@ 10% of that for 3 before any signal due to 5 was observed. We have determined that 4 and 5 are in equilibrium (approached from both 4 and 5) with K_{eq}=@ 2.0 under these conditions.

After all of 3 was consumed, the ratio of 4/5 was 4.4 (± 0.2) indicating that some direct cyclization of 3 occurred. Treatment of methyl cinnamate with one to three equivalents of N-methylhydroxylamine gave only 4 and 5 but no 3. After 2 hours the 4/5 ratio was 1.31, and when all the starting ester was consumed the ratio was 1.89 (± 0.03). No trace of 3 even by TLC could be found in these experiments.

Neutralization of the hydrochloride of 3 with triethylamine in ether, removal of salt and solvent gave an oil which subsequently solidified. Complete removal of triethylamine was assured by repeated trituration with benzene and solvent removal. The residue was refluxed in bromobenzene for 5 hours and the formation of 4 followed by the IR bands of 4 at 1790-1780 $cm.^{-1}$. Removal of part of the solvent followed by n.m.r. clearly showed 4 was present by the CH_3N signal at δ 2.54 (authentic sample comparison). Likewise when 3 was generated and heated at @100° without solvent, 4 was formed, obtainable in 45% yield after 5 hours, by extraction with pet ether. This is a substantial recovery of 4 under much milder conditions than those used by Anselme.

Reasons for the enhanced cyclization of 3 over the hydrazide probably lie in the relatively enhanced nucleophilicity of the nitrogen lone pair of 3 over the lone pair in a hydrazide [6]. This is surprising because hydrazine is a better α-nucleophile than hydroxylamine toward p-nitrophenylacetate [7]. However, the delocalization of the amide lone pair affects the availability of the amino-lone pairs in hydrazides. In contrast [8,9] hydroxamic acids are excellent nucleophiles. In the present case 3 should resemble a hydroxamic acid in nucleophilicity because esters do not delocalize the oxygen lone pairs as well as amides delocalize the nitrogen lone pairs [10]. Thus resonance form I is more important than II in 3 as expressed in the $\nu_{C=O}$ of 3 of 1735 cm^{-1}, typical of esters.

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