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MANGANESE-MEDIATED ALLYL ADDITION TO ENOLIZABLE ALDEHYDE AND KETONES. AN APPROACH FOR INTRODUCTION OF ACETONYL SIDE CHAIN AT C(9) OF ANTHRACYCLINE ANTIBIOTICS

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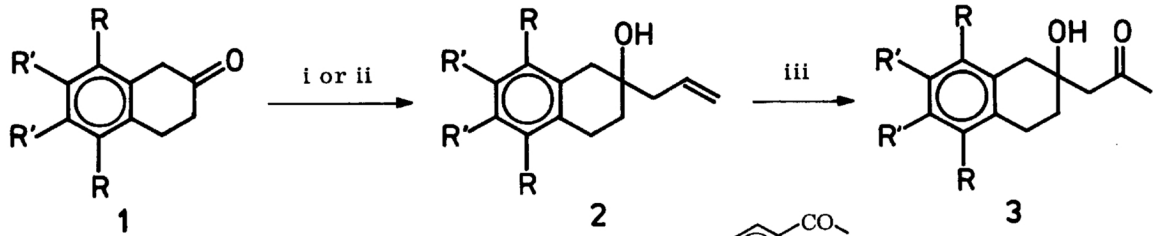
Allyl addition to enolizable aldehyde and ketones is achieved efficiently with manganese reagents generated by the reaction of allyl bromide with $MnCl_2$-$LiAlH_4$ or Mn powder. The Wacker oxidation of the β-tetralone adducts gives an acetonyl moiety typical to an anti-tumor antibiotic, feudomycin.

Addition of carbon nucleophiles to carbonyl carbons sometimes turns out to be a tough synthetic obstacle due to facile enolization of the carbonyl groups. Organometallic reagents of main group elements often encounter this side reaction. In order to solve the problem, organotransition metal reagents are introduced by transmetallation, and thus methyl,[1] vinyl,[2] and ethynyl[2,3] groups are successfully connected to enolizable carbonyl carbons. We report herein that manganese-mediated allyl addition is effective for aldehyde and ketones which readily undergo enolate formation with conventional organomagnesium or -lithium reagents,[4] and this C-C bond forming reaction is particularly useful for attaching C_3 side chain at C(9) of anthracycline antibiotics.

Two manganese reagents were applicable: (A) allyl bromide/$MnCl_2$-$LiAlH_4$ (1 : 1) reagent[5] and (B) allyl bromide/Mn powder (10 μm).[6] For example, phenylacetaldehyde (1.41 mmol) was allowed to react with the Reagent A generated from lithium aluminium hydride (4.0 mmol), anhydrous manganese(II) chloride (4.0 mmol), allyl



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a: R = R' = H, **b**: R = OMe, R' = H, **c**: R = OH, R' =

i) Reagent A (CH_2=$CHCH_2Br$/$MnCl_2$-$LiAlH_4$ (1 : 1), THF, 0 °C - r.t.)

ii) Reagent B (CH_2=$CHCH_2Br$/Mn powder (10 μm), THF, reflux)

iii) O_2, $PdCl_2$-CuCl, aq DMF

bromide (2.0 mmol) in tetrahydrofuran (THF, 10 ml) at room temperature for 15 h (overnight). Workup followed by preparative TLC gave 1-phenyl-4-penten-2-ol in 77% yield. Similarly, cyclopentanone allyl adduct was obtained in 57% isolated yield. Both the manganese reagents are particularly useful for allyl addition to β-tetralone and its derivatives **1**. Results are given in the order of substrate, reagent, and isolated yield: **1a**, A, 78%; **1a**, B, 66%, **1b**, A, 98%; **1b**, B, 76%; **1c**, A, 61%.

The synthetic importance of this reaction is demonstrated by the conversion of the allyl moiety into acetonyl group by the Wacker process.[7] For example, **2a** was stirred under an oxygen atmosphere in the presence of palladium(II) chloride-copper(I) chloride catalyst system in aqueous dimethylformamide (DMF). Workup gave **3a** in 61% yield. Similarly, **3b** and (±)4-demethoxy-7-deoxyfeudomycinone (**3c**) were obtained in 71% and 85% yields from **2b** and **2c** respectively. The two-step method disclosed herein provides us with an easy access to a new class of anti-tumor anthracycline antibiotics such as feudomycin.[8] Synthetic studies thereupon are in progress in our laboratory.[9]

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