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ENAMINE SYNTHESIS OF 4-KETOALDEHYDES

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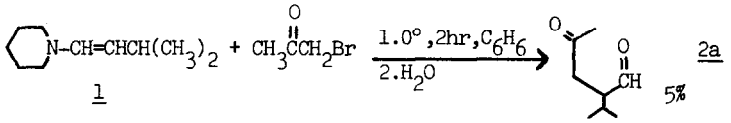
1,4-Dicarbonyl compounds are key precursors to a variety of important chemicals which include natural products of insect and plant origin as well as the biologically important prostaglandins.[1,2] A variety of pathways have been developed for the synthesis of 1,4-diketones.[1,3-5] However, few general synthetic methods exist for 4-ketoaldehydes.[1,3]

Although 1,4-diketones are readily prepared by the alkylation of ketone enamines with α-bromoketones,[5] the analogous reaction of aldehyde enamines and α-bromoketones has not been successfully exploited for the synthesis of 4-ketoaldehydes. This no doubt is a reflection of numerous reports of problems associated with C-alkylation of aldehyde enamines compared to ketone enamine alkylations.[6]

When we attempted to alkylate a 1.8 M solution of the piperidine enamine of isovaleraldehyde (1)[5] with bromoacetone (1.9 M) in benzene at 0° for 2 hr, only a 5% yield of 2-isopropyl-4-ketopentanal (2a) was obtained. Much tarry residue in addition to unreacted bromoacetone was also obtained. When these reagents were mixed without cooling, the exothermic reaction caused the benzene to reflux and only a tarry residue was obtained.

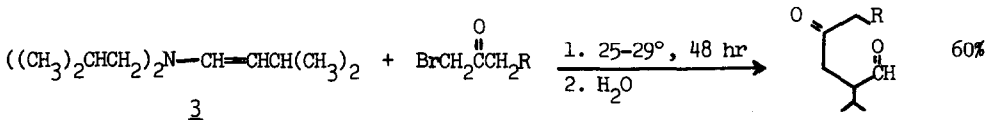


1 2a

The low yield of 2a and dominance of side reactions is consistent with previous aldehyde enamine chemistry.[6]

In order to moderate the reactivity of the enamine and inhibit N-alkylation, a sterically more demanding secondary amine was used to form the enamine of isovaleraldehyde.[7] The diisobutylamine enamine of isovaleraldehyde (3) was prepared in the usual manner.[5] It reacts with bromoacetone at room temperature either neat (48 hr) or in benzene solution (96 hr; 3, 1.8 M; bromoacetone, 1.2 M) to give a 60% yield of 2a. The preparation of

2-isopropyl-4-ketohexanal (2b) was also effected in 60% yield using 1-bromo-2-butanone.



2a, R = H

2b, R = CH_3

A variety of 4-ketoaldehydes should be readily accessible by this method. The nature of the substituents on the 2- and 5-positions of the 4-ketopentanal skeleton can be varied by appropriate choice of aldehyde enamine and 1-bromo-2-alkanone.

The sensitivity of competing pathways to temperature is illustrated by the observation that when a benzene solution of 3 (1.06 M) and bromoacetone (1.12 M) were refluxed for 1 hr, large amounts of tarry material and unreacted bromoacetone were obtained, and only 6% of 2a was produced.

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