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NEW USES OF AMINALS IN ORGANIC SYNTHESIS

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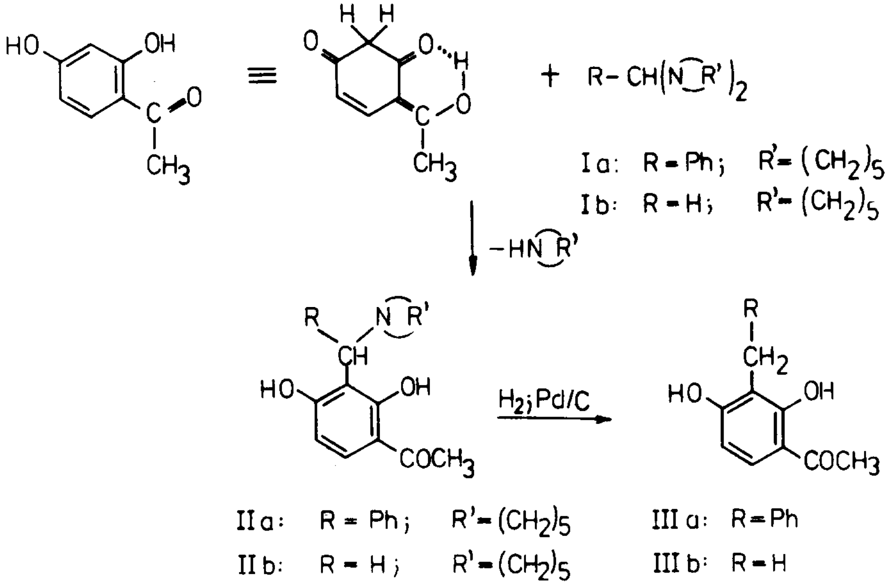
Aminals, though described during the early history of organic chemistry,[1] have been little investigated for use in synthesis. Their formation from an aldehyde and secondary amine, and their reactions with active methylene compounds led, however, to the questioning of the catalytic function of secondary amines in reactions of, e.g., the Knoevenagel or Mannich type,[2] and to pointing out the functionally aldehydic ("ammono-aldehyde") character of methylene-bis-amines.[3]

In our comparative experiments the use of aminals, instead of their components, has shown their superiority in effecting Claisen-Schmidt condensations, Knoevenagel and Mannich reactions. The same experience was reported for a Leuckart-Wallach reaction.[4] According to experiments in progress, it appears that most or all reactions of aldehydes with other compounds which are catalyzed by secondary amines can be effected, and often in better yields or more rapidly, if aminals are used; in fact, they may also accomplish reactions which are unpracticable with the components.

These results prompted us to extend the use of aminals to reactions with substances not regarded normally as active methylene compounds, such as suitably substituted phenols, acetophenones and flavonoids. For example, hydroxyl groups in meta position to each other, or to the oxygen atom of the hetero ring in flavonoids, afford suitable activation of the hydrogen atom between them for the reaction with aminals to result in nuclear substitution.

In our experiments so far piperidine has been used as the secondary amine and benzaldehyde or formaldehyde as the aldehyde component of the aminal, i.e. benzylidene-bis-piperidine (Ia) and methylene-bis-piperidine (Ib) have been investigated. As an example of ketones, 2',4'-dihydroxyacetophenone and Ia



gives 2',4'-dihydroxy-3'-[phenyl-(1-piperidyl)methyl]-acetophenone (IIa; m.p. 168-171°); the reaction product with Ib is 2',4'-dihydroxy-3'-(1-piperidylmethyl)acetophenone (IIb; m.p. 98-100°). Catalytic reduction of these products yields 2',4'-dihydroxy-3'-benzylacetophenone (IIIa) (3-benzylresacetophenone, m.p. 207-208°; lit.[5] m.p. 195-197°) and 2',4'-dihydroxy-3'-methylacetophenone (IIb) (3-methylresacetophenone, m.p. 157-158°; lit.[6] m.p. 156-157°), respectively.

As seen, the method offers a selective way of nuclear alkylation and aralkylation of hydroxyl-containing compounds, which is known to be notoriously difficult to achieve by the usual methods owing to the concomitant formation of the O-ethers.[7]

As an example in the flavone series, chrysin (5,7-dihydroxyflavone) has been used to synthesize 6-(phenylpiperidylmethyl)chrysin (m.p. 260-263°), 6- and 8-piperidylmethylchrysin (m.p. 196-200° and 203-204°, respectively), 6,8-bis(piperidylmethyl)chrysin (m.p. 175-179°), and 6-(phenylpiperidylmethyl)-8-(piperidylmethyl)chrysin (m.p. 187-193°). Notably, 8-(piperidylmethyl)chrysin could not be prepared by the Mannich reaction of unsubstituted chrysin.[8].

Analogously, 2',4',2-trihydroxychalcone gives with Ib 2',4',2-trihydroxy-3'-piperidylmethylchalcone (m.p. 197-203°).

Starting from the substances of type II, several new compounds have been prepared by carbonyl reactions, acetylation, alcoholysis of the amine rest, etc. Selective reduction of 8-(piperidylmethyl)chrysin gave 8-methylchrysin (m.p. 250-255°). Other experiments to obtain C-alkyl- and C-aralkyl-flavones, -flavanones and -dihydrochalcones, developing the method for the synthesis of natural C-substituted flavonoids, are in progress.

The IR, ^{1}H-, ^{13}C-spectra and elemental analyses are consistent with the structures given for all compounds reported herein.

The experiments so far do not prove that the actual role of the secondary amine is to form always an intermediate with the aldehyde instead of acting as a catalyst,[2] yet it is evident that the former is a possible route of these reactions.

The principle applied in this work can be extended to every case where an aldehyde is made to react with a compound containing an active hydrogen atom; in this way, besides effecting known reactions more efficiently, the use of aminals allow new, selective C-substitutions of aromatic compounds.

Details of the work in progress will be reported.

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