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THE REDUCTIVE ALKYLATION OF MELDRUM'S ACID

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Summary: Meldrum's acid can be reductively alkylated with borane·dimethylamine complex and aldehydes or ketones; borane·trimethylamine was used with cyclohexanone.

Several years ago we noted that Knoevenagel-type products derived from Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione; isopropylidene malonate) are readily reduced by sodium borohydride in methanol solution.[1] These reductions were so rapid that we felt that it might be possible to reductively alkylate Meldrum's acid in a one pot scheme. There are a few reports which describe the reductive alkylation of active methylene compounds under hydrogenating conditions[2] and with potassium tetracarbonylhydridoferrate.[3] Preliminary work with sodium borohydride and aliphatic aldehydes in alcohol gave low yields; only moderate yields (30-60%) were obtained with borohydride in acetic acid media. These reactions seemed to be complicated by the concomitant reduction of the aldehyde to alcohol. Consistently good to high yields were obtained with both aliphatic and aromatic aldehydes only after we used borane·dimethylamine[4] as the reducing agent. This method is particularly important for the aliphatic aldehydes since the Knoevenagel products in most cases can only be made by special methods[5] due to the predominance of a subsequent Michael addition with the formation of bis-adducts.[6] For the ketones, the results were less satisfactory, although reasonable yields could be obtained with those of low molecular weight by using them as both reactant and solvent, and with the more reactive cyclohexanone. With cyclohexanone, borane·trimethylamine had to be used in order to avoid low yields which were apparently due to extensive reduction of the ketone. The lower yields obtained generally with the ketones might be attributed to their lower reactivity towards Meldrum's acid in the Knoevenagel condensation; this would then favor their reduction to alcohols. For optimum yields, an excess of the carbonyl compound had to be employed in all cases. Also, at least for the results obtained with the aromatic aldehydes and especially the ketones, it appears that the borane complex or something released from it acts not only as a reducing agent but as a catalyst or promoter of the Knoevenagel reaction as well (a solution of Meldrum's acid in acetone alone shows no sign of reaction after several days).[7]

Some representative procedures are as follows. Until more is known concerning the nature of these borane complexes, we suggest that the entire procedure be conducted in a hood behind a safety shield. Since some gas evolution may occur, the reactions should be conducted in a vented vessel.

Isopropylidene benzylmalonate: Borane·dimethylamine, 0.59 g, 10 mmoles, was dissolved in 25 ml of methanol and 1.44 g, 10 mmoles, of Meldrum's acid was added with stirring. After the solid dissolved, 2 ml of benzaldehyde was added with continued stirring. After ten minutes an additional 1 ml of aldehyde (total 30 mmoles) was added. After ten additional minutes the reaction mixture was poured onto ca. 60 ml of ice-water, made acidic with HCl, and the crystalline product removed by filtration and washed with water. The product, mp 79-80, lit. mp 80-1,[8] weighed 2.21 g (94% yield) and was quite pure as judged by IR, NMR, and TLC. A similar procedure was used with the aliphatic aldehydes. For the higher molecular weight aldehydes the product can be most conveniently isolated by selective extraction from ether by aqueous potassium carbonate followed by acidification of the extract.

Isopropylidene isopropylmalonate: Meldrum's acid, 1.44 g, 10 mmoles, was added to 4 ml of acetone with stirring. Borane·dimethylamine, 0.59 g, 10 mmoles, was then added and the mixture allowed to stir overnight. The solution was then poured onto 50 ml of ice-water, made acidic with HCl, and the crystalline product removed by filtration and washed with water. The product, mp 99-101, lit. mp 104-5,[1] weighed 1.33 g (72% yield), and produced an NMR spectrum identical to that which was previously obtained.[1] A similar procedure was used with 2-butanone and cyclopentanone.

Isopropylidene cyclohexylmalonate: Borane·trimethylamine, 0.73 g, 10 mmoles, was dissolved in 12 ml of methanol and 1.44 g, 10 mmoles, of Meldrum's acid was added with stirring. Cyclohexanone, 3 ml, 29 mmoles, was added and the mixture stirred overnight. The reaction mixture was then poured onto ca. 60 ml of ice-water and acidified with HCl. The crystalline product was removed by filtration and washed with water. The product weighed 1.40 g (62% yield) and had mp 128-9, lit mp 129.5-30.5.[8]

The products (Table) were generally obtained pure directly from the reaction mixture as judged by melting point and thin layer chromatography. The monosubstituted isopropylidene malonates can be easily hydrolyzed and decarboxylated to the corresponding monocarboxylic acids[6] or they can be used as starting materials in a variety of recently developed synthetic methods.[6,9]

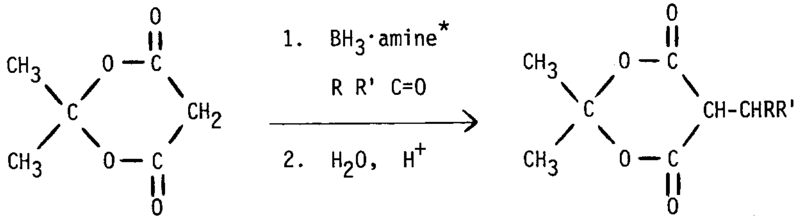

Table. Reductive Alkylation of Meldrum's Acid.

R	R'	yield (%)	mp(crude)	mp(recryst.)**	lit. mp
CH_3	H	87	106-9	106-8	107-9[10]
CH_3CH_2	H	70	76-8	78-80	80-1[11]
$CH_3(CH_2)_2$	H	82	58-9	58-60	57-8[9b]
$CH_3(CH_2)_6$	H	77	65-7	65-6	***
$CH_2=CH(CH_2)_8$	H	66	59-61	57-8	***
Phenyl	H	94	78-80	79-80	80-1[8]
$PhCH_2$	H	84	109-11	110-12	114[12]
2-Furyl	H	88	92-3	90-2	92-3[1]
CH_3	CH_3	72	99-101	102-3	104-5[1]
CH_3	CH_3CH_2	52	76-8	78-9	79-80[13]
$-(CH_2)_4-$		58	86-8	92-3	***
$-(CH_2)_5-$		62	128-9	128-9	129.5-30.5[8]

* Borane·dimethylamine was used in all cases except with cyclohexanone where borane·trimethylamine was used.

** from heptane   *** Compound gave satisfactory analysis for carbon and hydrogen ($\pm$0.2%).

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