

3,3-ETHYLENEDIOXYBUTYLMAGNESIUMBROMIDE - A NUCLEOPHILIC 3-KETOBUTYL EQUIVALENT

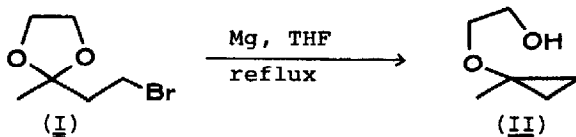
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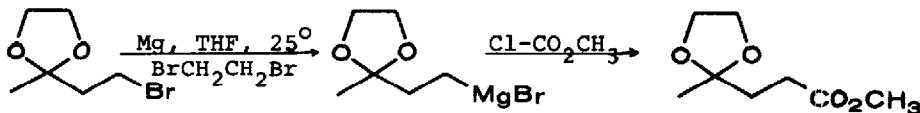
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The attachment of a 3-ketoalkyl group to an existing structure is an important method for the elaboration of cyclic systems.<sup>1</sup> Usually this group is introduced as an electrophilic species, as is exemplified by the Robinson Annelation reaction<sup>2</sup> with an alkyl vinyl ketone or its equivalent. This communication describes the preparation and some reactions of the title reagent, a versatile nucleophilic 3-ketobutyl equivalent.

It has been reported<sup>3</sup> that attempted preparation of this reagent from 2-methyl-2-( $\beta$ -bromoethyl)-1,3-dioxolane (I) and magnesium gave 1-methylcyclopropyl-(2-hydroxyethyl) ether (II):

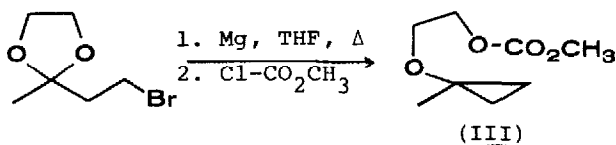


We have found, however, that the Grignard reagent is quite easily prepared using a three-fold excess of magnesium and a small amount of 1,2-dibromoethane in tetrahydrofuran, if the temperature is maintained at 25°. This reagent is a homogeneous olive-brown solution which reacts with excess methyl chloroformate to give the ethylene ketal of methyl levulinate:<sup>4</sup>



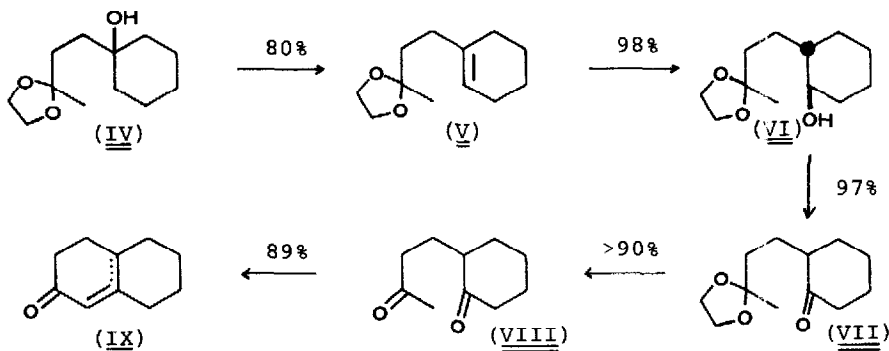
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If the halide is added to excess magnesium in refluxing tetrahydrofuran and then reflux continued for one hour, a heterogeneous mixture results. Addition of this mixture to excess methyl chloroformate gave the carbonate ester (III) [IR: 5.69 $\mu$ . NMR(CCl<sub>4</sub>): 0.35 $\delta$ , 0.72 $\delta$ , distorted triplets (4H); 1.36 $\delta$ , singlet (3H); 3.60 $\delta$ , multiplet (2H); 3.72 $\delta$ , singlet (3H); 4.11 $\delta$ , multiplet (2H)]:

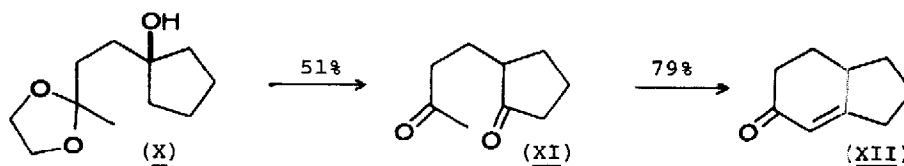


Reaction of the Grignard reagent [prepared from 1.2 eq. of (I)] with cyclohexanone in tetrahydrofuran solvent was exceedingly slow, complete consumption of the ketone occurring only after four hours at room temperature. After work-up with aqueous ammonium chloride solution and column chromatography, a 97% yield of the tertiary alcohol (IV) was obtained. The extremely low reactivity of this Grignard reagent is probably the result of internal solvation of magnesium by the dioxolane ring, along with inductive electron withdrawal from carbon-1 by the two oxygen atoms.

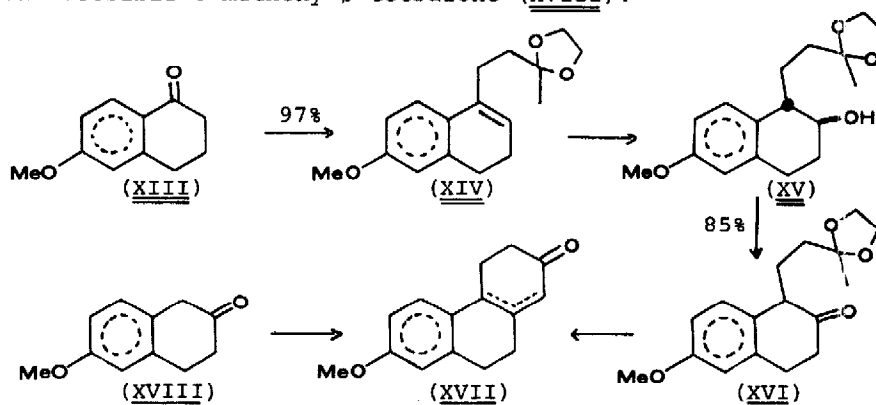
(IV) was dehydrated with phosphorous oxychloride-pyridine to the endocyclic olefin (V) [NMR(CCl<sub>4</sub>): 1.22 $\delta$ , singlet (3H); 1.3-2.2 $\delta$ , envelope (12H); 3.83 $\delta$ , singlet (4H); 5.35 $\delta$ , broad singlet (1H)] which was then hydroborated-oxidized<sup>5</sup> to the alcohol (VI) [IR: 3.0 $\mu$ , 9.50 $\mu$ . NMR(CCl<sub>4</sub>): 0.9-2.1 $\delta$ , envelope (12H); 3.2 $\delta$ , broad singlet (1H); 3.6 $\delta$ , multiplet (1H); 3.85 $\delta$ , singlet (4H)]. Oxidation with Collins reagent<sup>6</sup> then gave the ketal-ketone (VII) [IR: 5.81 $\mu$ . NMR(CCl<sub>4</sub>): 1.22 $\delta$ , singlet (3H); 1.0-2.5 $\delta$ , envelope (13H); 3.84 $\delta$ , singlet (4H)], identical to an authentic sample prepared from alkylation of the sodium enolate of cyclohexanone with (I). Deketalization with dilute aqueous perchloric acid in glyme afforded the diketone (VIII) in greater than 90% yield. Cyclization with 5% KOH in methanol under nitrogen gave, in 89% yield,  $\Delta^{1,9}$ -octalone (IX), identical to an authentic sample:<sup>7</sup>



Cyclopentanone reacted much more slowly with the Grignard reagent than did cyclohexanone. It was found that conducting the reaction in a 2:1 mixture of benzene and tetrahydrofuran increased the rate of addition significantly, and by use of this solvent a 96% yield of the tertiary alcohol (X) could be obtained. Dehydration with phosphorous oxychloride-pyridine, hydroboration-oxidation and then oxidation-deketalization with excess Jones reagent in acetone furnished, in 51% overall yield, the known diketone (XI), previously cyclized<sup>8</sup> to the hydrindenone (XII):



The above results describe a new annelating sequence whereby a 3-ketobutyl unit is attached to a ketone at the site of the carbonyl group, rather than next to it, as in a Robinson Annelation. The utility of this new procedure is illustrated by the preparation of the alkylated 6-methoxy- $\beta$ -tetralone derivative (XVI) from the readily available<sup>9</sup> 6-methoxy- $\alpha$ -tetralone (XIII). Ketal-ketone (XVI) is a precursor for the tricyclic enone (XVII)<sup>10</sup>, an intermediate for the synthesis of polycyclic compounds, heretofore prepared by Robinson Annelation of the relatively inaccessible 6-methoxy- $\beta$ -tetralone (XVIII):



Reaction of the Grignard reagent with (XIII) in benzene-THF (2:1) was complete in four hours at room temperature. After work-up with aqueous ammonium chloride solution, the crude product was distilled under high vacuum to provide a 97% yield of the olefin (XIV) [NMR( $\text{CCl}_4$ ): 1.27 $\delta$ , singlet (3H); 1.5-2.9 $\delta$ , multiplet (8H); 3.67 $\delta$ , singlet (3H); 3.83 $\delta$ , singlet (4H); 5.16 $\delta$ , triplet,  $J=5$  Hz. (1H); 6.55 $\delta$ , multiplet (2H); 7.08 $\delta$ , doublet,  $J=9$  Hz. (1H)]. Hydroboration-oxidation afforded the alcohol (XV) which was oxidized in about 85% overall yield from (XIV) with pyridine-sulfur trioxide complex in dimethylsulfoxide-triethylamine<sup>11</sup> to the ketal-ketone (XVI) [IR: 5.82 $\mu$ . NMR( $\text{CCl}_4$ ): 1.21 $\delta$ , singlet (3H);

1.2-2.2 $\delta$ , envelope (4H); 2.2-3.4 $\delta$ , multiplet (5H); 3.71 $\delta$ , singlet (3H); 3.78 $\delta$ , singlet (4H); 6.62 $\delta$ , multiplet (2H); 6.98 $\delta$ , doublet, J=9 Hz. (1H)].

The low reactivity of this Grignard reagent allows high selectivity in its reaction with various electrophiles. Controlled reaction of acid chlorides with the reagent gives very high yields of mono-ketalized 1,4-diketones, versatile intermediates for the synthesis of cyclopentenones, furans and other heterocycles. Thus, for example, *n*-hexanoyl chloride reacts with one equivalent of the reagent at 0° in THF to give 2,5-decanedione, 2-ethylene ketal.

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