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COPPER-CATALYZED CONJUGATE ADDITION OF GRIGNARD REAGENTS TO ISOPROPYLIDENE ALKYLIDENEMALONATES

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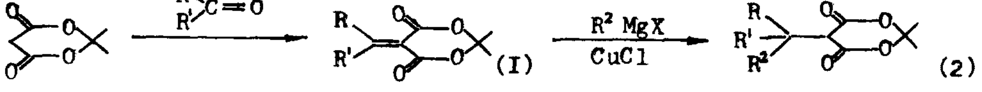
Summary: A new method for the synthesis of isopropylidene alkylmalonates involving conjugate addition of Grignard reagents to isopropylidene alkylidenemalonates was developed.

The isopropylidene malonate is an attractive alternative to the normal malonic esters in organic synthesis.In previous report[1], we found that alkylation of isopropylidene malonate under phase-transfer conditions takes place easily to give 5,5-dialkyl derivatives. In this paper, we wish to report a convenient method for the synthesis of monosubstituted isopropylidene malonates.

Because isopropylidene malonate has high acidity and rigid cyclic structure, it can condense easily with carbonyl compounds to give isopropylidene alkylidenemalonates[2]. Recently, Wright, et al[3]. reported that the carbon-carbon double bond of these compounds can be reduced by sodium borohydride to give isopropylidene alkylmalonates. This approach is not applicable to the preparation of tertiary alkyl substituted isopropylidene malonates. Since, under copper-catalysis, Grignard reagents can undergo conjugate addition to carbonyl compounds[4], we have studied the reactivity of isopropylidene alkylidenemalonates with Grignard reagents, in order to develop an effective general method for the synthesis of isopropylidene alkylmalonates. In our experiments we have found that, in the presence of cuprous chloride, the conjugate addition of Grignard reagents to isopropylidene alkylidenemalonates takes place rapidly with high yield.



Ia: R=H, R' =CH$_3$. Ib: R=H, R' =ph. Ic: R=CH$_3$, R' =CH$_3$.

Typical experimental procedure for the preparation of 2f serves as an illustration: Cuprous chloride (I.5 mmoles) was added to the ethereal solution of methyl magnesium iodide (40 mmoles) with stirring under nitrogen on an ice-salt bath. An ethereal solution of Ic (20 mmoles) was added dropwise over a period of about 45 minutes, then the reaction mixture was stirred in room temperature for 30 minutes. A cold solution of 2% sulfuric acid was added. The organic layer was saperated, and the aqueous layer was extracted with ether. After removal of solvent, the crude product was recrystallized from toluene-hexane.

We have successfully utilized this procedure for the synthesis of a number of monosubstituted isopropylidene malonates(See Table I).The structures of all products were confirmed by their I.R.spectra, N.M.R.spectra and elemental analyses.

Table I. Synthesis of Isopropylidene Alkylmalonates (2)

Substractes(I)	R^2MgX	Products(2)	Yield (%)	M.P.
Ia	CH_3MgI	2a	86	I02-I04 °C
Ia	C_2H_5MgBr	2b	83	79- 80 °C
Ia	phMgBr	2c	80	I03-I04 °C
Ib	CH_3MgI	2d	82	I03-I04 °C
Ib	phMgBr	2e	80	I45-I46 °C
Ic	CH_3MgI	2f	83	55- 56 °C
Ic	phMgBr	2g	80	83- 84 °C

Because substituted isopropylidene malonates are easily converted to carboxylic acids[5] or esters[6], the method described here is also efficient for the synthesis of β-branched carboxylic acids or their esters.

The application of isopropylidene malonate in synthesis will be further explored in our laboratory.

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