Allyl as Protective Group for the Acidic Hydrogen of Malonic Ester

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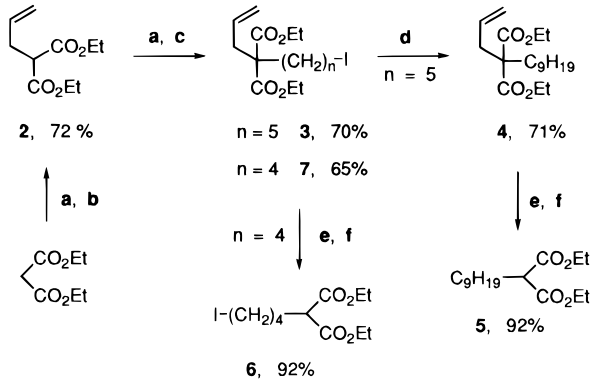
The malonic ester synthesis is one of the most fundamental methodologies in organic synthesis.[1] The reaction has been widely used for the preparation of mono- and disubstituted acetic acids *via* mono- and dialkylation, respectively, and subsequent hydrolysis and decarboxylation. The presence of two acidic hydrogens in the starting compound, however, sometimes causes difficulty in applying this methodology in organic synthesis. Thus, dialkylation becomes a significant side reaction in monoalkylations of malonic ester with reactive alkyl halides or α,ω-dihaloalkanes.[1a,2] Another problematic point is the fact that chemical transformations of functional groups which can be introduced through monoalkylation are somewhat limited because of the presence of an acidic hydrogen. It is, therefore, surprising that no protective group for the acidic hydrogen of malonic ester has been developed.[3]

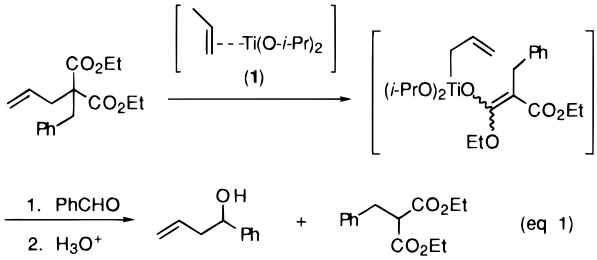
Recently, we found that allyl compounds $CH_2{=}CHCH_2X$ such as halides (X = Cl, Br, or I) or alcohol derivatives (X = $OCOCH_3$, $OCOOC_2H_5$, OTs) react with the titanium(II) compound (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), readily generated *in situ* by the reaction of Ti(O-*i*-Pr)$_4$ with 2 equiv of *i*-PrMgX (X = Cl, Br), to afford the corresponding allyltitanium compounds.[4] The reaction can be rationalized by a mechanism which involves ligand exchange of the coordinated propene in **1** with the olefinic moiety of the substrate and subsequent β-elimination. With these findings we anticipated that allyl compounds where X = RC(COOEt)$_2$ might also furnish allyltitaniums on treatment with **1**, since the RC(COOEt)$_2$ anion is stable and thus might be a sufficiently good leaving group.[5] If the reaction proceeds in excellent yield, as expected, the allyl group can be regarded as a protective group for the acidic hydrogen of malonic ester. We pursued this possibility.

First, we examined the expected elimination reaction. After addition of 4 equiv of *i*-PrMgCl to a mixture of diethyl allyl(benzyl)malonate and 2 equiv of Ti(O-*i*-Pr)$_4$ at −45 °C, the reaction mixture was stirred for 1 h at −45 °C and then treated with benzaldehyde (−45 to 0 °C for 1 h) to provide, after hydrolysis, diethyl benzylmalonate and 1-phenyl-3-buten-1-ol in 97 and 89% yield, respectively. This finding strongly indicated that the reaction proceeded according to eq 1 as expected.

Scheme 1[a]



[a] Reagents and conditions: (a) NaH (1.05 equiv), THF, 20 °C, 1 h; (b) allyl bromide (1.2 equiv), 20 °C, overnight; (c) I(CH$_2$)$_n$I (2.0 equiv), 20 °C, overnight; (d) Bu$_2$CuLi (1.2 equiv), THF, 0 °C, 4 h; (e) Ti(O-*i*-Pr)$_4$ (2.0 equiv), *i*-PrMgCl (4.0 equiv), Et$_2$O, −45 to −40 °C, 1 h; (f) 1 N HCl.



With this result in hand, we examined the potential applicability of the reaction in organic synthesis. The results described below show that the allyl group can indeed be conveniently used as a protective group for the acidic hydrogen of malonic ester.

Treatment of readily preparable and also commercially available diethyl allylmalonate (**2**) with NaH and then 1,5-diiodopentane in THF provided the monoiodide **3** in good yield. The reaction of **3** with Bu$_2$CuLi in ether gave the expected cross-coupling product **4** which upon reaction with **1** provided the deallylated poduct **5** quantitatively as shown in Scheme 1. In contrast, the reaction of diethyl 5-iodopentylmalonate (obtained similarly from sodium diethyl malonate and 1,5-diiodopentane in 57% yield) with Bu$_2$CuLi furnished **5** in only 10% yield but afforded diethyl cyclohexane-1,1-dicarboxylate in 90% yield presumably *via* deprotonation and cyclization of the resulting ester enolate. Although sodium diethyl malonate mainly underwent monoalkylation by treatment with 1,5-diiodopentane, it did not provide the corresponding monoalkylated product **6** by reaction with 1,4-diiodobutane in more than 5% yield, but afforded diethyl cyclopentane-1,1-dicarboxylate in 62% yield *via* intramolecular dialkylation.[6] Compound **6**, however, was readily

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(1) (a) Cope, A. C.; Holmes, H. L.; House, H. O. In *Organic Reactions;* Adams, R., Ed.; John Wiley & Sons: New York, 1957; Vol. 9, p 107. (b) House, H. O. *Modern Synthetic Reactions*; Benjamin: New York, 1972; p 492. (c) Mathieu, J.; Weill-Raynal, J. *Formation of C−C Bonds*; Georg Thieme Publishers: Stuttgart, 1975; Vol. 2, p 12.

(2) For some improvements to avoid dialkylation, see: Brandstrom, A.; Junggren, U. *Tetrahedron Lett.* **1972**, 473. Bram, G.; Fillebeen-Khan, T. *J. Chem. Soc., Chem. Commun.* **1979**, 522.

(3) *Protective Groups in Organic Chemistry*; McOmie, J. F. W., Ed.; Plenum Press: New York, 1973. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1991. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, p 631.

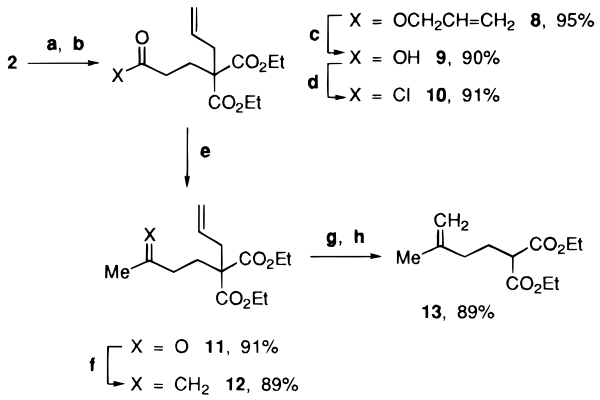
(4) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881.

(5) Reactions in which the malonate carbanion can be regarded as a leaving group have been reported as, for example, reactions of cyclopropane-1,1-dicarboxylates with nucleophiles; see: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66. Hiyama, T.; Morizawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2151. Burgess, K. *J. Org. Chem.* **1987**, *52*, 2946. However, there is no precedent to use this type of reactions for protection of malonates.

(6) It is known that cyclization of carbanions derived from (ω-haloalkyl)malonates to five-membered carbocycles is much faster than to six-membered ones, see: Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67. Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.

0022-3263/96/1961-2266$12.00/0

Scheme 2[a]



[a] Reagents and conditions: (a) NaH (1.05 equiv), THF, 20 °C, 1 h; (b) allyl 2-bromopropionate (1.2 equiv), 20 °C, overnight; (c) HCO_2H (3.5 equiv), NEt_3 (3.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), Bu_3P (10.0 mol %), THF, 40 °C, 1 h; (d) $(COCl)_2$ (2.5 equiv), benzene, 70 °C, 1 h; (e) Me_2CuLi (1.2 equiv), Et_2O, 0 °C, 1 h; (f) $Ph_3P{=}CH_2$ (1.4 equiv), THF, 0 °C, 1 h; (g) Ti(O-*i*-Pr)$_4$ (2.0 equiv), *i*-PrMgCl (4.0 equiv), Et_2O, −45 to −40 °C, 1 h; (h) 1 N HCl.

obtained by the reaction of **2** with 1,4-diiodobutane followed by deallylation of the resulting alkylated product **7** by treatment with **1**.

A series of the reactions, shown in Scheme 2, also indicates the usefulness as well as tolerance of the allyl protective group. Thus, the reaction of the sodium derivative of **2** with allyl 3-bromopropionate furnished the corresponding alkylated product **8** quantitatively, which on treatment with triethylammonium formate in the presence of a Pd catalyst[7] afforded **9** through deallylation of the allyl ester moiety. The acid **9** was converted into the acid chloride **10** and then to the ketone **11** by reaction with Me_2CuLi. (The ketone **11** was also synthesized in 88% yield by Michael addition of **2** to methyl vinyl ketone). Wittig methylenation of **11** furnished **12** which on treatment with **1** smoothly provided the monosubstituted malonate **13**. It should be noted that the Pd-catalyzed deallylation of the allyl ester moiety of diethyl [2-(carballyloxy)ethyl]malonate, obtained from sodium diethyl malonate and allyl 3-bromopropionate, did not proceed, presumably due to the presence of the acidic hydrogen. Also Wittig methylenation of diethyl (3-oxobutyl)malonate (prepared by Michael addition of diethyl malonate to methyl vinyl ketone) under the conditions applied to **11** provided the expected product in only 20% yield.

In conclusion, we have shown that the allyl group can be effectively used as a protective group for the acidic hydrogen of malonic ester. We hope that the present methodology might expand the applicability of the malonic ester synthesis.

Supporting Information Available: Experimental and spectral data for reaction products (7 pages).

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(7) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623.