Pergamon

Tetrahedron Letters 40 (1999) 5467–5470

TETRAHEDRON LETTERS

New Methods for the Selective Reduction of Disubstituted Malonates to the Corresponding Hydroxy-ester Derivatives

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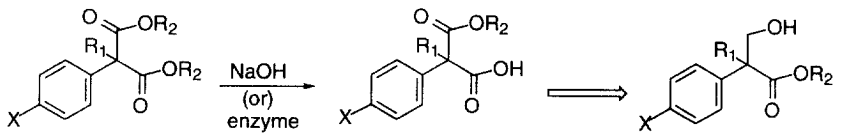
Received 30 October 1998; accepted 28 May 1999

Abstract: The reduction of alkylphenylmalonates and dialkylmalonates with LiAl(O-*t*-Bu)$_3$H proceeds with selective reduction of one of the ester functionalities to provide the hydroxy-ester derivatives in good yields.

The preparation of hydroxy-ester derivatives **1** has typically relied on the basic[1,2] or enzymatic[3] hydrolysis of malonates **2** to the corresponding monomalonate derivatives **3**, followed by reduction. Alkylation of the appropriate ester with gaseous paraformaldehyde also provides the corresponding hydroxy-ester derivatives.[4] Even though these protocols provide reasonable yields of the desired hydroxy-ester derivatives, alternative more direct and less costly approaches may provide routes to otherwise inaccessible derivatives. Herein are described the results of the selective and direct reduction of readily available disubstituted malonates to the corresponding hydroxy-esters using either LiAl(O-*t*-Bu)$_3$H or Buchwald's recently described titanium system.[5]

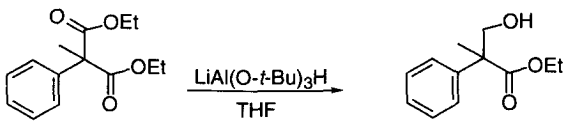
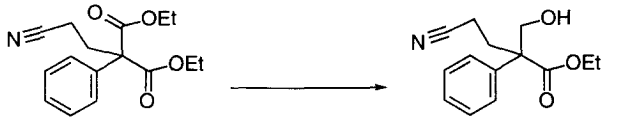
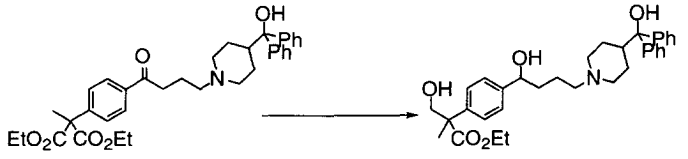
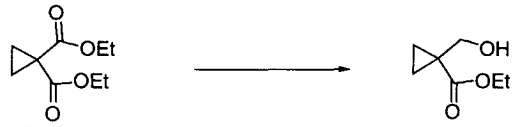


2 **3** **1**

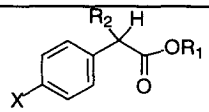
The use of LiAl(O-*t*-Bu)$_3$H for selective reductions of a wide variety of substrates has been well-documented with the stability of the ester functionality to this reagent often being a key feature.[6] However, the selective reduction of malonates **2** with hydride reagents has not been extensively studied. Attempts with $LiAlH_4$[7] and $NaBH_4$[8] provided low yields and primarily over-reduction of the malonate functionality, although one report describes the selective reduction of malonates to the corresponding aldehyde-esters using DIBAL-H at -78 °C.[9] It was hoped that the use of Red-Al® or LiAl(O-*t*-Bu)$_3$H would provide an intermediate aluminate species which would prevent further reduction due to the intrinsic steric nature of the aluminate species. Not too surprisingly, the reduction of malonate **2a** with 1.0 eq of Red-Al® (-78 °C) provided a complex mixture of products. However, when **2a** was treated with 1 eq of LiAl(O-*t*-Bu)$_3$H (-78 °C to room temperature), slow and incomplete conversion (28%) to the desired hydroxy-ester **1a** was observed after 18 h.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01100-4

Table: Reductions of Malonates with $LiAl(O\text{-}t\text{-}Bu)_3H$[a,b]

Entry		Yield (reaction time)[c]	
		Room Temperature	Reflux
1.	 **2a** → **1a**	85% (4 d)	76% (2 h)
2.	 **2b** → **1b**	74% (20 h)	40% (2 h)[d]
3.	 **2c** → **1c**	64% (5 d)	73% (2 h)
4.	 **2d** → **1d**	n.d.	69% (2 h)
5.	 **2e** → **1e**	67% (2 d)[e]	n.d.
6.	 **5** → **6**	n.d.	72% (24 h)[f]
7.	 **7** → **8**	n.d.	61% (2 h)[g]

[a] See Typical Procedures for reaction conditions. [b] A small amount of compound **4** was generally observed. [c] Isolated yields; n.d. = not done. [d] Mixture of **1b**, starting material and diol was observed. [e] 10 eq of $LiAl(O\text{-}t\text{-}Bu)_3H$ was used. [f] 2.5 eq of $LiAl(O\text{-}t\text{-}Bu)_3H$ was used. [g] 2.2 eq of $LiAl(O\text{-}t\text{-}Bu)_3H$ was used.



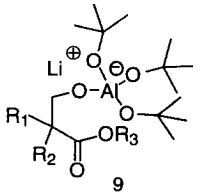
4 (6-8%)

Increasing the amount of LiAl(O-*t*-Bu)$_3$H to 5 eq now provided complete reduction of **2a** after 4 days to give an 85% yield of the desired hydroxy-ester derivative **1a**. None of the diol product resulting in over-reduction was observed; however, in all cases a small amount of ester **4** was seen by GC-MS analysis of the crude reaction mixtures. This result is remarkable because LiAl(O-*t*-Bu)$_3$H has generally been reported to be unreactive to the ester functionality.[6] In a similar fashion, reduction of dimethyl 4-bromophenyl malonate **2b** provided the desired hydroxy-ester **1b** in 74% yield.

Alkyl-substitution does not appear to be problematic as reduction of the *n*-propyl analog **2c** provided the desired hydroxy-ester derivative **1c** in 64% yield. Initially, the reactions were performed at room temperature and required 2-5 days for completion. In order to speed up the conversion, the reaction of **2c** with 5 eq of LiAl(O-*t*-Bu)$_3$H was conducted in THF at reflux. Under these conditions, the reaction was complete in 1 h, no over-reduction was observed, and a 73% yield of **1c** was obtained. Reaction of **2a** likewise proceeded smoothly at reflux to provide the desired hydroxy-ester **1a**. However, the reaction of **2b** containing the dimethyl ester functionality at reflux was not very selective even when only 2.1 eq of LiAl(O-*t*-Bu)$_3$H was used, because a mixture of **1b**, starting material and diol was obtained. Thus, elevated temperatures for the reduction of dimethyl malonates should be avoided and are not necessary as this reduction was complete after 18 h at room temperature. Interestingly, the reduction of **2d** with a nitrile functionality in the molecule demonstrates the potential chemoselectivity of this reaction. In this case, reduction of only the malonate to give the desired alcohol **1d** (69%) was observed even when the reaction was performed with 5 eq of LiAl(O-*t*-Bu)$_3$H at reflux. Finally, conversion of malonate **2e** to the corresponding hydroxy-ester was problematic under the usual protocols because a substantial amount of decarboxylation was observed in the saponification step. However, reaction of **2e** with 10 eq. of LiAl(O-*t*-Bu)$_3$H for 2 d at room temperature provided a 67% yield of hydroxy-ester **1e** with the desired reduction of the keto-group also obtained.

Having established a protocol for the reduction of the alkylphenylmalonates **2**, reductions of simple dialkylmalonate derivatives were investigated. Thus, reduction of diethyl diethylmalonate **5** with 5 eq of LiAl(O-*t*-Bu)$_3$H at reflux resulted in over-reduction providing a mixture of the desired hydroxy-ester (**6**) and the corresponding diol. However, when 2.5 eq of LiAl(O-*t*-Bu)$_3$H was used, smooth conversion to the desired hydroxy-ester **6** (72%) was observed. Likewise, reduction of the cyclopropyl analog **7** provided the desired hydroxy-ester **8** (61%).

Some comments on the nature of the aluminate intermediate are warranted. The above results suggest that the stability of the aluminate intermediate **9** is dictated by the steric bulk of the various substituents. In the case of diethyl malonate derivatives, one can obtain reduction of only one ester group by controlling the temperature and stoichiometry of LiAl(O-*t*-Bu)$_3$H. However, in the case of dimethyl malonate derivatives, the steric hindrance is insufficient and over-reduction occurs at elevated temperatures.



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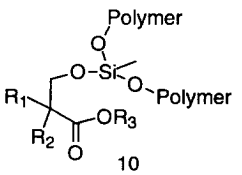

10

With the recent report by Buchwald on the catalytic reduction of lactones to the corresponding lactol derivatives using "Cp_2TiH",[5] the use of this system for the reduction of malonates **2** was explored. It was anticipated that the intermediate silyl-protected alcohol **10** (bound to the polymer) would behave in a similar fashion to the aluminate intermediate and sterically hinder over-reduction. Quite nicely, treatment of methylphenylmalonate **2a** with poly(methylhydrosiloxane) (PMHS) and the *in situ* formed titanocene intermediate provided the desired hydroxy-ester **1a** in 52% yield after work-up with Bu_4NF. Unfortunately, reflux temperatures were required for the reaction to proceed, as no reaction was observed at room temperature after 24 h. Nevertheless, a good yield of hydroxy-ester **2a** was obtained.[10]

In conclusion, new methods for the direct and selective reduction of malonate derivatives to the corresponding hydroxy-ester derivatives have been developed. The mild reaction conditions utilized for the $LiAl(O\text{-}t\text{-}Bu)_3H$ system should have many applications for the synthesis of other hydroxy-ester derivatives which possess sensitive functionality in the molecule.

Typical Procedures

Reduction of 2a with $LiAl(O\text{-}t\text{-}Bu)_3H$ at Room Temperatue: To a solution of 250 mg (1.0 mmol) of **2a** in 3 mL of THF under N_2 at -78 °C was added 5 mL of a 1.0 M solution of $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF by syringe over 20 min. The solution was allowed to warm to room temperature. After 4 d, GC-MS showed a 96:4 mixture of **1a** and **4a**. 10% $KHSO_4$ was carefully added. EtOAc was added and the organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography using an EtOAc / heptane gradient gave 176 mg (85%) of **1a**.

Reduction of 2d with $LiAl(O\text{-}t\text{-}Bu)_3H$ at Reflux: To a solution of 303 mg (1.0 mmol) of **2d** in 5 mL of THF under N_2 at room temperature was added 5 mL of a 1.0 M solution of $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF by syringe over 2 min. The solution was heated to reflux. After 2 h, GC-MS showed a 95:5 mixture of **2d** and **4d**. Following work-up, flash chromatography using an EtOAc / heptane gradient gave 180 mg (69%) of **1d**: ^1H NMR ($CDCl_3$) δ 7.42-7.20 (m, 5), 4.24 (q, 2, J = 7 Hz), 4.18 (m, 1), 3.92 (m, 1), 2.40-2.17 (m, 5), 1.78 (m, 1), 1.61 (m, 1), 1.26 (t, 3, J = 7 Hz); IR (neat) 3486, 3472, 2230, 1724 cm^{-1}; MS (APCI) m/z (relative intensity) 262 ($M + H^+$, 100).

Reduction of 2a with "Cp_2TiH" and PMHS:[5] To a solution of of Cp_2TiCl_2 (15 mg, 0.08 mmol) in 2 mL of THF under nitrogen was added a 1.0 M THF-solution of EtMgBr (0.15 mL, 0.15 mmol). After 5 min, PMHS (0.43 mL, 7.5 mmol eq of hydride) was added. After 5 min, malonate **2a** (750 mg, 3 mmol) was added and the reaction was heated to reflux. After 18 h, the mixture was cooled to room temperature and 1.0 M THF solution of $n\text{-}Bu_4NF$ (0.3 mL, 0.3 mmol) was introduced. After 5 h, water and EtOAc were added. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography using an EtOAc / heptane gradient gave 327 mg (52%) of **1a**.

References and Notes

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[4] For example, see: Domagala, J. M.; Bach, R. D. *J.Org. Chem.* **1979**, *44*, 2429.

[5] Verdaguer, X.; Hansen, M. C.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *62*, 8522; Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641; Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323.

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[8] Jokela, R.; Taipale, T.; Ala-Kaila, K.; Lounasmaa, M. *Heterocycles*, **1986**, *24*, 2265.

[9] Davis, C. R.; Swenson, D. C.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 6843.

[10] This catalytic reduction is currently being explored further.