Tetrahedron Letters,Vol.26,No.22,pp 2603-2606,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

PREPARATION OF α,β-DEHYDRO-β-AMINO ACID DERIVATIVES BY TIN-PROMOTED ADDITION OF MALONATES TO SIMPLE NITRILES

Frank Scavo and Paul Helquist*

Department of Chemistry, University of Notre Dame,
Notre Dame, Indiana 46556 U.S.A.

Summary: Simple aliphatic and aromatic nitriles undergo reaction with malonate esters in the presence of tin(IV) chloride to give derivatives of α,β-dehydro-β-amino acids. The same products are obtained through use of bromomalonate esters.

α,β-Dehydro-β-amino acid derivatives have many potential applications as biologically active compounds and as precursors of substituted β-amino acids, heterocyclic systems, and other classes of valuable compounds.[1] Conceptually, many of these dehydro derivatives should be available by the addition of malonates or other appropriate carbon nucleophiles to nitriles. However, this approach has largely been limited in the past to specially activated, electron-deficient nitriles such as cyanoformates and cyanogen, often in the presence of Lewis acids.[2-4] We now wish to report that this limitation is very easily overcome and that these addition reactions can actually be accomplished with simple, readily available nitriles.

Equimolar amounts of dialkyl malonates and nitriles undergo reaction in the presence of tin(IV) chloride in 1,2-dichloroethane at reflux. Completion of the reaction is indicated by the formation of a white precipitate after a few minutes. This solid is apparently a tin complex of the addition product, although we have not actually determined the structure of any of these initially obtained products. The solids are air-stable and may either first be isolated by routine filtration or may be hydrolyzed directly to obtain the final products. The imine derivatives 1 apparently tautomerize to give the observed final products of structure 2

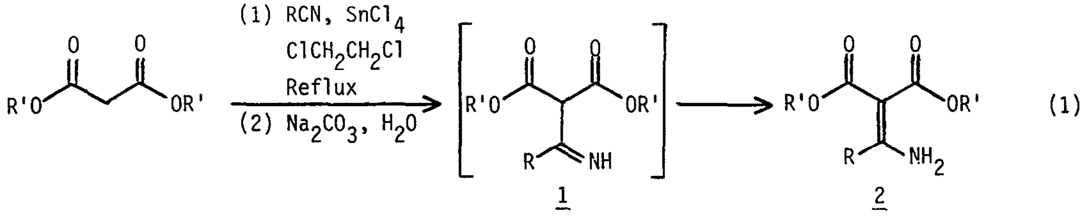


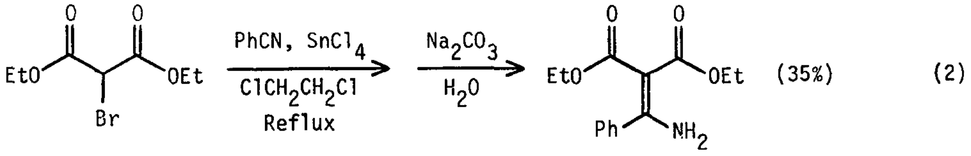
Table. Tin(IV)-Promoted Addition of Dimethyl Malonate to Nitriles (eq. 1).

R	Time (min)	Yield of 2 (%)[a]	mp (°C)
CH_3	50	45	83-84
CH_2CH_3	37	55	Oil
Ph	26	57	130-131
CH=CHPh	32	43	87-89
$CH=CHCH_3$	48	17	97-99

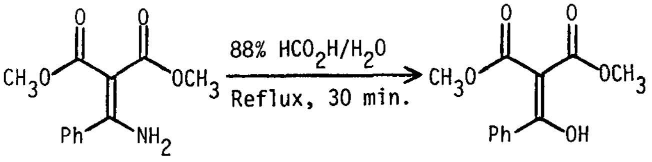
[a] All yields are for isolated, crystalline products except for the second entry.

(equation 1). Our results are summarized in the Table.

An interesting point is that the same products are obtained when a bromomalonate is used in place of the simple malonate (equation 2). We assume that this reaction is due to coordination of the bromomalonate to tin followed by nucleophilic attack on the thus activated bromine substituent to generate a tin malonate which then undergoes reaction with the nitrile. This result is interesting in light of the earlier generation of metalated malonates by reaction of bromomalonates with reducing agents such as zinc-copper couple and tin(II) chloride.[1a,g,5] Also, our observations contrast with a report by others in which a tin(IV)-promoted reaction of nitriles with an α-halocarbonyl system proceeds via substitution of halide at carbon by the nitrile.[6]



A further observation is that the nitrile-derived adducts 2 undergo facile hydrolysis (e.g. in aqueous formic acid) to give the corresponding tricarbonyl derivatives in the expected enolic form 3 (equation 3).



3

(3)

In conclusion, we have devised a very straightforward method for the preparation of dehydro-β-amino acid derivatives. We are currently studying the scope of this method, optimizing the yields, and investigating several applications of the products.

A sample procedure is as follows: Dimethyl malonate (5.0 g, 38 mmol), benzonitrile (3.9 g, 38 mmol), and 1,2-dichloroethane (20 mL) were placed in a 100-mL round-bottom flask equipped with a reflux condenser and a magnetic stirring bar. After the apparatus was flushed with nitrogen, $SnCl_4$ (17.8 g, 8.9 mL, 76 mmol) was added at once with a syringe, and the mixture was heated at reflux. A golden yellow-colored solution formed quickly followed in about 15 min by the appearance of white precipitate. After an additional 10 min, the mixture was cooled and then filtered to give 13.5 g of white solid. The filtrate was evaporated, leaving additional white solid (1.58 g). The combined solids were dissolved in acetone (100 mL), and satd. aq. Na_2CO_3 (70 mL) was added until a pH of 7 was reached. The resulting white solid was removed by filtration and was washed with CH_2Cl_2 (4x100 mL). The combined filtrates were dried over anhyd. $MgSO_4$ and evaporated to leave a white crystalline residue which was recrystallized from EtOAc/hexanes to give 5.11 g (57%) of colorless needles: mp 130-131 °C; IR (KBr) 3400, 3280, 1670, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 9.30 (br, 1 H), 7.67 (s, 5 H), 5.50 (br s, 1 H), 3.89 (s, 3 H), 3.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 168.2, 168.1, 164.6, 137.2, 129.8, 128.3, 126.5, 93.0, 51.1, 50.9; MS (70 eV) m/e (%) 235 (22), 204 (31), 104 (22), 69 (100). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.26; H, 5.58. Found: C, 61.21; H, 5.64.

Acknowledgement. We are pleased to acknowledge the financial support of this work by the National Science Foundation (CHE 8120466).

References

1. (a) Meyers, A. I.; Sircar, J. C. In "The Chemistry of the Cyano Group"; Rappoport, Z., Ed.; Interscience: London, 1970; pp. 383-386. (b) Bodnarchuk, N. D.; Kolomoets, D. P.; Gavrilenko, B. B.; Derkach, G. I. *Fiziol. Aktiv. Veskchestva* **1972**, 13; *Chem. Abstr.* **1973**, *79*, 4886x. (c) Ghosal, S.; Chaudhuri, R. K.; Tiwari, M. P.; Singh, A. K.; Wehrli, F. W. *Tetrahedron Lett.* **1974**, 403. (d) Ganem, B. *J. Am. Chem. Soc.* **1976**, *98*, 224. (e) Howe, R. K.; Gruner, T. A.; Carter, L. G.; Franz, J. E. *J. Heterocyc. Chem.* **1978**, *15*, 1001. (f) Celerier, J.-P.; Deloisy, E.; Kapron, P.; Lhommet, G.; Maitte, P. *Synthesis* **1981**, 130. (g) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833. (h) Basato, M.; Corain, B.; Veronese, A. C.; D'Angeli, F.; Valle, G.; Zanotti, G. *J. Org. Chem.* **1984**, *49*, 4696.
2. For the effect of electron-withdrawing groups on nitriles in general see: (a) Grivas, J. C.; Taurins, A. *Can. J. Chem.* **1958**, *36*, 771. (b) Cramer, F.; Pawlzik, K.; Baldauf, H. J. *Chem. Ber.* **1958**, *91*, 1049. (c) Schaeffer, F. C. In ref. 1a, p. 286.
3. For addition of malonates and related nucleophiles to activated nitriles see ref. 1a,b,g,h. See also (a) Bodnarchuk, N. D.; Gavrilenko, B. B.; Derkach, G. I. *J. Org. Chem. USSR* **1968**, *4*, 1645. (b) Iimori, T.; Nii, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1979**, 2525. (c) Ube Industries, Ltd. Japanese Patent 81 71 050, 1981; *Chem. Abstr.* **1981**, *95*, 169789m. (d) Basato, M.; Corain, B.; Cofler, M.; Veronese, A. C.; Zanotti, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1593.
4. For some alternative approaches to dehydro β-amino acid derivatives see ref. 1d-g. See also: Singh, H.; Cheema, A. S. *Chem. Ind. (London)* **1976**, 413.
5. (a) Ube Industries, Ltd. Japanese Patent 81 71 049, 1981; *Chem. Abstr.* **1981**, *95*, 169790e. (b) Ube Industries, Ltd. Japanese Patent 81 87 542, 1981; *Chem. Abstr.* **1981**, *96*, 20461m.
6. Lora-Tamayo, M.; Madronero, R.; Leipprand, H. *Chem. Ber.* **1964**, *97*, 2230.

(Received in USA 18 March 1985)