

Ni-Catalyzed Homocoupling of 3-Halopropenoates in the Presence of Water: Formation of Hexenedioates

Martin Kotora,* Hiroshi Matsumura, and Tamotsu Takahashi*

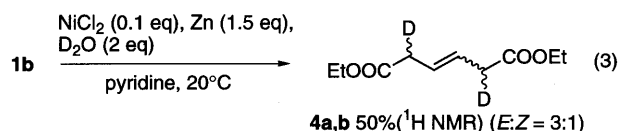
Catalysis Research Center and Graduate School of Pharmaceutical Sciences, Hokkaido University
and CREST, Science and Technology Corporation (JST), Sapporo 060-0811

(Received September 16, 1999; CL-990794)

Homocoupling of (*Z*)-3-halopropenoates using a catalytic amount of NiCl_2 and Zn in the presence of water in pyridine afforded a mixture of (*Z*)- and (*E*)-3-hexenedioates.

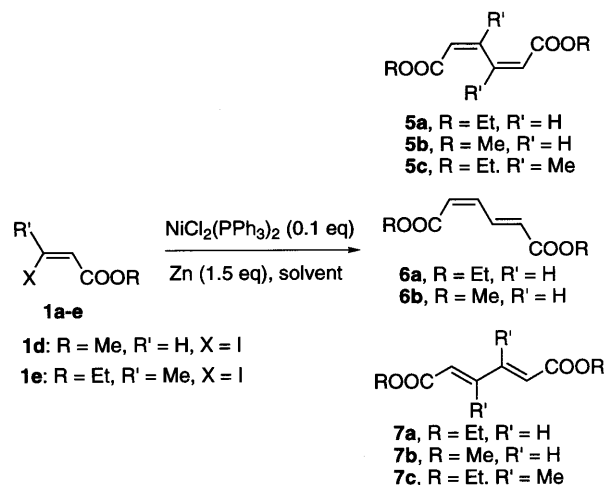
Homocoupling of organic halides is a well-established route for the preparation of various symmetrical compounds and is mediated or catalyzed in the presence of a reductant by a number of transition metals such as Pd, Ni, etc.¹ Dimerization of 3-halopropenoic acids and their derivatives is of interest, because the corresponding hexadienedioic acid derivatives are biologically active compounds.^{2,3} So far, three methods have been reported. The first two dimerization methods used stoichiometric amounts of $\text{Ni}(\text{COD})_2$ in DMF ⁴ or copper(I) thiophene-2-carboxylate⁵ to give hexadienedioates with retention of the stereochemistry of the double bond. The third method was carried out with 40 mol% of NiCl_2 and Zn as a reductant in HMPA; however, in this case a loss of stereochemistry was observed.⁶ Nonetheless, a truly catalytic method for dimerization of these compounds has not been developed yet. In this regard, a potentially useful catalyst seemed to be $\text{NiCl}_2(\text{PPh}_3)_2$ which was successfully used in another case involving halopropenoates.⁷

During the course of our study on Ni-catalyzed reactions of halopropenoates, we found that when homocoupling of **1** was carried out in pyridine in the presence of H_2O and a catalytic amount of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, the products were hexenedioates **2** but not hexadienedioates (Eq. 1). Moreover, the yield of this reaction depended on halogen in the starting material: thus, **1a** afforded **2** in 5%, **1b** in 50 (41% isol.), and **1c** in 80 (66% isol.) yield, respectively. This reaction also proceeded in the case of (*E*)-3-chloropropenoates (**3**) (35% yield) (Eq. 2). When the reaction was conducted with D_2O , the corresponding deuterated product **4** was obtained (Eq. 3).



This was a quite unexpected result, and we set out to find the reaction mechanism to explain the formation of **2**. It was clear that homocoupling products of 3-halopropenoates were formed in the first step. However, in order to verify the homocoupling of 3-halopropenoates, we carried out the following catalytic reactions, since truly catalytic dimerization reaction of 3-halopropenoates has not been known yet as described above.

Homocoupling of alkyl (*Z*)-3-halopropenoates in the presence of a catalytic amount of $\text{NiCl}_2(\text{PPh}_3)_2$ (10 mol%), Zn (1.5 equiv) in polar solvents proceeded with good selectivity to afford hexadienedioates **5-7** (Scheme 1 and Table 1).



Scheme 1.

Generally, the homocoupling proceeded in the several solvents studied; however, it was sensitive to the reaction conditions as well as to the quality of Zn. Thus, coupling of **1d** in the presence of Zn that was left exposed to air for a longer period of time (Entry 2) afforded substantial amount of isomerized products **6b** + **7b**. On the other hand, the use of freshly obtained Zn powder (Entry 1) resulted in the clean formation of **5a**. Concerning reactions in THF, remarkable improvement in yields was observed after treatment of the Zn suspension in THF with TMSCl (0.2 equiv) (Entries 5 and 6), although the formation of isomerized products **6b**+**7b** was observed. Homocoupling of **1e** also proceeded smoothly (Entry 6) and afforded the corresponding product **5c** in 99% yield. (*E*)-3-Iodopropenoate **3b** showed the same reactivity as *Z* isomers as

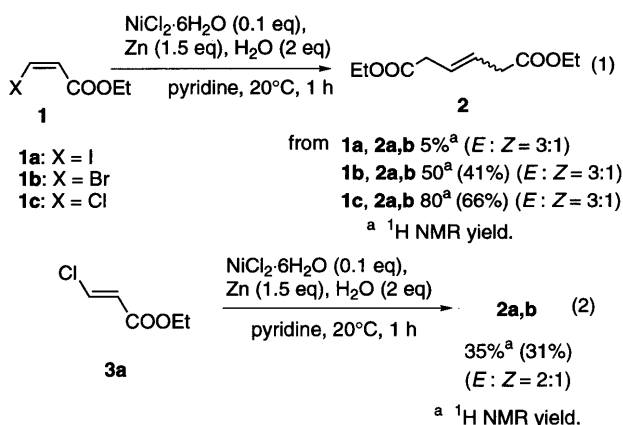
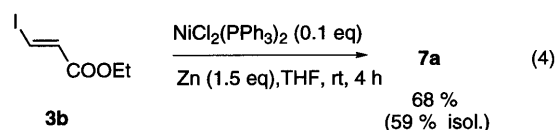


Table 1. Ni-catalyzed homocoupling of (Z)-3-iodopropenoates.

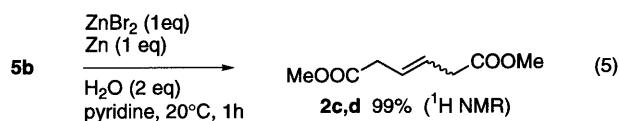
Entry	1	Solvent	t/h	Yield /% ^a		Combined yield ^b
				2	3 + 4	
1	1a	MeCN	3	5a, 82 (52)	6a+7a, - (21) ^c	82
2	1d	MeCN	6	5b, 53 (24)	6b+7b, 45 (10)	97
3	1d	DMPU	3	5b, 78 (50)	6b+7b, - (3) ^c	78
4	1d	THF	2	5b, 53 (20)	6b+7b, 15 (47) ^c	68
5	1a	THF ^d	1.5	5a, 62 (34)	6a+7a, 36 (26)	98
6	1c	THF ^d	1.5	5c, 99 (62)	7c, - (3) ^c	99

^a¹H NMR yields. Isolated yields are in parentheses. ^bCombined ¹H NMR yields. ^cFormed by isomerization of 5. ^dSuspension of Zn was stirred with 0.2 equiv of TMSCl in THF for 1 h prior to the addition of other reactants.

shown in eq (4). It is notable that only 7a was obtained in 68% NMR yield in the case of the E isomer 3b. Interestingly, although the analysis of the reaction mixture often indicated that only one isomer was formed, after the work-up isomerized products were isolated in considerably high yields. Obviously, the isomerization occurred during both work-up and purification on silica gel.

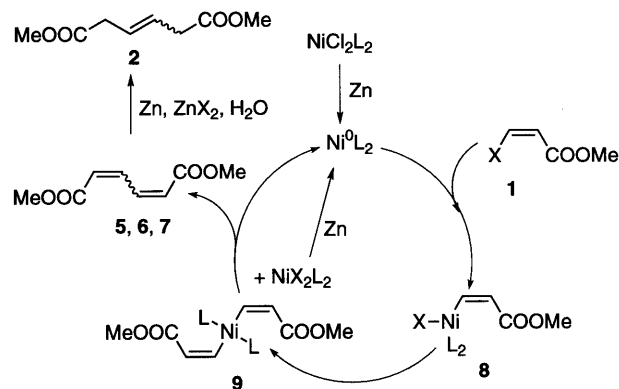


The origin of the reduction to 2 in the second step was puzzling. To clarify this point, we conducted a number of reactions of 5b with different combinations of the reactants used in the above-mentioned reaction. We found that 5b was quantitatively reduced to 2c,d in pyridine in the presence of zinc halide (1 equiv), Zn-powder (1 equiv), water (2 equiv), in just 1 h (Eq. 5). This clearly indicated that this reaction was a "dissolving metal" reduction.⁸ Reduction of activated double bonds under these conditions has been reported.⁹



Thus, the overall course of the homocoupling followed by the reduction (Scheme 2) is as follows: Zn reduces a nickel catalyst to a Ni⁰-species to which oxidative addition of (Z)-3-halo-

propenoate proceeds to give organo halonickel species 8 that undergoes disproportionation¹⁰ to a nickel halide and a diorgano nickel compound 9 that, in turn, undergoes reductive elimination to give a Ni⁰-species and the homocoupling products 5, 6, and 7. In the next phase the product is reduced by metallic zinc (dissolving metal mechanism) to give 2. The necessary zinc halide is formed in the reduction of the Ni-catalyst.

**Scheme 2.**

References

- For examples see: "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press Ltd., Oxford (1991), Vol. 3.
- M. R. Parsek, R. W. Ye, P. Pun, and A. M. Chakrabarty, *J. Biol. Chem.*, **269**, 11279 (1994).
- T. Hida, S. Tsubotani, N. Katayama, Y. Funabashi, H. Natsugari, and S. Harada, *J. Antibiot.*, **46**, 803 (1993).
- M. F. Semmelhack, P. Helquist, L. D. Jones, L. Ketter, L. Mendelson, L. S. Ryono, J. Gorzynski Smith, and R. D. Stauffer, *J. Am. Chem. Soc.*, **103**, 6460 (1981).
- S. Zhang, D. Zhang, and L. S. Liebeskind, *J. Org. Chem.*, **62**, 2312 (1997).
- K. Takagi and N. Hayama, *Chem. Lett.*, **1983**, 637.
- M. Kitora, M. Ishikawa, F.-Y. Tsai, and T. Takahashi, *Tetrahedron*, **55**, 4969 (1997).
- D. J. Pasto in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press Ltd., Oxford (1991), Vol. 8, p. 478.
- a) F. Toda and K. Iida, *Chem. Lett.*, **1976**, 695. b) K. Ohkata and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, **43**, 2204 (1970).
- K. Osakada and T. Yamamoto, *J. Synth. Org. Chem.*, **57**, 305 (1999).