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

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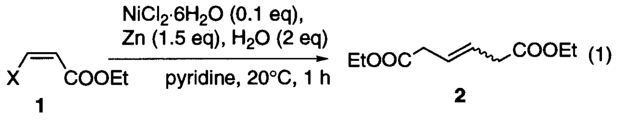
Homocoupling of (*Z*)-3-halopropenoates using a catalytic amount of NiCl$_2$ and Zn in the presence of water in pyridine afforded a mixture of (*Z*)- and (*E*)-3-hexenedioates.

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 Ni(COD)$_2$ in DMF[4] or copper(I) thiophene-2-carboxylate[5] 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 NiCl$_2$(PPh$_3$)$_2$ which was successfully used in another case involving halopropenoates.[7]

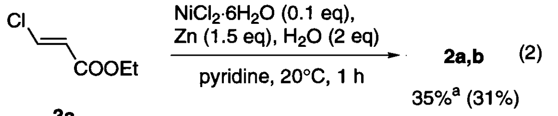
During the course of our study on Ni-catalyzed reactions of halopropenoates, we found that when homocoupling of **1** was carried out in pyridine in the presence of H$_2$O and a catalytic amount of NiCl$_2$·6H$_2$O, the products were hexenedioates **2** but not hexadienedioates (Eq. 1). Moreover, the 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$_2$O, the corresponding deuterated product **4** was obtained (Eq. 3).



1 **2**

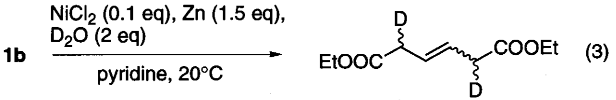
1a: X = I
1b: X = Br
1c: X = Cl

from **1a, 2a,b** 5%[a] (*E* : *Z* = 3:1)
1b, 2a,b 50[a] (41%) (*E* : *Z* = 3:1)
1c, 2a,b 80[a] (66%) (*E* : *Z* = 3:1)
[a] ^{1}H NMR yield.



3a **2a,b**

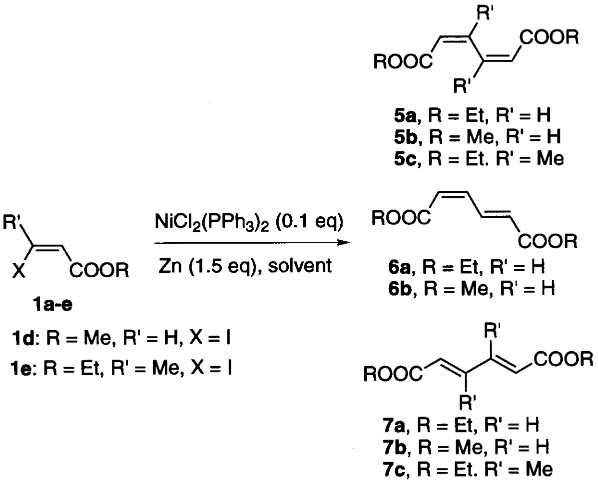
35%[a] (31%)
(*E* : *Z* = 2:1)
[a] ^{1}H NMR yield.



4a,b 50%(^{1}H NMR) (*E*:*Z* = 3:1)

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 truely 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 NiCl$_2$(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).



5a, R = Et, R' = H
5b, R = Me, R' = H
5c, R = Et. R' = Me

1a-e
1d: R = Me, R' = H, X = I
1e: R = Et, R' = Me, X = I

6a, R = Et, R' = H
6b, R = Me, R' = H

7a, R = Et, R' = H
7b, R = Me, R' = H
7c, R = Et. R' = Me

Scheme 1.

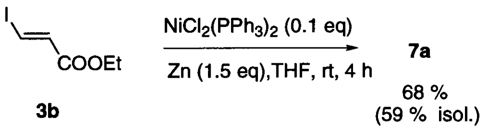
Generally, the homocoupling proceeded in the several solvents studied; however, it was sensitive to the reaction conditions as well as to the quality of Zn. Thus, coupling of **1d** in the presence of Zn that was left exposed to air for a longer period of time (Entry 2) afforded substantial amount of 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] 2	Yield /%[a] 3 + 4	Combined yield[b]
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

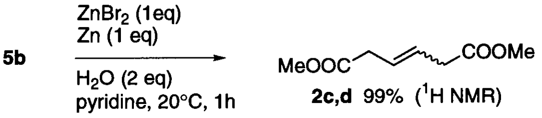
[a] ^{1}H NMR yields. Isolated yields are in parentheses. [b] Combined ^{1}H NMR yields. [c] Formed by isomerization of **5**. [d] Suspension of Zn was stirred with 0.2 equiv of TMSCl in THF for 1 h prior to the addition of other reactants.

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.



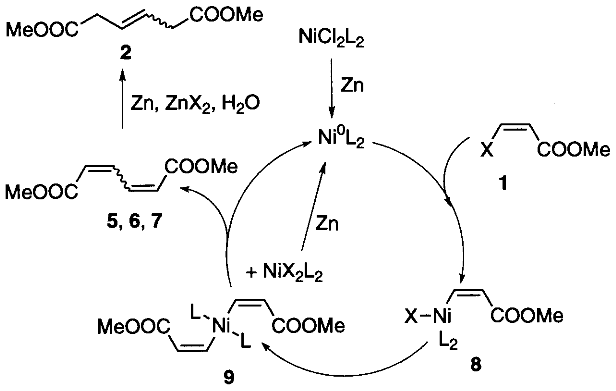
(4)

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 1h (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]



(5)

Thus, the overall course of the homocoupling followed by the reduction (Scheme 2) is as follows: Zn reduces a nickel catalyst to a Ni^0-species to which oxidative addition of (*Z*)-3-halopropenoate proceeds to give organo halonickel species **8** that undergoes disproportionation[10] to a nickel halide and a diorgano nickel compound **9** that, in turn, undergoes reductive elimination to give a Ni^0-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.

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