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Palladium-Catalyzed Cross-Coupling of 3-Iodobut-3-enoic Acid with Organometallic Reagents. Synthesis of 3-Substituted But-3-enoic Acids

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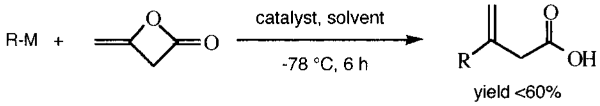
3-Substituted but-3-enoic acids were obtained in good yields under mild experimental conditions by palladium-catalyzed cross-coupling of 3-iodobut-3-enoic acid with organozinc or organotin compounds using $PdCl_2(MeCN)_2$ as catalyst and DMF as solvent.

Introduction

Intermediate compounds bearing two electrophilic centers have been widely used over the past few years as the key step in total synthesis.[1] Some bi-electrophiles containing a carboxylic function have proved to be valuable in the synthesis of terpenoic acid derivatives.[2] The most widely used of the series of but-3-enoic acid synthons is diketene whose opening by various organometallics leads to 3-substituted but-3-enoic acids (Scheme 1).[3]

However, this process does not allow the satisfactory introduction of vinylic and benzylic groups (especially in terms of yields given by vinylic organometallics), owing mainly to formation of polymers. Moreover, it is well-known that diketene decomposes violently in the presence of a base.[4] This is a limitation to obtaining high quantities of 3-substituted but-3-enoic acids. We therefore planned a new approach to this type of acids through the reactions between 3-iodobut-3-enoic acid and various organometallic compounds.

Scheme 1



Results and Discussion

Synthesis of 3-Iodobut-3-enoic Acid. Hydroiodation of the but-2,3-dienoic acid,[5] initially prepared by carbonatation reaction of allenylmagnesium bromide with hydroiodic acid, yielded only the nonconjugated 3-iodobut-3-enoic acid **(1)** at room temperature.[6] Increasing the temperature led to a mixture of **(1)** and the *E* and *Z* isomers of 3-iodobut-2-enoic acid.

Using an identical procedure, heating the but-3-ynoic acid at 70 °C for 6 h yielded 69% of iodovinylic acid **1** without any isomerization product (Scheme 2).

Reactivity of 3-Iodobut-3-enoic Acid. The reactivity of iodovinylic acid **1** was then studied through the substitution of the iodine atom.[7] The substitution reaction of **1** was carried out with various organometallic reagents. Preliminary experiments with Grignard reagents or organocuprates in various solvents (such as ether, THF, and HMPA) did not allow the expected substitution. On the basis of Negishi's work,[8] we decided to use organozinc reagents under palladium(II) catalysis in THF which provided poor yields of a mixture of the 3-substi-

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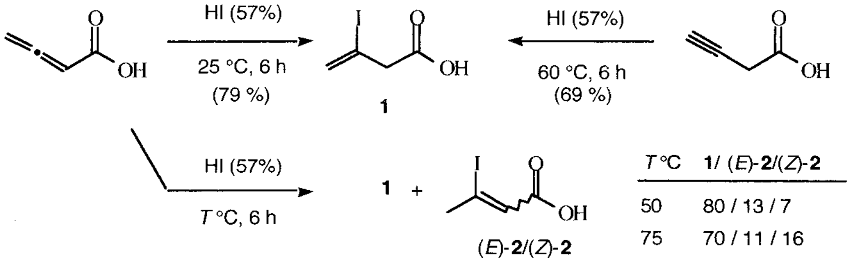
Scheme 2



Scheme 3

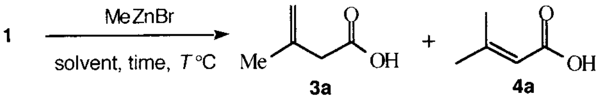


Table 1. Reaction of 1 with MeZnBr

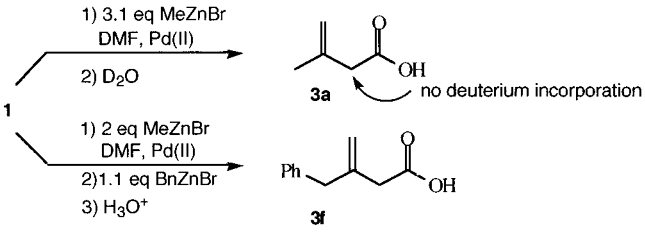
entry	MeZnBr (equiv)	solvent[a]	catalyst[b]	T (°C)	t (h)	**1**[c] (%)	**3a** (%)	**4a** (%)
1	8	A	none	20	24	100	0	0
2	8	A	D	20	148		90	10
3	6	A	D	20	17	14	80	4
4	3	A	D	0	6		0	0
5	3	A	D	5	12		0	0
6	3	B	D	50	48	50	50	
7	2.1	C	E	70	2.5		0	
					6		10	
					24		50	
8	2.1	C	E	20	36		30	
9	3	C	E	20	12		95	
10	3	C	E	40	12		97	

[a] A: ether/THF(2/1); B: THF; C: ether/DMF(1/1). [b] D: $PdCl_2(PhCN)_2$; E: $PdCl_2(MeCN)_2$. [c] Conversion rate determined by ^1H NMR.

tuted acids **3** and **4**. To optimize these first results, we tested various solvents and catalysts to obtain substitution of **1** by methylzinc bromide (generated by addition of zinc bromide to a solution of methylmagnesium iodide) (Scheme 3, Table 1).

We first found that palladium must be present to promote the cross coupling reaction (entry 1). In the presence a palladium salt and with a large excess of methylzinc bromide, the coupling product was obtained in a quantitative conversion over a period of 6 days (entry 2). Nevertheless, **3a** was obtained in a mixture with the conjugated acid **4a**, as already observed with substitution of other vinyl iodides.[9] Many attempts to avoid the formation of **4a** were performed. Low conversion rates were obtained by decreasing the equivalent number of zinc reagents, indicating the dependence of the reaction on a polar medium. To verify this hypothesis, THF was replaced by DMF. After 24 h, with 2.1 equivalents of methylzinc bromide, the reaction occurred with 50% yield exclusively providing **3a**. It should be noted that phosphine-free palladium complexes were more efficient than phosphine-ligated palladium which gave low conversion rates. Finally quantitative conversion rates were obtained within 12 h with 3 equivalents and in an ether – DMF solvent. The stoechiometry of the substitution reaction was also surprising. The first equivalent of methylzinc bromide unambiguously yielded the corresponding zinc carboxylate of **1**. As can be seen in Table 1, two other equivalents were necessary to complete the reaction efficiently. To understand more fully the role of the required third equivalent, we performed the experiments summarized in Scheme 4. Hypothetical deprotonation of the zinc carboxylate affording zinc ketene ketal by the second equivalent of organozinc reagent was excluded by deuteriolysis of the reaction where there was no incorporation of deuterium atoms in α-position of the carboxyle function. Experiments conducted on (*Z*)-3-iodopropenoic acid where the deprotonation reaction on C-2 atom was impossible under our experimental conditions exhibited identical trends in which 3 equiv of organozinc reagent were necessary to substitute the iodine atom.[10]

Scheme 4



Moreover, attempts performed with, first, 2 equiv of methylzinc bromide and 1 equiv of benzyl zinc bromide yielded exclusively the benzyl-substituted butenoic acid **3f**, indicating the inertness of the second organozinc equivalent. On the basis on these experiments, this can reasonably be explained by assuming the formation of a strong chelate **I** between the zinc carboxylate and the zinc reagent. The latter is ineffective during the transmetalation step of the catalytic cycle.

The best arrangement to produce substitution in good yields thus is the combination of 3 equiv of organozinc reagents with ether/DMF as the solvent and a complex of palladium(II) (with $PdCl_2(PhCN)_2$ instead of $PdCl_2(MeCN)_2$, the yields were nearly the same) (Scheme 6). The results are summarized in Table 2.

According to the results in Table 2, substitution reactions with alkyl, phenyl, alkynyl and benzyl groups occurred in good yields giving 3-substituted but-3-enoic acids **3a**–**i**. No isomerization product was obtained, giving the procedure general significance. Access to allylsilane **3h** (Table 2, entry 8), which has been very well studied by Itoh et al.,[3] occurs through reaction of **1** with

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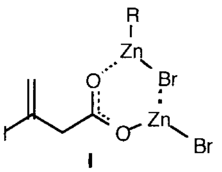
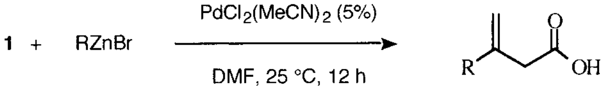
Scheme 5



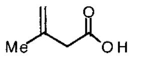
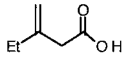
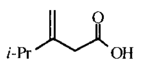
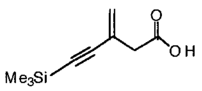
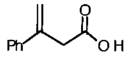
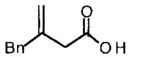
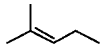
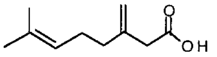
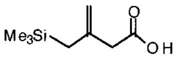
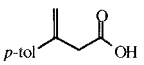
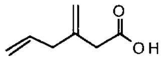
I

Scheme 6



3a-k

Table 2. Synthesis of 3-substituted but-3-enoic Acids

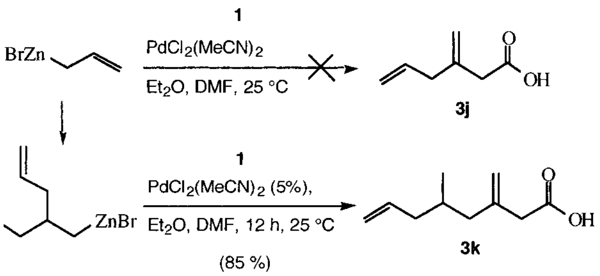
Entry	R[a]	N°	Product	Yield[b] (%)
1	Me	**3a**		80
2	Et	**3b**		90
3	*i*-Pr	**3c**		78
4	Me_3Si—≡	**3d**		85
5	Ph	**3e**		77
6	Bn	**3f**		81
7		**3g**		65
8	Me_3SiCH_2	**3h**		90
9	*p*-tolyl	**3i**		75
10	allyl	**3j**		81[c]

[a] RZnBr was prepared by reaction between the organomagnesium reagent (RMgCl or RMgBr) and anhydrous $ZnBr_2$ in etheral solution. [b] Yields obtained after purification on silica gel or crystallization. [c] Obtained by cross-coupling reaction (see the Experimental Section).

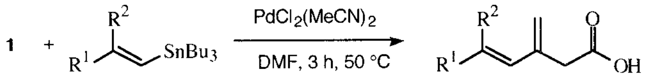
trimethylsilylmethylzinc chloride. In the case of allylzinc bromide only a small amount (3%) of the desired allyl substituted **3j** was obtained (Scheme 7).

The major product **3k** resulted from prior dimerization of allylzinc bromide and then subsequent substitution of iodovinylic acid. The carbozincation of allylzinc bromide, first studied by Courtois et al.,[11] can also be compared with the results of Lehmkohl[12] concerning the dimerization of allylmagnesium bromide. It should be noted that diacid resulting from a double substitution reaction was not observed probably due to the already evokated ligation of zinc reagent with zinc carboxylate. Finally, the dienyl acid **3j** was obtained by cross-coupling reaction between allyltributyltin and **1** using tetrakis(triphenylphosphine)palladium (0) as catalyst, with 81% yield.

Scheme 7



Scheme 8



5a-5f

Table 3. Cross-Coupling of 1 with Vinyltins

entry	R^1	R^2	vinyltin (equiv)	yield (%)	no.
1	H	H	1.2	75	**5a**
2	H	Ph	1.4	75	**5b**[b]
3	H	$(EtO)_2CHCH_2$	1.4	63	**5c**[b]
4	H	Me_3Si	1.2	80	**5d**[b]
5[a]	Me	Me	1.2	66	**5e**
6[a]	H	$SnBu_3$	1.2	66	**5f**[b]

[a] Tributylstannyl ester of **1** was used. [b] (*E*)-Isomer was obtained.

Introduction of Vinyl Units. The introduction of vinyl groups on the 3-iodobut-3-enoic acid **1** required the use of organozinc reagents in solutions of THF or HMPA (generated from organolithium or organomagnesium compounds in THF or HMPA solutions),[13] neither of which are appropriate in this reaction. Vinyltins were therefore used instead, together with 5% of dichlorobis-(acetonitrile)palladium(II) using DMF as solvent (Scheme 8, Table 3).[14] The mild experimental conditions of the Stille cross-coupling reaction led to good yields of dienes **5**, and no polymerization products were detected.

To avoid protonolysis of acid sensitive vinyltin reagents, iodovinylic acid **1** was used as its tributylstannylester (entries 5 and 6).[15] The synthetic potential of compounds **5a**−**f** has not yet been fully studied; however, compound **5a** undergoes Diels−Alder-type reactions with, for example, maleic anhydride or dimethyl acetylenedi-

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carboxylate, affording good yields of functionalized cycloadducts **6a** and **6b**.

Conclusion

In summary, the palladium-catalyzed cross-coupling reaction was extended to iodovinylic acid without any protection of the carboxylic acid function and allowed the synthesis of various 3-substituted but-3-enoic acids with fair to good yields. Applications of these new building blocks to the synthesis of natural products are currently under development and will be reported in due course.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all the compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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