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Stereospecific Synthesis of (*Z*) or (*E*)-3-Methylalk-2-enoic Acids

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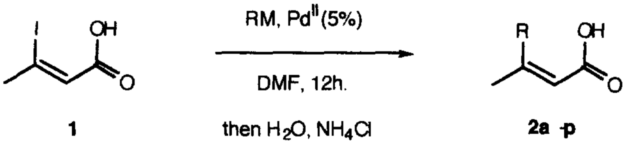
Abstract **:** The palladium catalysed coupling of organozinc or organotin reagents with 3-iodobut-2(or 3)-enoic acid is stereoselective and affords *Z* (or *E*)-3-methylalk-2-enoic acids. The method was applied to the synthesis of the *E* and *Z* stereoisomers of ocimenones and pseudo-tagetones.

The trisubstituted olefins bearing a functional group on their *Z* or *E* position have long retained the attention of a number of organic chemists, and the numerous applications of the total synthesis of natural products explain the great interest paid to the stereospecific synthesis of these types of molecules[2, 3, 4, 5]. For instance, numerous functionalized terpenic structures exhibit double bonds usually trisubstituted with a methyl group and an ester or an acid or a secondary alcohol groups. Among the efficient routes towards these molecules, the carbocupration[6] or the carboalumination[7] reactions of 3-methyl propiolate derivatives are worth noting ; however, these methods do not enable the preparation of *Z* olefins. For these reasons we planned to study a new approach towards this type of compound using 3-iodobut-2-enoic acids, which can be considered as a dication synthon with defined configuration.

The starting 3-iodobut-2-enoic acids were obtained by addition of hydroiodic acid on 3-methylpropiolic acid[8]. The addition on the triple bond occurs with clean *Z*-stereoselectivity and without any protection of the carboxylic function. It should be noted that temperature, reaction time and purity of hydroiodic acid are critically important parameters for the obtention of a pure *Z*-stereoisomer. Thus, when the reaction is performed at 100°C for 24h, the *E*/*Z* ratio increases up to 54/46 and pure *E*-stereoisomer is finally obtained by fractional crystallisation (petroleum ether/ether 9/1).

Reactivity of (*Z*)-3-iodobut-2-enoic acid, especially substitution with retention of the double bond stereochemistry of the iodo group by various organometallic reagents, has been studied. The experimental conditions applied here are derived from the systematic study carried on 3-iodobut-3-enoic acid[9]. We found that the best conditions for the iodo substitution are : 1) the use of organozinc or organotin reagents under palladium complexes catalysis[10] ; 2) the use of DMF as a solvent (very low yields were obtained or even no reaction at all with an ether or THF medium deprived of DMF).



According to the results shown in Table I the procedure is a general one. It can thus accommodate various alkyl, aryl and alkynyl groups. With organozinc reagents, 3 equivalents are required to achieve the reaction with quantitative conversion rates. With only two equivalents, the reaction occurs with a very low yield, even when the reaction time is increased.

Table I : Preparation of (*Z*)-3-methylalk-2-enoic acids[11]

entry	R	M(eq.)	catalyst[a]	solvent	T°C	reaction time (h.)	yield[b] (%)	2
1	Me	ZnBr (3.1)	A	ether/DMF (1/1)	rt	12	95	**2a**
2	Et	"	"	"	"	"	98	**2b**
3	*i*-Bu	"	"	"	"	"	80	**2c**
4	Me_3SiCH_2	"	"	"	"		58	**2d**
5	Ph	"	"	"	"	"	83	**2e**
6	*p*-Tol	"	"	"	"	"	78	**2f**
7	Bn	"	"	"	"	"	77	**2g**
8		"	"	"	"	"	85	**2h**
9	n-Bu—≡	"	"	"	"	"	70	**2i**
10	Me_3Si—≡	"	"	"	"	"	78	**2j**
10	vinyl	$SnBu_3$ (1.1)	B	DMF	rt	3	75	**2k**
11		"	"	"	"	"	65	**2l**
13	Ph	"	"	"	"	"	75	**2m**
14	$(EtO)_2CH$	"	"	"	"	"	63	**2n**
15	$(EtO)_2CH$	"	"	"	35	"	52	**2o**
16	Allyl	Cu[c] (1)	none	THF	-75	0.5	70	**2p**

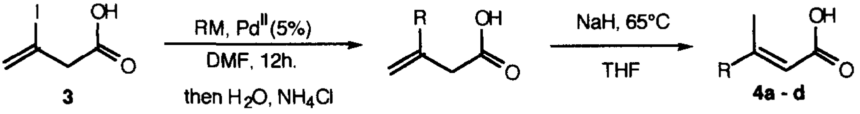
[a] A = $PdCl_2(PPh_3)_2$; B = $PdCl_2(MeCN)_2$

[b] yields obtained after purification on silica gel or crystallisation

[c] obtained by addition of 2 equivalents of allylmagnesium bromide on a THF suspension of CuI

So as to introduce the vinyl group, the reaction was performed with 1.1 equivalent of vinyltin reagents, which do not affect the carboxylic function under Stille's conditions[12]. The use of alkyl or vinylcuprate reagents has also permitted the transfer of an alkyl or vinyl group with good yields, though with partial isomerisation of the double bond (5-50%). Diallylcuprate is the only reagent that affords allylation product ; however **2p** was obtained with a *Z*/*E* ratio=96/4 .

Concerning the access to (*E*)-3-methylalk-2-enoic acids the following procedure was chosen. The starting iodo acid **3** reacts under similar conditions with different organometallic reagents affording 3-methylenalkanoic acids which upon treatment with sodium hydride (2.1 eq.) in THF[13], give the expected acids with a clean *E* stereocontrol.



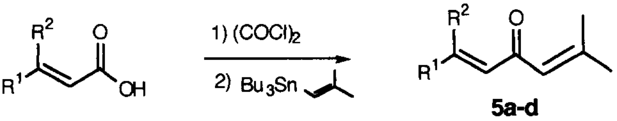
3

4a - d

E/Z > 95/5

4a R = Et (87%), **4b** R =Ph (97%), **4c** R = vinyl (80%),
4d R = 2-methylbut-2-enyl (81%)

Taking into account the numerous applications of compounds **2** and **4**, we decided to apply our strategy to the synthesis of very simple *E* or *Z* terpenoic structures. Acids **2b**, **2k**, **4a** and **4c**, when treated with oxalyl chloride afforded the corresponding acyl chlorides which are acylated with 1-tributylstannyl-2-methylpropene under palladium catalysis[14] giving (*Z*) and (*E*)-ocimenones (**5b** and **5d**) and (*Z*) and (*E*)-pseudo-tagetones (**5a** and **5c**) (previously obtained by pyrolysis of verbenol[15]).



5a-d

	[Pd^{II}] 5%, solvent		Yield (%)	E/Z
2b	$PdCl_2(MeCN)_2$, DMF	**5a**	68	0/100
2k	$BnPdCl(PPh_3)_2$, $CHCl_3$	**5b**	65	15/85 [16]
4a	$PdCl_2(MeCN)_2$, DMF	**5c**	70	100/0
4c	$PdCl_2(MeCN)_2$, DMF	**5d**	63	100/0

In summary, we have investigated a new general route of access to both (*Z*) and (*E*)-3-methylalk-2-enoic acids. Studies to modify the nature of the substituent in position 3 and to investigate the synthetic properties of the various acids **2** and **4** are currently underway.

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11. Typical procedure: preparation of compound **2g**. To an etheral solution of benzylmagnesium bromide, made from 0.729 g (3x10^{-2} at-g) of magnesium and 5.13 g (32 mmol) of benzyl bromide in 25 mL of anhydrous ether, 7 g (31 mmol) of zinc bromide are added. The solution is stirred overnight at room temperature. Then, 20 mL of DMF are added to the newly prepared organozinc until an homogeneous solution is obtained. Next, 1.27 g (10 mmol) of **1** diluted into 5 mL of DMF is added dropwise. At the end of the addition, 0.15 mg (0.5 mmol) of dichlorobis(acetonitrile)palladium(II) is added. The mixture is stirred for 12 h at 25 °C then hydrolysed with a cold solution of 1N hydrochloric acid and washed with a saturated solution of ammonium chloride. The etheral phase is treated at 0 °C with a solution of 1N sodium hydroxide. The aqueous solution obtained is acidified and extracted 3 times with ether. After usual work-up **2g** (2 g) is purified using column chromatography on silica gel (petroleum ether/ether 70/30 as an eluent).
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16. The use of $PdCl_2(PPh_3)_2$ or $PdCl_2(MeCN)_2$ in DMF leads to **5b** with a larger proportion of isomerisation products (30-50%)

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