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NEW AND EFFICIENT PROCEDURES FOR THE SYNTHESIS OF STEREODEFINED 2-(HETERO)ARYL AND 2-METHYL SUBSTITUTED ALKYL 2-ALKENOATES HAVING VERY HIGH STEREOISOMERIC PURITY[1]

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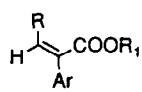
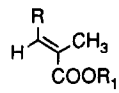
Abstract: Stereodefined 2-(hetero)aryl and 2-methyl substituted alkyl 2-alkenoates of general formula **1** and **2** have been synthesized with a high degree of stereoselectivity as well as in good overall yields starting from alkyl 2-alkynoates, **4**.

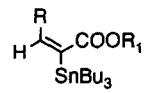
Recently, in the course of our continuing investigation into the synthetic utilities of stereodefined 1-alkenylstannanes bearing a functional substituent in the 1-position[2], we developed methods which allow to prepare efficiently and in very high stereoisomeric purity stereodefined 2-(hetero)aryl substituted alkyl 2-alkenoates, **1**, as well as alkyl (E)-2-methyl-2-alkenoates, (E)-**2**, and involve the use of regio- and stereoisomerically pure alkyl (E)-2-tributylstannyl-2-alkenoates , (E)-**3**, as precursors. These methods appear of particular interest since *i)* stereoisomerically pure esters **1** and (E)-**2** are valuable synthetic intermediates and *ii)* compounds **1** cannot be prepared using classical olefination methods such as the Horner-Emmons reaction or its modifications[3]. On the other hand, compounds (E)-**2** synthesized using this last reaction often contain not negligible amounts of the corresponding Z stereoisomers[3].



1



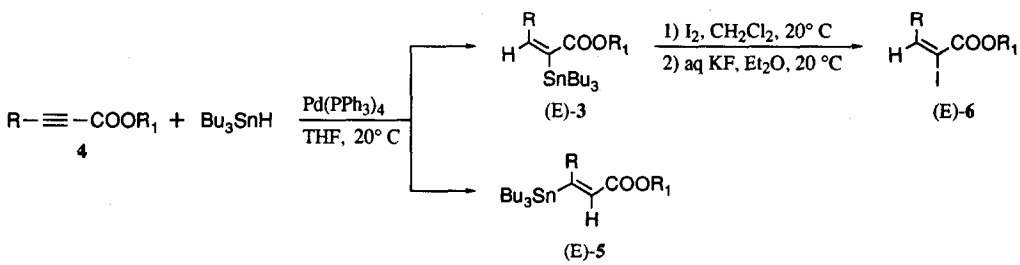
(E)-**2**



(E)-**3**

The synthesis of compounds (E)-**3**[4] was carried out by reaction between alkyl 2-alkynoates , **4**, and 1 equiv of Bu_3SnH in THF solution at 20 °C, in the presence of 2 mol% of $Pd(PPh_3)_4$ (Scheme 1) (Table 1)[5].

Scheme 1



This reaction also produced small amounts (2 - 8 %) of alkyl (E)-3-tributylstannyl-2-alkenoates, (E)-**5**,

which were separated from esters (E)-**3** by MPLC on silica gel[7]. Then, treatment of compounds (E)-**3** with an equimolar amount of iodine in CH_2Cl_2 solution at 20 °C gave stereospecifically the corresponding alkyl (E)-2-iodo-2-alkenoates, (E)-**6**, in 70 - 95 % yield (Scheme 1) (Table 1)[8].

Table 1

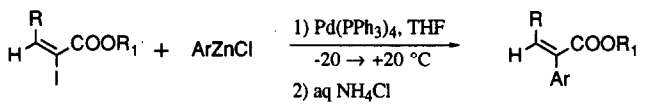
Compounds (E)-**3** and (E)-**6** Prepared

Products			Isolated yield (%)	Stereoisom. purity (%)	$[\alpha]_D^{25}$
	R	R_1			
(E)-**3a**	*n*-C_5H_{11}	CH_3	85	>98	—
(E)-**3b**	C_6H_5	C_2H_5	71	99	—
(S)(E)-**3c**[a)]	$C_2H_5CH(CH_3)$	C_2H_5	93	>99	+23.63 (c = 2.535, *n*-C_7H_{16})
(E)-**3d**	*t*-$BuMe_2SiOCH_2$	C_2H_5	84	99	—
(E)-**6a**	C_6H_5	CH_3	70	≥99	—
(E)-**6b**	*n*-C_5H_{11}	C_2H_5	89	>99	—
(S)(E)-**6c**	$C_2H_5CH(CH_3)$	C_2H_5	87	>99	+41.31 (c = 2.520, *n*-C_6H_{14})
(E)-**6d**	*t*-$BuMe_2SiOCH_2$	C_2H_5	95	>99	—

a) See Ref. 6

Finally, the iodo derivatives (E)-**6** were converted efficiently and stereospecifically to the desired 2-(hetero)aryl substituted esters of general formula **1** by reaction with THF solutions of 1.2 equiv of (hetero)arylzinc chlorides, in the presence of 10 mol% of $Pd(PPh_3)_4$ (Scheme 2).

Scheme 2

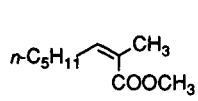


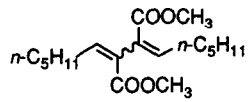
(E)-**6** **1**

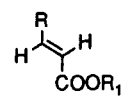
This procedure allowed the preparation of methyl (Z)-2-phenyl-2-octenoate, (Z)-**1a** (R = *n*-C_5H_{11}; Ar = Ph), ethyl (Z)-2,3-diphenyl-2-propenoate, (Z)-**1b** (R = Ph; Ar = Ph), and ethyl (E)-3-phenyl-2-thienyl-2-propenoate, (E)-**1c** (R = Ph; Ar = 2-thienyl) having 98-99 % stereoisomeric purity in 76, 82 and 73 % isolated yield, respectively.

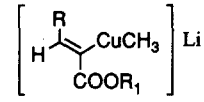
Interestingly, compounds **1** could not be obtained by direct cross-coupling reactions between compounds (E)-**3** and (hetero)aryl iodides, in the presence of catalytic amounts of palladium catalysts such as $(PPh_3)_2PdCl_2$ or $Pd(PPh_3)_4$.

On the basis of the successful results obtained in the synthesis of esters **1** starting from compounds (E)-**6**, it was also attempted to use a similar procedure for the synthesis of alkyl (Z)-2-methyl-2-alkenoates, (Z)-**2**. Thus, compound (E)-**6a** was reacted with a THF solution of 1.1 equiv of CH_3ZnCl, in the presence of 10 mol% of $Pd(PPh_3)_4$. This reaction, which was carried out for 4 h at -30 °C, 15 h at 20 °C and finally under reflux for 4 h, afforded compound (Z)-**2a** having 81 % stereoisomeric purity in 43 % yield. From the crude reaction mixture it was also possible to isolate 7,8-di(carbomethoxy)-6,8-tetradecadiene, **7**, in 19 % yield. A worse result, as regards either the yield or the stereoisomeric purity of (Z)-**2a**, was obtained when $PdCl_2$(dppf) was used as catalyst.


(Z)-2a

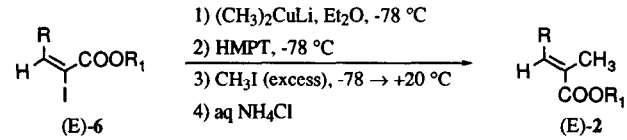

7


(E)-8


(Z)-9

On the other hand, it was surprisingly found that, on treatment of compounds (E)-**6** with a fourfold excess of $(CH_3)_2CuLi$ in Et_2O at -78 °C for 4 h, followed by addition of HMPT and a molar excess of methyl iodide, alkyl (E)-2-methyl-2-alkenoates, (E)-**2**, having very high stereoisomeric purity, were obtained in good yields[9] (Scheme 3).

Scheme 3

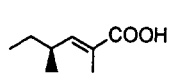


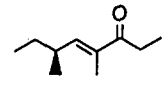
(E)-6 (E)-2

Compounds (E)-2			Isolated yield (%)	Stereoisom. purity (%)	$[\alpha]_D^{25}$
	R	R_1			
(E)-**2a**	n-C_5H_{11}	CH_3	96	>98	—
(E)-**2b**	C_6H_5	C_2H_5	87	>99	—
(S)(E)-**2c**	$C_2H_5CH(CH_3)$	C_2H_5	81	>99	+41.09 (c = 3.395, CH_3OH)

It was also observed that alkyl 2-alkenoates, (E)-**8**, having stereoisomeric purity higher than 99 %, were produced in very high yield by hydrolysis of the reaction mixtures obtained by treatment of compounds (E)-**6** with Et_2O solutions of 4 equiv of $(CH_3)_2CuLi$ at -78 °C for 4 h. Thus, these results suggested that the synthesis of compounds (E)-**2** involved the formation of the β-substituted (α-carbalkoxyvinyl)cuprate reagents having Z configuration, (Z)-**9**, a class of compounds for which some reactivity studies with various electrophiles have been already performed[10].

As shown in Scheme 3, this new and efficient procedure for preparing esters (E)-**2**, which involved a configurational inversion, was also employed to prepare compound (S)(E)-**2c**, $[\alpha]_D^{25}$ + 41.09 (c = 3.395, CH_3OH). Saponification of this ester, followed by acidification, allowed to obtain quantitatively (S)(E)-2,4-dimethyl-2-hexenoic acid, (S)(E)-**10**, $[\alpha]_D^{24}$ + 35.84 (c = 2.715, C_6H_6) [lit[11] $[\alpha]_D^{24}$ + 34.6 (c = 2.65, C_6H_6)], which is a useful precursor to (S)(E)-4,6-dimethyl-4-octen-3-one (manicone)[12], (S)(E)-**11**, an alarm pheromone component of ants in the genus *Manica*[13]. It may also be noted that compound **11** of unknown configuration represents a caste-specific substance present in the mandibular glands of male carpenter ants in the genus *Camponotus*[14].


(S)(E)-10


(S)(E)-11

Our studies are now directed toward the application of the above mentioned procedures for preparing stereodefined esters **1** and (E)-**2** to the synthesis of other stereodefined biologically active compounds.

REFERENCES AND NOTES

1. This work was supported by the Consiglio Nazionale delle Ricerche (CNR, Roma), Progetto Finalizzato *Chimica Fine* and by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).
2. *a)* Rossi, R.; Carpita, A.; Bellina, F.; De Santis, M. *Gazz. Chim. Ital.* **1991**, *121*, 261; *b)* Rossi, R.; Carpita, A.; Messeri, T. *Synth. Commun.* **1991**, *21*, 1875; *c)* Rossi, R.; Carpita, A.; Messeri, T. *Synth. Commun.* **1992**, *22*, 603.
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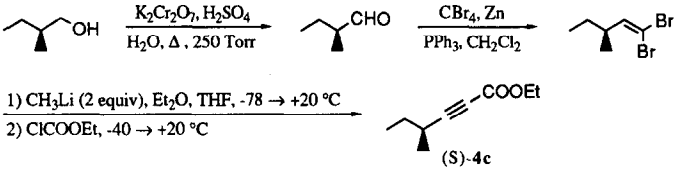
4. All new compounds were characterized by elemental analysis, ^1H NMR spectroscopy and mass spectrometry.
5. For Pd-catalyzed hydrostannation reactions of alkyl alkynoates, see: *a)* Cochran, J.C.; Bronk, B.S.; Terrence, K.M.; Phillips, H.K. *Tetrahedron Lett.* **1990**, *31*, 6621; *b)* Zhang, H.X.; Guibé, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 619.
6. Ethyl (S)-4-methyl-2-hexynoate, (S)-**4c**, $[\alpha]_D^{25}$ + 36.24 (c = 5.905, *n*-C_7H_{11}), which was used for preparing compound (S)(E)-**3c**, was synthesized starting from (S)-2-methyl-1-butanol having e.e. higher than 99.5 % by the following reaction sequence:



(S)-**4c**

7. Compounds (E)-**3** underwent partial stereomutation during distillation under reduced pressure.
8. For bromodestannylation of some trimethylstannyl-substituted stereodefined α,β-unsaturated esters, see: Cochran, J.C.; Terrence, K.M.; Phillips, H.K. *Organometallics* **1991**, *10*, 2411.
9. A typical procedure for the synthesis of compounds (E)-**2** is as follows: $(CH_3)_2CuLi$ (92.5 mmol) was prepared in Et_2O solution at - 78 °C according to the standard procedure. A solution of an alkyl (E)-2-iodo-2-alkenoate, (E)-**6** (26.49 mmol) in Et_2O (30 ml) was added and the reaction mixture was stirred for 4.5 h at -78 °C. GLC/MS analysis of a sample of this mixture, which was hydrolyzed with aq NH_4Cl, showed the presence of a new compound, which was identified as an alkyl (E)-2-alkenoate, (E)-**8**, as well as of a small amount of an ester, subsequently identified as (E)-**2**. HMPT (70 ml) and CH_3I (250 mmol) were sequentially added to the reaction mixture maintained at -78 °C and the resulting mixture was stirred for 0.5 h at -78 °C and then slowly warmed up to 20 °C. After stirring at this temperature for 14 h it was poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered, washed with an aqueous NH_4Cl solution, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel to give the desired compound (E)-**2**.
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