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Highly Regioselective Palladium-Mediated Synthesis of Stereoisomerically Pure (*Z*)- and (*E*)-Alkyl 2-Bromo-3-(hetero)arylpropenoates[1]

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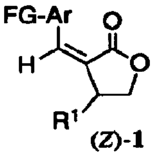
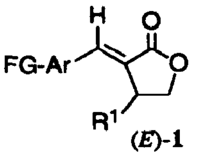
Abstract: Stereoisomerically pure (*Z*)- and (*E*)-alkyl 2-bromo-3-(hetero)arylpropenoates, (*Z*)- and (*E*)-**2**, have been efficiently and selectively prepared by Pd(0)-mediated cross-coupling reaction between (hetero)arylzinc halides, **5**, and easily available (*Z*)- and (*E*)-alkyl 2,3-dibromopropenoates, (*Z*)- and (*E*)-**4**, respectively. Compounds (*Z*)- and (*E*)-**2** serve as useful precursors to stereoisomerically pure trisubstituted (*E*)- and (*Z*)-α,β-unsaturated esters, respectively.

In the context of recent work on the synthesis of stereoisomerically pure (*Z*)- and (*E*)-α-arylidene-γ-butyrolactones, (*Z*)- and (*E*)-**1**[2], we required pure 3-(hetero)aryl substituted (*Z*)- and (*E*)-alkyl 2-bromopropenoates, (*Z*)- and (*E*)-**2**, in considerable amounts.



(*Z*)-**1**



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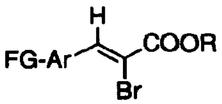
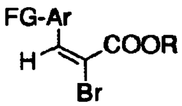


(*Z*)-**2**



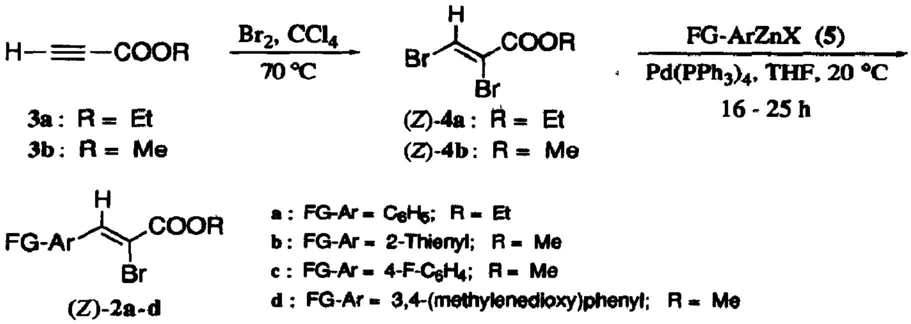
(*E*)-**2**

(FG = H or a functional group)

Surprisingly, we found that these α-bromo-α,β-unsaturated esters have rarely been used in the literature[3] and apparently no systematic investigation exists on their synthesis[4]. Thus, we developed simple methods which allowed us to prepare under mild conditions, in high overall yields and multigram quantities, stereoisomerically pure compounds (*Z*)- and (*E*)-**2** starting from commercially available materials. In this communication we describe these methods as well as the stereospecific and efficient conversion of compounds (*Z*)- and (*E*)-**2** to stereoisomerically pure trisubstituted (*E*)- and (*Z*)-α,β-unsaturated esters, respectively.

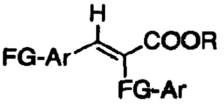
Compounds (*Z*)-**2** were synthetized according to the reaction sequence depicted in Scheme 1. In particular, alkyl propynoates, **3**, were reacted with 1.1 equiv. of bromine in CCl_4 at 70 °C for 1.5 h to afford pure (*Z*)-alkyl 2,3-dibromopropenoates[5], (*Z*)-**4**, in 75 - 83 % isolated yield after purification of the crude reaction mixtures by chromatography on silica gel. These compounds were then treated with 1.2 equiv. of (hetero)arylzinc halides, **5**, in THF solution at 20 °C for 16 - 25 h, in the presence of 5 mol % of $Pd(PPh_3)_4$, to give stereospecifically and in 77 - 85 % yield compounds (*Z*)-**2** not contaminated by the corresponding

(*E*)-alkyl 2,3-di-(hetero)arylpropenoates, **6**, or (*E*)-alkyl 3-bromo-2-(hetero)arylpropenoates, **7**.



a : FG-Ar = C_6H_5; R = Et
b : FG-Ar = 2-Thienyl; R = Me
c : FG-Ar = 4-F-C_6H_4; R = Me
d : FG-Ar = 3,4-(methylenedioxy)phenyl; R = Me

Scheme 1



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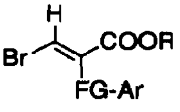
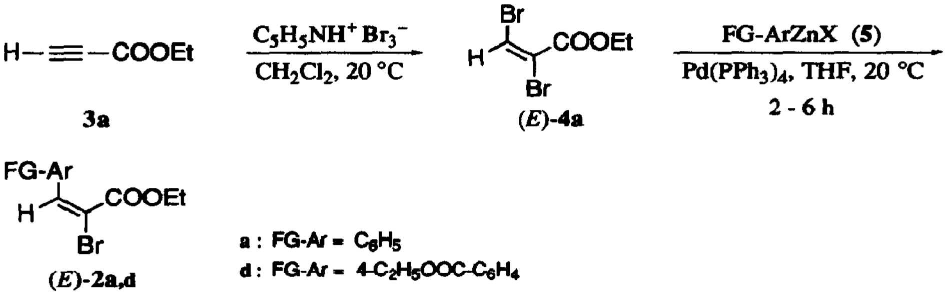


7

On the other hand, compounds (*E*)-**2** were synthetized using the reaction sequence illustrated in Scheme 2. Thus, ethyl propynoate, **3a**, was treated with a slurry of 1.3 equiv of pyridinium bromide perbromide in CH_2Cl_2 at 20 °C for 40 h to give pure (*E*)-ethyl 2,3-dibromopropenoate, (*E*)-**4a**, in 81 % isolated yield[5a]. The cross-coupling reaction between (*E*)-**4a** and 1.2 equiv of **5** in THF at 20 °C for 2 - 6 h, in the presence of 5 mol % of $Pd(PPh_3)_4$, gave selectively and stereospecifically the desired esters (*E*)-**2** in 52 - 79 % yield. The results of some Pd(0)-mediated reactions between compounds **5** and (*Z*)- or (*E*)-**4** are summarized in the Table.

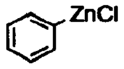
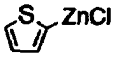
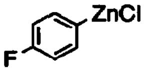
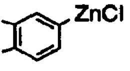
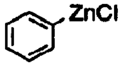
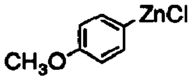
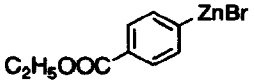


a : FG-Ar = C_6H_5
d : FG-Ar = 4-C_2H_5OOC-C_6H_4

Scheme 2

Interestingly, the stereochemical outcome of these reactions was different from that of the alkynylation of (*Z*)- and (*E*)-**4a** under the Sonogashira conditions[5a]. In fact, this reaction was stereoconvergent and produced (*Z*)-coupling products[5a].

Table. Synthesis of (*Z*)- and (*E*)-Alkyl 2-Bromo-3-(hetero)arylpropenoates, (*Z*)- and (*E*)-**2**, by Pd-Mediated Reaction between (Hetero)Arylzinc Halides, **5**, and (*Z*)- or (*E*)-**4** [a].

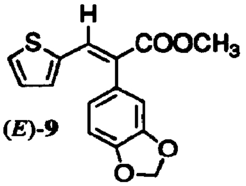
Entry	Alkyl 2,3-dibromo-propenoate, 4	Organozinc halide, 5 [b]	Reaction time (h)	Product 2	Isolated yield (%)
1	(*Z*)-**4a**	 (**5a**)	25.0	(*Z*)-**2a**	77
2	(*Z*)-**4b**	 (**5b**)	16.0	(*Z*)-**2b**	85
3	(*Z*)-**4b**	 (**5c**)	23.0	(*Z*)-**2c**	84
4	(*Z*)-**4b**	 (**5d**)	16.0	(*Z*)-**2d**	84
5	(*E*)-**4a**	 (**5a**)	2.0	(*E*)-**2a**	79
6	(*E*)-**4a**	 (**5e**)	2.5	(*E*)-**2e**	68
7	(*E*)-**4a**	 (**5f**)	6.0	(*E*)-**2f**	52

[a] These reactions were performed by treatment of a stirred slurry of compound **5** in THF cooled to -20 °C with 5 mol % of $Pd(PPh_3)_4$ followed by fast addition of compound (*Z*)- or (*E*)-**4**. The resulting mixtures were stirred at -20 °C for 15 min, at 0 °C for 15 min and then at 20 °C for the period of time reported in Table. [b] Compounds **5a**-**5e**, which were used in a 0.3 M THF solution, were prepared by reaction of the corresponding (hetero)aryl magnesium bromides with a slurry of $ZnCl_2$ in THF at 0 °C. Compound **5f**, which was used as 0.11 M THF solution, was prepared from ethyl 4-bromobenzoate according to the procedure reported in Ref. 6

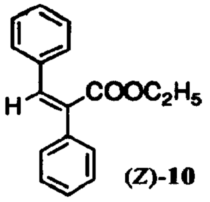
It is also worth noting that compounds (*Z*)- and (*E*)-**2** proved to be able to undergo stereospecific Pd-mediated cross-coupling reactions either with compounds **5** or vinyltributylstannane, **8**. For example, treatment of (*Z*)-**2b** with 1.2 equiv of 3,4-(methylenedioxy)phenylzinc chloride, **5d**, in THF at 20 °C for 16 h and at 50 °C for 7.5 h, in the presence of 5 mol % of $Pd(PPh_3)_4$, gave pure (*E*)-**9** in 73 % yield. On the other hand, reaction between (*E*)-**2a** and phenylzinc chloride, **5a**, in THF at 20° C for 3 h, in the presence of 5 mol % of $Pd(PPh_3)_4$, afforded stereoisomerically pure (*Z*)-**10** in 88 % isolated yield. Moreover, treatment of (*Z*)-**2a** with 1.2 equiv of **8** in N-methylpyrrolidinone, in the presence of 5 mol % of $PdCl_2(PhCN)_2$, 10 mol % of CuI and 10 mol % of $AsPh_3$ for 46 h at 20 °C, gave pure (*E*)-**11** in 85 % isolated yield[7,8].

Thus, the coupling reactions involving compounds (*Z*)- or (*E*)-**2**, even though not optimized, allowed to prepare in satisfactory yields multigram quantities of stereoisomerically pure trisubstituted α,β-unsaturated esters[9], which include (*Z*)- and (*E*)-alkyl 2,3-diarylpropenoates[10]. On this subject it seems useful to mention that these last compounds cannot be synthetized in pure form by the Horner-Wadsworth-Emmons reaction[11].

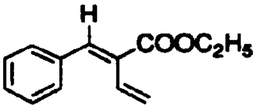
8



(*E*)-**9**



(*Z*)-**10**



(*E*)-**11**

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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).
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