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α-Methylene-β-amino Ketone Derivatives from β-Ketoallylsilanes

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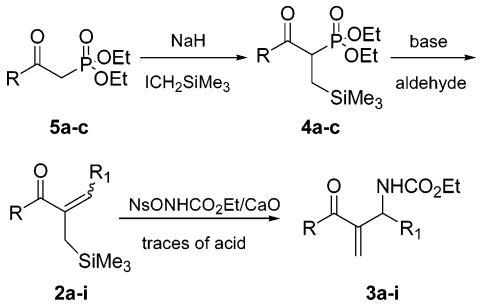
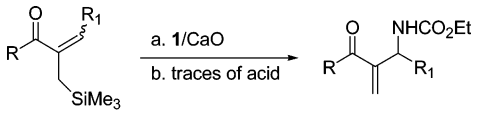


β-Ketoallylsilanes are synthesized by the Horner−Emmons reaction starting from novel silylated ketophosphonates and various aldehydes. The reactions of β-ketoallylsilanes with $NsONHCO_2Et$ and CaO produce α-methylene-*N*-(ethoxycarbonyl)-β-amino ketones through the ring opening of the intermediate aziridine, which is favored by the presence of the trimethylsilyl group. With chiral β-ketoallylsilanes we obtained a stereoselective amination reaction with a 90% diastereomeric excess. α-Methylene-*N*-(ethoxycarbonyl)-β-amino ketones are isolated in 39−60% yields and characterized.

β-Amino carbonyl moieties are found as structural subunits of natural and synthetic products such as alkaloids and poliketides[1] and can be used in the synthesis of 1,3-amino alcohols and β-amino acids.[2] Some β-amino ketone derivatives such as α-alkyl-β-dimethylaminopropiophenones are reported to have analgesic and bacteriostatic properties.[3] In addition, unsaturated β-amino ketones are interesting products, i.e., N-substituted α-(aminomethyl)acrylophenones are reported to be weak inhibitors of colchicine binding and markedly decrease the serum cholesterol, triglyceride, and phospholipid levels of rats.[4] Therefore, the development of methods for the preparation of these compounds is an attractive objective in chemical synthesis. In the recent literature, some α,β-unsaturated β-amino ketones were synthesized by the aza Baylis−Hillman reaction of *N*-sulfonated imines with methyl vinyl ketone in the presence of catalytic amounts of Lewis bases such as triphenylphosphine or DABCO.[5]

SCHEME 1. Amination Reaction of 2



We propose here a new approach to α,β-unsaturated β-amino ketone derivatives, based on our previous results, obtained in the amination reaction of electron-poor olefins, using ethyl *N*-{[(4-nitrobenzene)sulfonyl]oxy}carbamate ($NsONHCO_2Et$) **1**. In recent years, we have reported that the reaction of either β-silylated α,β-unsaturated carboxylates[6a] or phosponates[6b] with **1** and solid CaO gives rise to *N*-(ethoxycarbonyl)-β-amino-α-methylene esters, through the formation of an intermediate aziridine and its subsequent ring opening. On these bases, we felt that the extension of the above amination procedure to other functionalized allylsilanes, as compounds **2,** could result in a new approach to *N*-(ethoxycarbonyl)-β-amino-α-methylene ketones such as **3** (Scheme 1).

Allylsilanes have emerged as useful intermediates in organic synthesis. They are extensively used in carbonyl addition reactions[7] and coupling reactions[8] and have been recently employed as key intermediates for the total synthesis of natural products.[9] In particular, allylsilanes bearing a carbonyl group at the β-position, as in **2**, are interesting because they can react either with nucleophiles[10] or with electrophiles.[11] Known literature procedures for their synthesis, catalyzed by transition-metal complexes, are those reported by Kang and co-workers, who proposed a methodology based on the palladium-catalyzed cross-coupling of 2-trimethylstannyl-3-trimethylsilylpropene with organic halides[12] or the new phosphine-free palladium-catalyzed three-component assembly of allenes, acyl chlorides, and hexamethyldisilane, recently developed by Cheng's group. This procedure led to the synthesis of some new β-ketoallylsilanes in good yields.[13] Another efficient palladium-catalyzed

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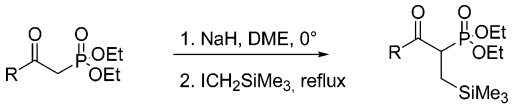
TABLE 1. Synthesis of Substrates 2: Conditions and Yields

Entry	R	R_1	Method[a]	**2** total isolated yield (%)	*Z*/*E*
a	Ph	H	A	85%	-
b	Me	H	A	70%	-
c	Et	H	A	75%	-
d	Me	Ph	B	30%	7/1
e	Et	Ph	B	35%	7/1
f	Me	Me	B	38%	7/1
g	Et	Me	B	35%	7/1
h	Me		B	44%	10/1
i	Et		B	40%	10/1

[a] Method A: 50% NaOH/CH_2Cl_2/37% H_2CO. Method B: NaH/DME/aldehyde/anhydrous conditions.

SCHEME 2. Synthesis of Novel Silylated *β*-Ketophosphonates 4



synthesis has recently been reported by Kabalka and consists of the reaction of the Baylis−Hillman acetate adduct with hexamethyldisilane.[14]

In our case, *β*-ketoallylsilanes **2** were prepared by the Horner−Emmons reaction between aldehydes and novel silylated *β*-ketophosphonates **4**. These last compounds were synthesized in turn by alkylation of commercially available *β*-ketophosphonates **5** with iodomethyltrimethylsilane in the presence of NaH, according to the procedure reported for the alkylation of the triethylphosphonoacetate (see Scheme 2).[15]

After chromatography on silica gel, products **4a**−**c** were isolated in a yields ranging from 40 to 45% (see the Experimental Section for full spectroscopic characterization). Byproducts **6** and **7** were also found (Figure 1).

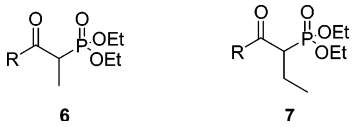


FIGURE 1. Byproducts of the synthesis of **4**

The best reaction conditions were found using DME as solvent and 7−8 h of heating. All attempts to improve the yields of alkylation reaction, e.g., by using THF or toluene as solvent, failed; in the first case, the reflux temperature was too low to promote the reaction, and in the second one, higher temperature and long reaction times led to extensive decomposition.

With the novel silylated ketophosphonates **4** in hand, we proceeded to prepare the allylsilanes **2** through the Horner−Emmons reaction (Table 1). For substrates **2a**−**c,** the Horner−Emmons reaction was carried out in a two-phase system using 50% aqueous NaOH as base in CH_2Cl_2 and a 37% formaldehyde aqueous solution (method A). For the substrates **2d**−**g**, we needed NaH in dry DME at room temperature (method B) to obtain the desired allylsilanes (Scheme 3). In these last cases, we obtained the *Z* isomer as the main product and only a very small amount of the *E* isomer. The *Z* isomers were separated and purified by chromatography on silica gel. Spectroscopic data confirm their structure.

Starting from the good results obtained in the synthesis of *β*-ketoallylsilanes **2a**−**g**, we focused our interest on chiral substrates. In particular, using the D-glyceraldehyde acetonide, we prepared the (*S*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-trimethylsilanylmethyl-3-alken-2-ones **2h** and **2i** (Table 1) using the hypothesis that the presence of a resident chiral *γ*-carbon in the acetonide structure should allow the stereoselective introduction of the aziridine ring in the reaction with $NsONHCO_2$-Et, providing a new route to optically active *β*-amino ketone derivatives after ring opening and removal of the trimethylsilyl group.

The amination reactions on substrates **2** (*Z* isomers) were carried out in CH_2Cl_2 by adding $NsONHCO_2Et$ and CaO portionwise, according to the reported procedure,[6] reaching the molar ratio shown in Table 2. After addition of 3−6 equiv of reagents and short reaction times, we observed the complete disappearance of the starting material and the formation of the intermediate *N*-(ethoxycarbonyl)aziridine, detected in the crude reaction mixture by ^{1}H NMR.

In the presence of traces of acid, removal of the trimethylsilyl group occurred and the corresponding unsaturated *β*-amino ketone derivatives **3** were isolated. In all cases, the trimethylsilyl group plays a key role in driving and facilitating the aziridine ring opening (Scheme 4).

All compounds **3a**−**i** were purified by chromatography on silica gel, and their structure was confirmed by ^{1}H NMR and ^{13}C NMR analysis.

The amination reaction performed on the chiral substrates **2h** and **2i** (mixture of *Z*/*E* isomers = 10/1) was highly diastereoselective; in fact, we obtained one diastereomer with a 90% of diastereomeric excess in both reactions. The main diastereomer was easily isolated by chromatography on silica

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SCHEME 3. Synthesis of Allylsilanes 2

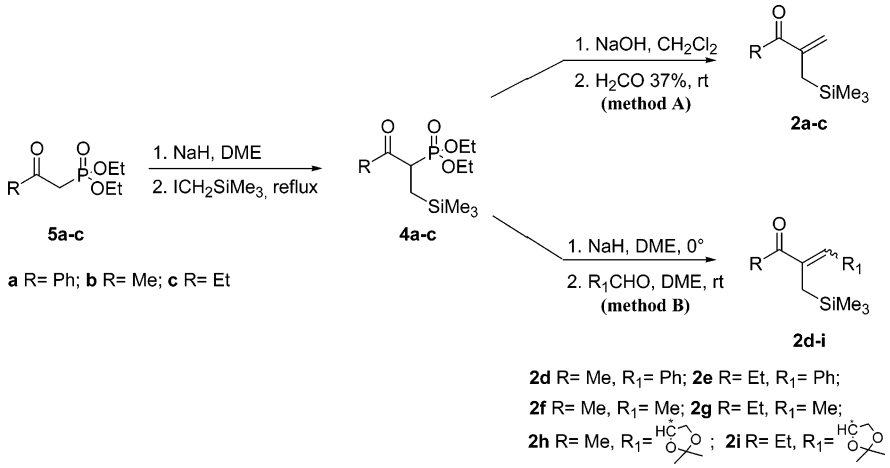
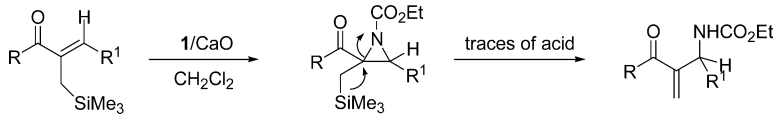


TABLE 2. Synthesis of *β*-Amino Ketone Derivatives 3: Conditions and Yields

Entry	R	R_1	**2**/NsONHCO$_2$Et/CaO	**3** isolated yields (%)	Diastereomeric ratio
a	Ph	H	1:3.5:3.5	39%	-
b	Me	H	1:3.5:3.5	31%	-
c	Et	H	1:3.5:3.5	34%	-
d	Me	Ph	1:6:6	41%	-
e	Et	Ph	1:6:6	30%	-
f	Me	Me	1:4:4	34%	-
g	Et	Me	1:4:4	44%	-
h	Me		1:5.5:5.5	60%	95/5
i	Et		1 :5.5 :5.5	45%	95/5

SCHEME 4. Synthesis of *β*-Amino Ketone Derivatives 3



gel with high purity, **3h**, $[\alpha]^{20}_D = +10.7$ (*c* 3,$CHCl_3$); **3i**, $[\alpha]^{20}_D = +7.1$ (*c* 3.6,$CHCl_3$). As far as the stereoselectivity of the reaction is concerned, in the hypothesis that the amination reaction occurs by an aza Michael mechanism,[16] we believe that products are formed preferentially through a *β-re* attack on compounds **2h**−**i** according to that reported by other authors for similar chiral *γ*,*δ*-dialkoxy unsaturated ketones.[17]

Removal of the isopropylidene protecting group in **3h** and **3i** could allow us to get precursors of unsaturated optically active amino derivatives as amino alcohols or 3-branched-amino sugars.[17] Thus, we are encouraged to continue our investigation in this field.

In conclusion, in this work we propose a new simple synthetic route for the preparation of α-methylene-*β*-amino ketone derivatives by the amination reaction of *β*-ketoallylsilanes obtained in turn from readily available *β*-ketophosphonates and aldehydes. Using an optically active aldehyde such as D-glyceraldehyde acetonide, this route allowed us to obtain new chiral *β*-ketoallylsilanes and, after amination reaction, optically active *β*-amino ketone derivatives with a very good diastereomeric excess.

Experimental Section

General Procedure for the Synthesis of Silylated Ketophosphonates 4a−c. (2-Oxo-1-trimethylsilanylmethylpropyl)phosphonic Acid Diethyl Ester (4b). To 60% NaH (495 mg, 11.34 mmol; suspension in mineral oil) in anhydrous DME (12 mL) was added ketophosphonate **5b** (2 g, 10.30 mmol) in anhydrous DME (6 mL) dropwise, under argon at 0 °C. After 1 h at 0 °C and 1 h at room temperature, a solution of iodomethyltrimethylsilane (8.8

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g, 41.20 mmol) in anhydrous DME (21 mL) was added, and the resulting mixture was heated to 70 °C. After being stirred for 7−8 h, the mixture was poured into saturated ammonium chloride solution, and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent evaporation, the crude was purified by chromatography on silica gel (hexane/acetone = 7/3) to obtain the product **4b** as a yellowish oil (1 g, 4 mmol, 40% yield): IR ($CHCl_3$) 1719, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ −0.07 (s, 9H), 0.83−0.99 (m, 1H), 1.20−1.38 (m, 7H), 2.29 (s, 3H), 3.14 (ddd, J = 24.9 Hz, J = 11.7 Hz, J = 2.2 Hz, 1H), 3.98−4.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −1.6, 12.3 (d, J_{CCP} = 6.1 Hz), 16.2 (d, J_{CCOP} = 7.6 Hz), 30.7, 49.0 (d, J_{CP} = 122.1 Hz), 62.5 (d, J_{COP} = 3.0 Hz), 62.7 (d, J_{COP} = 3.0 Hz), 203.7; GC−MS *m*/*z* 280 [M^+] (5.7%), 165 (100); HRMS calcd for $C_{11}H_{25}NaO_4PSi$ *m*/*z* 303.1157, found *m*/*z* 303.1150.

General Procedure for the Synthesis of β-Ketoallylsilanes 2a−c (Method A). 1-Phenyl-2-trimethylsilanylmethylpropenone (2a).[12] To a stirred solution of the substrate **4a** (300 mg, 0.88 mmol) in dichloromethane (1 mL) was added dropwise a 50% (w/w) sodium hydroxide aqueous solution (1.05 mL). After 1 h at room temperature, a 37% (w/w) formaldehyde aqueous solution (73 mg, 0.90 mmol) was added dropwise, and the resulting heterogeneous mixture was stirred for 6 h. Then the mixture was extracted with dichloromethane, and the organic phase was dried over Na_2SO_4 and evaporated under vacuum. The product **2a** was obtained pure as a yellow oil (163 mg, 0.75 mmol, 85% yield): IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 9H), 2.03 (s, 2H), 5.50 (s, 1H), 5.72 (s, 1H), 7.39−7.75 (m, 5H); GC−MS *m*/*z* 218 [M^+] (14.2), 73 (100).

General Procedure for the Synthesis of β-Ketoallylsilanes 2d−i (Method B). 4-Phenyl-3-trimethylsilanylmethylbut-3-en-2-one (2e). To 60% NaH (81 mg, 1.86 mmol; suspension in mineral oil) in anhydrous DME (1.5 mL) was added the substrate **4c** (390 mg, 1.33 mmol) in anhydrous DME (0.3 mL) dropwise, under argon at 0 °C. After 1 h at 0 °C and 1 h at room temperature, a solution of benzaldehyde (310 mg, 2.93 mmol) in anhydrous DME (0.8 mL) was added at 0 °C, and the resulting mixture was stirred at room temperature. After being stirred for 10 h, the mixture was poured into saturated ammonium chloride solution, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4. After solvent evaporation, the crude was purified by chromatography on silica gel (hexane/diethyl ether = 98/2) to obtain the pure *Z* isomer (98 mg, 0.40 mmol) as a yellow oil, and a mixture of *E*/*Z* isomers (16 mg, 0.06 mmol) in a ratio of 4/1 (35% total yield). Spectral data of **2e (*Z*)**: IR ($CHCl_3$) 1672, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ −0.02 (s, 9H), 1.19 (t, J = 7.3 Hz, 3H), 2.18 (s, 2H), 2.86 (q, J = 7.3 Hz, 2H), 7.28−7.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −1.9, 8.4, 15.7, 29.3, 126.6, 127.3, 127.9, 133.4, 135.5, 140.0, 201.9; GC−MS *m*/*z* 246 [M^+] (18.8), 73 (100); HRMS calcd for $C_{15}H_{22}NaOSi$ *m*/*z* 269.1338, found *m*/*z* 269.1333.

General Procedure for the Synthesis of α-Methylene-β-amino Ketone Derivatives 3a−i. (2-Benzoylallyl)carbamic Acid Ethyl Ester (3a). To a stirred solution of the substrate **2a** (151 mg, 0.69 mmol) in CH_2Cl_2 (0.2 mL) were added $NsONHCO_2Et$ (201 mg, 0.69 mmol) and CaO (39 mg, 0.69 mmol) every hour, reaching the molar ratio substrate/$NsONHCO_2Et$/CaO up to 1:3.5:3.5. Because the reaction was exothermic, during the addition the flask was cooled in a water bath to avoid overheating. After 4 h, pentane was added. The organic phase was filtered, concentrated under vacuum and dissolved in $CHCl_3$. After 24 h, the solvent was evaporated, and the mixture was chromatographed on silica gel (hexane/ethyl acetate 6:4) to obtain the product **3a** as a yellow oil (63 mg, 0.27 mmol, 39% yield): IR ($CHCl_3$) 3500, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, J = 7.3 Hz, 3H), 4.07−4.17 (m, 4H), 5.33 (br, 1H), 5.79 (s, 1H), 6.11 (s, 1H), 7.40−7.75 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.4, 41.3, 59.7, 126.4, 127.1, 128.2, 131.2, 136.3, 143.1, 155.5, 196.2; GC−MS *m*/*z* 233 [M^+] (3.7), 105 (100); HRMS calcd for $C_{13}H_{15}NNaO_3$ *m*/*z* 256.0950, found *m*/*z* 256.0958.

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Supporting Information Available: General experimental methods, procedures for the synthesis of β-ketophosphonates **4a**−**c**, β-ketoallylsilanes **2a**−**i**, and β-amino ketone derivatives **3a**−**i**, their characterization data, and copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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