HIGHLY STEREOSELECTIVE SYNTHESIS
OF SOME β-BRANCHED α-(PHENYLSULFONYLMETHYL)
ACRYLIC COMPOUNDS

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(Reçu le 8 Novembre 2008, accepté le 12 Janvier 2009)

ABSTRACT: Substitution reaction of β-branched Baylis-Hillman bromides with sodium benzenesulfinate in absolute ethanol at room temperature, produces in S_N2 process and high stereoselectivity, the corresponding allyl phenyl sulfinates in good yields.

Key words: Baylis-Hillman derivatives, nucleophilic substitution, allyl phenyl sulfones.

The Baylis-Hillman method is now considered as a simple organic reaction leading to carbon-carbon formation [1-3]. In most cases, the reaction provides functionalized alcohols 1 and 2 [4-7] which can be transformed into polyfunctionalized derivatives. In order to extend the potential synthetic utility of this class of acrylic compounds, we investigated the electrophilic reactivity of some allyl bromides 3 and 4 [8-12].

Due to their easy conversion into homoallyl alcohols and α,β-unsaturated ketones or ketones [13] via a reductive desulfonylation using low-valent Titanium reagents [14]; we have shown that the reaction-coupling of functional allyl bromides 3 or 4 and commercially available benzenesulfinates, in absolute ethanol, and at room temperature, could be appropriate for the easy synthesis of various β-branched α-(phenylsulfonylmethyl) acrylic compounds 5 and 6 in good yields (Scheme 1, Table 1).

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Table 1: β-Branched α-(phenylsulfonylmethyl) acrylic compounds 5 and 6 synthetised.

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<th>Yield (%)</th>
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(*) Stereochemical assignments and isomeric purities were based on the difference in chemical shifts and integration ratio of vinylic protons in ¹H NMR analysis.
Several methods for the synthesis of simple ally sulfones have been reported from the reaction of alcohols or allyl acetates and sodium benzenesulfinate in the presence of a catalytic amounts of Pd(OAc)$_2$ [15] or Pd-Graphite [16] in refluxing THF [17]. However, functionalized allyl sulfones of type 5 and 6 were either rarely described, or required relatively delicate operating conditions [18,19]. Initial investigation on the prepared allyl sulfones 5 and 6 indicated that the reaction proceeds through an usual tandem nucleophilic addition-elimination reactions 2x(S$_{N2}'$) [19-21] leading to the most substituted sulfones in the presence of an excess of sodium sulfinate which undergoes an isomerisation leading to compounds 5 and 6.

Moreover, it seems that the stereochemistry of the obtained allyl sulfones 5 or 6 depends on the size of the alkyl or aryl group R. The ethoxycarbonyl one, being more bulky than the corresponding cyano group, allowed the isolation of allyl sulfones 5 in Z configuration in the first case and E in the second family of allyl sulfones 6.

In conclusion, this work shows that the nucleophilic substitution of functional allyl bromide of type 3 or 4 in the presence of sodium phenylsulfinate proceeds via a double Michael reaction. The examination of the experimental conditions showed that it was possible to use a polar protic solvent as the ethanol instead of a complexant like polyethylene oxide 400 (PEO 400) [19].

**EXPERIMENTAL**

Reaction progress and purity of products were monitored by TLC on silica gel plates (Fluka Kieselgel 60F$_{254}$) and Merck silica gel 60 (70-230 mesh) for flash chromatography. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-300 ($^1$H: 300 MHz, $^{13}$C: 75 MHz) in CDCl$_3$ solution as solvent with TMS as an internal reference. The allyl products were obtained in satisfactory to excellent yields by using 2.1 equivalents of the benzenesulfinic acid sodium salt (97%) purchased from Fluka Chemie GmbH.

**Allyl Bromides 3 or 4; General Procedure:**

Phosphorus tribromide (PBr$_3$) (5.7 g, 1.9 mL, 20 mmol) was added to a stirred solution of 2-(1-hydroxyalkyl) acrylic compound 1 or 2 in anhydrous ether Et$_2$O (40 mL) at -10°C. The temperature was allowed to rise to 20°C and stirring was continued for 1 h. Water (25 mL) was then added at -10°C and the mixture was extracted with hexane (3 x 20 mL). The organic layer was washed with brine (2 x 15 mL) and dried over MgSO$_4$. The solvent was evaporated and the remaining oil was distilled in vacuo.

**Phenyl allyl sulphones 5 and 6; Typical procedure:**

To benzenesulfinic acid sodium salt 2.1 eq (0.832 g; 5.07 mmol) dissolved in 6 mL of absolute ethanol was added dropwise to ethyl α-(bromomethyl) acrylate (0.5 g; 2.42 mmol) diluted in 5 mL of dry dichloromethane. The mixture was stirred during 6 h at room temperature then concentrated to reduce the excess of ethanol. After quenching with water (10 mL) and extraction with dichloromethane, the combined organic layers were washed with brine, dried over MgSO$_4$, and...
filter and evaporate under reduce pressure. The crude product was purified by column chromatography on silica gel (diethyl ether / petroleum ether, 2:8).

**(E,Z)-Ethyl 2-(phenylsulfonylmethyl)but-2-enoate 5a**

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.14 (t, 3H, CH$_3$CH$_2$O, $J = 7.35$ Hz); 1.83 (d, 3H, CH$_2$CH=C, $J = 7.35$ Hz); 3.94 (q, 2H, -OC$_2$H$_5$, $J = 7.35$ Hz); 4.26 (s, 2H, -CH$_2$SO$_2$); 6.28 (q, 1H, CH$_3$CH=, $J = 7.35$ Hz (E-isomer)); 7.24 (q, 1H, CH$_3$CH=C, $J = 7.35$ Hz (Z-isomer)); 7.53-7.86 (m, 5H, aromatic H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.03 (CH$_3$CH=C); 15.30 (CH$_3$CH$_2$O); 53.70 (-CH$_2$SO$_2$); 61.10 (CH$_3$CH$_2$O); 122.01 (aromatic CH); 129.00 (aromatic CH); 129.40 (CH$_3$CH=C); 133.80 (aromatic CH); 138.80 (CH$_3$CH=C); 146.30 (aromatic C); 165.40 (CH$_3$CH$_2$O).

**(E,Z)-Ethyl 2-(phenylsulfonylmethyl)pent-2-enoate 5b**

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.05 (t, 3H, CH$_3$CH$_2$-CH=, $J = 7.35$ Hz); 1.14 (t, 3H, CH$_3$CH$_2$O, $J = 7.35$ Hz); 2.24 (qd, 2H, CH$_3$CH$_2$-CH=, $J = 7.35$ Hz, $J = 7.35$ Hz); 3.94 (q, 2H, O-CH$_2$-CH$_3$, $J = 7.35$ Hz); 4.26 (s, 2H, -CH$_2$SO$_2$); 6.08 (t, 1H, CH$_3$CH$_2$-CH=C, $J = 7.35$ Hz (E-isomer)); 7.10 (t, 1H, CH$_3$CH$_2$-CH=C, $J = 7.35$ Hz (Z-isomer)); 7.53-7.85(m, 5H, aromatic H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 13.21 (CH$_3$CH$_2$O); 14.22 (CH$_3$CH$_2$CH=C); 23.02 (CH$_3$CH$_2$CH=C); 53.93 (-CH$_2$SO$_2$); 61.11 (CH$_3$CH$_2$O); 120.24 (aromatic CH); 128.71 (aromatic CH); 128.93 (CH$_3$CH$_2$CH=C); 133.72 (aromatic CH); 138.94 (aromatic C); 152.80 (CH$_3$CH$_2$CH=C); 165.62 (CH$_3$CH$_2$O).

**(E,Z)-Ethyl 2-(phenylsulfonylmethyl)hex-2-enoate 5c**

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.93 (t, 3H, CH$_3$CH$_2$-CH$_2$, $J = 7.35$ Hz); 1.14 (t, 3H, CH$_3$CH$_2$O, $J = 6.99$ Hz); 1.46 (qt, 2H, CH$_3$CH$_2$-CH$_2$, $J = 7.35$ Hz, $J = 7.35$ Hz); 2.19 (td, 2H, CH$_2$CH$_2$-CH=, $J = 7.35$, $J = 7.71$ Hz); 3.94 (q, 2H, OCH$_2$CH$_3$, $J = 6.99$ Hz); 4.26 (s, 2H, -CH$_2$SO$_2$); 6.12 (t, 1H, CH$_3$CH$_2$-CH$_2$-CH=C, $J = 7.71$ Hz (E-isomer)); 7.12 (t, 1H, CH$_3$CH$_2$-CH$_2$-CH=C, $J = 7.71$ Hz (Z-isomer)); 7.53-7.85 (m, 5H, aromatic H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 13.80 (CH$_3$CH$_2$O); 13.87 (CH$_3$CH$_2$CH=C); 21.60 (CH$_3$CH$_2$CH$_2$); 31.20 (CH$_3$CH$_2$CH$_2$); 54.65 (-CH$_2$SO$_2$); 60.82 (CH$_3$CH$_2$O); 120.84 (aromatic CH); 128.81 (aromatic CH); 128.96 (CH$_3$CH$_2$CH=C); 133.7 (aromatic CH); 138.91 (aromatic C); 151.44 (CH$_3$CH$_2$CH=C); 165.61 (CH$_3$CH$_2$O).

**(E,Z)-Ethyl 4-methyl-2-(phenylsulfonylmethyl)pent-2-enoate 5d**

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.47 (d, 6H, CH$_3$CH, $J = 6.60$ Hz); 0.63 (t, 3H, CH$_3$CH$_2$O, $J = 6.99$ Hz); 2.21 (m, 1H, =CH-CH(CH$_3$)$_3$); 3.42 (q, 2H, OCH$_2$CH$_3$, $J = 6.99$ Hz); 3.80 (s, 2H, -CH$_2$SO$_2$); 5.12 (d, 1H, (CH$_2$)$_3$CH-CH=C, $J = 10.65$ Hz (E-isomer)); 6.37 (d, 1H, (CH$_2$)$_3$CH-CH=C, $J = 10.65$ Hz (Z-isomer)); 7.02-7.35 (m, 5H, aromatic H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 13.82 (CH$_3$CH$_2$O); 21.05 ((CH$_3$)$_2$CH=); 28.44 ((CH$_3$)$_2$CH); 54.62 (-CH$_2$SO$_2$); 60.46 (CH$_3$CH$_2$O); 118.47 (CH=C); 128.80 (aromatic CH); 128.90 (aromatic CH); 133.60 (aromatic CH); 139.09 (aromatic C);156.32 (CH=C); 165.46 (CH$_3$CH$_2$O).

**(E,Z)-Ethyl 2-(phenylsulfonylmethyl)hept-2-enoate 5e**

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.90 (t, 3H, CH$_3$CH$_2$CH$_2$(CH$_2$)$_2$, $J = 6.96$ Hz); 1.14 (t, 3H, CH$_3$CH$_2$O, $J = 6.99$ Hz); 1.37 (m, 4H, CH$_3$(CH$_2$)$_2$-CH$_3$); 2.21 (dt, 2H, CH$_2$CH$_2$CH=C, $J = 7.71$ Hz, $J = 7.71$ Hz); 3.94 (q, 2H, O-CH$_2$CH$_3$, $J = 6.99$ Hz); 4.26 (s, 2H, -CH$_2$SO$_2$); 6.12 (t, 1H, -CH$_2$CH=C, $J = 7.71$ Hz (E-isomer)); 7.12 (t, 1H, -CH$_2$CH=C, $J = 7.71$ Hz (Z-isomer)); 7.53-7.85 (m, 5H, aromatic H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 13.81 (CH$_3$CH$_2$O); 14.05 (CH$_3$(CH$_2$)$_3$); 22.45 (CH$_3$CH$_2$(CH$_2$)$_2$); 29.30 (CH$_3$(CH$_2$)$_2$CH$_3$); 30.34 (CH$_3$(CH$_2$)$_2$CH$_2$CH); 54.04 (-CH$_2$SO$_2$); 61.10 (CH$_3$CH$_2$O); 120.68 (aromatic CH); 129.00 (aromatic CH); 129.12 (CH=C); 133.73 (aromatic CH); 138.92 (aromatic C); 151.61 (CH=C); 165.61 (CH$_3$CH$_2$O).
(E,Z)-Ethyl 4-methyl-2-(phenylsulfonylmethyl)hex-2-enoate 5f

\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 0.76 (t, 3H, CH\(_3\)CH\(_2\)CHCH\(_3\), J = 7.35 Hz); 0.92 (d, 3H, CH\(_3\)CH\(_2\)CHCH\(_2\)CH\(_3\), J = 6.60 Hz); 1.04 (t, 3H, CH\(_3\)CH\(_2\)O, J = 6.99 Hz); 1.29 (m, 2H, CH\(_3\)CH\(_2\)CHCH\(_2\)CH\(_3\)); 2.41 (m, 1H, (CH\(_3\)CH\(_2\)CH(CH\(_2\))C=H); 3.81 (s, 2H, -CH\(_2\)-SO\(_2\)); 4.18 (q, 2H, OCH\(_2\)CH\(_3\), J = 6.99 Hz); 6.17 (d, 1H, CH\(_3\)CH\(_2\)CH(CH\(_2\)(CH\(_3\))=CH=C, J = 11.01 Hz (E-isomer)); 6.77 (d, 1H, CH\(_3\)CH\(_2\)CH(CH\(_3\))=CH=C, J = 11.01 Hz, (Z-isomer)); 7.43-7.76 (m, 5H, aromatic H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 11.66 (CH\(_3\)CH\(_2\)CH); 14.06 (CH\(_3\)CH\(_2\)); 18.95 (CH\(_3\)CH\(_2\)CH(CH\(_3\))); 29.94 (CH\(_3\)CH\(_2\)CH); 35.64 (CH\(_3\)CH\(_2\)CH(CH\(_3\))); 54.07 (-CH\(_2\)-SO\(_2\)); 60.80 (CH\(_3\))=C, J = 6.99 Hz); 1.29 (m, 2H, CH\(_3\)CH\(_2\)CHCH\(_2\)CH=, J = 7.35 Hz, (E-isomer)); 7.43-7.76 (m, 5H, aromatic H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 12.98 (CH\(_3\)CH\(_2\)O); 18.95 (CH\(_3\)CH2CH(=)); 59.63 (-CH\(_2\)-SO\(_2\)); 104.03 (CH=); 119.47 (CH=C); 128.96 (aromatic CH); 130.18 (aromatic CH); 134.03 (aromatic CH); 139.05 (aromatic C); 156.21 (CH=C); 165.70 (CH\(_3\)CH\(_2\)O).
(E-isomer); 6.65 (t, 1H, CH₃-CH₂-CH=, J = 7.71 Hz (Z-isomer)); 7.61-7.90 (m, 5H, aromatic H). ¹³C NMR (75 MHz, CDCl₃): δ 12.44 (CH₃CH₂); 25.49 (CH₃CH₂); 59.50 (CH₂SO₂); 102.39 (CH=C); 115.50 (CN); 128.88 (aromatic CH); 129.78 (aromatic CH); 134.51 (aromatic CH); 137.24 (aromatic C); 159.60 (aromatic C).

(E,Z)-2-(Phenylsulfonylmethyl)hex-2-enenitrile 6c
¹H NMR (300 MHz, CDCl₃): δ 0.85 (t, 3H, CH₃-CH₂-CH₂-CH=, J = 6.96 Hz); 1.35 (m, 2H, CH₃-CH₂-CH₂-CH=); 2.29 (td, 2H, CH₃CH₂CH₂CH=, J = 7.35 Hz, J = 7.71 Hz); 6.31 (t, 1H, CH₃-CH₂-CH₂-CH=, J = 7.71 Hz (E-isomer)); 6.68 (t, 1H, CH₃CH₂CH₂CH=, J = 7.71 Hz (Z-isomer)); 7.61-7.90 (m, 5H, aromatic H). ¹³C NMR (75 MHz, CDCl₃): δ 13.44 (C₃H₃CH₂); 21.26 (CH₃CH₂); 33.82 (CH₃CH₂CH₂); 59.43 (CH₂SO₂); 102.91 (CH=C); 115.74 (CN); 128.56 (aromatic CH); 129.56 (aromatic CH); 134.45 (aromatic CH); 137.24 (aromatic C); 158.31 (CH=C).

(E,Z)-5-Methyl-2-(phenylsulfonylmethyl)hex-2-enenitrile 6d
¹H NMR (300 MHz, CDCl₃): δ 0.85 (d, 6H, (C₃H₃)₂CH-CH₂-CH=, J = 6.99 Hz); 1.68 (m, 1H, (CH₃)₂CH-CH₂-CH=); 2.23 (dd, 2H, (CH₃)₂CH-CH₂-CH=, J = 7.35, J = 7.74); 3.98 (s, 2H, CH₂SO₂); 6.38 (t, 1H, (CH₃)₂CH-CH₂-CH=, J = 7.74 (E-isomer)); 6.70 (t, 1H, (CH₃)₂CH-CH₂-CH=, J = 7.74 (Z-isomer)); 7.56-7.91 (m, 5H, aromatic H). ¹³C NMR (75 MHz, CDCl₃): δ 22.08 ((C₃H₃)₂CH); 28.02 ((CH₃)₂CH); 40.79 ((CH₃)₂CHCH₂); 59.45 (CH₂SO₂); 103.46 (CH=C); 118.14 (CN); 128.61 (aromatic CH); 129.54 (aromatic CH); 134.42 (aromatic CH); 137.40 (aromatic CH); 157.44 (CH=C).

(E,Z)-2-(Phenylsulfonylmethyl)oct-2-enenitrile 6e
¹H NMR (300 MHz, CDCl₃): δ 0.78 (t, 3H, CH₃-CH₂-(CH₂)₃-CH=, J = 6.81 Hz); 1.08-1.27 (m, 6H, CH₃-(CH₂)₃CH₂-CH=); 2.25 (td, 2H, CH₃-(CH₂)₂CH₂CH=, J = 7.35 Hz, J = 7.71 Hz); 3.84 (s, 2H, CH₂SO₂); 6.25 (t, 1H, CH₃-(CH₂)₂CH₂CH=, J = 7.71 Hz (E-isomer)); 6.58 (t, 1H, CH₃-(CH₂)₂CH₂CH=, J = 7.71 Hz (Z-isomer)); 7.48-7.82 (m, 5H, aromatic H). ¹³C NMR (75 MHz, CDCl₃): δ 14.42 (CH₃CH₂); 22.55 (CH₃CH₂); 27.56 (CH₃CH₂CH₂CH₂); 31.13 (CH₃CH₂CH₂CH₂CH₂); 32.11 (CH₃CH₂CH₂CH₂CH₂); 59.66 (CH₂SO₂); 102.99 (CH=C); 118.20 (CN); 129.58 (aromatic CH); 129.99 (aromatic CH); 134.42 (aromatic CH); 137.40 (aromatic CH); 157.44 (CH=C).

(E)-3-Phenyl-2-(phenylsulfonylmethyl)acrylonitrile 6f
¹H NMR (300 MHz, CDCl₃): δ 4.05 (s, 2H, CH₂SO₂); 7.09 (s, 1H, PhCH=); 7.43-7.94 (m, 10H, aromatic H). ¹³C NMR (75 MHz, CDCl₃): δ 61.38 (CH₂SO₂); 98.03 (CH=C); 117.05 (CN); 128.84 (aromatic CH); 129.07 (aromatic CH); 129.30 (aromatic CH); 130.66 (aromatic CH); 132.45 (aromatic CH); 134.66 (aromatic C); 137.53 (aromatic C); 151.89 (aromatic C).

(E)-3-(3-Fluorophenyl)-2-(phenylsulfonylmethyl)acrylonitrile 6g
¹H NMR (300 MHz, CDCl₃): δ 4.06 (s, 2H, CH₂SO₂); 7.10 (s, 1H, PhCH=); 7.13-7.94 (m, 9H, aromatic H). ¹³C NMR (75 MHz, CDCl₃): δ 61.27 (CH₂SO₂); 97.67 (CH=C); 97.70 (CN); 116.23 (aromatic CH); 116.52 (aromatic CH); 117.12 (aromatic CH); 128.81 (aromatic CH); 129.67 (aromatic CH); 131.58 (aromatic CH); 134.73 (aromatic CH); 137.58 (aromatic C); 150.57 (aromatic C); 162.66 (CH=C); 166.03 (aromatic CF).
REFERENCES