Synthesis of 4-Isobutylbenzaldehyde an Important Intermediate for the Fragrance (+)- and (-)-Silvial®

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Abstract: The synthesis of 4-isobutylbenzaldehyde, a valuable precursor for the fragrance Silvial® (3-(4-isobutylphenyl)-2-methylpropanal), is reported. Three different synthetic approaches are reported starting either from 4-isobutylbenzoic acid (via benzyl alcohol, or via acyl chloride), or by Suzuki-Miyaura cross-coupling reaction between 4-bromobenzaldehyde and 2-methylpropylboronic acid.

Keywords: Fragrance synthesis, Acyl chloride, Benzyl alcohol, Palladium catalyst, Suzuki-Miyaura cross-coupling.

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1. Introduction

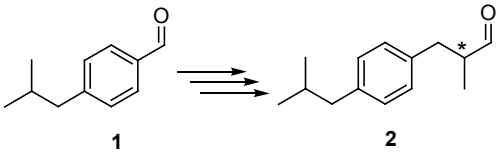
It is now well known that the human nose perceives in different ways the olfactory notes of the two enantiomers of a chiral molecule; in fact they may be different both in quality and in intensity [1-10]. The possibility to synthesize and obtain stereoisomers having different odour profile has become of increasing interest in perfumery due to the continuous demand for new olfactive notes. Moreover, there are environmental and safety concerns arising from the increasing use of odorants and their interaction with the ecosystem and human beings [11]. In fact, exclusive manufacture and use of the most olfactory active stereoisomer of a perfumery raw material, would lead to lower consumption and dispersion of these compounds in the environment.

Silvial®, according to the odour profile reported by Givaudan, is a "powerful, vibrant muguet ingredient with a slight citrus under tone and a fresh aldehydic touch".

Odorants displaying floral notes (citrus, muguet, lily-of-the-valley, etc.) are of particular interest in perfumery as they are widely appreciated and used [12,13].

Spurred by our interest in developing practical synthetic routes to enantiomerically enriched fragrances [14-16], we are currently developing an enantioselective catalytic route to this valuable fragrance. To the best of our knowledge the odour profile of the two enantiomers of Silvial® has yet to be disclosed, and only the racemate is commercialized by Givaudan.

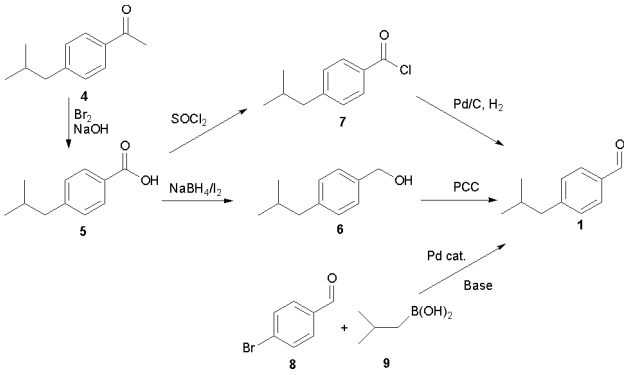
Studies are currently in progress in order to synthesize enantiomerically enriched Silvial®, according to a multi-step synthetic strategy in which the key intermediate is 4-isobutylbenzaldehyde (**1**) (Scheme 1).



Scheme 1. Chemical structures of 4-isobutylbenzaldehyde and Silvial®.

Although the starting product **1** is commercially available, it is rather expensive so we thought it interesting to develop alternative synthetic approach-

es for **1**, in particular, we found it appealing to use as starting compounds either 4-isobutylacetophenone or 4-bromobenzaldehyde which are commercially available and inexpensive.
In this work, we wish to report the results of our investigations on some synthetic pathways to the sought key intermediate **1** (Scheme 2).



Scheme 2. The approaches developed for the synthesis of 4-isobutylbenzaldehyde (**1**).

In Scheme 2 are reported our synthetic approaches to **1**: 4-isobutylacetophenone (**3**) is easily converted into the corresponding acid (**4**) by the treatment with Br_2 and NaOH (haloform reaction). 4-Isobutylbenzoic acid (**4**) may then react according to two different reaction pathways to give the desired aldehyde, either by reduction/oxidation *via* benzyl alcohol **5** or by acylation and reduction *via* acyl chloride **6**. Alternatively, aldehyde **1** may be obtained by Suzuki-Miyaura cross-coupling carried out in the presence of aryl halide **7** and alkyl boronic acid **8**, catalysed by a Pd complex [17-25].

2. Results and Discussion

According to literature, there are two different ways to obtain 4-isobutylbenzoic acid (**4**) from the inexpensive readily available 4-isobutylacetophenone (**3**). S. Gurunath et al. reported that **4** was obtained in good yield (72%) by reacting **3** in the presence of Re_2O_7, *tert*-butylhydroperoxide and acetic acid at 100 °C [26]. A more straightforward synthesis was disclosed by J.B. Summers et al. which obtained **4**, albeit with modest yields (about 38%), by treating **3** with sodium hypochlorite [27].

The alternative synthesis proposed by us in Scheme 2 is similar to the one reported by S.D. Wyrick for [(*N*-alkyl-l-oxo-1H,3H-isoindolin-5-yl) oxy]butanoic acids, and related derivatives [28]. The reaction of **3** was carried out in the presence of bromine and a base (NaOH) employing a mixture dioxane/water (1.0/1.5 vol/vol) as the solvent; after heating at 40 °C, **4** is recovered in high yield (87%).

The carboxylic acid **4** may be converted into **1** according to two different pathways: i) *via* reduction to benzyl alcohol **5** followed by partial oxidation; ii) by reaction with thionyl chloride and reduction in the presence of Pd/C and H_2. According to the benzyl alcohol pathway, benzoic acid **4** was reduced with $NaBH_4/I_2$ to give alcohol **5** in good yield (74%) [29,30]; then, following a well established protocol [14], alcohol **5** was partially reoxidized to the corresponding aldehyde **1** in high yield (85%). The sequence of reactions is carried out with no formation of by-products and easy recovery of the product.

Another possible route to **1** is by way of the corresponding acyl chloride **6**. Alkyl and acyl chlorides are commonly employed both as synthetic intermediates and as final products by fine chemistry industry [31,32]. The reaction usually takes place between a carboxylic acid and thionyl chloride.

According to literature [33,34], we carried out the reaction between acid **4** and a large excess of $SOCl_2$ in the absence of a solvent [33,35] under reflux. The formation of the acyl chloride is confirmed by ^1H NMR spectroscopy in which after total removal of the thionyl chloride the OH singlet of the acid is not more present and the aromatic proton resonances are shifted to lower fields indicating total conversion of **4** to **6**.

It is of crucial importance that no $SOCl_2$ remains in the reaction crude prior to hydrogenation, to avoid palladium deactivation [33,35]. It is to point out that the Pd catalyst, required for the hydrogenation of the acyl chloride **6** to give **1**, must be highly selective, due to possible aldehyde reduction to the corresponding alcohol **5**; this is usually obtained by partially deactivating the Pd catalyst. If we consider the surface of a fresh 10% Pd/C catalyst, only ca. 2% of the total carbon surface available is occupied by Pd, thus the carbon surface may adsorb organic substrates or undesired molecules such as water which could be responsible of side product formation [33]. Most important is the effect of pre-treatment and reaction conditions on the Pd itself which may lead to drastic changes to the catalyst surface area: for example literature data report that a decrease of the

metal surface area of over 75% is obtained by refluxing the Pd/C catalyst in xylene for 4 h [33]. Similar results are achieved pre-treating the Pd/C with organic bases. In all cases, in this work we have chosen to pre-treat the catalyst with *N*,*N*-diisopropylethylamine, as reported in the experimental section.

A first experiment (**Protocol A**) was carried out at 1 atm P(H_2) and room temperature: after 24 h the reaction conversion of **6** to **1** is 77%; traces of alcohol **5** were also present, probably because of the long reaction time.

Accordingly, next experiments were carried out at shorter reaction times (**Protocols B** and **C**). After 3 h at 85 °C, 50% conversion of **6** to **1** is obtained with no formation of alcohol **5**. Best results were achieved increasing the hydrogen pressure to 4 atm, reaching 85% conversion of **6** in 3 h at room temperature.

An alternative promising possibility is the synthesis of **1** *via* Suzuki-Miyaura reaction of 4-bromobenzaldehyde (**7**) and 2-methylpropylboronic acid (**8**) in the presence of a Pd catalyst.

In recent years there has been increasing interest in S-M cross-coupling reaction as synthetic way to carbon-carbon bond formation due to the high tolerance towards many functional groups, low toxicity, high stability and prompt availability of boronic acids, low cost of the reagents [17-25].

As a matter of fact, we have long been interested in S-M cross-coupling reaction and in the synthesis of Pd complexes to be employed in the reaction [36-39].

In Table 1 are reported the results obtained for the coupling reaction of **7** and **8** in the presence of different palladium catalysts. At first, the coupling reaction was carried out in the presence of a commercially available Pd catalyst, $PdCl_2(PPh_3)_2$ with reaction conditions similar to those employed in the literature [40,41].

Table 1. Suzuki-Miyaura coupling of 4-bromobenzaldehyde (**7**) with 2-methylpropylboronic acid (**8**) in the presence of different palladium catalyst[(a)].

Cat.	Pd (mmol)	Ligand (mmol)	Base	Conv. (%)[(b)]
$PdCl_2(PPh_3)_2$	0.02	0	K_2CO_3	0
$[PdCl_2(PN)]$[(c)]	0.02	0	K_2CO_3	0
$Pd_2(dba)_3$/$[(t\text{-Bu})_3PH]BF_4$	0.01	0.02	K_3PO_4	0
$Pd(OAc)_2$/$[(t\text{-Bu})_3PH]BF_4$	0.05	0.1	K_3PO_4	0

[(a)] Reaction conditions: **7**: 1.0 mmol, **8**: 1.5 mmol, base: 3.9 mmol, solvent: toluene (15 mL), t: 21 h, T: 110 °C. [(b)] Conversion as determined by GLC (internal standard: *n*-undecane). [(c)] $[PdCl_2(PN)]$: $[PdCl_2(C_9H_6NOP(C(CH_3)_3)_2)]$ (Fig. 1).

Albeit prolonged reaction times, no product formation was observed. According to our experience in the use of Pd complexes containing iminophosphine ligands [42,43] the reaction between **7** and **8** was carried out in the presence of a very active catalyst containing a P,N-ligand which we have recently developed (Figure 1)[43]; nevertheless also in this case no reaction conversion was achieved.

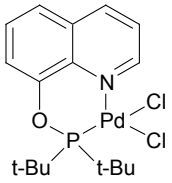


Fig. 1. $[PdCl_2\{8\text{-(di-}tert\text{-butylphosphinooxy)quinoline}\}]$.

Frequently, these reactions are performed employing a commercial Pd(0) or Pd(II) complex and a phosphine ligand leading to *in situ* formation of the catalytically active species.

The cross-coupling between **7** and **8** was carried out using either $Pd_2(dba)_3$ or $Pd(OAc)_2$ in the presence of $[(t\text{-Bu})_3PH]BF_4$. In fact, according to a widely used protocol the air stable phosphonium salt is converted *in situ* in the highly air sensitive $(t\text{-Bu})_3P$ which is one of the most active phosphine ligands used in coupling reactions [20]. Unfortunately with both catalyst precursors no reaction was observed.

In conclusion, in this work we tested three different ways to synthesize aldehyde **1**. Both approaches based on the use of 4-isobutylacetophenone (**3**) allowed us to obtain the sought aldehyde, but only the one based on the reduction/selective oxidation sequence allowed to obtain good yield in the desired product. When the intermediate is the acyl chloride species, in no cases we achieved conversions higher than 85%.

Although we were unsuccessfull in preparing aldehyde **1** *via* Suzuki-Miyaura cross-coupling reaction, this remains in our opinion the most promising synthetic approach thus we are further working in order to find out an efficient catalyst for the reaction. In fact, a huge variety of catalysts is nowadays available even commercially.

3. Experimental

3.1. General materials and methods

Solvents were purchased from Aldrich and purified according to literature [44]. All other

reagents (Aldrich) were used without further purification. All products were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AC300 spectrometer operating at 300.21 and 75.44 MHz, respectively. Gas Chromatography-Mass Spectrometry (GC-MS) analyses were performed on a Hewlett-Packard 5890 SERIES II gas chromatograph interfaced with a HP 5971 quadrupole mass detector. Gas Liquid Chromatography (GLC) analyses were performed on an Agilent 6850 gas chromatograph equipped with a Flame Ionization Detector (FID).

3.2. Synthesis of 4-isobutylbenzoic acid (4)

Compound **4** was prepared as reported by S.D. Wyrick et al. [28]. A 1 L three-neck round-bottom flask, fitted with a magnetic stirring bar, a reflux condenser, and an addition funnel, was charged, under inert atmosphere, with 17.6 g (100 mmol) of 4-isobutylacetophenone (**3**), 200 mL of 1,4-dioxane, and a solution of NaOH 5M (62.5 g, 1.56 mol, in 310 mL of water). Then 20 mL (390 mmol) of Br_2 were slowly added; after the addition was complete, the flask was heated at 40 °C for 45 min and then cooled to room temperature. Under vigorous stirring, 60.3 g (579 mmol) of $NaHSO_3$ were added followed by 60 mL of HCl conc., the reaction mixture was extracted with dichloromethane (3×150 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum, affording 15.5 g of a white solid (87% yield) which was characterized by ^{1}H, ^{13}C NMR and GC-MS.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 11.35 (bs, 1H, OH), 8.05 (d, 2H, arom, *J*=8.1 Hz), 7.27 (d, 2H, arom, *J*=8.1 Hz), 2.57 (d, 2H, CH_2CH, *J*=7.0 Hz), 1.93 (m, 1H, CH, *J*=7.0 Hz), 0.93 (d, 6H, CH_3, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 172.2, 148.4, 130.2, 129.3, 126.9, 45.5, 30.2, 22.4. MS (EI): m/z (%) 178 $[M]^+$, 136, 91, 77.

3.3. Synthesis of 4-isobutylbenzyl alcohol (5)

Compound **5** was prepared as reported by M.J. McKennon et al. [29]. A 500 mL three-neck round-bottom flask, fitted with a magnetic stirring bar, a reflux condenser, and an addition funnel, was charged, under inert atmosphere, with 5.60 g (148.2 mmol) of sodium borohydride and 200 mL of anhydrous THF. Once no more hydrogen formation was observed, 10.0 g (56.1 mmol) of 4-isobutylbenzoic acid (**4**) were added dropwise in 1 h at 0 °C. Finally, 14.25 g (56.1 mmol) of iodine dissolved in 50 mL of THF were slowly added dropwise over 30 min resulting in vigorous hydrogen evolution. After the addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h and then cooled to room temperature; eventually, methanol was slowly added until the reaction mixture became clear (150 mL). After stirring for 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of 200 mL of 20% aqueous KOH. The solution was stirred for 4 h and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum, affording 6.78 g of a white solid (74% yield) which was characterized by ^{1}H, ^{13}C-NMR and GC-MS.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.28 (d, 2H, arom, *J*=7.5 Hz), 7.16 (d, 2H, arom, *J*=7.5 Hz), 4.64 (s, 2H, CH_2OH), 2.50 (d, 2H, CH_2CH, *J*=6.9 Hz), 1.89 (m, 1H, CH, *J*=6.9 Hz), 0.93 (d, 6H, CH_3, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 141.2, 138.2, 129.3, 126.9, 65.2, 45.1, 30.3, 22.4. MS (EI): m/z (%) 164 $[M]^+$, 121, 107, 91, 77.

3.4. Synthesis of 4-isobutylbenzaldehyde (1) from 5

Compound 1 was prepared as reported by A. Abate et al. [2]. A 100 mL two-neck round-bottom flask, fitted with a magnetic stirring bar, a reflux condenser, and an addition funnel, was charged, with 1.0 g (6.0 mmol) of 5 in 10 mL CH_2Cl_2 and 2.60 g (12.1 mmol) of pyridinium chlorochromate in 20 mL CH_2Cl_2, the resulting suspension was stirred for 2 h then diluted with diethyl ether (10 mL). The mixture was filtered on a short silica gel column (eluent: diethyl ether), evaporation of the solvents affording 0.83 g of 1 (85% yield) which was characterized by ^{1}H, ^{13}C-NMR and GC-MS.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 9.98 (s, H, CHO), 7.80 (d, 2H, arom, *J*=8.1 Hz), 7.31 (d, 2H, arom, *J*=8.1 Hz), 2.56 (d, 2H, CH_2, *J*=6.9 Hz), 1.92 (m, 1H, CH, *J*=6.9 Hz), 0.92 (d, 6H, CH_3, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 192.0, 149.2, 134.5, 129.7, 45.6, 30.1, 22.3. MS (EI): m/z (%) 162 $[M]^+$, 120, 91, 77.

3.5. Synthesis of 4-isobutylbenzyl chloride (6)

Compound **6** was prepared as reported by J.A. Peters et al. and C.Y. Zang et al. [34,35]. A 100 mL two-neck round-bottom flask, fitted with a magnetic stirring bar, a reflux condenser, and an addition funnel, was charged, under inert atmosphere, with 900 mg (5.1 mmol) of **5** and after cooling at 0 °C, 15 mL of thionyl chloride were added dropwise in 20 min; the flask was then heated to 110 °C for 1 h and finally cooled to room temperature. Excess $SOCl_2$ was removed under vacuum affording a yellow oil which was used without further purification. The product was characterized by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.04 (d, 2H, arom, *J*=8.3 Hz), 7.30 (d, 2H, arom, *J*=8.3 Hz), 2.58 (d, 2H, CH_2, *J*=6.9 Hz), 1.94 (m, H, CH), 0.93 (d, 6H, CH_3, *J*=6.9 Hz).

3.6. Synthesis of 4-isobutylbenzaldehyde (1) from 6

The synthesis of **1** from **6** was carried out according to three different protocols, here after reported.

Protocol A: compound **1** was prepared as reported by J.A. Peters et al. [34]. A 100 mL two-neck round-bottom flask, fitted with a magnetic stirring bar, a reflux condenser, and an addition funnel, was charged, under inert atmosphere, with 85 mg (0.08 mmol) of 10% Pd/C, 25 mL of anhydrous AcOEt and 355 µL (2.04 mmol) of *N*,*N*-diisopropylethylamine, the flask was saturated with H_2 at room temperature for 1 h; the reaction mixture was then cooled to 0 °C and 330 mg (1.7 mmol) of 4-isobutylbenzyl chloride (**6**) in 15 mL of anhydrous AcOEt were added dropwise; the flask was again saturated with H_2 at room temperature for 24 h. The reaction mixture was filtered and the solvent was removed by rotary evaporation giving a yellow oil which was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were acidified with HCl 10% (3×20 mL), washed with H_2O (2×20 mL), dried with $MgSO_4$, and, after filtration, the solvent was removed by rotary evaporation giving 280 mg of a yellow oil which was characterized by ^{1}H NMR to calculate the conversion (77%) and yield in **1** (73%); 4% of alcohol **5** was also formed.

Protocol B: compound **1** was prepared as reported by J.A. Peters et al. [34]. A 100 mL two-neck round-bottom flask, fitted with a magnetic stirring bar, a reflux condenser, and an addition funnel, was charged, under inert atmosphere, with 85 mg (0.08 mmol) of 10% Pd/C, 25 mL of anhydrous AcOEt and 355 µL (2.04 mmol) of *N*,*N*-diisopropylethylamine, the flask was saturated with H_2 at room temperature for 1 h; the reaction mixture was then cooled to 0 °C and 330 mg (1.7 mmol) of 4-isobutylbenzyl chloride (**6**) in 15 mL of anhydrous AcOEt were added drop wise; the flask was again saturated with H_2 and the mixture was heated to 85 °C for 4 h. After cooling to room temperature, the reaction crude was filtered and the solvent was removed by rotary evaporation giving a yellow oil which was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were acidified with HCl 10% (3×20 mL), washed with H_2O (2×20 mL) dried with $MgSO_4$, and, after filtration, the solvent was removed by rotary evaporation giving 260 mg of a yellow oil which was characterized by ^{1}H NMR, to calculate the conversion of **6** (50%) and yield in **1** (50 %).

Protocol C: a 150 mL stainless steal autoclave, fitted with a magnetic stirring bar, was charged, under inert atmosphere, with 85 mg (0.08 mmol) of 10% Pd/C, 25 mL of anhydrous AcOEt and 355 µL (2.04 mmol) of *N*,*N*-diisopropylethylamine, the autoclave was saturated with H_2 at room temperature for 1 h. Finally, the hydrogen was vented off and 330 mg (1.7 mmol) of 4-isobutylbenzyl chloride (**6**) in 15 mL of anhydrous AcOEt were added, under inert atmosphere. The autoclave was pressurized with 4 atm of H_2 at room temperature for 3 h. The reaction crude was filtered and the solvent was removed by rotary evaporation giving a yellow oil which was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were acidified with HCl 10% (3×20 mL), washed with H_2O (2×20 mL) dried with $MgSO_4$, and, after filtration, the solvent was removed by rotary evaporation giving 290 mg of a yellow oil which was characterized by ^{1}H NMR, to calculate the conversion of **6** (85%) and yield in **1** (85 %).

3.7. Synthesis of 4-isobutylbenzaldehyde (1) from 4-bromobenzaldehyde (7) and 2-methylpropylboronic acid (8) (run 4 of Table 1)

In a typical experiment, a 50 mL glass reactor was charged with 185.2 mg (1.0 mmol) of 4-bromobenzaldehyde (**7**), 154.0 mg (1.5 mmol) of 2-methylpropylboronic acid (**8**), 828.0 mg (3.9 mmol) of K_3PO_4, 160 mg of *n*-undecane (1.0 mmol, as gas chromato-

graphic internal standard), 15 mL toluene and 450 µL of H_2O. Finally, under inert atmosphere, were added 36.6 mg (0.1 mmol) of tricyclohexylphosphine tetrafluoroborate and 11.0 mg (0.05 mmol) of $Pd(OAc)_2$. The mixture was heated, under magnetic stirring, at 110 °C for 21 h. After cooling to room temperature and filtration, the raw reaction mixture was analyzed by GLC for the computation of reaction conversion (100%). The mixture is then treated with AcOEt (15 mL) and brine, the organic extracts were dried with $MgSO_4$, and, after filtration, the solvent was removed by rotary evaporation giving 131 mg (yield 81%) of a yellow oil which was characterized by GLC, GC-MS, ^{1}H NMR and ^{13}C NMR.

4. Acknowledgements

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