



Synthesis of 2,2-Dimethyl-3-(3-methyl phenyl)propanal and Its Derivatives

JIANSHUI ZHANG¹, RUI HUANG¹, QIAN YAN², XIAHUA PAN¹, FENG LIU¹ and WENHUA OU^{1,*}

¹School of Perfume and Aroma Technology, Shanghai Institute of Technology, Shanghai, P.R. China

²School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai, P.R. China

*Corresponding author: Fax: +86 21 60873134; Tel: +86 21 60873134; E-mail: ouwenhua72@hotmail.com

(Received: 28 October 2011;

Accepted: 7 September 2012)

AJC-12099

An alternative approach to the synthesis of 2,2-dimethyl-3-(3-methylphenyl)propanal and its derivatives was described. 2,2-Dimethyl-3-(3-methylphenyl) propanal and its derivatives were obtained in middle yields from various substituted alkylaromatics, *via* bromination and alkylation. Its feature of fragrance was green, reminiscent of leaves, with flowery-aldehydic aspects.

Key Words: Lilial, Bromination, Alkylation, Bromomethylation, Muguet odor.

INTRODUCTION

Since flowers from lily of the valley (muguet) plant were very small in amount and the essential oils were difficult to obtain by extracting from these flowers, it is not possible to produce blossom oil from this plant. In addition, components with the characteristic of muguet odor had not been reported yet by obtaining from the plant^{1,2}. Therefore, perfumers had to rely on the synthetic substitutes, such as Lylal, Lilial to create the scent of this type. However, the odor of these materials were showed considerable difference compare to that of the living flowers³. In the past few years⁴⁻⁷, perfumers discovered that 2,2-dimethyl-3-(3-methylphenyl)propanal (Fig. 1) and its reduction had an elegant scent of powerful floral, fresh, green flowery perfume and lily of the valley note such as majantol. Few reports were found about synthesis of these compounds. Herein, we presented the synthesis of these compounds and evaluated the corresponding odoriferous characteristics.

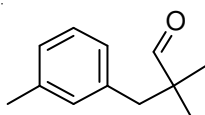


Fig. 1. Structure of 2,2-dimethyl-3-(3-methylphenyl)propanal

Hafner *et al.*⁶ reported the synthesis of 2,2-dimethyl-3-(3-methylphenyl) propanal from 3-methyl benzyl chloride (Fig. 2).

In the above-mentioned report, isobutyraldehyde was alkylated with benzylic halides to get 2,2-dimethyl-3-(3-methylphenyl)propanal in moderate yields by using phase-

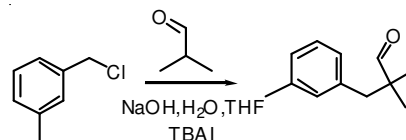


Fig. 2. Synthetic method of 2,2-dimethyl-3-(3-methylphenyl) propanal

transfer catalyst (tetrabutyl ammonium iodide). However, it suffered from the low yields, the high cost and the low selectivity.

It was well known that bromomethyl-substituted aryl derivatives are more active than the corresponding chloromethyl compounds in organic transformations. The present report described an alternative method to the alkylation reaction which used bromomethyl-substituted aryl compounds instead of the chloromethyl substrates. The reaction was completed in short time and in good yield. Consequently, we studied a variety of different bromomethyl-substituted aryl substrates by reacting with isobutyraldehyde in the presence of PTC (phase-transfer catalyst) to obtain a series of compounds (Fig. 3). Among those compounds, compound **3c** and **3d** were synthesized for the first time. The bromomethyl-substituted aryl compounds could be obtained easily from bromo-methylation of aromatic compounds.

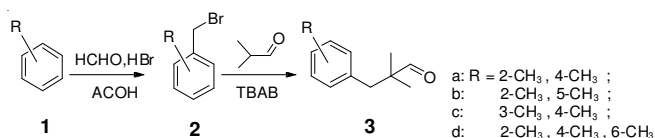


Fig. 3. Synthesis of 2,2-dimethyl-3-(3-methylphenyl)propanal and its derivatives

EXPERIMENTAL

The following reagents and solvents used in this preparation were sourced from some chemical company in China and used without further purification.

Cautions: The toxicity and the lachrymatory properties of the bromomethylated products require the use of an efficient hood and protective gloves.

General procedure for bromomethylation: To a mixture of aromatic compound (0.30 mol), paraformaldehyde (9.24 g; 0.30 mol) and 100 mL of glacial acetic acid was added 60 mL of a 40 wt % HBr/acetic acid solution rapidly. The mixture was kept for 2 h at 50 °C and then poured into 100 mL of water. The product was filtered off and dried in vacuum.

1-(Bromomethyl)-2,4-dimethylbenzene (2a): m.p. 27-31, yield: 62 %; IR (KBr, ν_{\max} , cm^{-1}): 3050, 2960, 2975, 2872, 1492, 1475, 1387, 1171; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.30 (s, 3 H, Ar- CH_3), 2.35 (s, 3 H, Ar- CH_3), 4.33 (s, 2 H, Ar- CH_2), 6.83-6.91 (m, 3 H, Ar-H); m/z (EI, 70 eV): 198 [M^+], 118 [M^+-Br].

2-(Bromomethyl)-1,4-dimethylbenzene (2b): m.p. 33-35, yield: 74 %; IR (KBr, ν_{\max} , cm^{-1}): 3030, 2965, 2915, 2877, 1486, 1460, 1395, 1055; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.33 (s, 3 H, Ar- CH_3), 2.35 (s, 3 H, Ar- CH_3), 4.35 (s, 2 H, Ar- CH_2), 6.95-7.05 (m, 3 H, Ar-H); m/z (EI, 70 eV): 198 [M^+], 118 [M^+-Br].

4-(Bromomethyl)-1,2-dimethylbenzene (2c): m.p. 27-30, yield: 58 %; IR (KBr, ν_{\max} , cm^{-1}): 3035, 2945, 2905, 2825, 1435, 1460, 1315, 1078; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.33 (s, 3 H, Ar- CH_3), 2.37 (s, 3 H, Ar- CH_3), 4.28 (s, 2 H, Ar- CH_2), 6.95-7.13 (m, 3 H, Ar-H); m/z (EI, 70 eV): 198 [M^+], 118 [M^+-Br].

2-(Bromomethyl)-1,3,5-trimethylbenzene (2d): m.p. 42-44 °C, yield: 90 %; IR (KBr, ν_{\max} , cm^{-1}): 3120, 2988, 2912, 2875, 1615, 1482, 1424, 1386, 1155, 906; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.25 (s, 3 H, Ar- CH_3), 2.35 (s, 3 H, Ar- CH_3), 4.42 (s, 2 H, Ar- CH_2), 6.82 (s, 2 H, Ar-H); m/z (EI, 70 eV): 212 [M^+], 132 [M^+-Br].

General procedure for alkylation: 7.2 g (0.18 mol) of powdered technical grade NaOH and 0.5 g of tetrabutylammonium bromide was suspended in 100 mL of toluene under N_2 at 70 °C, a mixture of 0.15 moles of the above bromide and 13 g (0.18 mol) of isobutyraldehyde was added dropwise to this pre-mix within a period of 1 h while stirring vigorously. The reaction mixture was then maintained at a temperature of 70 °C. After the reaction was completed (monitored by GC), the NaBr and NaOH was then filtered off and washed with two portions of toluene (20 mL \times 2 mL). The filtrate was washed with 100 mL water. After separating the phase and removing the solvents, the end product was obtained by fractional distillation.

2,2-Dimethyl-3-(2,4-dimethylphenyl)propanal (3a): Yield: 65 %; IR (KBr, ν_{\max} , cm^{-1}): 3022, 2970, 2925, 2872, 1731, 1610, 1470, 1386, 1390; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.16 (s, 6H, C(CH_3)), 2.29 (d, 6H, Ar- CH_3), 2.81 (s, 2H, Ar- CH_2), 6.93-7.28 (m, 3H, Ar-H), 9.60 (s, 1H, CH=O); m/z (EI, 70 eV): 190 [M^+], 172 [$\text{M}^+-\text{H}_2\text{O}$], 131 [$\text{M}^+-(\text{CHO} + 2\text{CH}_3)$], 119 [$\text{C}_9\text{H}_{11}^+$].

2,2-Dimethyl-3-(2,5-dimethylphenyl)propanal (3b): Yield: 70 %; IR (KBr, ν_{\max} , cm^{-1}): 3040, 2965, 2925, 2872,

1726, 1616, 1510, 1470, 1390; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.01 (s, 6 H, C(CH_3)), 2.71 (d, 6 H, Ar- CH_3), 2.81 (s, 2 H, Ar- CH_2), 6.85-7.27 (m, 3 H, Ar-H), 9.61 (s, 1 H, CH=O) m/z (EI, 70 eV): 190 [M^+], 172 [$\text{M}^+-\text{H}_2\text{O}$], 131 [$\text{M}^+-(\text{CHO} + 2\text{CH}_3)$], 119 [$\text{C}_9\text{H}_{11}^+$].

2,2-Dimethyl-3-(3,4-dimethylphenyl)propanal (3c): Yield: 67 %; IR (KBr, ν_{\max} , cm^{-1}): 3040, 2965, 2925, 2872, 1726, 1610, 1496, 1470, 1386, 1156; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.10 (s, 6 H, C(CH_3)), 2.29 (d, 6 H, Ar- CH_3), 2.90 (s, 2 H, Ar- CH_2), 6.83-7.07 (m, 3 H, Ar-H), 9.61 (s, 1 H, CH=O); m/z (EI, 70 eV): 190 [M^+], 172 [$\text{M}^+-\text{H}_2\text{O}$], 131 [$\text{M}^+-(\text{CHO} + 2\text{CH}_3)$], 119 [$\text{C}_9\text{H}_{11}^+$].

2,2-Dimethyl-3-(2,4,6-trimethylphenyl)propanal (3d): Yield: 65 %; IR (KBr, ν_{\max} , cm^{-1}): 2970, 2925, 2872, 1726, 1616, 1510, 1474, 1390, 1200, 1125, 1028, 855; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 0.97 (s, 6 H, 2C(CH_3)), 2.29 (s, 9 H, Ar- CH_3), 2.91 (s, 2 H, Ar- CH_2), 6.86 (s, 2 H, Ar-H), 9.55 (s, 1 H, CH=O). m/z (EI, 70 eV): 204 [M^+], 145 [$\text{M}^+-(\text{CHO} + 2\text{CH}_3)$], 133 [$\text{C}_{10}\text{H}_{13}^+$].

Detection method: The progress of reactions and the purity of compounds synthesized were checked by thin-layer chromatography (TLC) and gas chromatography (GC). Melting points were determined with a SGW X-4 micro melting point apparatus. IR spectra were determined as KBr pellets on a Bruker Vertex 70 spectrophotometer. $^1\text{H NMR}$ spectra were recorded using a Bruker-AMX 400 MHz spectrometer in CDCl_3 with tetramethylsilane as internal standard. ESIMS was recorded on Dionex MSOPlus mass spectrometer.

RESULTS AND DISCUSSION

First we selected various aryl compounds as starting materials and prepared the corresponding bromide (**2a-2d**) by classic bromomethylation. Because of methyl substituent effect, the yield of **2a**, **2b**, **2d** was better than the yield of **2c** in the bromomethylation.

We studied alkylation of isobutyraldehyde by checking some phase-transfer catalysts in next step. Table-1 showed that the tetrabutylammonium bromide is better as phase-transfer catalyst in the alkylation. And we obtained the corresponding alkylation products in middle yield (Table-2).

Analysis of the influence of the position of the methyl group of the aromatic ring in the molecule on the odour of the compound: The introduction of methyl into 3- or 5-position

TABLE-1
THE EFFECT OF DIFFERENT PHASE
TRANSFER CATALYSTS ON REACTION

Phase transfer catalyst	Conversion (%)	Time (h)	Yield (%)
Benzyltriethylammonium chloride (TEAC)	73	10	47
Tetrabutylammonium bromide (TBAB)	100	4	72
Tetrabutylammonium iodide (TBAI)	100	4	63
Tetrabutylammonium hydrogen sulphate (TBAHS)	100	5	69
PEG-400	56	5	^a
No catalyst	36	10	^a

^aThe Amount of product was too small.

TABLE-2
ALKYLATION OF VARIOUS DERIVATIVES AND ODOUR
DESCRIPTION OF THE PRODUCT

Entry	Substrate	Product	Yield (%)	Odour description
1			65	Very weak flowery, guaiacol like odor
2			70	Green, melon, Muguet
3			67	Floral, green, fresh and marine
4			65	Moss

of aromatic ring (compound **3b,3c**) their odour characteristic are also very similar with strong fresh-floral, aqueous-aldehydic and lily flowers. However, when methyl substituted in 2, 4 or 6 position (compound **3a,3d**), The odor of those compounds was found to be considerably less intense than that of compound **3b, 3c**, lacked the aqueous-aldehydic freshness, but possessed soil or other sensory character. The result was shown that introduction of a methyl group in *meta*-position of the aldehyde chain, the odor of the compound was more obvious muguet odor (Table-2).

Conclusion

An alternative procedure of the synthesis of 2-dimethyl-3-(3-methylphenyl) propanal and its derivatives was presented. We obtained this kind of scented compounds from various substituted alkylaromatics, *via* bromination and alkylation. Its feature of fragrance was green, reminiscent of leaves, with flowery-aldehydic aspects. This synthesis method solved the question in obtaining this kind of scented compounds.

REFERENCES

1. J.P. Morelli and S.W. Waite, US Patent No. 6013 618 (2000).
2. G. Preti, C.J. Wysocki and L.C. Smith, Worldwide Patent No. WO/2003/061609 (2003).
3. K.J. Rossiter, *Chem. Rev.*, **96**, 3201 (1996).
4. N. Andreas and T. Mcgee, Worldwide Patent No. WO/2005/079573 (2005).
5. P.A. Canizares, German Patent No. DE3531585 (1985).
6. W. Friedrich, W. Gebauer, W. Hafner, E. Markl and M. Regiert, German Patent No 4968668, Appl. 07/382,646 (1990).
7. T. Schmid, J.O. Daiss, R. Ilg, H. Surburg and R. Tacke, *Organometallics*, **22**, 4343 (2003).