# Efficient chemoselective addition of Grignard reagents to carbonyl compounds in 2-methyltetrahydrofuran

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Compared with tetrahydrofuran (THF) as a solvent for the addition reactions between Grignard reagents and carbonyl compounds 2-methyltetrahydrofuran affords the corresponding adducts in higher yields with higher chemoselectivities. Moreover, 2-methyltetrahydrofuran can be readily recycled and reused, which lowers the cost of the process and makes the reaction greener.

**Keywords:** 2-methyltetrahydrofuran, Grignard reactions, carbonyl compounds, alcohol synthesis

Solvents play important roles in organic synthesis and the replacement of toxic and volatile solvents such as benzene and dichloromethane by a variety of cleaner solvents has been evaluated recently.[1] The Grignard reaction is undoubtedly one of the most important carbon-carbon bond-forming reactions in organic synthesis as well as in medicinal chemistry.[2] The traditional solvents such as $Et_2O$ and THF have been widely used for the preparation of Grignard reagents. However, the hazardous properties of $Et_2O$ such as flammability and proneness to the formation of peroxides limit its application in industry, while THF, due to its complete miscibility with water, involves high costs in recycling and drying. Therefore, the development of new and environmentally benign solvents for the Grignard reaction was desirable.

Among various solvents, 2-methyltetrahydrofuran (2-MeTHF) has proved to be a greener and more environmentally friendly solvent than THF, due to its specific characteristics such as ready availability from renewable resources, being suitable for the preparation of higher concentrations of bromine-

containing Grignard reagents, and being readily recoverable.[3] Very recently, Schmalz and co-workers[4] reported that significant increase in enantioselectivities could be achieved when the reactions were carried out in 2-MeTHF instead of $Et_2O$ or THF.

Grignard reactions are often accompanied by so-called abnormal reactions such as reduction, enolisation, and pinacol coupling, and the corresponding products are shown in Scheme 1 respectively as **a**, **b**, **c**. This prompted us to design a procedure to suppress abnormal reactions by using 2-MeTHF as solvent. Herein, we report comparative results of Grignard reactions carried out in 2-MeTHF and THF and make an assessment of the prospects of the former for its applications both in laboratory practice and in industry.

Initially, we investigated the reaction between carbonyl compounds (**1**) and $n$-BuMgBr (**2a**) using 2-MeTHF and THF respectively as the solvent as $n$-BuMgBr is one of the most typical structures to generate the side products (Table 1).[5] It was found that a small amount of 2-MeTHF was enough to afford a clear solution of Grignard reagent (its concentration

**Table 1** The Grignard reactions of $n$-BuMgBr with aldehydes and ketones in 2-MeTHF and THF[a]



| Entry | $R^1$ | $R^2$ | THF | | 2-MeTHF | |
|---|---|---|---|---|---|---|
| | | | **3** | **4** | **3** | **4** |
| 1 | $C_6H_5$ | H | 79 | 0 | 86 (**3a**) | 0 |
| 2 | $p$-ClC$_6$H$_4$ | H | 85 | 0 | 87 (**3b**) | 0 |
| 3 | $p$-MeOC$_6$H$_4$ | H | 81 | 0 | 95 (**3c**) | 0 |
| 4 | $C_6H_5$ | Me | 53 | 31 | 72 (**3d**) | 20 |
| 5 | $p$-ClC$_6$H$_4$ | Me | 63 | 22 | 64 (**3e**) | 20 |
| 6 | $p$-MeOC$_6$H$_4$ | Me | 71 | 15 | 90 (**3f**) | 5 |
| 7 | $C_6H_5$ | Et | 53 | 31 | 85 (**3g**) | 11 |
| 8 | $p$-ClC$_6$H$_4$ | Et | 48 | 41 | 59 (**3h**) | 29 |

[a]All reactions were carried out in THF or 2-MeTHF under nitrogen atmosphere using substrates **1** (20 mmol) and $n$-BuMgBr **2a** (24 mmol).
[b]Isolated yields based on **1**.



**Scheme 1**

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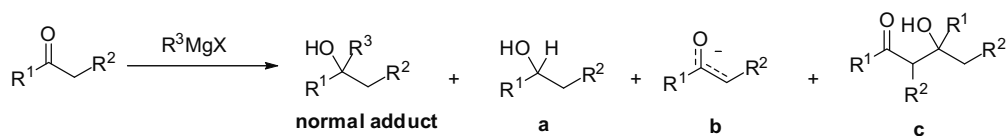
can reach up to 3 mol L$^{-1}$ in 2-MeTHF, but only about 1 mol L$^{-1}$ in THF). Most of the substrates, especially the ones with electron-donating groups at the *para*-position of aromatic rings, showed higher chemoselectivities and higher yields of the alcohols **3** could be obtained in 2-MeTHF than in THF (Table 1, entries 3 and 6).

Prompted by these intriguing results, a series of carbonyl compounds (including an ester) and a nitrile were reacted with *n*-BuMgBr so as to demonstrate the generality of the Grignard reactions in 2-MeTHF. Studies were also carried out with the Grignard reagents derived from benzyl chloride, allyl bromide, and bromobenzene. The results are illustrated in Table 2 and Scheme 2. As expected, all the aldehydes generated the addition products **3** in excellent yields (Table 2, entries 1–6, 13, 15, 17) and the troublesome reduction reaction was not observed when 2-MeTHF was used as the solvent. The Grignard reaction of ketones was equally effective to afford good to excellent yields of the desired products (Table 2, entries 7–12, 14, 16). The addition of Grignard reagents to ester **5** and nitrile **7** in 2-MeTHF (Scheme 2) afforded the corresponding products with good yields and good chemoselectivities.

On the other hand, 2-MeTHF can not only be used as reaction solvent, but also as the extraction solvent and it can be readily recovered according to a known procedure. Grignard reactions in the recycled 2-MeTHF were investigated and the

results are summarised in Table 2. To our delight, comparable high yields of the desired products were obtained.

In the light of the encouraging results, we attempted to apply the Grignard reaction in the synthesis of tramadol hydrochloride **9**, which is a non-addictive, non-opioid analgesic agent used for the treatment of moderate to moderately severe pain. Tramadol hydrochloride **9** is traditionally prepared by treatment of 3-methoxyphenylmagnesium bromide **2e** with 2-[(dimethylamino)methyl]cyclohexanone **10** in THF, followed by precipitation as the hydrochloride in different solvents.[6] We investigated this reaction both in 2-MeTHF and THF under similar reaction conditions. Compared with previous reported methodologies, the present protocol featured less solvent, a shorter reaction time and higher conversion (Table 3).

In summary, addition reactions between carbonyl compounds and Grignard reagents proceeded more smoothly in 2-MeTHF than in THF. The higher chemoselectivities, better yields of the adducts, together with the easy recycling and reuse of the solvent make 2-MeTHF a good alternative to THF. The methodology presented here may contribute to the development of green strategy in industry.

## Experimental

Starting materials and solvents were purchased from commercial sources and used without additional purification. Melting points were determined with a Büchi B-540 capillary melting point apparatus

**Table 2**   The results of Grignard reactions in 2-MeTHF[a]



| Entry | R$^1$ | R$^2$ | R$^3$ MgBr | Time/h | Product **3**, yield/%[b] |
|---|---|---|---|---|---|
| 1 | Furan-2-yl | H | *n*-Bu MgBr (**2a**) | 1 | **3i** (91, 90[c]) |
| 2 | *p*-FC$_6$H$_4$ | H | **2a** | 2 | **3j** (79) |
| 3 | Thiophene-2-yl | H | **2a** | 1 | **3k** (92) |
| 4 | 3,4-(OCH$_2$O)C$_6$H$_3$ | H | **2a** | 1.5 | **3l** (90) |
| 5 | *i*-C$_4$H$_9$ | H | **2a** | 1.5 | **3m** (89) |
| 6 | 4-Methylthiazole-5-yl | H | **2a** | 1.5 | **3n** (88) |
| 7 | -(CH$_2$)$_4$- | | **2a** | 1 | **3o** (72) |
| 8 | *m*-ClC$_6$H$_4$ | Et | **2a** | 2 | **3p** (58) |
| 9 | Furan-2-yl | Me | **2a** | 1.5 | **3q** (89, 87[c]) |
| 10 | Pyridin-2-yl | Me | **2a** | 1.5 | **3r** (78) |
| 11 | Me | Me | Bn MgCl (**2b**) | 1.5 | **3s** (75) |
| 12 | -(CH$_2$)$_5$- | | **2b** | 2 | **3t** (87) |
| 13 | Ph | H | Allyl MgBr (**2c**) | 1 | **3u** (96, 95[c]) |
| 14 | Ph | Me | **2c** | 1.5 | **3v** (94, 93[c]) |
| 15 | Ph | H | Ph MgBr (**2d**) | 2 | **3w** (89, 87[c]) |
| 16 | Ph | Me | **2d** | 2 | **3x** (78, 78[c]) |
| 17 | Furan-2-yl | H | **2d** | 1.5 | **3y** (97) |

[a]The reactions were carried out at room temperature under nitrogen atmosphere using carbonyl compounds (20 mmol) and Grignard reagents (24 mmol).
[b]Isolated yields based on **1**.
[c]The reactions were carried out in the recycled 2-MeTHF.
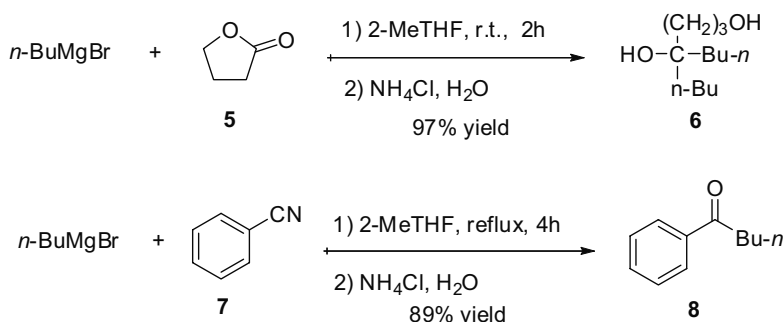


**Scheme 2**

**Table 3**  The preparation of tramadol hydrochloride (**9**) in 2-MeTHF and THF[a]
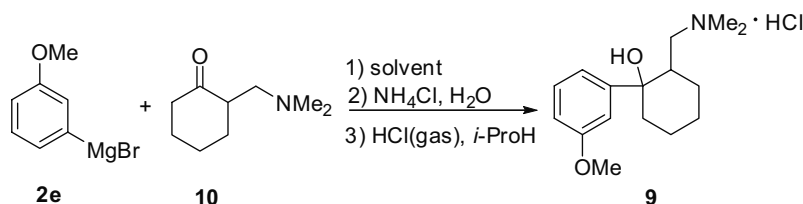


| Entry | Solvent | Amount/mL | Time/h | Yield/%[b] |
|---|---|---|---|---|
| 1 | 2-MeTHF | 50 | 6 | 82 |
| 2 | THF | 65 | 8 | 67 |

[a]Both reactions were carried out under nitrogen atmosphere using **10** (0.1 mol) and **2e** (0.12 mol).
[b]Isolated yields based on **10**.

and are uncorrected. IR spectra were recorded on a Nicolet Avatar-370 instrument. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AVANCE III-500 spectrometer and Varian Mercury plus-400 with tetramethylsilane (TMS) as an internal standard. Mass spectra were measured with a Finnigan Trace DSQ instrument. High resolution mass spectral (HRMS) analyses were measured on an APEX (Bruker) mass III spectrometer using ESI (electrospray ionisation) techniques. For chromatography silica-gel was purchased from Qingdao Haiyang Chemical Co., Ltd. (200–300 mesh). All spectroscopic data of the products were identical to those of authentic samples.

The recovery and drying of 2-MeTHF were accomplished in a distillation set-up consisting of a reboiler, a fractionation tower and an overhead condenser with a liquid-liquid decanter. The aqueous 2-MeTHF (1.5 L) was added to the set-up. Then azeotropic distillation was carried out for 5-8 h to remove the residual water gradually until no more water phase appeared in the overhead decanterat 60 °C. The water phase was recycled to the next batch. The dry 2-MeTHF was collected and when measured the reboiled product had less than 300ppm water. The total recycled yield was about 95%.

*General procedure for the synthesis of 3 in 2-MeTHF.*
A mixture of the aryl or alkyl halide (24.0 mmol) in anhydrous 2-MeTHF (15 mL) was added dropwise to magnesium turnings (25.2 mmol, 0.6 g) {preactivated by 1,2-dibromoethane (0.5 mmol)} under nitrogen atmosphere at room temperature. The mixture was cooled in an ice bath to 0 °C and then the carbonyl compounds (20.0 mmol) in anhydrous 2-MeTHF (5 mL) was added dropwise within 15 minutes and the mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and quenched with saturated NH4Cl. The layers were separated and the aqueous phase was extracted twice with 2-MeTHF (2 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and the crude product was purified by column chromatography to give **3**. The physical and spectroscopic data are as follows.

*1-Phenylpentan-l-ol* (**3a**): Yellow oil.[7] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 7.34 (d, $J$ = 6.0 Hz, 2H, ArH), 7.30 (t, $J$ = 6.0 Hz, 2H, ArH), 7.26–7.23 (m, 1H, ArH), 4.59 (t, $J$ = 6.4 Hz, 1H, CH), 2.23 (br s, 1H, OH), 1.77–1.64 (m, 2H, CH2), 1.38–1.19 (m, 4H, 2 × CH2), 0.87 (t, $J$ = 6.8 Hz, 3H, CH3).

*1-(4-Chlorophenyl)pentan-l-ol* (**3b**): Light-yellow oil. [8] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 7.32–7.24 (m, 4H, ArH), 4.62 (dd, $J_1$ = 6.4 Hz, $J_2$ = 12.8 Hz, 1H, CH), 2.00 (br s, 1H, OH), 1.79–1.61 (m, 2H, CH2), 1.39–1.18 (m, 4H, 2 × CH2), 0.88 (t, $J$ = 7.2 Hz, 3H, CH3).

*1-(4-Methoxyphenyl)pentan-l-ol* (**3c**): Colourless crystals.[9] m.p. 41.3–42.1 °C. ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 7.26–7.23 (m, 2H, ArH), 6.88–6.85 (m, 2H, ArH), 4.58 (t, $J$ = 7.0 Hz, 1H, CH), 3.79 (s, 3H, OCH3), 1.99 (br s, 1H, OH), 1.82–1.75 (m, 1H, CH2–Ha), 1.70–1.63 (m, 1H, CH2–Hb), 1.38–1.17 (m, 4H, 2 × CH2), 0.87 (t, $J$ = 7.0 Hz, 3H, CH3).

*2-Phenylhexan-2-ol* (**3d**): Yellow oil.[10] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 7.42 (d, $J$ = 7.6 Hz, 2H, ArH), 7.32 (t, $J$ = 7.6 Hz, 2H, ArH), 7.22 (t, $J$ = 7.6 Hz, 1H, ArH), 1.92 (br s, 1H, OH), 1.82–1.76 (m, 2H, CH2), 1.54 (s, 3H, CH3), 1.29–1.10 (m, 4H, 2 × CH2), 0.84 (t, $J$ = 7.2 Hz, 3H, CH3).

*2-(4-Chlorophenyl)hexan-2-ol* (**3e**): Yellow oil.[11] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 7.36 (d, $J$ = 6.4 Hz, 2H, ArH), 7.29 (d, $J$ = 6.4 Hz, 2H, ArH), 2.58 (br s, 1H, OH), 1.82–1.72 (m, 2H, CH2), 1.53 (s, 3H, CH3), 1.29–1.05 (m, 4H, 2 × CH2), 0.84(t, $J$ = 7.2 Hz, 3H, CH3).

*2-(4-Methoxyphenyl)hexan-2-ol* (**3f**): Yellow oil.[12] ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 7.35–7.32 (m, 2H, ArH), 6.86–6.83 (m, 2H, ArH), 3.78 (s, 3H, OCH3), 2.10 (br s, 1H, OH), 1.80–1.72 (m, 2H, CH2), 1.52 (s, 3H, CH3), 1.25–1.11 (m, 4H, 2 × CH2), 0.84 (t, $J$ = 7.0 Hz, 3H, CH3).

*3-Phenylheptan-3-ol* (**3g**): Yellow oil.[13] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 7.37 (d, $J$ = 7.2 Hz, 2H, ArH), 7.33 (t, $J$ = 7.2 Hz, 2H, ArH), 7.22 (t, $J$ = 7.2 Hz, 1H, ArH), 1.89–1.73 (m, 4H, 2 × CH2), 1.70 (br s, 1H, OH), 1.29–1.00 (m, 4H, 2 × CH2), 0.83 (t, $J$ = 7.2 Hz, 3H, CH3), 0.75 (t, $J$ = 7.2 Hz, 3H, CH3).

*3-(4-Chlorophenyl)heptan-3-ol* (**3h**): Yellow oil. ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 7.32–7.27 (m, 4H, ArH), 1.85–1.71 (m, 5H, 2 × CH2, OH), 1.29–1.01 (m, 4H, 2 × CH2), 0.82 (t, $J$ = 7.5 Hz, 3H, CH3), 0.74 (t, $J$ = 7.5 Hz, 3H, CH3); ^{13}C NMR (125 MHz, CDCl3, δ, ppm): 144.7, 132.0, 128.1 (2 × CH), 127.0 (2 × CH), 77.0, 42.3, 35.4, 25.6, 23.1, 14.0, 7.7; IR (neat): 3497, 2961, 2936, 2874 cm$^{-1}$; MS (EI): $m/z$ (%) 226.1 (M$^+$, 5), 197.1 (100), 169.0 (100), 151.0 (25), 111.0 (28), 77.0 (18); HRMS Calc. for C13H19ClO, 226.1124. Found 226.1113.

*1-(Furan-2-yl)pentan-l-ol* (**3i**): Brown oil.[14] ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 7.36 (d, $J$ = 1.5 Hz, 1H, ArH), 6.32 (dd, $J_1$ = 2.0 Hz, $J_2$ = 3.0 Hz, 1H, ArH), 6.22 (d, $J$ = 3.0 Hz, 1H, ArH), 4.65 (t, $J$ = 7.0 Hz, 1H, CH), 2.10 (br s, 1H, OH), 1.87–1.82 (m, 2H, CH2), 1.42–1.26 (m, 4H, 2 × CH2), 0.90 (t, $J$ = 7.0 Hz, 3H, CH3).

*1-(4-Fluorophenyl)pentan-l-ol* (**3j**): Yellow oil.[15] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 7.31–7.28 (m, 2H, ArH), 7.05–7.00 (m, 2H, ArH), 4.63 (t, $J$ = 6.8 Hz, 1H, CH), 1.97 (br s, 1H, OH), 1.80–1.64 (m, 2H, CH2), 1.40–1.19 (m, 4H, 2 × CH2), 0.88 (t, $J$ = 7.2 Hz, 3H, CH3).

*1-(Thiophen-2-yl)pentan-l-ol* (**3k**): Yellow oil.[16] ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 7.23 (dd, $J_1$ = 2.5 Hz, $J_2$ = 3.5 Hz, 1H, ArH), 6.95–6.94 (m, 2H, ArH), 4.88 (t, $J$ = 7.0 Hz, 1H, CH), 2.24 (br s, 1H, OH), 1.88–1.79 (m, 2H, CH2), 1.44–1.25 (m, 4H, 2 × CH2), 0.90 (t, $J$ = 7.0 Hz, 3H, CH3).

*1-(3,4-Dimethylenedioxyphenyl)pentan-l-ol* (**3l**): Light yellow oil.[17] ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 6.84 (s, 1H, ArH), 6.75 (d, $J$ = 1.5 Hz, 2H, ArH), 5.92 (s, 2H, CH2), 4.53 (t, $J$ = 7.0 Hz, 1H, CH), 2.11 (br s, 1H, OH), 1.77–1.72 (m, 1H, CH2–Ha), 1.65–1.61 (m, 1H, CH2–Hb), 1.36–1.18 (m, 4H, 2 × CH2), 0.87 (t, $J$ = 7.0 Hz, 3H, CH3).

*2-Methyloctan-3-ol* (**3m**): Yellow oil.[18] ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 3.69–3.64 (m, 1H, CH), 1.82–1.73 (m, 1H, CH), 1.73 (br s, 1H, OH), 1.44–1.21 (m, 8H, 4 × CH2), 0.93–0.90 (m, 9H, 3CH3).

*1-(4-Methylthiazol-5-yl)pentan-l-ol* (**3n**): Yellow oil. ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 8.55 (s, 1H, ArH), 4.96 (t, $J$ = 7.0 Hz, 1H, CH), 3.55 (br s, 1H, OH), 2.35 (s, 3H, CH3), 1.89–1.86 (m, 1H, CH2–Ha), 1.73–1.68 (m, 1H, CH2–Hb), 1.40–1.22 (m, 4H, 2 × CH2), 0.89 (t, $J$ = 7.0 Hz, 3H, CH3); ^{13}C NMR (125 MHz, CDCl3, δ, ppm): 150.7, 148.1, 136.9, 67.3, 39.5, 27.8, 22.4, 15.1, 14.0; IR (neat): 3280, 2958, 2931, 2861 cm$^{-1}$; MS(ESI): $m/z$ 186.1 [M + 1]$^+$, HRMS Calc. for C9H15NOS, 185.0874. Found 185.0879.

*1-Butylcyclopentan-l-ol* (**3o**): Light-yellow oil.[17] ^{1}H NMR (400 MHz, CDCl3, δ, ppm): 1.83–1.78 (m, 2H, CH2), 1.66–1.52 (m, 8H, 4 × CH2), 1.45–1.22 (m, 5H, 2 × CH2, OH), 0.92 (t, $J$ = 6.8 Hz, 3H, CH3).

*3-(3-Chlorophenyl)heptan-3-ol* (**3p**): Yellow oil. ^{1}H NMR (500 MHz, CDCl3, δ, ppm): 7.42 (s, 1H, ArH), 7.23–7.20 (m, 2H, ArH), 7.19–7.16 (m, 1H, ArH), 2.15 (br s, 1H, OH), 1.85–1.72 (m, 4H, 2 × CH2), 1.29–0.99 (m, 4H, 2 × CH2), 0.82 (t, $J$ = 7.0 Hz, 3H, CH3), 0.74 (t, $J$ = 7.0 Hz, 3H, CH3); ^{13}C NMR (125 MHz, CDCl3, δ, ppm): 148.5, 134.1, 129.2, 126.4, 125.9, 123.7, 77.1, 42.3, 35.4, 25.6, 23.1, 14.0, 7.7; IR (neat): 3475, 2960, 2935, 2872 cm$^{-1}$; MS (EI): $m/z$ (%) 226.1 (M$^+$, 4), 197.0 (100), 169.0 (97), 151.0 (22), 111.0 (50), 77.0 (58); HRMS Calc. for C13H19ClO, 226.1124. Found 226.1118.

*2-(Furan-2-yl)hexan-2-ol* **(3q)**: Yellow oil.[19] ^{1}H NMR(400 MHz, CDCl$_3$, δ, ppm): 7.34 (d, $J$ = 1.2 Hz, 1H, ArH), 6.30 (dd, $J_1$ = 2.0 Hz, $J_2$ = 3.2 Hz, 1H, ArH), 6.18 (d, $J$ = 2.0 Hz, 1H, ArH), 1.86–1.79 (m, 2H, CH$_2$), 1.53 (s, 3H, CH$_3$), 1.30–1.20 (m, 4H, 2 × CH$_2$), 0.87 (t, $J$ = 7.0 Hz, 3H, CH$_3$).

*2-(Pyridin-3-yl)hexan-2-ol* **(3r)**: Brown oil.[20] ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm): 8.52–8.51 (m, 1H, ArH), 7.72–7.69 (m, 1H, ArH), 7.33 (d, $J$ = 9.0 Hz, 1H, ArH), 7.21–7.18 (m, 1H, ArH), 5.21 (br s, 1H, OH), 1.86–1.73 (m, 2H, CH$_2$), 1.51 (s, 3H, CH$_3$), 1.36–1.20 (m, 4H, 2 × CH$_2$), 0.82 (t, $J$ = 7.5 Hz, 3H, CH$_3$).

*1,1-Dimethyl-2-phenylethanol* **(3s):** Yellow oil.[21] ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 7.30–7.19 (m, 5H, ArH), 2.75 (s, 2H, CH$_2$), 1.72 (s, 1H, OH), 1.21 (s, 6H, 2 × CH$_3$).

*1-Benzylcyclohexanol* **(3t)**: Light-yellow crystals. M.p. 55.3–56.4 °C (lit.,[22] 55–56 °C); ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 7.32–7.20 (m, 5H, ArH), 2.75 (s, 2H, CH$_2$), 1.63–1.41 (m, 9H, 4 × CH$_2$, OH), 1.27 (t, $J$ = 6.8 Hz, 2H, CH$_2$).

*1-Phenylbut-3-en-1-ol* **(3u)**: Yellow oil.[23] ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 7.35–7.32 (m, 4H, ArH), 7.30–7.23 (m, 1H, ArH), 5.83–5.72 (m, 1H, CH), 5.15–5.10 (m, 2H, CH$_2$), 4.68 (t, $J$ = 8.8 Hz, 1H, CH), 2.52–2.44 (m, 2H, CH$_2$), 2.25 (br s, 1H, OH).

*2-Phenylpent-4-en-2-ol* **(3v)**: Light-yellow oil.[24] ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 7.44 (d, $J$ = 7.6 Hz, 2H, ArH), 7.34 (t, $J$ = 7.6 Hz, 2H, ArH), 7.25–7.22 (m, 1H, ArH), 5.67–5.58 (m, 1H, CH), 5.12 (t, $J$ = 9.6 Hz, 2H, CH$_2$), 2.68 (dd, $J_1$ = 7.6 Hz, $J_2$ = 14.0 Hz, 1H, CH$_2$–Ha), 2.50 (dd, $J_1$ = 7.6 Hz, $J_2$ = 14.0 Hz, 1H, CH$_2$–H$_b$), 2.04 (br s, 1H, OH), 1.54 (s, 3H, CH$_3$).

*Diphenylmethanol* **(3w)**: Colourless crystals. M.p. 65.1–66.0 °C (lit.,[25] 65–66 °C). ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm): 7.39–7.37 (m, 4H, ArH), 7.35–7.32 (m, 4H, ArH), 7.28–7.25 (m, 2H, ArH), 5.84 (s, 1H, CH), 2.14 (br s, 1H, OH).

*1,1-Diphenylethanol* **(3x)**: Colourless crystals. M.p. 79.3–79.8 °C (lit.,[26] 78–80 °C). ^{1}H NMR(500 MHz, CDCl$_3$, δ, ppm): 7.48–7.45 (m, 4H, ArH), 7.38–7.35 (m, 4H, ArH), 7.31–7.28 (m, 2H, ArH), 2.31 (br s, 1H, OH), 2.00 (s, 3H, CH$_3$).

*(2-Furyl)phenylmethanol* **(3y)**: Brown oil.[27] ^{1}H NMR(400 MHz, CDCl$_3$, δ, ppm): 7.43–7.31 (m, 6H, ArH), 6.30 (dd, $J_1$ = 2.0 Hz, $J_2$ = 3.2 Hz, 1H, ArH), 6.10 (d, $J$ = 3.2 Hz, 1H, ArH), 5.81 (s, 1H, CH), 2.55 (br s, 1H, OH).

*4-Butyloctane-1,4-diol* **(6)**: Light yellow oil.[28] ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 3.64 (t, $J$ = 5.6 Hz, 2H, CH$_2$), 2.54 (br s, 2H, 2 × OH), 1.64–1.43 (m, 8H, 4 × CH$_2$), 1.34–1.23 (m, 8H, 4 × CH$_2$), 0.93–0.89 (m, 6H, 2 × CH$_3$).

*1-Phenylpentan-1-one* **(8)**: Light yellow oil.[29] ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 7.96 (m, 2H, ArH), 7.57–7.53 (m, 1H, ArH), 7.47–7.43 (m, 2H, ArH), 2.96 (t, $J$ = 7.2 Hz, 2H, CH$_2$), 1.76–1.69 (m, 2H, CH$_2$), 1.46–1.37 (m, 2H, CH$_2$), 0.95 (t, $J$ = 7.2 Hz, 3H, CH$_3$).

*Tramadol hydrochloride* **(9)**: Colourless crystals. m.p. 179.5–180.3 °C (lit.,[30] 180–181 °C). ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 11.47 (br s, 1H, HCl), 7.32–7.28 (t, $J$ = 8.0 Hz, 1H, ArH), 7.09 (s, 1H, ArH), 7.00 (d, $J$ = 2.4 Hz, 1H, ArH), 6.80 (dd, $J_1$ = 2.4 Hz, $J_2$ = 8.0 Hz, 1H, ArH), 3.83 (s, 3H, OCH$_3$), 3.04–2.98 (m, 1H, CH), 2.67 (d, $J$ = 5.2 Hz, 3H, CH$_3$), 2.61–2.55 (m, 2H, CH$_2$), 2.46 (d, $J$ = 5.2 Hz, 3H, CH$_3$), 2.44 (s, 1H, OH), 2.14–1.42(m, 8H, 4 × CH$_2$).

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