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Microwave-assisted methylation of phenols with tetramethylammonium chloride in the presence of K_2CO_3 or Cs_2CO_3

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Dedicated to the memory of the late Professor Ljubo Golič

ABSTRACT

We have evaluated the potential of using tetramethylammonium chloride (Me_4NCl) as an alternative methylating agent for phenols under microwave-assisted conditions. Its chemical behavior was tested in a reaction with 2-naphthol in the presence of various bases and solvents. The method was then applied in 1,2-dimethoxyethane or toluene under heterogeneous conditions for the O-methylation of a series of phenolic compounds. We found that many simple phenols can be methylated in the presence of K_2CO_3, whereas some other less-reactive phenols require the presence of the more reactive Cs_2CO_3.

1. Introduction

Many reagents already exist for the O-methylation of phenols. Methyl iodide, dimethyl sulfate, and diazomethane are the most commonly used.[1] Methyl chloride and methyl bromide are gases at room temperature, which means they have a very limited usability. However, the above reagents present serious toxicological and carcinogenic risks due to their volatility and their ability to methylate nucleic acids in living organisms.[2] Diazomethane, as well as being a very toxic gas, presents additional risks due to its explosive nature, and needs to be freshly prepared in special apparatus prior to use. As a consequence, trimethylsilyldiazomethane has been proposed as a less-hazardous alternative to diazomethane.[3] Sulfonic acids' methyl esters, especially methyl *p*-toluenesulfonate, are suitable reagents for laboratory-scale reactions.[4] Trimethyl phosphite and trimethyl phosphate were also found to be efficient for methylating phenols.[5] Finally, these methylations can also be achieved using methanol under standard Mitsunobo conditions.[6]

Environmental and toxicological concerns have resulted in an increased interest in new methylating reagents in general, of which dimethyl carbonate seems to be the most promising for industrial use. It is inexpensive, nontoxic, biodegradable and requires only catalytic amounts of bases for reactions involving methylations.[7] The O-methylation of phenols generally requires temperatures of 120–200 °C, but more convenient methods have also been described.[8] The O-methylation of phenol with other, less-reactive esters under harsh conditions has also been reported.[9] On the other hand, onium salts, such as trialkylsulfonium and trialkylselenonium salts,[10] and tetraalkylammonium salts can also be used for alkylations. Over a century ago it was shown that the phenolate salts of quaternary amines decompose on strong heating into phenyl alkyl ethers and tertiary amines.[11] Tetramethylammonium, phenyltrimethylammonium and other quaternary amine hydroxides have long been known as reagents in gas-chromatography analysis, and used for the on-column derivatization of phenols, thiols, carboxylic acids, amines, and acidic NH groups.[12] Regardless of their relatively common use in gas chromatography, there have only been relatively few reports of quaternary amines being used as alkylating reagents in preparative synthesis. Phenyltrimethylammonium salts, being some of the most reactive, have found limited use in the O-methylation of phenols, particularly phenolic morphinans, where methyl iodide or dimethyl sulfate might cause quaternization at the tertiary amine function.[13] Other quaternary salts, however, have mostly been neglected as alkylating reagents, primarily because of their much lower reactivity. For example, betaine (2-trimethylammonioacetate) was reported to methylate a wide assortment of simple phenols under harsh conditions (200–230 °C), with the evolution of CO_2 and trimethylamine, applying CaO as a base.[14] Tetramethylammonium hydroxide (Me_4NOH) was reported to be a useful reagent for the methylation of estradiol and estriol, giving excellent yields of products with *O*-methylated phenolic groups.[15] When using a tenfold excess of Me_4NOH it was possible to *O*-methylate, not only phenolic, but also the aliphatic hydroxy groups of the two steroids. A report in Chinese was published on the O-, N-, and S-alkylation of some carboxylic acids, amines, anilines, and thiophenol, with

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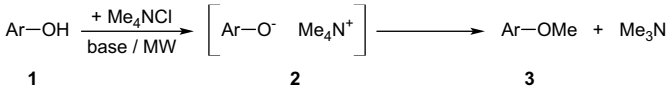
several quaternary ammonium halides at 160 °C in 1-methyl-2-pyrrolidinone (NMP) as a solvent.[16] However, when searching for preparative procedures of phenolic compounds O-alkylation with tetramethylammonium halides we only found two patents: one describing the methylation of 3,4-dihydroxybenzaldehyde with Me_4NBr and KOH to give isovanillin in an 11% yield[17] and the other describing the methylation of 4-phenylphenol with Me_4NCl and K_2CO_3 in NMP at 160 °C with a nearly quantitative yield.[18]

During our work we were in need of small amounts of some simple, substituted methyl aryl ethers. We were, however, surprised to find so little information in the scientific literature related to tetramethylammonium salts as methylating reagents and thus decided to explore this method further. The possibility of avoiding the use of carcinogenic reagents for such routine laboratory preparations was attractive enough for us to try using Me_4NCl under heterogeneous reaction condition in conjunction with a microwave-accelerated reaction.[19,20] Me_4NCl is an inexpensive, nonvolatile crystalline solid (mp >300 °C), and though quite toxic if ingested, it presents no such toxicity hazards originating from volatility, as is the case with diazomethane, methyl iodide, and dimethyl sulfate. But most importantly, Me_4NCl is not a suspected carcinogen. Its molecular weight is also low enough to make its use as a methylation reagent practical and economical on the basis of its weight. The side products of its use in methylation are trimethylamine, which leaves the reaction mixture as a gas, and the chloride salt of the base employed.

2. Results and discussion

We report here the results of our investigation of the methylation of a series of phenols **1** with tetramethylammonium chloride toward aryl methyl ethers **3** via tetramethylammonium phenolates **2** (Scheme 1).



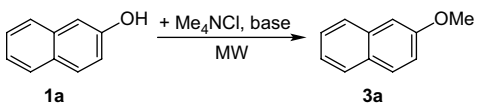
Scheme 1. Methylation of phenols using Me_4NCl.

We first investigated the influence of the base used on the conversion in a model system of 2-naphthol (**1a**) and Me_4NCl in a 1:1 ratio in 1,2-dimethoxyethane (DME) as a solvent (0.5 mmol substrate in 2 mL solvent); 1 mol equiv of the base was used (Table 1). The reactions involved 10 min of microwave heating in a standard, closed reaction vessel (10 mL) at 145 °C (according to the IR sensor of the microwave reactor). The reaction mixture was then acidified and analyzed by means of HPLC and the conversion established by the use of authentic standards. No 2-methoxynaphtalene (**3a**) could be detected in the absence of the base (entry 1). Nucleophilic organic bases like pyridine and 1,4-(diazabicyclo[2.2.2]octan) (DABCO) also did not give detectable amounts of 2-methoxynaphthalene (entries 2 and 3). The use of Cs_2CO_3, KOH, and NaOH gave the best results (entries 9, 10, and 11). $LiOH\cdot H_2O$ gave negligible conversions (entry 6), perhaps due to the presence of hydration water or as a reflection of the Lewis-acid nature of lithium salts in aprotic solvents. The inhibition of the methylation by the presence of water might also explain the somewhat better performance of NaOH in comparison to KOH pellets, which generally contain up to 15% of water. In addition, K_2CO_3 (entry 8) was somewhat less efficient than Cs_2CO_3, KOH, and NaOH. However, since our aim was to develop a method suitable for a microwave reactor, we had to avoid the use of alkali hydroxides since they represent a hazard because of the very high microwave absorption in their melts and their ability to etch the walls of the reaction vessel (which can result in the reaction vessel exploding when under pressure). Using alkali hydroxides also inevitably narrows the spectrum of tolerated functional groups. On the other hand, Cs_2CO_3 seems to be too expensive to be used in any preparative method involving simple, reactive substrates. We therefore decided to investigate the scope and the limitations of the use of K_2CO_3 as the base of choice for simple substrates, and the application of Cs_2CO_3 for the more precious ones.

Table 2 shows the influence of the choice of solvent on the same system using K_2CO_3 as a base. Water as a solvent gave the lowest conversion to 2-methoxynaphthalene, even though it is the only solvent that efficiently dissolves Me_4NCl as well as the base (entry 1). Among the alcohols, 2-propanol was the best solvent (entries 2, 3, and 4). Though *N*,*N*-dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP), and acetonitrile perform excellently as solvents in classical S_N2-type *O*-alkylations of phenols, in this reaction they were inferior to all the less-polar, aprotic solvents tested (entries 5, 6, and 7). In fact, 1,2-dimethoxyethane (DME), ethyl acetate, and toluene all gave better results (entries 8, 9, and 10). DME was thus selected as the solvent of choice because of its complete inertness under the conditions used and due to its relative volatility, making the isolation easier. For comparison, in some cases toluene was also applied as a solvent.

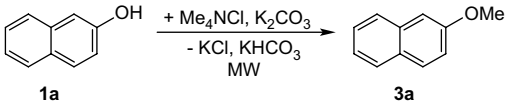
Such alkylations, where both the nucleophile and the alkylating reagent are charged ions, are of a less-common type (designated as type-III S_N2 by Smith and March).[21] The detrimental effects of the water on the reaction conversion can be explained on the basis of

Table 1
Influence of the base on the methylation of 2-naphthol with Me_4NCl in DME at 145 °C



Entry	Base	Conversion %
1	—	0
2	Pyridine	0
3	DABCO	0
4	$Mg(OH)_2$	<1
5	Li_2CO_3	<1
6	$LiOH\cdot H_2O$	~1
7	Na_2CO_3	3
8	K_2CO_3	40
9	Cs_2CO_3	63
10	KOH	67
11	NaOH	82

Table 2
Influence of the solvent on the methylation of 2-naphthol with Me_4NCl using K_2CO_3 as a base at 145 °C



Entry	Solvent	Conversion %
1	Water	<1
2	MeOH	<1
3	EtOH	5
4	2-PrOH	16
5	DMF	17
6	MeCN	20
7	NMP	27
8	DME	40
9	AcOEt	46
10	PhMe	51

Table 3
Methylation of phenols with Me_4NCl in the presence of K_2CO_3 or Cs_2CO_3 under microwave irradiation for 25 or 60 min at 145 °C

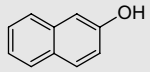
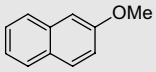
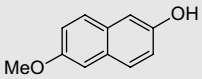
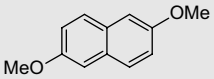
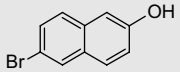
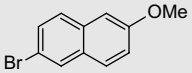
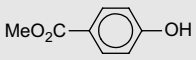
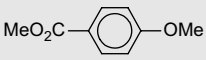
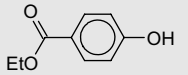
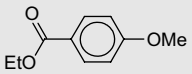
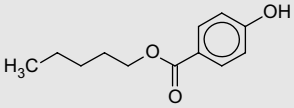
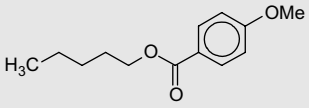
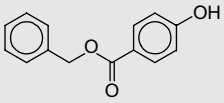
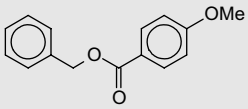
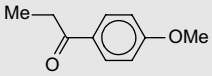
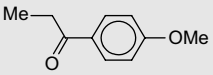
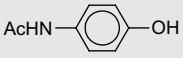
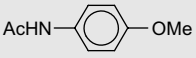
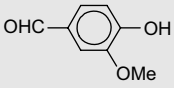
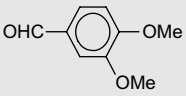
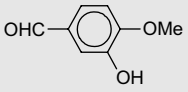
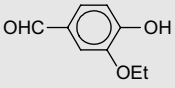
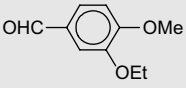
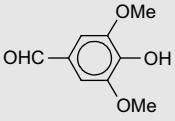
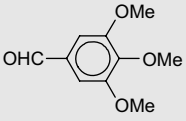
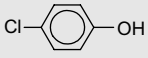
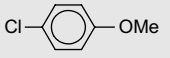
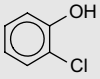
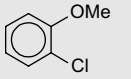
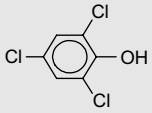
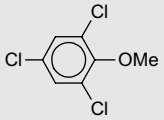
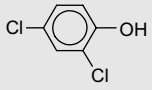
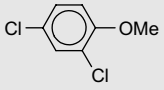
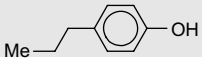
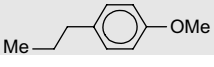
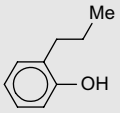
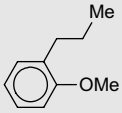
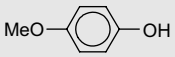
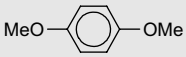
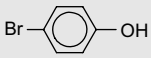
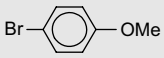
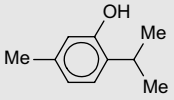
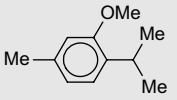
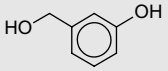
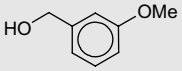
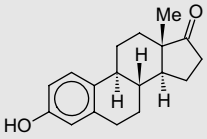
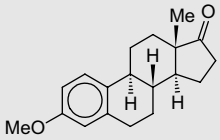
Entry	Phenol		Product		Solvent	Reaction time (min)	Yield[a] (%) using K_2CO_3	Yield[a] (%) using Cs_2CO_3
1		(**1a**)		(**3a**)	DME	25	87	—
2		(**1b**)		(**3b**)	DME	25 60	66 78	57 85
3		(**1c**)		(**3c**)	DME	60	91	92
4		(**1d**)		(**3d**)	DME	25	54	—
5		(**1e**)		(**3e**)	DME	25	74	—
6		(**1f**)		(**3f**)	DME	25	71	—
7		(**1g**)		(**3g**)	DME PhMe	25 25	28 61	— —
8		(**1h**)		(**3h**)	DME	25	98	—
9		(**1i**)		(**3i**)	DME	25	65	—
10		(**1j**)		(**3j**)	DME	25	60	45
11		(**1k**)			DME	25	19	92
12		(**1l**)		(**3l**)	DME	25 60	39 —	48 96
13		(**1m**)		(**3m**)	DME PhMe	25 60	33 38	96 —
14		(**1n**)		(**3n**)	DME	25 60	27 68	— —
15		(**1o**)		(**3o**)	DME	60	55	—
16		(**1r**)		(**3r**)	DME	60	59	85
17		(**1s**)		(**3s**)	PhMe	25	58	—
18		(**1t**)		(**3t**)	DME	25	61	—

Table 3 (*continued*)

Entry	Phenol		Product		Solvent	Reaction time (min)	Yield[a] (%) using K_2CO_3	Yield[a] (%) using Cs_2CO_3
19		(**1u**)		(**3u**)	DME	25	54	—
20		(**1v**)		(**3v**)	DME	25 60	38 78	— —
21		(**1w**)		(**3w**)	DME	60	76	—
22		(**1x**)		(**3x**)	DME	60	71	—
23		(**1y**)		(**3y**)	DME	60	43	72
24		(**1z**)		(**3z**)	DME	60 120	— 61	44 90

[a] Isolated yields are given.

the solvation of both the nucleophile (phenoxide anion) and electrophile (ammonium cation). Since only the unsolvated ions can efficiently interact in an S_N2 nucleophilic substitution, the solvation represents a barrier, inhibiting the formation of the reaction transition state. However, when the reaction is performed in aprotic, nonpolar solvents, unsolvated opposite ions are free to associate in an ion-pair complex, where the S_N2 reaction can produce a neutral molecule.

The solvation of the tetramethylammonium cation by polar, aprotic solvents (DMF, acetonitrile, and NMP) might explain their lower efficiency in comparison with the less-polar, aprotic solvents (DME, ethyl acetate, and toluene). On the other hand, we would expect a much more dramatic solvation effect when using protic solvents, which are able to solvate both the phenoxide anion as well as the tetramethylammonium cation. The formation of an ion-pair complex in such protic solvent is less likely, thus explaining the unusually low conversions observed in water and methanol. In accordance with this hypothesis, nonpolar, aprotic solvents gave the best conversions in the methylation of 2-naphthol, even though such media are most unfavorable in view of the lower solubility of Me_4NCl and K_2CO_3.

Finally, we performed a series of preparative O-methylations of various simple phenols to evaluate the potential of Me_4NCl for synthetic use. The reactions were performed under heterogeneous conditions using K_2CO_3 as the base and DME or toluene as the solvent in the microwave reactor. For an easier comparison of the results, the reaction time used was generally 25 or 60 min. As shown in Table 3, longer reaction times often lead to yield improvements, unless the substrate is unstable in the reaction conditions.

We observed a marked influence of the phenol substitution on the isolated reaction yields. However, simple generalizations are hard to draw, especially when considering the heterogenous nature of the reaction. Nevertheless, phenols *para* substituted with a carbonyl group consistently gave better results. For example, *p*-hydroxypropiophenone (**1h**) gave an almost quantitative yield of **3h**. *p*-Hydroxybenzoic acid esters (**1d–g**) gave moderate yields of the products, except for the methyl ester (**1d**), which underwent partial hydrolysis, as indicated by the chromatographic detection of *p*-hydroxybenzoic acid among the reaction products. In the methylation of benzyl *p*-hydroxybenzoate (**1g**) we observed a much better yield when using toluene (61%) as opposed to DME (28%). The influence of the carbonyl group at the *para* position is particularly evident in the methylations of vanillin (**1j**) and isovanillin (**1k**), leading to the identical product (**3j**), but in 60% and 19% yields, respectively. This effect might be attributed to the increased acidity of the phenolic group in vanillin, resulting in a faster consumption of the carbonate under the heterogeneous conditions used.

Chlorophenols (**1n–1r**) gave low yields for short reaction times, but prolonging the reaction time to 60 min resulted in better yields. A similar effect of prolonged heating was also observed with *p*-methoxyphenol (**1v**) and *p*-bromophenol (**1w**).

No methylation of the benzylic alcohol group was observed during the methylation of 3-hydroxybenzyl alcohol (**1y**), but the reaction gave a relatively low yield (43%) of 3-methoxybenzyl alcohol (**3y**), even after prolonged heating.

Steric factors appear to be of some importance, as indicated by the low yield of syringaldehyde (**1m**) methylation (33%, entry 13) as opposed to vanillin (60%, entry 10), though the electronic and chelating factors of the additional methoxy group could also play an important role. Nevertheless, thymol (**1x**) with the isopropyl group at the *ortho* position, required longer reaction times than the other alkyl substituted phenols, like **1t** and **1u**, in order to give comparable yields, thus additionally indicating some steric influence on the reaction (entries 18, 19, and 22).

We were unable to obtain reproducible yields from *p*-nitrophenol methylation under such conditions. The yields varied from 15–41% (not shown in Table 3), apparently due to decomposition to a tarry material.

Based on an optimization study, cesium carbonate, which is an excellent base in aprotic solvents,[22] was expected to give better results, and some less-simple or problematic substrates certainly warrant its use. Syringaldehyde (**1m**), which gave poor yields using K_2CO_3 in both DME and toluene, gave excellent yields in DME with Cs_2CO_3 as a base. Similar improvements, though less dramatic, were obtained for 2,4,6-trichlorophenol (**1r**) and 3-hydroxybenzyl

alcohol (**1y**). Substituted 2-naphthol substrates like **1b** and **1c**, which after prolonged heating gave good results with K_2CO_3 as a base, also performed well under such conditions. However, the most surprising results were obtained with vanillin (**1j**) and isovanillin (**1k**), whose performance under such conditions was the opposite of what was obtained with K_2CO_3 as a base. While isovanillin gave an excellent improvement with Cs_2CO_3, vanillin gave a poorer yield than that obtained with K_2CO_3. Similarly, 3-ethoxy-4-hydroxybenzaldehyde (**1l**), a compound homologous to vanillin, gave only a slight improvement using Cs_2CO_3, though excellent yields were obtained with a longer reaction time. Estrone (**1z**), a phenolic steroid, gave a good yield of *O*-methylestrone (**3z**) in 2 h of reaction time. Reaction time of 1 h did not give satisfactory yield, perhaps indicating that more complex phenols generally require longer reaction times under such conditions. When we tried to methylate *p*-nitrophenol, a violent decomposition occurred, resulting in a sudden pressure increase, which was shown to be dangerous to the microwave equipment.

The reaction mixtures were diluted with ethyl acetate, insoluble solids removed by filtration, and the corresponding product was isolated using radial chromatography. However, the isolation of several phenols can also be simplified by performing an extraction with diethyl ether and removing the unreacted phenols by washing the extract with 2 M aqueous sodium hydroxide. This method often resulted in products of comparable purity.

To evaluate the possibility of scaling up the reactions we used the standard 80 mL microwave reaction vessel. All the reaction components were scaled up 25-times, again using 2-naphthol (**1a**) as the model substrate (50 mmol; 7.2 g) applying K_2CO_3 as a base and DME as a solvent. The reaction proceeded sluggishly at 145 °C and even prolonging the reaction time up to 2 h gave only a 37% of isolated yield of 2-methoxynaphthalene (**3a**). Heating the reaction mixture for 3 h at 160 °C was required to achieve an 89% isolated yield of **3a**. Thus, for scaling up this heterogeneous reaction harsher reaction conditions are required than those used at 2 mmol scale.

3. Conclusions

We have developed a new method for the microwave-assisted O-methylation of phenolic compounds using tetramethylammonium chloride as a noncarcinogenic reagent. The heterogeneous reaction conditions with potassium carbonate as a base generally give moderate to excellent yields that can generally be improved by using cesium carbonate when required. Nonpolar, aprotic solvents were found to be the best for this reaction. *CAUTION:* We do not recommend using nitrophenols as substrates under such microwave conditions because of the possibility of their rapid decomposition.

4. Experimental

4.1. General

Microwave reactions were conducted using a focused microwave unit (Discover by CEM Corporation, Matthews, NC). The machine consists of a continuous, focused microwave power-delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel via the septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature controller mounted under the reaction vessel. Large scale reaction was conducted in a hermetically closed 80 mL glass vessel equipped with an external temperature controller measuring the temperature trough a fiber optic immersed in the reaction media. All the reaction mixtures were stirred with a Teflon-coated magnetic stirring bar in the vessel. High-performance liquid chromatography was performed on a Nucleosil C-18 column using an acetonitrile/water mobile phase and a UV detector at 254 nm. NMR spectra were recorded on a Bruker Avance DPX 300-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard at 29 °C. MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Melting points are uncorrected and were measured on a Kofler micro hot stage. All reagents used were commercially available or prepared using published methods. Potassium and cesium carbonates were finely ground and dried at 150 °C for 12 h.

4.2. General procedure for the methylation of phenols with trimethylammonium chloride

Into a 10-mL microwave reaction vessel was added the phenolic substrate (2 mmol), tetramethylammonium chloride (290 mg, 2.5 mmol), anhydrous base (2.5 mmol K_2CO_3 or Cs_2CO_3), and the solvent (2 mL; 1,2-dimethoxyethane or toluene; see Table 3). The reaction vessel was purged with argon before closing and irradiated in the microwave reactor for the specified time at 145 °C with magnetic stirring (the microwave power limit was set to 50 W for K_2CO_3 and 100 W for Cs_2CO_3 based reactions). The vessel was vented in a fume hood to remove the trimethylamine. The reaction mixture was diluted with ethyl acetate (5 mL), the solids filtered off and then washed with additional ethyl acetate (2×5 mL). The filtrate was evaporated in vacuo and the product isolated with radial chromatography using petroleum ether/ethyl acetate or petroleum ether/diethyl ether as eluents. The product identity was confirmed by ^{1}H NMR and IR spectroscopy as well as mp, where applicable.

4.3. Analytical and spectroscopic data of products

*4.3.1. 2-Methoxynaphthalene (**3a**)*[23]

Mp 70–71 °C (lit.[23] 71–72 °C); ^{1}H NMR δ 3.92 (s, 3H), 7.10–7.18 (m, 2H), 7.33 (m, 1H), 7.43 (m, 1H), 7.75 (m, 3H); IR (KBr) 1632, 1597, 1506, 1476, 1462 cm^{-1}.

*4.3.2. 2,6-Dimethoxynaphthalene (**3b**)*[24]

Mp 149–151 °C (lit.[24] 149 °C); ^{1}H NMR δ 3.90 (s, 6H), 7.07–7.16 (m, 4H), 7.64 (d, J=8.7 Hz, 2H); IR (KBr) 1603, 1503, 1453, 1389, 1234 cm^{-1}.

*4.3.3. 2-Bromo-6-methoxynaphthalene (**3c**)*[25]

Mp 101–103 °C (lit.25 105–107 °C); ^{1}H NMR δ 3.91 (s, 3H), 7.09 (d, J=2.5 Hz, 1H), 7.16 (dd, J_1=2.5 Hz, J_2=8.9 Hz, 1H), 7.49 (dd, J_1=2.0 Hz, J_2=8.7 Hz, 1H), 7.62 (m, 2H), 7.91 (d, J=1.7 Hz, 1H); IR (KBr) 1626, 1587, 1499, 1387, 1266 cm^{-1}.

*4.3.4. Methyl 4-methoxybenzoate (**3d**)*[26]

Mp 47–48 °C (lit.[26] 48 °C); ^{1}H NMR δ 3.86 (s, 3H), 3.88 (s, 3H), 6.92 (AA′XX′, J=9.0 Hz, 2H), 7.99 (AA′XX′, J=9.0 Hz, 2H); IR (KBr) 1711, 1609, 1512, 1430, 1321 cm^{-1}.

*4.3.5. Ethyl 4-methoxybenzoate (**3e**)*[27]

^{1}H NMR δ 1.38 (t, J=7.2 Hz, 2H), 3.86 (s, 3H), 4.34 (q, J=7.2 Hz, 2H), 6.91 (AA′XX′, J=8.4 Hz, 2H), 8.00 (AA′XX′, J=8.4 Hz, 2H); IR (NaCl) 1711 br, 1607, 1513, 1462, 1367 cm^{-1}.

*4.3.6. Pentyl 4-methoxybenzoate (**3f**)*[28]

^{1}H NMR δ 0.93 (t, J=7.1 Hz, 3H), 1.30–1.49 (m, 4H), 1.76 (m, 2H), 3.86 (s, 3H), 4.28 (t, J=6.7 Hz), 6.9 (d, J=9.0 Hz, 2H), 7.97 (d, J=9.0 Hz, 2H); IR (NaCl) 1712, 1607, 1512, 1465 cm^{-1}.

*4.3.7. Benzyl 4-methoxybenzoate (**3g**)*[28]

^{1}H NMR δ 3.85 (s, 3H), 5.34 (s, 2H), 6.91 (AA′XX′, J=9.0 Hz, 2H), 7.29–7.47 (m, 5H), 8.03 (AA′XX′, J=9.0 Hz, 2H); IR (NaCl) 1711, 1606, 1581, 1511, 1456 cm^{-1}.

*4.3.8. 1-(4-Methoxyphenyl)propan-1-one (**3h**)*[29]

Mp 25–27 °C (from petroleum ether) (lit.[29] 27 °C); ^{1}H NMR δ 1.21 (t, J=7.2 Hz, 3H), 2.95 (q, J=7.2 Hz, 2H), 3.87 (s, 3H), 6.93 (AA′XX′, J=9.0 Hz, 2H), 7.95 (AA′XX′, J=9.0 Hz, 2H); IR (KBr) 1679, 1602, 1510, 1460, 1418 cm^{-1}.

*4.3.9. N-(4-Methoxyphenyl)acetamide (**3i**)*[30]

Mp 128–130 °C (lit.[30] 129–130 °C); ^{1}H NMR δ 2.15 (s, 3H), 3.79 (s, 3H), 6.85 (AA′XX′, J=9.0 Hz, 2H), 7.14 (br s, 1H), 7.38 (AA′XX′, J=9.0 Hz, 2H); IR (KBr) 1650, 1606, 1560, 1512 cm^{-1}.

*4.3.10. 3,4-Dimethoxybenzaldehyde (**3j**)*[31]

Mp 41–43 °C (lit.[31] 42 °C); ^{1}H NMR δ 3.95 (s, 3H), 3.97 (s, 3H), 6.98 (d, J=8.1 Hz, 1H), 7.42 (d, J=1.8 Hz, 1H), 7.46 (dd, J_1=8.1 Hz, J_2=1.8 Hz, 2H), 9.86 (s, 1H); IR (KBr) 1686 br, 1587 br, 1513, 1466, 1424 cm^{-1}.

*4.3.11. 3-Ethoxy-4-methoxybenzaldehyde (**3l**)*[32]

Mp 47–49 °C (lit.[32] 49.5–50.5 °C); ^{1}H NMR δ 1.49 (t, J=7.0 Hz, 3H), 3.96 (s, 3H), 4.17 (q, J=7.0 Hz, 2H), 6.98 (d, J=8.2 Hz, 1H), 7.43 (dt, J_1=8.2 Hz, J_2=1.9 Hz, 2H), 9.85 (s, 1H); IR (KBr) 1691, 1677, 1599, 1511, 1440 cm^{-1}.

*4.3.12. 3,4,5-Trimethoxybenzaldehyde (**3m**)*[33]

Mp 72–74 °C (lit.[33] 72–74 °C); ^{1}H NMR δ 3.94 (s, 6H), 3.95 (s, 3H), 7.14 (s, 2H), 9.87 (s, 1H); IR (KBr) 1686, 1588, 1506, 1459, 1425 cm^{-1}.

*4.3.13. 4-Chloroanisole (**3n**)*[34]

^{1}H NMR δ 3.78 (s, 3H), 6.82 (AA′XX′, J=9.0 Hz, 2H), 7.23 (AA′XX′, J=9.0 Hz, 2H); IR (NaCl) 1594, 1581, 1493, 1462, 1441 cm^{-1}.

*4.3.14. 2-Chloroanisole (**3o**)*[34]

^{1}H NMR δ 3.90 (s, 3H), 6.91 (m, 2H), 7.22 (m, 1H), 7.35 (m, 1H); IR (NaCl) 1589, 1487, 1463, 1450, 1436 cm^{-1}.

*4.3.15. 2,4,6-Trichloroanisole (**3r**)*[35]

Mp 61–63 °C (lit.[35] 61–62 °C); ^{1}H NMR δ 3.88 (s, 3H), 7.30 (s, 2H); IR (KBr) 1551, 1472, 1418, 1385, 1370 cm^{-1}.

*4.3.16. 2,4-Dichloroanisole (**3s**)*[36]

^{1}H NMR δ 3.88 (s, 3H), 6.84 (d, J=8.8 Hz, 1H), 7.19 (dd, J_1=8.8 Hz, J_2=2.5 Hz, 1H), 7.36 (d, J=2.5 Hz, 1H); IR (NaCl) 1489, 1463, 1440, 1292, 1263 cm^{-1}.

*4.3.17. 1-Methoxy-4-propylbenzene (**3t**)*[37]

^{1}H NMR δ 0.92 (t, J=7.3 Hz, 3H), 1.61 (m, 2H), 2.52 (t, J=7.5, 2H), 3.78 (s, 3H), 6.82 (AA′XX′, J=8.7 Hz, 2H), 7.09 (AA′XX′, J=8.7 Hz, 2H); IR (NaCl) 1613, 1512, 1465, 1300, 1246 cm^{-1}.

*4.3.18. 1-Methoxy-2-propylbenzene (**3u**)*[38]

^{1}H NMR δ 0.95 (t, J=7.4 Hz, 3H), 1.59 (m, 2H), 2.58 (t, J=7.6, 2H), 3.81 (s, 3H), 6.80–6.91 (m, 2H), 7.09–7.20 (m, 2H); IR (NaCl) 1601, 1494, 1462, 1439, 1242 cm^{-1}; MS (EI) m/z 150 (M^+, 32), 121 (100), 91 (81); HRMS (EI) calcd for $C_{10}H_{14}O$ [M]$^+$ 150.1045, found 150.1048.

*4.3.19. 1,4-Dimethoxybenzene (**3v**)*[39]

Mp 54–56 °C (lit.[39] 54–56 °C); ^{1}H NMR δ 3.77 (s, 6H), 6.84 (s, 4H); IR (KBr) 1638, 1510, 1468, 1439, 1298, 1240 cm^{-1}.

*4.3.20. 4-Bromoanisole (**3w**)*[40]

^{1}H NMR δ 3.79 (s, 3H), 6.78 (AA′XX′, J=9.0 Hz), 7.37 (AA′XX′, J=9.0 Hz); IR (NaCl) 1579, 1489, 1461, 1290, 1246 cm^{-1}.

*4.3.21. 2-Methoxy-4-methyl-1-isopropylbenzene (**3x**)*[41]

^{1}H NMR δ 1.19 (d, J=6.9 Hz, 6H), 2.32 (s, 3H), 3.27 (sept., J=6.9 Hz, 1H), 3.81 (s, 3H), 6.67 (s, 1H), 6.74 (d, J=7.8 Hz, 1H), 7.09 (d, J=7.8 Hz, 1H); IR (NaCl) 1612, 1580, 1504, 1460 cm^{-1}.

*4.3.22. (3-Methoxyphenyl)methanol (**3y**)*[42]

^{1}H NMR δ 1.82 (br s, 1H), 3.81 (s, 3H), 4.66 (s, 2H), 6.83 (m, 1H), 6.92 (m, 2H), 7.27 (t, J=8.1 Hz, 1H); IR (NaCl) 1595, 1490, 1457, 1264 cm^{-1}.

*4.3.23. O-Methylestrone (**3z**)*[8f]

Mp 167–168.5 °C (lit.[8f] 168 °C); ^{1}H NMR δ 0.91 (s, 3H), 1.34–1.72 (m, 6H), 1.87–2.6 (m, 7H), 2.90 (m, 2H), 3.78 (s, 3H), 6.64 (d, J=2.8 Hz, 1H), 6.72 (dd, J_1=8.6 Hz, J_2=2.8 Hz, 1H), 7.20 (d, J=8.6 Hz, 1H); IR (KBr) 2914, 1738, 1608, 1503, 1453 cm^{-1}; α^{25}_{546} +133 (c 5, $CHCl_3$).

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References and notes

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