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Article

Quantitative Methylation of Lignin Monomers Using Tetrabutylammonium Hydroxide and MeI and Applications in Organic Synthesis

Yajie Zuo, Siying Zhu, Yi Liu, Jingjing Zhao, Shiyi Zhang, and Chongmin Zhong*

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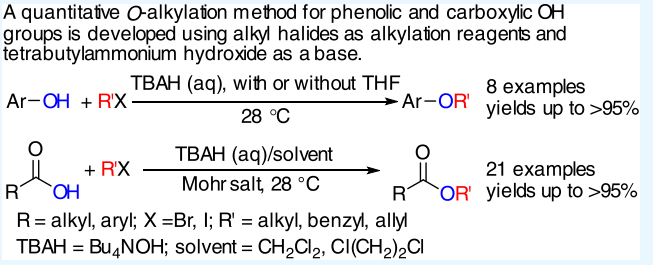
ABSTRACT: Efficient *O*-alkylation of phenols and carboxylic acids has essential applications in organic synthesis. A mild alkylation method for phenolic and carboxylic OH groups is developed using alkyl halides as alkylation reagents and tetrabutylammonium hydroxide as a base, and lignin monomers can be fully methylated in quantitative yields. Additionally, phenolic and carboxylic OH groups can be alkylated by different alkyl halides in one pot in different solvent systems.



INTRODUCTION

Lignin compounds are phenolic polymers found only in the cell walls of vascular plants. Lignin and its partial degradation products occur in such natural environments as soils, sediments, and natural waters. Monomers in lignin are connected by C−C and C−O bonds, which are highly resistant to microbial degradation and hydrolysis.[1] Therefore, lignin is the main component of soil organic matter (SOM). Lignin in the soil gradually decomposes to CO_2, which plays a vital role in the global carbon cycle.[2]

The commonly used method for lignin analysis in environmental samples was developed by Hedges and Ertel in 1982,[3] which was modified by Kögel and Bochter in 1985.[4] The method uses CuO in 2 M NaOH to oxidize lignin in environmental samples at 170 °C to phenolic monomers, which, after series of cleanup procedures, are analyzed immediately by gas chromatography (GC) after derivatization with *N*,*O*-bis(trimethylsilyl) trifluoroacetamide (BSTFA). Because lignin monomers are air- and light-sensitive, the analytical process is quite time-consuming and few laboratories have established a routine analytical method for lignin analysis in geological samples.

In the 1990s, a technique called thermally assisted hydrolysis and methylation (THM) was applied to characterize lignin components in wood samples.[5−8] The sample mixture containing lignin and tetramethylammonium hydroxide (TMAH) is loaded in a pyrolyzer and then heated at 250−710 °C; the methylated products are separated and analyzed with GC−MS. Because the reactions are carried out at high temperatures, in addition to the eight methylated lignin monomers, many other pyrolysis products are methylated and give a complicated GC profile, which makes the quantification inaccurate. Additionally, such functional groups as aldehydes, acetyls, and C═C double bonds in monomers are sensitive to strong alkalines at high temperatures.[9] Therefore, a new method that can transform lignin into methylated monomers under more mild conditions is desired.

Besides the application of methylated lignin monomers to lignin analysis, the *O*-alkylated lignin monomers have also found wide applications in the synthesis of bioactive compounds. Nakamura et al. methylated the two OH groups in vanillic acid separately,[10] first methylating carboxylic acid in refluxing methanol using sulfuric acid as a catalyst and then methylating the phenolic OH group with iodomethane/K_2CO_3 in refluxing acetone. 4-Hydroxycinnamic acid was methylated by Baltas et al. in a similar method.[11] Even though methylation of phenolic and/or carboxylic OH groups in several lignin monomers with iodomethane/K_2CO_3 in DMF is efficient, quantitative methylation methods for all lignin monomers have not been reported.[12,13]

Phase-transfer catalysis is widely used to alkylate phenolic and carboxylic OH groups with alkyl halides at mild conditions.[14−19] Liotta utilized tetrabutylammonium hydroxide (TBAOH) and MeI to methylate acidic hydroxyl groups in coal in THF.[20] Piccolo et al. investigated *O*-alkylation of a lignite humic acid by 20% TBAOH and alkyl halides in THF.[21] Soleiman-Beigi et al. exploited for the first time the application of TBAOH and alkyl halides in organic synthesis.[22] However, 20% TBAOH aqueous solution could only alkylate phenols

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and benzyl alcohols in ca. 80% yields and at 50 °C. Therefore, synthetic applications of TBAOH and alkyl halides in *O*-alkylation of phenolic and carboxylic hydroxyl groups have, to our knowledge, not been fully demonstrated.

Ester formation from carboxylic acid is one of the most practiced reactions in organic synthesis. In recent years, new methods for preparing esters have emerged. Čebular et al. used *N*-bromosuccinimide (NBS) as the catalyst to prepare esters at 70 °C from corresponding acids and alcohols.[23] Cobb and Brittain et al. utilized pentafluoropyridine to convert carboxylic acids to acyl fluoride intermediates, which were then transformed into esters via alcoholysis.[24] However, only moderate yields were obtained in most cases. Yasmin et al. reported a new access to esters using a deep eutectic solvent as an alkylation reagent.[25] However, high temperatures (140 °C) and moderate yields limit their application in organic synthesis. Liu and Xi et al. utilized streptozotocin, a DNA-alkylating reagent, to transform various carboxylic acids, sulfonic acids, and phosphorous acids into their methyl esters at room temperature, and yields of up to 97% were obtained. However, streptozotocin is an expensive chemical (ca. $100/1 g) and can only be used in small-scale synthesis.[26]

In this work, we report a quantitative methylation method for lignin monomers using TBAOH and alkyl halides at room temperature. This new *O*-alkylation procedure will not only be applied to lignin analysis but also find applications in chemical synthesis.

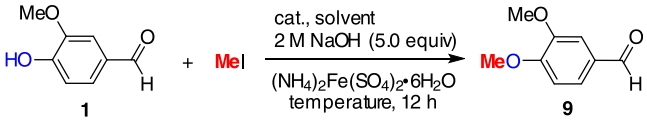
RESULTS AND DISCUSSION

Methylation of Lignin Monomers with TMAH at High Temperatures. The eight monomers, produced in alkaline CuO oxidation and used as an estimation of the various contributing plant types, are vanillin (**1**), acetovanillone (**2**), vanillic acid (**3**), syringaldehyde (**4**), acetosyringone (**5**), syringic acid (**6**), *p*-coumaric acid (**7**), and ferulic acid (**8**) (Chart S1).

Abraham et al. used TMAH to pyrolytically methylate simple carboxylic acids and phenols at high temperatures (225−400 °C),[27−29] and the yields of completely methylated products reached up to 95%. To test whether TMAH can methylate lignin monomers, we mixed 1.0 mmol of lignin monomers and 5.0 mmol of TMAH·5H_2O in a 25 mL autoclave and conducted the pyrolytic methylation under a N_2 atmosphere at high temperatures for 3 h (Table S1). At 250 °C, vanillin (**1**) and acetovanillone (**2**) produced 20 and 23% methylated products, respectively. However, *p*-coumaric acid (**7**) did not produce any dimethyl product. At 300 °C, all three monomers produced no completely methylated products. All of the reactions produced a large amount of brown oil, scarcely soluble in dichloromethane (DCM) and ethyl acetate. No monomers were recovered in these reactions. Therefore, TMAH cannot efficiently methylate lignin monomers, probably due to aldehyde, acetyl, and C=C double-bond functional groups in the monomers, which likely underwent Cannizzaro reaction, aldol condensation, and polymerization, respectively, under basic and high-temperature conditions.

Methylation of Vanillin by MeI and Phase-Transfer Catalysts. Using vanillin (**1**) as the model compound, the reaction conditions were screened in terms of phase-transfer catalysts, equivalents of MeI,[30] solvent, and temperature (Table 1). Mohr's salt is added to remove the oxygen dissolved in solvents. We first investigated the effects of solvents in the presence of 0.1 equiv of Bu_4NI and 2 equiv of MeI at 27 °C (entries 1−6), and the reaction in DCM gave the best yield (62%, entry 5). Phase-transfer catalysts were then screened using 5.0 equiv of MeI (entries 7−12). Bu_4NCl and Bu_4NBr gave similar and best yields (77%, entries 7−8). Increasing the amount of Bu_4NCl to 0.2 equiv further improved the yield to 86% (entry 13). The reactions at 40 °C had no noticeable effect on yields (entries 14 and 15), but 10.0 equiv of MeI increased the yield to 94% (entry 16).

Table 1. Methylation of Vanillin by MeI and Phase-Transfer Catalysts[a]



entry	catalysts (equiv)	MeI (equiv)	solvents	temp. (°C)	yields (%)[b]
1	Bu_4NI (0.1)	2	toluene	27	0
2	Bu_4NI (0.1)	2	ether	27	28
3	Bu_4NI (0.1)	2	anisole	27	53
4	Bu_4NI (0.1)	2	ethyl acetate	27	20
5	Bu_4NI (0.1)	2	DCM	27	62
6	Bu_4NI (0.1)	2	$CHCl_3$	27	10
7	Bu_4NCl (0.1)	5	DCM	27	76
8	Bu_4NBr (0.1)	5	DCM	27	76
9	Bu_4NHSO_4 (0.1)	5	DCM	27	74
10	$(Et_3)BnNCl$ (0.1)	5	DCM	27	40
11	$[C_5H_5NC_{16}H_{31}]Cl$ (0.1)	5	DCM	27	28
12	$MeP(Ph_3)I$ (0.1)	5	DCM	27	57
13	Bu_4NCl (0.2)	5	DCM	27	86
14	Bu_4NCl (0.2)	5	DCM	40	86
15	Bu_4NCl (0.2)	10	DCM	40	84
16	Bu_4NCl (0.2)	10	DCM	27	94

[a]0.5 mmol vanillin, 1.25 mL of 2 M NaOH aqueous solution; 0.5 mmol of Mohr salt was used as an oxygen scavenger. [b]NMR yield using 4-methylbiphenyl as an internal standard.

Methylation by MeI and TBAOH. TBAOH was used instead of NaOH and the phase-transfer catalyst to further improve the yield (Table 2). We are surprised to find that, in the presence of 5.0 equiv of TBAOH and 10.0 equiv of MeI, vanillin was quantitatively methylated (Table 2, entry 1). *p*-Coumaric acid with both phenolic and carboxylic OH groups was also quantitatively methylated (entry 2). Reducing the amounts of TBAOH and MeI to 3.0 equiv, respectively, *p*-coumaric acid could still be quantitatively methylated (entries 3−5). Further reducing the amount of TBAOH and MeI resulted in decreased yields (entries 6−7). $(NH_4)_2Fe(SO_4)_2\cdot 6H_2O$ (Mohr salt) was used as an oxygen scavenger. Reducing the amount of Mohr salt from 0.5 to 0.1 equiv resulted in a slightly decreased yield (entry 8). Mohr salt also reacted with iodide ions to form deep-green $[FeI_4]^{2-}$ complex ions, which adhered to the glass wall on the top of the solution. If the mixture of NaOH and Bu_4NI was used instead of TBAOH, the yield decreased to 40% (entry 9). When 5.0 equiv of TBAOH and 10.0 equiv of MeI were used, DCM could be omitted (entry 10). However, when 5.0 equiv of MeI was used, the reaction mixture formed a muddy state, reducing the yield to 80% (entry 11). When 1.0 M TBAOH was used instead of 1.36 M TBAOH to dilute the reaction mixture (in the absence of DCM), the yield dramatically decreased to 25% (entry 12).

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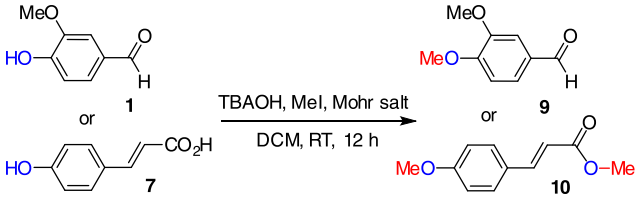
Table 2. Methylation of Lignin Monomers by MeI and TBAOH

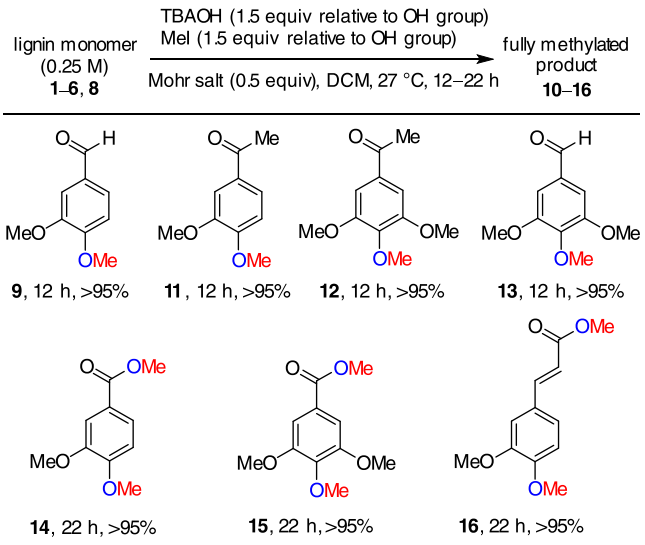


entry	lignin monomer	TBAOH (equiv)	MeI (equiv)	Mohr salt (equiv)	yields (%)[b]
1	**1**	5	10	0.5	>95
2	7	5	10	0.5	>95
3	7	5	5	0.5	>95
4	7	3	4	0.5	>95
5	7	3	3	0.5	>95 (>95)[c]
6	7	2.5	2.5	0.5	88
7	7	2.2	2.2	0.5	74
8	7	4	4	0.1	95
9	7	3[d]	3	0.5	40
10	7	5[e]	10	0.5	>95
11	7	5[e]	5	0.5	80
12	7	5[e,f]	5	0.5	25

[a]Conditions: substrates, 0.5 mmol; CH_2Cl_2, 2.0 mL; 1.36 M TBAOH (40 wt % TBAOH in water); 27 °C, 12 h. [b]NMR yield using 4-methylbiphenyl as the internal standard. [c]Isolated yield. [d]1 mL of NaOH aqueous (1.5 M) and 3.0 equiv of Bu_4NI were used instead of Bu_4NOH. [e]CH_2Cl_2 was not used. [f]2.5 mL of 1.0 M Bu_4NOH aqueous was used.

Substrate Scope. The optimized reaction conditions are summarized in Table 3. Under the optimized conditions, all of the other seven monomers shown in Chart S1 were quantitatively methylated. The methylation rates for vanillic acid, syringic acid, and ferulic acid are slow, and 22 h is needed for quantitative methylation

Table 3. Substrate Scope



Besides MeI, other alkylation reagents were also examined, and the results are shown in Figure 1. Dimethylsulfate could methylate *p*-coumaric acid and afforded **10** quantitively in 22 h. Allyl bromide, benzyl bromide, ethyl iodide, and butyl bromide are all appropriate alkylation reagents and could provide corresponding alkylated products **17**–**20** quantitively within 22 h. Ethyl 2-bromoacetate could alkylate vanillin and provide **21** in a yield of 95%. 1-Bromo-4-chlorobutane could also alkylate both phenolic and carboxylic OH groups and gave the chloro-functionalized product **22** in a yield of 93%. This result also shows that alkyl chlorides are not appropriate alkylation reagents under the reaction conditions.

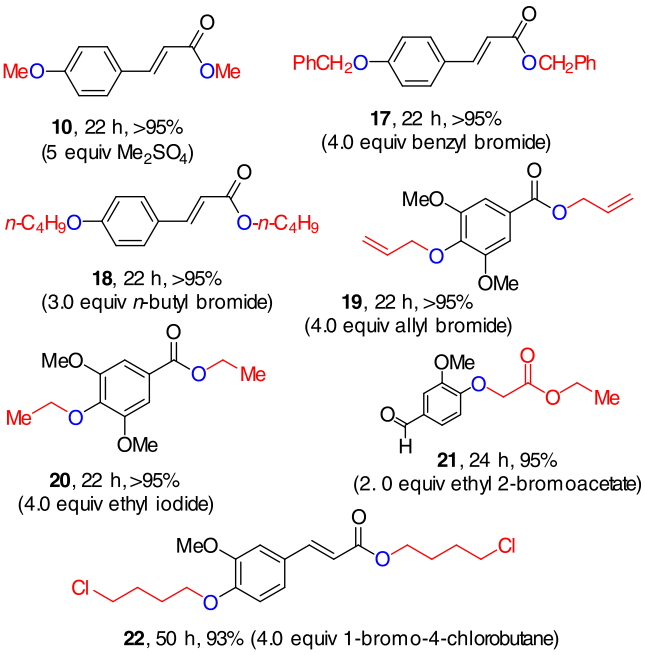


Figure 1. Alkylation of lignin monomers with alkyl halides other than MeI.

Unsymmetric Alkylation of Lignin Monomers. Encouraged by the success in symmetrically alkylating lignin monomers (**3**, **6**–**8**), we plan to alkylate the four monomers unsymmetrically with different alkyl halides. Thin-layer chromatography (TLC) analysis of the reaction mixture (Table 2, entry 5) showed that both phenolic OH only methylated (**35**) and carboxylic OH only methylated intermediates existed in the system before the completion of the reaction.[31] Therefore, a reaction condition that can selectively alkylate phenolic OH or carboxylic OH group should be identified. Because carboxylic esters hydrolyze easily in a NaOH aqueous ethanol solution at room temperature, we envisioned that the alkylation of the carboxylic OH group should be suppressed in a homogeneous

TBAOH aqueous solution.[32] Indeed, we found that the phenolic OH group in *p*-coumaric acid could be quantitatively methylated by 2.0 equiv of MeI in TBAOH/THF or TBAOH only (2.0 equiv TBAOH in all cases), and the carboxylic OH group was left intact (Scheme 1). After the reaction was completed within 0.5 h, excess MeI was completely removed by extraction with hexane. Then, 2.0 mL of DCM, 2.0 equiv of another alkyl halide, 0.25 equiv of Mohr salt, and an additional 1.0 equiv of TBAOH were added. The formed mixture was stirred at 28 °C until TLC analysis showed that the monomethylated intermediate was completely converted to the final product **23**.

Using the procedure outlined in Scheme 1, monomers **3**, **6**, and **8** were also unsymmetrically alkylated in good to

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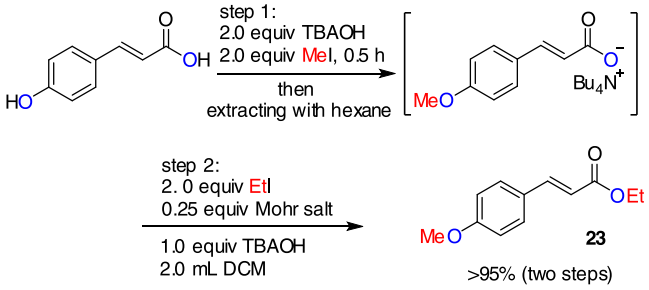
Scheme 1. One-Pot Unsymmetric Alkylation of *p*-Coumaric Acid with Two Different Alkyl Halides



quantitative yields (Figure 2). Syringic acid (**6**) was transformed to **24** (step 1: MeI; step 2: EtI) and **25** (step 1: EtI; step 2: MeI) both in quantitative yields. Ferulic acid (**8**) was alkylated by MeI and allyl bromide in sequence to form **26**, and by allyl bromide and MeI in sequence to form **27**, respectively, both in a yield of 78%. Vanillic acid (**3**) was first alkylated by *n*-butyl bromide and then by MeI to give compound **28** in a yield of 85%.

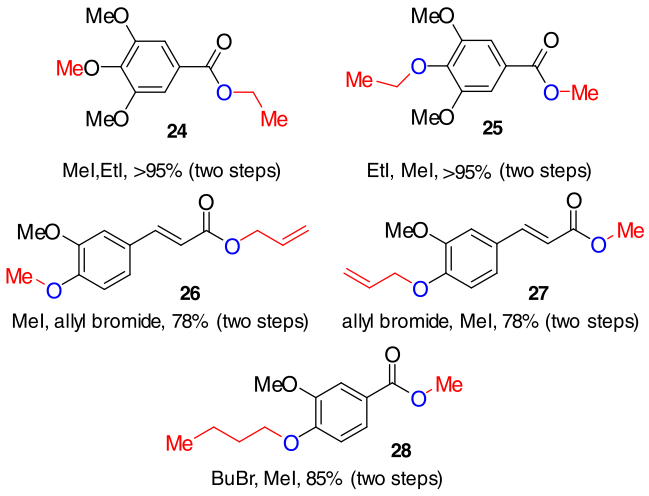


Figure 2. One-pot unsymmetric alkylation of monomers **3**, **6**, and **8**.

The alkylation of **3** with *n*-butyl bromide produced a trace amount of dialkylation products, which can be removed from the system by extraction with ether.

***O*-Alkylation of Carboxylic Acid.** The success in the alkylation of carboxylic acids in lignin monomers drives us to apply the method to alkylate more general carboxylic acids, and the results are outlined in Figure 3. 3-Phenylpropionic acid and 2-iodobenzoic acid were transformed into methyl and benzyl esters (**29** and **30**), respectively, both in a quantitative yield. Alcohol-functionalized long-chain halide, 11-bromoundecan-1-ol, could also efficiently alkylate 3-phenylpropionic acid and produced **31** in good yield. Binary carboxylic acids, oxalic acid and 2-methylmalonic acid, and tricarboxylic acid, citric acid, were all efficiently alkylated to form their corresponding esters (**32**, **33**, and **34**) in good to excellent yields. Further solvent screening shows that 1,2-dichloroethane is better than DCM for alkylating polybasic carboxylic acid.

The effect of Mohr salt on the alkylation of carboxylic acids was further examined. For the alkylation of 3-phenylpropionic acid with MeI, the addition of 0.13 equiv of Mohr salt resulted

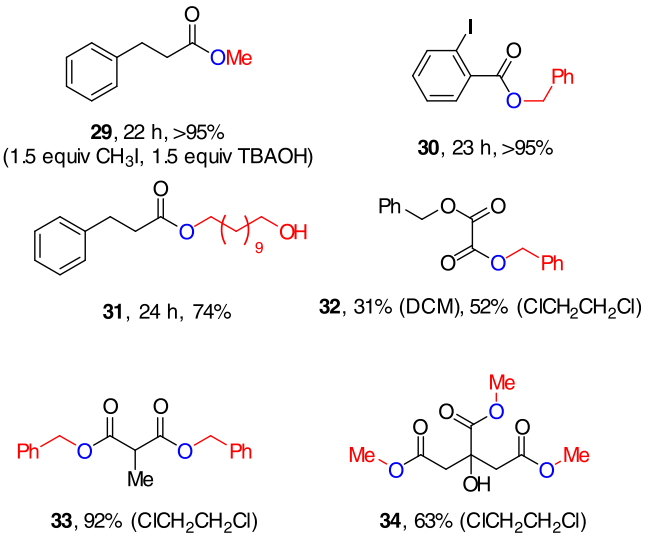


Figure 3. *O*-alkylation of carboxylic acid.

in a quantitative formation of **29**, in contrast to a yield of 94% in the absence of Mohr salt.

Preparative synthesis was also studied. Vanillic acid (6.0 mmol, 1.009 g) was alkylated by ethyl iodide (3.0 equiv) under the standard condition shown in Table 3, and the product (**37**) was obtained in a yield of 98%, in contrast to a yield of 79% in the absence of Mohr salt (see the Supporting Information).

In summary, a biphasic system composed of DCM (or 1,2-dichloroethane) and TBAOH aqueous solution can be used to efficiently alkylate phenolic and carboxylic OH groups with alkyl halides (iodides or bromides) at room temperature. When the reaction was conducted in a homogeneous TBAOH aqueous or TBAOH/THF solution, only the phenolic OH group was selectively alkylated. Such functionals in alkyl halide as alcohol, Cl, C=C double bond, and ester groups are all tolerated by the reaction. The addition of Mohr salt helps improve yields in the alkylation of carboxylic OH groups. Traditional quaternary ammonium salts together with NaOH aqueous solution cannot efficiently alkylate lignin monomers. The alkylation method for lignin monomers will find applications in organic synthesis and organic component analysis in geological samples.

EXPERIMENTAL SECTION

Materials and Methods. TMAH was obtained as the pentahydrate from Innochem Co, China. TBAH was obtained as a 40 wt % aqueous solution from Energy Chemical Co., China. Vanillin, acetovanillone, vanillic acid, syringaldehyde, syringic acid, and ferulic acid were purchased from Energy Chemical Co., China. Acetosyringone and *p*-coumaric acid were purchased from Aladdin Co., China. All solvents are analytically pure and were used as received. Higher-temperature reactions were carried out in a 25 mL batch autoclave of stainless steel with PPL lining in a nitrogen atmosphere. Room-temperature reactions were carried out in a 10 mL screw reaction tube equipped with a septum cap under an atmosphere of nitrogen. Column chromatography was performed with a 100−200-mesh silica gel. NMR spectra were taken in $CDCl_3$ on an Avance neo 400 M (^{1}H: 400 MHz; ^{13}C: 100 MHz) or an Advance Bruker Avance III 500 M (^{1}H: 500 MHz; ^{13}C: 126 MHz) spectrometer, and the resonances were referenced to TMS in ^{1}H NMR and 77.26 ppm of $CDCl_3$

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in ^{13}C NMR. High-resolution mass spectra were recorded on a Thermo Scientific Q Exactive. All of the reactions shown in figures, tables, and schemes were conducted one time; therefore, only one number was reported for the yields of each reaction.

General Procedure A: Methylation with TMAH (Table 1). In a PPL container of an autoclave were added 1.0 mmol of lignin monomers, 5.0 mmol of TMAH·$5H_2O$, and a stir bar. The container was purged with nitrogen by evacuating and filling-back nitrogen three times. The autoclave was sealed and heated to the specified temperature. After stirring at that temperature for 3 h, the autoclave was cooled down to room temperature in cold water. The mixture was acidified to pH 2 with 2 M HCl and extracted with ethyl acetate (3 mL × 6). After drying with anhydrous Na_2SO_4, the solution was evaporated under reduced pressure. The residue was analyzed by ^1H NMR using 4-methylbyphenyl as the internal standard.

General Procedure B: Methylation with MeI and Phase-Transfer Catalysts (Table 2). In a 10 mL screw reaction tube were added 0.5 mmol of lignin monomer **1**, phase-transfer catalyst, 0.25 mmol (98 mg) of Mohr salt, and a stir bar. The tube was sealed with a septum cap and connected to a vacuum-nitrogen line through a needle. The reaction tube was purged with nitrogen by evacuating and filling-back nitrogen three times. Solvent was added through the septum with a syringe, and the mixture was stirred for 10 min. Then, 2 M NaOH (5 equiv, 1.25 mL) and MeI were added. The mixture was stirred at room temperature for 12 h. Then, the mixture was acidified with 2 M HCl. The organic phase was separated, and the water phase was extracted with ether (2 mL × 6). The organic phases were combined and dried with anhydrous Na_2SO_4. The solution was evaporated under reduced pressure, and the residue was washed with ether and filtered through a pad of silica. The ether solution was evacuated again, and the residue was analyzed by ^1H NMR using 4-methylbyphenyl as the internal standard.

General Procedure C: Methylation by MeI and TBAH (Table 3 and Figure 1). In a 10 mL screw reaction tube were added 0.5 mmol of lignin monomer, 0.25 mmol (98 mg) of Mohr salt, and a stir bar. The tube was sealed with a septum cap and connected to a vacuum-nitrogen line through a needle. The reaction tube was purged with nitrogen by evacuating and filling-back nitrogen three times. Then, 2.0 mL of DCM was added through the septum with a syringe, and the mixture was stirred for 5 min. TBAH (1.5 M, 40 wt % aqueous solution) and MeI were added. The mixture was stirred at 28 °C for 12−22 h. Then, the mixture was acidified to pH ≈ 7 with 1 M HCl. The organic phase was separated, and the water phase was extracted with DCM (2.0 mL × 6). The organic phases were combined and dried with anhydrous Na_2SO_4. The solution was passed through a pad of silica gel using ether as an eluent. The solution was evaporated under reduced pressure. The residue was purified by silica gel column chromatography.

General Procedure D: One-Pot Unsymmetric Alkylation of Lignin Monomers (3, 6−8). *First Step: Alkylation of Phenolic OH Groups.* In a 10 mL screw reaction tube were added 0.5 mmol of lignin monomer and a stir bar. The tube was sealed with a septum cap and connected to a vacuum-nitrogen line through a needle. The reaction tube was purged with nitrogen by evacuating and filling-back nitrogen three times. TBAH (735 μL, 2.0 equiv, 1.36 M, 40 wt % aqueous solution) and alkyl halide (2.0 equiv) were added through the septum with syringes. The mixture was stirred at 28 °C for 0.5−24 h. When TLC analysis showed that the substrate disappeared, the solution was extracted with hexane four times. Then, the aqueous solution was evaporated under reduced pressure to remove extraction agents.

Second Step: Alkylation of Carboxylic OH Group. Mohr salt (0.125 mmol, 49 mg) and a stir bar were added to the reaction mixture. The tube was sealed with a septum cap and connected to a vacuum-nitrogen line through a needle. The reaction tube was purged with nitrogen by evacuating and filling-back nitrogen three times. Then, 2.0 mL of DCM, TBAH (1.0 equiv, 370 μL), and alkyl halide (2.0 equiv) were added through the septum with syringes. The progression of the reaction was monitored by TLC. When the reaction was complete, the organic phase was separated, and the water phase was extracted with ether (2 mL × 6). The organic phases were combined and dried with anhydrous Na_2SO_4. After filtration, the solution was evaporated under reduced pressure, and the residue was washed with ether and filtrated through a pad of silica. The ether solution was evacuated again, and the residue was purified by silica gel column chromatography.

General Procedure E: Alkylation of Binary and Ternary Carboxylic Acids. In a 10 mL screw reaction tube were added 0.5 mmol of carboxylic acid and a stir bar. The tube was sealed with a septum cap and connected to a vacuum-nitrogen line through a needle. The reaction tube was purged with nitrogen by evacuating and filling-back nitrogen three times. 1,2-Dichloroethane (2 mL), TBAH (1.36 M, COOH/TBAH = 1:2), and alkyl halide (COOH/halide = 1:2) were added through the septum with syringes. The mixture was stirred at 28 °C for 24 h. Then, the mixture was acidified to pH ≈ 7 with 2 M HCl. The organic phase was separated, and the water phase was extracted with ethyl acetate (2 mL × 6). The organic phases were combined and dried with anhydrous Na_2SO_4. The solution was evaporated under reduced pressure, and the residue was washed with ether and filtrated through a pad of silica. The ether solution was evacuated again, and the residue was purified by silica gel column chromatography.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07920.

Experimental details, product characterization, and copies of NMR spectra (PDF)

NMR spectroscopy data (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Chongmin Zhong − *College of Chemistry and Pharmacy, Northwest A&F University, Yangling 712100, China;* orcid.org/0000-0003-0684-5269; Email: zhongcm@nwsuaf.edu.cn

Authors

Yajie Zuo − *College of Natural Resources and Environment, Northwest A&F University, Yangling 712100, China*

Siying Zhu − *College of Natural Resources and Environment, Northwest A&F University, Yangling 712100, China*

Yi Liu − *College of Chemistry and Pharmacy, Northwest A&F University, Yangling 712100, China*

Jingjing Zhao − *College of Chemistry and Pharmacy, Northwest A&F University, Yangling 712100, China*

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Shiyi Zhang − *College of Chemistry and Pharmacy, Northwest A&F University, Yangling 712100, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c07920

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript

Notes

The authors declare no competing financial interest.

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(30) MeI and other alkylating reagents used in this study are carcinogenic or potentially carcinogenic. Therefore skin contact and vapor inhalation should be avoided by carrying out the reactions in a well-ventilated fume hood.
(31) The two intermediates were identified by comparing their proton NMR spectra with that of carboxylic OH only methylated intermediate (**36**) produced through esterification. See Supporting Information for details.
(32) A control experiment using benzoic acid was conducted under the condition of step 1 shown in Scheme 1. After 0.5 h reaction, the solution was neutralized to pH ∼7 and extracted with ether. TLC analysis showed that no detectable methyl benzoate was found in the ether layer.