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One-Pot Alkylation-Sulfonylation of Diphenol †

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Abstract

The selective derivatization of the hydroxyl group in phenols is of paramount importance in synthetic chemistry. Alcohol was employed as the alkylating agent for converting phenol to alkyl aromatic ethers mediated with sulfonyl chloride-potassium carbonate. Diphenol underwent a one-pot alkylation-sulfonylation in the alcohol–sulfonyl chloride–K_2CO_3 system. Such process enabled the non-symmetrical derivatization of phenolic hydroxyl groups in diphenols.

Keywords: one-pot; alkylation-sulfonylation; diphenol; green alkylating agent; solvent-free

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1. Introduction

Phenolic hydroxyl group, occurring in various pharmaceutical and natural molecules, has been concerned as efficient skeleton or functional group for derivation of aromatic moiety [1]. Due to the broad synthetic application and highly sensitive reactivities, the selectivity-controlling of protection and derivatization of hydroxyl groups is an innegligible challenge to achieve the desired chemical conversion [2]. Alkylation of phenolic -OH group is not only a simple functional group transformation [3,4], the alkyloxy groups are key scaffolds dictating the properties of the final molecules [5]. However, the common alkylation reagents, such as halides, alkyl sulfates and sulfonates have been confined for their environmental toxicity, potential danger to health [7,8].

In the previous work, alkyl sulfonyloxyphenyl ether could be synthesized selectively via sequential procedure of monodesulfonation of diphenol bissulfonate-alkylation [9]. Observation of the in situ formation of phenoxy anion indicated the feasibility of direct alkylation of the phenolic hydroxyl group. Herein, methods for the alkylation of phenolic hydroxyl groups in phenols and the alkylation-sulfonylation of diphenols were described, utilizing alcohols as alkylating agents in the presence of sulfonyl chloride.

2. Results and Discussion

2.1. Alkylation of Phenol Using Alcohols as Alkylating Agents

To evaluate the feasibility of the alkylation using alcohols as alkylating agents, the model substrate *o*-bromophenol was treated with 2.5 mL of methanol, excess potassium carbonate, and *p*-toluenesulfonyl chloride (*p*-TsCl) based on prior work [9]. The mixture was subjected to ultrasound-assisted reaction for 6 h. TLC monitoring indicated that the

desired alkylated product was not obtained. Subsequently, the reaction was carried out under heating reflux for 5 h, after which TLC analysis showed complete consumption of the starting phenol. Following standard workup, the corresponding methylated product, *o*-bromoanisole (**1a**), was obtained (Figure 1). Substrate scope investigation demonstrated that this reaction condition was applicable to the alkylation of various phenols, providing an effective approach for the synthesis of a series of alkyl aromatic ethers **1a-d** using alcohols as alkylating agents (Figure 2).

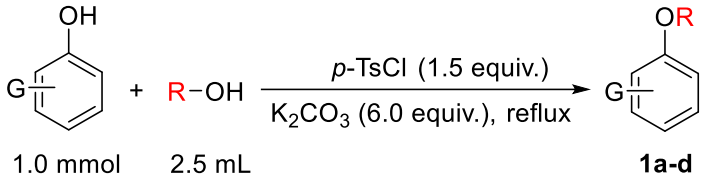

Figure 1. Alkylation of phenol using alcohols as alkylating agents.

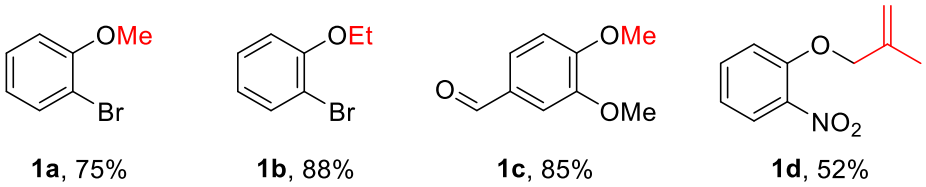

Figure 2. Synthesis of alkyl aromatic ethers **1a–d**.

As illustrated in Figure 2, the sulfonyl chloride-mediated alkylation of phenols with alcohols is a viable strategy (Figure 2). A variety of phenols bearing diverse substituents including sensitive groups such as formyl and nitro could be converted to alkylated products under standard conditions highlighting the system's broad functional group tolerance.

2.2. One-Pot Alkylation-Sulfonylation of Diphenol

Based on the results of the sulfonyl chloride-mediated alkylation of phenols with alcohols, resorcinol was employed as the model substrate to investigate the reactivity and selectivity of its two phenolic hydroxyl groups under the alcohol–TsCl–K_2CO_3 system. It is noteworthy that the formation of 3-methoxyphenyl sulfonate was observed in 60% yield. This indicated that under the current conditions, the two phenolic hydroxyl groups of resorcinol underwent alkylation and sulfonylation, respectively (Figure 3).

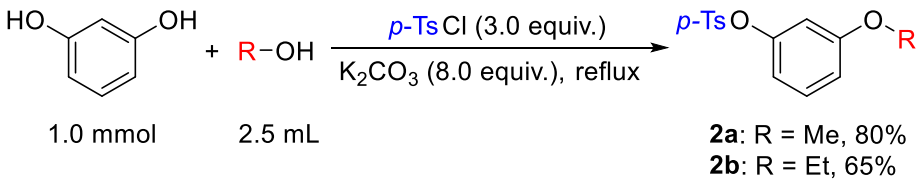

Figure 3. Synthesis of alkyloxyphenyl sulfonate **2a–b**.

In this weakly basic reaction system, the alcohol served a dual role as both the alkylating agent and the solvent.

3. Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DMX500 in $CDCl_3$ solutions and with tetramethyl silane as internal standard. Melting points were recorded on Micro melting point meter X5.

3.1. 1-Bromo-2-Methoxybenzene 1a [10]

Colorless oil, 75% isolated yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.26 (ddd, *J* = 9.0, 1.6, 0.7 Hz, 1H), 6.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.80 (td, *J* = 7.7, 1.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz,$CDCl_3$) δ 155.9, 133.4, 128.6, 121.8, 112.0, 111.7, 56.2.

3.2. 1-Bromo-2-Ethoxybenzene 1b [11]

Colorless oil, 88% isolated yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.27–7.25 (ddd, *J* = 7.4, 1.6, 0.8 Hz, 1H), 6.82 (td, *J* = 7.7, 1.4 Hz, 1H), 6.81 (m, 1H), 4.09 (t, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 133.4, 128.4, 121.7, 113.3, 112.2, 64.8, 14.7.

3.3. 3,4-Dimethoxybenzaldehyde 1c [12]

White solid, 85% isolated yield; m.p. 41–42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.46 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 154.5, 149.6, 130.2, 126.9, 110.4, 108.9, 56.2, 56.0.

3.4. 1-((2-Methylallyl)oxy)-2-Nitrobenzene 1d [13]

Light green oil, 65% isolated yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.1 Hz, 1.7 Hz 1H), 7.52–7.47 (m, 1H), 7.08–7.06 (m, 1H), 7.05–7.01 (m, 1H),5.14–5.01 (m, 2H), 4.56 (s, 2H),1.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 139.6, 134.1, 125.8, 120.5, 114.8, 113.5, 72.6, 19.3.

3.5. 3-Methoxyphenyl 4-Methylbenzenesulfonate 2a [9]

White solid, 80% isolated yield; m.p. 54–55 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.16 (t, *J* = 8.2 Hz, 1H), 6.78 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.59–6.54 (m, 2H), 3.72 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 150.5, 145.3, 132.5, 129.9, 129.7, 128.9, 114.3, 113.1, 108.2, 55.5, 21.7.

3.6. 3-Ethoxyphenyl 4-Methylbenzenesulfonate 2b [9]

Colorless oil, 65% isolated yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.3 Hz, 1H), 6.67 (ddd, *J* = 8.4, 2.4, 0.7 Hz, 1H), 6.47 (t, *J* = 2.3 Hz, 1H), 6.43 (ddd, *J* = 8.1, 2.2, 0.8 Hz, 1H), 3.83 (q, *J* = 8.0 Hz, 2H), 2.35 (s, 3H), 1.27 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 150.5, 145.3, 132.5, 129.8, 129.7, 128.5, 114.1, 113.6, 108.7, 63.7, 21.7, 14.6.

4. Conclusions

A green protocol for the *O*-alkylation of phenols was developed, utilizing alcohols as alkylating agents in the presence of a weak base (K_2CO_3) and a sulfonyl chloride. This system enabled highly selective alkylation-sulfonylation of diphenols, allowing for the introduction of distinct groups onto different oxygen atoms. This strategy provided a novel approach for the non-symmetric derivatization of phenolic hydroxy groups. The successful synthesis of allyl ether 1d not only offered a versatile handle for arene functionalization via Claisen rearrangement but also presented a potential synthetic route to natural products containing allyl aryl ether motifs, such as eugenol. This method employed low-toxicity, readily available alcohols and mild K_2CO_3, offering a green, efficient, and operationally simple alternative.

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References

1. Reitzer, F.; Allais, M.; Ball, V.; Meyer, F. Polyphenols at interfaces. *Adv. Colloid Interface Sci.* **2018**, *257*, 31–41.
2. Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. Protection (and deprotection) of functional groups in organic synthesis by heterogeneous catalysis. *Chem. Rev.* **2004**, *104*, 199–250.
3. Tian, Z.; Gong, Q.; Huang, T.; Liu, L.; Chen, T. Practical electro-oxidative sulfonylation of phenols with sodium arenesulfinates generating arylsulfonate esters. *J. Org. Chem.* **2021**, *86*, 15914–15926.
4. Sun, X.; Zhang, F.; Yan, K.; Feng, W.; Sun, X.; Yang, J.; Wen, J. Electrochemical-in-situ-oxidative sulfonylation of phenols with sulfinic acids as an access to sulfonylated hydroquinones. *Adv. Synth. Catal.* **2021**, *363*, 3485–3490.
5. Liargkova, T.; Eleftheriadis, N.; Dekker, F.; Voulgari, E.; Avgoustakis, C.; Sagnou, M.; Mavroidi, B.; Pelecanou, M.; Hadjipavlou-Litina, D. Small multitarget molecules incorporating the enone moiety. *Molecules* **2019**, *24*, 199.
6. Hämmerling, S.; Thiele, G.; Steinhauer, S.; Beckers, H.; Müller, C.; Riedel, S. A very strong methylation agent:[Me2Cl][Al (OTeF5) 4]. *Angew. Chem. Int. Ed.* **2019**, *58*, 9807–9810.
7. Dor, Y.; Cedar, H. Principles of DNA methylation and their implications for biology and medicine. *Lancet* **2018**, *392*, 777–786.
8. Hämmerling, S.; Thiele, G.; Steinhauer, S.; Beckers, H.; Müller, C.; Riedel, S. Ultrasonic Cavitation Facilitates Rapid Synthesis of Trisubstituted Pyrazole Scaffolds through Michael Addition/Domino Cyclization. *Angew. Chem. Int. Ed.* **2019**, *58*, 9807–9810.
9. Ma, J.; Li, Y.; Wu, P.; Zhao, J.; Zheng, W. Ultrasound-mediated monodesulfonation of polyphenol sulfonate and one-pot generation of alkyl aryl ether under solvent-free conditions. *ChemistrySelect* **2023**, *8*, e202300659.
10. Massah, A.R.; Mosharafian, M.; Momeni, A.R.; Aliyan, H.; Naghash, H.J.; Adibnejad, M. Solvent-free Williamson synthesis: An efficient, simple, and convenient method for chemoselective etherification of phenols and bisphenols. *Synth. Commun.* **2007**, *37*, 1807–1815.
11. Sadygov, O.A.; Alimardanov, K.M.; Chalabiev, C.A. Induced bromination of aromatic hydrocarbons by alkali metals bromides and sodium hypochlorite. *Russ. J. Org. Chem.* **2005**, *41*, 1631–1636.
12. Iioka, R.; Yorozu, K.; Sakai, Y.; Kawai, R.; Hatae, N.; Takashima, K.; Tnabe, G.; Wasada, H.; Yoshimatsu, M. Synthesis of azepino [1,2-a] indole-10-amines via [6+1] annulation of ynenitriles with Reformatsky reagent. *Eur. J. Org. Chem.* **2021**, *2021*, 1553–1558.
13. Liu, Z.; Luan, N.; Lu, H.; Liang, A.; Li, J.; Zou, D. Boron-promoted ether interchange reaction: Synthesis of alkyl nitroaromatic ethers from methoxynitroarenes. *Eur. J. Org. Chem.* **2020**, *2020*, 702–707.