An Efficient Strategy for Protecting Dihydroxyl Groups of Catechols

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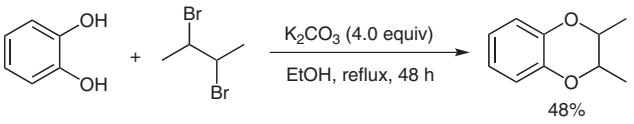
Abstract: A novel strategy for protecting dihydroxyl groups of catechols has been developed. Base-mediated cyclizations of catechols with 1,3-dibromopropane provided the corresponding benzo[*b*]1,4-dioxepans, and herefrom the protecting group was easily cleaved by aluminum chloride. The preparation of the antibacterial and antifungal agent 4-(2-aminothiazol-4-yl)benzene-1,2-diol from catechol reliably verified its availability amenable to various harsh reaction conditions.

Key words: catechols, protection, *ortho*-dihydroxyl, 1,3-dibromopropane, benzo[*b*]1,4-dioxepans, deprotection, aluminum chloride

Organic molecular architectures containing a catechol moiety have exhibited broad biological activities[1] with the important drugs like apomorphine,[2] L-dopa,[3] tolcapone,[4] entacapone,[5] dopexamine,[6] norepinephrine,[7] etc. Owing to high reactivity, dihydroxyl groups of catechols generally need to be protected in the synthesis of complex molecules as frequently encountered. Fortunately, many classical methods have been developed for this purpose, including methylene,[8] dimethyl,[9] dibenzyl,[10] acetonylidene,[11] diphenylmethylene,[12] alkyl orthoformate,[13] 2-Boc-ethylidene,[14] and cyclic borate protection methods.[15] Among these methods, the removal of the methylene and dimethyl groups often need hypertoxic boron tribromide and cryogenic treatment.[8,9a] The dibenzyl strategy often requires troublesome Pd-catalyzed deprotection.[16] While the acetonylidene strategy can not suffer from the ordinary reagents hydrogen halide[17] and *p*-toluenesulfonic acid,[18] the alkyl orthoformate method has also the same drawbacks.[19] Moreover, the diphenylmethylene protecting group is often assembled under high temperature (180 °C).[12] In addition, the expensive *tert*-butyl propynoate is a prerequisite for the 2-Boc-ethylidene strategy.[14] As known to all, the cyclic borate protecting group, susceptible to weak base, is severely limited.[15]

Therefore, a tolerant, concise, and versatile protection strategy remains to be developed for providing the synthesis of biologically relevant and diverse catechols, in which the protecting group should be readily installed, sufficiently tolerate various harsh reaction conditions, and be mildly cleaved in the end. In this letter, a convenient and efficient approach was suggested for protecting dihydroxyl groups of catechols using inexpensive 1,3-dibromopropane as a gentle protecting reagent and cheap aluminum chloride as a facile deprotecting reagent. Furthermore, the potential antibacterial and antifungal agent 4-(2-aminothiazol-4-yl)benzene-1,2-diol was prepared to verify the availability of this methodology.[1g,20]

It is well known that the isopropyl group has properly served as a hydroxyl protecting group for phenols.[21] For this reason, we envisioned that 2,3-dibromobutane, containing two isopropyl moieties, might be a suitable reagent to protect dihydroxyl groups of catechols via 2,3-dimethylbenzo[*b*]1,4-dioxanes. Unfortunately, in the model reaction we acquired 2,3-dimethylbenzo[*b*]1,4-dioxane in a low yield of 48% (Scheme 1). We thought that the intramolecular torsion of 2,3-dimethylbenzo[*b*]1,4-dioxane should be responsible for the difficult cyclization of catechol and 2,3-dibromobutane.



Scheme 1 Unsatisfactory cyclization of catechol and 2,3-dibromobutane

During the concurrent synthesis of vanillin and isovanillin, we found that the *n*-propyl group acts as an excellent hydroxyl protecting group for phenols with outstanding protecting and deprotecting properties too.[22] Inspired by the work, again we proposed 1,3-dibromopropane as a protecting reagent to catechols, considering to flexible seven-membered scaffold of benzo[*b*]1,4-dioxepan. As expected, the model cyclization reaction of catechol (1.0 equiv) and 1,3-dibromopropane (1.3 equiv) gave an excellent yield of 92% in the presence of potassium carbonate (3.5 equiv). Previously, this cyclization has never functioned as a protection strategy, despite the fact that it was mentioned once.[23]

Subsequently, we concentrated on the cleavage of the 1,3-propylidene group to estimate this novel strategy, and accordingly **2a** was chosen as a representative cleavage reaction for optimizing deprotection (Table 1). Based on the previous work (2.1 equiv aluminum chloride relative to 1.0 equiv *n*-propyl protecting group),[22] we initially attempted 4.2 equivalents of aluminum chloride to cleave the protecting group in dichloromethane at room temper-

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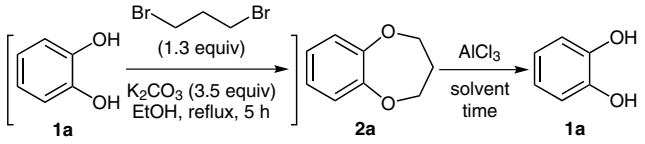
ature, however, the deprotection invalidly proceeded in 8% yield (Table 1, entry 1). Further, the deprotection at reflux in dichloromethane or chloroform still maintained the unacceptable yields of 13% and 16%, respectively (Table 1, entries 2 and 3). Besides, the tested polar solvents acetone and acetonitrile showed to be ineffective (Table 1, entries 4 and 5). Finally, we turned our attention to the usual solvent benzene possessing good dissolving capability and moderate boiling point, wherein the reactions occurred as the wonderfully improved results (Table 1, entries 6–8). The best yield was gained at reflux with 3.0 equivalents of aluminum chloride for four hours (90%, Table 1, entry 7).

Table 1 Optimization of the Deprotection Conditions[a]



Entry	Solvent	Time (h)	Temp	$AlCl_3$ (equiv)	Yield of **1a** (%)[b]
1	CH_2Cl_2	10	25 °C	4.2	8
2	CH_2Cl_2	10	reflux	4.2	13
3	$CHCl_3$	10	reflux	4.2	16
4	acetone	10	reflux	4.2	6
5	MeCN	10	reflux	4.2	0
6	PhH	4	reflux	4.2	86
7	PhH	4	reflux	3.0	90
8	PhH	6	reflux	2.3	88

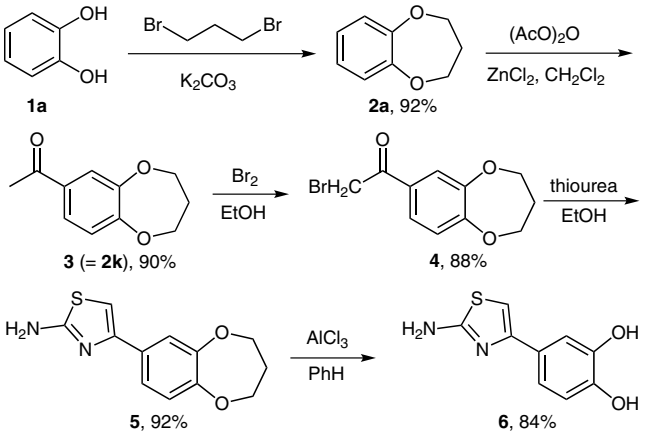
[a] Deprotections performed with solvents (10 mL), **2** (3.0 mmol), and aluminum chloride at the appropriate temperature for the specified time.
[b] Isolated yield.

With the optimized conditions in hand, then the scope of substrates was examined for the strategy. As shown in Table 2, various catechols underwent the discrete cyclization and deprotection reactions generally in good to excellent yields. Meanwhile, the reactions were well compatible with a wide range of substituents, such as electron-donating MeO and Me, as well as electron-withdrawing Br, F, PhCO, MeCO, EtOCO, NC, and benzo substituents.

In the cyclizations,[24] the catechols with electron-donating groups invariably gave good yields (Table 2, entries 2–7, 84–88%, i), but slightly lower than the yield of the model reaction (92%, Table 2, entry 1, i). On the other hand, the catechols with electron-withdrawing groups generally achieved excellent yields (91–95%, Table 2, entries 8–14, i), similar or superior to the yield of the model reaction. It is reasoned that enhanced acidity of catechols by electron-withdrawing groups will be in favor of the cyclizations.

In the deprotections,[25] the 1,3-propylidene group on the benzo[*b*]1,4-dioxepans **2** containing electron-donating group(s) was cleaved in good yields (83–86%) within the optimal specified time (Table 2, entries 2–7, ii), but less than in the model reaction (90%, Table 2, entry 1, ii). Particularly, it was observed that the simultaneous transalkylation and deprotection of **2g** gave the product **1a** (Table 2, entry 7, ii).[26] In contrast, for compounds **2** containing electron-withdrawing group(s), the excellent yields were generally obtained, equal or superior to the yield of the model reaction (Table 2, entry 1, ii and entries 8–14, 90–95%, ii).

To further verify the availability of this strategy, the promising antibacterial and antifungal agent 4-(2-aminothiazol-4-yl)benzene-1,2-diol (**6**) was prepared from catechol via five-step reactions (Scheme 2).[1g,20] First, the 1,3-propylidene protecting group has proved to be robust in the environment of the strong base potassium carbonate. Next, the Friedel–Crafts acylation of **2a** with an excellent yield of 90% definitely demonstrated the stability of the protecting group against the strong Lewis acid zinc chloride, sharply comparing with the congeneric aluminium chloride. Moreover, it was impressive that the protecting group was unaffected by hydrogen bromide generated in the bromination (offering **4** in outstanding 88% yield) and Hantzsch thiazole synthesis (offering **5** in an excellent yield of 92%). Finally, the desired product **6** was smoothly synthesized in good yield (84%) using the accomplished deprotection method (see Supporting Information for the detailed procedure). Thus, the study already demonstrated that this strategy exhibits remarkable performances.

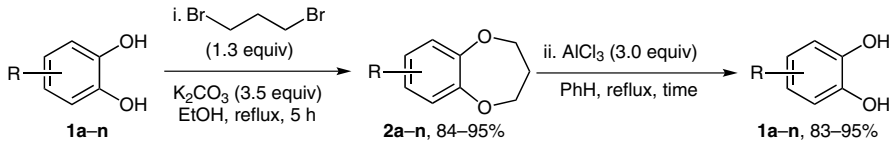


Scheme 2 Synthesis of 4-(2-aminothiazol-4-yl)benzene-1,2-diol **6** from catechol[27]

In conclusion, we have firstly developed a novel strategy for protecting dihydroxyl groups of catechols. The protecting group was easily installed and removed with a wide scope of catechols in good to excellent yields. The antibacterial and antifungal agent **6** was achieved in five steps with an overall yield of 56% from catechol employing this protecting strategy. This strategy unambiguously indicated its remarkable tolerances under various harsh

conditions including potassium carbonate as strong base, bromine and acetic anhydride as highly reactive reagents, hydrogen bromide as strong Brønsted acid, and zinc chloride as Lewis acid. We expected that this methodology has great potential for the application in organic synthesis.

Table 2 Cyclizations and Deprotections of the Different Substituted Catechols[a]



1a–n **2a–n**, 84–95% **1a–n**, 83–95%

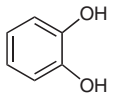
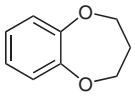
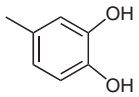
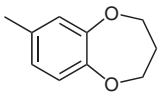
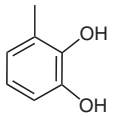
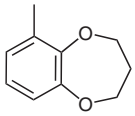
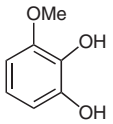
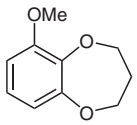
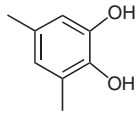
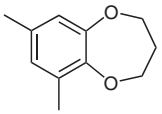
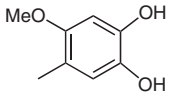
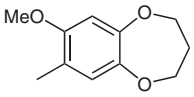
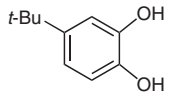
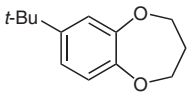
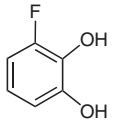
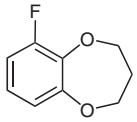
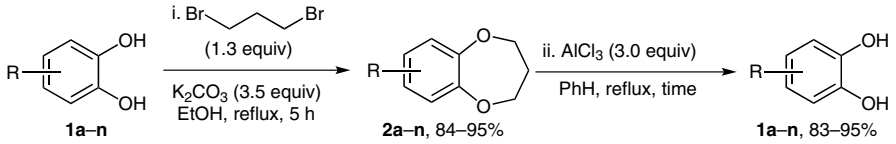
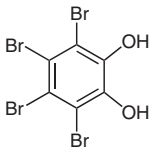
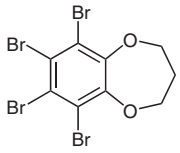
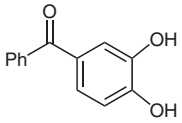
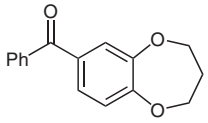
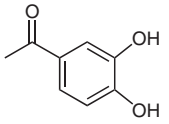
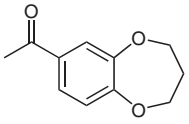
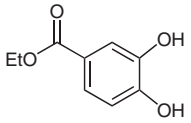
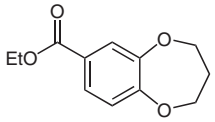
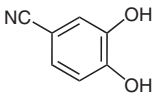
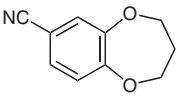
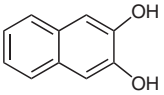
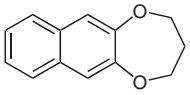
Entry	1	2	Isolated yields (%) i	ii (time, h)[b]
1	 **1a**	 **2a**	92	90 (4.0)
2	 **1b**	 **2b**	88	86 (1.0)
3	 **1c**	 **2c**	88	86 (1.0)
4	 **1d**	 **2d**	86	83 (1.0)
5	 **1e**	 **2e**	86	84 (1.0)
6	 **1f**	 **2f**	85	83 (1.0)
7	 **1g**	 **2g**	84	83 (1.0)[c]
8	 **1h**	 **2h**	91	92 (1.0)

Table 2 Cyclizations and Deprotections of the Different Substituted Catechols[a] (continued)



Entry	1	2	Isolated yields (%) i	ii (time, h)[b]
9			91	91 (0.7)
	1i	**2i**		
10			93	94 (1.0)
	1j	**2j**		
11			93	93 (3.5)
	1k	**2k**		
12			91	90 (1.0)
	1l	**2l**		
13			95	95 (5.0)
	1m	**2m**		
14			92	92 (5.0)
	1n	**2n**		

[a] (i) Cyclizations performed with EtOH (15 mL), **1** (5.0 mmol), K_2CO_3 (17.5 mmol), and 1,3-dibromopropane (6.5 mmol) at reflux for 5 h; (ii) deprotections performed with benzene (10 mL), **2** (3.0 mmol), $AlCl_3$ (9.0 mmol) at reflux for the specified time.
[b] Indicated in parentheses as the optimal specified time.
[c] Catechol **1a** as the product of this deprotection.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(24) **General Cyclization Procedure**
To EtOH (15 mL) were added in turn catechols **1** (5.0 mmol), K_2CO_3 (2.42 g, 17.5 mmol) and 1,3-dibromopropane (0.66 mL, 6.5 mmol), then the mixture was heated at reflux for 5 h. The resulting mixture was filtered and concentrated to acquire the crude product, the purification of which by column chromatography afforded the corresponding product **2** with PE–EtOAc (30:1, v/v) as eluents.
Representative Compound 2a
Colorless liquid, 0.69 g (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (quint, *J* = 5.6 Hz, 2 H, CH_2), 4.22 (t, *J* = 5.6 Hz, 4 H, CH_2), 6.90–6.95 (m, 2 H, Ar), 6.96–7.01 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.9, 70.5 (2 C), 121.6 (2 C), 123.3 (2 C), 151.2 (2 C) ppm. ESI-HRMS: *m/z* [M + H$^+$] calcd for $C_9H_{11}O_2$: 151.0759; found: 151.0757.
(25) **General Deprotection Procedure**
A solution of benzo[*b*]1,4-dioxepans **2** (3.0 mmol) in benzene (10 mL) was treated by anhyd $AlCl_3$ (1.20 g, 9.0 mmol), and the mixture was heated to reflux for specified time. Then, the reaction mixture was quenched by sat. aq NH_4Cl (20 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed by sat. brine (2 × 20 mL) and concentrated to provide the crude product, the purification of which by column chromatography afforded the corresponding product **1** with PE–EtOAc (10:1, v/v) as eluents.
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(27) **Synthetic Procedures for Compounds 4–6**
Compound 4
Bromine (0.17 mL, 3.4 mmol, dissolved in 2 mL EtOH) was added dropwise to a stirred solution of **3** (0.50 g, 2.6 mmol) in EtOH (8 mL), and the mixture was stirred at r.t. for 1 h. Then, the solvent was removed to get the crude product, the purification of which by column chromatography afforded the pure product **4** with PE–CH_2Cl_2 (15:1, v/v) as eluents; white solid; mp 72–74 °C; 0.62 g (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (quint, *J* = 5.6 Hz, 2 H, CH_2), 4.28 (t, *J* = 5.6 Hz, 2 H, CH_2), 4.34 (t, *J* = 5.6 Hz, 2 H, CH_2), 4.37 (s, 2 H, CH_2), 7.00 (d, *J* = 8.4 Hz, 1 H, Ar), 7.57 (d, *J* = 8.4 Hz, 1 H, Ar), 7.60 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.79, 30.81, 70.2, 70.4, 121.6, 122.7, 124.7, 129.1, 150.6, 156.0, 189.8 ppm. ESI-HRMS: *m/z* [M + H$^+$] calcd for $C_{11}H_{12}O_3Br$: 270.9970; found: 270.9975.
Compound 5
A solution of **4** (0.54 g, 2.0 mmol) and thiourea (0.18 g, 2.4 mmol) in absolute EtOH (12 mL) was refluxed for 2 h. After removal of the solvent, the residue was treated with aq NaOH (1 mol/L, 10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phase was concentrated to provide the crude product, the purification of which by column chromatography afforded the pure product **5** with PE–EtOAc (4:1, v/v) as eluents; light yellow solid; mp 174–177 °C, 0.46 g (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (quint, *J* = 5.2 Hz, 2 H, CH_2), 4.22 (t, *J* = 5.2 Hz, 4 H, CH_2), 5.05 (s, 2 H, NH_2), 6.60 (s, 1 H, thiazole), 6.97 (d, *J* = 8.4 Hz, 1 H, Ar), 7.34 (d, *J* = 8.4 Hz, 1 H, Ar), 7.40 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.8, 70.6 (2 C), 102.1, 119.3, 121.1, 121.7, 130.3, 150.5, 151.0, 151.2, 167.1. ESI-HRMS: *m/z* [M + H$^+$] calcd for $C_{12}H_{13}N_2O_2S$:

249.0698; found: 209.0693.

Compound 6

A solution of **5** (0.40 g, 1.6 mmol) in benzene (8 mL) was treated by anhyd $AlCl_3$ (0.64 g, 4.8 mmol), and the mixture was heated to reflux for 10 h. Then, the mixture was quenched by sat. aq NH_4Cl (20 mL). Then aq NaOH (1 mol/L) was added to keep pH 7. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed by sat. brine (2 × 20 mL), and then concentrated to provide the crude product, the purification of which by column chromatography afforded the pure product **6** with PE–EtOAc (2:1, v/v) as eluents; yellow solid; mp 228–231 °C; 0.28 g (84% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.64 (s, 1 H, thiazole), 6.69 (d, J = 8.0 Hz, 1 H, Ar), 6.92 (s, 2 H, OH), 7.06 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H, Ar), 7.19 (d, J = 2.0 Hz, 1 H, Ar), 8.90 (s, 2 H, NH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 98.3, 113.3, 115.4, 116.9, 126.8, 144.8, 144.9, 150.3, 167.7 ppm. ESI-HRMS: m/z [M + H$^+$] calcd for $C_9H_9N_2O_2S$: 209.0385; found: 209.0381.

