Regiospecific Amination of Veratrole *via* *o*-Benzoquinone Bis(dimethyl acetal)

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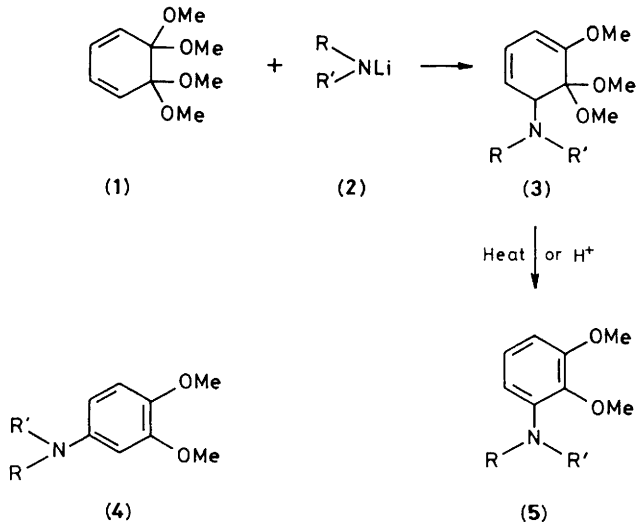
The bis(dimethyl acetal) of *o*-benzoquinone reacts with *N*-substituted lithium amides to afford 3-aminoveratroles selectively.

The bisacetal of *o*-benzoquinone (a stable equivalent of *o*-benzoquinone) is available *via* electrochemical oxidation of veratrole[1] and acts as an umpolung reagent of veratrole.[2] We report here that *N*-substituted lithium amides can attack the acetal to give 3-aminoveratroles selectively, a convenient preparation of which has not previously been reported despite their use in the synthesis of naturally occurring compounds such as 2-quinolone alkaloids.

When the bis(dimethyl acetal) (**1**) was stirred with 2 equiv. of HMeNLi (**2a**) in diethyl ether under an argon atmosphere for 3 h, *N*-methyl-2,3-dimethoxyaniline (**3a**) was formed in a 66% yield (Scheme 1). Similar reactions of (**1**) with lithium salts of benzylamine (**2b**), allylamine (**2c**), and *N*-methylaniline (**2d**) also gave the corresponding 3-aminoveratroles (**5b**)—(**5d**) (Table 1). The unsubstituted salt $LiNH_2$ (**2e**), however, did not react with the acetal (**1**). In no case was formation of the regioisomer (**4**) observed, in contrast with the nucleophilic addition of amines to *o*-quinones yielding 4-aminocatechols.[3]

The acetal (**1**) underwent similar nucleophilic substitutions with secondary alkylaminolithiums such as lithium di-isopropylamide (**2f**), which is well known to be a strong base but a weak nucleophile. However, the product was not the expected (**5f**) (R = R′ = Pr^i) but 5-(di-isopropylamino)-1,6,6-trimethoxy-1,3-cyclohexadiene (**3f**) (76% yield) which was isolated as an oil by column chromatography (SiO_2–CH_2Cl_2)



Scheme 1

a; R = H, R′ = Me
b; R = H, R′ = $PhCH_2$
c; R = H, R′ = CH_2=$CHCH_2$
d; R = Me, R′ = Ph
e; R = R′ = H
f; R = R′ = Pr^i
g; R = R′ = Et
h; R = H, R′ = Ph

Table 1. Synthesis of 3-aminoveratroles (**5**) by the reaction of *o*-benzoquinone bis(dimethyl acetal) (**1**) with lithium amides (**2**).

RR′NLi (**2**)	Temp. /°C	Time /h	% Yield	B.p. of (**5**) /°C (torr)
MeNHLi	0	3	66	80—81 (0.8)
$PhCH_2NHLi$	room temp.	13	69	126—128 (0.1)
CH_2=$CHCH_2NHLi$	0	3	84	115—116 (2)
Ph(Me)NLi	0	5	64	oil
NH_2Li	0	5	0	

and whose structure was established by i.r., mass, and n.m.r. spectral analyses. The lithium salts of diethylamine (**2g**) and aniline (**2h**) also give the respective cyclohexadiene (**3g**) and (**3h**). These compounds (**3**) could be quantitatively converted into the corresponding 3-aminoveratroles (**5**) by treatment with a catalytic amount of trifluoroacetic acid or on heating in toluene.

The reactions listed in Table 1 may also proceed through the corresponding cyclohexadiene intermediates (**3a**)—(**3d**), which are probably less stable than (**3f**)—(**3h**).

It is well known that free amines possess strong nucleophilicity and in many cases act more efficiently as nucleophiles than their lithium salts. In the system described here, however, the opposite is observed, and lithium amides (**2**) act as nucleophiles while the free amines of the salts (**2**) give no reaction with the acetal (**1**).

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References

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3 For a review, see K. T. Finley in 'The Chemistry of the Quinonoid Compounds,' Part 2, ed. S. Patai, Wiley, New York, 1974, p. 877.