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Synthesis of *o*-chlorophenols *via* an unexpected nucleophilic chlorination of quinone monoketals mediated by *N*,*N*′-dimethylhydrazine dihydrochloride†

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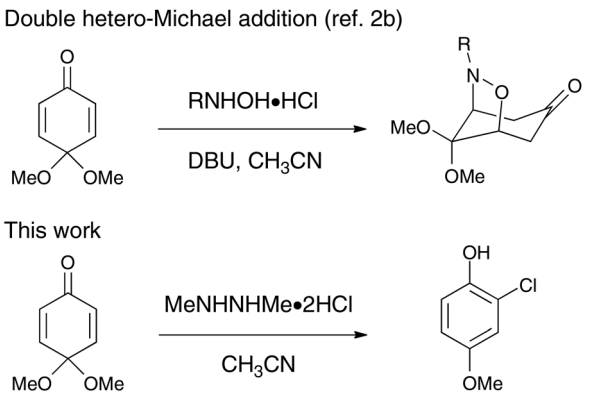
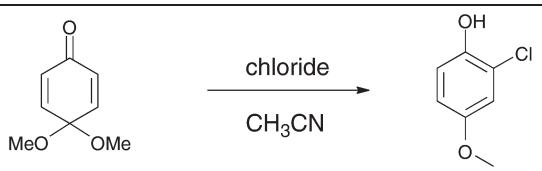
An unexpected nucleophilic chlorination of a quinone monoketal while carrying out a pyrazolidine synthesis has led to a general preparation of multisubstituted phenols. The products are obtained in good to high yields under mild conditions. The bridged pyrazolidines that were the original targets are obtained in the presence of a protic solvent.

Quinone monoketals are quinone equivalents with both carbonyls and double bonds being differentiated. They are important building blocks in the synthesis of structurally complex molecules.[1] Recently we were interested in heterocycle synthesis from nucleophilic addition to quinonoids.[2] We have developed a Fischer indole synthesis *via* coupling of quinone monoketals and monosubstituted aliphatic hydrazines through a 1,2-addition, aromatization, isomerization and cyclization process.[2a] We also have demonstrated a synthesis of bridged isoxazolidines *via* a double hetero-Michael addition between *N*-substituted hydroxylamines and quinone monoketals.[2b] To our surprise, when we extended the nucleophile to commercially available *N*,*N*′-dimethylhydrazine dihydrochloride, under the same conditions (DBU, CH_3CN, room temperature), the expected pyrazolidine was not obtained. Aside from the recovered starting material, a product was isolated in 2% yield. This product was shown to be a chlorophenol from MS and NMR spectra (Scheme 1). After comparison of the spectra with those of an authentic sample, the product was character-



Scheme 1 Unexpected formation of chlorophenols.

Table 1 Screening of the chloride source



2a **3a**

Entry	Chloride	Temperature (°C)	Time	Yield[a] (%)
1	**1a**	25	1 h	82
2	**1b**[b]	25	1 h	80
3	**1c**	25	1 h	62
4	**1d**	25	1 h	56
5	HCl (1 M)	25	1 h	55
6	**1a**	**Reflux**	**20 min**	**99**
7	Pyr·HCl[b]	Reflux	1 h	83
8	TMSCl	Reflux	1 h	32
9	Et_3N·HCl	Reflux	1 h	0
10	TBAC[c]	Reflux	1 h	0
11	$ZnCl_2$	Reflux	1 h	0

[a] Isolated yield. [b] Much lower yields for substituted quinone monoketals. [c] Tetrabutylammonium chloride.

MeNHNHMe·2HCl **1a** | MeONHMe·HCl **1b** | H_2NNH_2·HCl **1c** | *sec*-$BuNHNH_2$·2HCl **1d**

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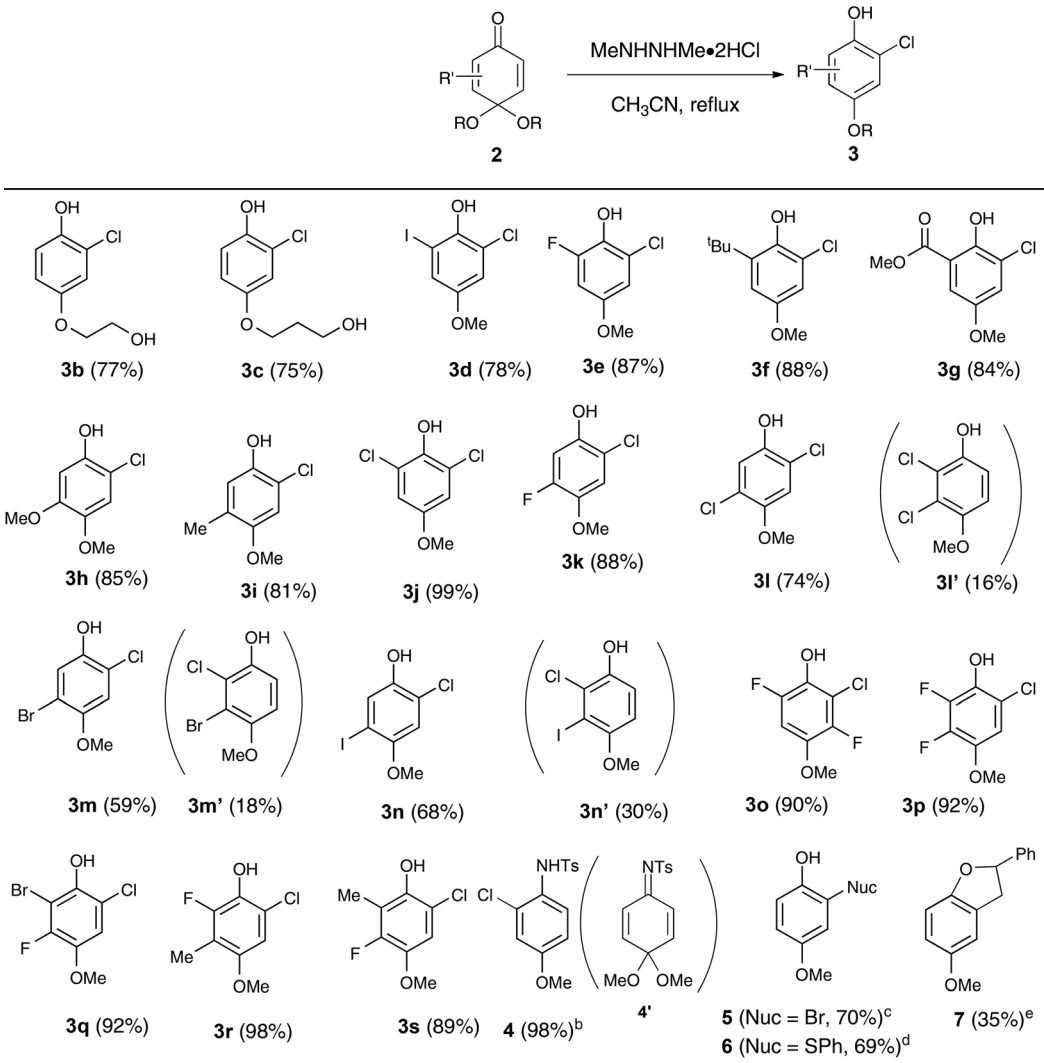
ized unambiguously as 2-chloro-4-methoxy-phenol **3a**,[3] presumably *via* a formal S_N2' substitution by chloride at the α-position of the carbonyl group and an ensuing aromatization. When the reaction was run in the absence of DBU at room temperature, **3a** was obtained in 82% yield, and upgraded to 99% yield under refluxing conditions (*cf.* Table 1). It is well known that quinone monoketals can undergo acid-catalyzed allylic substitution with carbon nucleophiles such as electron-rich arenes.[4] To the best of our knowledge, there are few precedents where halide is reported to undergo nucleophilic addition to quinone monoketals possibly *via* allylic substitution[5a] or 1,4-addition.[5b,c] Herein, we report our results on the regioselective synthesis of chlorophenols *via* a nucleophilic chlorination of quinone monoketals.

We first investigated a variety of hydrochloride salts of organic bases and inorganic chlorides for their effectiveness for this transformation (Table 1). Although different chloride sources can effect this nucleophilic chlorination, it was found that *N*,*N*′-dimethylhydrazine dihydrochloride gave the best result under reflux conditions (CH_3CN as the solvent).

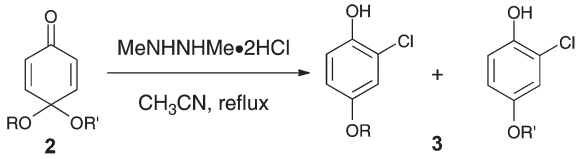
With optimized conditions identified, we then explored the scope of quinone monoketals. All quinone monoketals are prepared in one step from commercial phenols by PIDA oxidation according to Tamura–Kita–Pelter protocol.[6] As shown in Table 2, quinone monoketals with at least one unsubstituted *alpha* carbon to the keto group are good substrates for this nucleophilic chlorination. Quinone ethylene monoketal and quinone trimethylene monoketal both afforded chloroalcohols in good yields (**3b** & **3c**). Their structures were characterized unambiguously by X-ray crystallography.[7] Generally, monosubstituted quinone dimethyl monoketals gave chlorophenols as one regioisomer (**3d–3k**), except in the cases of **3l–3n**, where

Table 2 Scope of quinone monoketals[a]



[a] Yields in parentheses are isolated yields. [b] Quinone imine ketal as starting material. [c] TMSBr as bromide source (MeNHNHMe·2HBr gave lower yield). [d] PhSH + $NH_2NH_2{\cdot}H_2SO_4$. [e] Styrene as nucleophile.

Table 3 Substitution of mixed quinone monoketals



2t (R = Me, R′ = Et)	**3a** (R = Me): **3t** (R′ = Et) 85% (1 : 3.5)[a]
2u (R = Me, R′ = ^{i}Pr)	**3a** (R = Me): **3u** (R′ = ^{i}Pr) 85% (1 : 7.5)[a]
2v (R = Me, R′ = propargyl)	81%[b] (**3a** as sole product)
2w (R = Me, R′ = TBS)[c]	**3a** (R = Me) 25%[b] **3w** (R′ = TBS) 46%[b]

[a] NMR ratio of an inseparable mixture. [b] Isolated yield. [c] The crude NMR ratio of **3a**/**3w** is 1 : 1.6.

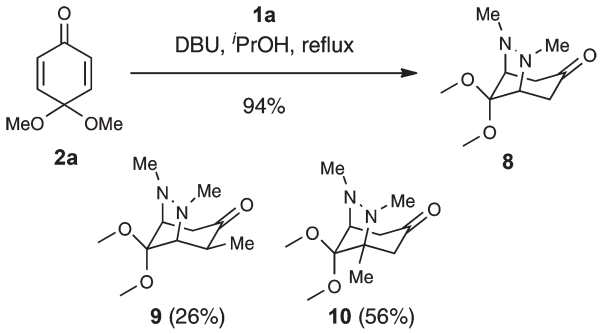
two regioisomers were obtained. Quinone monoketal with an electron-withdrawing methoxycarbonyl group still led to *ortho*-chlorophenol **3g**, instead of a *meta*-phenol through 1,4-addition to the β-carbon of the unsaturated ester, which attests to the generality of this method. Multisubstituted chlorofluorophenols were synthesized in high yields, as demonstrated in **3o–3s**, which otherwise would be obtained with difficulty.[8] Quinone imine ketal **4′**[9] is a good substrate for our nucleophilic chlorination to afford *ortho*-chloroanilide **4** as the sole product. Other nucleophiles, such as bromide, thiophenol[10] and styrene,[10,11] can also undergo this allylic substitution (**5–7**).

Mixed quinone monoketals gave a mixture of inseparable products. The major products are those where methanol acted as a better leaving group[12] (Table 3, **2t–2u**). On the other hand, for methyl propargyl mixed quinone monoketal **2v**, the sole product is **3a** due to propargyl alcohol acting as a better leaving group. Mixed quinone monoketal **2w**[13] may offer an evidence for the relative leaving ability of methanol and *tert*-butyldimethylsilanol in the quinone monoketal setting. The ratio of **3a** to **3w** is *ca.* 1 : 1.6 from proton NMR of the crude products, while 1 : 1.8 for isolated products, which implies methanol is a slightly better leaving group than *tert*-butyldimethylsilanol.[14]

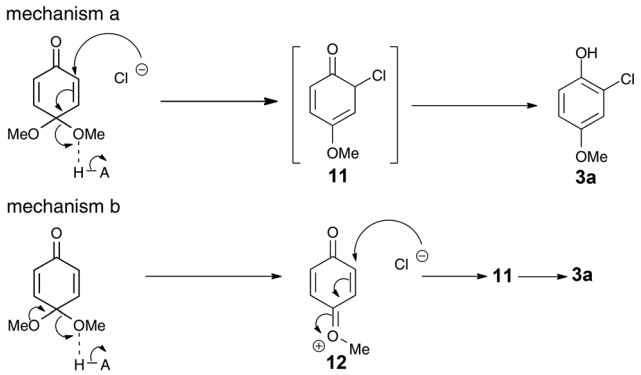
After screening the solvents, it was found that the expected bridged pyrazolidine could be obtained under basic conditions when a protic solvent was used. 2-Methyl and 3-methyl quinone monoketals also gave pyrazolidines in moderate yields (Scheme 2).

For the mechanistic speculation, this chlorination can be rationalized by either a direct S_N2'-type substitution (mechanism a) or a regioselective 1,4-addition to the preformed more electron-withdrawing oxocarbenium cation[15] (mechanism b), which is reminiscent of the mechanism of the Thiele reaction (Scheme 3).[16]

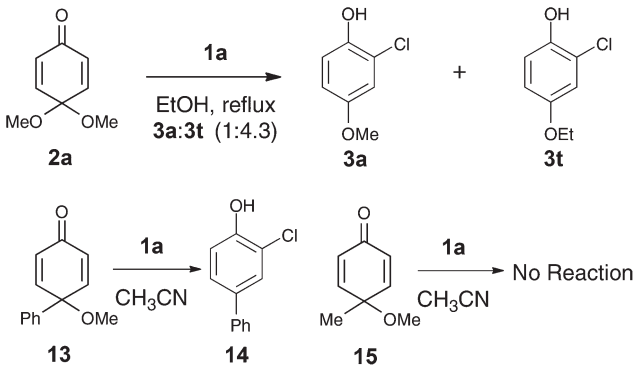
Circumstantial evidence favoring cation mechanism b includes: (1) scrambling experiments which incorporated solvent; (2) fast 1,4-addition of HCl to benzoquinone;[17] and (3)



Scheme 2 Expected bridged pyrazolidine synthesis.



Scheme 3 Possible mechanisms.



Scheme 4 Experiments favoring mechanism b.

quinol ether **13** gave the expected substitution while **15** did not (Scheme 4).

Conclusions

In summary, we have demonstrated an unexpected nucleophilic chlorination of quinone monoketals mediated by *N*,*N*′-dimethylhydrazine dihydrochloride. It provides a simple way to make multisubstituted phenols regioselectively. Moreover,

the relative ability of methoxy and siloxy as leaving group was also studied using mixed quinone monoketals as the substrates.

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