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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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Abstract

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, CH₃CN, 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 characterized 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 (CH₃CN 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 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, thiophenol¹⁰ 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 group¹² (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 cation¹⁵ (mechanism b), which is reminiscent of the mechanism of the Thiele reaction.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) 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Double hetero-Michael addition (ref. 2b)

This work

Scheme 1.

Unexpected formation of chlorophenols

Scheme 2.
Expected bridged pyrazolidine synthesis

Scheme 3.
Possible mechanisms

Scheme 4.
Experiments favoring mechanism b.

Table 1

Screening of the chloride source

entry	chloride	Temperature (°C)	time	yield (%) ^a
1	1a	25	1 hr	82
2	1b ^b	25	1 hr	80
3	1c	25	1 hr	62
4	1d	25	1 hr	56
5	HCl (1 M)	25	1 hr	55
6	1a	reflux	20 min	99
7	Pyr•HCl ^b	reflux	1 hr	83
8	TMSCl	reflux	1 hr	32
9	Et ₃ N•HCl	reflux	1 hr	0
10	TBAC ^c	reflux	1 hr	0
11	ZnCl ₂	reflux	1 hr	0

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

MeNHNHMe•2HCl	MeONHMe•HCl	H ₂ NNH ₂ •HCl	sec-BuNHNH ₂ •2HCl
1a	1b	1c	1d

Table 2

Scope of quinone monoketals ^a ^aYields in parentheses are isolated yields.^bQuinone imine ketal as starting material.^cTMSBr as bromide source.^dPhSH + NH₂NH₂·H₂SO₄.^estyrene 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>i</i> Pr)	3a (R = Me): 3u (R' = <i>i</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

^aNMR ratio of an inseparable mixture.^bIsolated yield.^cThe crude NMR ratio of **3a/3w** is 1:1.6.