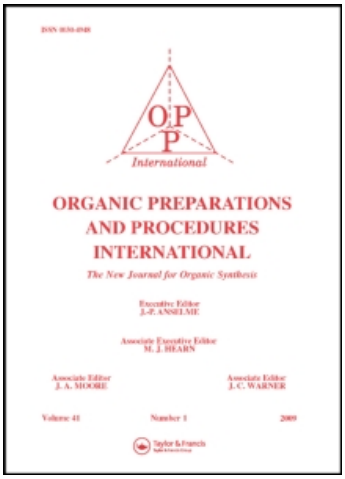

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Sundberg, R. J. , Theret, M. -H. and Wright, L.(1994) 'OXIDATION OF AMINES BY DICHLORODICYANOQUINONE (DDQ) WITH TRAPPING BY TRIMETHYLSILYL CYANIDE', Organic Preparations and Procedures International, 26: 3, 386 — 389
To link to this Article: DOI: 10.1080/00304949409458446
URL: http://dx.doi.org/10.1080/00304949409458446

OXIDATION OF AMINES BY DICHLORODICYANOQUINONE (DDQ) WITH TRAPPING BY TRIMETHYLSILYL CYANIDE

Submitted by (09/07/93)

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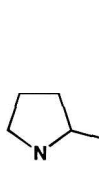
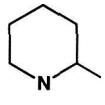
We recently reported the facile oxidative fragmentation of the *iboga* alkaloid catharanthine by oxidation with DDQ in the presence of trimethylsilyl cyanide (TMSCN).[1] In order to provide a basis for mechanistic comparison we have now examined the reactivity of several simpler amines toward DDQ. The oxidation of triethylamine by chloranil was studied some time ago.[2] The product, 2-(2-diethylaminovinyl)-3,5,6-trichlorobenzoquinone, results from apparent nucleophilic substitution by an enamine oxidation product on chloranil. It has been proposed that oxidation of amines by quinones proceeds *via* a charge transfer complex and electron-transfer.[3] More recently, low yields (<10%) of 2-dialkylamino-3-cyano-5,6-dichlorobenzoquinones were isolated from the reaction of secondary amines with DDQ in CH_2Cl_2 in the dark.[4] TMSCN has proven to be a useful reagent for trapping imines formed by photooxidation of amines.[5] It appeared likely to be a useful reagent for trapping products formed by oxidation by DDQ since the resulting α-cyanoamines would be more difficult to oxidize than the starting amine. The amines studied were 1methyl- and 1-benzylpyrrolidine, 1-methyl- and 1-benzylpiperidine, 2-methyltetrahydroisoquinoline and N,N-dimethyl-*trans*-2-phenylcyclopropylamine. The procedure adopted was to allow the amine and DDQ to react in benzene, either at 25° or 80° (reflux) in the presence of 3 equiv of TMSCN and 0.1 equiv of $LiClO_4$. The product mixture was separated from DDQ-derived material by elution through basic alumina.

The products shown below all have previously been reported and were identified on the basis of spectroscopic data.[6] Authentic samples of **1e**, **2c**, **2e** and **2f** were prepared for comparison. The extent of conversion and product ratio was determined from the NMR spectrum. The results are summarized in Table 1.



1

a) R_1 = Me, X = H
b) R_1 = CH_2Ph, X = H
c) R_1 = CH_3, X = CN
d) R_1 = CH_2Ph, X = CN
e) R_1 = CNCHPh, X = H
f) R_1 = CH_2CN, X = H



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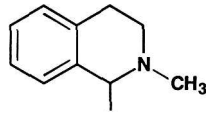
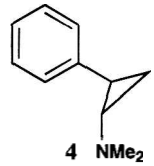


3

a) X = H
b) X = CN



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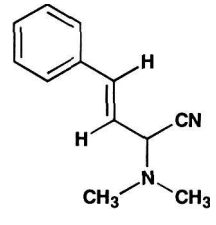

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TABLE 1. Yields of α-Cyanoamines by DDQ oxidation

Amine	Temp (°C)	Time (hrs)	Product	Yield (%)[a]	*exo/endo*	lit. Ref.
1a	25	1	**1c**	51	0:100	5a
1a	80	1	**1c**	40	0:100	5a
1b[b]	25	0.25	**1e, 1d**	59	5:95	5d, 5b
1b	80	1	**1e, 1d**	38	5:95	5d, 5b
2a[c]	25	3	**2f, 2c**	30	79:21	5a
2a	80	4	**2f**	40	100:0	5a
2b[b]	25	0.75	**2e, 2d**	19	87:13	5e, 5c
2b	80	24	–	0	—	–
3	25	2	**3b**	63	0:100	5f
3	80	2	**3b**	70	0:100	5f
4	25	4	–	0	—	
4	80	1.5	**5**	72	—	11

a) Estimated relative accuracy in conversion and product ratio is ± 10%. b) two equiv. c) C_6D_6

The pyrrolidines **1a** and **1b** showed a strong preference for endocyclic oxidation with yields in the range of 40-60%. The piperidines **2a** and **2b** were somewhat less reactive and the yields were lower. The major product from **2a** is the exocyclic aminonitrile **2f**. Similarly, the major product from **2b** was compound **2e** which was identified by comparison with a sample prepared by condensation of piperidine with benzaldehyde in the presence of TMSCN.[7] The relative reactivity pyrrolidine > piperidine is consistent with reactivity noted toward other oxidants.[8] The preference for endocyclic oxidation of pyrrolidines has also been noted in electrochemical cyanation[9] and ClO_2 oxidation.[10] The preference for exocyclic oxidation of 1-methylpiperidine is in the same direction, but more pronounced, as observed under those conditions. N-Methyltetrahydroisoquinoline was oxidized to the 1-cyano derivative in good yield. No trace of the exocyclic oxidation product was observed. N,N-Dimethyl-*trans*-2-phenylcyclopropylamine **4** was unreactive toward DDQ at 25° but was converted to the fragmentation product **5** at 80°. The product was identified by comparison of spectroscopic data with those previously published for 5.[11] Fragmentation was anticipated on the basis of previous studies on the oxidation of cyclopropylamines.[12]

These results raise interesting mechanistic questions which will require further study for clarification. Perhaps the most intriging issue is the preference for endocyclic oxidation of pyrrolidines, which in the case of **1b** outweighs the effect of benzylic activation. This is in contrast to photooxidation of **1b** which, under strongly alkaline conditions, leads to debenzylation.[13] It is also possible that TMSCN participates in the oxidation reaction, beyond functioning as a trapping agent, by O-silylation of the quinone.

EXPERIMENTAL SECTION

DDQ and TMSCN were purchased from Aldrich Chemical Company and used as received. Benzene was distilled from sodium-benzophenone ketyl and CH_2Cl_2 was distilled from P_2O_5.

Oxidation by DDQ.- A solution of DDQ (1.1 mmol, 1.1 eq), $LiClO_4$ (0.1 eq) and TMSCN (3 eq) was prepared in dry benzene (10 mL) and stirred for five minutes at room temperature; then the amine (1 mmol) was added. The solution turned deep brown and was stirred or heated for the period specified in Table 1. After the completion of the reaction period the mixture was eluted through basic alumina with CH_2Cl_2 and after careful evaporation of the solvent the product composition determined by ^{1}HNMR.

Preparation of Reference Samples.- Compound **2f** was prepared from piperidine by condensation with formaldehyde in the presence of NaCN[14] and **2c** was obtained from piperidine-2-carbonitrile[15] by reductive methylation with formaldehyde and $NaBH_3CN$.[16] Compounds **1e** and **2e** were prepared from the appropriate amine and benzaldehyde by condensation in the presence of TMSCN.[7]

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