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Thiourea catalysis of NCS in the synthesis of chlorohydrins

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Abstract

Thiourea catalysis of reactions utilizing *N*-succinimides is demonstrated with NCS chlorination of olefins in the presence of water to afford chlorohydrins.

Why are organohalides an important synthetic goal? They allow the incorporation of a variety of functional groups containing carbon, nitrogen, sulfur and oxygen.[1] In drug design halogen replacement of proton or methyl groups attached to carbon has often provided a more metabolically stable compound invariably without loss of biological activity.[2] Vicinal halohydrins have also been key intermediates to a number of marine natural products.[3] Synthetically halohydrins have been useful in 1,2-alkyl shift with formation of a ketone,[4] ring contraction with aldehyde formation mediated by silver oxide,[5] *cis*-diol formation via a ketene acetal[6] and epoxidation[7] among other reactions.

Chlorohydrins have been extensively prepared by epoxide opening with metal halides.[8] Alternatively, hypohalous acids and hypohalite reactions with an olefin also have provided halohydrins.[9] In addition $NaIO_4$/NaCl,[10] *N*-methylmorpholine-*N*-oxide/cyanuric chloride,[11] Pd(II)-complex/$CuCl_2$,[12] trichloroisocyanuric acid[13] and *N*-chlorosaccharins[14] have all proven good sources of chlorine to form chlorohydrins.

N-Halosuccinimides have constituted some of the most popular sources of halogens. Indeed, bromohydrins have been produced by olefin reaction with NBS in THF and water.[15] Interestingly, while NCS has been useful[16] for α-chlorination of carbonyl, thioether, sulfoxide, sulfone and chlorination of aromatic compounds or amines, the corresponding preparation of chlorohydrins from NCS is not documented in the literature. We wondered if an organocatalytic approach to this opportunity would prove effective.

A reinvigorated interest in organocatalysis[17,18] in recent years has resulted in a plethora of new catalytic processes often carried out with excellent stereoselectivity. Proline based systems have been successfully employed in the preparation of α-halocarbonyl,[19,20] while interest in thiourea catalytic applications has grown.

Urea and its derivatives[21] were first used to catalyze sulfoxide allylation[22] and Claisen rearrangements.[23] These catalysts then saw expanded utilisation in Diels–Alder,[24] 1,3-dipolarcycloaddition,[25] nitrone TMSCN addition,[26] Strecker,[27] Mannich,[28,29] aza-Henry,[30] hydrophosphonylation,[31] Pictet–Spengler[32] Michael addition,[33–35] Baylis–Hillman[36–38] and reductive amination[39] reactions. Several mechanisms have invoked thiourea hydrogen bonding capability with a carbonyl oxygen[40] and reactions with *N*-halosuccinimides were catalyzed by Brønsted acids[41] suggestive of mechanisms with Figure 1 as a key step.

Styrene (**1**) reacted with NCS in a wet solvent very slowly to give chlorohydrin **5** in a negligible yield (Table 1, entry 1) and unfortunately the addition of urea offered only marginal catalysis (Table 1, entry 2). A notable improvement was observed with the use of either thiourea (**2**) or *N*,*N*-dimethylthiourea (**3**) as catalysts.[42] Both gave a fast reaction with excellent regiocontrol (the other regioisomer was not observed) in moderate yields (Table 1, entries 3 and 4).

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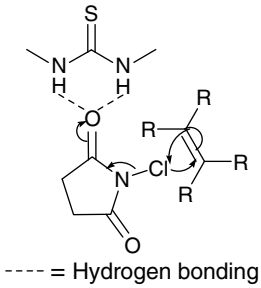


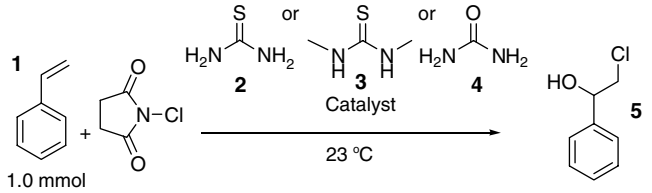
Fig. 1. Possible key step of the mechanism.

The investigation then focused upon optimisation of reaction conditions. Catalyst loading was altered with less catalyst responsible for a slower reaction (Table 1, entry 5) and more catalyst responsible for a faster reaction with slightly lower yield (Table 1, entry 6). Half the mass of NCS in a reaction gave a drastic increase in the reaction's duration and a significant loss of reaction yield (Table 1, entry 7). The replacement of THF with acetonitrile caused a minimal change of reaction yield (Table 1, entry 8); however, with water as the only solvent a slow reaction with a limited yield was observed (Table 1, entry 9).

The initial conditions prior to attempted optimisation proved to be the best. The reaction conditions were applied to a variety of substrates containing different substituted olefins (**9**–**14**) with varied electronic environments.

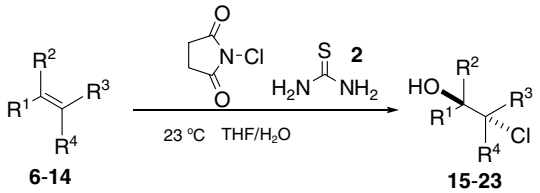
Styrene derivatives with replacement functional groups at the *para* position of the phenyl ring were studied. A

Table 1
Chlorination of styrene with thiourea/urea catalysts in water



Entry	Catalyst (Mol %)	NCS (mmol)	Solvent (3 cm^3)	Time (h)	Yield (%)
1	—	4.0	THF/H_2O (1:1)	12.0	5
2	**4** (20)	4.0	THF/H_2O (1:1)	36.0	21
3	**3** (20)	4.0	THF/H_2O (1:1)	3.0	54
4	**2** (20)	4.0	THF/H_2O (1:1)	3.0	69
5	**2** (10)	4.0	THF/H_2O (1:1)	9.0	67
6	**2** (50)	4.0	THF/H_2O (1:1)	1.5	57
7	**2** (20)	2.0	THF/H_2O (1:1)	48.0	46
8	**2** (20)	4.0	MeCN/H_2O (1:1)	3.0	66
9	**2** (20)	4.0	H_2O	10.0	43

Table 2
Chlorination of a variety of olefin substrates in water



Entry	Substrate	Time (h)	Product, Yield (%)
1	**6**	2.0	**15** (55)
2	**7**	1.0	**16** (60)
3	**8**	5.0	4 : 3 (34) **17a** : **17b**
4	**9**	1.0	**18** (82)
5	**10**	1.0	3 : 2 (53) **19a** : **19b**
6	**11**	1.5	**20** [a](56)
7	**12**	0.5	**21** [b](48)
8	**13**	1.5	**22** (32)
9	**14**	0.5	**23** [c](64)

[a] cis:trans ratio 5:6.
[b] cis:trans ratio 1.5:3.
[c] cis:trans ratio 2:9.

fluoro group (**6**) gave a reaction of decreased duration that afforded chlorohydrin (**15**) in a slightly reduced yield (Table 2, entry 1). Whilst a methyl group (**7**) gave a reaction three times faster (Table 2, entry 2). The phenyl functionality change to an aliphatic moiety such as *n*-hexyl (**8**) lead to a slower reaction with lower yield and unfortunately almost no regiocontrol (Table 2, entry 3). A digeminal olefin (**9**) gave excellent regiocontrol for formation of chlorohydrin with the highest yield observed, in a short reaction time (Table 2, entry 4). But a trisubstituted olefin showed markedly less regiocontrol with a notably lower yield (Table 2, entry 5). Olefins with a variety of electronic environments were exposed to the reaction conditions. A chlorohydrin was formed from stilbene (**11**) quite rapidly in moderate yield (Table 2, entry 6). Chalcone (**12**) chlorohydrination was faster with little change in the yield (Table 2, entry 7). Finally cycloalkenes were studied; the aliphatic methylcyclohexene gave a slower reaction with inferior yield (Table 2, entry 8) compared to aromatic indene (**13**) that reacted very rapidly, to provide the chlorohydrin in one of the higher yields of the substrates studied (Table 2, entry 9).

In summary, the organocatalysis of reactions involving *N*-succinimides have been demonstrated, with cheap and commercially available reagents. NCS showed unprecedented chlorination of olefins in the presence of water and gave chlorohydrins in moderate to good yields when catalyzed by thiourea or its derivatives. Work is currently focused towards other chlorination or bromination reactions using NCS or NBS and thiourea, in addition to the development of an asymmetric variant of the reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.211.

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42. This trend maybe ascribed to the difference in pK_a (urea is 26.9 and thiourea is 21.0, both in DMSO) given the earlier mechanistic speculation.