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Tetrahedron Letters 44 (2003) 8143–8147

TETRAHEDRON LETTERS

A mild, phosphine-free method for the conversion of alcohols into halides (Cl, Br, I) via the corresponding *O*-alkyl isoureas

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Received 9 July 2003; revised 30 August 2003; accepted 3 September 2003

Abstract—A novel procedure for the conversion of primary and secondary alcohols into the corresponding alkyl chlorides, bromides and iodides is described. The transformation is high-yielding in the case of chlorides and bromides, tolerates a range of functional groups, and does not rely on the use of phosphines.

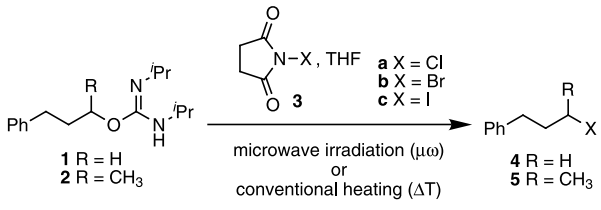
The transformation of alcohols into the corresponding halides represents an important functional group interconversion in organic synthesis. Various methods have been reported, either requiring a single operation or two separate reaction steps, to accommodate a wide structural variety of alcohol substrates.[1] The potential difficulties associated with the removal of the triphenylphosphine oxide by-product notwithstanding, the majority of alcohol to halide transformations is based on the use of triphenylphosphine. The displacement of sulfonates with a halide source usually requires a two-step operation. Perhaps the simplest methods involve hydrogen halide, thionyl halide or phosphorous halide reagents, though these methods only tolerate a rather limited range of substrate functionalisation. Hence, despite the wealth of available methods for alcohol to halide transformation, research towards the development of mild, selective methodologies, especially for non-allylic or benzylic alcohols, is still an active area in organic synthesis.[2]

As part of our ongoing interest in the development of synthetic and combinatorial applications of *O*-alkyl isoureas,[3] especially with attention to novel isourea activation strategies,[4] we discovered an unanticipated route to alkyl halides upon treatment of *O*-alkyl isoureas with *N*-halosuccinimides (NXS, X = Cl, Br, I, Scheme 1). *O*-Alkyl isoureas require activation prior to reaction, and the conversion to alkyl halides under conventional protic activation with a strong acid (CF_3SO_3H, equimolar) and excess tetrabutylammonium halide (Br, I) as the halide source has been described.[5] We have recently reported a novel activation method for *O*-alkyl isoureas to initiate halogenation reactions with acetyl halides (Cl, Br), a reaction which proceeded with inversion of configuration.[4]

In this communication, we report our findings regarding the reaction of *N*-halosuccinimides with *O*-alkyl isoureas, including the subsequent development of a practical one-pot procedure for the conversion of alcohols into the corresponding alkyl chlorides, bromides and iodides.

By reacting *O*-alkyl isourea **1** (Scheme 1), synthesised from 3-phenyl-1-propanol and diisopropylcarbodiimide (DIC), with *N*-bromosuccinimide (NBS) **3b** under microwave irradiation in THF as solvent, we were surprised to obtain **4b** in good yield (85%) after only 5 minutes reaction time. Hence, we were stimulated to investigate the scope of this reaction (Table 1).

Increasing the number of equivalents of NBS did not further improve the yield (entry 3 versus 2). When the reaction was carried out with thermal heating, the yield of **4b** improved to 92%, although the reaction time was



Scheme 1. Conversion of isoureas by *N*-halosuccinimides.

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doi:10.1016/j.tetlet.2003.09.024

Table 1. Synthesis of alkyl halides from *O*-alkyl isoureas

Entry	Isourea	X (**3**) (equiv.)	Temp (°C)	Time (min)	Yield (%)[a]
1	**1**	Cl (1.5)	160 (μω)	5	77
2	**1**	Br (1.0)	150 (μω)	5	85
3	**1**	Br (2.0)	150 (μω)	5	86
4	**1**	Br (1.0)	80 (ΔT)	4.5 h	77
5	**1**	Br (2.0)	80 (ΔT)	4.5 h	92
6	**1**	I (1.0)	150 (μω)	5	65
7	**1**	I (2.0)	150 (μω)	5	93
8	**2**	Cl (1.5)	160 (μω)	10	80[b]
9	**2**	Br (1.0)	160 (μω)	5	87[b]
10	**2**	Br (1.0)	80 (ΔT)	4.5 h	70[b]
11[c]	**2**	Br (2.0)	80 (ΔT)	4.5 h	96[b]
12	**2**	I (1.0)	150 (μω)	10	60[b]

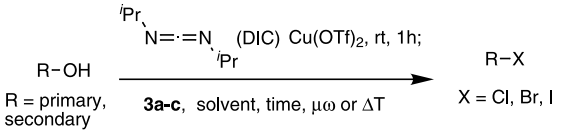
[a] Isolated yield after chromatography.
[b] Traces of elimination product (<5%) could be observed (GC).
[c] Dichloroethane was used as the solvent instead of THF.

much longer (entry 5) and 2 equiv. of NBS were required (entry 5 versus 4). The reaction worked with *N*-chlorosuccinimide (NCS) (entry 1) and *N*-iodosuccinimide (NIS) (entries 6, 7) as well. In order to obtain a good yield of the iodide, 2 equiv. of NIS were required, even when microwave irradiation was employed (93%, entry 7). We also investigated the reactivity of isourea **2**, derived from a secondary alcohol, under those conditions. We were delighted to find that under microwave irradiation, reaction of **2** with NCS (entry 8), NBS (entry 9) and NIS (entry 12) yielded the corresponding halides in good yields, again with very short reaction times. With conventional heating, the reaction worked equally well when 2 equivalents of NBS were used (entries 10, 11).

With the reactivity of the isoureas towards *N*-halosuccinimides established, the next stage was to investigate the possibility of using this procedure in a one-pot reaction process for the synthesis of alkyl halides from the corresponding alcohols, where the isourea would be synthesized in situ. To this end, a process was envisaged where the alcohol substrate would first be reacted with DIC and a copper-based catalyst to form the isourea, followed by the addition of *N*-halosuccinimide (Scheme 2). As a control experiment, 3-phenyl-1-propanol was treated with NBS (2 equiv.), and heated for 5 min at 150°C in the microwave oven. No 3-phenyl-1-bromopropane was formed under these conditions.

Some preliminary experiments were conducted to optimise the isourea formation. Whereas CuCl is the traditional choice as catalyst for isourea formation,[6] we found that $Cu(OTf)_2$ is superior in terms of reactivity. The improved activity is marked when secondary alcohols are used. Another benefit of the $Cu(OTf)_2$ catalyst is that it does not introduce chloride ions to the reaction mixture, which could lead to the formation of alkyl chloride side-products when NBS or NIS are used. The current optimal procedure for isourea formation is simply mixing the alcohol substrate with 1 equiv. of DIC and 1–2 mol% of $Cu(OTf)_2$ for 1 h at room temperature, without the use of any solvent. With solid alcohols, a small amount of THF was added. The reaction is easily monitored by IR (disappearance of the carbodiimide band at 2110 cm^{-1} and appearance of the isourea band at 1655 cm^{-1}). Provided complete conversion was achieved, the exact method of isourea preparation was of little consequence for the yield of the overall halogenation process.

The substrates that were used to investigate the halogenation process are shown in Figure 1, and the results for the conversion to the corresponding chlorides are listed in Table 2. DIC and $Cu(OTf)_2$ were added to the alcohol, and stirred for 1 h, followed by addition of solvent and 2 equiv. of NCS. All reactions were executed in a sealed tube. Conventional heating in THF or



Scheme 2. One-pot conversion of alcohols to alkyl halides.

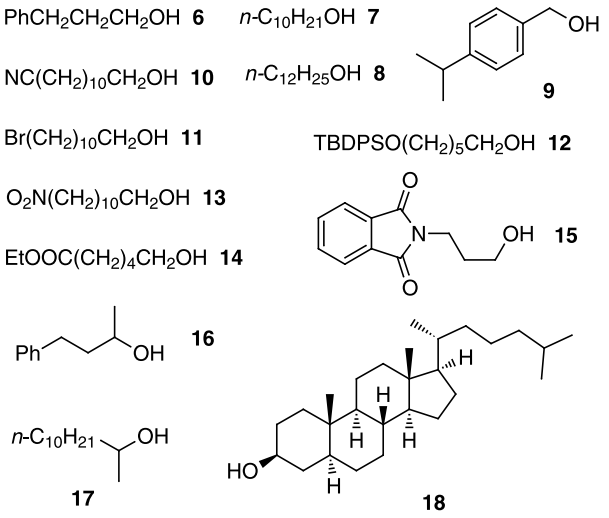


Figure 1. Substrates for the halogenation reaction.

Table 2. One-pot conversion of alcohols into alkyl chlorides

$$\text{R-OH} \xrightarrow[\text{3a (2 equiv.), conditions}]{\text{DIC (1 equiv.) Cu(OTf)}_2^{a}\text{, rt 1 h}} \text{R-Cl}$$

Entry	ROH	Solvent	Time (h)	Temp (°C)	Yield (%)[b]
1	**8**	THF	3.5	100 (ΔT)	85
2	**8**	Dioxane	3.5	100 (ΔT)	86
3	**8**	THF	5 min	160 (μω)	93
4	**14**	THF	4.5	100 (ΔT)	64
5	**15**	THF	4.5	100 (ΔT)	70
6	**16**	THF	3.5	100 (ΔT)	68[c]
7	**16**	Dioxane	3.5	100 (ΔT)	73[c]
8	**16**	THF	10 min	160 (μω)	74[c]
9	**17**	THF	3.5	100 (ΔT)	76 (7)
10	**17**	THF	10 min	160 (μω)	72 (15)
11[d]	**18**	THF	3.5	80 (ΔT)	36 (5)
12[d]	**18**	THF	21.5	80 (ΔT)	70 (10)
13[d]	**18**	THF	10 min	160 (μω)	72 (16)

[a] 1 mol% was used for primary alcohols, and 2 mol% was used for secondary alcohols.
[b] Isolated yield after chromatography. Yields in parentheses refer to elimination product (determined by NMR).
[c] Less than 5% of elimination product was formed (GC).
[d] 5 mol% of $Cu(OTf)_2$ was used for the isourea formation.

1,4-dioxane gave identical results (entries 1, 2). When microwave irradiation was employed, (entry 3), a slightly better yield was obtained after only 5 min. The reaction conditions tolerate the presence of ester and imide functional groups (entries 4 and 5). With secondary alcohols, the desired alkyl chloride was also obtained in good yields with minimal difference between thermal and microwave heating conditions (entries 6–8; 9–10; and 12–13), except with regard to the much shorter reaction time for the latter. Secondary *O*-alkyl isoureas required a longer microwave irradiation time for the halogenation reaction compared to primary isoureas, and typically some elimination product was found in the case of secondary alcohols. This side-reaction was found to be substrate-dependent. With **16**, only traces of elimination product were observed, both under thermal as under microwave conditions. However, with **17**, about 7% of elimination products were observed under thermal conditions, which increased to 15% under microwave irradiation. With 3β-cholestanol **18** as substrate, a much longer reaction time was required under thermal conditions (entries 11, 12), though a reaction time of 10 minutes was still sufficient under microwave irradiation (entry 13). Interestingly, only the corresponding α-chloride was obtained, indicating a clean inversion of configuration. We noticed that it is essential that moisture-free conditions are used. The presence of moisture can be easily detected as the copper triflate turns blue in the presence of water.

The results for the conversion of alcohols to alkyl bromides are shown in Table 3. Isourea formation, followed by reaction with NBS in refluxing 1,2-dichloroethane (DCE) gave the corresponding bromide in good yield (entry 1). When the reaction was conducted in THF using microwave heating, a similar yield was obtained after a reaction time of only 5 min (entry 2). When the isourea intermediate was synthesised by using CuCl instead of $Cu(OTf)_2$, a similar yield was obtained (entries 1, 4, 6, 8). When only 1 mol% of CuCl was used, we could not detect any alkyl chloride product but when 5 mol% of CuCl was used, GC-analysis revealed the formation of trace amounts of the corresponding alkyl chloride (ca. 3%).

When DCE and dioxane were compared as solvent (entries 4 and 5), an identical yield was obtained under standard reflux conditions, though the reaction appeared to be finished in a shorter time, though a higher reaction temperature was used in dioxane. A benzylic alcohol gave the corresponding bromide in good yield (entry 8).

A range of functional groups including nitrile, alkyl bromide, TBDPS–ether, nitro, ester and imide (entries 10–17) were tolerated under the reaction conditions. Secondary alcohols were also successfully transformed into the corresponding bromides (entries 18–23), with a negligible solvent-dependance. However, under microwave conditions (entries 20, 22), a slightly lower yield was obtained. The proportion of elimination product was lower compared to the alkyl chloride formation, and in the case of **17**, no elimination product was formed at all, as judged by GC analysis through comparison with an authentic sample. With 3β-cholestanol **18**, again only the 3α-isomer was formed. However, it was disappointing to observe that, when enantiopure 4-phenyl-2-butanol **16** was used, partial racemisation had occurred, presumably through a Finkelstein-type bromide exchange reaction.

The transformation of alcohols into alkyl iodides proved more difficult than expected, with yields that are lower compared to the bromination and chlorination reactions (Table 4, entries 1–4). When **11** was subjected to the reaction conditions, we found that Finkelstein reactions complicated the reaction outcome. Apart

Table 3. One-pot conversion of alcohols into alkyl bromides

$$\text{R-OH} \xrightarrow[\text{3b (2 equiv.), conditions}]{\text{DIC (1 equiv.) Cu(OTf)}_2^{a}\text{, rt 1 h}} \text{R-Br}$$

Entry	ROH	Solvent	Time (h)	Temp (°C)	Yield (%)[b]
1[d]	**6**	DCE	4.5	80 (ΔT)	87
2	**6**	THF	5 min	150 (μω)	83
3[c]	**6**	THF	5 min	150 (μω)	85
4[d]	**7**	DCE	4.5	80 (ΔT)	90
5	**7**	Dioxane	2	100 (ΔT)	90
6[d]	**8**	DCE	4.5	80 (ΔT)	90
7	**8**	THF	5 min	150 (μω)	87
8[d]	**9**	DCE	2	80 (ΔT)	85
9	**10**	THF	2	100 (ΔT)	88
10	**10**	THF	5 min	150 (μω)	76
11	**11**	THF	2	100 (ΔT)	90
12	**11**	THF	5 min	150 (μω)	88
13	**12**	THF	2	100 (ΔT)	81
14	**13**	THF	2	100 (ΔT)	89
15	**13**	THF	5 min	150 (μω)	93
16	**14**	THF	2	100 (ΔT)	82
17	**15**	THF	2	100 (ΔT)	85
18	**16**	DCE	4.5	80 (ΔT)	83[e]
19	**16**	Dioxane	2	100 (ΔT)	85[e]
20	**16**	THF	5 min	160 (μω)	72[e]
21	**17**	Dioxane	2	100 (ΔT)	92
22	**17**	THF	5 min	150 (μω)	77
23	**18**	Dioxane	2	100 (ΔT)	80[f]

[a] 1 mol% was used for primary alcohols, and 2 mol% was used for secondary alcohols.
[b] Isolated yield after chromatography.
[c] Isourea was formed at 100°C, 5 min, under microwave irradiation.
[d] Reaction time of 30 min for the isourea formation, and CuCl (1 mol%) was used.
[e] Trace amounts (<5%) of elimination products were formed (GC).
[f] An additional 9% yield of elimination product was isolated.

Table 4. One-pot conversion of alcohols into alkyl iodides

$$\text{R-OH} \xrightarrow[\text{3c (2 equiv.), conditions}]{\text{DIC (1 equiv.) Cu(OTf)}_2^{a}\text{, rt 1 h}} \text{R-I}$$

Entry	ROH	Solvent	Time (min)	Temp (°C)	Yield (%)[b]
1	**6**	THF	5	150 (μω)	56
2	**6**	THF	10	150 (μω)	44
3	**8**	THF	5	150 (μω)	73
4	**10**	THF	5	150 (μω)	73
5	**11**	THF	5	150 (μω)	See text

[a] 1 mol% was used for primary alcohols, and 2 mol% was used for secondary alcohols.
[b] Isolated yield after chromatography.

from the expected 1-bromo-11-iodoundecane product, 1,11-dibromoundecane and 1,11-diiodoundecane were found to be present (5:3:1 ratio by GC). The reaction of secondary alcohols proved low-yielding and the products were contaminated with a substantial amount of elimination side-product, as well as with other unidentified byproducts.

We have also tried to perform the transformation by mixing all ingredients (the alcohol, $CuCl_2$ (5 mol%), DIC, NBS and the solvent) from the beginning. With 3-phenyl-1-propanol, the corresponding bromide was obtained in 75% yield.

In summary, we have reported a general, high-yielding one-pot process for the conversion of primary and secondary alcohols to the corresponding alkyl chlorides and bromides.[7,8] The conversion to alkyl iodides gave low to moderate yields. The reaction product from secondary alcohols is typically contaminated with a small amount of elimination product. The reaction requires heating, with thermal heating at 80–100°C and microwave irradiation at 150–160°C to give similar results in terms of yield, but with a much shorter reaction time (5–10 min) in the microwave oven. A wide range of functional groups (see Fig. 1) survive the reaction conditions, but the excess halide ions in the

reaction mixture may lead to undesired Finkelstein reactions. The mechanism of this transformation is currently under investigation.

Acknowledgements

The authors thank Personal Chemistry for the donation of a Smith Synthesizer™. The authors acknowledge the supporting partners of the Southampton Combinatorial Centre of Excellence for financial support. The funding partners are: Amersham Health and Amersham Biosciences, AstraZeneca, Evotec OAI Ltd, GlaxoSmithKline, Eli Lilly, Merck Biosciences Inc., Organon, Pfizer and Roche. The authors thank Joan Street and Neil Wells for assistance with NMR-measurements and Julie Herniman and John Langley for assistance with mass spectrometry.

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7. Typical procedure for the one-pot halogenation reaction using conventional thermal conditions: a mixture of alcohol **6** (2.01 mmol), DIC (2.01 mmol) and $Cu(OTf)_2$ (1 mol%) was stirred for 1 h at room temperature. To the mixture was added DCE (3 mL) and NBS (4.01 mmol). The vial was sealed and the reaction mixture was heated at 80°C for 4.5 h. After cooling, the solvent was evaporated under vacuo. Flash chromatography on silica gel afforded the corresponding bromide (0.347 g, 87%).
8. Typical procedure for the one-pot halogenation reaction using microwave irradiation conditions: a mixture of alcohol **6** (1.12 mmol), DIC (1.14 mmol) and $Cu(OTf)_2$ (1–2 mol%) was stirred for 1 h at room temperature. To the mixture was added THF (2.5 mL) and NBS (2.22 mmol) and the reaction vial was sealed. After microwave irradiation at 150°C for 5 minutes, the mixture was subjected to work-up as described above, and the corresponding bromide (0.184 g, 83%) was obtained.