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A novel stereoselective one-pot conversion of alcohols into alkyl halides mediated by *N*,*N*′-diisopropylcarbodiimide

Stefano Crosignani, Brice Nadal†, Zhengning Li and Bruno Linclau*

Combinatorial Centre of Excellence, Chemistry Department, University of Southampton, Southampton SO17 1BJ, UK. E-mail: bruno.linclau@soton.ac.uk

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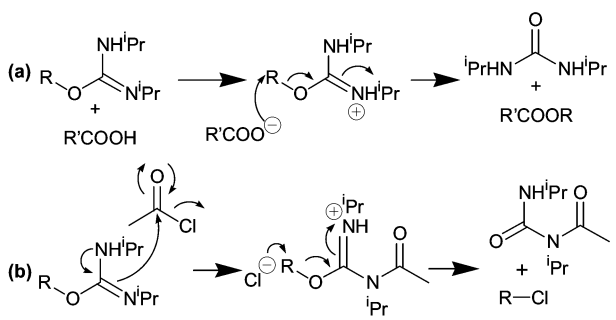
Alcohols can be converted in high yields to the corresponding alkyl halides in a one-pot procedure *via* the corresponding *O*-alkylisourea; very short reaction times are possible when microwave irradiation is used.

The reaction of alcohols with commercial carbodiimides to *N*,*N*′-diisopropyl (or dicyclohexyl)-*O*-alkylisoureas under copper (I) catalysis is well precedented.[1] *O*-Alkylisoureas are relatively stable compounds. Typical reactions using *O*-alkylisoureas require prior activation by acid–base reaction, which converts the isourea moiety to a leaving group. In a typical example (Scheme 1a), an isourea is protonated by a carboxylic acid, followed by nucleophilic substitution leading to an ester. Golding *et al.* described that when *O*-alkylisoureas are protonated by a very strong acid (CF_3SO_3H, equimolar) in the presence of excess tetrabutylammonium halide (Br, I), the corresponding alkyl halides are obtained.[2]

To the best of our knowledge, there is no precedent for the activation of isoureas other than through protonation. During our recent studies on the chemistry of solid-supported *O*-alkylisoureas,[3] we became interested in exploring new methods for the activation of *O*-alkylisoureas towards nucleophilic attack. With *O*-alkylisoureas being easily prepared from the corresponding alcohols,[1] the ultimate aim of the research was to investigate whether alternative activation methods would result in mild reaction conditions for the displacement of alcohols with nucleophiles under non-basic and extremely mild (CuCl or $Cu(OTf)_2$) acidic conditions.

In this communication, we wish to describe our results regarding activation of isoureas with acyl halides (Scheme 1b), which has led us to develop a practical, mild one-pot procedure for the conversion of alcohols to alkyl halides. The overwhelming majority of alcohol to alkyl halide transformations is currently achieved by phosphine based methods or *via* the corresponding sulfonates,[4] and halogenation *via* the corresponding isourea would provide the synthetic chemist an alternative at hand to carry out this transformation under non-basic, phosphine-free conditions whilst avoiding the use of strong acids such as in the Golding procedure.



Scheme 1 (a) The mechanism of acid-catalysed reactions of isoureas and (b) the proposed mechanism for the reaction of isoureas and acetyl chloride.‡

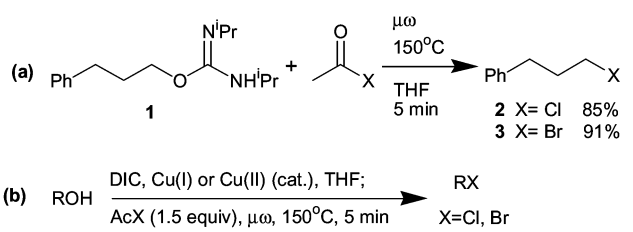
† ERASMUS exchange student, Université Paul Sabatier, Department de Chimie at Castres.

Preliminary experiments were conducted on purified isourea derivative **1** (Scheme 2a). Reaction of **1** with 1.5 equivalents of acetyl chloride (refluxing THF, 16 h) gave (3-chloropropyl)benzene in moderate yield (47%). As we recently described the beneficial effects of microwave irradiation for the reactions of isoureas with carboxylic acids,[3b] we decided to investigate if microwave irradiation could also improve the yields for this reaction. In effect, when **1** was treated with one equivalent of acetyl chloride at 150 °C for 5 min in a focused microwave oven, a yield of 78% was obtained, which could be raised to 85% using 1.5 equiv. of acetyl chloride. Similar results were obtained with acetyl bromide, giving (3-bromopropyl)benzene in 91% yield. Conversely, reaction of **1** with benzoyl fluoride did not lead to the corresponding fluoroalkane.

Having established the viability of the transformation, we next turned to develop a one-pot procedure from alcohols (Scheme 2b). To this end, the alcohol was first reacted with 1 equiv. of *N*,*N*′-diisopropylcarbodiimide (DIC) in the presence of CuCl (2 mol%). It is known[1] that this transformation requires several hours to complete but we found that a substantial reduction in reaction time could be achieved by microwave irradiation, with 5 min being an optimal reaction time at a temperature of 100 °C.§ After the isourea formation was complete, which was easily monitored by IR, acetyl chloride was added and the reaction mixture was subjected to identical conditions as in the preliminary experiment outlined in Scheme 2a. As can be seen in entries 1–5 (Table 1), very good isolated yields of the corresponding primary alkyl chlorides (after chromatography) were obtained. From the results, it is clear that the use of microwave irradiation in the first step gives a slightly better yield, although it is the vast reduction in reaction time that makes this method most appealing. Hence, we continued to use microwave irradiation for the first step when possible.

With propargylic alcohols, extensive decomposition was observed when the mixture was subjected to microwave irradiation. Nevertheless, the corresponding isourea could be quantitatively obtained by the conventional methods.[1] Subsequent treatment with acetyl chloride gave the propargylic chloride in good yield (entry 5). So far, we have not been able to achieve satisfactory results with allylic alcohols, but benzylic alcohols gave the corresponding chlorides in excellent yield (entry 4).

The mildness of the conditions ensures that acid-sensitive functionalities, such as acetals, are not touched (entry 5).



Scheme 2 (a) Reaction of *O*-alkylisourea with acetyl halides and (b) one-pot conversion of alcohols to haloalkanes.

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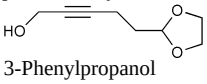
Table 1 One-pot conversion of alcohols into the corresponding halides (1 equiv. of DIC used in all cases)

Entry	Alcohol	Catalyst (mol%)	Activator	1 step	2 step	Yield
1	3-Phenylpropanol	CuCl (2%)	AcCl	RT, 16 h	150 °C, 5 min	93%
2	3-Phenylpropanol	CuCl (2%)	AcCl	100 °C, 5 min	150 °C, 5 min	100%
3	*N*-(3-Hydroxypropyl)phthalimide	CuCl (2%)	AcCl	100 °C, 5 min	150 °C, 5 min	92%
4	*p*-Nitrobenzyl alcohol	CuCl (2%)	AcCl	100 °C, 5 min	150 °C, 5 min	95%
5		CuCl (1%)	AcCl	RT, 16 h	150 °C, 5 min	82%
6	3-Phenylpropanol	$Cu(OTf)_2$ (2%)	AcBr	100 °C, 5 min	150 °C, 5 min	98%
7	6-Chlorohexan-1-ol	$Cu(OTf)_2$ (2%)	AcBr	100 °C, 5 min	150 °C, 5 min	96%
8	*N*-(3-Hydroxypropyl)phthalimide	$Cu(OTf)_2$ (2%)	AcBr	100 °C, 5 min	150 °C, 5 min	89%
9	*p*-Nitrobenzyl alcohol	$Cu(OTf)_2$ (2%)	AcBr	100 °C, 5 min	150 °C, 5 min	98%
10	4-Phenylbutan-2-ol	$Cu(OTf)_2$ (5%)	AcCl	100 °C, 5 min	140 °C, 5 min	80% (14%)[a]
11	4-Phenylbutan-2-ol	$Cu(OTf)_2$ (5%)	AcBr	100 °C, 5 min	120 °C, 5 min	95% (< 3%)[a]
12	Dihydrocholesterol	$Cu(OTf)_2$ (5%)	AcBr	RT, 16 h	150 °C, 5 min	80% (8%)[ab]
13	Dihydrocholesterol	CuCl (5%)	AcBr	RT, 16 h	150 °C, 5 min	Complex mixture
14	(*R*)-4-Phenylbutan-2-ol	$Cu(OTf)_2$ (5%)	AcBr	100 °C, 5 min	120 °C, 5 min	88% (< 3%)[ac]

[a] Elimination product (ratio determined by ^{1}H-NMR). [b] Only the 3-α isomer was observed. [c] $[\alpha]_D$ = +66.2° ($CHCl_3$, c = 0.85). A sample prepared using Ph_3P–CBr_4 had $[\alpha]_D$ = +64.7° ($CHCl_3$, c = 0.80).

Starting from a secondary alcohol (entry 10), the corresponding chloroalkane was found in good yield, however this was accompanied by some elimination product.

We reasoned that for bromination reactions the use of a different copper catalyst was advisable, as the chloride anion could cause a Finkelstein-type reaction with the alkyl bromide produced, which would result in product mixtures. It was found that copper (II) triflate was an excellent alternative. The use of this catalyst also gave an additional advantage in that it proved to be a better catalyst than CuCl: while the microwave-assisted isourea formation on secondary alcohols catalysed by CuCl requires long reaction times (20–30 minutes), $Cu(OTf)_2$ catalysed reactions are complete in 5 minutes. It was clear that the change in catalyst did not influence the second step in a negative way: high yields were obtained for primary alcohols (entries 6–9). Acetyl bromide proved to be superior to acetyl chloride when performing the reaction on secondary alcohols, giving lower levels of elimination (entries 11–12).

Kaulen has demonstrated that the acylation of secondary chiral *O*-alkylisoureas with carboxylic acids proceeds with inversion of configuration.[5] When the isourea of 3β-dihydrocholesterol¶ was reacted with acetyl bromide, only the 3α-bromo diastereoisomer was formed, which proves that an S_N2 inversion process is taking place (entry 12). When CuCl was used instead of $Cu(OTf)_2$ in conjunction with AcBr for the second step, a complex reaction mixture was obtained consisting of the desired 3α-bromo derivative, as well as the 3α-chloro, the 3β-bromo and the elimination products (entry 13). This clearly demonstrates that Finkelstein reaction does take place with chloride anions originating from the copper catalyst. Because of the presence of CuCl, there is more than 1 equiv. of halide ions present in the reaction mixture. As the chloride ions do react with the activated isourea, there are residual bromide ions which cause the formation of the 3-β-cholesterol derivative through Finkelstein reaction with the corresponding 3-α-bromo derivative. With $Cu(OTf)_2$ as catalyst instead of CuCl, no such epimerisation was observed.

Similar results were obtained for the bromination of enantiopure (*R*)-4-phenylbutan-2-ol (entry 14). No racemisation was observed, as evidenced by comparison of the optical rotation with a sample of (*S*)-4-phenyl-2-bromobutane, prepared from (*R*)-4-phenylbutan-2-ol using Ph_3P–CBr_4. This gives our method a clear advantage over the Golding method, where extensive racemisation was observed even after 30% conversion.

The observed inversion of configuration (entries 12, 14) is in accord with the proposed mechanism (Scheme 1b), which implies an S_N2 substitution in the second step. However so far the postulated *N*-acetylurea by-product has not been isolated. As no alkyl acetates have ever been detected, hydrolysis of the acetyl chloride to acetic acid and hydrochloric acid, with these acids as the actual reactants can be ruled out. This is further demonstrated by the fact that diisopropylurea, which would be the by-product of the reaction of hydrochloric or acetic acid with the isourea, is definitely not formed in any significant amount. Further work is under way in order to confirm the proposed mechanism.

In conclusion, we have demonstrated that non-protic activation of isoureas is possible, and has been used to develop a practical one-pot procedure for the conversion of alcohols into alkyl halides using readily available reagents. The reaction is stereoselective, suitable for primary (including propargylic and benzylic) and secondary alcohols, and acid sensitive groups survive. The use of microwave irradiation results in reaction times as short as 5 min per step. The mechanism of this novel isourea activation method is suggested, but not yet confirmed. Further work towards the confirmation of the mechanism and to widen the scope of the reaction is in progress.

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Notes and references

‡ Typical procedure: the substrate (2.0 mmol), *N*,*N*′-diisopropylcarbodiimide (2.0 mmol) and catalyst (0.1 mmol) are dissolved in anhydrous THF (2.0 mL) in a microwave vial. The vial is sealed and heated at 100 °C for 5 min under microwave irradiation. The acetyl halide is added (3.0 mmol) and the vial is heated at the appropriate temperature for 5 min under microwave irradiation. The resulting reaction mixture is directly purified by column chromatography.

§ Performing this step at higher temperatures led to incomplete reactions, suggesting that the copper catalyst decomposes under these conditions.

¶ Conversion of dihydrocholesterol under microwave irradiation did not proceed to completion, while performing this step at room temperature overnight afforded the desired isourea.

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