COMMUNICATION

Indium-mediated allylation reactions of α-chlorocarbonyl compounds and preparation of allylic epoxides

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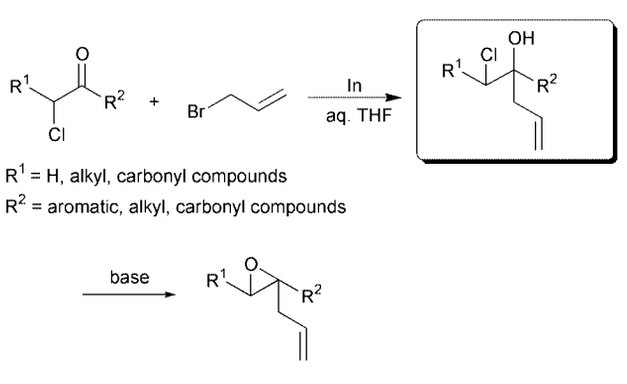
Indium-mediated allylation of α-chlorocarbonyl compounds with various allyl bromides in aqueous media gave the corresponding homoallylic chlorohydrins, which could be transformed into the corresponding epoxides in the presence of a base. These reactions were strongly dependent upon both the substituents at the carbon bearing chlorine and the allyl bromides used.

Introduction

Halohydrins constitute important intermediates in synthetic organic chemistry. They have usually been prepared by addition of hypohalous acids or hypohalites to alkenes or by opening epoxides by hydrohalic acids.[1] Recently, it has been reported that metal-mediated addition of haloallyl or halovinyl halides to ketones provided the corresponding halohydrin.[2] Reductive dehalogenation reactions of α-halocarbonyl compounds using metals in organic solvents have also been studied extensively.[3,4] To the best of our knowledge, however, metal-mediated allylation reactions of α-halocarbonyl compounds have never been reported presumably due to the competing dehalogenation reactions.

Herein, we wish to report the indium-mediated allylation of α-chlorocarbonyl compounds, which resulted in the corresponding homoallylic chlorohydrins, and synthesis of the corresponding epoxides from the thus prepared chlorohydrins (Scheme 1).



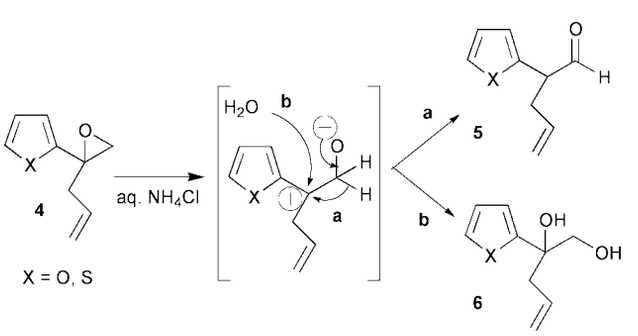
Scheme 1

Results and discussion

The results are summarized in Table 1. A general procedure for the allylation reaction is as follows: a mixture of an α-chlorocarbonyl compound (0.5 mmol), indium (0.6 mmol) and an allyl bromide (0.75 mmol) was stirred in 6 mL of aqueous THF (THF–H_2O = 1 : 3, v/v) at rt (or 50 °C). After stirring for the reaction times specified in Table 1, the mixture was extracted with ethyl acetate (10 mL × 2), dried and concentrated. Purification of the crude products by silica gel chromatography gave the desired products **1**. Since the dehalogenation occurred competitively, the allylation reactions were highly dependent upon the substrates. While the allylation reactions in entries 1, 3, and 5 proceeded at 50 °C to provide the homoallylic chlorohydrins **1** in modest to good yields with trace amounts of reduced products, those in entries 2 and 4 gave predominantly reduced products under the same reaction conditions. In the cases of entries 2 and 4, the desired allylated products were obtained in low yields at room temperature with the recovery of starting materials. Regarding allyl bromides, γ-substituted ones, *i.e.* crotyl bromide **C** and 4-bromo-2-methylbut-2-ene **D**, gave the corresponding products in relatively low yields. Transformation of chlorohydrins **1** to epoxides was achieved by using appropriate bases to give the corresponding epoxides (**2**) in good yields (Table 1).

As shown in Table 2, the allylation reactions of α-chlorocarbonyl compounds containing heterocycles and the conversion of the resulting chlorohydrins **3** to epoxides were examined under the same reaction conditions mentioned above. Allylation of chloroacetylthiophene (entry 1) and chloroacetylfuran (entry 2) proceeded similarly. The chlorohydrins **3** yielded the corresponding epoxide **4** by reacting with a base. In some cases, however, the first generated epoxide **4** was converted to the two compounds **5** and **6** after the epoxidation reaction was quenched with saturated NH_4Cl solution.

A plausible mechanism for the formation of **5** and **6** might involve two types of rearrangements after the cleavage of the C–O bond of the epoxides: path (a) hydride migration and path (b) addition of water molecule (Scheme 2).[5]



Scheme 2

In summary, we have accomplished the indium-mediated allylation of α-chlorocarbonyl compounds in aqueous media and the preparation of epoxides from the chlorohydrins obtained. Allylation of α-chlorocarbonyl compounds was

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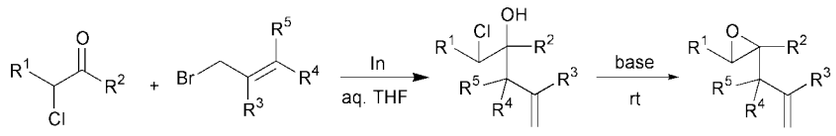
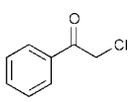
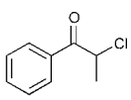
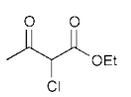
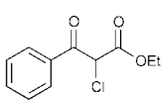
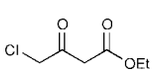
Table 1 Indium-mediated allylation reaction of α-chlorocarbonyl compounds and preparation of allylic epoxides



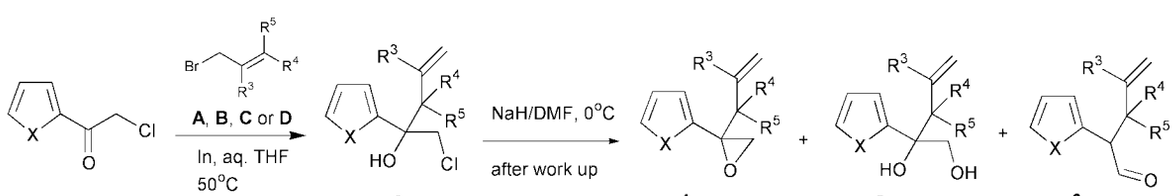
A $R^3 = R^4 = R^5 = H$
B $R^3 = CO_2CH_3$, $R^4 = R^5 = H$
C $R^3 = R^5 = H$, $R^4 = CH_3$
D $R^3 = H$, $R^4 = R^5 = CH_3$

1 **2**

Entry	Substrate	Bromide	Temp./°C	Time/h	Yield (**1**, %)[a]	Base/solvent	Time/h	Yield (**2**, %)[a]
1		**A**	50	4	88	DBU/THF	12	81
		B	50	1	85	DBU/THF	4	78
		C	50	5	55	DBU/THF	4	89
		D	50	3	38	DBU/THF	6	99
2		**A**	rt	5	27(39)[b] (48/52)[e]	NaH/DMF	4	79
		B	rt	3	31(35)[b] (45/55)[e]	NaH/DMF	4	nr[c]
		C	rt	5	34(39)[b] (48/52)[e]	NaH/DMF	4	nr[c]
		D	rt	5	nr	—	—	nr[c]
3		**A**	50	4	71(48/52)[e]	DBU/THF	12	93
		B	50	2	71(31/69)[e]	DBU/THF	12	67
		C	50	4	58(48/52)[e]	DBU/THF	8	98
		D	50	4	52(50/50)[e]	DBU/THF	8	nr[c]
4		**A**	rt	7	78(50/50)[e]	K_2CO_3/acetone	2.5	87
		B	rt	5	71(50/50)[e]	K_2CO_3/acetone	2.5	nr[c]
		C	rt	4	53(50/50)[e]	K_2CO_3/acetone	12	71
		D	rt	5	nr	—	—	—
5		**A**	50	2	97	NaH/DMF	1.5[d]	76
		B	50	2	93	NaH/DMF	—	nr[c]
		C	50	4	65	NaH/DMF	2[d]	90
		D	50	4	50	NaH/DMF	1[d]	71

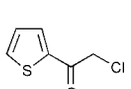
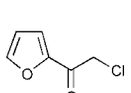
[a] Isolated yield. [b] Starting material recovered. [c] No reaction. [d] At 0 °C. [e] Diastereoisomers(%).

Table 2 Indium-mediated allylation reaction of α-chlorocarbonyl heterocycles and preparation of allylic epoxides



X = O, S

3 **4** **5** **6**

Entry	Substrate	Bromide	Time/h	Yield (**3**, %)[a]	Time/h	Yield (**4**, %)[a]	Yield (**5**, %)[a]	Yield (**6**, %)[a]
1		**A**	2.5	65	1.0	—	30	22
		B	1.5	99	2.0	97	—	—
		C	4.0	67	2.5	—	79	16
		D	3.5[b]	59	2.0	99	—	—
2		**A**	5.0	64	1.5	—	24	40
		B	4.0	73	0.5	—	21	61
		C	3.0	62	2.5	—	23	28
		D	5.0	53	7.0	66	—	—

[a] Isolated yield. [b] At rt.

strongly dependent upon both the substrates and the allyl bromides used. With respect to the epoxide formation, heterocyclic α-chlorocarbonyl compounds provided various products *via* rearrangements after the formation of epoxides.

Experimental

All starting materials were obtained commercially from Aldrich or prepared by the known methods. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian Gemini 300 NMR spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on either a VG70-VSEQ (VG ANALYTICAL, UK) or a Hewlett Packard MSD 5972 series spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Identification of the products was made on the basis of IR, ^{1}H NMR and mass evidence in comparison with authentic samples.

Allylation reactions of α-chlorocarbonyl compounds. General procedure

Method A. To a solution of 2-chloroacetophenone (309 mg, 2.0 mmol) in 25% aq. THF (5 mL) were added allyl bromide (260 μL, 3.0 mmol) and indium powder (276 mg, 2.4 mmol). The solution was stirred at 40–50 °C for 4 h. The reaction mixture was cooled at room temperature and quenched with 6 M

HCl. It was extracted with CH_2Cl_2, the organic layer was dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography of the residue (benzene–ethyl ether–hexane 2 : 1 : 6) gave the chlorohydrin (347 mg, 88%) and acetophenone (9.5 mg, 4%). δ_H(300 MHz; $CDCl_3$) 7.37 (m, 5H, Ar*H*), 5.61 (m, 1H, CH_2=C*H*CH_2-), 5.15 (t, 2H, C*H*$_2$=CHCH_2-), 3.85 (dd, J = 3.9, 9.1 Hz, 2H, -C*H*$_2$Cl), 2.71 (d, J = 7.5 Hz, 2H, CH_2=CHC*H*$_2$-), 2.45 (s, 1H, -O*H*).

Method B. To a solution of ethyl 2-chloro-3-oxo-3-phenylpropanoate (340 mg, 1.5 mmol) in 25% aq. THF (5 mL) were added allyl bromide (195 μL, 2.3 mmol) and indium powder (207 mg, 1.8 mmol). The solution was stirred at room temperature for 7 h. The reaction mixture was quenched with 6 M HCl, then was extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane–ethyl acetate 20 : 1) gave the chlorohydrin (313 mg, 78%). δ_H(300 MHz; $CDCl_3$) 7.42–7.27 (m, 5H, Ar*H*), 5.5 (m, 1H, CH_2=C*H*CH_2-), 5.05 (t, 2H, C*H*$_2$=CHCH_2-), 4.66 (s, 1H, CC*H*Cl), 3.97 (m, 3H, -OC*H*$_2$CH$_3$ and -O*H*), 2.85 (dd, J = 6.9, 13.9 Hz, 1H, C*H*$_2$=CHC*H*$_2$-), 2.7 (dd, J = 7.4, 13.9 Hz, 1H, CH_2=CHC*H*$_2$-), 0.95 (t, J = 7.14, 3H, -OCH$_2$C*H*$_3$).

Preparation of allylic epoxides. General procedure

Method A. The chlorohydrin (from bromide **A** and entry 1 in Table 1, 100 mg, 0.5 mmol), DBU (224 μL, 1.5 mmol) in THF were stirred at room temperature for 14 h. The reaction mixture was extracted with CH_2Cl_2 and washed 1 M HCl. The organic layer was dried and concentrated to give the epoxide (66 mg, 81%). δ_H(300 MHz; $CDCl_3$) 7.35 (m, 5H, Ar*H*), 5.8 (m, 1H, CH_2=C*H*CH_2-), 3.01 (d, J = 5.1 Hz, 1H, -C*H*$_2$OC), 2.9 (dd, J = 7.1, 15.0 Hz, 1H, CH_2=CHC*H*$_2$-), 2.78 (d, J = 5.3 Hz, 1H, -C*H*$_2$OC), 2.65 (dd, J = 7.6, 14.9 Hz, 1H, CH_2=CHC*H*$_2$-).

Method B. The chlorohydrin (from bromide **A** and entry 2 in Table 1, 93 mg, 0.44 mmol) was dissolved in DMF and NaH (80% dispersion in mineral oil, 40 mg, 1.32 mmol) was added. The resulting solution was stirred at room temperature for 4 h, then it was quenched with sat. NH_4Cl. Ethyl acetate was added to the reaction mixture and it was washed with H_2O. The organic layer was dried and concentrated to give the epoxide (60 mg, 79%). δ_H(300 MHz; $CDCl_3$) 7.3 (m, 5H, Ar*H*), 5.75 (m, 1H, CH_2=C*H*-), 5.16 (t, 2H, C*H*$_2$=CH-), 3.11 (q, 1H, C*H*$_2$OC), 2.84 (q, 1H, CH_2=CHC*H*$_2$-), 2.51 (q, 1H, CH_2=CHC*H*$_2$-), 0.99 (d, 3H, C*H*$_3$CHCl).

Method C. The chlorohydrin (from bromide **A** and entry 4 in Table 1, 142 mg, 0.5 mmol) was dissolved in acetone and K_2CO_3 (110 mg, 0.8 mmol) was added. The resulting solution was at room temperature for 2.5 h. The reaction mixture was extracted with CH_2Cl_2. The organic layer was dried and concentrated to give the epoxide (107 mg, 87%). δ_H(300 MHz; $CDCl_3$) 7.35 (m, 5H, Ar*H*), 5.73 (m, 1H, CH_2=C*H*CH_2-), 5.09 (t, 2H, C*H*$_2$=CHCH_2-), 4.3 (m, 2H, -OC*H*$_2$CH$_3$), 3.5 (s, 1H, COC*H*), 2.92 (dd, J = 7.1, 15.1 Hz, 1H, CH_2=CHC*H*$_2$-), 2.78 (dd, J = 7.1, 15.1 Hz, 1H, CH_2=CHC*H*$_2$-), 1.32 (t, 3H, -OCH$_2$C*H*$_3$).

Acknowledgement

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