## Communications to the Editor

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# A NOVEL ONE STEP CONVERSION OF ALCOHOLS INTO ALKYL BROMIDES OR IODIDES

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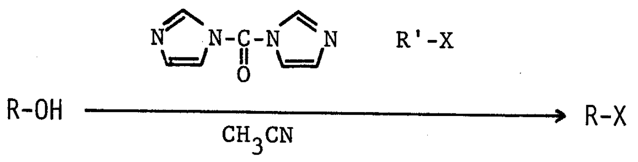
Alcohols are converted in high yields into alkyl bromides or iodides by a one step reaction with N,N'-carbonyldiimidazole and an excess of reactive halides such as allyl bromide or methyl iodide.

KEYWORDS——— alcohol; N,N'-carbonyldiimidazole; bromination; iodination; 1-alkoxycarbonylimidazole; 1-alkoxycarbonyl-3-substituted imidazolium salt; allyl bromide; methyl iodide

The conversion of alcohols into alkyl bromides or iodides[1-8] is frequently used in organic synthesis. Recently, Hanessian et al. reported the conversion of alcohols into alkyl iodides or chlorides using imidazolylsulfonate as an efficient leaving group.[9]

Previously we reported that 1-ethoxycarbonyl-3-substituted imidazolium salts formed in the reaction of 1-ethoxycarbonylimidazole with halides were unstable under heating, and the ethoxycarbonyl group of the salts were easily cleaved to give 1,3-disubstituted imidazolium compounds.[10] Furthermore, we examined the reaction of some 1-alkoxycarbonylimidazoles with an excess of halides with heating and found that it gave the corresponding alkyl bromides or iodides.

We report here a novel one step conversion of alcohols into alkyl bromides or iodides using oxycarbonylimidazolium moieties activated by quaternization of the nitrogen atom in the imidazole ring as efficient leaving groups.



R : primary or secondary alkyl
R'-X : allyl bromide, methyl iodide, etc.

A typical procedure is as follows (3-phenylpropyl bromide): To a solution of 3-phenylpropanol (1.36 g, 10 mmol) and N,N'-carbonyldiimidazole (CDI)[11] (1.62 g, 10 mmol) in dry acetonitrile (10 ml) was added allyl bromide (6.0 g, 50 mmol). The mixture was stirred for 30 min at room temperature and then refluxed for 1.5 h. After cooling, ether (70 ml) and water (30 ml) was added to the solution. The organic layer was washed with dil. HCl, aq. $NaHCO_3$, aq. $Na_2S_2O_3$ (in the case of iodides), and water, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give 1.96 g of oil. A solution of the oil in hexane (50 ml) was treated with $SiO_2$ (1 g), and evaporated under reduced pressure to give 1.92 g (97%) of 3-phenylpropyl bromide as a colorless oil. The results are summarized in the Table.

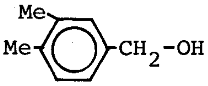
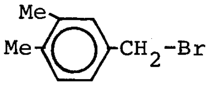
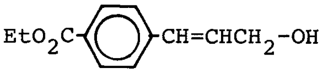
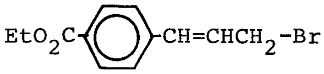
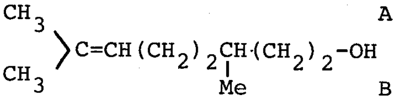
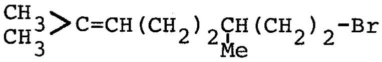
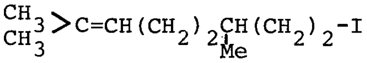
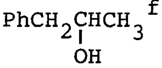
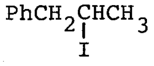
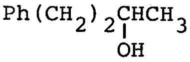
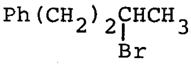
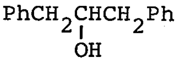
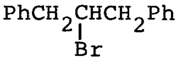
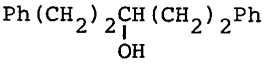
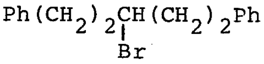
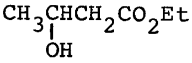
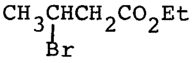
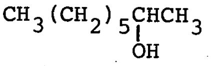
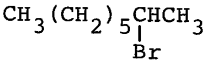
In this reaction any halide (R'-X) more reactive than the resultant halides (R-X) can be used as a reagent. In general halides such as allyl bromide or methyl iodide are preferable, because they are reactive and can be easily removed (low boiling points) after reaction. The amount of halides (R'-X) required is more than 3 eq of the alcohols. Acetonitrile is preferable as a solvent.

The merits of this reaction are (a) alkyl bromides or iodides can be obtained directly from alcohols using commercially available reagents (CDI and R'-X), (b) the resultant halides are easily isolated and purified by the simple operation, (c) the end of the reaction can be monitored by stopping the generation of carbon dioxide gas, and (d) the reaction conditions are mild and the reaction proceeds in neutral medium. This reaction is especially useful in bromination, and it is also useful in obtaining unstable bromides such as benzyl bromides or cinnamyl bromides.

The limitation of this reaction are (a) when the resultant halides (R-X) are more reactive than the added halides (R'-X), the yields are decreased because the resultant halides react with the imidazole compounds, but the addition of large excess of halides (R'-X) prevents this side reaction to some extent, (b) racemization occurres in the optically active alcohols, and (c) chlorination proceeds in low yields probably because of the low reactivities of the chlorides.

Although the detailed mechanism of the reaction is yet to be clarified, it seems likely that the halogenation proceeds through an initial formation of 1-alkoxycarbonylimidazoles (I) from alcohols and CDI, followed by the quaternization with halides (R'-X) to give 1-alkoxycarbonyl-3-substituted imidazolium salts (II), the oxycarbonylimidazolium moieties of which are efficient leaving groups. Subsequent cleavage of the compounds (II) with heating forms the carbenium ions ($R^+$) with decarboxylation, and they combine with halide ions ($X^-$) to give the alkyl halides (R-X).

Table. Conversion of Alcohols into Alkyl Bromides or Iodides

| Alcohol | R'-X[a]<br>(eq) | Condition[b]<br>(h) | Product | Yield[c]<br>(%) |
|---|---|---|---|---|
| $Ph-(CH_2)_3-OH$ | A (5) | 1.5 | $Ph-(CH_2)_3-Br$ | 97[d] |
| | B (5) | 2 | $Ph-(CH_2)_3-I$ | 96 |
| $Ph-(CH_2)_4-OH$ | A (5) | 1 | $Ph-(CH_2)_4-Br$ | 98 |
| $Ph-(CH_2)_5-OH$ | A (5) | 1 | $Ph-(CH_2)_5-Br$ | 98 |
|  | A (10) | 1 |  | 65[e] |
|  | A (10) | 1.25 |  | 60 |
| $CH_3-(CH_2)_{11}-OH$ | A (10) | 2 | $CH_3-(CH_2)_{11}-Br$ | 97 |
|  $(CH_3)_2C{=}CH(CH_2)_2CH(Me)(CH_2)_2-OH$ | A (5) | 2 |  $(CH_3)_2C{=}CH(CH_2)_2CH(Me)(CH_2)_2-Br$ | 83 |
| | B (5) | 2 |  $(CH_3)_2C{=}CH(CH_2)_2CH(Me)(CH_2)_2-I$ | 84 |
|  $PhCH_2CH(OH)CH_3$[f] | B (3) | 3 |  $PhCH_2CH(I)CH_3$ | 80 |
|  $Ph(CH_2)_2CH(OH)CH_3$ | A (5) | 3 |  $Ph(CH_2)_2CH(Br)CH_3$ | 94 |
|  $PhCH_2CH(OH)CH_2Ph$[f] | C (2) | 3 |  $PhCH_2CH(Br)CH_2Ph$ | 95 |
|  $Ph(CH_2)_2CH(OH)(CH_2)_2Ph$ | A (5) | 3 |  $Ph(CH_2)_2CH(Br)(CH_2)_2Ph$ | 87 |
|  $CH_3CH(OH)CH_2CO_2Et$ | A (5) | 3 |  $CH_3CH(Br)CH_2CO_2Et$ | 78 |
|  $CH_3(CH_2)_5CH(OH)CH_3$ [g] | A (5) | 3 |  $CH_3(CH_2)_5CH(Br)CH_3$[i] | 88 |
| [h] | A (5) | 3 | | 87 |

[a] A : $CH_2{=}CHCH_2Br$, B : $CH_3I$, C : $PhCH_2Br$.

[b] Refluxing time, after stirring for 0.5 h at r.t.

[c] Isolated yield.

[d] 3 eq halide gives 81% product.

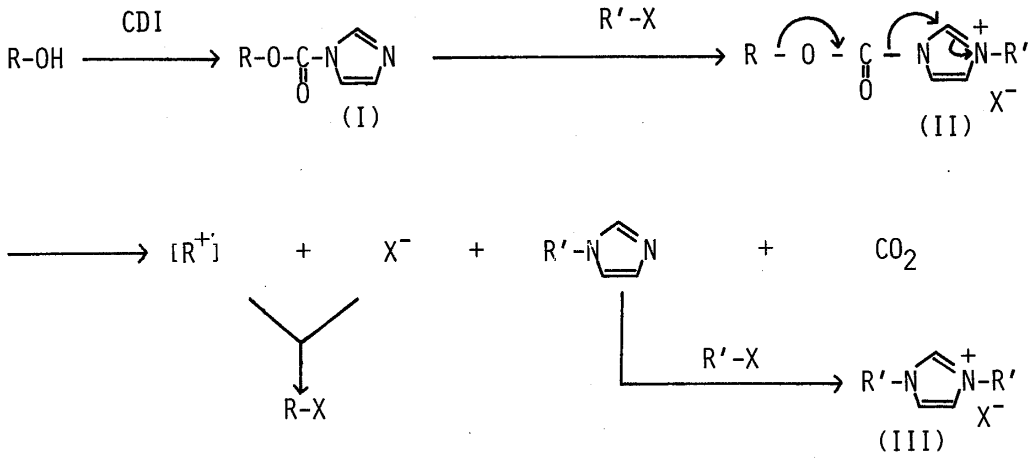
[e] 5 eq halide gives 38% product.

[f] Isolated alkoxycarbonylimidazoles were treated with halide.

[g] $[\alpha]_D^{22}$ $-10.7°$ ($c$ 1.0, EtOH).

[h] $[\alpha]_D^{22}$ $+10.2°$ ($c$ 0.99, EtOH).

[i] Racemate.



This mechanism is also suggested by the results that (a) 1-alkoxycarbonyl-3-substituted imidazolium salts (II) are obtained by the reaction of 1-alkoxycarbonylimidazoles (I) with halides (R'-X), (b) the reaction of the isolated compounds (II) with halides with heating gives the corresponding bromides or iodides (R-X), and (c) optically active alcohols give the racemate in this reaction.

## REFERENCES AND NOTES

1) G.A. Olah, B. G. B. Gupta, R. Malhotra, and S. C. Narang, J. Org. Chem., 45, 1638 (1980), and references therein.
2) R. O. Hutchins, D. Masilamani and C. A. Maryanoff, J. Org. Chem., 41, 1071 (1976).
3) A. K. Bose, and B. Lal, Tetrahedron Letters, 1973, 3937.
4) N. Furukawa, T. Inoue, T. Aida, and S. Oae, J. Chem. Soc., Chem. Commun., 1973, 212.
5) S. Kobayashi, M. Tsutsui, and T. Mukaiyama, Chem. Lett., 1976, 373, and references therein.
6) G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, J. Org. Chem., 44, 1247 (1979).
7) M. E. Jung, and P. L. Ornstein, Tetrahedron Letters, 1977, 2659.
8) S. Hanessian, Y. Leblanc, and P. Lavallée, Tetrahedron Letters, 23, 4411 (1982).
9) S. Hanessian and J. M. Vatèle, Tetrahedron Letters, 22, 3579 (1981).
10) T. Kamijo, R. Yamamoto, H. Harada, and K. Iizuka, Chem. Pharm. Bull., 31, 1213 (1983).
11) H. A. Staab, Angew. Chem. Int. Ed. Engl., 1, 351 (1962).

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