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# REACTIONS OF THE 2-ALKOXY-N-METHYLBENZOTHIAZOLIUM ION AND ITS SYNTHETIC UTILITY

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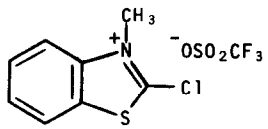
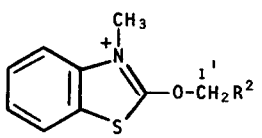
In a recent note[1] we described the use of 2-chloro-N-methylbenzothiazolium trifluoromethanesulfonate (I) for the preparation of compounds of the type $RCOXR^1$ (X = S, NH, and O).[2] The general procedure specified that $R^1XH$ be added to a mixture of $RCO_2H$, triethylamine, and I.[3] It was noted that I reacted non-selectively with both $RCO_2H$ and $R^1XH$, and addition of I to a mixture of the two substrates and triethylamine resulted in a substantial decrease in the yield of $RCOXR^1$. For instance, the reaction of I with a mixture of cyclohexanecarboxylic acid and a primary alcohol (X = O in $R^1XH$) provided a significant amount of the corresponding chloride ($R^1Cl$) at the expense of the ester. This observation immediately suggested the involvement of the 2-alkoxybenzothiazolium ion II and subsequent attack of the chloride ion on C(1') of II. In view of renewed interest[2] in this type of reaction intermediate, we have now prepared the previously uncharacterized species II and have investigated its reactions with various nucleophiles, $R^3YH$. This note delineates the criteria which $R^3YH$ normally meets when the formation of $R^2CH_2$-Y-$R^3$ proceeds in excellent yield.




I




II

$R^2$ = $CH_3CH_2$ or $C_6H_5CH_2CH_2$

Treatment of 2-chlorobenzothiazole with sodium n-propylate or 3-phenylpropylate,[4] followed by methylation of the resulting 2-alkoxybenzothiazole with methyl trifluoromethanesulfonate yielded II which is reasonably stable at room temperature with the usual precautions. To a 0.1M dichloromethane solution of II was added a 1:1 mixture of $R^3YH$ and base (0.1M in the same solvent) at room temperature. After several hours stirring, the product was processed in the usual manner. The isolated yield of $R^2CH_2$-Y-$R^3$ for each nucleophile is tabulated below. Triethylamine, which was simply used as an acid-scavenger in the previous work,[1] reacts with II to afford the corresponding quaternary ammonium salt and 3-N-methylbenzothiazolidone. Triphenylphosphine behaves in a similar manner. Alkanethiols such as n-butanethiol immediately form

Tables. Reactions of II with various nucleophiles.

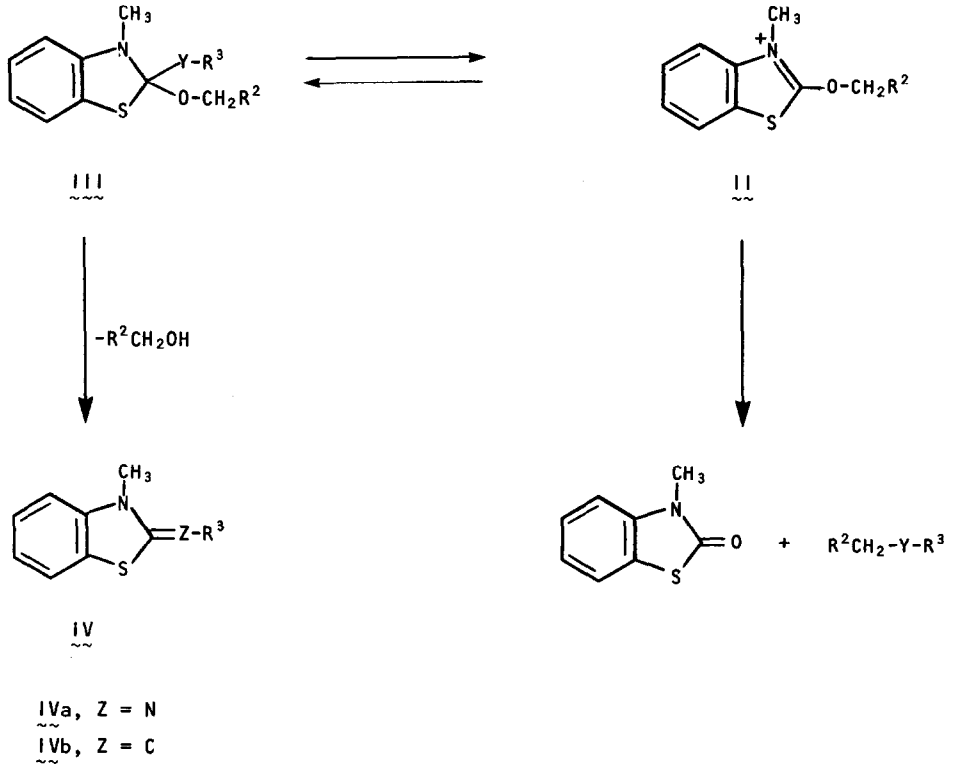
| $R^3YH$ and base / $R^2CH_2$ | $(C_2H_5)_3N$ | $(C_6H_5)_3P$ | $C_6H_5SH$ / $(C_2H_5)_3N$ | $C_4H_9SH$ | $C_6H_5CH_2NH_2$ / $(C_2H_5)_3N$ | $CH_3CO_2H$ / $(C_2H_5)_3N$ | $CF_3CO_2H$ / $(C_2H_5)_3N$ |
|---|---|---|---|---|---|---|---|
| $CH_3CH_2$ | 100% | 90 | 88[a] | -- | 0[c] | -- | -- |
| reaction time (hr) | (3) | (24) | (1) | | (1) | | |
| $C_6H_5CH_2CH_2$ | 100% | 85 | 100[a] | 0[b] | 0[c] | 95 | 80 |
| reaction time (hr) | (3) | (18) | (2) | (18) | (1) | (3) | (4) |

| $R^3YH$ and base / $R^2CH_2$ | $Cl^-$ / $(C_2H_5)_3\overset{+}{N}H$ | KCN / 18-crown-6 | $NaCH(CO_2C_2H_5)_2$ | $C_6H_5OH$ / $(C_2H_5)_3N$ | $p\text{-}NO_2C_6H_4OH$ / $(C_2H_5)_3N$ |
|---|---|---|---|---|---|
| $CH_3CH_2$ | -- | -- | 0[c] | 40 | 95 |
| reaction time (hr) | | | (1) | (5) | (2) |
| $C_6H_5CH_2CH_2$ | 80%[d] | 82[e] | 0[c] | 35 | 100 |
| reaction time (hr) | (2) | (6) | (1) | (5) | (2) |

[a] See reference 5.
[b] No observable mixed sulfide was generated with the triethylammonium, sodium, or thallium(I) salt of n-butanethiol.
[c] See text.
[d] Reagent I was reacted with a 1:1 mixture of the alcohol and triethylamine in acetonitrile.
[e] Refluxing acetonitrile.

intermediates of type III which are stable under the reaction conditions used but decompose rapidly during the work-up. Compound II and a primary amine apparently form intermediate III (Y = NH, for instance $R^3 = C_6H_5CH_2$), which (because of the proton attached to the nitrogen atom) undergoes elimination of $R^2CH_2OH$ to afford the final product IVa (Z = N) in 80-85% yield. Similarly, sodium malonate [Y = CH, $R^3 = (CO_2C_2H_5)_2$] gave IVb (Z = C) in 88% yield. Characteristic of the reactions of II with most of the remaining nucleophiles listed in the Table is the rapid disappearance of II (which indicates the likely formation of III), and the comparatively slow reaction to give $R^2CH_2\text{-}Y\text{-}R^3$ in excellent yield. These observations together with the results mentioned above lead to the following interpretation for the overall outcome of the $R^2CH_2\text{-}Y\text{-}R^3$ formation: (1) addition of $R^3YH$ (or $R^3Y^-$) to II is reversible, and (2) nucleophilic $S_N2$ type displacement at C(1') of II by $R^3YH$ (or $R^3Y^-$) proceeds faster than that by triethylamine. To effectively realize the above reversibility, $R^3Y^-$ must be a reasonably good leaving group and Y should not include a proton attached to carbon or to a heteroatom (eg., malonate and primary amines). The nucleophilic

attack of triethylamine can be suppressed by conversion into its conjugate acid [see equation (1)]. The high acidity of $R^3YH$ of course effects this conversion and at the same time $R^3Y^-$, usually a better nucleophile than $R^3YH$, becomes the species reacting at C(1') of II. Benzenethiol, carboxylic acids, $CN^-$, and $Cl^-$ all satisfy these conditions and yields of $R^2CH_2$-Y-$R^3$ are excellent. Phenols include a borderline case and present a good illustration of the reaction. Reaction of II with p-nitrophenol (pKa = 7.15) provides a quantitative yield of the corresponding ether, whereas that with phenol (pKa = 9.89) proceeds rather unsatisfactorily. Thus, the high nucleophilicity and good leaving propensity of $R^3Y^-$, and the high acidity (say pKa less than 8) of $R^3YH$ are required for the satisfactory synthesis of $R^2CH_2$-Y-$R^3$.




IVa, Z = N
IVb, Z = C

$$R^3YH + (C_2H_5)_3N \rightleftharpoons R^3Y^- + (C_2H_5)_3\overset{+}{N}\text{-}H \qquad (1)$$

Reactions of the benzothiazolium salt II or a 2-alkoxypyridinium salt[2] (and those involving these salts as intermediates) appear to follow the above reaction patterns which constitute the basis of their use for a variety of purposes, and serve as a guide for further modification of I and II.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. F.A. Souto-Bachiller, G.S. Bates, and S. Masamune, Chem. Commun., 719 (1976).

2. (a) The use of 2-halopyridinium salts to effect similar reactions has recently been reviewed. T. Mukaiyama, Angew. Chem. Int. Edit. Engl., 15, 94 (1976).

   (b) 2-Chloro- and 2-fluorobenzothiazolium tetrafluoroborates can also be utilized for the preparation of O-esters. T. Mukaiyama and K. Hojo, Chem. Lett., 267 (1976).

   (c) There are several other reagents similar to that discussed in this note. For example, N,N-dimethylformamidium chloride [$(CH_3)_2N^+=C(H)Cl\ Cl^-$] reacts with alcohols to give alkoxyimmonium salts [$(CH_3)_2N^+=C(H)OR\ Cl^-$] which upon thermolysis (ca. 100°) provide the corresponding alkyl chlorides. H. Eilingsfeld, M. Seefelder, and H. Weidinger, Ber., 96, 2671 (1963); R. Rätz and O.J. Sweeting, J. Org. Chem., 30, 438 (1965). For earlier examples of the utilization of the above reagent, see M. Zaoral and Z. Arnold, Tetrahedron Lett., No. 14, 9 (1960); K. Morita, S. Noguchi, and M. Nishikawa, Chem. and Pharm. Bull., 7, 896 (1959); Z. Arnold, Coll. Czech. Chem. Commun., 26, 1723 (1961).

   (d) 2-Alkoxypyridium salts which are apparently formed in situ from 2-fluoropyridium tosylate and alcohols react with sodium iodide to afford the corresponding alkyl iodides. S. Kobayashi, M. Tsutsui, and T. Mukaiyama, Chem. Lett., 373 (1976). For the use of 2-fluoro-3-ethylbenzothiazolium tetrafluoroborate instead of the above pyridium salt for the same operation, see K. Hojo and T. Mukaiyama, ibid., 619 (1976).

   (e) 2-Alkoxybenzothiazolium salts (generated in situ) can be used to effect inversion of configuration of hydroxy groups. T. Mukaiyama and K. Hojo, ibid., 893 (1976).

3. $RCO_2H$ is transformed mainly into RCOCl before the addition of $R^1XH$. See reference 1.

4. H. Gilman K.E. Lentz, and J.A. Beel, J. Am. Chem. Soc., 74, 1081 (1952).

5. For the analogous preparation of 2-pyridyl sulfides from alcohols by means of a 2-fluoropyridinium salt, see T. Mukaiyama et al., Chem. Lett., 1159 (1975).