Pergamon

Tetrahedron Letters, Vol. 35, No. 32, pp. 5887-5888, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01163-X

Copper-Assisted Substitution Reaction for Phenylthio Group of a 4-Phenylthioazetidinone Derivative

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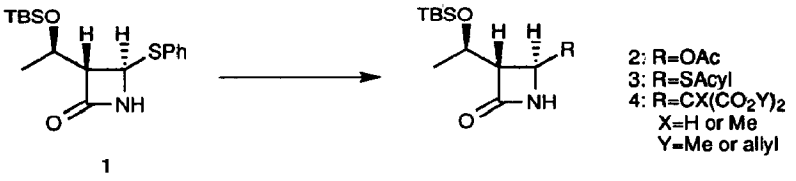
Abstract: The phenylthio group of 4-phenylthioazetidinone (**1**) was readily substituted with copper(I) salts of carboxylates, thiocarboxylates, and copper(I) enolates of malonates and β-ketoesters to give synthetic intermediates (**3** and **4**) for penem and carbapenem antibiotics.

3-(1-*t*-Butyldimethylsilyloxyethyl)-4-phenylthioazetidin-2-one (**1**)[1,2] which is now commercially produced from (*R*)-butane-1,3-diol in 6 steps[3] has been used as a synthetic intermediate for the synthesis of penem and carbapenem antibiotics. However, due to its poor ability as a leaving group, the phenylthio group must be converted to a more reactive phenylsulfinyl, phenylsulfonyl, or acetoxy group for substitution reactions with thiocarboxylates or enolates. Thus, the phenylsulfonyl group could be replaced by thiocarboxylates to give intermediates for penem synthesis (**3**),[4,5] while the phenylsulfinyl group was transformed to an intermediate for carbapenem synthesis.[6] We reported a facile conversion of phenylthioazetidinone (**1**) to acetoxyazetidinone (**2**) with copper(II) acetate in refluxing acetic acid.[3]

Here, we wish to report a versatile method for conversion of **1** to **2** as well as intermediates (**3** and **4**) for synthesis of penems and carbapenems using a copper(I) reagent under a mild condition.

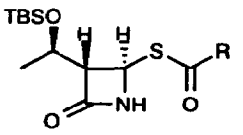


1

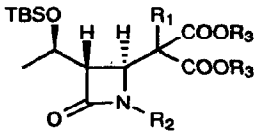
Copper(I) acetate was prepared from an equivalent amount of cuprous bromide-dimethylsulfide complex (CuBr-DMS) and sodium acetate in tetrahydrofuran (r.t., 15min) by copper-sodium metal exchange. This reagent facilitated the conversion of **1** to **2** in a high yield under a milder condition (r.t., 1.5hr) than copper(II) acetate (100°C, 45min), suggesting that copper(I) acetate formed *in situ* is more reactive to the phenythio group than copper(II) acetate. Since the copper ion has high affinity for a sulfur atom, the exchange of the metal ions between sodium thiocarboxylates and CuBr-DMS also led to generation of copper(I) thiocarboxylates.

1 was thus reacted (r.t., 1hr) with copper(I) thioacetate prepared from sodium thioacetate and CuBr-DMS (r.t., 15min) in tetrahydrofuran to afford acetylthioazetidinone (**5**) in 70% yield. Other thiocarboxylates such as thiobenzoate and thio-2-tetrahydrofuranoate[4] also readily reacted with **1** by the same procedure to provide corresponding thioesters (**6** and **7**) in similar yields. These results indicate that the copper atom of copper(I) thiocarboxylates has higher affinity for the sulfur atom of the phenylthio group than that of thiocarboxylates and thus accelerates the elimination of the phenylthio group. The copper(II) thiocarboxylates were also effective in this substitution reaction (r.t., 1hr) in tetrahydrofuran to give thioesters (**5-7**) although preparation of the thiocarboxylates from cupric oxide and thiocarboxylic acids in a 1:2 mole ratio required a high temperature

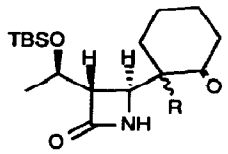
(reflux in tetrahydrofuran for 1hr). Hence, acylthioazetidinones (3), intermediates for penems, could be derived directly from the phenylthioazetidinone by use of copper(I) or (II) thiocarboxylates.



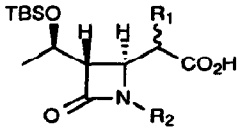
5: R=Me
6: R=Ph
7: R=2-Thf



8: R_1=R_2=H, R_3=Me
9: R_1=Me, R_2=H, R_3=allyl
10: R_1=F, R_2=H, R_3=Me
14: R_1=Me,R_2=CH_2CO_2PNB, R_3=allyl



11: R=CO_2allyl
13: R=H



12: R_1=Me, R_2=H
15: R_1=Me, R_2=CH_2CO_2PNB
PNB: *p*-nitrobenzyl

Unlike acetoxyazetidinone (2), phenylthioazetidinone (1) did not react with sodium dimethyl malonate at all due to the low reactivity of the phenythio group. However, the copper enolate of the malonate, generated by metal exchange with CuBr-DMS (1eq) at 0°C (15min) readily reacted with the phenylthioazetidinone in tetrahydrofuran (0°C, 15min). Thus, the copper ion facilitated the substitution giving azetidinone (**8**) in 74% yield. The same reaction with the copper(I) enolates of diallyl methylmalonate and dimethyl fluoromalonate at 25° (15min) afforded the corresponding azetidinones (**9** and **10**) in 82% and 92% yield, respectively. **1** also reacted with the copper enolate of 2-(allyloxycarbonyl)cyclohexanone in the same procedure (r.t., 15min) to give a diastereomeric mixture (1:1) of ketoester (**11**) in 88% yield. The intermediates (**4**) for the synthesis of carbapenem antibiotics were thus obtained from **1** by use of the copper-assisted reaction. Allyl esters (**9** and **11**) were converted to the α-epimer-rich compounds (3:1 for **12** and 2.5:1 for **13**) by deallylation[7] and decarboxylation in 80% yield while β-epimer-rich compound **15** (α:β=1:1.7) was obtained from N-alkylated diester (**14**).[8]

We demonstrated that the phenylthio group at C-4 of azetidinone (**1**) is readily substituted by copper salts of carboxylates, thiocarboxylates, and copper enolates of malonates and β-ketoesters under mild conditions. Thereby, readily available phenylthioazetidinone (**1**)[3] can serve as a common intermediate for the synthesis of penem and carbapenem antibiotics.

References and Notes

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8 The N-alkylated derivative of **11** was also converted to the β-epimer-rich compound(α:β=1:1.3). A similar result has been described for decarboxylation of N-TBS and N-Bn derivatives in a recent patent. Miura, T.; Murayama, T.; Yoshida, A. Japan Patent Appl. 5-155850, June 22, 1993.

(*Received in Japan* 23 *April* 1994; *accepted* 6 *June* 1994)