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# Zinc Halides-Mediated Nucleophilic Attack of Thioacid Salts in non Protic Media. A Key Step in the Total Synthesis of Penems.

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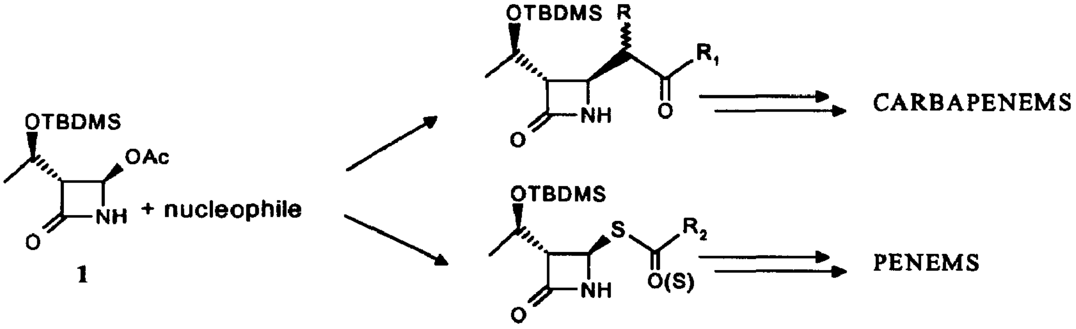
***Abstract:*** **High yield zinc halides-mediated reactions between thioacid salts and (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyl-oxy)ethyl]azetidin-2-one in non protic media are described.**

The development of practical high yield syntheses of compounds coming from the discovery is the fundamental step that allows candidates with an interesting pharmaceutical profile to become drugs. Furthermore, the definition of a versatile synthetic approach can open new perspectives in the search of new structures. The availability of (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]azetidin-2-one **1**[1] prompted several academic and industrial research groups to define total syntheses of non classical β-lactams in which the nucleophilic attack to the C-4 represents the key step.[2]

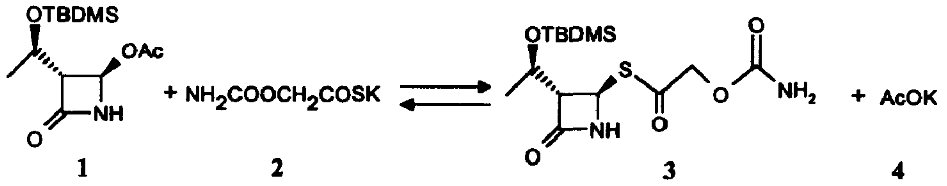


However, in the penem class,[3] when the nucleophilic attack of RCOS$^-$ was carried out in non aqueous media, low conversions and yields were generally observed. This outcome is related to the reversibility of the exchange process, in fact, there is a competition between RCOS$^-$ and the acetate anion generated during the reaction. To overcome this obstacle using nucleophiles ustable under the classical conditions ($H_2O$ as cosolvent in the presence of a base) it is necessary to follow semisynthetic approaches starting from penicillins[4] or less practical and more expensive C-4 substituted azetidinones.[5]

Herein, we report our studies on the metal-mediated nucleophilic attack of RCOSH salts in non protic media for the development of high yield straightforward approaches to the synthesis of penems starting from **1**.

We tested several metal salts as promoter of the reaction in organic solvent between **1** and **2**. The reaction product, azetidinone **3**, is the key intermediate in the total synthesis of Ritipenem and Ritipenem Acoxil.[3b] Compounds **2** and **3** are unstable under classical conditions.[6]

Table 1. Metal-mediated nucleophilic attack of **2** to **1**. Promoter and solvent effect.[a]

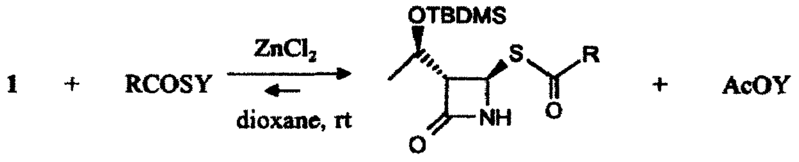


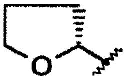
| Entry | Promoter | Solvent | t | Conversion[b] | 3 | |
|---|---|---|---|---|---|---|
| | | | h | % | 4R/4S[b] | yield, %[c] |
| 1[d] | | dioxane | 24 | 65 | ≥97/3 | 52 |
| 2 | $MgCl_2$ | dioxane | 48 | 60 | 86/14 | 25[e] |
| 3 | $FeCl_3$ | dioxane | 48 | 32 | ≥97/3 | 24 |
| 4 | $CoCl_2$ | dioxane | 24 | 47 | ≥97/3 | 40 |
| 5 | CuCl | dioxane | 24 | 2-3 | | |
| 6 | $ZnCl_2$ | dioxane | 18 | 100 | ≥97/3 | 93 |
| 7 | $ZnBr_2$ | dioxane | 18 | 100 | ≥97/3 | 96 |
| 8 | $ZnI_2$ | dioxane | 18 | 100 | ≥97/3 | 91 |
| 9 | $Zn(OAc)_2$ | dioxane | 24 | 10 | ≥97/3 | 7 |
| 10 | $ZnCO_3$ | dioxane | 24 | 61 | ≥97/3 | 43 |
| 11 | $ZnCl_2$ | $CH_3COCH_3$ | 2.5 | 100 | ≥97/3 | 93 |
| 12 | $ZnBr_2$ | AcOEt | 4 | 100 | ≥97/3 | 95 |
| 13 | $ZnI_2$ | $CH_3CN$ | 7 | 100 | ≥97/3 | 90 |
| 14 | $ZnCl_2$ | $CH_3OH$ | 24 | 100 | ≥97/3 | 9[f] |
| 15 | $ZnCl_2$ | $^t$BuOH | 25 | 24 | ≥97/3 | 17 |
| 16 | $ZnCl_2$ | $H_2O/CH_3COCH_3$ | 5 | 100 | ≥97/3 | 36[e] |

a. The reactions were carried out at room temperature using 1mmol of **1**, 1.5mmol of **2** and 1.5mmol of the metal salt in 7mL of solvent. b. Determined by $^1$H NMR and HPLC. c. Isolated yields of the 4R diastereoisomer. d. The reaction was carried out at 60°C. e. Extensive decomposition was observed. See ref 6. f. The product that came from diastereoselective nucleophilic attack of $CH_3OH$ was isolated in 89% yield.

Among the salts used at room temperature in dioxane (Table 1, entries 2-10), zinc halides gave the best results in terms of diastereoselectivity, yield, stability of starting materials and reaction products (entries 6-8). The performances of the zinc halide salts were similar and high yields were obtained using other reaction solvents such as $CH_3COCH_3$, AcOEt and $CH_3CN$ (entries 11-13). On the other hand, low yields were observed when the nucleophilic attack was carried out in $CH_3OH$ and $^t$BuOH or with $H_2O$ as cosolvent (entries 14-16). The high conversions and yields observed are related to the capability of the Zn(II) salt to coordinate the acetate anion favoring the shift of the reaction equilibrium to the right. It is worth noting that the reaction outcome was not dependent on the counterion used or the thioacid substitution (Table 2). The methoxymethyl (entry 4) and the tetrahydrofuranyl derivatives (entry 5) are intermediates in the total synthesis of FCE 25199[7] and Suflopenem Sodium,[24] respectively. The yields of the Zn(II)-mediated nucleophilic attack carried out in non protic media (entries 4 and 5) are consistently higher respect to the ones obtained under classical conditions.[8]

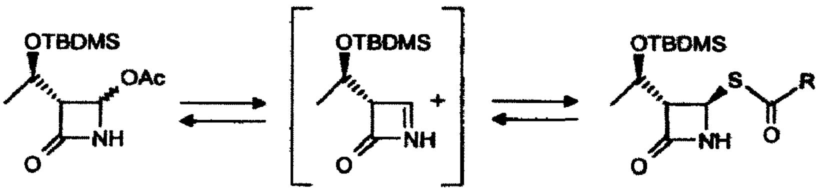
**Table 2.** Counterion and thioacid substitution effects.[a]



| Entry | R | Y | 4R/4S[b] | Yield, %[c] |
|---|---|---|---|---|
| 1 | $NH_2COOCH_2$ | Na | ≥97/3 | 93 |
| 2 | $NH_2COOCH_2$ | $Et_3NH$ | ≥97/3 | 92 |
| 3 | $CH_3$ | K | ≥97/3 | 95 |
| 4 | $CH_3OCH_2$ | $Et_3NH$ | ≥97/3 | 93 |
| 5 |  | $Et_3NH$ | ≥97/3 | 94 |

a. All reactions were carried out using the procedure of Table 1, in dioxane at rt until the conversion was complete. b. Determined by HPLC and $^1$H NMR of the crude. c. Isolated yield of the 4R diastereoisomer.

Except the $MgCl_2$-mediated reaction (Table 1, entry 2), the minor diastereoisomer was isolated in very low yield being the 4R/4S ratio always ≥97/3 irrespective of promoters, solvents and nucleophiles. Furthermore, the stereochemistry of 1 at C-4 was not important, in fact, the usual diastereoselectivity was observed using as starting material a 50/50 mixture of 4R and 4S azetidinone acetate.[4] This result is consistent with a mechanism centred on the formation of the iminium intermediate 5.



5

4R/4S ≥97/3

**Summing up, the zinc halides mediated nucleophilic attack of thioacid salts towards 1 is a general high yield procedure for the synthesis of key intermediates for total synthesis of penems.**

**Further studies on the catalytic version of the method are under way.**

### References and Notes

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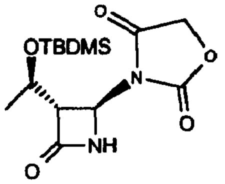
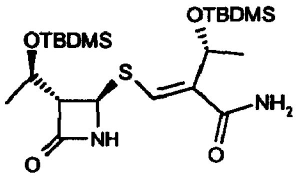
4. Perrone,E.; Franceschi,G. *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukas,G. and Ohno, M., Eds.; Springer-Verlag: Berlin,1990; p 613 and references therein.
5. Selected example: Cl: ref 2c. b. $PhS(O_2)$: Lang,M.; Prasad,K.; Holick,W.; Gosteli,J.; Ernest,I.; Woodward,R.B. *J. Am. Chem. Soc.* **1979**, *101*, 6296. c. PhCOO: Hanessian,S.; Bedeschi,A.; Battistini,C.; Mongelli,N. *J. Am. Chem. Soc.* **1985**, *107*, 1438. d. HCOO: Busch,F.R.; Dugger,R.W.; Quallich,G.J. *GB* 1992, 2252769 A. e. PhS(O): Kita,Y.; Shibata,N.; Yoshida,N.; Tohio,T. *Tetrahedron Lett.* **1991**, *32*, 2375.
6. Typical decomposition products are:





7. Alpegiani,M.; Bedeschi,A.; Zarini,F.; Della Bruna,C.; Jabes,D.; Perrone,E.; Franceschi,G. *J. Antibiotics* **1992**, *45*, 797.
8. The best yield of the nucleophilic attack of methoxythioacetic acid to 1 carried out in $CH_3COCH_3$/aqueous NaOH was 75%, Zarini,F. unreported results. The best yield of the nucleophilic attack of (R)-tetrahydrofuranyl-2-thiocarboxylic acid to 1 carried out in THF/aqueous NaOH was 82%.[2d]

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