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NEW CEPHALOSPORIN ACYLATING AGENTS DERIVED FROM SYN-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETIC ACID. APPLICATION TO THE SYNTHESIS OF CEFEPIME SULFATE

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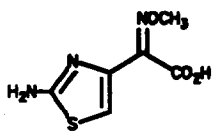
Summary: Activation of the title acid 1 as acyl derivatives of 1-methyl-5-mercaptotetrazole (13) and 2-methyl-5-mercapto-1,3,4-thiadiazole (9, 14) and subsequent acylation of penultimate 4 (X = Cl, I) gave good yields of cefepime sulfate 5.

Many activated derivatives of the title acid 1,[1] useful in preparing beta-lactams of current medicinal interest, have been reported in the patent literature. Perhaps the most prominent and frequently employed are the 1-



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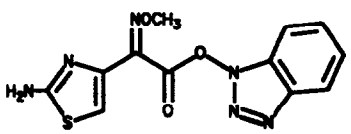

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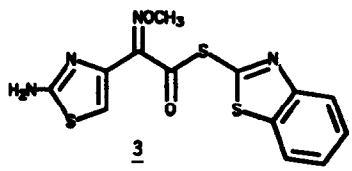

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hydroxybenzotriazolyl (HOBT) and 2-mercaptobenzothiazolyl (HSBT) esters 2[2] and 3,[3] respectively. Both were used to prepare our antibiotic candidate cefepime 5,[4,5] isolated initially as its sulfate salt,[5] from penultimate 4[5] (eq 1). For different reasons,[6] it became necessary to pursue new acylating agents.

Based on processing advantages noted in substituting 3 for 2 in preparing 5, mercaptan activation of 1 was desirable. Since bulk quantities of thiols 6 and 7 were available, and their toxicities well documented,[8] esters 8 and 9 were proposed for study. A literature search revealed that the related 2-tritylaminothiazoles 10 and 11 were known, and were efficient acylating agents.[9]

As an initial approach, reactions of 1 with 12[10] and Ph_3P[11-14] or $(EtO)_3P$[15,16] under various conditions gave insignificant conversions to 8 (HPLC). However, coupling of 1 with 6 and DCC (1 equiv each) in acetone gave the isomeric acylating agent 13 in a modest 35% yield (eq 2).[17] Acylation at the 3-position of 6 is proposed based on IR spectral data and on computer generated versus observed ^{13}C chemical shifts for 8/13, and on the predominance of 6 in solution as the tautomeric 4H-1-methyl-5-thionotetrazole.[10,18]

Acylation of 4 (X = I) with 13 (1.5 equiv)[19] gave a 72% yield of 5. Alternatively, preparation of 13 *in situ* in DMF (eq 2) followed immediately by acylation of 4 (X = Cl)[20] afforded 5 in 66% yield.

Ester 9 was analogously prepared in THF in 24% yield from 1, 7 and DCC (1 equiv each).[21] Again, IR and ^{13}C spectral data inferred 9 as the adduct structure rather than 14. Acylation of 4 (X = I) with 1.5 equiv 9[22] gave 5 in 73% yield. Also, as was observed with 13, isolation of 9 prior to acylation was unnecessary. Thus, *in situ* formation of 9 in DMF or THF and acylation of 4 (X = I)[20,22] gave 5 in 54% and 58% yields, respectively.

An alternative synthesis of 9 was realized by reaction of 1 with Ph_3P and disulfide 15[23] (1.2 equiv each) in either THF or acetone. After 15 min, filtration of THF insoluble by products and acylation of 4 (X = I)[22] afforded a 58% yield of 5.

Finally, reaction of 1 with 15 and Ph_3P (1.2 equiv each) under conditions favoring N-acylation (1 equiv Et_3N, cat. Et_4NBr, acetone, 4.5 hr)[13] gave mainly 14 (HPLC area% ratio 14/9 = 11/1). Filtration of acetone insoluble by products and acylation of 4 (X = I)[24] gave 5 in 56% yield.

In summary, replacement of 2 with acylating agents 9, 13 and 14 in syntheses of 5 from 4 was demonstrated. Use of these reagents does not require protection of the 2-amino group, as in 10 and 11, thus reducing process steps. Also, the observed 6-fold acylation rate enhancements of 4 as well as the total solubility of 6 and 7 during work up favors use of 9, 13 and 14 over 2. Additional applications on the use of these new acylating agents are being pursued.

References and Footnotes

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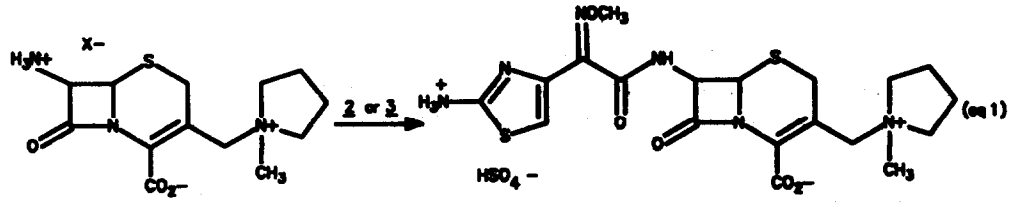
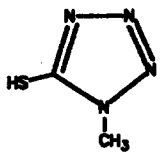


4 (X = Cl, I) 5 (eq 1)



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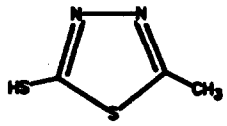

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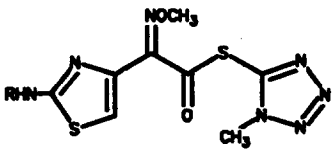
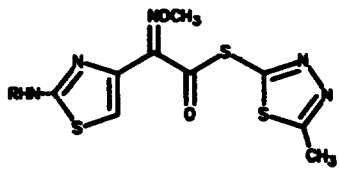


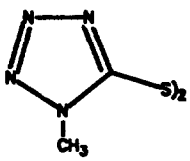
8 (R = H)

10 (R = Ph_3C)



9 (R = H)

11 (R = Ph_3C)



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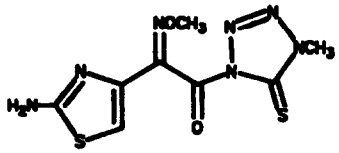
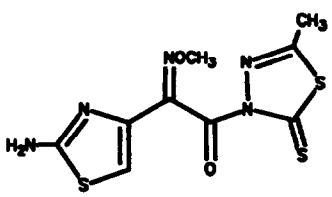
1 —(6, DCC, ACETONE)→



13 (eq 2)



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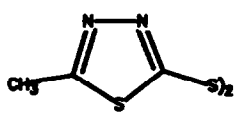

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16. Hubschwerein, C.N. US 4576751, Mar 18, 1986.
17. The low yield was due to coprecipitation of 13 with DCU during the coupling step. The product was isolated after addition of 4 volumes of Skelly B to the acetone filtrate.
18. McCleverty, J.A. Transition Met. Chem., 1984, 9, 139.
19. Acylation conditions: i) aq acetone, 2N NaOH, pH 6.5, 30 min; ii) methyl isobutyl ketone; iii) 2.8 equiv 4N sulfuric acid.
20. Acylation conditions: i) aq DMF, 2N NaOH, pH 6.5, 30 min; ii) CH_2Cl_2 wash; iii) 2.8 equiv 4N sulfuric acid.
21. The product was isolated after addition of the filtered THF process stream into 10 volumes of Skelly B.
22. Acylation conditions: i) aq THF, 2N NaOH, pH 6.5, 30 min; ii) methyl isobutyl ketone; iii) 2.8 equiv 4N sulfuric acid.
23. Oba, T.; Tanaka, T.; Okumura, N.; Watanabe, K.; Bannai, K.; Ohtsu, A.; Naruchi, T.; Kurozumi, S.; Toru, T. Eur. patent appl. 22634, Jan 21, 1981; pg 110, example 62.
24. Acylation conditions: i) aq acetone, 2N NaOH, pH 6.5, 0-5°C, 1 hr; ii) methyl isobutyl ketone; iii) 2.8 equiv 4N sulfuric acid.

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