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REACTIONS OF TMSI WITH CEPHALOSPORIN ESTERS

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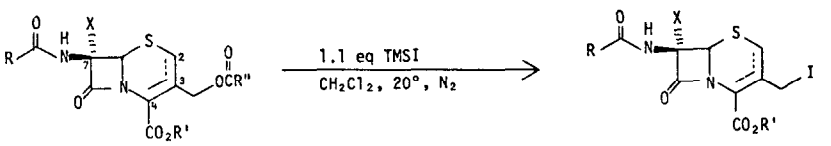
ABSTRACT: The direct synthesis of 3-iodomethyl cephalosporin esters from 3-acetoxy- and 3-carbamoylmethyl analogues may be achieved using TMSI. The "one-pot" conversion of sodium cephalothin into a C-3 heterocycle-substituted cephalosporin may also be performed using TMSI-mediated chemistry.

3-Iodomethyl cephalosporins are useful intermediates in the preparation of a variety of heterocycle-substituted cephalosporin antibiotics, but their accessibility, in comparison to the chloro and bromo analogues, has been limited by the necessity for multi-step syntheses.[1,2] This report presents a simple method for the direct generation of these iodinated substrates by treatment of 3-acetoxymethyl or 3-carbamoylmethyl cephalosporins with iodotrimethylsilane (TMSI).[3]

SCHEME I

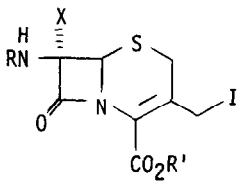
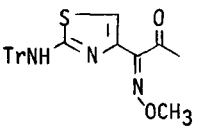
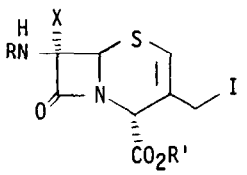


1 2

In a typical reaction, benzyl 7α-methoxy-7β-phenylacetamido-3-acetoxymethyl-3-cephem-4-carboxylate, 1c, (0.33 g, 0.65 mmol) in 4 ml of anhydrous CH_2Cl_2 was treated with TMSI (0.1 ml, 0.7 mmol) at 20°C for 1 h. The mixture was then sequentially extracted with ice cold solutions of 10% $Na_2S_2O_3$, 10% $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. 3-Iodomethyl cephalosporin 2c was recovered [95%, 0.36 g, δ 4.32 ($CDCl_3$) (s), $-CH_2I$] and was stable indefinitely when stored at -10°C.

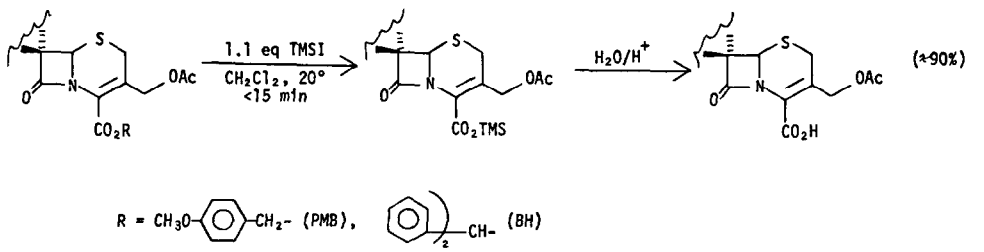
Table 1 displays a number of 3-iodomethyl cephalosporins prepared by this method. Note that the integrity of the double bond in Δ^2- and Δ^3-cephems is retained in the iodinated products, and the geometry of the syn-methoxime in 2e is also maintained. Also of interest is the relative unreactivity of the benzyl and tert-butyl esters in 1b, 1c, and 1f toward TMSI as compared to the allylic acetate moiety.[4] This is not the case, though, for cephalosporins possessing the p-methoxybenzyl (PMB) or benzhydryl (BH) esters both of which are efficiently cleaved with TMSI faster than the allylic acetate (Scheme II).

TABLE I. Conversion of Cephalosporins into C-3 Iodomethyl Derivatives with TMSI

Product[a]		R	R'	X	Yield (%)[b]
	a.	Phenoxyacetyl	PNB	H	92
	b.	Phenylacetyl	benzyl	H	96
	c.	Phenylacetyl	benzyl	$-OCH_3$	95
	d.	Thiophenacetyl	methyl	$-OCH_3$	90[c]
	e.		methyl	H	76[d]
	f.	Thiophenacetyl	tert-butyl	H	61

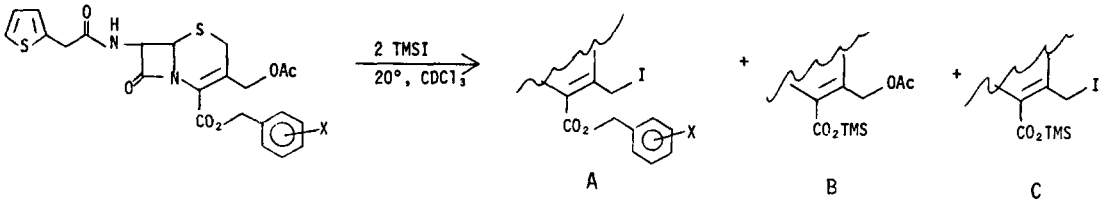
[a]All iodo-compounds gave satisfactory spectral analyses, including parent ions (M^+) and $M-127)^+$ ions upon EI/MS.
[b]Isolated yields.
[c]This iodide was derived from the carbamate, rather than the acetate.
[d]This experiment was conducted using 2 eq. TMSI, since 1 eq. interacts with the methoxime side chain by NMR analysis and can be reversed upon aqueous workup.

SCHEME II



The chemistry of cephalosporins is indeed subtle. To further demonstrate this fact, the reactions of three additional methyl-substituted benzyl esters with TMSI were compared with the PMB and benzyl systems.

TABLE II. TMSI Cleavage[a] of Ceph-Benzyl Esters[b]



A B C

X	Time	Ratio of Products A	B	C
H	24 h	1	0	0
ortho-CH_3	15 min	2	1	0
	30 min	1	0	3
para-CH_3	15 min	2	1	0
	30 min	1	0	4
meta-CH_3	15 min	1	0	0
	3 h	0	0	1
para-OCH_3	15 min	0	0	1

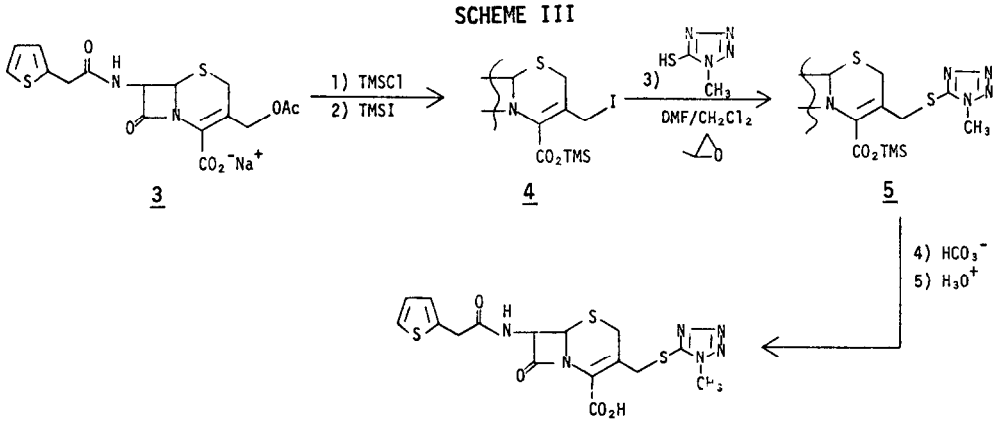
[a]Ratios determined by NMR analysis.
[b]The tert-butyl ester usually requires 1-3 h for complete removal.

From the results shown above in Table II, the relative reactivity toward TMSI of various cephalosporin esters may be tentatively formulated as follows in decreasing order:

> BH, PMB > C-3 acetoxy- or carbamoylmethyl > t-butyl > m-methylbenzyl > benzyl >> p-nitrobenzyl (PNB), methyl.

Further utility of TMSI in the cephalosporin field can be demonstrated in the "one-pot" synthesis of N-methyltetrazolylthiomethyl acid 6 (Keftet®) from sodium cephalothin 3 (Keflin®) as shown in Scheme III.[5] The water-soluble salt 3 is converted to the CH_2Cl_2-soluble trimethylsilyl ester.[6] Then, following TMSI (3 eq) treatment in CH_2Cl_2 at 20°C for 1-2 h, the crude iodocephalosporin is diluted with DMF and propylene oxide (acid scavenger). N-Methyltetrazolthiol (1.5 eq) is then added, and within 1 h reaction is complete. Trimethylsilyl ester 5 can be isolated after extraction workup[7] and then be hydrolyzed to the final product by careful basification with cold saturated $NaHCO_3$, then reacidification and extraction into EtOAc.

SCHEME III



3 4 5 6 (70% overall)

In conclusion, we have demonstrated the utility of TMSI in cephalosporin chemistry, including a room temperature C-3 substitution technique complementing existing procedures.

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References

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2. (a) U. S. Patent 3,658,799; (b) S. Karady, T. Y. Cheng, S. H. Pines, and M. Sletzinger, Tetrahedron Lett., 2625 (1974); (c) U. S. Patent 4,042,585.
3. (a) M. F. Jung and M. A. Lyster, J. Am. Chem. Soc., 99, 968 (1977); (b) M. F. Jung and M. A. Lyster, Chem. Commun., 315 (1978); (c) W. C. Groutas and D. Felker, Synthesis, 861 (1980).
4. These results should be compared to the a) desacetoxycephalosporin system: A. Mangria and A. Scandroglio, Tetrahedron Lett., 5219 (1978) and b) to the 7-pyrrolocephalosporin system in which the reported 45% yield of the 3'-acetoxycephalosporin acid was probably due to competing formation of the neutral 3'-iodomethylcephalosporin tert-butyl ester: A. Nudelman, F. Braun, and E. Karoly, J. Org. Chem., 43, 3788 (1978).
5. "Cephalosporanic Acids: A New Look at Reactions at the C-3' Position", L. D. Hatfield, J. W. Fisher, J. M. Dunigan, R. W. Burchfield, J. M. Greene, J. A. Webber, R. T. Vasileff, and M. D. Kinnick, Proceedings of the Royal Society (1980), in press.
6. British Patent 1,244,191.
7. W. J. Wheeler, D. R. Finley, and H. E. Osborne, J. Antibiot. 33, 72 (1980).
8. NMR δ ($CDCl_3$) of 4: 4.33 (brd s, 2H, $-CH_2STet$), 3.65 (brd s, 2H, C-2 methylene), 0.10 (s, 9H).
9. NMR δ (d_6-DMSO) of 5: 3.71 (d, J=6 Hz, 2H, C-2 methylene), 3.95 (s, NCH_3, 3H), 5.0 (d, J=5 Hz, 1H, C-6 methine), 5.67 (c of d of d, J=5 Hz and 9 Hz, 1H, C-7 methine). Rf 0.45 (4:1 EtOAc/HOAc).

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