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REACTIONS OF ORGANOCUPRATES WITH VINYL-TRIFLATES AND RELATED CEPHEMS: A NOVEL APPROACH TO 3-SUBSTITUTED CEPHALOSPORINS

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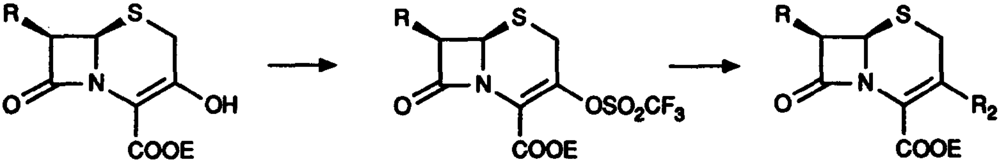
Abstract: Vinyl-triflates and related 3-substituted cephems readily undergo addition-elimination reactions with a variety of organocuprates to form new carbon-carbon bonds. This chemistry presents a novel approach to the synthesis of 3-alkyl, 3-aryl, and 3-alkenylcephalosporins.

Reactions on substrates containing carbon bound leaving groups by organocuprates are conceptually among the most straightforward operations for the formation of new carbon-carbon bonds.[1] Several years ago, Mc Murry demonstrated that enol-trifluoromethanesulfonates (enol-triflates) underwent *regio* and *stereo* specific coupling in high yield with a wide variety of organocuprate reagents.[2] In connection with our ongoing research on semi-synthetic cephalosporins, we were looking into methods to gain a convenient access to 3-alkyl, -aryl, and -alkenyl cephems without going through cumbersome procedures. Since 3-hydroxycephems **1** are readily available,[3] we decided to take advantage of Mc Murry's chemistry and explore the reactions of trifloxycephems **2a** with a variety of organocuprates in order to synthesize our target compounds.[4] (**Scheme 1**)

Scheme 1



1 **2** **3**

The starting 3-trifloxycephem **2a** was prepared by treating 3-hydroxycephem **1** with triflic anhydride in the presence of *N,N*-diisopropylethylamine at -78 °C. Treatment of **2a** with Me_2CuLi (lower-order cuprate) or $Me_2Cu(CN)Li_2$ (higher-order cuprate) provided the desired product, in a satisfactory yield, but as a mixture of Δ^2/Δ^3-cephems (entries 1&2, **Table 1**). However, admixing the same cuprates with 2.0 equivalents of $BF_3 \cdot Et_2O$ suppressed the isomerization (entries 3&4, **Table 1**).

Base-catalyzed isomerization of Δ^2/Δ^3-cephems is known.[5] The isomerization is most likely induced by the cuprate itself as cuprates are known to be basic in nature.[1b] On the other hand, the organo-copper reagents generated along with $BF_3 \cdot Et_2O$ afford altogether different reactive species (cuprate-Lewis acid combination)[6] which not only participate in the addition-elimination reactions effectively but, most importantly, prevent the base-catalyzed isomerizations.

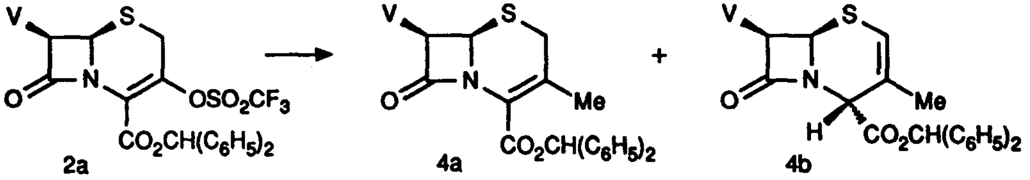


Table 1

Entry	Cuprate	Ratio of 4a:4b (NMR)	%Yield
1	Me_2CuLi	1:1	65
2	$Me_2Cu(CN)Li_2$	2:3	65
3	$Me_2CuLi/BF_3{\cdot}Et_2O$	100:0	65
4	$Me_2Cu(CN)Li_2/BF_3{\cdot}Et_2O$	98:2	85

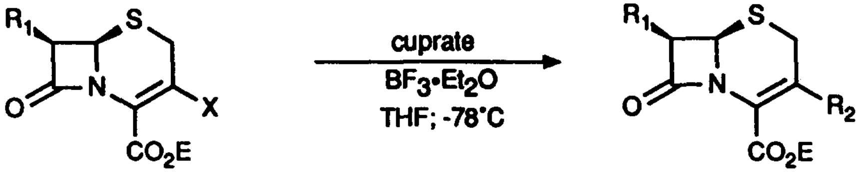
V=$NHCOCH_2OC_6H_5$

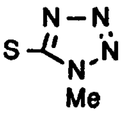
The chemistry was extended further by treating **2a** with a variety of organocuprates including alkyl, aryl, vinyl, and (*Z*)-propenyl reagents (**Table 2**). *A stereospecific reaction (>98%)* was observed between **2a** and (*Z*)-di-1-propenylcuprate (entries 8, 9 & 11, **Table 2**). We also explored the potential of other vinylic sulfonates[7] to engage in reactions and discovered that vinyl tosylate and nosylate (*p*-nitrobenzenesulfonate) also reacted equally well with the cuprates to form carbon-carbon bonds (entries 10, 11 & 12, **Table 2**). Interestingly, the displacement of mercapto-1-methyl-tetrazole[8] to yield the corresponding product in high yield (entry 13, **Table 2**) was also observed.

In summary, we have developed a facile method to synthesize a variety of 3-alkyl, 3-aryl, and 3-alkenyl cephalosporins[9] from accessible starting materials. Furthermore, we have also demonstrated the utility of lower and higher order cuprates for substituting C-C for C-X bonds at the C3 sp^2 carbon in cephalosporins.[10] We are continuing our endeavors to delineate the scope of this chemistry.

Acknowledgement. We would like to thank Professor Gary Posner for helpful discussions and Ms. Char Lloyd for typing this manuscript.

Table 2



Entry	X	E	R1	Cuprate	R2	% Yield [a]
1	OTf	PMB	G	Me_2CuLi	Me	75
2	OTf	DPM	V	Et_2CuLi	Et	75
3	OTf	DPM	V	n-Bu_2CuLi	n-Bu	60
4	OTf	DPM	V	t-Bu_2CuLi	t-Bu	70
5	OTf	DPM	V	Ph_2CuLi	Ph	65
6	OTf	DPM	V	$(CH_2{=}CH)_2CuLi$	$CH_2{=}CH$	35
7	OTf	DPM	V	$(CH_2{=}CH)_2(CN)Li_2$	$CH_2{=}CH$	42
8	OTf	DPM	V	( $)_2CuLi$[b]		29
9	OTf	DPM	V	( $)_2Cu(CN)Li_2$[b]		55[c]
10	OTs	DPM	V	Me_2CuLi	Me	62
11	OTs	DPM	V	( $)_2Cu(CN)Li_2$[b]		59[c]
12	ONs	DPM	V	Me_2CuLi	Me	35
13		PMB	G	Me_2CuLi	Me	81

[a] Unoptimized isolated yields after chromatography.
[b] Cuprate prepared by transmetallation reaction: ref 11
[c] Isolated as a mixture of Δ^2-and Δ^3-cephems (1:1)
V = $NHCOCH_2OC_6H_5$; G = $NHCOCH_2C_6H_5$
DPM = $CH(C_6H_5)_2$; PMB = $CH_2C_6H_4$-p-OCH_3

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7. The sulfonates were prepared according to the literature procedures: Spitzer, W. A. *United States Patent*, **1976**, # 3,985,737.

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9. All new compounds were fully characterized by IR, NMR, MS, and HRMS, or combustion analyses.

10. A typical procedure for the cuprate reaction is as follows: In a 10-mL flask under argon or nitrogen was added CuI or CuCN (0.75 mmol) followed by dry THF (1.5 mL) and the slurry was cooled to -78 °C. Using a syringe, the alkyllithium (1.5 mmol) was added dropwise and the mixture was allowed to warm until homogenous. The reaction mixture was re-cooled to -78 °C and immediately $BF_3 \cdot Et_2O$ (1.5 mmol) was added, followed by (0.34 mmol) of **2a**. The mixture was stirred for 2-5 hrs at -78 °C before quenching in saturated NH_4Cl solution. The pure compounds were isolated by flash chromatography.

11. (*Z*)-1-(Propenyl)$_2$Cu(CN)Li$_2$ and (*Z*)-1-(propenyl)$_2$CuLi were prepared by transmetallation between (*Z*)-propenyl-tri-*n*-butylstannane and higher-order cyanocuprate or lower-order cuprate, as described in: Behling, J.R.; Babiak, K.A.; Ng, J.S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

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