Tetrahedron Letters, Vol.30, No.3, pp 337-340, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CARBACEPHEMS AND 4-METHYLENE-AZETIDIN-2-ONES BY COPPER-MEDIATED AMIDE NITROGEN-VINYLIC CARBON RING CLOSURE

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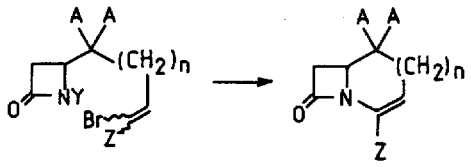
Abstract : Treatment of N-alkyl or N-aryl 3-bromo-3-buteneamides under modified Ullmann-Goldberg conditions results in the direct formation of highly strained N-substituted 4-methylene-azetidin-2-ones in fair to good yields. In the same manner, 4-(4'-bromobuten-3'-enyl) azetidinone derivatives provides carbacephems.

Recently, we described the synthesis of benzocarbapenem- and benzocarbacephem-derivatives by a copper promoted intramolecular aromatic substitution[1]. In spite of the failure of an analogous copper I mediated synthesis of penems[2], we attempted the extension of this type of N-C bond formation from aryl to vinylic bromides.

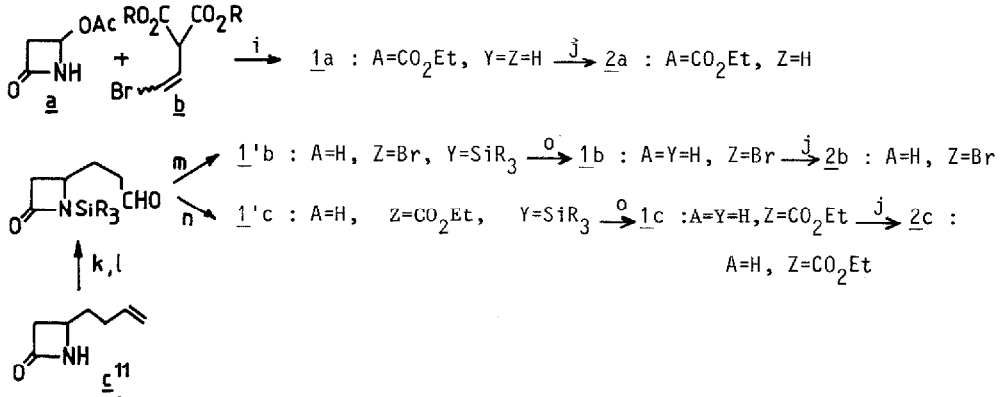
First, we examined the possibility of a new access to carbacephem or carbapenem rings, 2 or 4, starting from 4-(bromoalkenyl) azetidinones, 1 or 3. Treatment of the easily available[3] 4-(4'-bromobut-3'-enyl) azetidinone, 1a, by copper powder at 110°C in DMF for 1 h gave the carbacephem 2a[4]. The yield of the reactions albeit low (20-33 %), depends on the amount of the Z stereoisomer in the E/Z mixture of the starting compound 1a[5]. Moreover, the recovered malonate 1a contains a larger percentage of the E isomer than the starting one. Therefore, the Z-bromide is probably the reactive specie[9] and cyclization conditions allow a slow E$\rightleftharpoons$Z isomerisation of 1a. Other examples of cyclization are shown on scheme 1. Poor yields (10-20%) of carbacephems 2b and 2c (unstable compound), along with starting compounds 1b and 1c and unidentified decomposed products were obtained.

From some homologous 4-(3'-bromoprop-2'-enyl) azetidinones 3 no carbapenem 4 was isolated. These fused five-membered ring azetidinones are probably too fragile to survive in the conditions of the reaction.



1 : n=1
3 : n=0

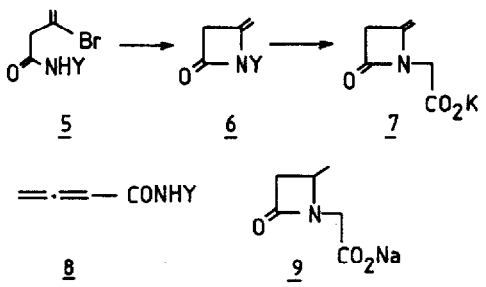
2 : n=1
4 : n=0



i) NaH, THF[3] j) Cu, DMF, 110-120°C k) $tBu\emptyset_2SiCl$[12], $CH_3CONHCH_3$, Et_3N[13] in situ
l) OsO_4NaIO_4, THF-H_2O[14] m) $\emptyset_3P$, CBr_4, Et_3N[15] n) $\emptyset_3P{=}CBrCO_2Et$[16] o) 0.04 M KF, MeOH

Scheme 1

Then, we considered the synthesis of 4-methylene azetidin-2-ones, 6, from acyclic precursors, 5, by a 4-exo-trig cyclization (Scheme 2). To the best of our knowledge, 4-methylene-azetidinones are unknown. Some alkyl-, aryl- or alkyloxycarbonyl-substituted derivatives have been recently described[3,17]. Structure 6 might be endowed with a particular reactivity as a result of the combined effects of ring strain (presence of the sp_2 C-4) and the enamine functionality.



Scheme 2

Entry	Y	Yield (%)
6a	$CH_2C_6H_5$	23
6b	$OCH_2C_6H_5$	12
6c	$4\text{-}CO_2Et\text{-}C_6H_4$	85
6d	$2\text{-}CH_3\text{-}5\text{-}CO_2Bu^t\text{-}C_6H_3$	66
6e	$2\text{-}CH_3\text{-}C_6H_4$	73
6f	$4\text{-}CH_3O\text{-}C_6H_4$	46
6gα	CH_2CO_2bzl	31
6gβ	$CH_2CO_2Bu^t$	42
6gγ	CH_2CO_2allyl	37

Table 1

Differently substituted secondary amides, 5, have been prepared by conventional methods starting from 3-bromo-but-3-enoic acid, easily obtained from 3-butyn-1-ol[18]. When treated by copper powder (5 equiv.) at 130-135°C for 20-50 mn in DMF,bromovinyl acetamide, 5, (0.28 mmoles) effectively gave β-lactam, 6[4], in 12-85 % yield (Table 1).

A certain correlation between yields of 6 and the NH acidity of the starting amides, 5, may be observed. However, the stability of the product 6 probably plays a role. Use of an ultrasonic probe[19] in the reaction mixture lowered substantially the temperature required for the cyclization, but the procedure suffered from a lack of repeatability.

The presence of an allenic intermediate on the reaction pathway has been ruled out since diene, 8, did not lead to any ring closure under a variety of conditions. By the way, all attempts to carry out heterocyclization of 1 or 5 with assistance of Ni[20] or Pd[21] instead of copper powder failed.

It is noteworthy that azetidinones, 6, display high $\nu_{C=O}$ IR stretching frequencies (1780-1795 cm^{-1}), one of the criteria of the reactivity of the β-lactam ring[22], and the alkaline hydrolysis of 6e is a rather fast process.

Glycinates, 6g, were prepared as the simplest precursors which would provide 4-methylene azetidin-2-one with a free carboxylic group. Hydrogenolysis (H_2,Pd/C,EtOH-AcOEt,aq.$NaHCO_3$) of the benzyl ester, 6gα , could not be carried out chemoselectively, and led to the fully reduced compound, 9. The acidic conditions (CF_3CO_2H-CH_2Cl_2) for the cleavage of the tertbutyl ester function of 6gβ induced the ring opening of the β-lactam nucleus. Finally, allyl ester 6gγ proved to be a well suited precursor as the allyl protecting group was nicely cleaved with $Pd(PPh_3)_4$[23] to potassium salt 7[4], with 95 % yield.

In preliminary biological assays, compound 7 exhibited neither antimicrobial, nor β-lactamase inhibiting properties[24]. Further studies aimed at introducing judicious side chain at C-3 are currently in progress.

Conclusion : In DMF, activated copper[1,25] promotes an intramolecular nucleophilic vinylic (S_NV) substitution[26] of a bromine atom by the nitrogen of a neighbouring amide or β-lactam group. Cyclization yields depend on the stability of the product in the reaction conditions.

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(Received in France 29 September 1988)