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SYNTHESIS OF 4-SUBSTITUTED 2-AZETIDINONES

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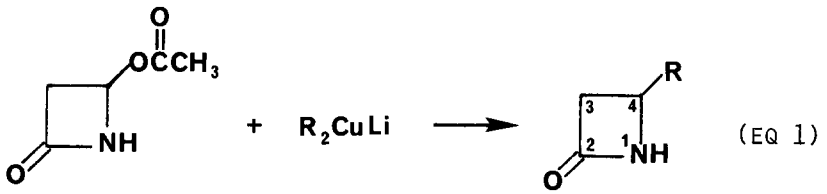
Summary: 4-Substituted 2-azetidinones were obtained in excellent yields from the reaction of various cuprates with 4-acetoxy-2-azetidinone.

Since the discovery of thienamycin[1] and other related carbapenem antibiotics,[2] few reports[3] have appeared on the carbon-carbon bond formation at the 4-position of 2-azetidinone. In general, the readily available material, 4-acetoxy-2-azetidinone (1)[4] has been used as the starting material in these reports, however, in many cases, the yields were low.[3] We report here a facile method for the introduction of alkyl, aryl, allyl and alkenyl groups at the 4-position of 2-azetidinone in excellent yields.

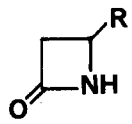
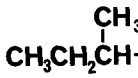
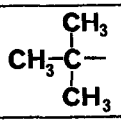
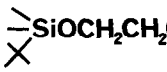
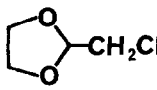
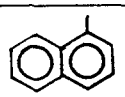
When azetidinone 1 was treated with 1 equivalent of the cuprates in ether : dimethyl sulfide (1:1) at -50 ∿ -30°C, only 20 ∿ 30% yields of the corresponding 4-substituted 2-azetidinones were obtained (eq. 1). However if two equivalents of the cuprates were used, excellent yields (71 - 98%) were achieved. The results are summarized in Table 1.



1 (EQ 1)

The Stoichiometric organocopper compounds (RCu) did not give any products. Neither ether nor tetrahydrofuran alone as the solvent in the displacement reaction of 1 with cuprates

TABLE 1. REACTIONS OF 4-ACETOXY-2-AZETIDINONE (1) WITH HOMOCUPRATES.

ENTRY	$R_2Cu^- M^+$		 ISOLATED YIELD (%)[5]
	R	M	
1	$CH_3CH_2CH_2CH_2-$	Li	2 (94)
2		Li	3 (96)
3		Li	4 (90)
4		Li	5 (98)
5		MgBr	6 (92)
6	$CH_2=CH-$	Li	7 (83)
7		Li	8 (95)
8		Li	9 (82)
9		Li	10 (80)
10	$CH_2=CHCH_2-$	Li	11 (71)[6]

gave appreciable amount of the products. When divinylcuprate was generated from vinylmagnesium bromide, a low yield of the displacement product was formed, however, the dialkylcuprate (entry 5) which was made from the corresponding alkylmagnesium bromide gave an excellent yield of β-lactam (6). Finally an attempt to replace the extra equivalent of cuprate with 1 equivalent of base by adding a solution of 1 equivalent of lithium diisopropylamide (LDA) in ether (-78°C) and a solution of 1 equivalent of lithium dibutylcopper in ether : dimethyl sulfide (1:1) (-78°C) simultaneously into a solution of 1 equivalent of 1 in ether at -78°C was unsatisfactory (low yield of 2). It is possible that LDA reacts with lithium dibutylcopper faster than β-lactam 1. We speculate that one equivalent of the cuprate is removing the acidic N-H proton while another equivalent of the cuprate is displacing the acetoxy group.

The following experimental procedure for the preparation of 5 from 1-t-butyldimethylsilyloxy-3-lithiopropane[7] is representative.

To a stirred mixture of 0.884 g (3.50 mmol) of CuI·MeSMe[8] in 10 mL of ether under argon at -20°C was added a solution of 1-t-butyldimethylsilyloxy-3-lithiopropane (7.0 mmol) in 10 mL of ether. The reaction solution was stirred at -20°C for 15 min and then 20 mL of dimethyl sulfide was added. This cuprate solution was cooled to -50°C and to this a solution of 0.226 g (1.75 mmol) of azetidinone 1 in 6 mL of ether was added. The resulting reddish solution was stirred at -50°C for 30 min., poured into a mixture of 80 mL of sat. NH_4Cl and 20 mL of conc. NH_4OH, stirred for 10 min., and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (E. Merck; 230 - 400 mesh; elution with CH_2Cl_2 - acetone 9 : 1) to give 0.420 g (98% yield) of 5; MS (70 eV), chemical ionization, 244 (M + 1); (EI) 244 (M + 1), 186, 156, 144, 101, 84, 75, 59; IR (neat) ν 3300 (m, N-H), 2900 (s), 1730 (s, C=O), 1460 (w), 1250 (m), 1100 (s), 840 (s), 780 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.04 (broad s, 1H, NH), 3.64 (m, 3H, CH_2O and CHN), 3.05 (d,d,d, 1H, J = 14.7, 5.0, 2.2 Hz, C-3-H), 2.56 (d,d,d, 1H, J = 14.7, 2.2, 1.3 Hz, C-3-H), 1.69 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 0.9 (s, 9H, CMe_3), 0.04 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 168.3 (s, C=O), 62.4 (t, CH_2O), 47.8 (d, CH-N), 43.3 (t, $\underline{C}H_2$-C=O), 32.1 (t, CH-$\underline{C}H_2$-CH_2-), 29.3 (t, CH_2-$\underline{C}H_2$-CH_2), 25.8 [q, 3C, C($\underline{C}H_3$)$_3$], 18.1 (s, $\underline{C}Me_3$), -5.5 (q, Si$\underline{C}H_3$).

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References and notes

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