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AN ALTERNATIVE ROUTE TO 4-BENZOYL-2-AZETIDINONES

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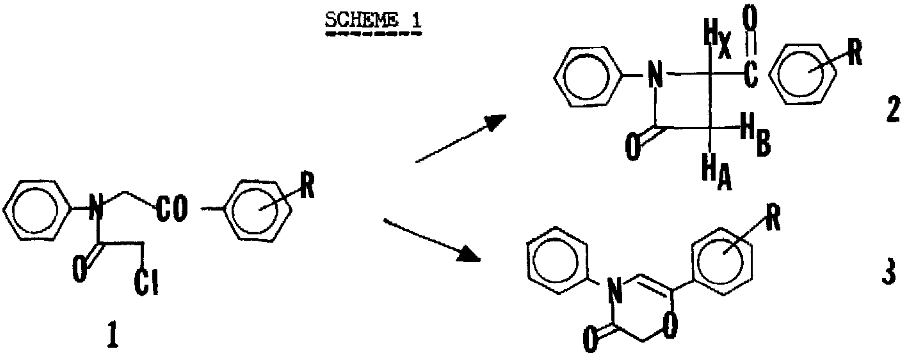
Cyclodehydrohalogenation by terminal N_1-C_4 bond formation affords N-aryl-4-benzoyl-2-azetidinones from 3-benzoyl-3-bromopropionanilides in an unequivocal annelation process.

The chemistry of 2-azetidinones continues to attract the interest of many research groups, and a substantial proliferation of data has occurred in recent years.[1-7] The current work stems from a report by Chatterjee et. al.[8] claiming the synthesis of two novel 2-azetidinones from substituted N-chloroacetyl-N-phenacylanilines, in yields ranging from 75 - 80 % (isolated). However, we had reported in earlier publications[9] that the cyclization of of such phenacylamines (1) was an ambiguous process which afforded both 2-azetidinones (2) and 1,4-oxazin-3-ones (3). The reaction coordinate was heavily dependent on aryl ring substituents (Scheme 1).

SCHEME 1



In our hands, the yield of the 2-azetidinones by Chatterjee's route[8] was consistently lower, was always accompanied by oxazine, e.g. (3a)[10], and was solvent dependent, with increasing amounts of oxazine paralelling increasing solvent polarity.[11]

We wish to describe an alternative approach to the synthesis of 4-benzoyl-2-azetidinones using terminal N_1-C_4 bond formation[12] (Scheme 2). Thus, bromination of 3-benzoylpropionic acid in ether at 0-5°C afforded quantitative yields of 3-benzoyl-3-bromopropionic acid, which was smoothly condensed to its anilide in dichloromethane (dried over Davison 4A molecular Sieves) with DCC in yields ranging from 80 - 95 %. The anilides were subjected to the action of various bases (triethylamine, sodium methoxide, n-butyllithium, and Amberlite IRA 400, OH^-).

The results are summarised in Table (I). The base of choice was discovered to be the anion exchange resin with which only 2-azetidinones were formed by cyclodehydrohalogenation, without any concomitant 1,2-elimination to trans-2-benzoylacrylanilide. With triethylamine no 2-azetidinone formation was observed. The overall efficiency of the conversion to beta-lactams by this route is about 28 - 60 %[13] based on starting 3-benzoylpropionic acid, but the process affords uncontaminated lactams with the base of choice without subsequent need for chromatographic purification.[14]

SCHEME 2

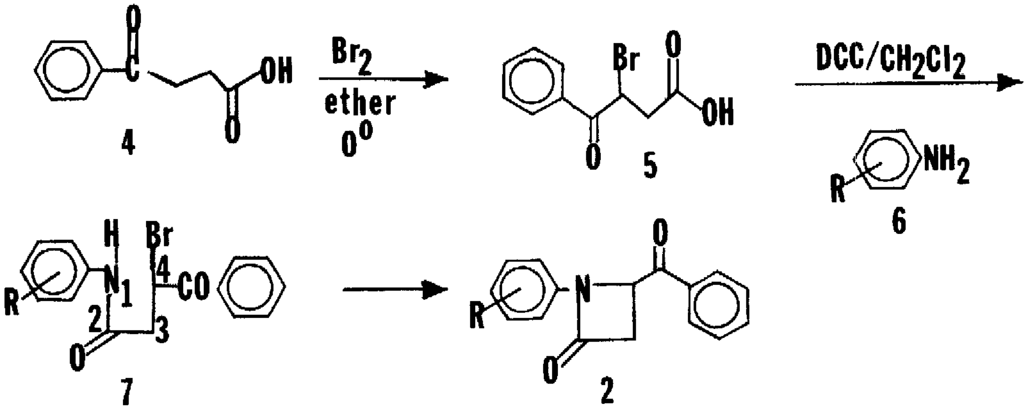
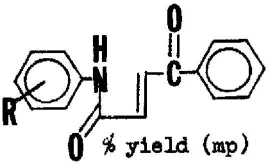
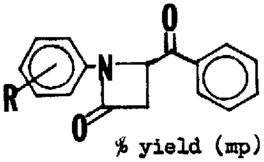


Table 1

Base	Solvent	R	Time (mins.)	Temp. °C	 % yield (mp)	 % yield (mp)
$(C_2H_5)_3N$	Benzene	H	60	80	91 (159 - 160)	-
NaOMe	Ethanol	H	60	22	48	35[8]
n-BuLi	THF	H	90	- 30	40	28
Amberlite IRA-400	Ethanol	H	5-10	22	-	60
"	"	4-CH_3	"	"	-	60 (172-174)
"	"	4-Cl	"	"	-	28 (142-143)
"	"	3-CF_3	"	"	-	55 270-272)

Experimental Procedure

N-(4-Tolyl)-4-benzoyl-2-azetidinone : To 2.0g of 3-benzoyl-3-bromo-4'-methylpropionanilide was added 15.0 ml of anhydrous (Linde 3A Sieves) ethanol and the crystalline solid was dissolved with stirring. The solution was passed over a 25g / 30 cm long column of Amberlite IRA - 400 anion exchange resin (base form) column which had been thoroughly washed with anhydrous ethanol. The starting material cyclized to product on the column and was eluted with 200 ml of anhydrous ethanol. Elution of the beta-lactam was monitord by thin layer chromatography. When elution was completed the fractions were combined and evaporated *in* - *vacuo* to give 1.19g (78 %) of required title compound. Crystallization from 2-propanol/hexane afforded analytically pure solid, mp 172-174° (Lit.[8] 174-175°), yield 0.91g (60 % recovery).

IR (Nujol) $\bar{\nu}_{CO}$ 1745 (2-azetidinone); 1692 (4-benzoyl).

Anal. Calcd. for $C_{17}H_{15}NO_2$ (265.29) % C 76.96, H 5.70, N 5.28;

Found C 77.12, H 5.94, N 5.06

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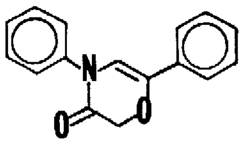
(10)



mp 73-75°; M^+ m/e = 251; IR (Nujol) $\bar{\nu}_{CO}$ 1695

NMR ($CDCl_3$) ppm δ : 4.8 (s, 2H); 6.5 (s, 1H), 7.4 (broad, aromatic, 10H).

(11) In methanol containing 5 % water, the oxazine was the major product by tlc examination ($R_f = 0.52$, silica-gel, 2.5 % $MeOH/CHCl_3$) and by isolation.

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(13) All yields are based upon *isolated*, crystalline, chromatographically homogeneous material. In addition to IR and NMR spectroscopy, the 2-azetidinones and all of the intermediates were characterized by combustion analysis and mass spectral fragmentation. We thank Mr. Paul Unger for the spectral data and Mr. George Maciak for the combustion analyses.

(14) Since the completion of our work a related cyclization has been reported by Professor Wasserman:

H. H. Wasserman, D. J. Hlasta, A. W. Tremper, and J. S. Wu, *Tetrahedron Letters*, 549 (1979).

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