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4-Benzoyloxy-2-azetidinone, a Convenient Synthon for β - Lactam Intermediates

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4 - BENZOYLOXY - 2 - AZETIDINONE, A CONVENIENT SYNTHON FOR β - LACTAM INTERMEDIATES.

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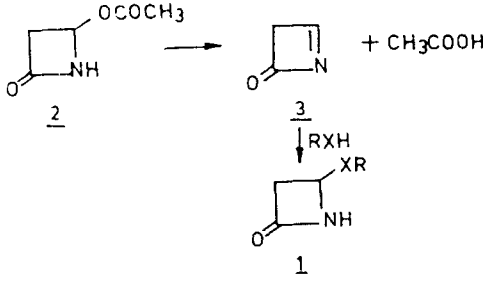
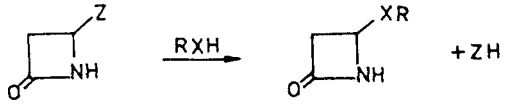
Abstract : 4 - Heterosubstituted - 2 - azetidenones were prepared in excellent yields from 4 - benzoyloxy - 2 - azetidenone(**4**), a much cheaper and stabler substrate compared to more common 4 - acetoxy - 2 - azetidenone (**2**).

4 - Substituted - 2 - azetidenones (**1**) are important intermediates for the synthesis of ß - lactam antibiotics[1] and inhibitors for Human Leukocyte Elastase[2]. Their common starting material is 4 - acetoxy - 2 - azetidinone[3] (**2**) in which the acetate group can be replaced by a variety of oxygen, sulphur and related nucleophiles. The reaction presumably occurs via the reactive acylimine[4] (**3**) which is then trapped by the nucleophile present (Scheme 1).



Scheme 1

The use of **2** is however limited by the following disadvantages : 1) the commercially available material is costly ($ 2.13 per gm. Aldrich) and is not very pure either, 2) the yields in many cases are not satisfactory[5] and 3) very often more than stoichiometric amount of **2** is necessary. This may be attributed to its thermal instability. On the other hand, the analogous 4 - benzoyloxy - 2 - azetidinone (**4**) is a stable crystalline solid, which is commercially available and comparatively much cheaper ($0.34 / mmol,Aldrich). Also **4** is expected to be more reactive than the acetoxy counterpart **2** as benzoate is a better leaving group (pK_a of benzoic acid is 4.2 while acetic acid has a higher pK_a of 4.8[6]). We realized that the better thermal stability coupled with higher reactivity of **4** may be of advantage and may lead to better yields in substitution reactions. Thus we carried out several displacement reactions with various oxygen and sulphur nucleophiles using both **2** and **4** as starting materials and the results are shown in Table 1.



2, Z = $OCOCH_3$
4, Z = OCOPh

5 . XR = SPh
6 . XR = SO_2Ph
7 . XR = $OCH_2CH = CH_2$
8 . XR = $OCH_2C \equiv CH$
9 . XR = $OCH_2CH_2NO_2$
10 . XR = OCH_2CH_2CN
11. XR = OCH_2Ph
12. XR = $OCH_2CH=CHPh$
13. XR = $OCH_2C \equiv C.CH_2OH$

Table 1

Entry	Product	Yield from 2	Yield from 4
1	**5**	78	95
2	**6**	90	93
3	**7**	76	86
4	**8**	56	70
5	**9**	45	76
6	**10**	50	80
7	**11**	45	70
8	**12**	38	78
9	**13**	35	52

Table I reveals that as expected, in all the cases, there was a marked improvement of yield when **4** was used as the synthon. The most striking of them is in the preparations of 4 - oxa derivatives. The other notable feature is shorter reaction time ($\sim$ 6 hrs) in comparison to the time (>20 h) taken when **2** is used as the starting material.

In conclusion we have demonstrated that **4** is a more convenient and economic synthon compared to **2** for the preparation of various 4 - hetero substituted ß - lactams. Presently we are investigating the displacement reactions of **4** with carbon necleophiles and the results will be reported later.

Experimental

The ^{1}H NMR spectra were recorded in varian EM 390 machine at 90 MHz. The IR spectra were obtained from Perkin Elmer (Model 3100) instrument. 4 - Acetoxy and 4 - benzoyloxy - 2 - azetidenone were purchased from Aldrich Chemical Company.

4 - Phenylthio and 4 - phenylsulphonyl azetidenones were prepared following the literature procedures [7,8]. The various 4 - oxa substituted ß - lactams **7** to **13** were prepared by zinc acetate mediated displacement slightly modifying the literature procedure[9] as described below :

Zinc acetate dihydrate (0.5eq) was first converted to the anhydrous form by refluxing with benzene using Dean - Stark apparatus. **2** or **4** was then added followed by the appropriate alcohol (1.1eq) and the solution was refluxed using a vertical condenser till all the starting material is consumed. The solution was then filtered through a plug of Si-gel and the filtrate was evaporated. The oily residue obtained was chromatographed over Si-gel (60 - 120 mesh). Elution with solvents (hexane - ethylacetate) of increasing polarity afforded the title compounds.

The known compounds were characterised by comparison with authentic samples. The new compounds were fully characterised by NMR and IR spectral data which are mentioned below.

For **9** : IR(neat, cm^{-1}) 3255, 2937, 1765, 1662, 1558, 1371, 1285, 1189, 1143, 1096, 842, 771.
^{1}HNMR ($CDCl_3$, δ) 7.20 (1H, **br**, NH), 5.05

(1H, dd, J = 2.2, 5.1 Hz, H - 4), 4.50 (2H, **t**, J = 6.0 Hz, CH_2NO_2), 4.02 (2H, **t**, J = 6.0 Hz, OCH_2), 3.10 (1H, ddd, J = 15.0, 5.1, 1.5 Hz, H - 3), 2.78 (1H, dd, J = 15.0, 2.2 Hz, H - 3).

For **10** : IR(neat, cm^{-1}) 3300, 2931, 2254, 1767, 1547, 1416, 1360, 1139, 943, 620
^1H NMR ($CDCl_3$, δ) 7.30 (1H, **br**, NH), 5.01 (1H, **dd**, J = 5.0, 2.1 Hz, H - 4), 3.61 (2H, **t**, J = 7.0 Hz, CH_2), 3.08 (1H, **ddd**, J = 15.1, 5.0, 1.5 Hz, H-3), 2.78 (1H, dd, J = 15.1, 2.1 Hz, H-3), 2.52 (2H, **t**, J = 7 Hz, CH_2CN).

For **11**: IR (neat, cm^{-1}) 3300, 2934, 1769, 1497, 1456, 1414, 1352, 1285, 1184, 1089, 1032, 952, 743.
^1H NMR ($CDCl_3$, δ) 7.30 (6 H, **br**, Ph, NH), 5.01 (1H, **dd**, J = 5.1, 2.2 Hz, H - 4), 4.40 (2H, **s**, OCH_2), 3.01 (1H, **ddd**, J = 15.2, 5.1, 1.5 Hz, H - 3), 2.70 (1H, **dd**, J = 15.2, 2.2 Hz, H - 3).

For **12**: IR (neat, cm^{-1}) 3365, 2310, 1757, 1447, 1413, 1380, 1268, 1192, 1082, 970, 767, 609.
^1H NMR ($CDCl_3$, δ) 7.80(1H, **br**, NH),5.10 (1H, **dd**, J = 5.2, 2.2 Hz, H - 4), 4.23 (4H, **brs**, OCH_2 . C = C - CH_2), 3.18 (1H, **ddd**, J = 15.2, 5.2, 1.5 Hz, H - 3), 2.80 (1H, **dd**, J = 15.2, 2.2 Hz, H - 3).

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