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Synthesis of N^1-unsubstituted β-lactams : Introducing N^1-(1′-thiophenyl)benzyl as an N-protecting group

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Abstract : A diastereoselective synthesis of (±) *cis*-β–lactams (**5** & **6**) *via* cycloaddition reaction of N^1-(α-thiophenyl)benzyl imines (**3**) with acid chlorides (**4**) in the presence of triethyl amine is described. Deprotection of N^1-(α-thiophenyl)-benzyl group was achieved in good yields by oxidation using potassium persulfate.
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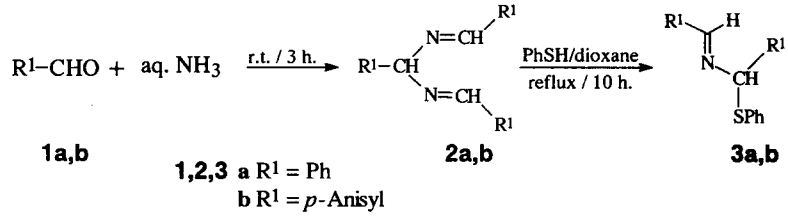
N-Unsubstituted β-lactams are intermediates in the synthesis of monocyclic and bicyclic β-lactam antibiotics.[1] As a part of our ongoing project on β-lactam synthon method[2] for the synthesis of natural and unnatural products, we were interested in developing methods for the preparation of NH-β-lactams. Generally, the selection of N^1-protective groups in β-lactam synthesis is based on the ease of selective removal of these groups at the appropriate stage. Benzyl,[3] allyl,[4] silyl[5] and *p*-methoxyphenyl[6] groups are often used for N^1-protection and can be removed under various conditions to get N-H β-lactams. In this communication we report the utility of (α-thiophenyl)benzyl as an N^1-protective group and its oxidative removal using potassium persulfate to yield N-unsubstituted β-lactams.

The starting hydrobenzamide[7] [1-phenyl-N,N′-bis(phenylmethylene)methane diamine (**2a**) & 1-*p*-anisyl-N,N′-bis-(*p*-anisylmethylene)methane diamine (**2b**)] were readily obtained in excellent yields by stirring a mixture of aromatic aldehydes (**1a,b**) with a 10 fold excess of aq. ammonia solution (30%) for 3 h. The reaction of **2a,b** with thiophenol in refluxing dioxane afforded imines **3a,b** in good yield[8] (Scheme 1).

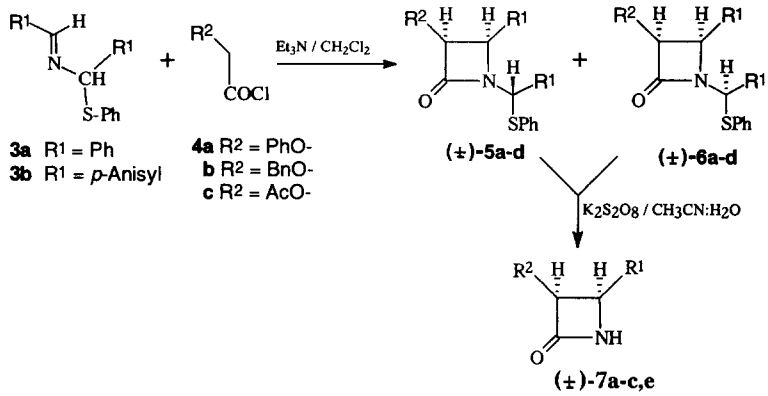
Scheme 1



1a,b **1,2,3** **a** R^1 = Ph **b** R^1 = *p*-Anisyl **2a,b** **3a,b**

Cycloaddition reaction of the imines **3a,b** with various acid chlorides (**4a-c**) in presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-β-lactams[9] (**5a-d** & **6a-d**)[10] in 50-79% yield (Table 1, Scheme 2). The diastereomeric ratio was determined by the HPLC[11] and ^{1}H NMR analyses of crude reaction mixtures. The major (**5**) and minor (**6**) diastereomers were separated by crystallization.

Sheme 2



The relative stereochemistry of the major diastereomer **5a** was established as 3*S*, 4*R*, 1′*S* by single crystal X-ray analysis[12] (Fig. 1).

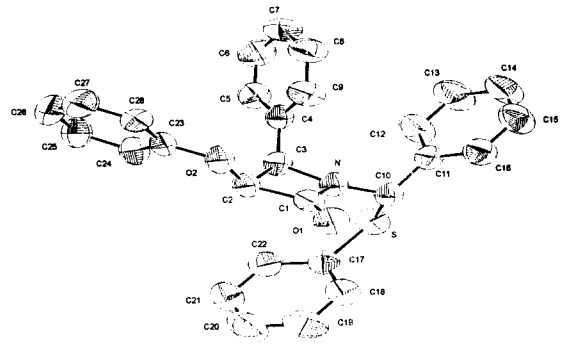


Fig. 1. The ORTEP diagram of the β-lactam **5a**

The chiral acid chloride (**4d**, R^2 = *l*-menthyl), on reaction with imine **3a** under similar reaction conditions gave a diastereomeric mixture of four *cis*-β-lactams in the ratio of 35:35:18:12 (HPLC, ^{1}H NMR). One of the diasteromers was isolated in the pure form by crystallization (acetone-petroleum ether) from the mixture.

Individual diastereomers **5** or **6**, or a mixture of **5** & **6**, reacted with potassium persulfate (aceto-nitrile/water, reflux, 4 h) to give the N-unsubstituted β-lactams (**7**)[13] in good yields (Scheme 2, Table 1).

Table 1. Synthesis of β-lactams **5a-e** & **6a-e** and N^1-unsubstituted β-lactams **7a,b,d,e.**

Compd.	R^1	R^2	Compound 5 & 6			Compound 7	
			Yield[a] (%)	Ratio[b] of 5 & 6	m.p. of 5 (°C)	yield[c] (%)	m.p. (°C)
a	Ph	PhO	74	74:26	214-215	70	159-160
b	Ph	BnO	58	64:36	119-120	64	188-189
c	Ph	AcO	50	74:26	153-154	--	--
d	Anisyl	PhO	79	83:17	157-159	70	165-167
e	Ph		62	35:35:18:12[d]	158-160[e]	65	173-174[f]

[a] Isolated yields of diastereomeric mixture of **5** & **6**; [b] Ratio of **5** & **6** from HPLC and ^1H NMR spectral data; [c] Isolated yield; [d] Ratio of four diastereomers; [e] M.p. of one of the pure diastereomer isolated from the mixture by crystallization; [f] Prepared from the pure diastereomer obtained by crystallization.

In summary, we have introduced (α-thiophenyl)benzyl as a novel N-protective group in β-lactam molecules, which can be removed *via* mild oxidative conditions tolerated by most common organic functional groups.

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9. The formation of the *cis-* isomer only was observed as confirmed from ^{1}H NMR analysis ($J_{3,4}$ = 4-5 Hz) of the crude reaction mixture.

10. *Typical procedure for β-lactams 5a & 6a* : A solution of the acid chloride (**4a**, 320 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of imines (**3a**, 450 mg, 1.5 mmol) and triethylamine (600 mg, 6 mmol) in CH_2Cl_2 (15 mL) at 0°C. The reaction mixture was then allowed to warm to r.t. and stirred further for 13 h. The usual work gave a diastereomeric mixture of β-lactams (**5a** & **6a**) in 74% yields. The major diastereomer **5a** was separated by crystallization from pet. ether - acetone.

    (5a) : M. p. 214-215 °C. ^{1}H NMR : δ 5.0 (d, J = 5 Hz, 1H); 5.2 (d, J = 5 Hz, 1H); 6.47 (s, 1H); 6.8 (d, J = 10 Hz, 2H); 6.83 (t, J = 10 Hz, 1H); 6.95 - 7.70 (m, 17H). ^{13}C NMR : 61.20, 62.34, 81.22, 115.64, 122.00, 127.55, 127.85, 128.08, 128.22, 128.57, 128.81, 129.08, 129.42, 132.49, 133.03, 135.07, 156.87, 165.98. IR : 1740 cm^{-1}. Anal. for Cald $C_{28}H_{23}O_2NS$: C, 76.86; H, 5.30; N, 3.20; S, 7.33. Found : C, 76.68; H, 5.37; N, 3.27.

    (6a) : Isolated as an oil. ^{1}H NMR : δ 4.45 (d, J = 5 Hz, 1H); 5.2 (d, J = 5 Hz, 1H); 6.15 (s, 1H); 6.6 (d, J = 10 Hz, 2H); 6.85 (t, J = 10 Hz, 1H); 6.95 - 7.60 (m, 17H). ^{13}C NMR : 63.23, 63.93, 80.30, 115.56, 121.95, 127.84, 128.06, 128.64, 128.75, 129.05, 129.44, 132.28, 133.04, 133.54, 135.78, 156.79, 164.91. IR : 1740 cm^{-1}.

11. HPLC : Perkin-Elmer 410-pump. H.P. 1050 MWD at 254 nm connected to H-P 3396 Ser-II integrater. Col. MN-C-18, 8 mm, 4 mm X 100 mm length. Solvent system (v/v): 80 : 20 (MeOH :H_2O) flow rate 1.5 mL/min.

12. For details see : Srirajan, V.; Bhawal, B.M; Puranik, V.G. *Acta. Cryst. C* (in press).

13. *Typical procedure for 3-Phenoxy-4-phenylazetidin-2-one (7a)* : A mixture of **5a** (0.088 g, 0.2 mmol), acetonitrile (8 mL), water (3 mL), and potassium persulfate (0.162 g, 0.6 mmol) was refluxed for 4 h. The solvent was removed by distillation under reduced pressure and the residue on usual work up gave **7a** in 70% yield. M.p. 159-160 °C. ^{1}H NMR : δ 5.05 (d, J = 4.8 Hz, 1H,); 5.5 (dd, J = 4.8 & 5.5 Hz, 1H,); 6.6 (bs, 1H,); 6.8 (two d, J = 9 Hz, 2H,); 6.9 (t, J = 9 Hz, 1H,); 7.10-7.40 (m, 7H,). IR : 2800 - 3500, 1770 cm^{-1}. Anal. Cald for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found : C, 75.51; H, 5.73; N, 5.62.

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