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Trans Diastereoselective Synthesis of 3-Alkyl Substituted β-Lactams *via* the Acid Chloride-Imine Reaction of Nonactivated Acid Chlorides

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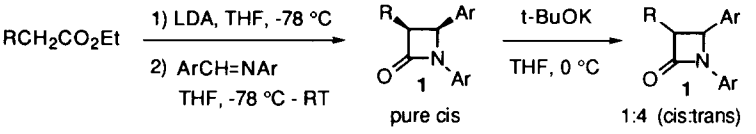
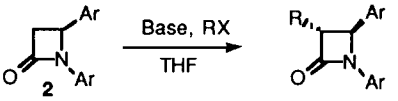
Abstract: New conditions for the acid chloride-imine reaction of nonactivated alkyl acid chlorides provide 3-alkyl substituted β-lactams in good yields with high trans selectivity.

We required ready access to both cis and trans diastereomers of 3-alkyl β-lactams such as **1** to further our SAR studies in the area of cholesterol absorption inhibition.[1] The requisite cis β-lactams are readily accessible *via* the well established ester enolate-imine condensation procedure.[2] Initially we prepared the corresponding trans diastereomers by potassium t-butoxide epimerization of cis **1**. Unfortunately this process typically gave a 1:4 (cis:trans) mixture of β-lactams. Though the diastereomers were separable by recrystallization, flash chromatography or more frequently by HPLC, we desired a highly selective route to trans β-lactams.



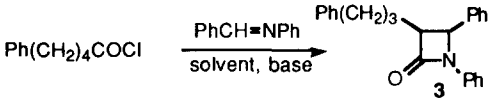
Attempts to prepare trans 3-alkyl β-lactams by alkylation of **2**[3] were only successful with MeI as the electrophile (88%, LDA, -78 °C); other aliphatic halides (Br, I) were unreactive at temperatures below -30 °C regardless of base (LDA, LICA or LHMDS) or additives (HMPA). Warming the reaction above - 30 °C resulted in decomposition of **2**.



The acid chloride-imine reaction has been extensively employed in the preparation of β-lactams.[4] In most cases acid chlorides activated with N, O, S, halogen, aryl or alkenyl at the alpha position are utilized and cis selectivity is typically observed. In contrast there have been relatively few examples of the use of nonactivated aliphatic acid chlorides in the synthesis of β-lactams.[5] Bose reported trans selectivity when propionyl chloride was added to a methylene chloride solution of imine (PhCH=NPh) and triethylamine (50% yield).[6] Application of this methodology to substrates appropriate to our needs

afforded β-lactam **3** with excellent trans selectivity but in low yield ~14% (Table 1, entry 2). We found that by modification of reaction conditions (solvent, base, temperature), 3-alkyl β-lactams could be conveniently prepared with excellent trans stereoselectivity and good chemical yield. The stereoselectivity was determined by ^{1}H NMR (trans: ~4.6 ppm, 1H, d J=2 Hz, CHN; cis: ~5.2 ppm, 1H, d, J=5-6 Hz, CHN) and/or HPLC. The reaction is performed in higher boiling solvents at relatively dilute concentrations (0.1M to imine) and tertiary amines are employed as bases as exemplified by entries 4, 6 and 7.[7] The use of more concentrated conditions leads to the formation of side products and lower yields of β-lactams. Higher yields of β-lactam may be obtained if excess acid chloride is employed (entry 8), however in some cases products presumably arising from the self condensation of excess acid chloride may complicate the isolation of β-lactams. Use of pyridine as the base results in a loss of stereoselection and a reduction in yield (entries 5 and 9). However, employment of pyridine as both the base and solvent improves the chemical yield, although stereoselectivity is poor (entry 10).

Table 1: Modification of Reaction Conditions.[a]



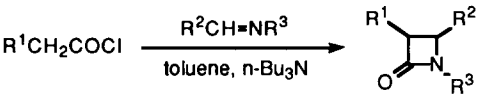
Entry	Solvent (BP)	Base	Temp.	cis: trans[b]	Yield (%)[c]
1	CH_2Cl_2 (40 °C)	Et_3N	RT	- -	0
2	CH_2Cl_2	Et_3N	reflux	trans[d]	14
3	$Cl(CH_2)_2Cl$ (83 °C)	Et_3N	reflux	trans[d]	40
4	$Cl(CH_2)_2Cl$	n-Bu_3N	reflux	trans[e]	58
5	$Cl(CH_2)_2Cl$	Pyridine	reflux	60:40	28
6	Toluene (111 °C)	Et_3N	reflux	4:96	51
7	Toluene	n-Bu_3N	reflux	8:92	57
8	Toluene	n-Bu_3N	reflux	5:95	76[f]
9	Toluene	Pyridine	reflux	55:45	<5[g]
10	Pyridine (115 °C)	Pyridine	reflux	58:42	80

a) RCOCl (1.0 eq) added to a soln of imine (1.0 eq) and base (2.0 eq) in solvent (0.1M to imine) at the indicated temperature, overnight. b) ratio determined by ^{1}H NMR (400 MHz) of crude reaction mixtures. c) Isolated yields, purified by flash chromatography on silica gel. d) cis diastereomer not detected by 400 MHz ^{1}H NMR of crude reaction mixture. e) Trace of cis diastereomer, not integratable by NMR. f) RCOCl (2.0 eq) added to a soln of imine (1.0 eq) and base (3.0 eq) in solvent (0.1M to imine) at the indicated temperature, overnight. g) determined by NMR, not isolated

In most cases, imine formation and the subsequent acid chloride-imine reaction are carried out sequentially in a one pot operation when toluene is utilized as the solvent. However, in a few examples the one pot procedure fails. In those cases recrystallization of the imine prior to use in the acid chloride-imine reaction, usually leads to successful β-lactam formation. The generality of the method is

demonstrated in Table 2. R^1 may be alkyl or branched alkyl. R^2 and R^3 can be aryl substituted with electron donating or withdrawing groups. The potent cholesterol absorption inhibitor, Sch 47949, is easily prepared by this route, initially as a 3:97, cis:trans mixture (entry 9). A single recrystallization provides pure trans Sch 47949. The possibility of epimerization of initially formed cis to trans β-lactams was ruled out by refluxing tributylamine and a pure cis β-lactam in toluene. No epimerization was observed by ^1H NMR. The use of nonactivated acid chlorides can also be extended to imines where R^2 or $R^3 \neq$ Ar entries (6, 12 and 13). When R^3 is benzyl trans selectivity is maintained (entry 6), subsequent hydrogenation affords trans 3-alkyl-N-unsubstituted β-lactams. Entries 12 and 13 provide rapid access to β-lactams readily amenable to elaboration at C-4. Notably, in these examples the acid chloride-imine reaction proceeds at room temperature and cis selectivity is observed.[5c]

Table 2: 3-Alkyl ß-Lactams via Acid Chloride-Imine reaction.[a]



Entry	R^1	R^2	R^3	cis:trans[b]	Yield(%)[c]
1	CH_3	Ph	Ph	4:96	37
2	CH_3CH_2	Ph	Ph	5:95	40
3	$(CH_3)_2CH$	Ph	Ph	5:95	39
4	t-Bu	Ph	Ph	5:95	41
5	$Ph(CH_2)_3$	Ph	Ph	8:92	57
6	$Ph(CH_2)_3$	Ph	$PhCH_2$	4:96	65
7	$Ph(CH_2)_3$	4-MeOPh	Ph	2:98	88
8	$Ph(CH_2)_3$	Ph	4-MeOPh	5:95	58
9	$Ph(CH_2)_3$	4-MeOPh	4-MeOPh	3:97	45
10	$Ph(CH_2)_3$	4-FPh	Ph	4:96	56
11	$Ph(CH_2)_3$	Ph	4-FPh	5:95	61
12	$Ph(CH_2)_3$	COPh-4-OMe	4-MeOPh	cis	83[d]
13	$Ph(CH_2)_3$	CHO	4-MeOPh	cis	90[e]

a) Acid chloride (1.0 eq) is added to a refluxing solution of imine (1.0 eq) and n-Bu_3N (2.0 eq) in toluene (0.1 M to imine). Mixture is refluxed overnight b) Cis/trans ratios were determined by ^1H NMR (400 MHz) of crude reaction mixtures. c) Isolated yields, purified by flash chromatography on silica gel. d) Acid chloride (2.0 eq) is added to a room temperature solution of imine(1.0 eq) and n-Bu_3N (2.2 eq) in toluene. e) Acid chloride (2.0 eq) is added to a room temperature solution of 4-MeOPhN=CH-CH=NPh-4-OMe in toluene[5c], Acid hydrolysis of reaction mixture provides R_3= CHO.

Numerous attempts have been made to explain and predict the stereochemical outcome of the acid chloride-imine reaction.[8] As evidenced by the data presented in the Tables 1 and 2, the factors affecting

the stereochemistry are complex. Diverse reaction paths appear to be operational that are sensitive to the substitution of the acid chloride and imine, temperature, base, solvent and concentration.

Although the acid chloride-imine reaction is a well established method for the synthesis of β-lactams, modifications which improve the yield, provide stereocontrol, shorten synthetic routes and/or lead to previously inaccessible β-lactams are important in light of the biological significance of β-lactams.[1,9] The methodology described in this paper fills a gap in the existing arsenal of methods to prepare β-lactams by providing rapid access to 3-alkyl substituted β-lactams with high trans stereoselectivity without the need for the introduction and removal of activating groups at the alpha position of the acid chloride. The tolerance of this method to substitution changes coupled with the stereoselectivity observed, should make it useful to those working in this area.

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7. **General Methods:** The appropriate aldehyde (5.0 mmol) and amine (5.0 mmol) in toluene (~0.1 M to amine) are refluxed with azetropic removal of water via a Dean-Stark trap. Imine formation is monitored by ^{1}H NMR of a small aliquot of the reaction (~10 ppm, CHO, imine ~8 ppm, CH=N). Upon complete imine formation, base (10.0 mmol) followed by the acid chloride (5.0 mmol, neat or in toluene) are added sequentially and reflux is continued overnight.[notes1 and 2] The solution is cooled to room temperature, quenched by the addition of 1M HCl and stirred ~15 min to hydrolyze any unreacted imine. The resulting mixture is transfered to a separatory funnel, diluted with ethyl acetate, washed with 1M HCl, $NaHCO_{3(sat.)}$, water and brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel chromatography.[note 3] Representative data given for **1,4-Bis-(4-Methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone (Entry 9, Table 2): Trans diastereomer Rel (3R, 4S),^{1}H NMR:** (300 MHz, CD_3Cl) 7.23(9H, m, Ar), 6.90(2H, d, J=9Hz, Ar), 6.78(2H, d, J=9Hz, Ar), **4.56 (1H, d, J=2Hz, CHN)**, 3.81(3H, s, OCH_3), 3.74(3H, s, OCH_3), 3.07(1H, m, CHCO), 2.65(2H, t, J=7Hz, $ArCH_2$), 1.90(4H, m, CH_2CH_2). **Anal.** Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.43; H, 6.48; N, 3.32. **Cis diastereomer Rel (3R, 4R): ^{1}H NMR:** (300 MHz, CD_3Cl) 7.20(7H, m, Ar), 6.99(2H, d, J=7Hz, Ar), 6.87(2H, d, J=9Hz, Ar), 6.79(2H, d, J=9Hz, Ar), **5.11(1H, d, J=6Hz, CHN)**, 3.83(3H, s, OCH_3), 3.75(3H, s, OCH_3), 3.52(1H, dt, J=6,7 Hz,CHCO), 2.43 (2H, m, $ArCH_2$), 1.43 (4H, m, CH_2CH_2). **Anal.** Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.44; H, 6.42; N, 3.29. **HPLC**: Dynamax 60A Silica Column, 10% EtOAc/hexanes, 1.5 mL/min, Trans; Rt= 19.0 min, Cis; Rt= 20.8 min. **Note 1**: Progress of the reaction is monitored by ^{1}H NMR (aldehyde CH ~ 10 ppm and imine CH ~ 8 ppm vs β-lactams C-4 proton 5.2-4.5 ppm). If sigificant quantity of imine is evident additional base and acid chloride may be sequentially added. **Note 2**: If the one pot procedure fails, prepare and recrystallize the imine prior to use in the acid chloride imine reaction. **Note 3:** If unreacted aldehyde and ß-lactam are not separable by TLC, dissolve reaction mixture in THF dilute by 50% with methanol and treat with excess sodium borohydride (2 molar eqs) to reduce aldehyde to alcohol which is usually easily removable from ß-lactam by chromatogaphy. When gas evolution ceases, quench with 1M HCl, dilute with ethyl acetate, wash with 1M HCl, water and brine, dry over Na_2SO_4, concentrate and chromatograph on silica gel.
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