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A NOVEL, GENERAL, TOTALLY STEREOSELECTIVE ONE-POT SYNTHESIS OF *cis*-3-SUBSTITUTED 4-FORMYLAZETIDIN-2-ONES

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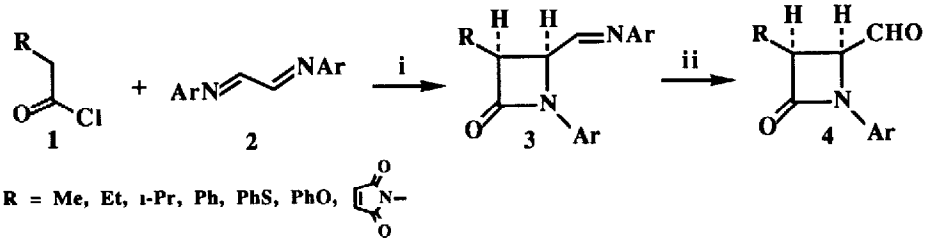
Summary. *A general , totally stereoselective one-pot synthesis of* cis-*3-substituted-4-formylazetidin-2-ones based upon the reaction of acid chlorides and 1,4-*bis-*(4-methoxyphenyl)-1,4-diazabuta-1,3-diene, as synthetic equivalent of the corresponding unknown α–formylimine, has been developed*

Appropriately *cis*-substituted 4-formylazetidin-2-one derivatives are versatile building blocks[1] for the synthesis of biologically active β-lactam antibiotics,[2] including *trans*- and *cis*-carbapenems,[3] monobactams and isocepham antibiotics [4] Routes to such valuable intermediates have hitherto involved either oxidative degradation or multistep functional group transformation from appropriate 4-substituted β-lactams (ie, 4-styryl -,[1b,1c,1e,5] 4-oxiranyl-,[1f] or 4-alkoxycarbonyl-β-lactams[1a,6])

The use of 1,4-diaza-1,3-dienes (α-diimines) in synthesis of 4-formylazetidin-2-ones by reaction with ester enolates has been reported by us[7] and others[8] However, this approach lacks generality since only a limited number of enolates (ie, α-disubstituted enolates) react to give β-lactams We now report, by using the acid chloride-imine approach,[9] a new, efficient, and one-pot procedure for the totally *cis*-stereoselective synthesis of 4-formylazetidin-2-ones, **4**, having alkyl, aryl or electron-withdrawing substituents (oxygen, sulfur or nitrogen) at C-3 (see **Scheme**) This method is based on the use of 1,4-*bis*-(4-methoxyphenyl)-1,4-diazabuta-1,3-diene (glyoxal diimine) **2**[10] as synthetic equivalent of the corresponding unknown α-formylmethanеimine Thus, treatment of the easily accesible α-diimine **2**[11] with several acid chlorides **1** in toluene at room temperature and in the presence of triethylamine afforded *cis*-4-imino-β-lactams, **3**,[12] which were *in situ* hydrolyzed in mild acid conditions, yielding the desired *cis*-4-formyl-β-lactams, **4**, in good to excellent yields (see **Table**)

It is noteworthy that exclusive *cis*-stereochemistry[13] was observed for all β-lactams **4** prepared It is known that *cis*- stereoselectivity is favoured when the bulk of the imine *N*-substituent is increased[14] or if 1-aza- or 2-aza-1,3-dienes are used as the imine moiety[15] in the acid chloride-imine approach to β-lactams The

stereochemical outcome found in the reaction described herein also shows a clear preference (to a *totally stereoselective* extent) for the *cis* stereochemistry when 1,4-diaza-1,3-diene, **2**, is used



i Et_3N, toluene, RT, 5 min - 6 h
ii. 5 % aqueous HCl, RT, 90 min

Scheme

On the other hand, no general methodology for the preparation of 3-alkyl-β-lactams (by using the acid chloride-imine approach) has been reported to date, low yields or low selectivities being usually obtained [3b, 16,17] The procedure in here allows for the synthesis of this class of compounds in highly efficient and totally stereoselective fashion [18] Therefore, the above results show a significant improvement in scope and efficency for diimine **2** related to other α-formylimine equivalents previously described An experimental procedure for the synthesis of compounds **4** is as follows A solution of the acid chloride [2 mmol for **3a-3d** or 1 mmol for **3e-3f**] in toluene (5 ml) was added dropwise to a vigorously stirred suspension of diimine **2** (1 mmol) in toluene (10 ml) and triethylamine [2 2 mmol for **3a-3d** or 1 1 mmol for **3e-3f**] at room temperature under argon The resulting mixture was stirred until complete reaction Then, 5 % aqueous HCl (10 ml) was added and the heterogeneous mixture was vigorously stirred for 1 5 hours The organic layer was diluted with toluene (25 ml) and successively washed with 5 % HCl (2 x 10 ml), water (10 ml), and brine (10 ml), and dried ($MgSO_4$) Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography (silica-gel, 70-230 mesh) or crystallization to yield **4**

In conclusion, the reaction of acid chlorides and 1,4-*bis*-(4-methoxyphenyl)-1,4-diazabuta-1,3-diene, as synthetic equivalent of the corresponding α–formylimine, provides a general and efficient easy entry into *cis*-3-substituted 4-formylazetidin-2-ones which in turn are suitable building blocks for β-lactam antibiotics The application of this methodology to more functionalized acid chlorides and other diimines, and their use in optically active β-lactam synthesis in now under progress

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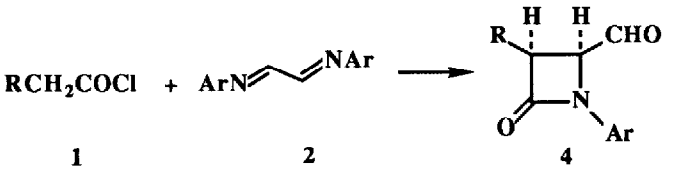
Table

One-Pot Preparation of* cis-*4-formylazetidin-2-ones



1 2 4

Compound[a,b]	R	Yield[c]	M.p./ °C[d]
4a	Me	90	118-120
4b	Et	73	90-91[e]
4c	*i*-Pr	80	91-93
4d	Ph	85	154-156
4e	PhS	80	153-154
4f	PhO	70	109-110
4g	Md[f]	55	200-202

[a] All compounds **4** were racemic mixtures and gave satisfactory spectral and analytical data [b] In all cases Ar = 4-$MeOC_6H_4$ [c] Yield of pure, isolated product based on diimine **2** [d] Recrystallized from EtOAc -hexane [e] Lit [6] m p 92-94 °C [f] Md = maleimidyl

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12. Although 4-ımıno-β-lactams **3** can be ısolated yıeldıng the correspondıng 4-formyl-β-lactams, **4**, upon hydrolysıs wıthout loss of stereoselectıvıty, the overall yıeld ıs often better for the one-pot procedure

13. Determıned by hıgh field (300 MHz) ^{1}H-NMR analysıs of the crude reactıon mıxtures No traces of the *trans* - ısomer were detected ın any case

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18. β-Lactam formatıon was not observed ın the reactıon of dıımıne **2** and acetyl chlorıde In thıs case complex reactıon mıxtures were obtaıned For an analogous behavıor see, for example (a) Iwamura, H , Tsuchımoto, M , Nishımura, S *Tetrahedron Lett* **1975**, 1405 (b) Maujeau, A , Chuche, J *Tetrahedron Lett* **1976**, 2905

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