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Indium triflate catalyzed reaction of diisopropyl diazomethylphosphonate with imines as a new approach to *cis*- and *trans*-aziridine-2-phosphonates

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Abstract—A new and efficient synthesis of *cis*- and *trans*-aziridine-2-phosphonates by metal-catalyzed aziridination reaction of diisopropyl diazomethylphosphonate and substituted aryl imines is reported. By exploring the influence of different Lewis acids employed as catalysts, imine nitrogen substituents, and the solvent effects we conclude that the best results are obtained when *N*-diphenylmethyl-substituted benzylimines are reacted with diisopropyl diazomethylphosphonate in methylene chloride at 0 °C in the presence of $In(OTf)_3$ as catalyst.
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2-EWG-substituted aziridines (Fig. 1) have emerged in recent years as useful building blocks for the synthesis of biologically important classes of compounds. Indeed, aziridine-2-carboxylates are widely utilized for the preparation of substituted α-aminoacids, diamine- and β-lactam derivatives.[1] Comparatively, less attention has been devoted to aziridine-2-phosphonates,[2] a bioisosterically related class of compounds, also useful as intermediates in the synthesis of biologically valuable molecules such as α-aminophosphonates, important in medicine and agriculture as enzyme inhibitors, antibiotics, clonal antibodies, pesticides and herbicides.[3]

Among the strategies developed for the preparation of aziridinyl-2-carboxylate derivatives, the metal-catalyzed reaction of ethyl diazoacetate (EDA) with imines has

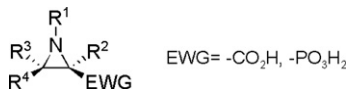

Figure 1. 2-EWG-substituted aziridine.

attracted considerable attention.[4] In this Letter, we describe the preparation of diisopropy-2-phosphonates by an analogous approach, that is, the hitherto unreported metal-catalyzed decomposition of a diazomethylphosphonate in the presence of aldimines.

In the planning of our work, we have made use of the knowledge gained in the optimization of the EDA-imines aziridination reaction and, in particular, in the definition of the crucial role played by the catalyst in the reaction outcome.[4c–e,g,n,p] In our case, in order to evaluate the effect of the catalyst on the aziridination reaction, we have investigated at first the reaction of diisopropyl diazomethylphosphonate (DIDAMP **1**)[5] with *N*-benzylidene aniline **2a**[6] in the presence of catalytic amounts of Lewis acids in methylene chloride both at room temperature and at 0 °C (Table 1).[7] The results show that *cis*- and *trans*-aziridine-2-phosphonates **3a** and **4a** can be formed in good to moderate yields with a variable diastereoselectivity. In particular, the best result in terms of both yield and diastereoselectivity was obtained when $In(OTf)_3$ was used as catalyst. Indeed, decomposition of DIDAMP **1** with **2a** in methylene chloride catalyzed by $In(OTf)_3$ at 0 °C (entry 6) resulted exclusively in the formation of diisopropyl *cis*-*N*-phenyl-3-phenylaziridin-2-ylphosphonate **3a** in 40% yield. Cis-selectivity, albeit with lower yield (20%), has also

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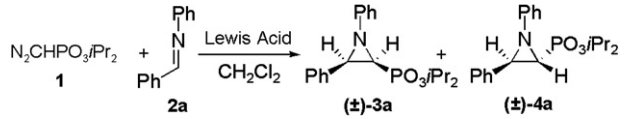
Table 1. Aziridine-2-phosphonates from DIDAMP **1** and *N*-benzylidene aniline **2a** catalyzed by various Lewis acids



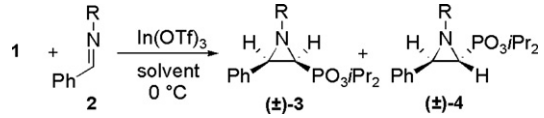
Entry	Lewis acid[a]	Temp	Yield[b] (%)	Cis/trans (**3a**/**4a**)[b]
1	$Zn(OTf)_2$	rt	66	1/1
2	$Cu(OTf)_2$	rt	>5	n.d.[c]
3	$In(OTf)_3$	rt	39	13/1
4	$Zn(OTf)_2$	0 °C	64	4/1
5	$Cu(OTf)_2$	0 °C	20	Cis only
6	$In(OTf)_3$	0 °C	40	Cis only

[a] 10 mol % with respect to imine.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] n.d. = not determined.

been achieved when **2a** was reacted with DIDAMP **1** in the presence of 10% $Cu(OTf)_2$ at 0 ° C (entry 5).

On the basis of these results, we then decided to use $In(OTf)_3$ as catalyst in order to examine both the influence of imines N-substitution and the solvent effect on the reaction outcome. Thus, a number of *N*-benzylidene amines **2b–d**[6] were reacted with **1** in the presence of 10% $In(OTf)_3$ in methylene chloride at 0 °C. As summarized in Table 2, the formation of *cis*-aziridines was again favoured. In particular, the aziridination reaction of *N*-(*p*MeOPh)- and *N*-(*p*CF_3Bn)-benzylimines **2b** and **2c** (entries 1 and 2) yielded diastereoselectively the corresponding *cis*-aziridines **3b** and **3c** in similar yields, whereas **2d** (entry 3) afforded both *cis*- and *trans*-aziridines **3d** and **4d** in 4/1 ratio and in higher overall yields. The influence of the solvent in the $In(OTf)_3$-catalyzed aziridination of DIDAMP **1** and (*N*-benzyhydryl)-benzylimine **2d** was explored next (Table 2). While the use of toluene (entry 4) led to similar results with respect to methylene chloride (entry 3), when the reaction was performed in THF longer reaction times were required (70 h vs 6 h) and a lower overall yield was obtained.

Table 2. $In(OTf)_3$-catalyzed aziridination reaction of DIDAMP **1** with differently N-substituted imines and solvents



Entry	**2**	R	Solvent	Cis/trans[a]	Isolated yield[b] (%)	
				(**3**/**4**)	**3**	**4**
1	**b**	*p*MeOPh	CH_2Cl_2	1/1	42	
2	**c**	*p*CF_3Bn	CH_2Cl_2	n.d.[c]	40	
3	**d**	$CHPh_2$	CH_2Cl_2	13/1	64	19
4	**d**	$CHPh_2$	Toluene	4/1	60	15
5	**d**	$CHPh_2$	THF	Cis only	39	11

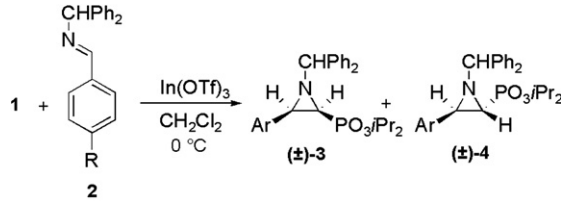
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Calculated after purification by flash chromatography on silica gel.
[c] n.d. = not determined.

We assume that this diminished catalytic power of the metal can be ascribed to the solvating properties of THF.

Having established that the best conditions for aziridination reaction with DIDAMP **1** involved the use of $In(OTf)_3$ as catalyst in methylene chloride at 0 °C, we decided to apply this system to study the effect on the reaction rate of diverse *para*-substituents at the benzylic moiety of imine.[6] The results reported in Table 3 indicate that the aziridines were formed in high overall yields (77–91%), and the reaction rate was influenced by the nature of the substituent at the benzylic group. In particular, we found out that compounds **2g–i** reacted faster with respect to unsubstituted benzylimine **2d**, while *p*Me-benzylimine **2e** reacted significantly slower (24 h). This behaviour could reflect a positive effect of electron-withdrawing substituents and a negative influence of electron-donor substituents on the benzylimine reactivity. The best yield (91%) and diastereoselectivity (6:1) was obtained for **2g** (Table 3, entry 4).

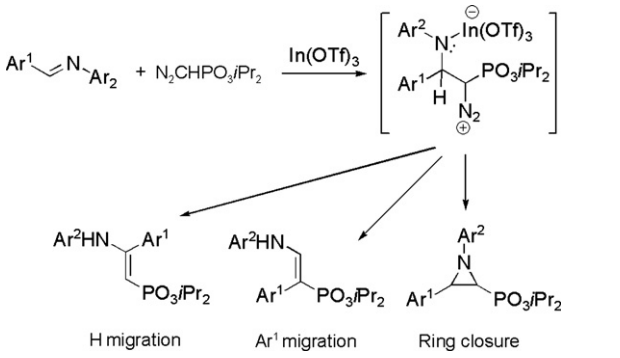
Two different mechanisms have been proposed for the metal-catalyzed aziridination reaction with EDA and imines depending on the properties of the metal.[4g] In the case of copper and rhodium catalysts the metal reacts with EDA to form a metal-carbene complex that attacks the imine nitrogen and affords the final aziridines through a planar azomethine ylide intermediate. Differently, $Zn(OTf)_2$, BF_3, $AlCl_3$ and $TiCl_4$ act as Lewis acids by activating imine for a nucleophilic attack by EDA at the α-carbon atom (most likely the rate-determining step) and the aziridine products are obtained after a second nucleophilic substitution with N_2 as the leaving group.[4f] It is noteworthy that some experimental evidences that we found in the reaction of DIDAMP **1** with aldimines in the presence of $In(OTf)_3$ as catalyst, such as the lack of DIDAMP dimers formation (products derived from carbene coupling), the isolation of

Table 3. Influence of various substituents at the benzyl moiety of the imine in the aziridination reaction



Entry	**2**	R	Time (h)	Cis/trans	Isolated yield[b] (%)	
				(**3**/**4**)[a]	**3**	**4**
1	**d**	H	6	4/1	58	19
2	**e**	*p*Me	24	4/1	40	16
3	**f**	*p*AcO	4	4/1	68	18
4	**g**	*p*Cl	3	6/1	79	12
5	**h**	*p*CF_3	2.5	2/1	54	28
6	**i**	*p*NO_2	2.5	2/1	53	27

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Calculated after purification by flash chromatography on silica gel.

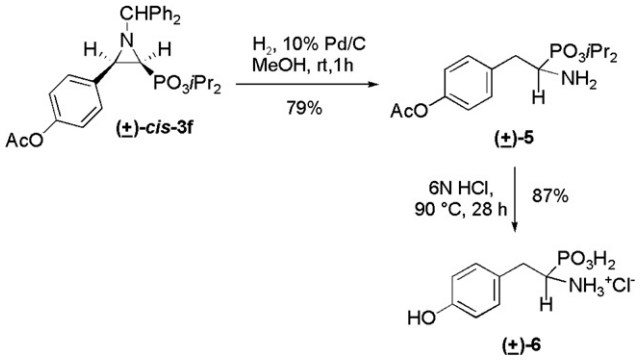


Scheme 1. Proposed mechanism for the $In(OTf)_3$ catalyzed aziridination reaction of aldimines with DIDAMP.

enamines as by-products, as well as the imine nitrogen substituent effect on the reaction rate could be compatible with the latter mechanism (Scheme 1). Moreover, those factors weakening the catalytic efficacy of the metal salt, such as the metal cation solvatation, were found to negatively affected the yield and the rate of the reaction.

Finally, we applied our synthetic route to (*N*-benzhydryl)-aziridine-2-phosphonates to the preparation of [1-amino-2-(4-hydroxy-phenyl)-ethyl]-phosphonic acid hydrochloride,[8] a phosphonic acid analog of the tyrosine (Scheme 2, (±)-**6**).[9] Hydrogenolytic cleavage of aziridine **3f**, obtained as reported before (Table 3, entry 3), was achieved in methanol under hydrogen flow in the presence of 10% palladium on carbon at room temperature to give the corresponding diisopropyl α-aminophosphonate (±)-**5** in 80% yield. Finally, hydrolysis of (±)-**5** by treatment with 6 N HCl at 90 °C afforded (±)[1-amino-2-(4-hydroxy-phenyl)-ethyl]-phosphonic acid hydrochloride (±)-**6**, in 87% yield.

In summary, a new catalytic method for the preparation of *cis*- and *trans*-aziridine-2-phosphonates has been developed. By examining the effects of the imine nitrogen substituent, that of the Lewis acid employed as catalyst, and the influence of the solvent on the reaction outcome, it is possible to conclude that the best results are obtained when (*N*-benzhydryl)-imines are let to react with DIDAMP **1** in the presence of $In(OTf)_3$ as catalyst



Scheme 2. Synthesis of (±)[1-amino-2-(4-hydroxy-phenyl)-ethyl]-phosphonic acid hydrochloride (±)**6**.

in methylene chloride at 0 °C. The utilization of the methodology above described for the preparation of aziridine-2-phosphonates of pharmaceutical interest is under way and the results will be reported in due time.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.042.

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