SYNTHESIS AND APPLICATION OF IONIC LIQUID PHASE-SUPPORTED β -AMINOCROTONATE FOR ACCESS TO ASYMMETRIC 1,4-DIHYDROPYRIDINES

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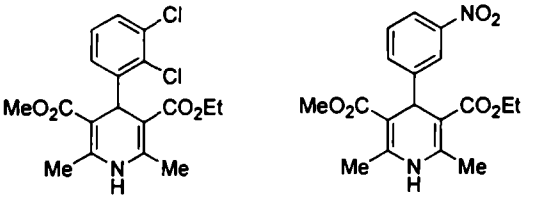
Abstract: Ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate or nitrendipine was prepared in four steps with high overall yield from ionic liquid phase bound b-aminocrotonate. The asymmetric 1,4-dihydropyridine scaffolds were built using a sequential approach according to ionic liquid-phase organic synthesis (IoLiPOS) methodology.

Key words: ionic liquid phase, b-aminocrotonate, 1,4-dihydropiridine, nitrendipine, regioselective detachment.

Introduction

The targets of organic synthesis are to produce useful organic compounds with high efficiency. With the advent of high throughput chemistry,[1] organic chemists have tended to focus on the efficiency of reactions, competences of synthetic strategies and separation protocols. The use of automated solid phase organic synthesis (SPOS) based on the original Merrifield method for the preparation of peptides[2] has proven its merit in the combinatorial chemistry area[3] by taking advantage of simple filtration techniques to wash off the by-products and excess reagents from the desired polymer bound product. Despite its great success, solid phase synthesis exhibits several shortcomings such as difficulties in reaction monitoring and the nature of the heterogeneous reaction due to hindered accessibility to the reactive sites[4] with non-polar solvents.[5] By replacing insoluble cross-linked resins with soluble polymer supports, the homogeneous reaction conditions of classical organic chemistry is still facilited due to their macromolecular properties[6]; however, limitations such as low loading capacity can restrict their applications.



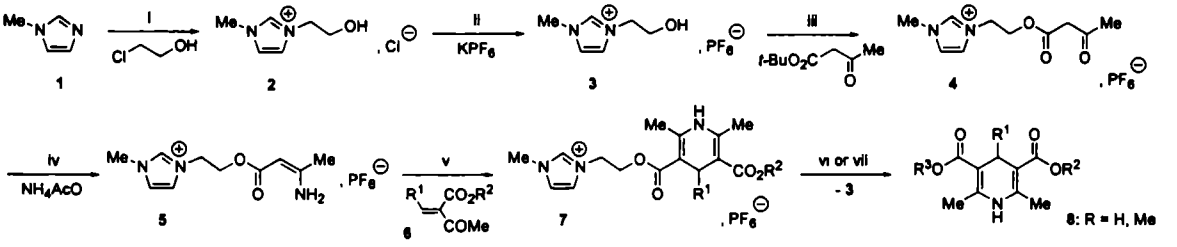
felodipine nitrendipine

Figure 1: chemical structure of felodipine and nitrendipine.

Recently, task-specific ionic liquids[7] (TSILs) and ionic liquid phases[8] (ILPs) - a subclass of TSILs - are receiving growing attention due to the advantages of the nature of homogeneous reaction, the wide range of solvent compatibility, the high loading capacity and the use of conventional spectroscopic analysis for reaction monitoring. Several groups have demonstrated the feasibility of ionic liquid-phases for homogeneous reaction conditions applied to the organic synthesis[9] of tetrahydroquinolines,[10] b-lactam library[11] *via* multistep reactions, 1,4-benzodiazepine-2,5-diones[12] to mention, but few recent examples. In connection with our research program on exploitation of ILPs as tools in ionic liquid phase organic synthesis (IoLiPOS) methodology,[13] we choose to explore now a new approach to asymmetric 1,4-dihydropyridines (1,4-DHPs) because these compounds represent an important class in the field of drugs and pharmaceuticals.[14] As examples, felodipine and nitrendipine[15] (figure 1) represent effective medicines useful for the treatment of hypertension[16] and as muscle relaxant drugs.

Results and discussion

The overall strategy for the asymmetric 1,4-dihdropyridine targets is outlined in scheme 1. For this study, we have chosen to examine the reactivity of 1-(2-hydroxyethyl)-3-methyl imidazolium hexafluorophosphate **3** [HOC_2mim][PF_6] synthesized according to our previous method.[8] The ionic liquid phase bound b-ketoester **4** was prepared easily (93% yield) from *tert*-butyl acetoacetate and [HOC_2mim][PF_6] **3** under solventless microwave irradiation conditions[17] with a stoichiometry of 1 : 2.5 of ILP **3** / b-ketoester, after 10 min.[18] at 170°C[19] (at 150 W in the Synthewave® 402 reactor).[20] The step 4 is the preparation of the key intermediate **5** for elaboration of 1,4-dihydropyridine moiety.



Scheme 1: Preparation of asymmetric 1,4-dihydropyridines **8** *via* ILP bound β-aminocrotonate **5**.

Reagents and reaction conditions: (i) chloroethanol 1 equiv., mw, 180°C, 60 W, 10 min. (ii) KPF_6 1 equiv., MeCN, 25°C, 18 h. (iii) *tert*-butylacetoacetate 2.6 equiv., mw, 170°C, 150 W, 10 min. (iv) NH_4OAc 3 equiv. 110°C, 1 h. (v) **6** 1 equiv., EtOH, reflux, 16 h. (vi) LiOH 1 equiv., THF/H_2O (6:4), reflux, 18 h then HCl 3M. (vii) MeONa 0.5 equiv., MeOH, reflux, 16 h.

Table 1: Results of reaction conditions evaluated for the preparation of ionic liquid phase supported β-aminocrotonate **5**.

Entry	NH_4OAc (equiv.)	React. temp (°C)	React. time (hour)	Conversion (%)		Method of heating
				4 -> **5**[a]	**5** -> **3**[b]	
1	2	110	0.5	100	20	μω[c]
2	3	110	0.33	100	50	oil bath[d]
3	2	110	1	92	-	oil bath[d]
4	1.5	110	1	87	-	oil bath[d]
5	1.5	110	16	100	-	oil bath[d]
6	3	110	1	100	5	oil bath[d]

[a] Conversion of **4** into **5** estimated by ^1H NMR (200 MHz, in DMSO d^6). [b] Conversion of **5** into **3** by hydrolysis estimated by ^1H NMR (200 MHz, in DMSO d^6). [c] Reaction realized in a Synthewave® 402 microwave reactor (Prolabo, Merck Eurolab group). [d] Reactions were run in a thermostated oil bath at 110°C, variation ±1°C.

The common methods for the synthesis of b-amino-a,b-unsaturated esters are based on the use ammonium acetate in toluene with azeotropic removal of water,[21] or montmorillonite K-10 under microwave.[22] On the basis of the recent work of Martin's group,[23] the preparation of ILP bound b-amino acetate **5** was tried under several experimental conditions (Table 1). Among the conditions studied (entry 6), we found that reaction of **4** with 3 equiv. of ammonium acetate in EtOH at 110°C gave good conversion (95%) after 1 hour *via* conventional heating method. Examination of the crude reaction mixture by ^1H NMR shows the presence of ILP **3** (5%) formed in the hydrolysis reaction[24] of ILP bound 3-aminocrotonate **5** but, we consider that this may not be a problem for the next reactions.

Most of the preparation for the asymmetric 1,4-DHPs involves a three component, one-step cyclocondensation, because multi component reactions (MCRs) constitute an attractive synthetic strategy for combinatorial chemistry.[25] For this project, we decided to develop a sequential approach *via* the ILP-bound b-aminocrotonate **5**.
In step 5, a stoichiometric mixture of **5** and the Knoevenagel building-block[26] **6a** (R^1 = *p*-ClC_6H_4, R^2 = Me) was found to react completely in refluxed EtOH for 16 h to produce in 72% yield the 1,4-DHP **7a** grafted on ionic liquid-phase after purification by washings with Et_2O/AcOEt (9:1) and water (Table 1). In order to obtain the 1,4-DHP scaffold, the bound product **7a** was subjected to cleavage by saponification with LiOH (1 equiv.) in a mixture of THF/H_2O (3:2) at 80°C for 18 h followed by controlled acidification with a solution of 3M HCl. Owing to the small quantities of the starting ILP-bound 1,4-DHP **7a** (~ 500 mg) used in the cleavage step, the 1,4-DHP **8a** (R^1 = *p*-ClC_6H_4, R^2 = Me, R^3 = H) was purified by flash-filtration on silica gel using CH_2Cl_2/MeOH (9:1) as washing eluent (76% yield). The structure of the expected 1,4-DHP **8a** was ascertained by conventional techniques (^1H, ^{13}C NMR and HRMS) and confirmed the regioselectivity of the cleavage.

Table 2: Results for the preparation of asymmetric 1,4-dihydropyridines **8**.

Product	R^1	R^2	R^3	Yield (%)[a]	Overall yield (%)[b]
5	-	-	-	95	-
7a	*p*-ClC_6H_4	Me	-	72	68
8a	*p*-ClC_6H_4	Me	H	76	52
7b	*m*-$NO_2C_6H_4$	Et	-	77	73
8b	*m*-$NO_2C_6H_4$	Et	Me	92	67

[a] Yield of isolated product. [b] Overall yield of isolated product **8** calculated from methylimidazole **1**.

To further demonstrate the effectiveness and the applicability of functionalized ILP **5** in a sequential synthesis of an asymmetric 1,4-DHP after regioselective detachment from the ILP, we have finally examined the synthesis of nitrendipine. By utilising this ILP-phase methodology, reaction of **6b** (R^1 = *m*-$NO_2C_6H_4$, R^2 = Et) with b-aminocrotonate **5** gave the bound precursor of nitrendipine **7b** in good yield (77%). Following water and Et_2O/AcOEt (4:1) washings of the IL-phase, the bound nitrendipine **7b** was treated with 0.5 equiv. of MeONa in MeOH and finally provided the desired ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate **8b** which was separated from the ILP **3** by flash filtration on a small pad of alumina gel AcOEt/CH_2Cl_2 (1:1) as eluent and was eluted (R_f = 1) in high yield (**8b:** 92%). The structure of nitrendipine **8b**[27] was confirmed by ^1H, ^{13}C and HRMS.

Conclusion

In summary, we have shown that b-aminocrotonate bound to ionic liquid-phase can be readily prepared and used in 1,4-dihydropyridine syntheses on the basis of ionic liquid-phase organic synthesis (IoLiPOS) methodology. This approach was confirmed by the sequential synthesis of nitrendipine with an overall yield of 67% from [HOC_2mim][PF_6] ionic liquid-phase **3**. This methodology offers considerable advantages because detachment from the ionic liquid-phase is regioselective and it is possible to build asymmetric 1,4-dihydropyridines from ionic liquid-phase bound b-aminocrotonates. The further use of this functionalized ionic liquid phase as starting point of asymmetric 1,4-DHP synthesis is ongoing in our laboratory.

Acknowledgements

One of us (J.C.L.) wishes to thank the "Ministère de la Recherche et de l'Enseignement Supérieur" for a research fellowship. We also thank Merck Eurolab Prolabo (Fr.) for providing the Synthewave 402® microwave apparatus.

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27. *Selected spectral data for ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8b**) or nitrendipine:* Yield = 92%. mp = 140-142°C, brown powder. R_f = 1 (CH_2Cl_2/AcOEt: 1/1). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) d = 1.22 (t, 3H, J = 7.1 Hz, CH_3CH_2O); 2.35 (s, 3H, Me); 2.36

(s, 3H, Me); 3.64 (s, 3H, C*H*$_3$O); 4.09 (dq, 2H, J = 7.2, 3.7 Hz, CH$_3$C*H*$_2$O); 5.09 (s, 1H, H-4); 5.90 (br s, 1H, N*H*); 7.37 (t, 1H, H-5', Ar); 7.63 (dt, 1H, J = 7.7, 1.1 Hz, H-4', Ar); 7.99 (dq, 1H, J = 8.1, 1.1 Hz, H-6', Ar); 8.11 (t, 1H, J = 1.9 Hz, H-2', Ar). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) d = 14.12 (*C*H$_3$CH$_2$); 19.25 (*C*H$_3$); 19.30 (*C*H$_3$); 39.66 (*C*H, C-4); 51.02 (*C*H$_3$O); 59.91 (CH$_3$*C*H$_2$O); 102.67-102.96 (C-3, C-5); 121.20 (C-4', Ar); 122.74 (C-2', Ar); 128.57 (C-5', Ar); 134.27 (C-6', Ar); 145.08-145.32-148.06 (C-1', C-2, C-6); 149.74 (C-3', Ar); 167.11 (C=O, CO_2Me); 167.61 (C=O, CO_2Et). HRMS, ***m/z*** = 361.1350 found (calculated for $C_{18}H_{20}N_2O_6$ = 360.1321, $M^{+\cdot}$).

Received on February 2, 2009