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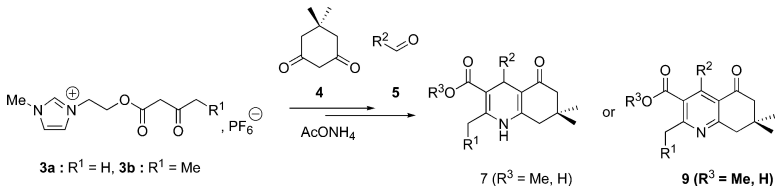

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Liquid-Phase Synthesis of Polyhydroquinoline Using Task-Specific Ionic Liquid Technology

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A new strategy for the synthesis of polyhydroquinolines from task-specific ionic liquids (TSIL) as a soluble support was developed. The preparation of the polyhydroquinolines by a three-component reaction was achieved by using ionic liquid-phase bound β-oxo esters. These starting functionalized esters were synthesized by a solventless transesterification without catalyst under microwave irradiation. The structure of the intermediates in each step was verified routinely by spectroscopic analysis, and after oxidation of the polyhydroquinolines grafted on the TSIL with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or after cleavage (transesterification, saponification−acidification), the target compounds were obtained in good yields and high purities.

Introduction

1,4-Dihydropyridine (1,4-DHP) derivatives have been widely explored as a consequence of their pharmacological profile and as the most important calcium channel modulators.[1] Nifedipine[2] represents the prototype 1,4-DHP structure found useful in both antianginal and antihypertensive treatment that has been approved for clinical use. The 1,4-DHP structures have been introduced in condensed systems such as quinoline[3] or quinolinone. These hexahydroquinolinones exhibit positive inotropic activities on electrically stimulated left atria of guinea pigs.[4] For the synthesis of hexahydroquinolinones, the key step is the unsymmetrical Hantzsch reaction[5] between acetoacetate and ammonia or a synthetic equivalent of ammonia and aromatic aldehyde to give the condensed dihydropyridine structure after dehydration of the unstable tetrahydropyridine. Experimentally, the preparation of the 1,4-DHPs involves a three-component, one-step cyclocondensation, because multicomponent reactions[6] (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step, and the diversity can be achieved simply by varying the reacting components. Owing to their convergence and productivity, the MCRs have attracted considerable attention from the point of view of combinatorial chemistry. The use of combinatorial chemistry techniques has become commonplace to generate compounds for the screening and identification of new drug leads. Over recent years, solution-phase chemistry has indicated an increasing interest for lead discovery and optimization tools for library generation in drug discovery.[7] It offers many advantages over solid-phase approaches, such as easy manipulation, reduction in validation time, and unlimited scale-up potential. Liquid-phase synthesis retains many of the advantages of conventional solution chemistry and still permits the fairly easy purification of the product. Liquid phases offer several advantages: (1) the purification is possible after each step, (2) the reactions may be realized in homogeneous solution, and (3) the large excess of reagents typically used in solid-phase supported synthesis is normally not required. Soluble polyethylene glycol (PEG) and others polymers (PEG-grafted polystyrene supports) have been employed successfully in the synthesis of oligopeptides.[8] Some limitations that were expressed for the use of soluble polymers supports include the following: (1) low loading capacity, (2) limited solubility in peptide synthesis, and (3) aqueous solubility and insolubility in ether solvents.[9]

Ionic liquids (ILs), room temperature salts, have recently received more and more attention as ecofriendly reaction media in organic synthesis. The increasing number of papers published in recent years[10] is a consequence of their peculiar properties, such as negligible vapor; an ability to dissolve organic, inorganic, and sometimes polymeric materials; no miscibility with nonpolar solvents; reasonable thermal and chemical stability; and good electrical conductivity. Recently, more attention has been focused on a subclass of ILs with

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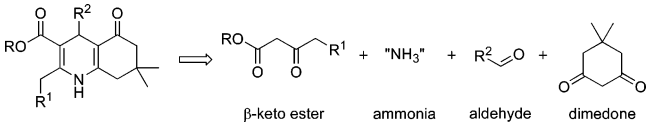


Figure 1. Components used for the synthesis of 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-3-carboxylate.

functional groups, so-called "task-specific ionic liquids" (TSILs),[11] and their applications in ionic liquid-supported organic synthesis. The basic idea of our laboratory[12] and others groups[13] was to replace solid- or liquid-phase supports with a functionalized TSIL. This new approach of liquid-phase-supported organic synthesis (LPOS) has been successfully demonstrated by the synthesis of small molecules and has several advantages, including a high active site/material ratio (high loading capacity), easy monitoring with standard analytical methods, and routine product isolation by simple extraction and washings. In view of the emerging importance of TSILs as alternatives to classical soluble polymeric matrices in combinatorial chemistry, we report here our results about the application of TSILs as soluble support in a liquid-phase traceless synthesis of polyhydroquinolines.

Results and Discussion

Attachment to the Task-Specific Ionic Liquid. For this study, the polyhydroquinoline moiety can be built from β-keto ester, ammonia, or a synthetic equivalent of ammonia, aromatic aldehyde, or dimedone (Figure 1), and the carboxylate function is used as the site of attachment to the liquid support.

As a suitable model reaction for ionic liquid-phase-supported organic synthesis, we have chosen to use β-keto ester bound to the ionic liquid phases (ILPs) as a novel task-specific ionic liquid. The starting ILPs **1**(**a**, **b**) with $X = BF_4$, PF_6 used in Scheme 1, readily available from the reaction of 1-methylimidazole and 2-chloroethanol,[14] were chosen as a suitable ionic liquid support for polyhydroquinoline synthesis. In this first step, the liquid-phase bound β-keto esters **3**(**a**−**c**) were prepared by transesterification[15] of methyl or *tert*-butyl[16] β-oxo carboxylates **2**(**a**,**b**) with the ionic liquid-phases [HOC_2mim][PF_6] **1a** and [HOC_2mim][BF_4] **1b** under solvent-free microwave irradiations. Transesterification with acetoacetate is somewhat different as compared to the usual esters. Mechanistic studies that such acetoacetylations proceeded by the initial formation of a highly reactive oxoketene[18] have been demonstrated. The rate-limiting step of the transesterification is elimination of the alcohol from the starting β-oxo ester **2**, and subsequent trapping of the oxo ketene with alcohols (i.e., a hydroxy-functionalized resin[18a,b] or a hydroxy ionic liquid[18c]) produces the transacetoacetyled compound. This step is accomplished generally by thermolysis[16] and more recently under microwave irradiations.[18a,c]

Table 1. Results for the Preparation of ILPs **3**(**a**−**c**) by Transesterification

product **3**	anion	R^1	yield (%)[a]
3a	PF_6	H	90
3b	PF_6	Me	92
3c	BF_4	H	90

[a] Yield of isolated product.

Table 2. Solubility of ILPs **1**(**a**, **b**) and **3**(**a**−**c**) in Some Common Solvents

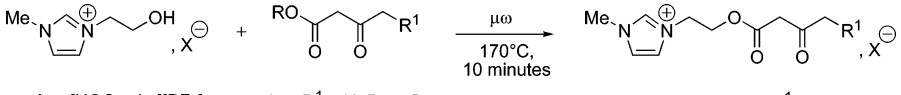
	solubility[a] in				
product	Me_2CO	CH_2Cl_2	AcOEt	H_2O	Et_2O
1a	misc	misc	misc	misc	imisc
1b	misc	imisc	imisc	misc	imisc
3a	misc	imisc	imisc	imisc	imisc
3c	misc	imisc	imisc	pm	imisc

[a] misc, miscible; imisc, immiscible; pm, partially miscible.

The use of microwave irradiations ($\mu\omega$) as an alternative mode of heating reaction mixtures has been observed to dramatically reduce reaction times and affect product ratio and yields.[19] As a suitable transformation to illustrate the concept of microwave-assisted liquid-phase synthesis, we have developed an array of experiments with different reaction temperatures under microwave, and the results revealed that the optimal reaction conditions were obtained after 10 min with a stoichiometry of 1/2.6 of ILP **1a**/*tert*-butylacetoacetate **2a** and 1/4 of ILP **1a**/methyl-3-oxopentanoate **2b** to produce, respectively, the ILPs **3**(**a**, **b**). Note that in this microwave flash heating process, there is no need to use a catalyst, such as 4-dimethylaminopyridine (DMAP), as is often used in the literature, and the optimal reaction mixture was 170 °C, just below the boiling point of the reagents **2**(**a**,**b**). For safety reasons, a 6-min heating ramp was performed before the temperature was maintained at the selected maximum value of 170 °C (at 150 W in the Synthewave 402 reactor with **2a** and at 60 W in the Discover CEM reactor with **2b**). As can be seen from inspection of the data presented in Table 1, the ionic liquid-phase bound β-oxo esters **3**(**a**−**c**) were prepared in good yields (90−92%) after washings with AcOEt (1/5 w/v).

In Table 2, the solubility of the ILP bound β-oxo esters **3a** and **3c** and the starting ILPs **1**(**a**, **B**) are presented. It can be observed that the ionic liquids **1**(**a**,**b**) are miscible with acetone and water. For the other solvents (dichloromethane, AcOEt, and diethyl oxide), **1a** ($X = PF_6$) is fully miscible. On the other hand, **1b** ($X = BF_4$) is insoluble. Additionally, the ILP-bound esters **3a** and **3c** are immiscible in dichloromethane, AcOEt, and Et_2O and also show good solubility in acetone. It was found that **3a** is insoluble in water, and

Scheme 1. Preparation of β-Keto Ester Bound to the Ionic Liquid Phases by Transesterification from ILPs **1(a**, **b)** under Microwave Irradiations

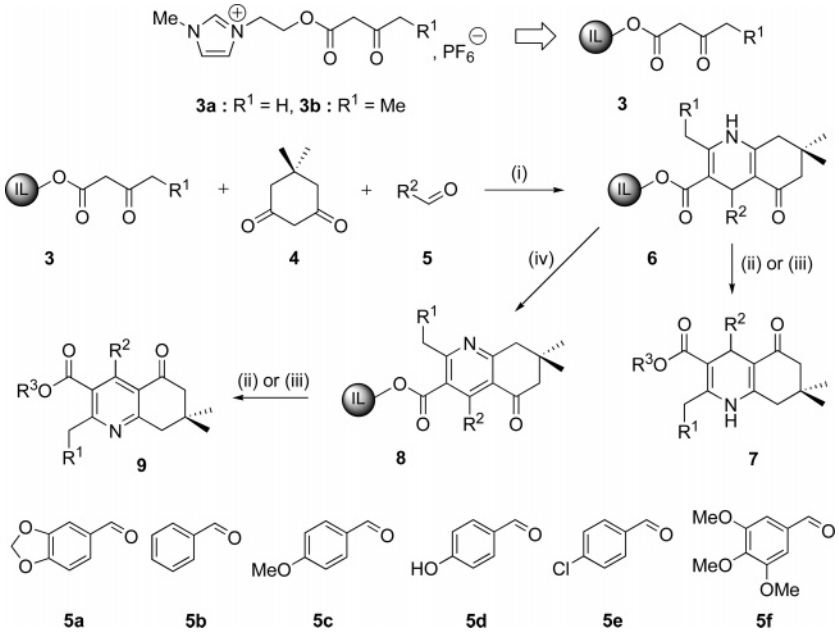


1a : [HOC_2mim][PF_6]
1b : [HOC_2mim][BF_4]

2a : R^1 = H, R = t-Bu
2b : R^1, R = Me

3a : X = PF_6, R^1 = H
3b : X = PF_6, R^1 = Me
3c : X = BF_4, R^1 = H

Scheme 2. Three-Component Reaction, Oxidation, Detachment from the ILP[a]



[a] Reagents and reaction conditions : (i) **4** 1 equiv, **5** 1.1 equiv, NH_4OAc 1.5 equiv, neat, 90 °C, 20 min; (ii) MeONa 1 equiv, MeOH, reflux, 18 h; (iii) LiOH 1 equiv, THF/H_2O (2:1), reflux, 20 h, then 3 M HCl; (iv) DDQ 1.1 equiv, CH_2Cl_2, reflux, 2 h.

3c is partially miscible. The ILPs bound β-oxo esters **3**(**a**, **b**) with PF_6 anion are the preferred precursors, because after microwave dielectric heating, the excess of β-oxo esters **2**(**a**, **b**) and eventually unreacted starting ILP **1a** were eliminated easily by washings with AcOEt. Finally, the structure of ILPs **3**(**a**−**c**) was ascertained by mass spectrometry and proton NMR, confirming that the major compound is the expected β-oxo esters **3**.

Solventless Three-Component Synthesis of Polyhydroquinoline, Oxidation and Detachment from the TSIL. With the selected ILP bound β-oxo esters **3**(**a**, **b**) with PF_6 anion in hand, we have examined the polyhydroquinoline synthesis under neat conditions (Scheme 2). After several experiments, the optimal results were obtained at 90 °C, and a stoichiometry of 1/1/1.1/1.5 of ILP-bound β-oxo ester **3**/dimedone **4**/aldehyde **5**/ammonium acetate was found to react completely without solvent in the one-pot three-component condensation. To our surprise, there was no need for a catalyst to improve the product yields and to optimize the reaction conditions, as reported in literature.[20] Progress of one-pot cyclization was easily monitored by proton NMR spectroscopy and showed that optimized reaction conditions were achieved with a reaction time of 20 min. This study was realized with a variety of substituted aromatic aldehydes **5** carrying either an electron-donating or -withdrawing substituent for the introduction of diversity into the polyhydroquinoline moiety, and a 7-member model library was constructed.

Owing to the small quantities of the starting IL-phase bound β-oxo esters **3** (5.6 mmol) used in the three-component synthesis of the polyhydroquinoline, the purification of the IL-phase **6** by the simple and classical washings with an appropriate solvent is not suitable, but we have discovered that flash filtration on alumina gel using dichloromethane (DCM) followed by DCM/MeOH (4/1) as washing eluen afforded the desired IL-phases **6** ($R_f \sim 0.9$) in good yields and high purities.

Table 3. Results for the Preparation of Various Polyhydroquinolines after the Three-Component Reactions on ILPs, Oxidation, and Detachment

compd	starting products	R^1	R^2	R^3	yield (%)[a]
6a	**3a** + **5a**	H	3,4-$(CH_2O_2)C_6H_3$		96
6b	**3a** + **5b**	H	C_6H_5		88
6c	**3a** + **5c**	H	4-$MeOC_6H_4$		91
6d	**3a** + **5d**	H	4-HOC_6H_4		85
6e	**3b** + **5a**	Me	3,4-$(CH_2O_2)C_6H_3$		91
6f	**3a** + **5e**	H	4-ClC_6H_4		83
6g	**3a** + **5f**	H	3,4,5-$(MeO)_3C_6H_2$		90
7a	**6a** + MeONa	H	3,4-$(CH_2O_2)C_6H_3$	Me	92
7b	**6a** + LiOH, HCl	H	3,4-$(CH_2O_2)C_6H_3$	H	82
8a	**6a** + DDQ	H	3,4-$(CH_2O_2)C_6H_3$	Me	80
9a	**8a** + MeONa	H	3,4-$(CH_2O_2)C_6H_3$	H	80

[a] Yield of isolated product.

The structure of ILPs **6**(**a**−**g**) was ascertained by conventional techniques (^1H, ^{13}C NMR, IR), and the purity was controlled by HRMS. As can be seen from the results of Table 3, the desired polyhydroquinolines **6**(**a**−**g**) grafted on the ILPs were prepared in yields ranging from 83 to 96% (Table 3). The experiments demonstrate that the task-specific ionic liquids bound β-oxo esters **3**(**a**, **b**) can be readily functionalized under solventless conditions and that they constitute an excellent auxiliary for the synthesis of small functionalized molecules.

After demonstrating the feasibility of our protocol for the preparation of functionalized polyhydroquinolines grafted on task-specific ionic liquid by a three-component cyclization, we have finally explored two methods for the cleavage: (a) In the first approach and as an example, the ILP **6a** was treated with sodium methoxide (1 equiv) in refluxed MeOH for 18 h, and the reaction was easily monitored by ^1H NMR (Figure 2) or TLC. After completion of the cleavage, the

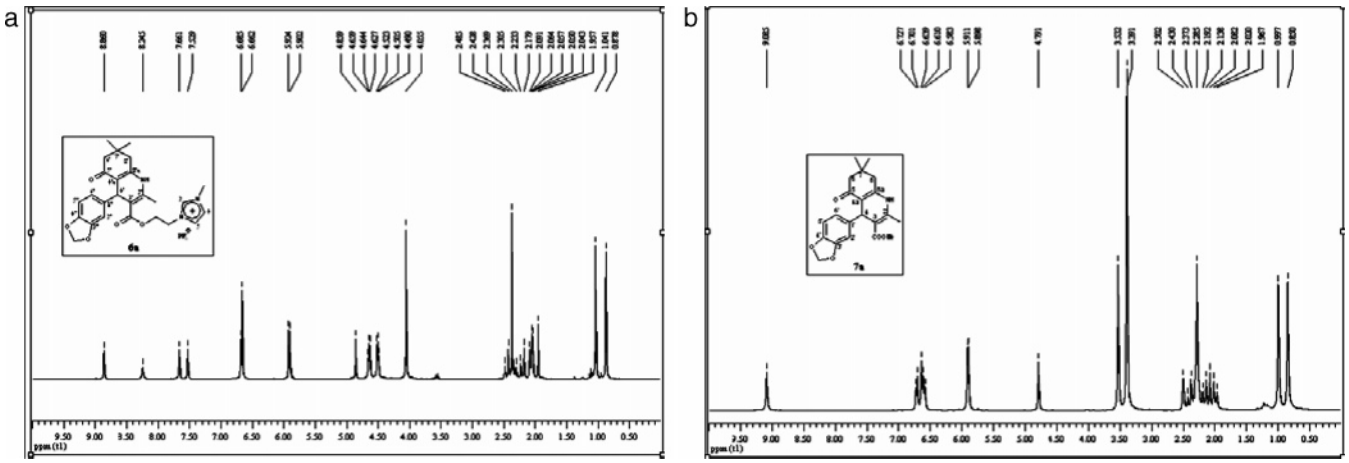


Figure 2. ^{1}H NMR spectrum of polyhydroquinoline before and after transesterification. (a) ^{1}H NMR spectra of **6a** in $(CD_3)_2CO$ after the three-component reaction. (b) ^{1}H NMR spectra of **7a** in $(CD_3)_2CO$ after transesterification of **6a** in MeOH with 1.1 equiv of MeONa.

solvent was removed in vacuo, and the expected ester **7a** (80% yield) was purified by chromatography on alumina gel using DCM/AcOEt (1/1) as eluent (R_f = 0.9). (b) In the second method, saponification of **6a** with 60% LiOH in THF at room temperature, followed by controlled acidification with a solution of 3 M HCl, afforded the acidic derivative of polyhydroquinoline **7b** in only 80% yield after chromatography on alumina gel using DCM/MeOH (9/1) as eluent. The two moderate yields (80%) obtained in the cleavage methods were due to the different partition of the products **7**(**a**, **b**) between the alumina gel and various organic solvents. It is also worth noting that after cleavage, the starting ILP **1a** issued from **6a** could be easily eluted after chromatography and regenerated with MeOH as eluent in nearly quantitative yield (~98%).

To further demonstrate the effectiveness and the applicability of functionalized task-specific ionic liquid in a three-component, liquid-phase, traceless synthesis of polyhydroquinoline, we set out to explore the oxidation[21] of ionic liquid-phase-bound polyhydroquinolines **6**. To the best of our knowledge, oxidation of polyhydroquinolines has not been explored in conventional solution organic synthesis and in solid-/liquid-phase synthesis. However, the aromatization of Hantzsch 1,4-dihydropyridines has been extensively studied, and the usual reagents were ceric ammonium nitrate;[22] clay-supported cupric nitrate[23] (clay cop); pyridinium chlorochromate;[24] $Bi(NO_3)_2$;[25] $Mn(OAc)_3$;[26] I_2/MeOH;[27] and more recently, $Zr(NO_3)_2$.[28] Most of the known methods suffer from longer reaction times, higher temperatures, the use of excess reagent, and the formation of side products.

On the other hand, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) appeared to be an appropriate reagent to aromatize Hantzsch 1,4-DHPs,[29] as reported by the group of Vanden Eynde. With that highly reactive quinone,[30] we could oxidize the polyhydroquinoline **6a** grafted on the ILP bearing the piperonyl group in the 2-position under very mild conditions (under refluxed dichloromethane) with short reaction time (2 h) from only 1.1 equiv of DDQ. The corresponding bound tetrahydroquinoline (THQ) **8a** was obtained quantitatively (^{1}H NMR of the crude reaction mixture), and a large excess of DDQ was not necessary. The expected THQ **8a** was separated from $DDQH_2$ by flash filtration on a small pad of alumina gel with DCM/MeOH (9/1) as eluent and was eluted in high yield (**8a**: 92%, R_f = 0.2). Subsequent cleavage of the THQ **8a** by transesterification (MeONa, 1 equiv in refluxed MeOH, 18 h) led to the THQ methyl ester **9a** in satisfied yield (82%).

Conclusion

In summary, a novel solution phase approach to polyhydroquinolines has been developed on the basis of an ionic liquid-phase strategy with a generic protocol of coupling, detachment, and purification. On the basis of this new example of application, the TSIL technology offers several advantages in comparison to the other methods used and developed in solid- and liquid-phase organic synthesis. First, the attachment of the β-keto esters **3** was rapidly performed under microwave irradiation without a catalyst, and the ILP bound β-keto esters were easily purified by solvent washings. Second, the β-keto ester intermediate is quantitatively transformed into polyhydroquinoline by using a solventless three-component approach because the loading capacity of the ILP is very high. Good yields and high purities were obtained for the polyhydroquinolines bound to the ILPs by flash filtration on gel chromatography. Other advantages of the TSIL technology are that the structure and purity of each intermediate could be verified by routine spectroscopic methods. Furthermore, the cost of the starting TSILs **1** is probably lower than the solid and liquid support, and in large-scale synthesis, this may be an important economic consideration. To our knowledge, this liquid-phase synthesis of polyhydroquinoline has never been reported and may be a complement to those existing in the literature that involve conventional solution organic synthesis. This methodology should be compatible with high-throughput liquid-phase organic synthesis and automation technology. Further developments of new functionalized TSILs as new tools for LPOS is currently under investigation and will be reported in due course.

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Supporting Information Available. Details of experimental procedures and analytical data (^{1}H, ^{13}C NMR, HRMS, IR), elemental analysis for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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