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Microwave-assisted liquid-phase synthesis of methyl 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate using functional ionic liquid as soluble support

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Abstract—A microwave-assisted liquid-phase synthesis of methyl 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate was developed using functional ionic liquid as soluble support. IL-bound acetoacetate was treated with arylidenemalononitriles to give supported 4*H*-pyran derivatives. After cleavage, the target compounds were obtained in good yields and high purities without chromatographic purification.

Combinatorial chemistry has emerged as a powerful tool to generate large numbers of compounds for the screening of functional molecules.[1] In the field of combinatorial chemistry, solid-phase organic synthesis (SPOS) has been accepted as an efficient method for high-throughput synthesis.[2] Despite its great success, solid-phase synthesis still exhibits several shortcomings such as the nature of heterogeneous reaction and difficulties in reaction monitoring. By replacing insoluble cross-linked resins with soluble polymer supports, the familiar reaction conditions of classical organic chemistry are reinstated, and yet product purification is still facilitated due to their macromolecular properties.[3] Non-crosslinked polystyrene and poly(ethylene glycol) (PEG) are the most common and useful soluble polymers for liquid-phase organic synthesis.[4] However, there is a main limitation about the use of soluble polymer supports, namely, low loading capacity. Fluorous synthesis, which successfully integrates liquid-phase reaction conditions with the phase-tag separations, has been recently introduced as a 'beadless' high-speed synthetic technology.[5] This is based on the concept that fluorinated reagents preferentially dissolved in perfluoroalkanes, the fluorous phase. But the expense of perfluoroalkane solvents, limitation in solvent selection, and the need for specialized reagents may limit its general applications. So, the idea of searching alternative soluble supports for high-throughput organic synthesis has been advocated.

Recently, more attentions in room temperature ionic liquids research have been paid on the functionalized ionic liquids with special tasks.[6] Functionalized ionic liquids have been introduced as soluble supports in liquid-phase organic synthesis.[7–10] It has the advantages of the nature of homogeneous reaction, high loading capacity, wide range of solvents, simple monitoring technology, and low cost.

Microwave-assisted reactions have become an established tool in organic synthesis.[11] Deetlefs and Seddon[12] reported that microwave irradiation could accelerate synthetic reaction for the preparations of ionic liquids. Hoffmann et al.[13] found that ionic liquids could efficiently absorb microwave energy by which the reaction rate could be accelerated remarkably. Fraga-Dubreuil et al. reported the synthesis of functionalized ionic liquid under microwave irradiations[9] and one-pot three-component condensation under microwave dielectric heating.[10]

Polyfunctionalized 4*H*-pyrans constitute a structural unit of a number of biologically interesting compounds which possess various pharmacological activities.[14] In this letter, we report our results about the application of functional ionic liquid as soluble support in the

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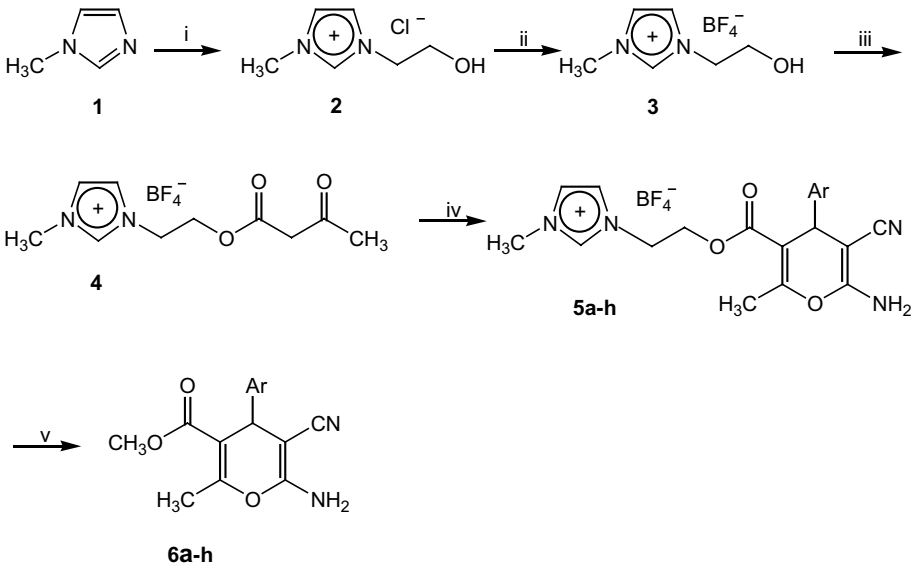

Scheme 1. Reagents and conditions: (i) chlorohydrin (2 equiv), N_2, microwave 200 W, reflux, 2 min; (ii) $NaBF_4$ (2 equiv), CH_3CN, 80 °C, 24 h; (iii) ethyl acetoacetate (3 equiv), microwave 200 W, reflux, 10 min; (iv) arylidenemalononitriles (2 equiv), pyridine, acetonitrile, microwave 200 W, reflux, 15–20 min; (v) sodium methoxide, methanol, room temperature, 6 h.

liquid-phase synthesis of methyl 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylates (Scheme 1).

Strohmeier and Kappe[15] reported the transesterification of standard polystyrene Wang resin with ethyl acetoacetate both under conventional and microwave conditions in solid phase organic synthesis. In our research, ionic liquids 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([2-hydemim][BF_4]) **3** was treated with ethyl acetoacetate under microwave irradiation to offer intermediate **4**. As indicated by IR monitoring, only 10 min was needed for the transformation from **3** to **4**. in contrast, it would take 3 h for the same conversion under conventional condition. Cyclization between IL-bound acetoacetate **4** and arylidenemalononitriles gave bound 4-*H* pyran derivatives **5a**–**h**. The excess reactant, arylidenemalononitriles, could be removed by simple extraction with the mixture of petroleum ether and dichloromethane (1:1 v/v), due to the immiscibility between ionic liquid phase and the mixture of petroleum ether and dichloromethane. Finally, the **5a**–**h** was treated with sodium methoxide in methanol for 6 h at room temperature. On completion of the cleavage step (monitored by TLC), the methanol in reaction mixture was removed in vacuo, and the product was extracted from the residue with dichloromethane. After the removal of dichloromethane, methyl 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylates **6a**–**h** were obtained in high yields and purities without further purification (Table 1).

To recover the hydroxyl-functionalized ionic liquid [2-hydemim][BF_4], the residue after extraction was washed twice with dichloromethane, and then acetone was added. The precipitate was removed and the filtrate was concentrated in vacuo to give regenerated [2-hydemim][BF_4]. The IL-bound acetoacetate **4** was synthesized in the same way described previously using recovered [2-hydemim][BF_4] and employed in the next run. The yield of **6a** maintained at 87–90% in the first six cycles.

Table 1. IL-supported liquid-phase synthesis of 4*H*-pyrans

Entry	Ar	Time[a] (min)	Yield[b] (%)	Final yield[c] (%)	Purity[d] (%)
1	C_6H_5	20	95	88	96
2	4-OH–C_6H_4	20	93	84	98
3	4-OCH_3–C_6H_4	20	94	86	98
4	4-Cl–C_6H_4	15	97	91	99
5	4-CH_3–C_6H_4	20	93	86	97
6	3-NO_2–C_6H_4	15	96	90	99
7	3-Br–C_6H_4	15	96	90	98
8	4-OH–3-OCH_3–C_6H_3	20	94	85	95

[a] Reaction time of step iv, Scheme 1.
[b] Yields of **5a**–**h** based on **4**.
[c] Isolated yields of final products **6a**–**h** based on **4**.
[d] Determined by HPLC.

In conclusion, the use of hydroxyl-functionalized ionic liquids as soluble supports in liquid-phase synthesis of the title compounds offers considerable advantages: firstly, the reaction is performed in homogeneous solution; secondly, higher loading capacity is achieved due to lower molecular weight of functionalized ionic liquid; thirdly, because the intermediates can be purified by simple extraction, the presented methodology is compatible with automatic manipulation; fourthly, the desired products can be obtained in high yields and purities without further chromatographic purification. Finally, the recovered ionic liquid after cleavage can be reused in another cycle without losing its activity.

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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.2005.03.197.

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