Liquid-phase organic synthesis of imidazo[1,2-*a*]pyridine derivatives using PEG-supported sulfonyl chloride

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Reaction of PEG-bound sulfonic acid with thionyl chloride formed the difunctionalised PEG-supported sulfonyl chloride, which was treated with α-hydroxyketones, followed by treatment with 2-aminopyridine in the presence of potassium carbonate efficient to afford imidazo[1,2-*a*]pyridines in good yields with a facile work-up procedure.

Keywords: liquid-phase organic synthesis, PEG-bound sulfonyl chloride, imidazo[1,2-*a*]pyridine

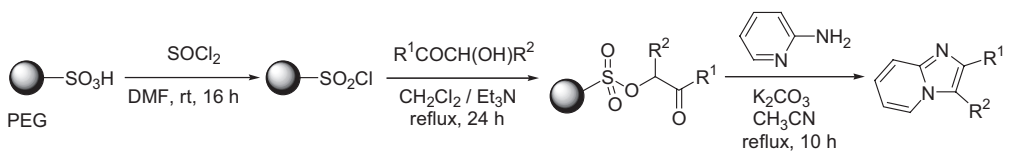
Recently, preparation of pharmacologically relevant heterocyclic compounds using combinatorial techniques was shown to be an effective way of developing drug candidates.[1] The use of soluble polymer support in combinatorial synthetic methodologies facilitates the library synthesis[2-4] and overcomes the difficulties experienced in solid-phase organic synthesis (SPOS) reactions.[5] Furthermore, progress of soluble polymer supported reactions is easily monitored using routine analytical techniques such as TLC, IR and ^{1}H NMR.[6] Imidazo[1,2-*a*]pyridine derivatives have long been widely used as local anesthetic[7] and antiulcer agents,[8,9] for whitening fine fabrics,[10] as anthelmintic or bacteriostatic agents,[11] and as fluorescent materials.[12] They are also versatile intermediates for synthetic transformations.[13-15] Hence, many synthetic methods for the imidazo[1,2-*a*]pyridine are well documented.[16-25] Recently, preparation of imidazo[1,2-*a*]pyridine using SPOS methodology has also been reported.[26] However, to our knowledge, the synthetic route to the imidazo[1,2-*a*]pyridines on soluble polymer supports has rarely been reported. Based on our previous study on the use of PEG-bound sulfonic acid for the preparation of 1,1-diacetates,[27] we report here an efficient liquid-phase organic synthesis (LOPS) of imidazo[1,2-*a*]pyridines with PEG-bound sulfonyl chloride (Scheme 1).

The synthesis of a sulfonyl chloride linker on PEG polymer (average mass 4000) was first investigated. As previously reported, the dimesylation from PEG 4000 with methanesulfonyl chloride was carried out and then conversion to the corresponding dibromide resin, which was further treated with 4-hydroxybenzenesulfonic acid and sodium hydroxide,[28,29] followed by treatment with concentrated HCl to form the difunctionalised PEG-supported sulfonic acid **1** in our published method.[27] Then reaction of PEG-supported sulfonic acid **1** with thionyl chloride in *N,N*-dimethylformamide gave the difunctionalised PEG-sulfonyl chloride resin **2** in 78% overall yield, and all steps were monitored using solution ^{1}H NMR spectroscopy. The loading rate of the sulfonyl chloride group was estimated as 0.50 mmol/g, based on chlorine elemental analysis. This reagent was then treated with various α-hydroxyketones in the presence of triethylamine in dichloromethane to generate the corresponding PEG-bound α-sulfonyloxy ketones **3**, where the polymer species are easily obtained through precipitation by addition of propan-2-ol to the mixtures and then with simple filtration. The linking reaction to the PEG support was also monitored by the IR absorption bands at 1371 cm^{-1} (S–O stretch of –SO_2C1), which was shifted to 1352 cm^{-1} (–SO_2–O–) as well as by the appearance of typical carbonyl absorptions near 1670–1695 cm^{-1}. Having obtained PEG-bound α-sulfonyloxy ketone **3**, the cyclocondensation reaction of resin **3** with 2-aminopyridine, the key for the success of this protocol was investigated. To optimise the reaction conditions, several solvents like dichloromethane, acetonitrile, *N,N*-dimethylformamide or diethyl ether and various bases such as potassium carbonate, sodium carbonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were performed. After a series of experiments, the cyclisation in refluxing acetonitrile in the presence of potassium carbonate was carried out efficiently to furnish the corresponding imidazo[1,2-*a*]pyridines **4** in moderate to good yields, as shown in Table 1. From Table 1, for substrates α-hydroxyketones, with substitution of an electron-withdrawing group or an electron-donating group on the aromatic ring resulted in no obvious effect on the reaction yields. However, the yields of imidazo[1,2-*a*]pyridine **4i** (Table 1, entry 12) were relatively lower under the same reaction conditions, which might be ascribed to its larger steric restriction of

Table 1 The yields of imidazo[1,2-*a*]pyridines **4**

Entry	R^1	R^2	Products	Yield/%[a]
1	C_6H_5	H	**4a**	80
2	C_6H_5	H	**4a**	79[b]
3	C_6H_5	H	**4a**	80[c]
4	C_6H_5	H	**4a**	78[d]
5	*p*-$CH_3C_6H_4$	H	**4b**	81
6	*p*-$CH_3OC_6H_4$	H	**4c**	78
7	*p*-ClC_6H_4	H	**4d**	75
8	*p*-BrC_6H_4	H	**4e**	74
9	*p*-FC_6H_4	H	**4f**	75
10	*p*-$NO_2C_6H_4$	H	**4g**	70
11	2-furyl	H	**4h**	73
12	C_6H_5	CH_3	**4i**	60

[a]Yields refer to the isolated pure products based on PEG-bound disulfonyl chloride. [b]With the first regenerated resin. [c]With the second regenerated resin. [d]With the fourth regenerated resin.



Scheme 1

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the corresponding ketone. After finishing the reaction, the recovered PEG-bound sulfonic acid potassium salt was precipitated with cold diethyl ether and was easily converted to PEG-bound sulfonic acid **1** again by treatment with conc. HCl. Therefore the covered polymeric sulfonic acid **1** can be used repeatedly for the preparation of the present imidazo[1,2-*a*] pyridines without obvious decreasing of the yield, as shown in Table 1 (entries 1–4).

In summary, a mild, efficient and environmentally benign preparation of imidazo[1,2-*a*]pyridines from the reaction of a cheap and recyclable PEG-bound sulfonyl chloride with α-hydroxyketones, followed by treatment with 2-aminopyridine in the presence of potassium carbonate was successfully carried out.

Experimental

Melting points were determined on X_4 melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard. FT–IR spectra were taken from a Perkin-Elmer SP One FT–IR spectrophotometer. PEG-bound sulfonic acid prepared according to our report method.[27] The other reagents were purchased from commercial sources and were used without further purification. DMF was distilled from calcium hydride and CH_2Cl_2 was distilled from phosphorous pentoxide immediately prior to use.

Preparation of PEG-bound sulfonyl chloride **2**; *general procedure*
Under a nitrogen atmosphere, to PEG 4000 disulfonic acid **1** (10.0 g, 2.30 mmol) in thionyl chloride (10 ml, 154.3 mmol) was added DMF (5 ml). After 16 h with stirring at room temperature, the solvent was removed *in vacuo* and the crude product dissolved in hot propan-2-ol (100 ml). The solution was cooled to 0°C, and the precipitate formed collected by filtration. The precipitation step was repeated, the combined precipitates washed with propan-2-ol (10 ml), and Et_2O (50 ml), and then dried *in vacuo* to afford PEG-bound sulfonyl chloride **2** as a white solid (9.50 g, 95%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.39–3.89 (m, PEG CH_2), 4.23 (t, J = 4.6 Hz, 4 H, CH_2OAr), 7.08 (d, J = 8.9 Hz, 4 H, ArH), 7.95 (d, J = 8.9 Hz, 4 H, ArH). FT–IR (KBr) υ 3032, 2944, 1600, 1545, 1371, 1105, 824 cm^{-1}.

Preparation of imidazo[1,2-a]pyridines (**4a–i**); *General procedure*
To a solution of α-hydroxy ketone aldehyde (4.0 mmol) in anhydrous dichloromethane (10.0 ml) was added PEG 4000 sulfonyl chloride **2** (4.35 g, 1.0 mmol) and Et_3N (2.0 mmol), and the reaction mixture was heated at reflux for 24 h under an N_2 atmosphere. The solvent was removed *in vacuo*, and the crude product dissolved in hot propan-2-ol (100 ml). The precipitation step was repeated, the combined precipitates washed with propan-2-ol (10 ml), and Et_2O (50 ml), and then dried *in vacuo* to afford PEG-bound α-sulfonyloxy ketone **3** as a white solid in nearly quantitative yield. To a solution of **3** (1.0 mmol) and 2-aminopyridine (3.0 mmol) in MeCN (20 ml), K_2CO_3 (1.24 g, 9 mmol) was added, and the reaction mixture was refluxed for 10 h under an N_2 atmosphere. Then the solvent was removed under vacuum, and diethyl ether (200 ml) was added with vigorous stirring and the mixture was cooled to 0°C. The recovered PEG-bound sulfonic acid potassium salt was collected by filtration, washed with cold diethyl ether (2 × 20 ml). The filtrate was washed water (each of 10 ml), dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel; hexane-EtOAc, 3 : 1) to afforded pure imidazo[1,2-*a*]pyridine **4**.

2-Phenylimidazo[1,2-a]pyridine (**4a**): Colourless solid; m.p. 131–132°C (Lit.[25] m.p. 130–32°C); ^{1}H NMR: δ = 8.13 (d, J = 6.8 Hz, 1 H), 7.96 (d, J = 7.2 Hz, 2 H), 7.86 (s, 1 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 1 H), 7.18 (t, J = 7.5 Hz, 1 H), 6.78 (t, J = 6.7 Hz, 1 H); IR (KBr): ν = 3033, 1633, 1600, 1510, 1440, 1080, 922, 745, 690 cm^{-1}.

2-(4-Methylphenyl)imidazo[1,2-a]pyridine **(4b)**: Pale yellow solid; m.p. 143–144°C (Lit.[24] m.p. 144–145°C); ^{1}H NMR: δ = 8.12 (d, J = 6.7 Hz, 1 H), 7.86 (d, J = 8.2 Hz, 2 H), 7.83 (s, 1 H), 7.64 (d, J = 9.0 Hz, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.16 (t, J = 7.9 Hz, 1 H), 6.77 (t, J = 6.7 Hz, 1 H), 2.38 (s, 3 H); IR (KBr): ν = 3132, 3035, 2875, 1633, 1600, 1513, 1454, 1378, 1082, 990, 828, 745 cm^{-1}.

2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine **(4c)**: Yellow solid; m.p. 133–134°C (Lit.[30] m.p. 136°C); ^{1}H NMR: δ = 8.08 (t, J = 6.7 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 2 H), 7.80 (s, 1 H), 7.62 (d, J = 9.0 Hz, 1 H), 7.14–7.16 (m, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.76 (t, J = 6.7 Hz, 1 H), 3.85 (s, 3 H); IR (KBr): ν = 3132, 3031, 2872, 1634, 1600, 1510, 1445, 1376, 1080, 842, 766, 690 cm^{-1}.

2-(4-Chlorophenyl)imidazo[1,2-a]pyridine **(4d)**: Yellow solid; m.p. 202–203°C (Lit.[24] m.p. 205–206°C); ^{1}H NMR: δ = 8.12 (d, J = 6.8 Hz, 1 H), 7.89 (d, J = 8.8 Hz, 2 H), 7.83 (s, 1 H), 7.62 (d, J = 8.9 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.18 (t, J = 7.1 Hz, 1 H), 6.76 (t, J = 6.8 Hz, 1 H); IR (KBr): ν = 3033, 1635, 1600, 1512, 1470, 1401, 1172, 1080, 836, 770 cm^{-1}.

2-(4-Bromophenyl)imidazo[1,2-a]pyridine **(4e)**: Yellow solid; m.p. 215–217°C (Lit.[31] m.p. 215–216°C); ^{1}H NMR: δ = 8.11 (d, J = 6.8 Hz, 1 H), 7.85–7.83 (m, 2 H), 7.82 (s, 1 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.57–7.55 (m, 2 H), 7.20–7.18 (m, 1 H), 6.79 (t, J = 6.8 Hz, 1 H); IR (KBr): ν = 3034, 1634, 1601, 1510, 1474, 1401, 1169, 1080, 835, 772 cm^{-1}.

2-(4-Fluorophenyl)imidazo[1,2-a]pyridine **(4f)**: Yellow solid; m.p. 163–164°C (Lit.[32] m.p. 165–166°C); ^{1}H NMR: δ = 8.12 (d, J = 6.8 Hz, 1 H), 7.94–7.91 (m, 2 H), 7.81 (s, 1 H), 7.63 (d, J = 9.1 Hz, 1 H), 7.17–7.11 (m, 3 H), 6.78 (t, J = 6.8 Hz, 1 H); IR (KBr): ν = 3032, 1634, 1600, 1513, 1475, 1401, 1169, 1080, 835, 772 cm^{-1}.

2-(4-Nitrophenyl)imidazo[1,2-a]pyridine **(4g)**: Yellow solid; m.p. 266–267°C (Lit.[30] m.p. 269°C); ^{1}H NMR: δ = 8.29 (d, J = 8.9 Hz, 2 H), 8.17 (d, J = 6.8 Hz, 1 H), 8.13 (d, J = 8.9 Hz, 2 H), 8.01 (s, 1 H), 7.67 (d, J = 9.0 Hz, 1 H), 7.25–7.23 (m, 1 H), 6.84 (t, J = 6.8 Hz, 1 H); IR (KBr): ν = 3037, 1640, 1599, 1520, 1500, 1110, 1082, 851, 744, 696 cm^{-1}.

2-(2-Furyl)imidazo[1,2-a]pyridine **(4h)**: Brown solid; m.p. 91–92°C (Lit.[24] m.p. 90–91°C); ^{1}H NMR: δ = 8.11 (d, J = 6.8 Hz, 1 H), 7.80 (s, 1 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.47 (d, J = 1.7 Hz, 1 H), 7.19 (t, J = 7.8 Hz, 1 H), 6.90 (d, J = 3.2 Hz, 1 H), 6.79 (t, J = 6.8 Hz, 1 H), 6.51–6.52 (dd, J = 3.5, 1.8 Hz, 1 H); IR (KBr): ν = 3089, 1636, 1608, 1486, 1236, 1082, 965, 745, 690 cm^{-1}.

3-Methyl-2-phenylimidazo[1,2-a]pyridine **(4i)**: Colourless solid; m.p. 91–92°C (Lit.[33] m.p. 90–91°C); ^{1}H NMR: δ = 7.91 (d, J = 6.8 Hz, 1 H), 7.81–7.779 (m, 2 H), 6.66–6.64 (d, J = 9.0 Hz, 1 H), 7.48–7.45 (m, 2 H), 7.36–7.34 (m, 1 H), 7.19–7.16 (t, J = 7.9 Hz, 1 H), 6.87–6.84 (t, J = 6.8 Hz, 1 H), 2.65 (s, 3 H); IR (KBr): ν = 3130, 3032, 1633, 1608, 1510, 1444, 1081, 920, 741, 693 cm^{-1}.

We gratefully acknowledge financial support from the National Natural Science Foundation of China (No. 20562005) and NSF of Jiangxi Province (No. 0620021 and No. 2007GZW0185).

Received 3 February 2008; accepted 3 May 2008
Paper 08/5085 *doi: 10.3184/030823408X320638*

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