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A facile solid-phase synthesis of 3,4,6-trisubstituted-2-pyridones using sodium benzenesulfinate as a traceless linker

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Abstract—A facile and traceless solid-phase synthesis of 3,4,6-trisubstituted-2-pyridones has been developed using polystyrene sodium benzenesulfinate resin. The chemistry is applicable to combinatorial library synthesis.

One of the challenges of solid-phase synthesis of compounds for drug discovery is developing synthetic routes that provide access to the target compound without leaving any trace of the tether that was used to link the starting reagent to the solid support. This is because complications may arise if these appendages are redundant and affect the activities of the compounds. In this regard, one of our interests is to develop the sulfone linker via polystyrene/1% divinylbenzene sodium sulfinate **1** as a traceless linker and to explore its new applications in solid-phase organic synthesis (SPOS). Earlier reports from other laboratories[1] and ours[2] have demonstrated the use of **1** as a solid support for SPOS and have shown the resulting sulfone linker derived from **1** to be a versatile and robust tether that offers a variety of on-resin functionalization or cleavage with additional changes.

2-Pyridones represent a unique class of pharmacophore, which are observed in various therapeutic agents[3] and antibiotics.[4] They are also versatile precursors for the construction of complex natural products,[5] pyridines[6] and larger pyridone systems such as those found in the nitroguanidine insecticide Imidacloprid[7] and subtype selective $GABA_A$ receptor agonists.[8] Consequently, methodologies for the preparation of pyridones have attracted much attention from both industry and academia, and various solution-phase syntheses of these compounds have been reported.[9,10] In recent years, synthetic methods for the preparation of 2- and 4-pyridones on solid-phase have also been examined.[11] To the best of our knowledge, only one of these reports concerns the traceless preparation of these compounds. In this report, 4-pyridones were prepared through condensation of resin-bound acylpyridiniums with Grignard reagents.[11e] We herein report the application of **1** for the convenient traceless syntheses of 2-pyridones. The key steps in our synthesis include (i) sulfinate *S*-alkylation, (ii) sulfone anion alkylation with an epoxide, (iii) γ-hydroxyl sulfone → γ-ketosulfone oxidation and (iv) traceless product release by a one-pot elimination–cyclization process (Scheme 1).

Polystyrene/1% divinylbenzene sodium benzenesulfinate (**1**) in NBu_4I/KI/DMF was reacted with an alkyl or aryl bromide at room temperature. The formation of **2** was easily monitored by IR spectroscopy for the appearance of the sulfone stretches (**2a**: ν_{asym} 1313.5 cm^{-1} and ν_{sym} 1150.4 cm^{-1}). Alkylation of **2** with an alkyl or aryl epoxide gave **3**, which could not be reliably analyzed by IR spectroscopy. Hence we proceeded to oxidize **3** with the Jones' reagent to give resin **4**. This transformation was monitored by IR spectroscopy for the appearance of the carbonyl stretch (**4a**: ν_{max} 1687.7 cm^{-1}). Treatment of **4** with potassium *tert*-butoxide/DMSO and 2-cyanoacetamide in air at 50 °C gave 3-cyano-2-pyridones in 28–48% overall yields.[12] Similarly, reactions with malonamide or methyl malonate monoamide gave pyridine-3-carboxylic acids and pyridine-3-carboxylic acid amides in 20–49% overall yields. However, in the cases of **4f** and **4i**, where R^1 and R^2 are both alkyl groups, it was observed that reactions at 50 °C gave the intermediates, 6-hydroxy-6-methyl-2-oxo-4-propyl-piperidine-3-carbonitrile[13] and 6-hydroxy-6-methyl-2-oxo-4-propyl-piperidine-3-carboxylic acid, respectively. Aromatization

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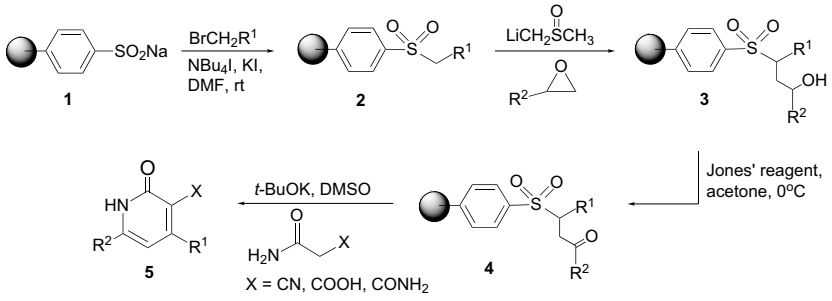

Scheme 1.

was achieved only when the reaction mixtures were heated at 70 °C. It was noted that for combinations where R^2 is an alkyl group, the corresponding 2-pyridones were obtained in lower yields. This would be expected as the protons on these methyl groups are acidic and could readily be removed under basic conditions to generate enolates which, in turn, could undergo side-reactions.

To provide an additional diversity in this library, we carried out the elimination–cyclization process under nitrogen. Decyanative aromatization due to 'oxygen starvation' occurred and 2-pyridones (**5l–o**) were obtained exclusively (Table 1).

In summary, this letter demonstrates a general protocol for the regiospecific solid-phase synthesis of 3,4,6-trisubstituted-2-pyridone derivatives using polystyrene/1% divinylbenzene sodium sulfinate as a traceless linker. Product **5** precipitated from water under acidic conditions and could be expediently purified without the need for column chromatography.[12] Since a variety of reagents can be used in steps (i), (ii) and (iv), the overall strategy is applicable for library generation.

Table 1. Solid-phase synthesis of 3,4,6-trisubstituted-2-pyridones

Entry	X	R^1	R^2	% Yield[a]
5a	CN	Ph	Ph	43
5b	CN	*p*-BrPh	Ph	45
5c	CN	*p*-MeOPh	Ph	48
5d	CN	Ph	Me	29
5e	CN	*p*-MeOPh	Me	28
5f	CN	$CH_3CH_2CH_2$	Me	14[b]
5g	COOH	Ph	Ph	46
5h	COOH	Ph	Me	20
5i	COOH	$CH_3CH_2CH_2$	Me	12[b]
5j	$CONH_2$	Ph	Ph	49
5k	$CONH_2$	Ph	Me	26
5l	H	Ph	Ph	49
5m	H	*p*-BrPh	Ph	44[c]
5n	H	Ph	Me	28
5o	H	*p*-BrPh	Me	25

[a] Purified yield calculated based on original loading of the resin. Purities were >97% as evaluated by NMR.

[b] Yield obtained after further purification by flash chromatography.

[c] Crystallographic data (excluding structure factors) of **5m** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 239935.

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12. Typical experimental procedure: Resin **1** (2.1 mmol/g, 100–200 mesh) was obtained from Tianjin Nankai Hecheng Science and Technology Co Ltd, China. The resin (1 g) was swollen under nitrogen in 20 mL DMF for 30 min. Alkyl or aryl bromide (5 equiv), KI (5 equiv) and tetrabutylammonium iodide (1 equiv) were added and the mixture was shaken at room temperature for 24 h. The resin was then filtered and washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), ethanol (20 mL × 2), CH_2Cl_2 (20 mL × 2) and diethyl ether (20 mL × 2), and dried overnight in a vacuum oven at 40 °C to afford resin **2**. *n*-BuLi (5 equiv) was added to DMSO (10 equiv) in THF (10 mL), at 0 °C, and the mixture was stirred for 5 min. The resulting dimsyl anion solution was transferred to a suspension of resin **2** (0.3 g, 1 equiv) in THF (8 mL) at room temperature and the mixture was shaken for 1 h. Epoxide (8 equiv) was added and the mixture was shaken for a further 12 h, after which, the reaction was quenched with 10% HCl and filtered. The resin was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), ethanol (20 mL × 2), CH_2Cl_2 (20 mL × 2) and diethyl ether (20 mL × 2), and dried overnight in a vacuum oven at 40 °C to afford resin **3**. Jones' reagent (10 equiv) was added to a suspension of resin **3** (0.3 g, 1 equiv) in acetone (8 mL), at 0 °C, and the mixture was shaken for 24 h. The resin was filtered and washed sequentially with H_2O (20 mL × 2), CH_2Cl_2 (20 mL × 2) and diethyl ether (20 mL × 2), and dried overnight in a vacuum oven at 40 °C to afford resin **4** as light green coloured beads. Resin **4** (1 g) was swollen in 20 mL DMSO for 1 h. *t*-BuOK (9 equiv) and the amide (12 equiv) were added and the resulting mixture was heated at 50 °C in air for a further 8 h, after which the resin was filtered and washed with DMF (5 mL × 2) and H_2O (5 mL × 2). The combined washings were diluted with H_2O (80 mL) and 2 M HCl was added until pH 2 was achieved. The precipitate formed was filtered, washed with water and dried under vacuum to give **5**. Compounds **5a**,[14] **5e**[14] and **5l**[9] have been reported previously.[14] **5b**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.83 (s, 1H, CH), 7.53 (m, 3H, ArH), 7.69 (m, 2H, ArH), 7.76 (m, 2H, ArH), 7.87 (m, 2H, ArH), 12.60 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 162.1, 160.9, 131.4, 130.1, 128.6, 127.5, 126.7, 123.7, 116.5, 103.7, 95.4. HRMS (EI): Calcd for $C_{18}H_{11}BrN_2O$ 350.0055, Found 350.0050. **5c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 6.79 (s, 1H, CH), 7.12 (d, J = 8.7 Hz, 2H, MeOArH), 7.55 (m, 3H, ArH), 7.74 (d, J = 8.7 Hz, 2H, MeOArH), 7.90 (m, 2H, ArH), 12.70 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 162.2, 161.1, 159.2, 151.0, 132.3, 131.1, 129.9, 128.9, 127.7, 116.8, 114.2, 105.9, 97.5, 55.4. HRMS (EI): Calcd for $C_{19}H_{14}N_2O_2$ 302.1055, Found 302.1052. **5d**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 6.33 (s, 1H, CH), 7.55 (m, 5H, ArH), 12.5 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 161.4, 160.1, 152.2, 136.1, 130.3, 128.8, 127.9, 116.6, 106.5, 97.3, 19.1. HRMS (EI): Calcd for $C_{13}H_{10}N_2O$: 210.0793, Found 210.0789. **5f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, J = 7.3 Hz, 3H, CH_3), 1.68 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 3.11 (m, 2H, CH_2), 6.27 (s, 1H, CH), 13.1 (br s, 1H, NH). ^{13}C NMR (500 MHz, $CDCl_3$): 160.7, 160.5, 152.1, 135.9, 106.8, 97.6, 36.9, 24.1, 19.4, 14.8. HRMS (EI): Calcd for $C_{10}H_{12}N_2O$ 176.0950, Found 176.0951. **5g**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.71 (s, 1H, CH), 7.46 (m, 8H, ArH), 7.87 (m, 2H, ArH), 12.99 (br, 1H, COOH). ^{13}C NMR (500 MHz, DMSO-d_6): 166.5, 162.5, 153.0, 148.1, 138.4, 132.9, 130.4, 128.9, 128.3, 127.6, 127.4, 118.3, 107.9. HRMS (EI): Calcd for $C_{18}H_{13}NO_3$ 291.0895, Found 291.0894. **5h**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.89 (s, 3H, CH_3), 6.41 (s, 1H, CH), 7.45 (m, 3H, ArH), 7.65 (m, 2H, ArH), 12.78 (br, 1H, COOH). ^{13}C NMR (500 MHz, DMSO-d_6): 164.1, 163.1, 161.2, 136.9, 136.5, 126.7, 126.5, 126.1, 117.4, 103.9, 21.2. HRMS (EI): Calcd for $C_{13}H_{11}NO_3$ 229.0739, Found 229.0738. **5i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, J = 7.3 Hz, 3H, CH_3), 1.75 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 3.21 (m, 2H,CH_2), 6.92 (s, 1H, CH), 11.28 (br, 1H, NH), 15.13 (br s, 1H, COOH). ^{13}C NMR (500 MHz, $CDCl_3$): 166.9, 165.4, 165.1, 138.3, 116.5, 110.5, 37.5, 23.8, 19.5, 14.9. HRMS (EI): Calcd. for $C_{10}H_{13}NO_3$ 195.0895, Found 195.0897. **5j**: ^{1} H NMR (300 MHz, DMSO-d_6): δ 4.87 (m, 2H, NH_2), 6.66 (s, 1H, CH), 7.49 (m, 6H, ArH), 7.73 (m, 2H, ArH), 7.81 (m, 2H, ArH), 11.95 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 167.4, 163.7, 161.2, 151.8, 149.6, 138.5, 129.9, 128.8, 128.7, 128.5, 128.2, 127.8, 127.0, 106.8. HRMS (EI): Calcd for $C_{18}H_{14}N_2O_2$ 290.1055, Found 290.1053. **5k**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 4.91 (m, 2H, NH_2), 6.50 (s, 1H, CH), 7.41 (m, 3H, ArH), 7.58 (m, 2H, ArH), 11.83 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 167.4, 164.8, 161.1, 137.5, 136.9, 128.7, 128.5, 128.1, 127.9, 104.6, 19.3. HRMS (EI): Calcd for $C_{13}H_{12}N_2O_2$ 228.0899, Found 228.0894. **5m**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.68 (m, 1H, CH), 7.00 (m, 1H, CH), 7.49 (m, 3H, ArH), 7.67 (m, 2H, ArH), 7.70 (m, 2H, ArH), 7.89 (m, 2H, ArH), 11.7 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 167.0, 155.4, 148.1, 137.1, 133.3, 131.6, 130.3, 129.9, 127.9, 125.3, 114.6, 107.4. HRMS (EI): Calcd for $C_{17}H_{12}BrNO$ 325.0102, Found 325.0101. **5n**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 6.34 (m, 1H, CH), 6.37 (m, 1H, CH), 7.47 (m, 3H, ArH), 7.65 (m, 2H, ArH), 11.6 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 163.3, 151.9, 145.8, 137.5, 129.3, 128.9, 126.6, 112.7, 103.1, 18.8. HRMS (EI): Calcd for $C_{12}H_{11}NO$ 185.0841, Found 185.0839. **5o**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 6.33 (m, 2H, CH), 7.64 (m, 4H, ArH), 11.6 (br, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): 163.2, 150.5, 146.0, 136.6, 131.8, 128.7, 122.7, 112.7, 102.7, 18.7. HRMS (EI): Calcd for $C_{12}H_{10}BrNO$ 262.9946, Found 262.9945.
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