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Synthesis of Methyl N-Aryl Oxamate Using Soluble Polymer Support

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Abstract: A variety of methyl N-aryl oxamates were synthesized using poly(ethylene glycol) (PEG) as a soluble polymer support and a monoproctection group with excellent yields.

Keywords: Methyl N-aryl oxamate, soluble polymer support, synthesis

The oxalyl group has been reported in a variety of biologically active series. In particular, oxamic acid esters have been found to be potent, orally active anti-allergy agents.[1–4] It is typically made using traditional solution-phase synthesis, which treats the requisite arylamines with an alkyloxalyl chloride in the presence of a base. The purification of products for further modification is difficult.

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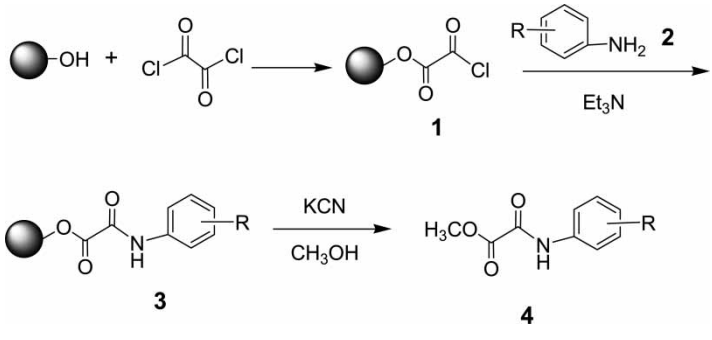
Liquid-phase synthetic approaches using soluble polymer support couple the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis) with those of solid-phase methods (use of excessive reagents, easy workup, and easy purification of products).[5,6] Poly(ethylene glycol) (PEG) is among the most studied soluble polymers for organic synthesis.[7–9] PEG support is soluble in most organic solvents such as DMF, dichloromethane, acetonitrile, and toluene. However, it has a strong tendency to precipitate in certain solvents such as diethyl ether, isopropyl alcohol, and cold ethanol. Hence purification is performed by simple precipitation, filtration, and washing of the polymer matrix. UV, IR, and NMR could be used readily to analyze the configuration of the polymer-supported intermediates and products without preliminary cleavage of the growing structure.

Keeping these facts in mind, in continuation of our efforts to utilize soluble polymer-supported systems in organic synthesis,[10–14] we report herein the new method of synthesizing methyl N-aryl oxamate using PEG as soluble polymer support. The synthetic route is illustrated in Scheme 1.

We anchored oxalyl chloride on PEG to yield a novel PEG-bound reactive acid chloride, one of which oxalyl groups was protected by PEG. PEG was used as a soluble polymer support and monoprotection group.

Considering the balance between loading capacity and the solubility profile of the resulting polymer derivatives, we chose dihydroxy PEG of molecular weight 3400 as support. PEG reacted with excess of oxalyl chloride in dried CH_2Cl_2 to give PEG-bound acid chloride **1** through ester linkage. The reaction proceeds to completion as evidenced by the disappearance of absorption for the hydroxy at 3469 cm^{-1} in the IR spectrum. Then, PEG-bound acid chloride was treated with various aromatic amines at rt to give PEG-bound oxamic acid ester **3**. The appearances of absorption for acylamide and aryl group in IR spectrum are clear evidence for the formation of **3**. Treatment of **3** with 1% KCN in methanol resulted in a very efficient cleavage from PEG support to provide the corresponding crude product **4**, which was purified by chromatography.



Scheme 1.

To establish the scope of this reaction, a variety of arylamines was investigated. Table 1 includes representatire examples.

It is note worthy that the reaction is easily carried out using PEG as a soluble polymer support and monoprotection group. The PEG-bound intermediates were easily isolated and purified by simple precipitating, filtering, and washing with Et_2O to remove the unreacted low molecular materials and by-products, avoiding tedious workup procedures, in contrast to using conventional, nonpolymeric reagent methods. TLC could be used to detect the low molecular reagent and by-product to confirm their complete removal. The configuration of PEG-bound product was easily analyzed with routine analytical methods (UV, IR, NMR) without following the cleave-and-analysis technique, or spectral analysis technique, in contrast to insoluble polymers as polymer supports.

In summary, we have successfully developed the new liquid-phase combinatorial synthesis of methyl N-aryl oxamate from oxalyl chloride and arylamine using PEG as soluble polymer support in excellent yields.

EXPERIMENTAL

All organic solvents and bases were dried by standard methods. PEG and PEG-bound compounds were melted at 80°C in a vacuum for 30 min before use to remove traces of moisture. IR spectra were recorded on a IR spectrum one (PE) spectrometer; ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity Inova 600 spectrometer in $CDCl_3$ using TMS as internal standard. Elemental analyses were done on a PE 2400 CHN analyzer. Melting points were measured on a WRS-1A digital melting-point apparatus and are uncorrected.

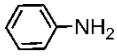
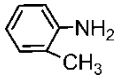
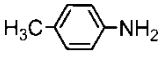
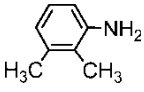
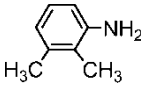
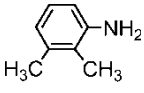
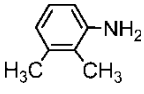
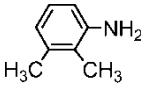
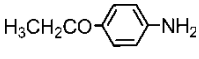
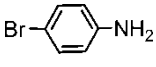
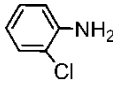
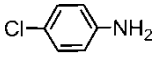
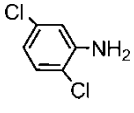
Preparation of PEG-Bound Acid Chloride 1

A solution of PEG (12.00 g, 6.96 mmol) in CH_2Cl_2 (40 mL) was added dropwise to an ice-cold solution of oxalyl chloride (2.44 mL, 14 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred at rt for 3 h. The resulting mixture was concentrated to remove the solvent and excess of oxalyl chloride; the residue, PEG-bound acid chloride, was used to proceed to the next reaction.

General Procedure for Preparation of PEG-Bound N-Aryl Oxamate Esters 3

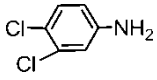
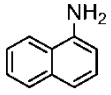
PEG-bound acid chloride **1** (3.00 g) was redissolved in CH_2Cl_2 (15 mL) and added dropwise to a solution of arylamine (5.22 mmol) and triethylamine

Table 1. Synthesis of methyl N-aryl oxamate using PEG as soluble polymer support

Product **4**	Substrate ($ArNH_2$) **2**	Mp (°C)	Yield (%)[a]
4a		106.6–108.2	89
4b		78.4–79.7	92
4c		147.0–147.4	93
4d		102.1–102.6	95
4e		75.2–76.0	94
4f		93.1–94.5	95
4g		78.4–79.8	94
4h		52.3–53.6	96
4i		147.5–148.1	98
4j		164.9–166.4	92
4k		86.8–88.0	90
4l		164.2–164.8	91
4m		124.2–125	90

(*continued*)

Table 1. Continued

Product **4**	Substrate ($ArNH_2$) **2**	Mp (°C)	Yield (%)[a]
4n		160.6–161.9	91
4o		104.7–106.4	97

[a]Isolated yields.

(0.36 mL, 2.16 mmol) in CH_2Cl_2 at rt with stirring. After 4 h, the resulting mixture was washed with H_2O and the aqueous phase was extracted with CH_2Cl_2 (30 mL × 3). Combined organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated, and precipitated with cold Et_2O (300 mL). The precipitate was filtered, washed with cold Et_2O (30 mL × 3), and dried under vacuum to afford **3**.

General Procedure for Preparation of Methyl N-Aryl Oxamate 4

Compound **3** was treated with 1% KCN in CH_3OH at rt for 5 h. After removing CH_3OH, the residue was redissolved in CH_2Cl_2 (3 mL); the detached PEG was precipitated by adding cold Et_2O and removed by filtering. Then, the combined filtrate was evaporated to give crude product, which was purified by column chromatography on silica gel (EtOAc–*n*-hexane, 1:3) to give the desired pure product **4**.

Data

4a: Methyl N-phenyl oxamate. IR: 3342 (NH), 1729 (CO), 1698 (CONH) cm^{-1}; ^1H NMR: d = 3.979 (s, 3 H, CO_2CH_3), 7.202 (m, 1 H, ArH), 7.400 (m, 2 H, ArH), 7.651 (m, 2 H, ArH), 8.864 (s, 1 H, NH); ^{13}C NMR: d = 54.583, 120.305 (2 C), 126.095, 129.738 (2 C), 136.669, 154.013, 161.958; anal. calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.15; H, 5.12; N, 7.78.

4b: Methyl N-(2-methylphenyl) oxamate. IR: 3383 (NH), 1727 (CO), 1678 (CONH) cm^{-1}; ^1H NMR: d = 2.330 (s, 3 H, Ar-CH_3), 3.978 (s, 3 H, CO_2CH_3), 7.132 (m, 1 H, ArH), 7.226 (d, 1 H, J = 7.8 Hz, ArH), 7.270 (m, 1 H, ArH), 8.020 (d, 1 H, J = 7.8 Hz, ArH), 8.819 (s, 1 H, NH); ^{13}C NMR: d = 17.954, 54.541, 122.193, 126.431, 127.491, 128.910,

131.088, 134.674, 154.055, 162.076; anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.06; H, 5.68; N, 7.09.

4c: Methyl N-(4-methylphenyl) oxamate. IR: 3338 (NH), 1726 (CO), 1696 (CONH) cm^{-1}; ^1H NMR: d = 2.342 (s, 3 H, Ar-CH_3), 3.970 (s, 3 H, CO_2CH_3), 7.189 (d, 2 H, $J = 8.4$ Hz, ArH), 7.535 (d, 2 H, $J = 8.4$ Hz, ArH), 8.827 (s, 1 H, NH); ^{13}C NMR: d = 21.455, 54.534, 120.252 (2 C), 130.211 (2 C), 134.136, 135.883, 153.883, 162.038; anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.98; H, 5.79; N, 7.33.

4d: Methyl (2,3-dimethylphenyl) oxamate. IR: 3240 (NH), 1741 (CO), 1682 (CONH) cm^{-1}; ^1H NMR: 2.205 (s, 3 H, Ar-CH_3), 2.317 (s, 3 H, Ar-CH_3), 3.978 (s, 3 H, CO_2CH_3), 7.065 (d, 1 H, $J = 7.8$ Hz, ArH), 7.145 (t, 1 H, $J = 7.8$ Hz, ArH), 7.718 (d, 1 H, $J = 7.8$ Hz, ArH), 8.802 (s, 1 H, NH); ^{13}C NMR: d = 13.960, 21.032, 54.465, 121.014, 126.637, 128.487, 128.681, 134.334, 138.088, 154.341, 162.198; anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.54; H, 6.70; N, 6.84.

4e: Methyl (2,4-dimethylphenyl) oxamate. IR: 3342 (NH), 1738 (CO), 1691 (CONH) cm^{-1}; ^1H NMR: d = 2.286 (m, 6 H, Ar-CH_3), 3.974 (s, 3 H, $COOCH_3$), 7.047 (m, 2 H, ArH), 7.828 (m, 1 H, ArH), 8.743 (s, 1 H, NH). ^{13}C NMR: d = 17.904, 21.375, 31.377, 54.450, 122.430, 127.976, 129.135, 131.767, 132.080, 136.306, 154.089, 162.168; anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 64.01; H, 6.45; N, 6.58.

4f: Methyl (3,4-dimethylphenyl) oxamate. IR: 3341 (NH), 1743 (CO), 1685 (CONH) cm^{-1}; ^1H NMR: d = 2.271 (s, 3 H, Ar-CH_3), 2.298 (s, 3 H, Ar-CH_3), 3.992 (s, 3 H, CO_2CH_3), 7.147 (d, 1 H, $J = 7.8$ Hz, ArH), 7.407 (d, 2 H, $J = 7.8$ Hz, ArH), 8.795 (s, 1 H, NH); ^{13}C NMR: d = 19.773, 20.376, 54.476, 117.780, 121.491, 130.665, 134.407, 134.613, 138.065, 153.849, 162.099; anal. calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.81; H, 6.28; N, 6.84.

4g: Methyl (2,6-dimethylphenyl) oxamate. IR: 3337 (NH), 1740 (CO), 1688 (CONH) cm^{-1}; ^1H NMR: d = 2.249 (s, 6 H, Ar-CH_3), 3.990 (s, 3 H, CO_2CH_3), 7.147 (m, 3 H, ArH), 8.398 (s, 1 H, NH); ^{13}C NMR: d = 18.942 (2 C), 54.438, 128.559 (2 C), 128.922 (2 C), 132.499, 135.501, 154.787, 161.851; anal. calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.57; H, 6.19; N, 6.30.

4h: Methyl (2,5-dimethylphenyl) oxamate. IR: 3344 (NH), 1739 (CO), 1689 (CONH) cm^{-1}; ^1H NMR: d = 2.279 (s, 3 H, Ar-CH_3), 2.340 (s, 3 H, Ar-CH_3), 3.977 (s, 3 H, CO_2CH_3), 6.938 (d, 1 H, $J = 7.8$ Hz, ArH), 7.089 (d, 1 H, $J = 7.8$ Hz, ArH), 7.823 (s, 1 H, ArH), 8.765 (s, 1 H, NH);

^{13}C NMR: d = 17.507, 21.619, 54.469, 122.826, 125.878, 127.228, 130.875, 134.456, 137.321, 154.032, 162.160; anal. calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.61; H, 6.39; N, 6.80.

4i: Methyl (4-propionylphenyl) oxamate. IR: 3344 (NH), 1725 (CO), 1705 (CONH) cm^{-1}; ^{1}H NMR: d = 1.412 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 3.963 (s, 3 H, CO_2CH_3), 4.032 (m, 2 H, J = 7.2 Hz, OCH_2 CH_3), 6.900 (d, 2 H, J = 9.0 Hz, ArH), 7.554 (d, 2 H, J = 9.0 Hz, ArH), 8.777 (s, 1 H, NH); ^{13}C NMR: d = 15.253, 54.431, 64.169, 115.396, 121.854 (2 C), 129.707, 153.765, 157.079, 162.114; anal. calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.22; H, 5.67; N, 6.14.

4j: Methyl (4-bromophenyl) oxamate. IR: 3346 (NH), 1743(CO), 1688 (CONH) cm^{-1}; ^{1}H NMR: d = 3.983 (s, 3 H, CO_2CH_3), 7.508 (d, 2 H, J = 8.4 Hz, ArH), 7.561 (d, 2 H, J = 8.4 Hz, ArH), 8.864 (s, 1 H, NH); ^{13}C NMR: d = 54.713, 118.932, 121.823 (2 C), 132.782 (2 C), 135.726, 154.013, 161.725; anal. calcd. for $C_9H_8BrNO_3$: C, 41.89; H, 3.12; N, 5.43. Found: C, 41.82; H, 3.07; N, 5.59.

4k: Methyl (2-chlorophenyl) oxamate. IR: 3366 (NH), 1736(CO), 1682 (CONH) cm^{-1}; ^{1}H NMR: d = 3.999 (s, 3 H, CO_2CH_3), 7.141 (m, 1 H, ArH), 7.336 (m, 1 H), 7.435 (d, 1 H, J = 7.8 Hz, ArH), 8.453 (d, 1 H, J = 8.4 Hz, ArH), 9.476 (s, 1 H, NH); ^{13}C NMR: d = 54.736, 121.709, 123.955, 126.496, 128.418, 129.784, 133.606, 154.039, 161.451; anal. calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; N, 6.56. Found: C, 50.77; H, 3.81; N, 6.42.

4l: Methyl (4-chlorophenyl) oxamate. IR: 3349 (NH), 1745 (CO), 1688 (CONH) cm^{-1}; ^{1}H NMR: d = 3.985 (s, 3 H, CO_2CH_3), 7.362 (d, 2 H, J = 9.0 Hz, ArH), 7.620 (d, 2 H, J = 9.0 Hz, ArH), 8.892 (s, 1 H, NH); ^{13}C NMR: d = 54.486, 121.268 (2 C), 129.572 (2 C), 130.956, 134.961, 153.751, 161.479; anal. calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; N, 6.56. Found: C, 50.52; H, 3.63; N, 6.73.

4m: Methyl (2,5-dichlorophenyl) oxamate. IR: 3344 (NH), 1725 (CO), 1705 (CONH) cm^{-1}; ^{1}H NMR: d = 4.007 (s, 3 H, CO_2CH_3), 7.119 (m, 1 H, ArH), 7.346 (d, 1 H, J = 8.6 Hz, ArH), 8.516 (d, 1 H, J = 8.6 Hz, ArH), 9.452 (s, 1 H, NH); ^{13}C NMR: d = 54.804, 121.617, 122.033, 126.446, 130.463, 134.262, 134.464, 154.047, 161.199; anal. calcd. for $C_9H_7Cl_2NO_3$: C, 43.58; H, 2.84; N, 5.65. Found: C, 43.63; H, 3.05; N, 5.49.

4n: Methyl (3,4-dichlorophenyl) oxamate. IR: 3342 (NH), 1731 (CO), 1696 (CONH) cm^{-1}; ^{1}H NMR: d = 3.988 (s, 3 H, CO_2CH_3), 7.436 (d, 1 H, J = 8.4 Hz, ArH), 7.477 (d, 1 H, J = 8.4 Hz, ArH), 8.859 (s, 1 H, NH); ^{13}C NMR: d = 55.287, 119.534, 122.006, 127.463, 128.916, 132.167,

134.269; anal. calcd. for $C_9H_7Cl_2NO_3$: C, 43.58; H, 2.84; N, 5.65. Found: C, 44.06; H, 2.91; N, 5.76.

4o: Methyl (naphthalen-5-yl) oxamate. IR: 3390 (NH), 1712 (CO), 1705 (CONH) cm^{-1}; ^1H NMR: d = 4.024 (s, 3 H, CO_2CH_3), 7.549 (m, 3 H, ArH), 7.754 (d, 1 H, $J = 7.8$ Hz, ArH), 7.888 (t, 2 H, $J = 7.2$ Hz, ArH), 8.168 (d, 1 H, $J = 7.2$ Hz, ArH), 9.411 (s, 1 H, NH); ^{13}C NMR: d = 54.644, 120.049, 120.374, 126.198, 126.522, 126.789, 127.007, 127.228, 129.406, 131.111, 134.437, 154.585, 162.145; anal. calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.33; H, 4.95; N, 6.40.

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