Clay catalyzed conversion of isatoic anhydride† to 2-(*o*-aminophenyl)oxazolines

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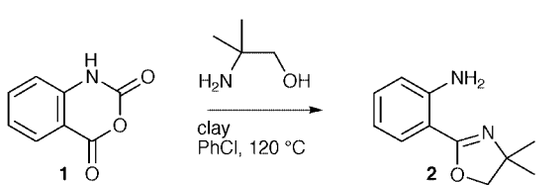
A simple and environmentally safe procedure for the preparation of 2-(*o*-aminophenyl)oxazolines from isatoic anhydride is presented. A series of chiral derivatives of the title compound is prepared in moderate yield *via* natural kaolinitic clay catalyzed reactions with optically pure 2-aminoalcohols. Reaction of polymer-supported isatoic anhydride under these conditions with chiral 2-aminoalcohols proceeds to furnish polymer-anchored analogues.

Introduction

Oxazoline is an important functionality as a protecting group[1] in organic synthesis. The optically active aromatic oxazolines are used extensively to control the stereochemistry in many asymmetric transformations.[2] In our previous communications[3] we have demonstrated the use of natural kaolinitic clay as an efficient catalyst for the preparation of 2-oxazolines from nitriles. We wish to present the application of this catalyst to the conversion of isatoic anhydride, **1**, to 2-(*o*-aminophenyl)-oxazolines. Chiral analogues of these compounds have been used in asymmetric synthesis.[4] The chemistry of **1** has been reviewed at length by Coppola;[5] the example of the preparation of 2,3-dihydrobenzothiazol from **1** and 2-aminothiophenol[6] is mentioned therein. Coppola has also recently reported the preparation of polymer-supported isatoic anhydride and its use as a scavenger of amines.[7] We have an interest in the preparation of polymer-supported, chiral oxazoline based ligands for application in heterogeneous asymmetric catalytic reactions. We wish to report our results on the reactions of polymer-supported isatoic anhydride under these conditions to furnish the polymer-anchored title compound.

Results and discussions

Reaction of **1** with 2-aminoalcohol was carried out in dry chlorobenzene at 120 °C in the presence of acidic kaolinitic clay[8] as the catalyst to furnish 2-(*o*-aminophenyl)oxazoline (Scheme 1). We presume that the Lewis acidic sites of the



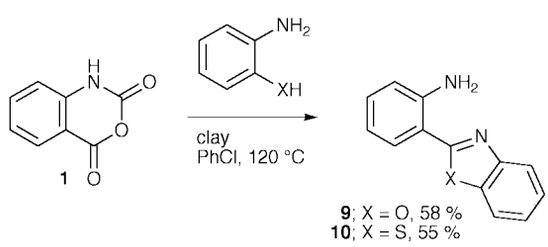
Scheme 1

catalyst assist the nucleophilic attack of the amino group on C-4 of **1**, which is followed by cyclization to give the oxazoline. The final product is formed by the loss of carbon dioxide to give the free amine.

† The IUPAC name for isatoic anhydride is (2*H*)-3,1-benzoxazine-2,4-(1*H*)-dione.

A series of derivatives of 2-(*o*-aminophenyl)oxazolines were synthesized with different 2-aminoalcohols and the results are summarized in Table 1. Commercially available Montmorillonite K10 was also found to be an efficient catalyst and the reaction was found to proceed much more quickly when carried out under microwave conditions (entry 1). However, experiments with $ZnCl_2$ gave a slightly lower yield (entry 1) for this reaction. As we were interested in chiral derivatives of this type of compound, different optically pure 2-aminoalcohols were used for this reaction to furnish the desired products in low to moderate yields. Slightly modified reactions with an excess of **1** showed some improvement in the conversion as is evident from entries 4 to 7. The amino oxazoline from entry 6 was converted to its NHTs derivative, the optical rotation of which was in accord with the reported value,[4a] indicating no loss of optical purity during the reaction.

The catalytic conversion of **1** also works with 2-aminophenol and 2-aminothiophenol (Scheme 2) with the formation of **9** and



Scheme 2

10, respectively; only a little amount of disulfide was formed in latter case.

Our continuing aim is the preparation of polymer-supported oxazolinyl ligands for heterogeneous asymmetric catalysis. We prepared the polymer-supported isatoic anhydride **11** from chloromethylated styrene–divinylbenzene polymer (4.8 equiv. Cl^- g^{-1}) by the procedure described by Coppola.[7] A sample of **11** was exposed to 2.5 equivalents of D-2-aminobutanol and a catalytic amount of kaolinitic clay in chlorobenzene to afford polymer-anchored amino oxazoline **12** (Scheme 3).

The FT-IR analysis of the polymer beads of **12** showed a peak at 3419 cm^{-1} and the absence of the two carbonyl peaks at 1778 and 1725 cm^{-1} of the polymer **11** indicated successful conversion. Two more chiral polymer-supported amino oxazolines **13** and **14** were prepared by the same method using L-isoleucinol and L-phenylalaninol as the aminoalcohols.

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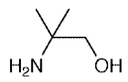
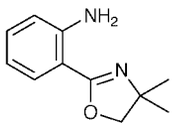
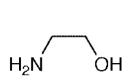
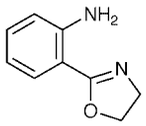
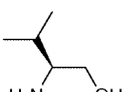
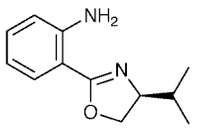
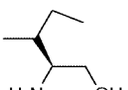
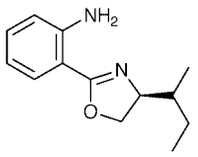
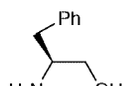
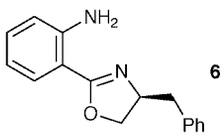
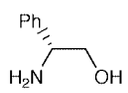
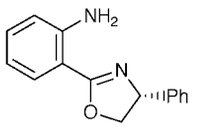
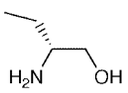
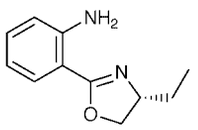
Table 1 Catalytic conversion of isatoic anhydride to 2-(*o*-aminophenyl)oxazolines[a]

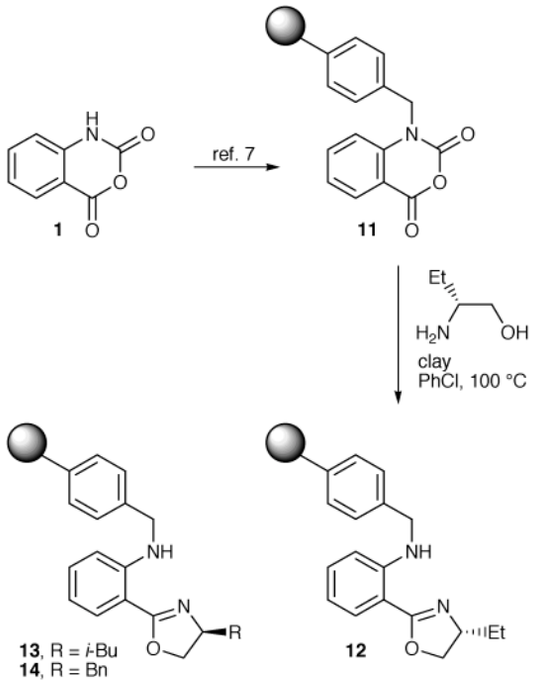
Entry	Aminoalcohol	Product		Yield (%)[b]
1			**2**	65 70[c] 45[d] 55[e]
2			**3**	40 45[c]
3			**4**	41[f]
4			**5**	50 55[f]
5			**6**	58[f]
6			**7**	35 62[f]
7			**8**	70[f]

[a] Isatoic anhydride was heated in dry chlorobenzene under Ar with 2-aminoalcohol (2.5 eq.), catalyst (20% w/w) for 20 h. [b] Isolated yield. All the compounds were characterized by usual spectral methods. [c] With microwave irradiation in a domestic oven for 20 min. [d] With $ZnCl_2$ (5 mol%). [e] With Montmorillonite K10 (20% w/w). [f] With 2 eq. of isatoic anhydride.

Thus in this paper we have presented a simple and efficient procedure for preparation of 2-(*o*-aminophenyl)oxazolines from isatoic anhydride. We have also presented our initial results on the preparation of the polymer-supported title compounds.

Experimental

Melting points were recorded on a Büchi melting point B-540 apparatus and are uncorrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on a Bruker AC 200 NMR spectrometer (200 MHz). Mass spectra were recorded on a Finnigan MAT 1020B 70 eV GC-MS (EI) instrument. The FT-IR spectra were recorded on a ATI-Mattson Res. Series 1 spectrometer and Microanalyses were carried out on a Carlo-Erba instrument. Optical rotations were measured on a JASCO DIP-181 digital polarimeter at 24 °C and are reported in units of 10^{-1} deg cm^2 g^{-1}. Kaolinitic clay was received from RRL, Trivandrum as a gift sample,[8b] and



Scheme 3

Montmorillonite K10 and isatoic anhydride were purchased from Aldrich Chemicals. Merrifield resin, the copolymer of chloromethylpolystyrene cross-linked with 1% divinylbenzene, with loading of 4.8 equiv. Cl^- g^{-1} resin was obtained from Ion Exchange (India) Ltd. as a gift sample. Optically pure amino alcohols were prepared from chiral amino acids by the known procedure.[9] Chlorobenzene was distilled over CaH_2 and stored over activated molecular sieves.

2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 2

A mixture of **1** (0.50 g; 3.06 mmol), 2-amino-2-methylpropan-1-ol (0.68 g; 7.64 mmol) and kaolinitic clay (0.10 g) was stirred in chlorobenzene (5 mL) at *ca.* 120 °C for 20 h. After completion of the reaction, the catalyst was filtered off and the product purified by column chromatography on neutral alumina to afford compound **2** as a white solid (0.38 g; 65%). Mp 103.6–106.0 °C; IR ν 3439, 3187, 3151, 1401, 1329, 1185, 752 cm^{-1}; ^{1}H NMR δ 1.35 (s, 6H), 4.05 (s, 2H), 6.35 (br s, 2H), 6.65 (m, 1H), 7.15–7.25 (m, 2H), 7.65–7.70 (m, 1H); MS *m*/*z* (%) 190 (M$^+$, 91), 175 (100), 145 (51), 130 (65), 118 (76), 92 (20), 65 (13). Calcd. for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.74. Found: C, 69.58; H, 7.31; N, 14.89%.

The same procedure was followed for the preparation of all the 2-(*o*-aminophenyl)oxazolines using the appropriate amino-alcohol as listed in Table 1.

2-(4,5-Dihydro-1,3-oxazol-2-yl)aniline 3

Light yellow oil. IR ν 3379, 3187, 3120, 1625, 1390, 1260, 747 cm^{-1}; ^{1}H NMR δ 4.00–4.12 (m, 2H), 4.12–4.25 (m, 2H), 6.05 (br s, 2H), 6.55–6.85 (m 2H), 7.15 (m, 1H), 7.70 (m, 1H); MS *m*/*z* (%) 162 (M$^+$, 100), 130 (48), 118 (70), 106 (55), 92 (20), 65 (20). Calcd. for $C_9H_{10}N_2O$: C, 66.66; H, 6.17; N, 17.28. Found: C, 66.45; H, 6.28; N, 17.42%.

2-(4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 4

Pale yellow oil. $[\alpha]_D$ −1.35 (0.85, $CHCl_3$); IR ν 3395, 3288, 2955, 1686, 1633, 1598, 1456, 1047, 746 cm^{-1}; ^{1}H NMR δ 0.90–1.10 (2 d, J = 7.8 Hz, 6H), 1.65–1.90 (m, 1H), 3.95–4.20 (m, 2H), 4.22–4.40 (m, 1H), 6.50 (br s, 2H), 6.55–6.80 (m 2H), 7.10–7.30 (m, 1H), 7.60–7.72 (m, 1H); MS *m*/*z* (%) 204 (M$^+$, 50), 193 (10), 161 (100), 133 (32), 119 (25), 106 (10), 92 (15). Calcd. for

$C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.72. Found: C, 70.91; H, 7.82; N, 13.64%.

2-(4-*sec*-Butyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 5

Pale yellow oil. $[a]_D$ +7.94 (1.26, $CHCl_3$); IR *v* 3462, 3283, 2960, 1634, 1599, 1491, 1046, 969, 748 cm^{-1}; ^1H NMR δ 0.88 (d, J = 6.0 Hz, 3H), 0.93 (t, J = 6.0 Hz, 3H), 1.15–1.40 (m, 1H), 1.50–1.80 (m, 2H), 4.00 (m, 1H), 4.15–4.40 (m, 2H), 6.15 (br s, 2H), 6.52–6.55 (m 2H), 7.10–7.30 (m, 1H), 7.65–7.75 (d, J = 8.0 Hz, 1H); MS *m*/*z* (%) 218 (M^+, 45), 187 (10), 161 (100), 133 (40), 118 (18), 106 (10), 92 (8). Calcd. for $C_{13}H_{18}N_2O$: C, 71.56; H, 8.27; N, 12.84. Found: C, 71.10; H, 8.71; N, 12.20%.

2-(4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 6

Light yellow thick oil. $[a]_D$ +26.54 (1.04, $CHCl_3$); IR *v* 3448, 3320, 3042, 2901, 1629, 1480, 1200, 1150, 769 cm^{-1}; ^1H NMR δ 2.75 (dd, J = 14.0 and 8.0 Hz, 1H), 3.15 (dd, J = 14.0 and 6.0 Hz, 1H), 4.05 (m, 1H), 4.30 (m, 1H), 4.50–4.70 (m, 1H), 6.15 (br s, 2H), 6.60–6.75 (m, 3H), 7.15–7.45 (m, 5H), 7.65 (m, 1H); MS *m*/*z* (%) 252 (M^+, 80), 224 (2), 160 (40), 131 (40), 118 (90), 91 (50), 83 (100), 71 (2). Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.22; H, 6.39; N, 11.52%.

2-(4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 7

Yellow oil. $[\alpha]_D$ +5.66 (1.06, $CHCl_3$); IR *v* 3463, 3365, 2955, 1685, 1630, 1590, 1495, 1037, 753, 697 cm^{-1}; ^1H NMR δ 4.15 (m, 1H), 4.68 (m, 1H), 5.45 (m, 1H), 6.15 (br s, 2H), 6.70 (m 2H), 7.35 (m, 6H), 7.80 (d, J = 8.0 Hz, 1H); MS *m*/*z* (%) 238 (M^+, 94), 218 (8), 207 (48), 193 (3), 180 (10), 160 (25), 147 (18), 131 (28), 118 (96), 91 (55), 83 (100), 77 (37), 65 (20). Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.17; H, 5.91; N, 11.20%.

2-(4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 8

Light yellow oil. $[a]_D$ −7.45 (1.45, $CHCl_3$); IR *v* 3440, 3290, 2948, 1660, 1450, 1052, 748 cm^{-1}; ^1H NMR δ 1.05 (t, J = 8.0 Hz, 3H), 1.55–1.85 (m, 2H), 3.85–4.00 (m, 1H), 4.20–4.45 (m, 2H), 6.20 (br s, 2H), 6.60–6.80 (m 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H); MS *m*/*z* (%) 190 (M^+, 91), 175 (100), 161 (45), 133 (40), 118 (76), 106 (60), 92 (20), 65 (13). Calcd. for $C_{11}H_{14}N_2O$: C, 69.53; H, 7.97; N, 13.99. Found: C, 69.47; H, 7.37; N, 14.73%.

2-(1,3-Benzoxazol-2-yl)aniline 9

Dark viscous oil. IR *v* 3481, 3370, 3013, 2942, 1686, 1482, 1293, 1243, 1156, 1100, 750 cm^{-1}; ^1H NMR δ 5.75 (br s, 2H), 7.20–7.35 (m, 2H), 7.62–7.72 (m, 4H), 7.80–7.95 (m, 2H); MS *m*/*z* (%) 210 (M^+, 3), 151 (81), 119 (100), 92 (55), 75 (2), 65 (12). Calcd. for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.76; N, 13.33. Found: C, 74.48; H, 4.26; N, 13.61%.

2-(1,3-Benzothiazol-2-yl)aniline 10

Brown solid. Mp 164.3–166.0 °C; IR *v* 3377, 3057, 3011, 2955, 2921, 2855, 1685, 1580, 1297, 1210, 759, 741, 665 cm^{-1}; ^1H NMR δ 5.85 (br s, 2H), 6.90–7.15 (m, 2H), 7.30–7.60 (m, 4H), 7.80–8.10 (m, 2H). MS *m*/*z* (%) 210 (M^+, 3), 151 (81), 119 (100), 92 (55), 75 (2), 65 (12). Calcd. for $C_{13}H_{10}N_2S$: C, 69.03; H, 4.42; N, 12.39; S, 14.16. Found: C, 68.70; H, 4.21; N, 12.00; S, 14.60%.

Polymer-supported amino oxazoline 12 (Scheme 3)

A mixture of **11** (0.50 g; with about 1.6 mmol of isatoic anhydride), D-2-aminobutanol (0.36 g, 4.00 mmol) and kaolinitic clay (0.10 g; 20% w/w) was agitated in dry chlorobenzene (3 mL) at 100 °C for 24 h. The resin beads were isolated and washed with organic solvents [water–THF (50:50, 25:75, 10:90 and 0:100) followed by acetone, methanol and dichloromethane] and dried under high vacuum. The polymer **12** was characterized by FT-IR analysis. IR *v* 3419, 3212, 2918, 2852, 1621, 1570, 1425, 1322, 1213, 769 cm^{-1}.

Polymer-supported amino oxazoline 13 (Scheme 3)

Prepared by the same process as for **12** but with L-isoleucinol as the 2-aminoalcohol. IR *v* 3388, 3282, 2918, 2853, 1616, 1500, 1456, 1369, 1218, 742 cm^{-1}.

Polymer-supported amino oxazoline 14 (Scheme 3)

Prepared by the same process as for **12** but with L-phenylalaninol as the 2-aminoalcohol. IR *v* 3460, 3309, 2955, 2867, 1590, 1495, 1037, 753, 697 cm^{-1}.

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