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POLYMER-SUPPORTED SYNTHESIS OF 7-HYDROXY-10-SUBSTITUTED ISOALLOXAZINES

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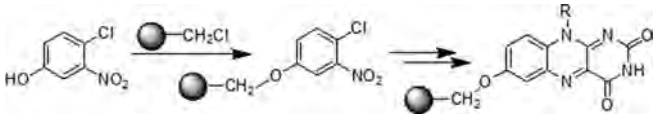
ABSTRACT Polymer-supported organic synthesis has emerged as an important area of synthetic chemistry. In recent times, a large number of polymer-supported syntheses of heterocycles have appeared. In this article, we report the simple and facile synthesis of 7-hydroxy-10-substituted isoalloxazines using Merrifield resin as polymer support.



KEYWORDS Flavin, Isoalloxazine, Merrifield resin, Polymer-supported, Flavin monooxygenases.

INTRODUCTION

The polymer supported organic synthesis is a powerful method for the synthesis of heterocyclic molecules.[1-5] The concept of polymer-supported synthesis was first realized when Merrifield published his synthesis of L-leucyl-L-alanylglycyl-L-valine through attachment of the intermediate to a polymer backbone.[6] Soon this concept was utilized by organic chemists for the synthesis of diverse group of compounds having diverse applications.[1-5] In this method of synthesis, an inert insoluble polymer is coupled to one of the substrates usually through a reaction dependent stable covalent bond. This method is advantageous over the conventional solution-phase method due to the ease of product isolation through only filtration and further gets cleaved from the polymer support. A hindrance to polymer-supported reactions has been the lack of analytical methods to establish the degree to which the expected product has formed.[7-9] The synthesis has also been carried out using polymer-support reagents and/or catalysts and soluble polymer supports.[10-12]

10-Substituted isoalloxazines (or flavins) are cofactors of flavin monooxygenases (FMOs). FMOs are redox enzymes and find their applications in electron transfer; metabolic processes, regulation of neurotransmitters, and many other biological activities.[13,14] The isoalloxazines also possess antimalarial activities and act as inhibitors of glutathione reductase.[15,16] The acidic cyclocondensation of 2-substituted aminoanilines with alloxan monohydrate is a useful method for the synthesis of 10-substituted isoalloxazines.[17-20] Herein, we report an easy and facile synthesis of 7-hydroxy-10-substituted isoalloxazines using Merrifield resin as polymer support.

RESULTS AND DISCUSSION

The Merrifield resin (chloromethylated styrene-divinylbenzene copolymer, 2% cross-linked, 2.50 mequiv of Cl/g, **1**) was reacted with 4-chloro-3-nitrophenol (**2**) in the presence of sodium methoxide in dry tetrahydrofuran (THF) to give polymer supported chloronitrobenzene **3**. The reaction of **3** with substituted amines/anilines (**4**) in dichloromethane - THF (1:1 v/v) gave polymer-supported nitroanilines **5**. The reduction of **5** with $SnCl_2$ gave polymer-supported diamines **6**. The appearance of absorption between 3400-3500 cm^{-1} for primary amine in Fourier transform infrared (FTIR) spectroscopy indicated the formation of resin bound diamines **6**.[21] The cyclocondensation of diamines

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6 with alloxan monohydrate **7** in the presence of dilute HCl in ethanol gave the polymer-supported isoalloxazines **8** (**Scheme 1**). The formation of the polymer-supported isoalloxazines was characterized by FTIR spectroscopy. The appearance of strong peaks in the regions 1640-1660 and 1710-1730 cm^{-1} confirms the presence of two carbonyl groups (C=O) in the molecule which is attributed to the carbonyls at positions 2 and 4, respectively of the isoalloxazine ring.[21,22] Another broad peak in the region 3460-3420 cm^{-1} is due to the presence of -NH group at position 3 of the isoalloxazine ring.[21,22] The polymer-support from compound **8** was cleaved using trifluoroacetic acid (TFA) in dichloromethane to give 7-hydroxy-10-substituted isoalloxazines (**9**) in 74-81% yields. The formation of **9** was confirmed by different spectroscopic data such as ultraviolet (UV)-visible, FTIR, ^1H nuclear magnetic resonance (NMR) spectroscopy, and elemental analysis (experimental section).

In conclusion, the present polymer-supported synthetic method is an efficient and free from tedious workup process for the synthesis of 7-hydroxy-10-substitutedisoalloxazines in good yields. This is more attractive and advantageous in comparison to their solution phase synthesis where each synthetic step requires tedious purification process including column chromatography. This is an environmental friendly method of synthesis.

EXPERIMENTAL SECTION

All melting points are uncorrected and were recorded on Thomas-Hoover Unimelt Capillary melting point Apparatus. FTIR spectra were recorded on Perkin-Elmer FTIR spectrophotometer (ATR mode) (ν in cm^{-1}). The absorption spectra were recorded on Perkin-Elmer UV-260 spectrophotometer, and absorption maxima were expressed in nm. ^1H NMR was recorded on Bruker Avance 300 spectrometer using tetramethyl silane as an internal reference (chemical shift in ppm). Elemental analysis was carried out in a Heraeus CHN analyzer. Merrifield resin, alloxan monohydrate, and 4-chloro-3-nitrophenol were obtained from Sigma-Aldrich and used without further purifications.

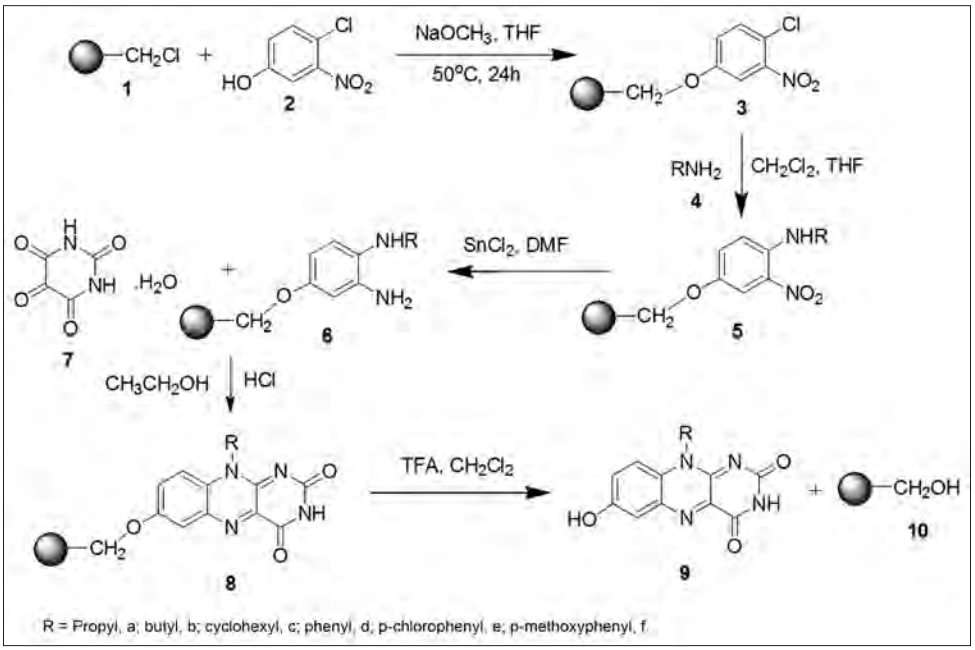
Coupling of merrifield resin (1) with 4-chloro-3-nitrophenol (2)

Merrifield resin (**1**) was taken in dry THF (THF, 100 mL). To this, 4-chloro-3-nitrophenol (**2**) (4.34 g, 25 mmol) and sodium methoxide (25 mmol) were added and the reaction mixture was stirred with heating at 50°C for 24 h. The solvent was removed under reduced pressure. The reaction mixture was partitioned with water and chloroform and filtered to give the polymer-supported chloronitrobenzene **3**. 1.93 g (11.12 mmol) of the compound **2** was recovered unreacted after the reaction, which shows that approximately 13 mmol is the theoretical loading capacity of the resin **3**. The yields of the final compounds were calculated based on the theoretical loading.

General method for the synthesis of polymer-supported N-substituted-2-nitroanilines (5)

Substituted amines/anilines (**4**) (13 mmol) and polymer-supported chloronitrobenzene **3** were taken in CH_2Cl_2-THF (50 mL, 1:1 v/v) at room temperature and the suspension was stirred for 24 h. The reaction mixture was filtered and washed subsequently with THF and CH_2Cl_2; dried in vacuo to give polymer-supported N-substituted-2-nitroanilines compounds (**5**). The FTIR data of the synthesized compounds recorded in KBr is given in cm^{-1}.

- Polymer supported N-propyl-2-nitroaniline (**5a**). 3320, 2928, 2919, 1550, 1543, 1418, 1333, 1237, 867, 735.
- Polymer supported N-butyl-2-nitroaniline (**5b**). 3331, 2931, 2893, 1545, 1432, 1335, 1242, 888, 812, 742.
- Polymer supported N-cyclohexyl-2-nitroaniline (**5c**). 3318, 2922, 2899, 1515, 1438, 1336, 1246, 1150, 826, 665.



Scheme 1: Synthesis of 7-hydroxy-10-substituted isoalloxazines

- Polymer supported N-phenyl-2-nitroaniline (**5d**). 3328, 2929, 2901, 1570, 1520, 1440, 1338, 1322, 1246, 848, 821.
- Polymer supported N-(4'-chlorophenyl)-2-nitroaniline (**5e**). 3320, 2931, 2900, 1565, 1516, 1430, 1348, 1262, 1250, 856, 751.
- Polymer supported N-(4'-methoxyphenyl)-2-nitroaniline (**5f**). 3309, 2922, 2880, 1540, 1435, 1343, 1280, 1287, 1243, 1141, 850, 759.

General method for the synthesis of polymer-supported N-substituted-2-aminoanilines (6)

To the polymer-supported nitro compounds (**5**) were added $SnCl_2.H_2O$ (14 mmol) and dimethylformamide (DMF) (DMF, 50 mL) at room temperature. The suspensions were stirred at room temperature for 24 h, filtered and washed subsequently with H_2O, CH_2Cl_2 and methanol (CH_3OH). The residue was dried in vacuo to give polymer-supported diamino compounds (**6**). The FTIR data of the synthesized compounds recorded in KBr is given in cm^{-1}.

- Polymer supported N-propyl-2-aminoaniline (**6a**). 3434, 3325, 2932, 2829, 1365, 1245, 1103, 918, 846, 765.
- Polymer supported N-butyl-2-aminoaniline (**6b**). 3430, 3342, 2992, 2833, 1375, 1251, 1100, 979, 856, 727.
- Polymer supported N-cyclohexyl-2-aminoaniline (**6c**). 3438, 3322, 2915, 2860, 1448, 1243, 1145, 1111, 1051, 856.
- Polymer supported N-phenyl-2-aminoaniline (**6d**). 3455, 3341, 3320, 2965, 1433, 1247, 1118, 849, 780, 765.
- Polymer supported N-(4'-chlorophenyl)-2-aminoaniline (**6e**). 3444, 3390, 3311, 2930, 1500, 1490, 1268, 1251, 881.
- Polymer-supported N-(4'-methoxyphenyl)-2-aminoaniline (**6f**). 3440, 3329, 3310, 2990, 2828, 1438, 1411, 1290, 1236, 1131, 929, 856.

General method for the synthesis of 7-polymer-supported 10-substituted isoalloxazines (8)

To the polymer-supported diamine **6** taken in ethanol (50 mL), alloxan monohydrate (**7**) (13 mmol) and dilute hydrochloric acid (2 mL) were added. The suspension was stirred at room temperature for 12 h, filtered and washed with H_2O, CH_2Cl_2 and methanol (CH_3OH). The residue was dried in vacuo to give the polymer-supported isoalloxazines (**8**). The FTIR data of the synthesized compounds recorded in KBr is given in cm^{-1}.

- Polymer supported 10-propylisoalloxazine (**8a**). 3433, 3312, 3155, 1729, 1680, 1660, 1573, 1519, 1445, 1334, 1243, 1236, 1131, 834, 776.
- Polymer supported 10-butylisoalloxazines (**8b**). 3442, 3308, 2969, 1722, 1675, 1663, 1522, 1519, 1458, 1399, 1303, 1241, 1236, 1115, 990, 842, 777.
- Polymer supported 10-cyclohexylisoalloxazine (**8c**). 3450, 3332, 2926, 2833, 1720, 1680, 1635, 1575, 1560, 1433, 1356, 1243, 1178, 1111, 981, 879, 794.
- Polymer supported 10-phenylisoalloxazine (**8d**). 3445, 3300, 3159, 3030, 2928, 2854, 1716, 1653, 1625, 1571, 1591, 1555, 1457, 1405, 1305, 1240, 1120, 975, 878, 753.
- Polymer supported 10-(4'-chlorophenyl)isoalloxazine (**8e**). 3442, 3310, 3016, 2950, 2866, 1722, 1658, 1622, 1581, 1466, 1375, 1278, 1143, 988, 856, 781.
- Polymer supported 10-(4'-methoxyphenyl) isoalloxazine (**8f**). 3429, 3313, 2926, 2855, 1721, 1672, 1623, 1540, 1500, 1400, 1368, 1290, 985, 867.

General method for the cleavage of isoalloxazines (9) from 7-polymer-supported 10-substituted isoalloxazines (8)

To the polymer-supported isoalloxazines **8**, TFA and CH_2Cl_2 (1:1 v/v) (5 mL) were added and contents were stirred for 3 h at room temperature. The suspension was filtered and washed with mixture of CH_3CH_2OH-CH_3OH (1:1 v/v 30 mL). The filtrate was concentrated under reduced pressure to give the desired products (**9**), which was recrystallized from CH_3CH_2OH.

7-Hydroxy-10-propylisoalloxazine (9a)

Yield: 77%; mp.: >300°C; UV-visible (DMSO) λ_{max}/nm: 429, 340, 280; IR (KBr) cm^{-1}: 3460, 3027, 2842, 1714, 1659, 1580, 1551, 1429, 1256, 1098, 884, 836, 773; ^1H NMR (DMSO-d_6) δ: 1.23 (3H, t, CH_3), 1.80-1.86 (2H, m, CH_2), 4.64 (2H, t, $N_{10}CH_2$), 7.78 (1H, d, H-9, J = 8.7 Hz), 8.03 (1H, bs, H-3), 8.46 (1H, d, H-8, J = 8.8 Hz), 8.80 (1H, s, H-6); elemental analysis for $C_{13}H_{12}N_4O_3$ (%): Found C 57.25; H 4.49; N 20.69, calculated C 57.35; H 4.44; N 20.58.

7-Hydroxy-10-butylisoalloxazine (9b)

Yield: 77%; mp.: >300°C; UV-visible (DMSO) λ_{max}/nm: 435, 330, 287; IR (KBr) cm^{-1}: 3470, 3169, 2952, 1720, 1660, 1555, 1519, 1343, 1250, 1236, 1099, 843, 769; ^1H NMR (DMSO-d_6) δ: 0.87-1.92 (7H, m, CH_3, $(CH_2)_2$), 4.65 (2H, t, $N_{10}CH_2$), 7.55-9.03 (3H, m, H-9, H-8, H-6); elemental analysis for $C_{14}H_{14}N_4O_3$ (%): Found C 58.69; H 4.99; N 19.63, calculated C 58.73; H 4.93; N 19.57.

7-Hydroxy-10-cyclohexylisoalloxazine (9c)

Yield: 80%; mp.: >300°C; UV-visible (DMSO) λ_{max}/nm: 431, 333, 280; IR (KBr) cm^{-1}: 3424, 3027, 2843, 1713, 1659, 1581, 1531, 1429, 1256, 1098, 889, 849; ^1H NMR (DMSO-d_6) δ: 1.15-2.08 (10H, m, cyclohexyl-H), 4.17-4.19 (1H, m, $N_{10}CH$), 7.81 (1H, d, H-9, J = 8.8 Hz), 8.22 (1H, bs, H-3), 8.57 (1H, d, H-8, J = 8.9 Hz), 8.88 (1H, s, H-6); elemental analysis for $C_{16}H_{16}N_4O_3$ (%): Found C 61.61; H 5.20; N 17.82 calculated C 61.53; H 5.16; N 17.94.

7-Hydroxy-10-phenylisoalloxazine (9d)

Yield: 81%; mp.: >300°C; UV-visible (DMSO) λ_{max}/nm: 445, 334, 283; IR (KBr) cm^{-1}: 3452, 3223, 2926, 1718, 1654, 1588, 1420, 1380, 1279, 1189, 907, 816; ^1H NMR (DMSO-d_6) δ: 6.97 (1H, d, H-9, J = 8.2 Hz), 7.35-7.79 (5H, m, 10-phenyl H), 7.84 (1H, d, H-8, J = 8.1 Hz), 8.23 (1H, s, H-6); elemental analysis for $C_{16}H_{10}N_4O_3$ (%): Found C 62.64; H 3.39; N 18.37 calculated C 62.74; H 3.29; N 18.29.

7-Hydroxy-10-(4'-chlorophenyl)isoalloxazine (9e)

Yield: 74%; mp.: >300°C; UV-visible (DMSO) λ_{max}/nm: 432, 337, 288; IR (KBr) cm^{-1}: 3420, 3399, 3065, 2933, 1725,

1660, 1575, 1399, 1289, 1199, 846; ^{1}H NMR (DMSO-d_6) δ: 7.66 (1H, d, H-9, J = 9.0 Hz), 7.74-7.76 (2H, m, H-2', H-6'), 7.91-7.93 (2H, m, H-3', H-5'), 8.21 (1H, d, H-8, J = 8.9 Hz), 8.60 (1H, bs, H-3), 8.82 (1H, s, H-6); elemental analysis for $C_{16}H_9N_4O_3Cl$ (%): Found C 56.39; H 2.55; N 16.52 calculated C 56.40; H 2.66; N 16.44.

7-Hydroxy-10-(4'-methoxyphenyl)isoalloxazine (9f)

Yield: (77%); mp.: >300°C; UV-visible (DMSO) λ_{max}/nm: 432, 341, 281; IR (KBr) cm^{-1}: 3424, 3326, 2921, 1725, 1660, 1607, 1499, 1469, 1219, 1177, 1040, 833; ^{1}H NMR (DMSO-d_6) δ: 4.16 (3H, s, OCH_3), 7.61 (1H, d, H-9, J = 9.0 Hz), 8.11-8.13 (2H, m, H-3', H-5'), 8.20-8.23 (2H, m, H-2', H-6'), 8.31 (1H, d, H-8, J = 9.0 Hz), 8.70 (1H, s, H-6); elemental analysis for $C_{17}H_{12}N_4O_4$ (%): Found C 60.77; H 3.65; N 16.51 calculated C 60.71; H 3.60; N 16.66.

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