Amberlite IR-120 H⁺ Resin, an Efficient and Recyclable Solid Phase Catalyst for the Synthesis of 2, 3-Disubstituted Quinazolin-4(3H)-Ones: A Greener Approach

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ABSTRACT

A highly efficient synthesis of 2,3-disubstituted quinazolin-4(3H)-ones via Amberlite IR 120 H⁺ resin. Amberlite IR 120 H⁺ is a commercially available, heterogeneous and recoverable catalyst to synthesize the 2,3-disubstituted quinazolin-4(3H)-ones in excellent yields.

Keywords: MCR strategy, Amberlite IR 120 H⁺ resin, Quinazolin-4(3H)-ones, Greener approach, Reusability.

INTRODUCTION

Quinazolines, quinazolinones frequently encountered chemical structure in several naturally occurring alkaloids and are of significant importance in medicinal chemistry due to their wide range of pharmacological activities these molecules acquired an important role in the medicinal chemistry. In general, these quinazolin-4(3H)-ones alkaloids have gained profound interest owing to their promising biological activity viz., anti-cancer, anti-convulsant, anti-bacterial, anti-ulcer, anti-fungal, analgesic, anti-inflammatory and anti-hypertensive. Rutaecarpine (Fig. 1, entry-A), a natural occurring alkaloid containing indolopyridoquinazolinone core structure was first isolated from Evodia Rutaecarpa by Asahina and co-workers in 1915.

Evodiamine (Fig. 1, entry-B), is a quinazolin-carboline alkaloid isolated from the fruit of Evodia rutaecarpa which is widely utilized in Chinese medicine as an antidote for several health disorders such as resisting tumour, antinociception, weight loss, protecting heart and reducing blood pressure.

Previously, these type of compounds were synthesized by using silica-sulfuric acid, p-TSA,
Magnetic Fe₃O₄ Nanoparticles, Montomorillonite K₁₀, Amberlite IR 120 His Industrial Grade Strong Acid Cation Exchange Resin. It was previously used for various chemical transformations. It is a nonhazardous and cheap catalyst. In the present invention we prepared various 2, 3-disubstituted quinazolin-4(3H)-ones by using Amberlite IR-120 H⁺ Resin in good yields. So the Amberlite IR 120 H⁺ was found to be the best recoverable heterogeneous catalyst for the synthesis of Quinazoline-4(3H)-one derivatives.

RESULTS AND DISCUSSION

Total 11 number of quinazoline-4(3H)-one derivatives were synthesized by treating isatoic anhydride with different aldehydes and amines as mentioned in the table-1. The obtained products were confirmed by NMR, IR and Mass.

Plausible mechanism

A step wise possible mechanism for the formation of 2, 3-disubstituted quinazolin-4(3H)-ones is illustrated in Fig. 2. The primary amine attack on carbonyl group of isatoic anhydride, followed by ring opening and decarboxylation provided the amide compound. The Nucleophile attack of amine to a carbonyl group of aldehyde and further dehydration under acidic medium provided the compound. Compound 5 cyclization and oxidation under air balloon to provided them as a solid compound.

Experimental section

All the reagents used in the present work were of Analytical Reagent/Laboratory Reagent grade. The ¹H and ¹³C NMR spectra were determined in CDCl₃/DMSO-d₆ solution using Varian Gemini 2000 model 200MHz instrument and Oxford magnet Varian Mercury 400MHz instrument. The ¹H chemical shift values were reported on the ³¹P scale in ppm, relative to TMS (δ = 0.00 ppm), while ¹³C chemical shifts relative to CDCl₃ and DMSO-d₆ (δ = 39.5 ppm) as internal standards. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as br (broad). Coupling constants (J) are given in hertz (Hz).

Mass spectra were run on an Agilent 1100 series LC system coupled to a triple quadrupole mass spectrometer (Agilent LC/MS/MS model 6410, Agilent Technologies Inc., Santa Clara, CA, USA) with electrospray ionization (ESI) source. The high-resolution mass spectra (HRMS) were determined using Waters LCT Premier time-of-flight mass spectrometer (Milford, USA) with ESI source.

Infrared spectra (IR) for all samples were recorded on Perkin Elmer 1650 FT IR spectrometer. All reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F₂₅₄), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (230-400 mesh) using distilled petroleum ether and ethyl acetate.

General procedure for the synthesis of disubstituted quinazolin-4(3H)-ones

In a 25 mL round bottom flask, isatoic anhydride (1.0 mmol), aldehyde (1.0 mmol), amine (1.1 mmol), Amberlite IR-120 H⁺ resin (300 mg) and water + Acetonitrile (20 mL) were heated to reflux under air balloon for 5 to 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, water (20 mL) and ethyl acetate (20 mL) were added and stirred for about 10 min, filtered and washed with ethyl acetate (20 mL) and both layers separated. The organic layer was washed with water (20 mL) and 10 %NaCl solution. The organic layer was dried with anhyd Na₂SO₄, and concentrated under reduced pressure. The crude
Table 1: Synthesis of 2.3-disubstituted quinazolin-4(3H)-ones

<table>
<thead>
<tr>
<th>S.No</th>
<th>Aldehyde (1)</th>
<th>Amine (2)</th>
<th>Product (3)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td></td>
<td>3a</td>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>FCHO</td>
<td></td>
<td>3b</td>
<td>7</td>
<td>88</td>
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<tr>
<td>3</td>
<td>FCHO</td>
<td></td>
<td>3c</td>
<td>6</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>NO2CHO</td>
<td>2a H₂N</td>
<td>3d NO₂</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>OCH₃CHO</td>
<td></td>
<td>3e O</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>ClCHO</td>
<td></td>
<td>3f Cl</td>
<td>6</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>NO₂CHO</td>
<td>2b H₂N</td>
<td>3g NO₂</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>BrCHO</td>
<td></td>
<td>3h Br</td>
<td>6</td>
<td>86</td>
</tr>
</tbody>
</table>
mass was recrystallized using methanol to afford the products in good yields (3a to 3k). The catalyst was recovered by washing with fresh water (2-3 times) and dried in vacuum oven at 50°C then it was reused for another cycle.

All the compounds gave satisfactory analytical and spectral data

3-hexyl-2-phenylquinazolin-4(3H)-one (3a):
Brown solid; Yield- 92%; IR (KBr) = 3345, 2928, 1642, 1525, 1449, 1302, 1159, 758 cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)): 8.34 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 5.2 Hz, 1H), 7.78-7.72 (m, 2H), 7.54-7.49 (m, 5H), 3.99-3.95 (m, 2H), 1.66-1.58 (m, 2H), 1.40-1.34 (m, 6H), 0.93-0.89 (m, 3H); 13C NMR (100 MHz, CDCl\(_3\)): \(\delta = 162.1, 156.2, 147.1, 135.5, 134.2, 133.6, 130.1, 129.7, 128.7, 128.4, 127.7, 127.3, 126.9, 126.7, 45.9, 30.9, 28.5, 26.2, 22.3, 13.8; HRMS: m/z calcd for C\(_{20}\)H\(_{23}\)N\(_2\)O (M+H) 308.1817, found: 308.1805.

2-(4-bromo-2,6-difluorophenyl)-3-hexyl quinazolin-4(3H)-one (3b)
Brown solid; Yield- 88%; IR (KBr) = 3325, 2856, 1681, 1525, 1491, 1073, 887, 761, 585, 527, cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.33\) (d, \(J = 7.6\) Hz, 1H), 7.78-7.72 (m, 2H), 7.54-7.49 (m, 5H), 3.99-3.95 (m, 2H), 1.66-1.58 (m, 2H), 1.40-1.34 (m, 6H), 0.93-0.89 (m, 3H); 13C NMR (100 MHz, CDCl\(_3\)): \(\delta = 162.1, 156.2, 147.1, 135.5, 134.2, 133.6, 130.1, 129.7, 128.7, 128.4, 127.7, 127.3, 126.9, 126.7, 45.9, 30.9, 28.5, 26.2, 22.3, 13.8; HRMS: m/z calcd for C\(_{20}\)H\(_{20}\)N\(_2\)O\(_2\)Br (M+H) 421.0721, found: 421.0749.

2-(4-fluorophenyl)-3-hexyl quinazolin-4(3H)-one (3c)
Brown solid; Yield- 84%; IR (KBr) = 3327, 2856, 1681, 1525, 1491, 1073, 887, 761, 585, 527, cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.33\) (d, \(J = 7.6\) Hz, 1H), 7.78-7.72 (m, 2H), 7.54-7.49 (m, 5H), 3.99-3.95 (m, 2H), 1.66-1.58 (m, 2H), 1.40-1.34 (m, 6H), 0.93-0.89 (m, 3H); 13C NMR (100 MHz, CDCl\(_3\)): \(\delta = 175.1, 134.3, 130.0, 129.9, 127.4, 127.1, 126.7, 121.3, 116.3, 116.0, 45.9, 31.0, 28.5, 26.2, 22.3, 13.8; HRMS: m/z calcd for C\(_{20}\)H\(_{20}\)N\(_2\)OF (M+H) 325.1716, found: 325.1717.

3-hexyl-2-(4-nitrophenyl) quinazolin-4(3H)-one (3d)
Yellow solid; Yield- 90%; IR (KBr) = 3325, 1676, 1547, 1310, 1076, 984, 857, 797, 745, 692, 452, cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.42-8.40\) (m, 2H), 7.82-7.76 (m, 4H), 7.58-7.43 (m, 2H), 3.98-3.95 (m, 2H), 1.67-1.52 (m, 2H), 1.42-1.35 (m, 2H), 0.92-0.88 (m, 3H); 13C NMR (100 MHz, CDCl\(_3\)): \(\delta = 161.7, 153.8, 148.4, 146.8, 141.4, 134.5, 131.2, 129.3, 128.5, 127.5, 126.9, 126.7, 124.0, 45.9, 31.0, 28.7, 26.2, 22.3, 13.8; HRMS: m/z calcd for C\(_{20}\)H\(_{20}\)N\(_2\)O\(_3\) (M+H) 352.1661, found: 352.1674.
3-hexyl-2-(4-methoxyphenyl) quinazolin-4(3H)-one (3e)

White solid; Yield: 82%; IR (KBr) 3337, 2923, 1682, 1512, 1446, 1278, 1006, 901, 662, 546, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ= 8.32 (d, J= 7.2 Hz, 1H), 7.74-7.70 (m, 1H), 7.50-7.46 (m, 2H), 7.31-7.26 (m, 2H), 7.04-7.00 (m, 1H), 6.87-6.83 (m, 1H), 4.02-3.98 (m, 2H), 3.88 (s, 3H), 1.62-1.56 (m, 2H), 1.25-1.18 (m, 6H), 0.86-0.79 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 162.3, 160.6, 156.1, 147.2, 134.1, 133.2, 128.0, 127.3, 126.7, 126.7, 120.8, 119.1, 114.1, 114.1, 55.4, 49.9, 31.0, 27.5, 26.3, 22.3, 13.8; HRMS: m/z calcd for C₂₁H₁₅N₂O₂ (M+H) 337.1916, found: 337.1916.

2-(2-chlorophenyl)-3-hexylquinazolin-4(3H)-one (3f)

White solid; Yield: 87%; IR (KBr) 3345, 2928, 1642, 1525, 1449, 1302, 1159, 758 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ= 8.36 (d, J= 8.4 Hz, 1H), 7.79-7.75 (m, 2H), 7.55-7.42 (m, 5H), 4.26-4.19 (m, 1H), 3.53-3.45 (m, 3H), 1.72-1.61 (m, 1H), 1.55-1.25 (m, 1H), 1.21-1.10 (m, 6H), 0.89-0.81 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 175.2, 161.8, 153.4, 147.2, 134.5, 134.2, 132.4, 131.0, 129.8, 129.8, 127.5, 127.2, 127.2, 126.8, 45.5, 30.9, 28.3, 26.3, 22.2, 13.8; HRMS: m/z calcd for C₂₁H₁₅N₂O₂Cl (M+H) 341.1421, found: 341.1406.

3-benzyl-2-(4-nitrophenyl) quinazolin-4(3H)-one (3g)

Yellow solid; Yield: 85%; IR (KBr)= 3232, 1676, 1543, 1310, 1076, 985, 857, 798, 744, 692, 451, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.05-8.01 (m, 1H), 7.76-7.74 (m, 1H), 7.33 (d, J= 5.2 Hz, 1H), 7.26-7.19 (m, 2H), 6.95-6.75 (m, 7H), 3.87 (s, 2H), 3.78 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 163.2, 162.6, 160.7, 160.2,

Fig. 2: of 2, 3-disubstituted quinazolin-4(3H)-ones formation
147.2, 134.3, 133.5, 132.1, 131.4, 129.7, 127.8, 127.4, 127.0, 126.9, 120.7, 119.0, 115.7, 114.1, 114.1, 113.9, 55.4, 55.2, 46.0; HRMS: m/z calcd for C_{23}H_{21}N_{2}O_{2} (M+H) 373.1552, found: 373.1548.

3-(4-methoxybenzyl)-2-(4-nitrophenyl) quinazolin-4(3H)-one (3j)
White solid; Yield- 82 %; IR (KBr) 3322, 1686, 1567, 1330, 1066, 984, 857, 797, 745, 692, cm
\(-1\); \(1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.41-8.38\) (m, 1H), 7.77-7.71 (m, 1H), 7.60-7.56 (m, 1H), 7.17 (d, J = 6.4 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.73-6.69 (m, 2H), 5.14 (s, 2H), 3.75 (s, 3H); \(1^3\)CNMR (100 MHz, CDCl\(_3\)): \(\delta = 162.0, 160.9, 159.1, 158.3, 146.9, 145.5, 134.6, 128.5, 127.9, 127.6, 127.6, 127.4, 126.9, 120.7, 119.0, 115.7, 114.1, 55.2, 46.0; HRMS: m/z calcd for C_{24}H_{22}N_{2}O_{3}F_{2}Br (M+H) 457.0363, found: 457.0367.

CONCLUSION

In conclusion, we have developed an efficient and environmentally benign synthetic method for the synthesis of 2, 3-disubstituted quinazolin-4(3H)-ones from isatoic anhydride, aldehyde and amines using Amberlite IR-120 H\(^{+}\) resin, a commercially available green and recyclable catalyst. The advantages of this method are simplicity of operation, clean reactions, and absence of side products, recyclable and high yields.

REFERENCES

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