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Nafion-H catalyzed cyclocondensation reaction for the synthesis of octahydroquinazolinone derivatives

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Abstract

A facile and environmentally friendly Nafion-H catalyzed multicomponent reaction for synthesis of octahydroquinazolinone derivatives is described. In order to improve the yield and selectivity, the effects of the mole proportion of reactants (cyclic β-diketones, urea and aldehydes) and solvents were investigated. The ability to reuse the catalyst, high yields and easy purification are important features of this process. Interestingly, under similar conditions, the use of nicotinaldehyde and isonicotinaldehyde as the aldehyde component of the reaction gives unexpected products that are distinct from Biginelli products. All of the products were characterized by ^{1}H NMR, ^{13}C NMR, EI-MS and IR, and the structure of one Biglnelli product (**4k**) was determined by single-crystal X-ray diffraction.

Keywords: Nafion-H; Biginelli reaction; Catalysis; Octahydroquinazolinone; Multicomponent reaction

1. Introduction

In recent years, dihydropyrimidinones (DHPMs) and their derivatives have occupied an important position in natural and synthetic organic chemistry, due mainly to their wide range of biological activities [1], such as antibacterial, antiviral, antihypertensive, antitumor effects and calcium channel blockers. Scaffold decoration of DHPMs is highly important for creating structural diversity to produce "drug-like" molecules for biological screening. The synthesis of DHPMs was first reported by Biginelli in 1893 [2] and has been reviewed recently [3]. Improved procedures and new Biginelli-like scaffolds have been reported over the past decade and a variant of the Biginelli condensation has been described for its application to the total synthesis of bioactive guanidine alkaloids [4]. Basically, these methods are all similar in the use of different Lewis acid catalysts as well as protic acid under classical reflux [5]. Other studies have focused on the use of ionic liquids [6], microwave irradiation [7] and combinatorial chemistry [8]. The use of boron compounds [9], TMSCl [10] and heterogeneous catalysts, such as tangstophosphoric acid [11], Zeolite [12], montmorillonite [13] and ion-exchange resins [14] have been reported. However, to the best of our knowledge, there have been relatively few reports of the synthesis of fused DHPMs from cyclic β-diketones.

Octahydroquinazolinone derivatives have exhibited potent antibacterial activity [15] and calcium antagonist activity [16]. More recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic β-diketones instead of open-chain dicarbonyl compounds, but with low yields of products (19–69%) using concentrated HCl as the catalyst [16]. Additional scaffolds, such as spiro-fused heterocycles and hexahydroxanthenes, were manufactured in those reactions [11,17].

Growing concern about environmental damage leads to an urgent requirement for the development of eco-friendly technology and economic processes. It is of great practical importance to synthesize octahydroquinazolinone derivatives by the Biginelli reaction using a solid acid catalyst, because of ability to modify the acid strength, ease of handling, recycling of the catalyst and environmental compatibility. Nafion-H, a perfluorinated resinsulphonic acid, has been found to be a suitable replacement for various homogeneous acid catalysts due to its acidic and stable nature [18]. The estimated Hammett (H_0) value for Nafion-H is comparable to that of 96–100% sulfuric acid ($H_0 = -12.0$) [19]. In view of the above obser-

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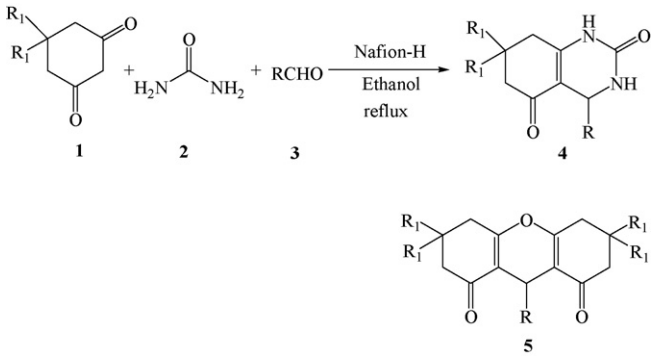


Scheme 1.

vation, and as a part of our program towards green synthesis [13a], we report a single-step and eco-friendly protocol for the synthesis of octahydroquinazolinone derivatives by the multicomponent reactions of cyclic β-diketones **1**, urea **2** and aldehydes **3** (Scheme 1) over Nafion-H with good yields and selectivity.

2. Experimental

All reagents and solvents were commercially available and were used as such. The Nafion-H catalyst (beads, 7–9 mesh) was provided by Shanghai Institute of Organic Chemistry, which has the ion exchange capacity as 0.83 meq g^{-1} and equivalent weight as 1205. Melting points were measured with an Electrothermal WRS-1B apparatus and are uncorrected. IR spectra were recorded with an AVATAR 370 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DM-500 or Gemini 2 000 (300 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were determined on an Agilent 5975 mass spectrometer.

2.1. General experimental procedure

A mixture of cyclic β-diketone (**1**, 2.6 mmol), urea (**2,** 2.4 mmol), aldehyde (**3**, 2.0 mmol), and Nifion-H (100 wt% of the reactants) in anhydrous ethanol (6 mL) was refluxed for an appropriate time as indicated by TLC. The reaction mixture was then poured into crushed ice with stirring, filtered and recrystallized several times from ethanol to afford pure products.

4-Phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**4a**): mp 308 °C (309 °C) [16b]; IR (KBr): 3218, 3098, 1697, 1650, 1604 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.77–1.96 (m, 2H), 2.15–2.26 (m, 2H), 2.44–3.33 (m, 2H), 5.18 (d, J = 3.30 Hz, 1H), 7.19–7.33 (m, 5H), 7.75 (s, 1H), 9.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.5, 154.6, 152.1, 144.8, 128.5, 127.3, 126.5, 108.7, 51.9, 36.5, 26.1, 21.0; EI-MS: m/z (%) = 243 (43), 242 (M^+, 70), 241 (26), 186 (17), 185 (13), 165 (100), 77 (11).

4-(4-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4b**): mp 298 °C (298 °C) [16b]; IR (KBr): 3222, 3093, 1697, 1652, 1604 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.68–1.80 (m, 1H), 1.89–1.92 (m, 1H), 2.18–2.23 (m, 2H), 2.25 (s, 3H), 2.42–2.50 (m, 2H), 5.13 (d, J = 2.84 Hz, 1H), 7.08–7.13 (m, 4H), 7.70 (s, 1H), 9.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.7, 154.7, 152.4, 142.2, 136.7, 129.3, 126.6, 109.2, 51.9, 36.8, 26.3, 21.2, 21.1; EI-MS: m/z (%) = 257 (26), 256 (M^+, 55), 255 (22), 241 (46), 200 (17), 185 (7), 165 (100), 91(12).

4-(3-Chlorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4c**): mp 312-313 °C (313–314 °C) [16b]; IR (KBr): 3 216, 3 099, 1 697, 1 649, 1 605 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81–1.95 (m, 2H), 2.21–2.27 (m, 2H), 2.41–2.51 (m, 2H), 5.19 (d, J = 3.02 Hz, 1H), 7.18–7.38 (m, 4H), 7.81 (s, 1H), 9.55 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.3, 154.9, 151.7, 147.1, 133.0, 130.4, 127.1, 126.3, 124.9, 108.0, 51.5, 36.3, 26.0, 20.8; EI-MS: m/z (%) = 278 (17), 277 (34), 276 (M^+, 47), 275 (12), 241 (41), 220 (9), 165 (100), 111 (8), 75 (6).

4-(4-Chlorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4d**): mp 290–291 °C (287–288 °C) [16b]; IR (KBr): 3220, 3093, 1696, 1652, 1607 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.79–1.94 (m, 2H), 2.19–2.26 (m, 2H), 2.43–2.51 (m, 2H), 5.17 (d, J = 3.03 Hz, 1H), 7.26 (d, J = 8.52 Hz, 2H), 7.37 (d, J = 8.52 Hz, 2H), 7.78 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.5, 154.8, 151.9, 143.7, 131.8, 128.5, 128.4, 108.3, 51.4, 36.4, 26.1, 20.9; EI-MS: m/z (%) = 278 (15), 277 (26), 276 (M^+, 39), 275 (13), 241 (39), 220 (11), 165 (100), 111 (9), 75 (10).

4-(2-Bromophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4e**): mp 291–292 °C (289 °C) [16b]; IR (KBr): 3 435, 3265, 3 093, 1700, 1640 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.86–1.97 (m, 2H), 2.11–2.23 (m, 2H), 2.48–2.52 (m, 2H), 5.55 (d, J = 2.74 Hz, 1H), 7.14–7.36 (m, 3H), 7.55 (d, J = 7.83 Hz, 1H), 7.61 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.1, 155.3, 151.1, 142.9, 132.9, 129.5, 129.3, 128.4, 122.6, 107.5, 52.8, 36.5, 26.1, 21.0; EI-MS: m/z (%) = 323 (5), 321 (M^+, 5), 241 (100), 165 (29).

4-(3-Bromophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4f**): mp 302 °C (304–305 °C) [16b]; IR (KBr): 3219, 3091, 1700, 1650, 1606 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.78–1.98 (m, 2H), 2.20–2.30 (m, 2H), 2.42–2.52 (m, 2H), 5.18 (d, J = 3.02 Hz, 1H), 7.22–7.45 (m, 4H), 7.80 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.3, 154.9, 151.7, 147.3, 130.7, 130.0, 129.2, 125.3, 121.6, 108.0, 51.5, 36.3, 26.0, 20.8; EI-MS: m/z (%) = 323 (10), 322 (22), 321 (M^+, 16), 320 (21), 241 (52), 165 (100).

4-(4-Bromophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4g**): mp 298 °C (297–298 °C) [16b]; IR (KBr): 3224, 3091, 1695, 1651, 1605 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.79–1.94 (m, 2H), 2.19–2.26 (m, 2H), 2.43–2.51 (m, 2H), 5.16 (d, J = 3.02 Hz, 1H), 7.20 (d, J = 8.24 Hz, 2H), 7.50 (d, J = 8.52 Hz, 2H), 7.78 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.2, 154.6, 151.7, 144.0, 131.3, 128.6, 120.2, 108.2, 51.4, 36.3, 26.0, 20.8; EI-MS: m/z (%) = 323 (6), 322 (17), 321 (M^+, 11), 320 (16), 241 (48), 165 (100).

4-(4-Nitrophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4h**): mp 301 °C (302–303 °C) [16b]; IR (KBr): 3220,

3094, 1695, 1655, 1613 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.95 (m, 2H), 2.20–2.27 (m, 2H),2.44–2.52 (m, 2H), 5.31 (d, J = 3.02 Hz, 1H), 7.52 (d, J = 8.79 Hz, 2H), 8.19 (d, J = 8.79 Hz, 2H), 7.90 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.5, 151.9, 151.7, 146.8, 127.8, 123.9, 107.7, 51.8, 36.4, 26.1, 20.8; EI-MS: m/z (%) = 288 (15), 287 (M$^+$, 43), 240 (13), 165 (100), 108 (7), 76 (7).

4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**4i**): mp 284 °C (279–280 °C) [16b]; IR (KBr): 3219, 3101, 1696, 1650, 1605 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.94 (m, 2H), 2.18–2.25 (m, 2H), 2.43–2.50 (m, 2H), 5.12 (d, J = 3.02 Hz, 1H), 6.86 (d, J = 8.79 Hz, 2H), 7.14 (d, J = 8.79 Hz, 2H), 7.68 (s, 1H), 9.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.4, 158.5, 154.3, 152.1, 137.0, 127.6, 113.8, 108.9, 55.3, 51.3, 36.5, 26.0, 21.0; EI-MS: m/z (%) = 273 (31), 272 (M$^+$, 76), 271 (33), 241 (68), 216 (30), 215 (17), 165 (100), 108 (19), 77 (17).

4-(4-Fluorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4j**): mp 297–281 °C (275–276 °C) [17e]; IR (KBr): 3264, 1704, 1672, 1624 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.80–1.88 (m, 1H), 1.90–1.95 (m, 1H), 2.17–2.27 (m, 2H), 2.41–2.46 (m, 2H), 5.17 (d, J = 2.59 Hz, 1H), 7.11–7.14 (m, 2H), 7.25–7.27 (m, 2H), 7.76 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.5, 162.4, 160.5, 154.8, 151.9, 141.0, 130.0, 128.4, 115.3, 114.8, 108.5, 51.3, 36.6, 26.1, 20.9; EI-MS: m/z (%) = 261 (14), 260 (M$^+$, 48), 259 (15), 239 (13), 217 (83), 204 (15), 165 (100), 133 (16), 95 (20), 75 (11).

4-(3-Fluorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4k**): mp 313 °C; IR (KBr): 3217, 3101, 1698, 1649, 1601 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.84 (m, 1H), 1.90–1.95 (m, 1H), 2.21–2.26 (m, 2H), 2.46–2.50 (m, 2H), 5.20 (d, J = 3.02 Hz, 1H), 7.00–7.09 (m, 3H), 7.34–7.38 (m, 1H), 7.80 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.7, 163.5, 161.5, 155.3, 152.1, 147.8, 130.8, 122.6, 114.3, 113.3, 108.4, 51.7, 36.7, 26.3, 21.1; EI-MS: m/z (%) = 261 (25), 260 (M$^+$, 42), 239 (55), 216 (17), 204 (100), 203 (87), 165 (72), 133 (67), 95 (86), 75 (39).

4-(2,4-Dichlorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**4l**): mp 286.5–287.8 °C (226.8–227.7 °C) [5c]; IR (KBr): 3245, 3097, 1695, 1649, 1608 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.85–1.93 (m, 2H), 2.14–2.22 (m, 2H), 2.46-2.51 (m, 2H), 5.53 (d, J = 2.47 Hz, 1H), 7.27–7.38 (m, 2H), 7.54 (s, 1H), 7.70 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.4, 155.8, 151.3, 140.7, 133.2, 132.9, 131.2, 129.2, 128.1, 107.0, 50.6, 36.7, 26.4, 21.3; EI-MS: m/z (%) = 311 (M$^+$, 6), 277 (40), 276 (19), 275 (100), 234 (25), 233 (13), 232 (73), 165 (78).

4-(4-Chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**4m**): mp 324.6–326.6 °C (>300 °C) [16c]; IR (KBr): 3247, 1707, 1674, 1617 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.87 (s, 3H), 1.01 (s, 3H), 2.02 (d, J = 16.00 Hz, 1H), 2.18 (d, J = 16.00 Hz, 1H), 2.26 (d, J = 17.00 Hz, 1H), 2.40 (d, J = 17.00 Hz, 1H), 5.15 (d, J = 3.00 Hz, 1H), 7.24 (d, J = 8.50 Hz, 2H), 7.37 (d, J = 8.50 Hz, 2H), 7.80 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.1, 152.7, 151.9, 143.8, 131.8, 128.5, 128.3, 107.2, 51.7, 49.9, 32.5, 28.9, 27.0; EI-MS: m/z (%) = 306 (16), 305 (22), 304 (M$^+$, 44), 269 (36), 220 (17), 193 (100), 137 (43).

9-(4-Methylphenyl)-1,8-dioxo-2,3,4,5,6,7-hexahydroxanthene (**5b**): mp 253.3-253.7 °C; IR (KBr): 1656, 1616 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.93–2.03 (m, 4H), 2.25 (s, 3H), 2.31–2.36(m, 4H), 2.56–2.66 (m, 4H), 4.77 (s, 1H), 7.02 (d, J = 7.90 Hz, 2H), 7.18 (d, J = 7.90 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.4, 163.7, 141.5, 135.8, 128.8, 128.2, 117.0, 37.0, 31.2, 27.1, 21.0, 20.3; EI-MS: m/z (%) = 309 (14), 308 (M$^+$, 61), 294 (15), 293 (72), 218 (15), 217 (100), 91 (34).

9-(3-Pyridyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydro-xanthene (**5n**): mp 243–244 °C; IR (KBr): 1673, 1649, 1618 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.87–1.96 (m, 4H), 2.26–2.31 (m, 4H), 2.61–2.71 (m, 4H), 4.55 (s, 1H), 7.23–7.25 (m, 1H), 7.54 (d, J = 7.85 Hz, 1H), 8.31 (d, J = 4.65 Hz, 1H), 8.43 (d, J = 1.90 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.7, 165.9, 149.9, 147.6, 140.3, 135.8, 123.7, 115.0, 36.7, 29.6, 26.8, 20.2; EI-MS: m/z (%) = 296 (9), 295 (M$^+$, 33), 239 (21), 238 (12), 218 (13), 217 (100), 78 (15).

9-(4-Pyridyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydro-xanthene (**5o**): mp 284–285 °C [20]; IR (KBr): 1673, 1649, 1617 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.87–1.97 (m, 4H), 2.27–2.32 (m, 4H), 2.61–2.68 (m, 4H), 4.56 (s, 1H), 7.19 (d, J = 5.85 Hz, 2H), 8.40 (d, J = 5.80 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.7, 165.9, 153.2, 149.7, 123.8, 114.6, 36.7, 31.3, 26.9, 20.2; EI-MS: m/z (%) = 296 (19), 295 (M$^+$, 40), 218 (18), 217 (100).

2.2. X-ray structure determination of **4k**

Monocrystals of **4k** suitable for X-ray analysis were grown at room temperature by slow evaporation of a solution containing ethanol. The selected crystal was mounted on an ENRAF-NONIUS CAD4 diffractometer equipped with graphite monochromated Mo Kα (λ = 0.71073 Å) radiation. The data were collected at 296 (2) K using the ω scan mode ($1.94° < \theta < 25.18°$). The structure was solved by direct methods and refined by full-matrix, least-squares method on F^2_{obs} with the SHELEL-97 software package. All non-H atoms were anisotropically refined. The hydrogen atoms were located by geometry calculation and riding on the related parent atoms.

Crystal data: $C_{14}H_{13}FN_2O_2$, M = 260.26, crystal size = 0.48 mm × 0.25 mm × 0.15 mm; crystal system: monoclinic, space group: $C2(c)$, a = 21.027(6) Å, b = 8.3110(16) Å, c = 14.027(3) Å, α = 90.000(16)°, β = 93.49(2)°, γ = 90.000(19)°, V = 2446.7(9) Å^3, Z = 8, Dc = 1.413 g/cm^3, $F(0\,0\,0)$ = 1088. A total of 2631 [(R_{int} = 0.0175)] independent data were collected (θ range for collection: 1.94–25.18°; completeness to 2θ = 25.18°, 100.0%; refinement method: full-matrix, least-squares on F^2; goodness of fit on F^2: 1.064; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0489, wR_2 = 0.1565; R indices (all data): R_1 = 0.0975, wR_2 = 0.1811; largest difference peak and hole: 0.793 and −0.413 e/A^3).

Table 1
Catalyst and solvent effect for multicomponent rections

Entry	Catalyst (wt% of the reactants)	Solvent	Time (h)	Yield of **4b** (%)
1	Nafion-H (30)	EtOH	10	41
2	Nafion-H (50)	EtOH	10	53
3	Nafion-H (80)	EtOH	10	62
3	Nafion-H (90)	EtOH	10	64
4	Nafion-H (100)	EtOH	10	66
5	Nafion-H (120)	EtOH	10	63
6	Montmorillonite KSF (10)	EtOH	10	20
7	Montmorillonite KSF (20)	EtOH	10	28
8	Montmorillonite KSF (30)	EtOH	10	31
9	Montmorillonite KSF (50)	EtOH	10	25
10	Montmorillonite KSF (90)	EtOH	10	14
11	Montmorillonite K10 (30)	EtOH	10	23
12	Nafion-H (100)	CH_3CN	10	55
13	Nafion-H (100)	MeOH	10	50
14	Nafion-H (100)	THF	10	58
15	Nafion-H (100)	$CHCl_3$	10	31
16	Nafion-H (100)	Benzene	10	Trace
17	Nafion-H (100)	Toluene	10	Trace

Reaction conditions: 1,3-cyclohexanedione (2.6 mmol), urea (2.4 mmol), 4-methylbenzaldehyde (2.0 mmol) in anhydrous, ethanol under refluxing.

Table 2
Multicomponent reactions of cyclic β-diketones, aldehydes and urea catalyzed by Nafion-H

Entry	R	Substrate	R_1	Product	Yield (%)[a,b]
1	C_6H_5	**3a**	H	**4a**	70 (46)
2	4-$CH_3C_6H_5$	**3b**	H	**4b**	66 (43)
3	3-ClC_6H_5	**3c**	H	**4c**	82 (62)
4	4-ClC_6H_5	**3d**	H	**4d**	76 (54)
5	2-BrC_6H_5	**3e**	H	**4e**	66 (44)
6	3-BrC_6H_5	**3f**	H	**4f**	68 (45)
7	4-BrC_6H_5	**3g**	H	**4g**	73 (44)
8	4-$NO_2C_6H_5$	**3h**	H	**4h**	67 (46)
9	4-$CH_3OC_6H_5$	**3i**	H	**4i**	74 (48)
10	4-FC_6H_5	**3j**	H	**4j**	75 (19) [17e]
11	3-FC_6H_5	**3k**	H	**4k**	68
12	2,4-$Cl_2C_6H_5$	**3l**	H	**4l**	88 (95) [5c]
13	4-ClC_6H_5	**3m**	CH_3	**4m**	72 (49) [16c]
14	3-Pyridine	**3n**	H	**5n**	77
15	4-Pyridine	**3o**	H	**5o**	81

Reaction conditions: cyclic β-diketones (2.6 mmol), aldehyde (2.0 mmol), urea (2.4 mmol) and Nafion-H (100 wt% of the reactants) in anhydrous ethanol under refluxing.

[a] Isolated yields.

[b] Numbers in parentheses refer to reported yields in literature [16b] unless indicated otherwise.

3. Results and discussion

3.1. Experimentation

First, various solid acids were examined in the model reaction of 1,3-cyclohexanedione (2.6 mmol), urea (2.4 mmol) and 4-methylbenzaldehyde **3b** (2.0 mmol) in ethanol and afforded 4-(4-methylphenyl)-1,2,3,4,5, 6,7,8-octahydroquinazoline-2,5-dione (**4b**) in various yields (Table 1). It can be seen from Table 1 that Nafion-H was the most efficient (Table 1, entries 1–11) of the three solid acids studied, and greater amounts of Nafion-H improve the result (Table 1, entries 1–5). Accordingly, a variety of reaction conditions were tried using Nafion-H as the catalyst to minimize side reactions and to improve the low yields that have been found even when using conc. HCl as the catalyst [16]. By adapting a 1:1.2:1 mole ratio of 1,3-cyclohexanedione, urea and 4-methylbenz-aldehyde, the reaction gave a mixture of **4b** and **5b** and the selective formation of **4b** can be achieved by increasing the amount of 1,3-cyclohexanedione and urea. The best results were obtained with a 1.3:1.2:1 ratio of 1,3-cyclohexanedione, urea and aldehyde. The effect of solvent on the reaction was studied (Table 1, entries 4, 12–17) and ethanol was found to be the best solvent when considering the reaction yields and environmental damage. The product could be purified easily by washing the solid residue with ethyl acetate after filtration, and the remaining catalyst could be used for further runs. No obvious decrease of the yield was observed for four successive reactions (66, 65, 67 and 64%), demonstrating that the Nafion-H catalyst can be recycled without significant loss of activity [21].

Having established the reaction conditions for this multicomponent reaction, we explored the scope and limitations of this reaction using different kinds of aromatic aldehydes and cyclic β-diketones. As shown in Table 2, the reactions can tolerate a wide range of aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents in the *ortho*, *meta* and *para* positions. Chloro-substituted substrates normally gave high yields (Table 2, entries 3, 4 and 12). The three-component condensation reactions proceeded smoothly and were complete within 8–12 h. Under these conditions, the yields were improved significantly compared with the reported reactions [16]. All the products were characterized on the basis of their spectroscopic data, such as ^{1}H NMR, ^{13}C NMR, EI-MS and IR spectra and physical data. Meanwhile, the structure was further confirmed by X-ray crystal structure analysis of compound **4k** (Fig. 1).

Since several pyridyl-containing compounds have remarkable pharmacological activities [22], we attempted to extend this reaction to nicotinaldehyde and isonicotinaldehyde. However, as shown in Table 2 (entries 14, 15), the reactions afforded mainly hexahydroxanthenes **5n** and **5o** [20], instead of the expected Biginelli products (**4n** and **4o**). The reason might be due to the strong electron-withdrawing property of pyridyl group and high acid-

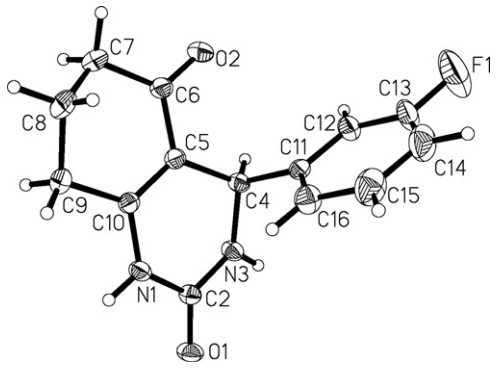
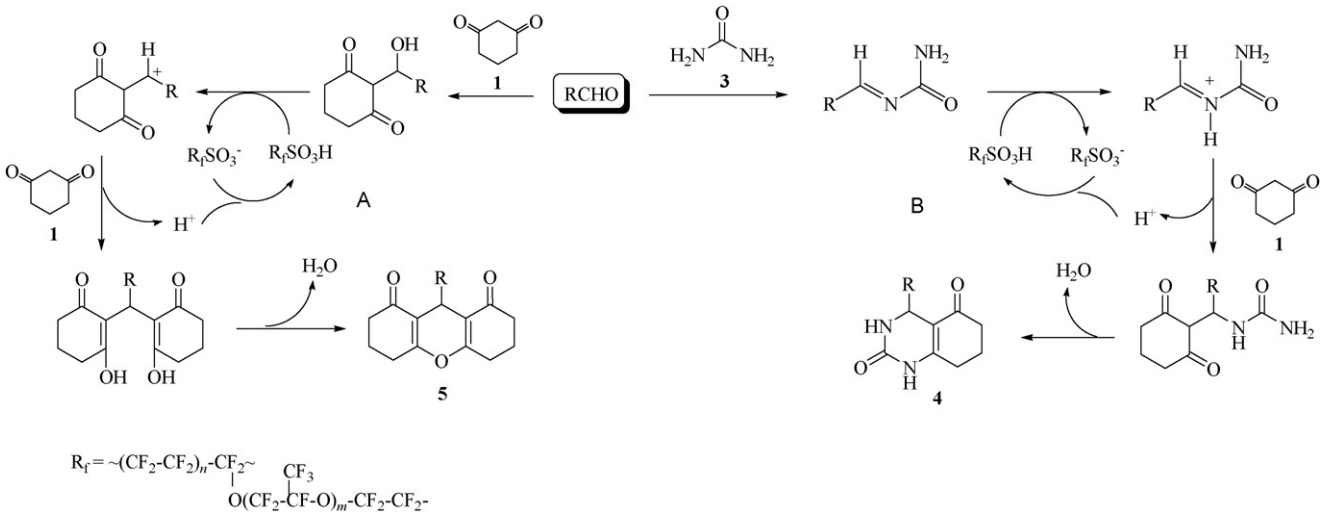


Fig. 1. The molecular structure and labeling scheme of **4k** with 30% probability of ellipsoids.



Scheme 2.

ity of 1,3-cyclohexanedione, which makes the reaction pathway favor the catalytic Cycle A (Scheme 2) and give the unexpected product **5**.

The mechanism of this multicomponent reaction is not clear at this stage. Similar to the reports by Folkers and Johnson [23], and Kappe [24] for the Biginelli reaction, the formation of product **4** may involve an acyl imine intermediate, the addition of cyclic β-diketone to the iminium ion, and subsequent cyclodehydration (Cycle B, Scheme 2).

*3.2. Structural description of 4-(3-fluorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazo-line-2,5-dione (**4k**)*

The structure and geometry of **4k** in the solid state were established by a single-crystal X-ray structure analysis (Fig. 1). The six-membered heterocyclic ring has the puckered boat conformation with C(4)–0.246 Å and N(1)–0.112 Å fully above the least-squares plane through C(2)/N(3)/C(5)/C(10), which is supported by the N(1)–C(2) bond length (1.384 Å) and the N(3)–C(2) bond length (1.333 Å). The dihedral angle between the benzene ring and the six-membered heterocyclic ring is 89.5°. The fluoro substituent on the C(4)-aryl ring is synperiplanar with respect to C(4)–H. The crystal packing diagram (not shown) shows intermolecular H-bondings between the carbonyl oxygen O(2) and N(1)–H with the following characteristics: N(1)–H···O(2) = 2.808 Å, H···O(2) = 1.957 Å, N(1)–H···O(2) = 164.5°, and between the amide oxygen O(1) and N(3)-H, with the following characteristics: N(3)–H···O(1) = 2.892 Å, H···O(1) = 2.044 Å, N(3)–H···O(1) = 167.9°.

4. Conclusion

We have developed a convenient, efficient and eco-friendly method for the direct synthesis of octahydroquinazoline derivatives over Nafion-H as the catalyst with good yields and selectivity. Importantly, the catalyst can be re-used several times. This successful reaction expands the synthetic scope of the multicomponent Biginelli reaction. The further applications of this reaction are being investigated in our laboratory.

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