Journal of Molecular Catalysis A: Chemical 360 (2012) 26–34

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Cellulose-SO_3H as a biodegradable solid acid catalyzed one-pot three-component Ugi reaction: Synthesis of α-amino amide, 3,4-dihydroquinoxalin-2-amine, 4*H*-benzo[*b*][1,4]thiazin-2-amine and 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives

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ARTICLE INFO

Article history:
Received 9 February 2012
Received in revised form 15 March 2012
Accepted 4 April 2012
Available online 12 April 2012

Keywords:
Biodegradable solid acid catalyzed
Three-compound Ugi reaction
Cellulose-SO_3H
α-Amino amide
Solid acid catalyzed

ABSTRACT

A variety of amines has become utilized in the three-compound Ugi reaction and synthesis of 3,4-dihydroquinoxalin-2-amine, 4*H*-benzo[*b*][1,4]thiazin-2-amine and 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in the presence of cellulose sulfuric acid as a biopolymer solid acid catalyst in ethanol at room temperature.

1. Introduction

Heterogeneous catalysts for the synthesis of fine chemicals have attracted considerable interest from both environmental and economical points. The solid acids have high turnover numbers and easily separated from reaction mixtures [1]. Cellulose and its derivatives, have some unique properties, which make them attractive alternatives for conventional synthetic organic or inorganic supports for catalytic applications [2]. The most frequently synthesized and used cellulose derivatives with functionalization patterns of high uniformity are important not only for comparison with statistically modified celluloses, but are particularly important as products with new properties and applications. Their importance also lies with respect to questions that remain open about the solution structure of cellulose derivatives and for the design of supramolecular architectures and has been widely studied during the past decades because of it is a biodegradable material and a renewable resource [3]. Recently, science and technology are shifting emphasis on environmentally friendly and sustainable resources and processes. In this regard, biopolymers are attractive candidates to explore for supported catalysis [4,5] alginate [6], gelatin [7,8], starch [9] and chistosan [10] derivatives are interesting support catalytic biopolymers.

In recent years, there has been much interest reported of a three-component Ugi reaction [11]. In particular; the groups of List [12] and Sutherland [11f] have introduced new catalytic three-component Ugi reaction to synthesis of α-amino acids by using an amine, a carbonyl compound, and an isocyanide. In this strategy, carbonyl compound condenses with an amine to form an imine intermediate (**A**). Then, the nucleophilic addition of isocyanide to iminium ions (**A**) to yield a nitrilium ion intermediate (**B**). Finally, water as an internal nucleophilic instead of carboxylic acids reaction with nitrilium ion **B** leads to the product α-amino acids (**C**) (Scheme 1).

2. Experimental

2.1. General

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR Spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in order:

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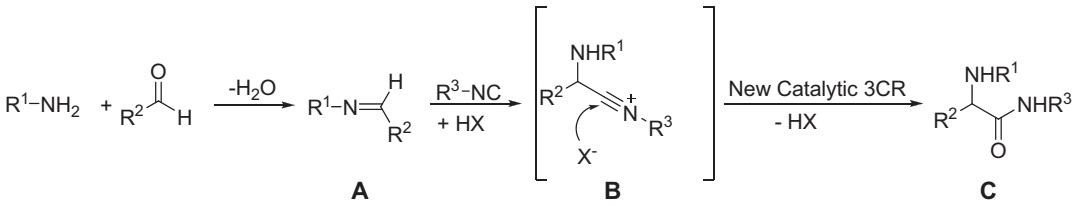
http://dx.doi.org/10.1016/j.molcata.2012.04.002



Scheme 1. Ugi three-component reaction.

number of protons, multiplicity and approximate coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal) and Ar (aryl). The ^{13}C NMR spectra were recorded at 75.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. Compounds **5a–j**, **6a–h**, **8d** and **8e** were new compounds whose structures were recognized by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Other products are known compounds and were characterized by IR and NMR spectroscopic data and their melting points are compared with reported values [13a,13b,16,17].

2.2. Synthesis of cellulose sulfuric acid

To a magnetically stirred mixture of cellulose (5.00 g, DEAE for column chromatography, Merck) in $CHCl_3$ (20 mL), chlorosulfonic acid (1.00 g, 9 mmol) was added dropwise at 0 °C during 2 h. After addition was complete, the mixture was stirred for 2 h until HCl was removed from reaction vessel. Then, the mixture was filtered and washed with methanol (30 mL) and dried at room temperature to obtain cellulose sulfuric acid as white powder (5.22 g). Sulfur content of the samples by conventional elemental analysis, was 0.55 mmol/g for cellulose sulfuric acid. The number of H^+ site of cellulose-SO_3H determined by acid–base titration was 0.50 meq/g [13k].

2.3. General procedure for the preparation of products *5a–j*, *6a–h*, *7a–k*, *10a–f* and *8a–e*

A solution of amines (1.00 mmol), carbonyl compounds (1.00 mmol) and isocyanide (1.00 mmol) was stirred for 2–48 h in the presence of cellulose sulfuric acid (0.10 g) in 3 mL of ethanol 96% at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), the precipitate was filtered off and washed with ethanol, and then crystallized from acetone to give products **5a–j, 6a–h, 7a–k, 8a–e** and **10a–f**.

2.4. Compounds characterization data

2.4.1. 2-(2-Bromophenyl)-N-cyclohexyl-2-(phenylamino)acetamide (*5a*)

Yellow oil. IR (KBr) cm^{-1}: 3501, 2932, 2854, 1661, 1601, 1497, 1439, 1349, 1316. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.70 (10H, m, 5CH_2 of cyclohexyl), 3.57 (1H, m, CH of cyclohexyl), 5.25 (1H, s, CH), 6.16 (1H, s, *J* = 7.9, NH), 6.60–8.00 (10H, m, CH-Ar and NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.1, 24.9, 25.6, 31.2, 32.5, 48.2, 61.1, 113.4, 117.3, 126.6, 128.1, 129.1, 129.5, 129.8, 134.0, 138.9, 147.6, 169.0. Anal. Calcd for $C_{20}H_{23}BrN_2O$: C, 62.02; H, 5.99; N, 7.23; found C, 62.00; H, 5.80; N, 7.13.

2.4.2. 2-(4-Chlorophenyl)-N-cyclohexyl-2-(phenylamino)acetamide (*5b*)

Cream powder; mp 168–169 °C. IR (KBr) cm^{-1}: 3461, 3051, 2931, 2855, 1678, 1608, 14501, 1438, 1355, 1302. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, 5CH_2 of cyclohexyl), 3.76 (1H, m, CH of cyclohexyl), 4.18 (1H, s, CH), 5.11 (1H, s, NH), 6.60–7.70 (10H, m, CH-Ar and NH). Anal. Calcd for $C_{20}H_{23}ClN_2O$: C, 70.06; H, 6.76; N, 8.17; found C, 70.06; H, 6.66; N, 8.10.

2.4.3. N-Cyclohexyl-2-(3-nitrophenyl)-2-(phenylamino)acetamide (*5c*)

Cream powder; mp 158–159 °C. IR (KBr) cm^{-1}: 3451, 2936, 2850, 1671, 1611, 1498, 1449, 1345, 1318. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, 5CH_2 of cyclohexyl), 3.67 (1H, m, CH of cyclohexyl), 4.45 (1H, s, CH), 5.151 (1H, s, NH), 6.30–8.30 (10H, m, CH-Ar and NH). Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89; found C, 67.97; H, 6.46; N, 11.80.

2.4.4. N-Tert-butyl-2-phenyl-2-(phenylamino)acetamide (*5d*)

Yellow oil. IR (KBr) cm^{-1}: 3384, 33420, 3180, 29350, 2855, 1670, 1600, 1523, 1307. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.24 (s, 9H), 4.44 (s, 1H), 4.56 (br s, NH), 6.45–7.40 (m, 11H, CH-Ar and NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.1, 50.6, 56.3, 65.4, 114.4, 114.6, 126.0, 128.5, 128.0, 139.1, 141.0, 152.6, 170.2. Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92; found C, 76.56; H, 7.80; N, 9.82.

2.4.5. 2-(4-Fluorophenyl)-2-(phenylamino)-N-(tosylmethyl)acetamide (*5e*)

Cream powder; mp 183 °C. IR (KBr) cm^{-1}: 3388, 3312, 3053, 2988, 2927, 1686, 1602, 1543, 1502, 1435, 1299. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.32 (3H, s, CH_3), 4.50–4.65 (2H, m, CH), 4.70–4.85 (2H, m, CH), 5.03 (1H, s, CH), 6.50–7.45 (14H, m, CH-Ar and NH), 10.50 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.5, 59.7, 60.3, 112.8, 113.6, 115.4, 115.6, 117.3, 128.7, 128.9, 129.2, 129.8, 129.9, 130.2, 134.7, 135.2, 144.8, 147.3, 171.6. Anal. Calcd for $C_{22}H_{21}FN_2O_3S$: C, 64.06; H, 5.13; N, 6.79; found C, 64.06; H, 5.09; 8; N, 6.89.

2.4.6. 2-(3-Nitrophenyl)-2-(phenylamino)-N-(tosylmethyl)acetamide (*5f*)

Cream powder; mp 187–188 °C. IR (KBr) cm^{-1}: 3336, 3054, 2930, 2866, 1694, 1603, 1534, 1435, 1351, 1314. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.27 (3H, s, CH_3), 4.61 (1H, dd, J_3 = 11.6 and 5.2, CH_2), 4.89 (1H, dd, J_3 = 13.8 and 7.2, CH_2), 5.26 (1H, s, CH), 6.58 (2H, ABq, J_3 = 7.6, CH-Ar), 6.62 (1H, s, NH), 7.03 (2H, ABq, J_3 = 7.1, CH-Ar), 7.09 (2H, ABq, J_3 = 7.2, CH-Ar), 7.37 (2H, ABq, J_3 = 7.4, CH-Ar), 7.65 (1H, dd, J_3 = 7.8 and 7.6, CH-Ar), 7.89 (1H, d, J_3 = 7.5, CH-Ar), 8.19 (1H, d, J_3 = 7.7, CH-Ar), 8.30 (1H, s, CH-Ar), 9.44 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.4, 59.4, 60.1, 113.7, 117.5, 122.4, 123.2, 128.6, 129.3, 129.8, 130.4, 141.6, 144.7, 146.9,

148.2, 170.7. Anal. Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56; found C, 60.12; H, 4.82; N, 9.56.

*2.4.7. 1-(Phenylamino)-N-(tosylmethyl)cyclohexanecarboxamide (**5g**)*

Brown powder; mp 187 °C. IR (KBr) cm^{-1}: 3370, 3051, 3007, 2936, 2857, 1672, 1600, 1496, 1388, 1316. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.20–1.90 (10H, m, $5CH_2$ of cyclohexyl), 2.44 (3H, s, CH_3), 4.68 (2H, s, CH_2), 6.65 (3H, m, CH-Ar), 6.90 (1H, s, NH), 7.18 (1H, d, J_3 = 7.0, CH-Ar), 7.31 (1H, ABq, J_3 = 7.5, CH-Ar), 7.73 (1H, ABq, J_3 = 7.6, CH-Ar), 7.92 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.7, 24.8, 31.0, 60.3, 112.8, 113.6, 115.4, 128.8, 129.2, 129.8, 134.2, 145.3, 171.5. Anal. Calcd for $C_{21}H_{26}N_2O_3S$: C, 65.26; H, 6.78; N, 7.25; found C, 65.16; H, 6.71; N, 7.20.

*2.4.8. 2-(Benzylamino)-2-(4-fluorophenyl)-N-(tosylmethyl)acetamide (**5h**)*

Brown powder; mp 120–121 °C. IR (KBr) cm^{-1}: 3330, 3058, 2935, 2855, 1679, 1613, 1530, 1434, 1358, 1318. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 2.36 (3H, s, CH_3), 3.39 (2H, s, CH_2), 4.50–4.70 (3H, m, CH_2 and CH), 5.58 (1H, s, NH), 7.00–8,00 (14H, CH-Ar and NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.2, 50.7, 61.0, 61.5, 115.5, 125.9, 128.1, 128.3, 128.5, 128.8, 128.9, 129.0, 129.3, 129.4, 129.5, 130.0, 130.1, 130.2, 130.6, 138.3, 145.3, 145.7, 171.0. Anal. Calcd for $C_{23}H_{23}FN_2O_3S$: C, 64.77; H, 5.44; F, 4.45; N, 6.57; found C, 64.70; H, 5.41; F, 4.45; N, 6.55.

*2.4.9. 2-(Benzylamino)-2-(2-bromophenyl)-N-(tosylmethyl)acetamide (**5i**)*

Cream powder; mp 180–181 °C. IR (KBr) cm^{-1}: 3360, 3334, 3168, 2932, 2850, 1678, 1590, 1528, 1445, 1355, 1302. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 2.27 (3H, s, CH_3), 4.50–4.70 (5H, m, $2CH_2$ and CH), 5.60 (1H, s, NH), 6.90–8.00 (14H, CH-Ar and NH). Anal. Calcd for $C_{23}H_{23}BrN_2O_3S$: C, 56.68; H, 4.76; N, 5.75; found C, 56.68; H, 4.76; Br, 16.39; N, 5.75.

*2.4.10. 2-(Allylamino)-N-tert-butyl-2-phenylacetamide (**5j**)*

Yellow liquid. IR (KBr) cm^{-1}: 3360, 3324, 3160, 2935, 2855, 1676, 1590, 1440, 1365. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.25 (9H, s, CH_3), 3.15 (m, 2H, CH_2), 5.00 (br, 1H, CH), 5.10 (br, 1H, CH), 5.75 (1H, s, NH), 6.95–7.60 (6H, CH-Ar and NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.2, 50.1, 50.4, 68.2, 115.7, 125.5, 135.5, 139.2, 167.5. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37; found C, 73.08; H, 9.01; N, 11.27.

*2.4.11. 2-(2-Hydroxyphenylamino)-2-(4-chlorophenyl)-N-cyclohexylacetamide (**6a**)*

Brown powder; mp 208 °C. IR (KBr) cm^{-1}: 3380, 3344, 3171, 3049, 2930, 2854, 1648, 1599, 1520, 1440, 1365, 1306. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, $5CH_2$ of cyclohexyl), 3.45 (1H, m, CH of cyclohexyl), 5.03 (1H, ABq, J = 7.8, CH), 5.37 (1H, ABq, J = 7.9, NH), 6.21 (1H, d, J_3 = 6.8, CH-Ar), 6.40 (1H, ddd, J_3 = 7.5, 7.5, J_4 = 1.3, CH-Ar), 6.51 (1H, ddd, J_3 = 7.2, 7.5, J_4 = 1.1, CH-Ar), 6.69 (1H, dd, J_3 = 7.6, J_4 = 1.2, CH-Ar), 7.37 (2H, ABq, J = 8.5, CH-Ar), 7.46 (2H, ABq, J = 8.5, CH-Ar), 8.27 (1H, d, J = 7.8, NH), 9.53 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.7, 24.8, 25.6, 32.4, 32.7, 48.1, 59.3, 111.3, 114.1, 117.2, 119.9, 128.8, 128.9, 132.4, 135.3, 139.5, 144.8, 169.7. Anal. Calcd for $C_{20}H_{23}ClN_2O_2$: C, 66.94; H, 6.46; N, 7.81; found C, 66.94; H, 6.46; N, 7.81.

*2.4.12. 2-(2-Hydroxy-5-methylphenylamino)-2-(4-chlorophenyl)-N-cyclohexylacetamide (**6b**)*

Brown powder; mp 203–204 °C. IR (KBr) cm^{-1}: 3394, 3349, 3188, 3033, 2930, 2856, 1656, 1602, 1524, 1408, 1356, 1306. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, $5CH_2$ of cyclohexyl), 2.02 (3H, s, CH_3), 3.48 (1H, m, CH of cyclohexyl), 5.02 (1H, ABq, J = 7.6, CH), 5.27 (1H, ABq, J = 7.7, NH), 6.06 (1H, s, CH-Ar), 6.21 (1H, d, J_3 = 7.8, CH-Ar), 6.56 (1H, d, J_3 = 7.8, CH-Ar), 7.38 (2H, ABq, J = 8.4, CH-Ar), 7.46 (2H, ABq, J = 7.1, CH-Ar), 8.24 (1H, d, J_3 = 7.48, NH), 9.26 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.3, 24.7, 24.8, 25.6, 32.4, 32.7, 48.0, 59.4, 112.1, 114.0, 117.4, 128.2, 128.8, 132.4, 135.2, 139.5, 142.6, 169.7. Anal. Calcd for $C_{21}H_{25}ClN_2O_2$: C, 67.64; H, 6.76; N, 7.51; found C, 67.62; H, 6.70; N, 7.41.

*2.4.13. 2-(2-Hydroxyphenylamino)-N-cyclohexyl-2-(4-methoxyphenyl)acetamide (**6c**)*

Black powder; mp 180–182 °C. IR (KBr) cm^{-1}: 3369, 3350, 3166, 2931, 2850, 1653, 1600, 1518, 1440, 1374, 1310. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, $5CH_2$ of cyclohexyl), 3.47 (1H, m, CH of cyclohexyl), 3.70 (3H, s, CH_3), 4.91 (1H, d, J = 7.5, CH), 5.26 (1H, d, J = 7.5, NH), 6.24 (1H, d, J_3 = 7.4, CH-Ar), 6.39 (1H, dd, J_3 = 7.2, 7.2, CH-Ar), 6.52 (1H, dd, J_3 = 7.3, 7.3, CH-Ar), 6.66 (2H, d, J_3 = 7.4, CH-Ar), 6.86 (2H, d, J_3 = 8.0, CH-Ar), 7.35 (2H, d, J_3 = 8.0, CH-Ar), 8.13 (1H, d, J_3 = 7.6, NH), 9.44 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.8, 24.9, 25.6, 32.5, 32.8, 48.0, 55.4, 59.5, 111.2, 114.0, 114.2, 116.9, 119.9, 128.2, 132.2, 135.7, 144.7, 159.0, 170.4. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90; found C, 71.16; H, 7.30; N, 7.85.

*2.4.14. 2-(2-Hydroxy-5-methylphenylamino)-N-cyclohexyl-2-(4-methoxyphenyl)acetamide (**6d**)*

Green powder; mp 175–178 °C. IR (KBr) cm^{-1}: 3394, 3349, 3930, 2856, 1651, 1605, 1519, 1451, 1305. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, $5CH_2$ of cyclohexyl), 2.00 (3H, s, CH_3), 3.44 (1H, m, CH of cyclohexyl), 3.68 (3H, s, CH_3), 4.87 (1H, d, J = 5.5, CH), 5.12 (1H, s, NH), 6.06 (1H, s, CH-Ar), 6.17 (1H, d, J_3 = 5.0, CH-Ar), 6.49 (1H, s, CH-Ar), 6.52 (2H, ABq, J_3 = 5.2, CH-Ar), 6.86 (2H, s, CH-Ar), 8.08 g (1H, s, NH), 9.16 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.3, 24.7, 24.8, 25.6, 32.5, 32.8, 47.9, 55.4, 59.5, 112.0, 113.8, 114.2, 117.1, 128.2, 132.3, 135.6, 142.5, 159.0, 170.4. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60; found C, 71.61; H, 7.60; N, 7.50.

*2.4.15. 1-(2-Hydroxyphenylamino)-N-cyclohexylcyclohexanecarboxamide (**6e**)*

Brown powder; mp 204–206 °C. IR (KBr) cm^{-1}: 3391, 3360, 3200, 3046, 2933, 2850, 1641, 1598, 1512, 1447, 1376. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.90 (20H, m, $10CH_2$ of cyclohexyl), 3.54 (1H, m, CH of cyclohexyl), 4.66 (1H, s, NH), 6.27 (1H, d, J = 6.6, CH-Ar), 6.30–6.60 (2H, m, CH-Ar), 6.73 (1H, d, J = 6.6, CH-Ar), 7.48 (1H, d, J = 7.4, NH), 9.58 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.2, 25.1, 25.4, 25.6, 31.4, 32.6, 47.8, 59.3, 114.3, 114.8, 118.0, 119.4, 133.6, 145.8, 175.0. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85; found C, 72.07; H, 8.90; N, 8.75.

*2.4.16. 1-(2-Hydroxyphenylamino)-N-cyclohexylcyclopentanecarboxamide (**6f**)*

Yellow powder; mp 219 °C. IR (KBr) cm^{-1}: 3393, 3065, 2947, 2853, 1675, 1604, 1558, 1515, 1449, 1376, 1331. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–2.40 (18H, m, $9CH_2$ of cyclohexyl and cyclopentyl), 3.54 (1H, m, CH of cyclohexyl), 4.88 (1H, s, NH),

6.00–7.50 (5H, m, CH-Ar and NH), 9.14 (1H, OH). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26; found C, 71.49; H, 8.60; N, 9.16.

2.4.17. 2-(5-Chloro-2-hydroxyphenylamino)-N-cyclohexyl-2-(2,4-dimethoxyphenyl)acetamide (**6g**)

Yellow powder; mp 190–192 °C. IR (KBr) cm^{-1}: 3390, 3350, 3177, 3023, 2936, 2858, 1670, 1609, 1408, 1346, 1310. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.80 (10H, m, $5CH_2$ of cyclohexyl), 3.50 (1H, m, CH of cyclohexyl), 3.72 (3H, s, CH_3), 3.85 (3H, s, CH_3), 5.14 (1H, s, CH), 5.25 (1H, s, NH), 6.28 (1H, s, CH-Ar), 6.40–6.75 (4H, m, CH-Ar), 7.16 (1H, d, J = 8.5, CH-Ar), 7.72 (1H, d, J = 7.9, NH), 9.79 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.2, 24.8, 25.6, 30.8, 31.7, 32.6, 48.0, 55.6, 56.0, 61.7, 98.9, 105.5, 110.7, 115.9, 119.3, 120.0, 123.5, 128.1, 129.7, 137.3, 143.6, 149.6, 172.7. Anal. Calcd for $C_{22}H_{27}ClN_2O_4$: C, 63.08; H, 6.50; N, 6.69; found C, 63.00; H, 6.35; N, 6.60.

2.4.18. 2-(5-Chloro-2-hydroxyphenylamino)-2-(4-chlorophenyl)-N-(tosylmethyl)acetamide (**6h**)

Brown powder; mp 195–196 C. IR (KBr) cm^{-1}: 3572, 3405, 3302, 3187, 3012, 2810, 1672, 1602, 1504, 1437. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 2.36 (3H, s, CH_3), 4.63 (1H, s, CH_2), 4.86 (1H, s, CH_2), 5.05 (1H, s, CH), 6.18 (1H, s, NH), 6.80–7.80 (12H, m, CH-Ar and NH), 10.01 (1H, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.5, 58.6, 65.7, 114.8, 116.4, 117.9, 123.0, 125.9, 128.6, 129.0, 129.1, 129.4, 129.9, 130.1, 130.7, 132.1, 134.4, 137.6, 143.7, 144.8, 170.6. Anal. Calcd for $C_{22}H_{20}Cl_2N_2O_4S$: C, 55.12; H, 4.21; N, 5.84; found C, 55.12; H, 4.20; N, 5.74.

2.4.19. 3-(4-Chlorophenyl)-N-(tosylmethyl)-4H-benzo[b][1,4]thiazin-2-amine (**8d**)

Yellow crystals; mp 108–109 °C. IR (KBr) cm^{-1}: 3340, 3065, 2936, 2850, 1667, 1610, 1538, 1431, 1349, 1311. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 2.34 (3H, s, CH_3), 4.75 (2H, s, CH_2), 7.35–7.65 (6H, m, CH-Ar), 8.00–8.15 (8H, m, CH-Ar and NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.5, 54.9, 122.1, 122.7, 123.5, 124.1, 126.3, 127.2, 128.1, 12.9, 130.0, 130.8, 132.1, 135.0, 136.5, 153.9, 166.4. Anal. Calcd for $C_{22}H_{19}ClN_2O_2S_2$: C, 59.65; H, 4.32; N, 6.32; found C, 59.55; H, 4.30; N, 6.22.

2.4.20. 3-(4-Methoxyphenyl)-N-(tosylmethyl)-4H-benzo[b][1,4]thiazin-2-amine (**8e**)

Yellow crystals; mp 96–97 °C. IR (KBr) cm^{-1}: 3335, 3045, 2935, 2860, 1674, 1600, 1530, 1445, 1355, 1310. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 2.34 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 4.77 (2H, s, CH_2), 6.95–7.10 (4H, m, CH-Ar), 7.30–7.45 (2H, m, CH-Ar), 7.50–7.60 (2H, m, CH-Ar), 8.00–8.20 (6H, m, CH-Ar and NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.6, 54.9, 56.8, 114.1, 115.7, 116.1, 121.8, 122.2, 125.9, 126.1, 126.5, 127.9, 128.6, 130.0, 134.7, 134.8, 154.1, 162.2, 167.5. Anal. Calcd for $C_{23}H_{22}N_2O_3S_2$: C, 62.99; H, 5.06; N, 6.39; found C, 62.99; H, 5.06; N, 6.29.

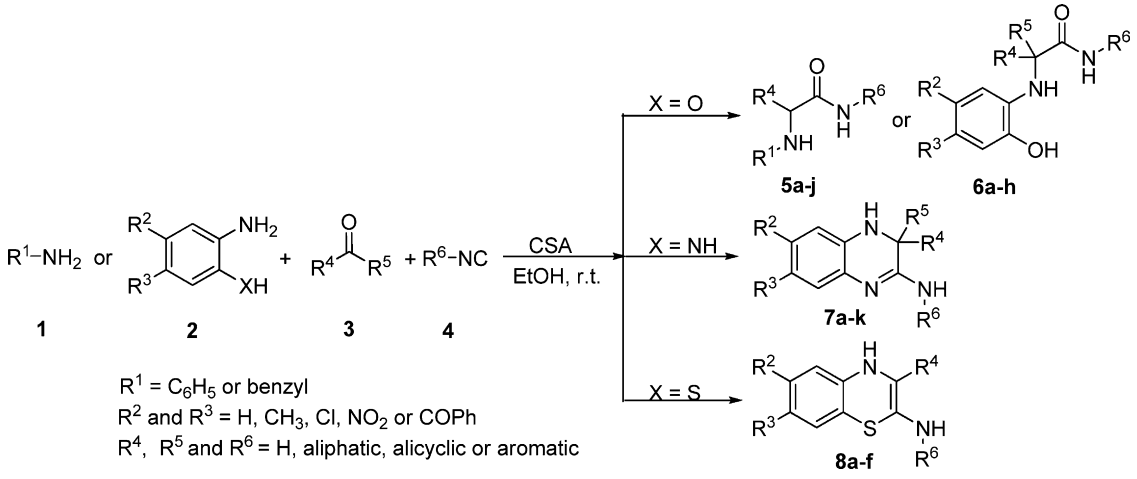
3. Results and discussion

During the course of our studies toward the development of new routes to the synthesis of organic compounds using green reaction mediums [13a–e] and introduction of cellulose-SO_3H for the first time as a biopolymer solid acid catalyst [13f–l], herein, we report the three-component Ugi reaction in which water acts as the internal nucleophile and synthesis of 3,4-dihydroquinoxalin-2-amine, 4*H*-benzo[*b*][1,4]thiazin-2-amine and 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in the presence of cellulose sulfuric acid (CSA) as a biodegradable solid acid catalyst (Scheme 2).

The catalyst is easily prepared by the reaction of chlorosulfonic acid with commercially available cellulose and the by-product, HCl gas, is easily removed from the reaction vessel [13k].

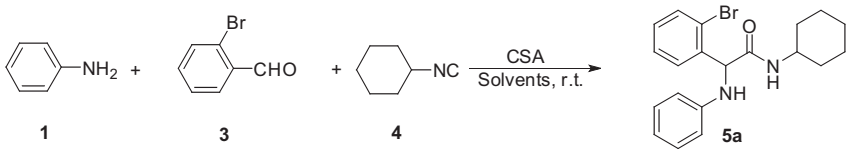
The newly designed reaction does not proceed in the absence of catalyst. Stirring aniline (**1**), 2-bromobenzaldehyde (**3**) and cyclohexyl isocyanide (**4**) at room temperature for 24 h in ethanol 96% resulted in no detectable quantities of the desired product (**5a**). Even refluxing the reaction mixture for 24 h did not result in the formation of product (**5a**). At this point, we started to investigate different catalysts for this reaction (Table 1). *p*-Toluenesulfonic acid and hydrogen chloride gave no conversion to the product either at room temperature or under refluxing conditions (Table 1, entries 1 and 2). Both of the silica sulfuric acid [14a] and xanthan sulfuric acid [14b] could promote this reaction, but with low conversion (Table 1, entries 3 and 4). Remarkably, we found cellulose sulfuric acid to be a highly active catalyst for the reaction, giving the desired product in 65% conversion (Table 1, entry 5).

In order to obtain the best conditions, aniline (**1**), 2-bromobenzaldehyde (**3**) and cyclohexyl isocyanide (**4**) in the presence of cellulose sulfuric acid in various organic solvents and water were allowed to react at room temperature. As can be seen from Table 2, commercially methanol 99% and ethanol 96% are the



Scheme 2. Synthesis of α-amino amide, 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile and 4*H*-benzo[*b*][1,4]thiazin-2-amine derivatives.

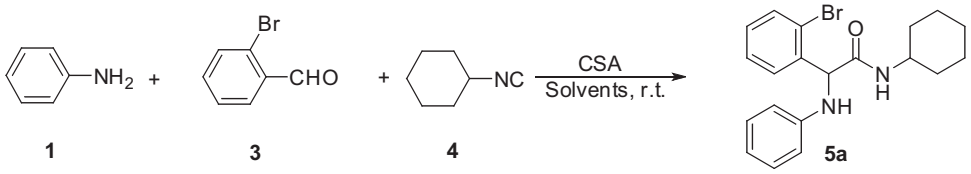
Table 1
Identification of an efficient catalyst for the three-component Ugi reaction.[a] .



Entry	Catalyst	Yields [%][b]
1	$TsOH{\cdot}H_2O$	0 (r.t.) 0 (reflux)
2	HCl	0
3	Silica sulfuric acid	8
4	Xanthan sulfuric acid	8
5	Cellulose sulfuric acid	65

[a] Reaction conditions: aniline (**1**, 1.0 mmol), 2-bromobenzaldehyde (**3**, 1.0 mmol), cyclohexyl isocyanide (**4**, 1.0 mmol), and catalyst were stirred in ethanol 96% (3.0 mL).
[b] Isolated yield.

Table 2
Optimization of the solvent for synthesis of 2-(2-bromophenyl)-*N*-cyclohexyl-2-(phenylamino)acetamide (4a).[a] .



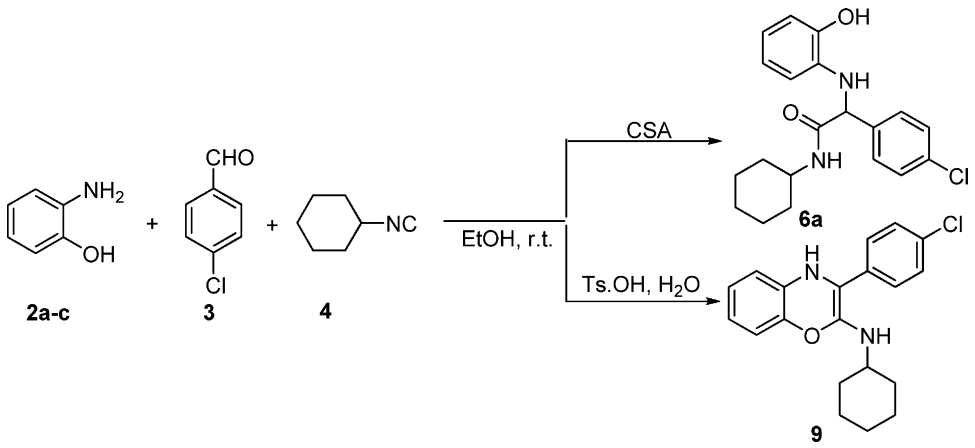
Solvents	Time [h]	Yields [%][b]
H_2O	24	–
CH_2Cl_2	24	–
$CHCl_3$	24	–
CH_3CN	24	–
C_6H_6	24	–
THF	24	15
MeOH 99%	24	65
Ethanol 96%	24	65
EtOH 100%	24	24

[a] Reaction conditions: aniline (**1**, 1.0 mmol), 2-bromobenzaldehyde (**3**, 1.0 mmol), cyclohexyl isocyanide (**4**, 1.0 mmol), and cellulose sulfuric acid (0.1 g) were stirred in solvent (3.0 mL).
[b] Isolated yield.

best solvents for the synthesis of compound 2-(2-bromophenyl)-*N*-cyclohexyl-2-(phenylamino)acetamide (**5a**) respect to yield and reaction times.

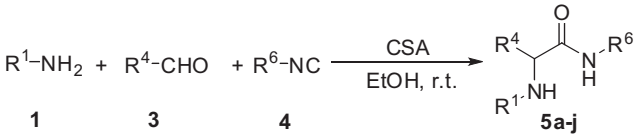
Using cellulose sulfuric acid as the best catalyst in ethanol as a solvent, we initiated a study to explore the scope of this new three-component reaction. Various amines (**1**), aldehydes (**3**) and isocyanides (**4**) were examined in this reaction and results showed in Table 3.

In order to investigate the scope and limitations of this reaction, we extended it to 2-aminophenols (**2a–c**) instead of amines (**1**). As indicated in Scheme 3, 2-aminophenol (**2a**) and 4-chlorobenzaldehyde (**3**) with cyclohexyl isocyanide (**4**) in the presence of cellulose sulfuric acid as a solid acid catalyst in ethanol lead to the synthesis of (**6a**) at room temperature for 48 h (Scheme 3). It is important to note, the previously reported product (**9**) was not obtained [15]. Even heating the reaction mixture at



Scheme 3. Synthesis of 2-hydroxy-α-amino amides derivatives.

Table 3
Catalytic three-component Ugi reaction of various amines, aldehydes and isocyanides.[a] .



1 3 4 5a-j

Entry	R^1	R^2	R^3	Product	Time [h]	Yield [%][b]
1	Ph	2-BrC_6H_4	*c*Hex	**5a**	48	65
2	Ph	4-ClC_6H_4	*c*Hex	**5b**	48	62
3	Ph	3-$NO_2C_6H_4$	*c*Hex	**5c**	48	60
4	Ph	Ph	*t*Bu	**5d**	48	60
5	Ph	4-FC_6H_4	*p*$TsSO_2CH_2$	**5e**	48	55
6	Ph	3-$NO_2C_6H_4$	*p*$TsSO_2CH_2$	**5f**	48	64
7	Ph	Cyclohexanone	*p*$TsSO_2CH_2$	**5g**	48	57
8	$PhCH_2$	4-FC_6H_4	*p*$TsSO_2CH_2$	**5h**	48	58
9	$PhCH_2$	2-BrC_6H_4	*p*$TsSO_2CH_2$	**5i**	48	60
10	Allyl	Ph	*t*Bu	**5j**	48	60

[a] Reaction conditions: amines (**1**, 1.0 mmol), aldehydes (**3**, 1.0 mmol), isocyanides (**4**, 1.0 mmol), and cellulose sulfuric acid (0.1 g) were stirred in ethanol 96% (3.0 mL).
[b] Isolated yield.

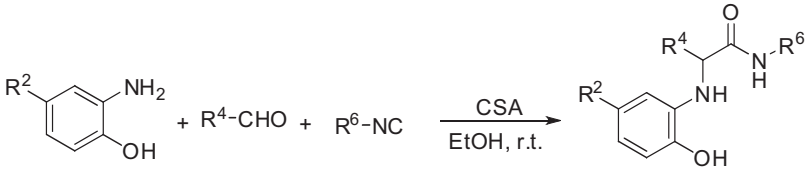
80 °C for 48 h did not formation of product **9**. In this regard, a variety of 2-aminophenols (**2a–c**) with aldehydes (**3**) and isocyanides (**3**) were reacted under similar conditions (Table 4).

In order to explore the range of this extension, the reaction of *o*-phenylenediamines (**2d–i**), 2,3-diaminomaleonitrile (**2h**) and 2-aminobenzenethiol (**2j**) with carbonyl compounds (**3**), and isocyanides (**4**) has been investigated in the presence of a catalytic amount of cellulose sulfuric acid in ethanol at room temperature for 2–48 h (Scheme 4). As indicated in Scheme 4, because of intramolecular nucleophilic attack of NH_2 and SH groups to the activated nitrile moiety interesting products such as 3,4-dihydroquinoxalin-2-amines **7a–k**, 1,6-dihydropyrazine-2,3-dicarbonitriles **8a–f** and 4*H*-benzo[*b*][1,4]thiazin-2-amines **8a–e** were obtained [13a,13b,16–18]. The reaction proceeds very cleanly under mild conditions at room temperature and no undesirable side reactions were observed under this reaction conditions. In this regard, a variety of *o*-phenylenediamines (**2d–h**), 2,3-diaminomaleonitrile (**2i**) and 2-aminobenzenethiol (**2j**) with carbonyl compounds (**3**), and isocyanides (**4**) were reacted under similar conditions (Table 5). So, we studied the reaction of 2,3-diaminomaleonitrile (**2i)** with cyclohexyl isocyanide and benzaldehyde (Scheme 4). However, due to high stability of the generated imine **11** from reaction of 2,3-diaminomaleonitrile and benzaldehyde, the nucleophilic attack by isocyanide did not occur [16].

Recyclability of the catalyst was examined, too. For this reason, catalyst which was recovered from reaction between 2,3-diaminomaleonitrile, cyclohexanone and cyclohexyl isocyanide by filtration; after drying the catalyst, it was reused. This procedure was carried out for four times. Results of these successive reactions are shown in Table 6. It is clear that by successive use of catalyst no decrease in reactivity or performance can be seen (Fig. 1).

The possible mechanism for the formation of α-amino amides, 3,4-dihydroquinoxalin-2-amine and 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in the presence of cellulose sulfuric acid as a promoter is shown in Scheme 5. It is conceivable that, the initial event is the formation of iminium **12** from an activated aldehyde or ketone **3** and an amine **2a–j** [19]. On the basis of the chemistry of reaction of isocyanides with imines, intermediate **13** was produced by nucleophilic attack of isocyanide **4** to activated iminium **12** [19,20]. When X = O intermediate **14** was produced by a nucleophilic attack of water molecule to nitrilium moiety **13** and led to the formation of products **5a–j** and **6a–h.** If X = NH or S, intermediate **15** was produced by an intramolecular nucleophilic attack of NH_2 or S to the activated nitrile moiety **13**. Tautomerization of

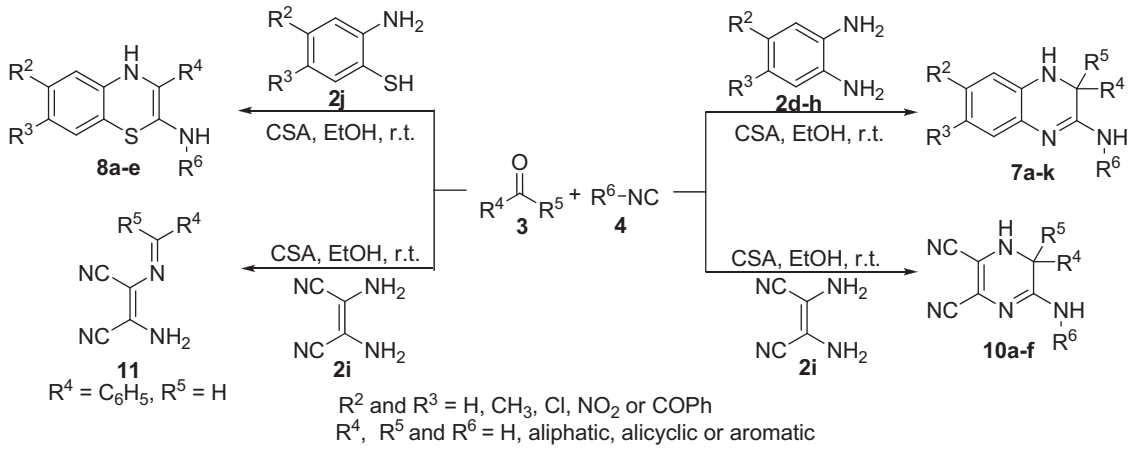
Table 4
Catalytic three-component Ugi reaction of different 2-aminophenols, aldehydes and isocyanides. .



2a-c 3 4 6a-h

Entry[a]	R	R^4	R^6	Product	Time [h]	Yield [%][b]
1	H	4-ClC_6H_4	*c*Hex	**6a**	48	75
2	Me	4-ClC_6H_4	*c*Hex	**6b**	48	70
3	H	4-$MeOC_6H_4$	*c*Hex	**6c**	48	74
4	Me	4-$MeOC_6H_4$	*c*Hex	**6d**	48	73
5	H	Cyclohexanone	*c*Hex	**6e**	48	61
6	H	Cyclopentanone	*c*Hex	**6f**	48	65
7	Cl	2,4-$MeOC_6H_4$	*c*Hex	**6g**	48	70
8	Cl	4-ClC_6H_4	*p*$TsSO_2CH_2$	**6h**	48	64

[a] Reaction conditions: 2-aminophenols (**2a–c**, 1.0 mmol), aldehydes (**3**, 1.0 mmol), isocyanides (**4**, 1.0 mmol), and cellulose sulfuric acid (0.1 g) were stirred in ethanol 96% (3.0 mL).
[b] Isolated yield.



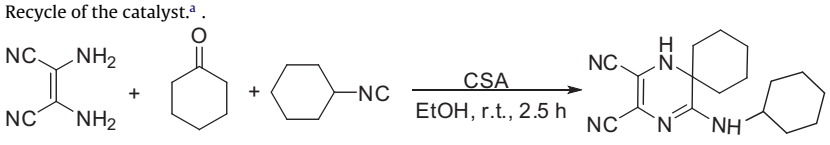
Scheme 4. Synthesis of 3,4-dihydroquinoxalin-2-amine **7a–k,** 1,6-dihydropyrazine-2,3-dicarbonitrile **10a–f** and 4*H*-benzo[*b*][1,4]thiazin-2-amine **8a–f** derivatives.

Table 5
Synthesis of 3,4-dihydroquinoxalin-2-amines, 1,6-dihydropyrazine-2,3-dicarbonitriles and 4*H*-benzo[*b*][1,4]thiazin-2-amines.

Entry[a]	Amine compound (**2d–j**)	Carbonyl compound (3)	R^6	Product	Time [h]	Yield [%][b]	Mp [°C]	
							Found	Reported
1	*o*-Phenylenediamine	Acetone	*c*Hex	**7a**	2	90	160–161	160–162b [13]
2	*o*-Phenylenediamine	Cyclohexanone	*t*Bu	**7b**	3	85	104–107	106–108 [16]
3	4-Methyl-*o*-phenylenediamine	Cyclohexanone	*c*Hex	**7c**	2	92	153–154	153–155 [17]
4	3,4-Diaminobenzophenone	Acetone	*c*Hex	**7d**	2.5	89	180–182	181–182b [13]
5	3,4-Diaminobenzophenone	Cyclohexanone	*c*Hex	**7e**	2.5	90	188–189	187–189b [13]
6	4-Nitro-1,2-phenylenediamine	Acetone	*c*Hex	**7f**	2.5	91	mp > 250	mp > 250b [13]
7	4-Nitro-1,2-phenylenediamine	Acetone	*t*Bu	**7g**	2.5	88	159–162	158–160b [13]
8	3,4-Diaminobenzophenone	4-Nitrobenzaldehyde	*c*Hex	**7h**	3	85	mp > 250	mp > 250b [13]
9	4,5-Dichloro-1,2-phenylenediamine	4-Methylbenzaldehyde	*t*Bu	**7i**	3	87	mp > 250	mp > 250b [13]
10	4-Nitro-1,2-phenylenediamine	Benzaldehyde	*c*Hex	**7j**	3	80	176–179	178–180b [13]
11	4-Nitro-1,2-phenylenediamine	4-Methoxybenzaldehyde	*c*Hex	**7k**	3	86	174–177	175–176b [13]
12	2,3-Diaminomaleonitrile	Acetone	*c*Hex	**10a**	2	95	256–258	255–258a [13]
13	2,3-Diaminomaleonitrile	Acetone	*t*Bu	**10b**	2	92	227–228	225–228a [13]
14	2,3-Diaminomaleonitrile	Acetone	$tBuCH_2C(Me_2)$	**10c**	2	88	148–151	150–151a [13]
15	2,3-Diaminomaleonitrile	Cyclohexanone	*c*Hex	**10d**	2.5	95	233	230–233a [13]
16	2,3-Diaminomaleonitrile	Acetophenone	*c*Hex	**10e**	2.5	87	231–233	231–233a [13]
17	2,3-Diaminomaleonitrile	4-Bromoacetophenone	*c*Hex	**10f**	3	88	mp > 250	mp > 250a [13]
18	2,3-Diaminomaleonitrile	Benzaldehyde	*c*Hex	**11**	3	90	203–206	204–205a [13]
19	2-Aminobenzenethiol	Benzaldehyde	*c*Hex	**8a**	48	80	191–193	192 [18]
20	2-Aminobenzenethiol	4-Methylbenzaldehyde	*c*Hex	**8b**	48	78	202–203	205 [18]
21	2-Aminobenzenethiol	Benzaldehyde	*t*Bu	**8c**	48	75	232–234	232 [18]
22	2-Aminobenzenethiol	4-Chlorobenzaldehyde	$pTsSO_2CH_2$	**8d**	48	81	108–109	–
23	2-Aminobenzenethiol	4-Methoxybenzaldehyde	$pTsSO_2CH_2$	**8e**	48	80	96–97	–

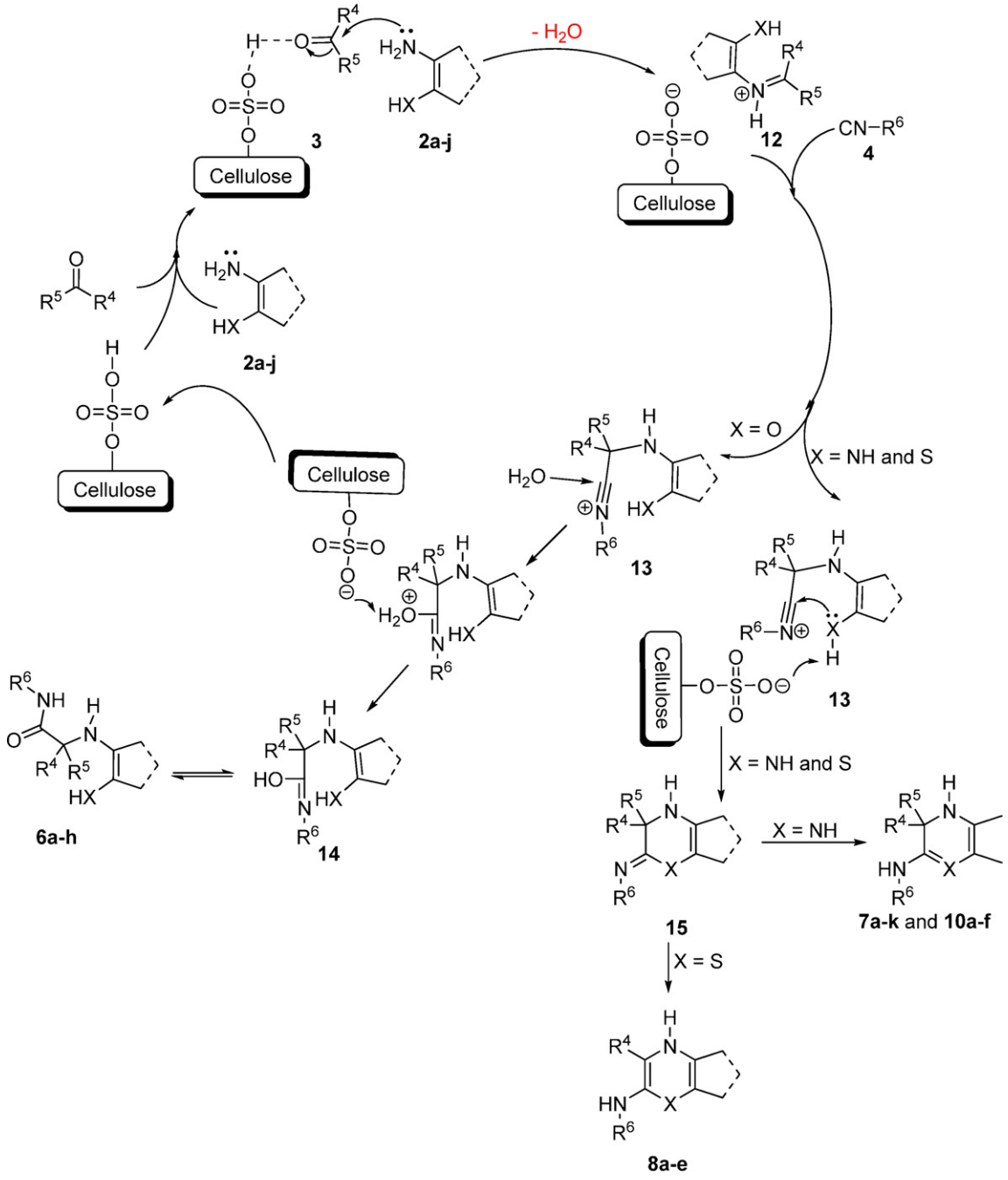
[a] Reaction conditions: amines (**2d–j**, 1.0 mmol), carbonyl compounds (**3**, 1.0 mmol), isocyanides (**4**, 1.0 mmol), and cellulose sulfuric acid (0.1 g) were stirred in ethanol 96% (3.0 mL).
[b] Isolated yield.

Table 6
Recycle of the catalyst.[a] .



Cycle	CSA [mg]	Yield [%]
1	10	95
2	9	93
3	9	91
4	8	90

[a] 2,3-Diaminomaleonitrile 1 mmol, cyclohexanone, cyclohexyl isocyanide 1 mmol in the presence of cellulose sulfuric acid (0.1 g) under ambient temperature in ethanol 96%.



Scheme 5. Proposed mechanism for the formation of products.

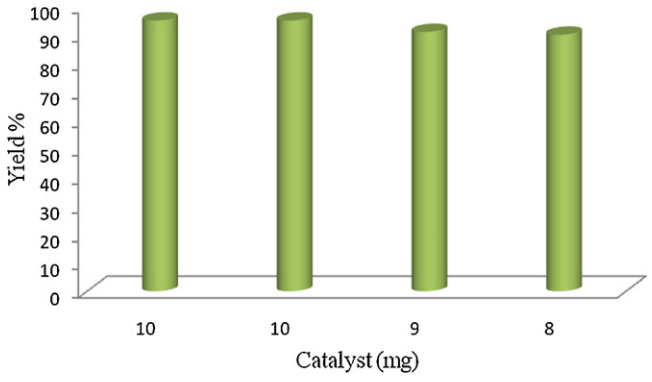


Fig. 1. Recycle of the catalyst.

intermediate **15** leads to the formation of products **7a–k**, **10a–f** and **8a–e**.

4. Conclusions

In summary, we reported cellulose sulfuric acid as a biodegradable biopolymer catalyzed three-component Ugi reaction leading to synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile and 4*H*-benzo[*b*][1,4]thiazin-2-amine derivatives in good yields upon mixing readily available substrates. The broad scope, operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the generation of different compounds with potential properties for medicinal chemistry programs.

Acknowledgement

We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

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