Article

Journal of the Brazilian Chemical Society

https://dx.doi.org/10.21577/0103-5053.20230168

J. Braz. Chem. Soc. **2024**, *35*, 4, e-20230168, 1-7

Synthesis of a Series of 4*H*-Pyran Derivatives with Multicomponent Reaction in DBSA/H_2O Microemulsion System

***Jun Wang,*[a] *Jialin Zang,*[b] *Dan Li*[c] *and Zhen Lv*[*,c,d]**

[a]*Academic Affairs Office, Qiqihar Medical University, 161006 Qiqihar, China*

[b]*The Second Affiliated Hospital of Qiqihar Medical University, 161006 Qiqihar, China*

[c]*College of Pharmacy, Qiqihar Medical University, 161006 Qiqihar, China*

[d]*College of Materials Science and Engineering, Jiamusi University, 154007 Jiamusi, China*

A series of 4*H*-pyran derivatives were synthesized through a three-component condensation reaction in a pot using aromatic aldehyde, cyclohexanedione, and malononitrile in the dodecyl benzenesulfonic acid/H_2O microemulsion system. This protocol is attractive because dodecyl benzenesulfonic acid microemulsion is superior for organic reaction due to its dual catalysis. On the one hand, dodecyl benzenesulfonic acid acts as a Brønsted acid to catalyze the reaction; on the other hand, it can form a microemulsion as surfactant to enlarge the boundary area and entrap water produced during esterification reaction. In addition, the reaction process is simple, with high liaison formation efficiency, good yields, and environmentally harmless reaction conditions. The dodecyl benzenesulfonic acid/H_2O microemulsion system was equally effective when used in consecutive reactions.

Keywords: 4*H*-pyran, dodecyl benzenesulfonic acid, green chemistry

Introduction

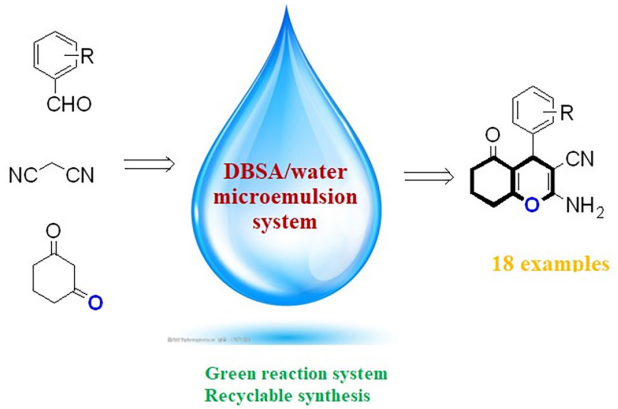
4*H*-Pyran, a heterocyclic system consisting of a fusion of a benzene ring and a pyran ring, is an essential structural component of natural compounds.[1-3] Various natural and synthetic derivatives of 4*H*-pyran possess critical biological and pharmacological applications, such as anti-inflammatory, anti-tumor, anti-oxidant, anti-microbial, cytotoxic, anti-HIV, anti-proliferative, and are used in the treatment of allergic bronchitis, anti-dysplasia and diabetes mellitus.[4-10] 4*H*-Pyran derivatives are potential calcium channel antagonists as well.[11-13] The synthesis of different 4*H*-pyran derivatives has become a popular area of research in organic synthesis. The reaction reagent was changed from organic solvent to water, and the synthesis method became effective and straightforward.[14-17]

As people pay more attention to the human living environment, more researchers are focusing on the research of organic synthesis that is not polluting to the environment (green synthesis). Green synthesis requires the use of non-toxic reagents, solvents, and catalysts in the synthesis process, of which water is considered to be the most ideal solvent in this regard.[18-20] It has the benefits of being inexpensive and easy to get, non-polluting and with little product loss.[21]

Recently, the application of dodecyl benzenesulfonic acid (DBSA) as a catalyst in organic synthesis reactions has received considerable attention and has been widely applied in the creation of natural compounds. The results showed that aldehydes and ketones are susceptible to condensation reactions in DBSA/H_2O microemulsion system. DBSA is a Brønsted acid, which has a strong solubilizing effect in addition to its excellent catalytic effect compared with other surfactants.[22-25] In addition, its acidity can accelerate the catalytic cyclization process, thus shortening the reaction time. These great properties are unmatched by other surfactants.

In this research, we found that 4*H*-pyran derivatives could be prepared in the DBSA/H_2O microemulsion system. The condensation reaction was carried out in water in the presence of DBSA, which acted both as a surfactant and as a catalyst for the formation of 4*H*-pyran derivatives. A series of 4*H*-pyran derivatives were synthesized with the green reaction system (Scheme 1).

*e-mail: pangmax27@163.com
Editor handled this article: Brenno A. D. Neto



Scheme 1. Synthesis of a series of 4*H*-pyran derivatives in DBSA/H_2O microemulsion system.

Experimental

All reagents and solvents were purchased from commercial sources (Energy, Shanghai, China) and used without further purification. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AVANCE NEO 600 spectrometer (Berlin, Germany). High-resolution mass spectrometry (HRMS) was recorded on waters UPLC G2-XS Qtof spectrometer (San Francisco, USA).

Chemistry

2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles (**2a-2r**)

A mixture of (1.2 mmol) aldehyde (**1a-1r**), (1.0 mmol) malononitrile and (1.2 mmol) cyclohexane-1,3-dione were stirred with DBSA (0.2 mmol) in water at 105 °C and refluxed for 75-150 min. After complete consumption of the starting materials, the reaction was cooled to room temperature. The solvent was removed and purified by recrystallization from ethanol to achieve the pure product.

Spectral data of the products

2-Amino-4-(3,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2a**)

White solid; yield: 90.4%; ^1H NMR (600 MHz, DMSO-d_6) δ 7.55 (d, *J* 8.3 Hz, 1H), 7.40 (dd, *J* 12.8, 2.1 Hz, 1H), 7.20-7.11 (m, 3H), 4.25 (s, 1H), 2.65-2.51 (m, 2H), 2.42-2.24 (m, 2H), 2.12 (dddd, *J* 34.6, 19.1, 14.2, 9.4 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.3, 165.0, 159.0, 146.3, 131.3, 131,0, 129.7, 129.6, 128.1, 119.9, 112.8, 57.5, 35.3, 34.7, 27.7, 20.7; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{12}Cl_2N_2O_2 + H]^+$: 335.0276, found: 335.0356.

2-Amino-5-oxo-4-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2b**)

White solid; yield: 91.2%; ^1H NMR (600 MHz, DMSO-d_6) δ 7.07 (d, *J* 7.9 Hz, 2H), 7.03 (d, *J* 8.1 Hz, 2H), 6.96 (s, 2H), 4.14 (s, 1H), 2.65-2.55 (m, 2H), 2.33-2.18 (m, 5H), 1.99-1.81 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.2, 164.7, 158.9, 142.3, 136.0, 129.3, 129.3, 127.5, 127.5, 120.2, 116.8, 114.4, 58.7, 36.8, 26.9, 21.0, 20.2; HRMS (EI) *m/z*, calcd. for $[C_{17}H_{16}N_2O_2 + H]^+$: 281.1212, found: 281.1289.

2-Amino-4-(4-isopropylphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2c**)

Brown solid; yield: 86.3%; ^1H NMR (600 MHz, DMSO-d_6) δ 7.15 (d, *J* 8.0 Hz, 2H), 7.07-7.04 (m, 2H), 6.97 (s, 2H), 4.15 (s, 1H), 2.83 (p, *J* 6.9 Hz, 1H), 2.66-2.56 (m, 2H), 2.34-2.22 (m, 2H), 2.00-1.83 (m, 2H), 1.17 (d, *J* 7.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.4, 164.9, 158.9, 146.9, 142.6, 127.4, 127.4, 126.7, 126.7, 120.3, 114.3, 58.8, 36.8, 35.4, 33.5, 26.9, 24.3, 24.3, 20.2; HRMS (EI) *m/z*, calcd. for $[C_{19}H_{20}N_2O_2 + H]^+$: 309.1525, found: 309.1429.

2-Amino-4-(4-(*tert*-butyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2d**)

White solid; yield: 88.6%; ^1H NMR (600 MHz, DMSO-d_6) δ 7.32-7.27 (m, 2H), 7.08-7.02 (m, 2H), 6.97 (d, *J* 9.4 Hz, 2H), 4.16-4.10 (m, 1H), 3.34 (s, 2H), 2.52-2.46 (m, 1H), 1.25 (s, 9H), 1.01 (dd, *J* 7.9, 6.3 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.3, 164.5, 159.0, 149.2, 142.2, 127.1, 127.1, 125.6, 125.5, 120.3, 114.0, 58.8, 35.5, 35.2, 34.7, 34.5, 34.3, 31.6, 27.8, 20.7; HRMS (EI) *m/z*, calcd. for $[C_{20}H_{22}N_2O_2 + H]^+$: 323.1681, found: 323.1753.

2-Amino-4-(4-(dimethylamino)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2e**)

Yellow solid; yield: 93.7%; ^1H NMR (600 MHz, DMSO-d_6) δ 6.97-6.80 (m, 4H), 6.65-6.55 (m, 2H), 4.13-3.93 (m, 1H), 3.33 (s, 2H), 2.84 (s, 6H), 2.50 (p, *J* 1.9 Hz, 2H), 2.38-2.21 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.2, 162.9, 158.8, 149.6, 133.1, 128.1, 128.1, 120.4, 114.5, 112.8, 112.8, 59.2, 44.9, 40.7, 35.0, 34.3, 28.0, 20.6; HRMS (EI) *m/z*, calcd. for $[C_{18}H_{19}N_3O_2 + H]^+$: 310.1477, found: 310.1531.

2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2f**)

White solid; yield: 92.9%; ^1H NMR (600 MHz, DMSO-d_6) δ 7.35 (dt, *J* 8.0, 1.6 Hz, 1H), 7.25 (td, *J* 7.5, 1.3 Hz, 1H), 7.22-7.14 (m, 2H), 7.02 (s, 2H), 4.70 (d, *J* 1.8 Hz, 1H), 2.64-2.56 (m, 1H), 2.46-2.32 (m, 1H),

2.27-2.17 (m, 1H), 2.13-1.99 (m, 1H), 1.03-1.01 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.0, 165.1, 159.0, 142.1, 132.5, 130.3, 129.8, 128.6, 127.9, 119.7, 113.0, 57.3, 40.1, 34.7, 27.9, 20.7; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{13}ClN_2O_2 + H]^+$: 301.0666, found: 301.0750.

2-Amino-4-(5-methylthiophen-2-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2g**)

Yellow solid; yield: 95.7%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.09 (d, *J* 9.9 Hz, 2H), 6.61 (t, *J* 3.1 Hz, 1H), 6.56 (t, *J* 2.2 Hz, 1H), 4.42 (s, 1H), 3.34 (s, 1H), 2.36-2.30 (m, 4H), 2.12 (d, *J* 10.0 Hz, 1H), 1.01 (t, *J* 6.4 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.0, 159.4, 159.3, 138.1, 138.0, 125.3, 124.1, 120.1, 114.2, 58.3, 34.6, 34.2, 27.8, 20.7, 15.4; HRMS (EI) *m/z*, calcd. for $[C_{15}H_{14}N_2O_2S + H]^+$: 287.0776, found: 287.0639.

2-Amino-4-(1*H*-indol-5-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2h**)

Yellow solid; yield: 93.8%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.29 (s, 3H), 6.90 (s, 3H), 6.37 (s, 1H), 4.24 (s, 1H), 2.61 (s, 2H), 2.36-2.16 (m, 2H), 1.90 (d, *J* 57.7 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.3, 164.1, 158.7, 135.8, 135.3, 127.9, 126.0, 121.1, 120.5, 118.8, 115.2, 111.6, 101.4, 59.7, 36.9, 35.9, 26.9, 20.3; HRMS (EI) *m/z*, calcd. for $[C_{18}H_{15}N_3O_2 + H]^+$: 306.1164, found: 306.1234.

2-Amino-5-oxo-4-(*o*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2i**)

White solid; yield: 90.5%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.13-7.07 (m, 2H), 7.04 (tt, *J* 7.4, 2.0 Hz, 1H), 6.97-6.92 (m, 3H), 4.46 (d, *J* 1.6 Hz, 1H), 2.65-2.57 (m, 1H), 2.45 (d, *J* 4.1 Hz, 3H), 2.42-2.32 (m, 1H), 2.31-2.20 (m, 1H), 2.13-2.01 (m, 1H), 1.01 (d, *J* 6.1 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.3, 164.4, 158.7, 144.1, 135.2, 130.3, 127.8, 126.9, 126.6, 120.2, 114.7, 58.6, 44.7, 34.6, 27.9, 20.7, 19.5; HRMS (EI) *m/z*, calcd. for $[C_{17}H_{16}N_2O_2 + H]^+$: 281.1212, found: 281.1255.

2-Amino-4-(2,5-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**2j**)

White solid; yield: 91.0%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.41 (d, *J* 8.5 Hz, 1H), 7.28 (dd, *J* 8.5, 2.6 Hz, 1H), 7.25 (d, *J* 2.6 Hz, 1H), 7.12 (s, 2H), 4.69 (d, *J* 1.4 Hz, 1H), 2.70-2.55 (m, 2H), 2.33-2.20 (m, 2H), 2.01-1.87 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.2, 166.0, 159.0, 144.2, 132.4, 131.5, 131.4, 129.9, 128.6, 119.5, 112.5, 56.5, 36.7, 33.6, 26.9, 20.2; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{12}Cl_2N_2O_2 + H]^+$: 335.0276, found: 335.0364.

2-Amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2k**)

White solid; yield: 87.3%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.08-7.05 (m, 2H), 6.95 (s, 2H), 6.85-6.81 (m, 2H), 4.14 (s, 1H), 3.71 (s, 3H), 2.63-2.56 (m, 2H), 2.34-2.18 (m, 2H), 2.00-1.79 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.3, 164.5, 158.8, 158.3, 137.3, 128.6, 128.6, 120.3, 114.5, 114.1, 114.1, 58.9, 55.4, 36.8, 35.0, 26.9, 20.2; HRMS (EI) *m/z*, calcd. for $[C_{17}H_{16}N_2O_3 + H]^+$: 297.1161, found: 297.1233.

2-Amino-4-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2l**)

Brown solid; yield: 92.9%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.49 (d, *J* 1.6 Hz, 1H), 7.09 (s, 2H), 6.32 (dd, *J* 3.2, 1.8 Hz, 1H), 6.06 (d, *J* 3.2 Hz, 1H), 4.33 (s, 1H), 2.63-2.56 (m, 2H), 2.33 (dd, *J* 8.0, 5.5 Hz, 2H), 2.01-1.85 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.0, 165.6, 159.7, 156.2, 142.2, 120.0, 111.9, 110.8, 105.6, 55.7, 36.6, 29.4, 26.9, 20.2; HRMS (EI) *m/z*, calcd. for $[C_{14}H_{12}N_2O_3 + H]^+$: 257.0848, found: 257.0927.

2-Amino-4-(3-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2m**)

White solid; yield: 89.9%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.37-7.34 (m, 1H), 7.26 (td, *J* 7.5, 1.3 Hz, 1H), 7.19 (q, *J* 1.8 Hz, 1H), 7.02 (s, 2H), 4.71 (s, 1H), 4.36 (t, *J* 5.1 Hz, 1H), 2.68-2.55 (m, 2H), 2.34-2.17 (m, 2H), 2.01-1.85 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.1, 165.5, 159.0, 142.2, 132.5, 130.2, 129.8, 128.5, 128.0, 119.7, 113.3, 56.5, 36.7, 33.1, 26.9, 19.0; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{13}ClN_2O_2 + H]^+$: 301.0666, found: 301.0738.

2-Amino-4-(2,3-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2n**)

White solid; yield: 93.1%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.55 (d, *J* 8.2 Hz, 1H), 7.41 (d, *J* 2.2 Hz, 1H), 7.20-7.12 (m, 3H), 4.26 (d, *J* 1.3 Hz, 1H), 2.69-2.55 (m, 2H), 2.35-2.22 (m, 2H), 1.99-1.86 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.4, 165.4, 158.9, 146.3, 131.2, 131.0, 129.7, 129.6, 128.1, 119.9, 113.2, 57.5, 36.7, 35.3, 26.9, 20.1; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{12}Cl_2N_2O_2 + H]^+$: 335.0276, found: 335.0353.

2-Amino-5-oxo-4-(quinolin-4-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2o**)

White solid; yield: 94.7%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.81 (d, *J* 4.6 Hz, 1H), 8.46 (d, *J* 8.6 Hz, 1H), 8.04 (d, *J* 8.4 Hz, 1H), 7.77 (t, *J* 7.6 Hz, 1H), 7.66 (t, *J* 7.7 Hz, 1H), 7.26 (d, *J* 4.5 Hz, 1H), 7.12 (s, 2H), 5.20 (s,

1H), 2.76-2.63 (m, 2H), 2.34-2.19 (m, 2H), 2.02-1.92 (m, *J* 5.9, 5.1 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.3, 165.9, 159.0, 151.7, 150.9, 148.3, 113.7, 57.8, 37.1, 36.3, 27.0, 20.3; HRMS (EI) *m/z*, calcd. for $[C_{19}H_{15}N_3O_2 + H]^+$: 318.1164, found: 318.1249.

2-Amino-4-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2p**)

White solid; yield: 89.6%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.55 (d, *J* 8.2 Hz, 1H), 7.41 (d, *J* 2.1 Hz, 1H), 7.24-7.05 (m, 3H), 4.26 (d, *J* 1.2 Hz, 1H), 2.70-2.46 (m, 3H), 2.37-2.19 (m, 2H), 2.00-1.81 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.4, 165.4, 158.9, 146.3, 131.2, 131.0, 129.7, 129.6, 128.1, 119.9, 113.2, 57.5, 36.7, 35.3, 26.9, 20.1; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{13}FN_2O_2 + H]^+$: 285.0961, found: 285.1093.

2-Amino-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2q**)

White solid; yield: 92.2%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.52 (d, *J* 2.2 Hz, 1H), 7.34 (dd, *J* 8.4, 2.2 Hz, 1H), 7.24 (d, *J* 8.4 Hz, 1H), 7.09 (s, 2H), 4.69 (s, 1H), 2.69-2.55 (m, 2H), 2.33-2.17 (m, 2H), 2.01-1.85 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.2, 165.7, 159.0, 141.4, 133.5, 132.1, 131.7, 129.0, 128.1, 119.6, 112.9, 56.8, 36.7, 32.9, 26.9, 20.2; HRMS (EI) *m/z*, calcd. for $[C_{16}H_{12}Cl_2N_2O_2 + H]^+$: 335.0276, found: 335.0355.

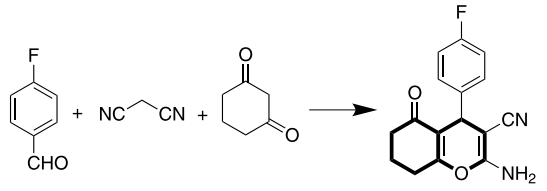
2-Amino-5-oxo-4-(*m*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2r**)

White solid; yield: 89.3%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.16 (t, *J* 7.5 Hz, 2H), 7.09 (t, *J* 7.6 Hz, 1H), 7.00 (d, *J* 1.7 Hz, 2H), 6.93 (t, *J* 1.3 Hz, 1H), 4.55 (s, 1H), 2.70-2.65 (m, 2H), 2.33-2.27 (m, 5H), 1.96-1.94 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.7, 165.2, 158.9, 145.2, 137.7, 128.7, 128.1, 127.7, 124.7, 120.2, 116.0, 58.7, 36.8, 35.8, 26.9, 21.5, 20.3; HRMS (EI) *m/z*, calcd. for $[C_{17}H_{16}N_2O_2 + H]^+$: 281.1212, found: 281.1251.

Results and Discussion

Conventional synthesis methods use a large number of organic reagents, which is a serious contradiction to the concept of green chemistry. Developing a green and efficient strategy to construct them was very meaningful. The pilot reaction involved the use of 4-fluorobenzaldehyde, malononitrile, and acetylacetone to synthesize 4*H*-pyran. The effects of the organic phase and DBSA on the reaction process as well as the product yields were investigated separately. We were surprised that the reaction of the substrate in the DBSA/H_2O microemulsion system was much more successful because of the other group (Table 1). The reaction process and product yield are greatly enhanced, and we are more confident in our ability to develop a green and efficient strategy to construct them.

Table 1. Comparison of reaction systems for the synthesis of 4*H*-pyran derivatives[a]

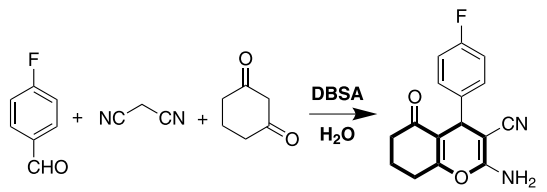


entry	Catalyzer	Solvent	time / h	Temperature / °C	Yield[b] / %
1	DBSA	H_2O	2	105	82.4
2	2- aminopyridine	CH_3OH	3.5	65	81.8
3	–	H_2O	2	105	–
4	–	CH_3OH	3.5	65	34.7

[a]Reaction conditions: 4-fluorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and cyclohexane-1,3-dione (1.0 mmol) were stirred with catalizers (0.2 mmol). [b]Yield of the pure product, purified by recrystallization from ethanol. DBSA: dodecylbenzenesulfonic acid.

In view of the fact that the DBSA-catalyzed synthesis of 4*H*-pyran works under very mild reaction conditions, we decided to complete a detailed study of the catalyst dosage. We then experimentally discovered that 0.2 mmol of DBSA catalyzed the reaction to proceed with the optimal yield of the resulting product (Table 2).

Table 2. Effect of catalyst dosage on target product yield for the synthesis of 4*H*-pyran derivatives[a]



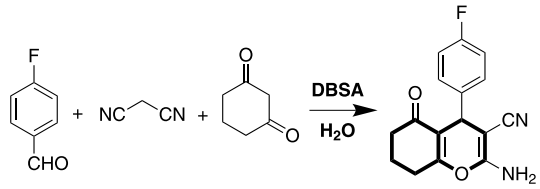
entry	Dosage / mmol	Yield[b] / %
1	0.1	82.4
2	0.2	84.2
3	0.3	83.9
4	0.4	84.1

[a]Reaction conditions: 4-fluorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and cyclohexane-1,3-dione (1.0 mmol) were stirred in water at 105 °C (2 h). [b]Yield of the pure product, purified by recrystallization from ethanol.

With the above reaction conditions in hand, the generality of reagents ratio for the synthesis of 4*H*-pyran derivatives was investigated (Table 3). From now on, the

results indicate that the maximum product yield is at a catalyst ratio of 1.2:1.0:1.2.

Table 3. Effect of raw material ratios on target product yields for the synthesis of 4*H*-pyran derivatives[a]



entry	Ratio	Yield[b] / %
1	1.0:1.0:1.0	86.0
2	1.1:1.0:1.1	87.1
3	1.2:1.0:1.2	89.3
4	1.1:1.1:1.0	86.7

[a]Reaction conditions: 4-fluorobenzaldehyde, malononitrile and cyclohexane-1,3-dione were stirred with DBSA (0.2 mmol) in water at 105 °C (2 h). [b]Yield of the pure product, purified by recrystallization from ethanol.

Under optimized reaction conditions, the 4-fluorobenzaldehyde reacted with malononitrile and cyclohexanedione by a one-pot method to obtain the corresponding (*S*)-2-amino-4-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile in excellent yields. Recycling experiments were performed using the DBSA catalyst for the synthesis of (*S*)-2-amino-4-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (Table 4). After completion of the reaction, the crude product was filtered and the filtrate was recycled to repeat the experiment. The results demonstrated that the catalyst's catalytic activity was stable and can be recycled.

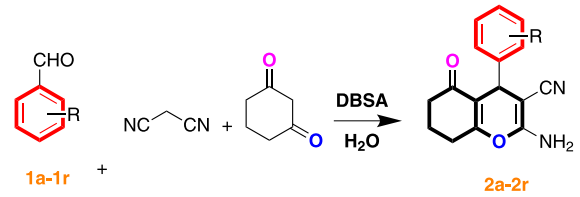
Table 4. Reusability of cata lysts for the synthesis of 4*H*-pyran derivatives[a]

Number	1	2	3	4	5
Yield[b] / %	89.3	84.7	88.1	89.6	88.9

[a]Reaction conditions: 4-fluorobenzaldehyde (1.2 mmol), malononitrile (1.0 mmol) and cyclohexane-1,3-dione (1.2 mmol) were stirred with DBSA (0.2 mmol) in water at 105 °C (2 h). [b]Yield of the pure product, purified by recrystallization from ethanol.

Taking into account the optimum reaction conditions, the generality of benzaldehydes in the synthesis of 4*H*-pyran derivatives was investigated (Table 5). Notably, a variety of benzaldehydes with diverse substituents at each position of the phenyl ring were suitable for the transformation, resulting in good yields of 4*H*-pyran derivatives (**2a-2r**). In order to show the diversity and inclusiveness of the reactions above, we attempted to introduce heterocyclic groups like thiophene, furan, indole, and quinoline into the 4*H*-pyran structure. Happily, compounds **2g**, **2h**, **2l** and **2o** exhibited higher product yields, as well as better reaction times than the substituted benzaldehydes, which is inextricably linked to the presence of the heteroatoms. All crude products were purified through ethanol recrystallization and confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS.

Table 5. Synthesis of polyfunctionalized 4*H*-pyran derivatives[a]



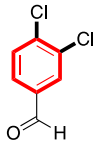
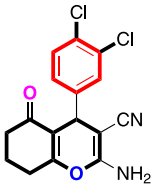
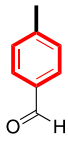
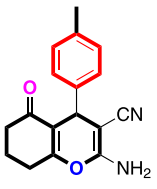
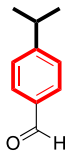
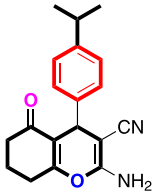
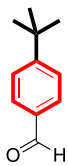
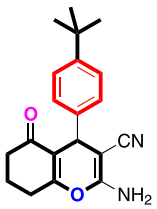
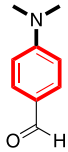
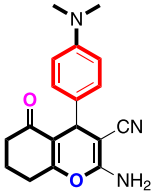
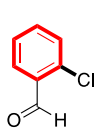
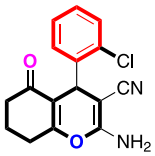
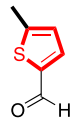
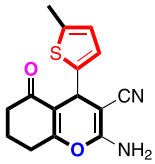
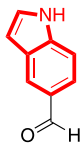
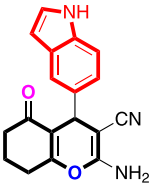
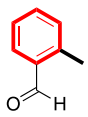
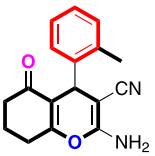
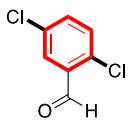
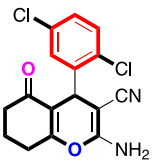
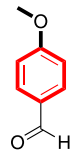
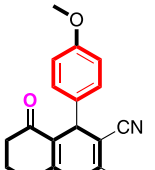
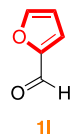
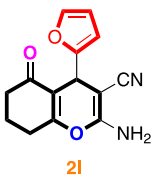
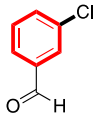
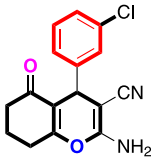
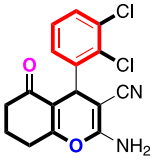
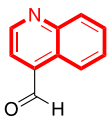
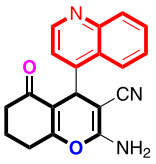
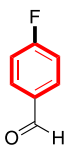
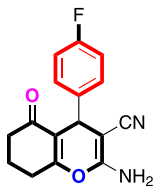
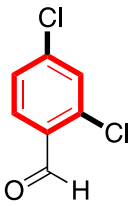
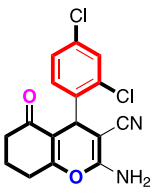
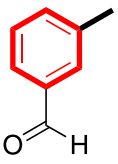
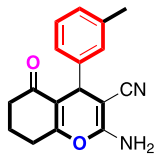
entry	Aldehyde	Compound	time[b] / min	Yield[c] / %
1	 1a	 2a	90	90.4
2	 1b	 2b	120	91.2
3	 1c	 2c	150	86.3
4	 1d	 2d	120	88.6
5	 1e	 2e	90	93.7

Table 5. Synthesis of polyfunctionalized 4*H*-pyran derivatives[a] (cont.)

6	 1f	 2f	120	92.9
7	 1g	 2g	75	95.7
8	 1h	 2h	75	93.8
9	 1i	 2i	120	90.5
10	 1j	 2j	90	91.0
11	 1k	 2k	120	87.3
12	 1l	 2l	75	92.9
13	 1m	 2m	120	89.9
14	 1n	 2n	90	93.1
15	 1o	 2o	75	94.7
16	 1p	 2p	120	89.6
17	 1q	 2q	90	92.2
18	 1r	 2r	120	89.3

[a]Reaction conditions: aldehyde (1.2 mmol), malononitrile (1.0 mmol) and cyclohexane-1,3-dione (1.2 mmol) were stirred with DBSA (0.2 mmol) in water at 105 °C. [b]Thin layer chromatography (TLC) assay reaction process. [c]Yield of the pure product, purified by recrystallization from ethanol.

Conclusions

In conclusion, a novel and efficient synthesis of 4*H*-pyran derivatives by DBSA catalyzed multicomponent reaction of aldehyde, malononitrile, and acetylacetone was developed in a microemulsion system. (*S*)-2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles (**2a-2r**) were synthesized and their structures were elucidated from ^{1}H NMR, ^{13}C NMR and HRMS data. Excellent yields, efficient response, use of DBSA as catalyst

and construction of the DBSA/H_2O microemulsion system, and no column chromatography involving environmentally incompatible organic solvents are some of the highlights of our synthesis method. Furthermore, compounds with electron-withdrawing groups had better reaction efficiency such as compounds **2g**, **2h**, **2l** and **2o**.

Supplementary Information

Supplementary data (NMR and HRMS) are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

We gratefully acknowledge the financial support by Qiqihar Science and Technology Program Joint Guidance Project (LSFGG-2022038), Fundamental Scientific Research Business Expenses of Colleges and Universities in Heilongjiang Province (2020-KYYWF-0023) and Qiqihar Institute of Medical Sciences Project (QMSI2020M-09).

References

1. Niknam, K.; Khataminejad, M.; Zeyaei, F.; *Tetrahedron Lett*. **2016**, *57*, 361. [Crossref]
2. Ramesh, R.; Jayamathi, J.; Karthika, C.; Malecki, J. G.; Lalitha, A.; *Polycyclic Aromat. Compd.* **2018**, 502. [Crossref]
3. Zang, J. L.; Bu, M.; Yang, J. F.; Han, L.; Lv, Z.; *J. Braz. Chem. Soc.* **2021**, *32*, 1780. [Crossref]
4. Amr, A. E.; Abdulla, M. M.; *Arch. Pharm. Chem.* **2006**, *339*, 88. [Crossref]
5. Amr, A. E.; Mohamed, A. M.; Mohamed, S. F.; Abdel-Hafez, N. A.; Hammam, A. E. G.; *Bioorg. Med. Chem*. **2006**, *14*, 5481. [Crossref]
6. Azzam, R. A.; Mohare, R. M.; *Chem. Pharm. Bull.* **2015**, *63*, 1055. [Crossref]
7. El-Sayed, N. N. E.; Zaki, M. E. A.; Al-Hussain, S. A.; Bacha, A. B.; Berredjem, M.; Masand, V. H.; Almarhoon, Z. M.; Omar, H. S.; *Pharmaceuticals* **2022**, *15*, 891. [Crossref]
8. Shafaei, F.; Najar, A. H.; *Comb. Chem. High Throughput Screening* **2020**, *23*, 446. [Crossref]
9. Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D.; *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6459. [Crossref]
10. Kidwai, M.; Poddar, R.; Bhardwaj, S.; Singh, S.; Luthra, P. M.; *Eur. J. Med. Chem.* **2010**, *45*, 5031. [Crossref]
11. Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A.; Pierre, A.; Atassi, G.; Renard, P.; *Bioorg. Med. Chem*. **2001**, *9*, 607. [Crossref]
12. El-Bana, G. G.; Salem, M. A.; Helal, M. H.; Alharbi, O.; Gouda, M. A.; *Mini-Rev. Org. Chem*. **2024**, *21*, 73. [Crossref]
13. El-Sayed, N. N. E.; Zaki, M. E. A.; Al-Hussain, S. A.; Bacha, A. B.; Berredjem, M.; Masand, V. H.; Almarhoon, Z. M.; Omar, H. S.; *Pharmaceuticals* **2022**, *15*, 891. [Crossref]
14. Maleki, B.; Baghayeri, M.; Abadi, S. A. J.; Tayebeea, R.; Khojastehnezhad, A.; *RSC. Adv.* **2016**, *6*, 96644. [Crossref]
15. Tabrizian, E.; Amoozadeh, A.; *Catal. Sci. Technol.* **2016**, *6*, 6267. [Crossref]
16. Khan, M. M.; Shareef, S.; Saigal; Sahoo, S. C.; *RSC. Adv.* **2019**, *9*, 26393. [Crossref]
17. Mukherjee, P.; Das, A. R.; *J. Org. Chem*. **2016**, *81*, 5513. [Crossref]
18. Sahoo, T.; Panda, J.; Sahu, J.; Sarangi, D.; Sahoo, S. K.; Nanda, B. B.; Sahu, R.; *Curr. Org. Synth.* **2022**, *17*, 426. [Crossref]
19. Kar, S.; Sanderson, H.; Roy, K.; Benfenati, E.; Leszczynski, J.; *Chem. Rev.* **2022**, *122*, 3637. [Crossref]
20. Vadgama, R. N.; Khatkhatay, A. B.; Odaneth, A. A.; Lali, A. M.; *Sustainable Chem. Pharm.* **2020**, *15*, 100203. [Crossref]
21. Trombino, S.; Sole, R.; Di Gioia, M. L.; Procopio, D.; Curcio, F.; Cassano, R.; *Molecules* **2023**, *28*, 2107. [Crossref]
22. An, D.; Miao, X. Z.; Ling, X. X.; Chen, X. X.; Rao, W. D.; *Adv. Synth. Catal.* **2020**, *362*, 1514. [Crossref]
23. Jing, L.; Li, X. J.; Han, Y. C.; Chu, Y.; *Colloids Surf., A* **2008**, *326*, 37. [Crossref]
24. Choi, J. W.; Han, M. G.; Kim, S. Y.; Oh, S. G.; Im, S. S.; *Synth. Met*. **2004**, *141*, 293. [Crossref]
25. Kumar, V.; Khandare, D. G.; Chatterjee, A.; Banerjee, M.; *Tetrahedron. Lett*. **2013**, *54*, 5505. [Crossref]

Submitted: July 30, 2023
Published online: October 18, 2023