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Aquivion PFSA as a Novel Solid and Reusable Acid Catalyst in the Synthesis of 2-Pyrrolidin-2-ones in Flow

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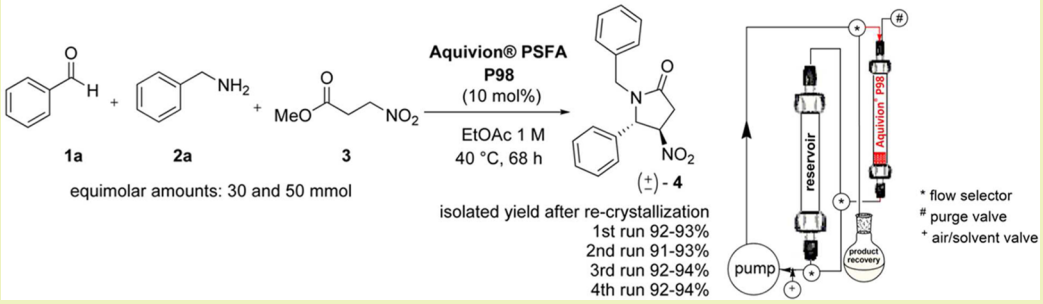
Supporting Information



ABSTRACT: A new protocol for the diasteroselective synthesis of pyrrolidin-2-ones **4**–**14** is presented. Aquivion PFSA effectively catalyzed the diasteroselective nitro-mannich/lactamization cascade reaction between the imine formed from aldehydes **1a**–**g** and amines **2a**–**b** with methyl 3-nitropropanoate **3**. The use of flow conditions allow a very efficient waste minimization confirmed by representative green metrics calculations.

KEYWORDS: *Acid catalysis, Multicomponent process, Waste minimization, Lactams*

INTRODUCTION

In the past few years, the request for more sustainable chemical processes characterized by lower environmental and safety concerns prompted the development of novel heterogeneous catalysts as suitable alternatives for corrosive and harmful mineral acids such as sulfuric and hydrofluoric acid.[1] Among the many solid acid catalysts available on the market, perfluorosulfonic acid (PFSA) resins have already demonstrated their effectiveness not only to catalyze organic reactions such as Friedel–Crafts acylation[2] and Fries rearrangement,[3] but also and more recently to valorize biomass[4] and for biofuels production.[5,6]

Aquivion PFSA is a perfluorinated copolymer obtained by free radical polymerization of tetrafluoroethylene and perfluoro-2-(fluorosulfonylethoxy) vinyl ether that displays a superacid character with a Hammett acidity (H_0) of about −12, a value that is comparable with pure sulfuric acid.[7] Furthermore, the high chemical inertness given by the perfluorinated structure allows Aquivion PFSA to withstand highly aggressive reaction conditions, thus resisting strong acids, bases, and oxidative as well as reductive environments. Moreover, Aquivion PFSA has the shortest side chain compared to its commercially available congeners. This feature increases its crystallinity, and the glass transition temperature (T_g) is raised to 140 °C allowing, when needed, the use at high reaction temperature.[8]

While some applications of this material have been reported in the frame of fuel cells or electrolyzers,[9,10] the use of Aquivion PFSA as solid acid catalyst in organic synthesis has never been explored. We have envisaged that its properties can make Aquivion PFSA a highly adaptive solid catalytic system for the definition of efficient protocols in the synthesis of fine chemicals. Accordingly, we have decided to further investigate this type of solid acid system.

Pyrrolidin-2-one moiety is a common motif of important biologically active products and pharmaceutical compounds.[11,12] Furthermore, due to its inherent reactivity, it is a key building block to directly access a large variety of heterocyclic systems.[13−16] Many synthetic protocols to obtain such molecules have been already developed and mainly relied on metal transition-catalyzed cyclization, acid-catalyzed cascade reaction, or β-lactams ring expansion.[17−21]

Some recent efficient approaches to 2-pyrrolidin-2-ones have been reported.[22−25] In more detail, recently, Dixon and co-

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workers have published a new stereoselective procedure for the synthesis of 2-pyrrolidin-2-ones employing a nitro-Mannich/lactamization cascade reaction of methyl 3-nitropropanoate with *in situ*-formed imine.[24,25] Even if the protocol yielded a large panel of desired product, the experimental conditions have not been optimized on the sustainability point of views, i.e., nitrogen atmosphere had to be applied throughout the process, toluene is used as solvent and over stochiometric amount of reactants, and benzoic acid are necessary for the reaction to go to completion. Accordingly, this reaction was chosen as the subject of the current investigation.

EXPERIMENTAL SECTION

Materials. Benzylamines were freshly distilled before undergoing reaction; aldehydes were washed with a water solution of K_2CO_3. All other solvents and reagents were used as obtained from commercial sources without further purification. GC-EIMS analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. Column chromatography was carried out using Silica gel 60, 230−400 mesh. NMR spectra were recorded on a Bruker DRX-AVANCE 400 MHz (^{1}H at 400 MHz and ^{13}C at 100.6 MHz) in $CDCl_3$ using TMS as the internal standard. IR spectra were recorded on a Bruker TENSOR 27. Elemental analysis were realized by using a FISONS instrument EA 1108 CHN. All melting points were measured with Buchi Melting Point 510 apparatus and are uncorrected.

*(±)-1-Benzyl-4-nitro-5-phenylpyrrolidin-2-one (**4**).* In a 2 mL vial equipped with a magnetic stirrer, benzaldehyde (**1a**) (2 mmol, 212 mg, 204 μL), benzylamine (**2a**) (2 mmol, 214 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 24 h. Then, it was diluted and washed with ethyl acetate (12 mL), and the catalyst was filtered off using a Celite pad. The filtrate was concentrated and crystallized in ethyl acetate (4 mL). 1-Benzyl-4-nitro-5-phenylpyrrolidin-2-one (**4**) was obtained as a white solid. (525 mg, 89%). TLC Rf (6 hexane/4 ethyl acetate) = 0.39. M.p. = 95−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.13 (dd, J = 18.0; 8.2 Hz, 1H), 3.23 (dd, J = 18.0; 3.2 Hz, 1H), 3.55 (d, J = 14.8 Hz, 1H), 4.84 (d, J = 2.1 Hz, 1H), 4.90 (m, 1H), 5.22 (d, J = 14.8 Hz, 1H), 7.12 (m, 4H), 7.30 (m, 2H), 7.45 (m, 2H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 34.5, 44.5, 65.3, 84.5, 126.4 (2C), 128.0, 128.2 (2C), 128.8 (2C), 129.5, 129.7 (2C) 134.6, 135.9, 170.0. GC-EIMS (*m*/*z*, %): 65 (14), 77 (11), 91 (100), 106 (66), 115 (27), 116 (20), 117 (40), 132 (20), 144 (12), 145 (10), 167 (11), 249 (26), 250 (73), 251 (14), 296 (11). Anal. Calcd for $C_{17}H_{16}N_2O_3$:C, 68.91; H, 5.44; N, 9.45. Found: C, 68.76; H, 5.32; N, 9.53. FT-IR (KBr, cm^{-1}): 1698, 1552, 1495, 1458, 1410, 1378.

*(±)-1-Benzyl-5-(4-chlorophenyl)-4-nitropyrrolidin-2-one (**5**).* In a 2 mL vial equipped with a magnetic stirrer, 4-chloro-benzaldehyde (**1b**) (2 mmol, 282 mg), benzylamine (**2a**) (1 mmol, 114 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 72 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated and purified on flash column chromatography (eluent 7 hexane/3 ethyl acetate). 1-Benzyl-5-(4-chlorophenyl)-4-nitro-5-phenylpyrrolidin-2-one (**5**) was obtained as a white solid. (535 mg, 81%). TLC Rf (6 hexane/4 ethyl acetate) = 0.39. M.p. = 126−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.10 (dd, J = 18.0; 8.3 Hz, 1H), 3.23 (dd J = 18.0; 3.3 Hz, 1H), 3.53 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 2.4 Hz, 1H), 4.85 (m, 1H), 5.20 (d, J= 14.8 Hz, 1H), 7.07 (m, 4H), 7.30 (m, 3H), 7.38 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 34.4, 44.6, 64.6, 84.3, 127.8, 128.1, 128.2 (2C), 128.9 (2C), 129.9 (2C), 134.3, 134.4, 135.6, 169.8. GC-EIMS (*m*/*z*, %): 65 (14), 91(100), 92 (10), 106 (77), 115 (28), 116 (16), 132 (21), 144 (21), 151 (19), 178 (11), 283 (15), 284 (43), 285 (13), 286 (15). Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.65; H, 4.42; N, 8.60. FT-IR (KBr, cm^{-1}): 1697, 1553, 1493, 1408, 1377.

*(±)-1-benzyl-5-(4-bromophenyl)-4-nitropyrrolidin-2-one (**6**).* In a 2 mL vial equipped with a magnetic stirrer, 4-bromo-benzaldehyde (**1c**) (2 mmol, 370 mg), benzylamine (**2a**) (2 mmol, 214 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg) and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 48h. The mixture was left under stirring at 40 °C for 24h then it was diluted and washed with ethyl acetate (12 mL) and the catalyst filtered off using a Celite pad. The filtrate was concentrated and crystallized in ethyl acetate. 1-benzyl-5-(4-bromophenyl)-4-nitro-5-phenylpyrrolidin-2-one (**6**) was obtained as a white solid. (711 mg, 92%). TLC Rf (6 hexane/4 ethyl acetate) = 0.34. M.p = 124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.11 (dd, J = 18.4; 8.3 Hz, 1H), 3.24 (dd, J = 18.4; 3.5 Hz, 1H), 3.53 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 2.3 Hz, 1H), 4.85 (m, 1H), 5.21 (d, J = 14.8 Hz, 1H), 7.05 (m, 4H), 7.30 (m, 3H), 7.58 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 34.4, 44.6, 64.7, 84.2, 123.7, 128.09(2C), 128.15, 128.19 (2C), 128.9 (2C), 132.9, 134.3, 135.0, 169.9. GC-EIMS (*m*/*z*, %): 65 (13), 91 (100), 92 (10), 106 (78), 115 (32), 116 (38), 132 (23), 144 (21), 322(13), 328 (37), 329 (19), 330 (37). Anal. Calcd for $C_{17}H_{15}BrN_2O_3$: C, 54.42; H, 4.03; N, 7.47. Found: C, 54.34; H, 4.09; N, 7.41. FT-IR (KBr, cm^{-1}): 1696, 1552, 1490, 1408, 1377.

*(±)-1-Benzyl-5-(3-chlorophenyl)-4-nitropyrrolidin-2-one (**7**).* In a 2 mL vial equipped with a magnetic stirrer, 3-chloro-benzaldehyde (**1d**) (2 mmol, 282 mg, 226 μL), benzylamine (**2a**) (2 mmol, 214 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 24 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated to obtain 1-benzyl-5-(3-chlorophenyl)-4-nitro-5-phenylpyrrolidin-2-one (**7**) as a yellow oil (626 mg, 95%). TLC Rf (6 hexane/4 ethyl acetate) = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.12 (dd, J = 18.4; 8.3 Hz, 1H), 3.23 (dd, J= 18.4; 3.2 Hz), 3.58 (d, J = 14.9 Hz, 1H), 4.82 (d, J = 2.3 Hz, 1H), 4.87 (m, 1H), 5.22 (d, J = 14.9 Hz, 1H), 7.06 (m, 3H), 7.14 (s, 1H), 7.31 (m, 3H), 7.38 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 34.4, 44.7, 64.7, 84.2, 124.6, 126.5, 128.18, 128.19, 128.9, 129.8, 131.0, 134.3, 135.8, 138.1, 169.9. GC-EIMS (*m*/*z*, %): 65 (15), 91(100), 106 (83), 115 (34), 116 (20), 132 (31), 144 (12), 151 (17), 201 (12), 283 (15), 284 (85), 285 (21), 286 (29), 330 (11). Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.63; H, 4.49; N, 8.56. FT-IR (cm^{-1}): 1700, 1553,1415, 1362.

*(±)-1-Benzyl-5-(4-methoxyphenyl)-4-nitropyrrolidin-2-one (**8**).* In a 2 mL vial equipped with a magnetic stirrer, 4-methoxybenzaldehyde (**1c**) (2 mmol, 272 mg, 244 μL), benzylamine (**2a**) (2 mmol, 214 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 218 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 48 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated and crystallized in ethyl acetate. 1-Benzyl-5-(4-methoxyphenyl)-4-nitro-pyrrolidin-2-one (**8**) was obtained as a white solid. (616 mg, 93%). TLC Rf (6 hexane/4 ethyl acetate) = 0.22. M.p. = 127−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.12 (dd, J = 18.1; 8.4 Hz, 1H), 3.21 (dd, J = 18.1; 3.6 Hz, 1H), 3.52 (d, J = 14.8, 1H), 3.84 (s, 3H), 4.77 (d, J = 2.5 Hz, 1H), 4.88 (m, 1H), 5.19 (d, J = 14.8 Hz, 1H), 6.95 (d, J = 8.6, 2H), 7.08 (m, 4H), 7.30 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 34.7, 44.4, 55.4, 64.9, 84.8, 115.0, 127.6, 127.8, 128.0, 128.2, 128.8, 134.7, 160.4, 169.8. GC-EIMS (*m*/*z*, %): 65 (11), 91 (100), 92 (12), 106 (37), 147 (45), 174 (18), 188 (12), 207 (13), 279 (37), 280 (23). Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.59; N, 8.63. FT-IR (KBr, cm^{-1}): 1697, 1546, 1518, 1415.

*(±)-4-Nitro-1-octyl-5-phenylpyrrolidin-2-one (**9**).* In a 2 mL vial equipped with a magnetic stirrer, benzaldehyde (**1a**) (2 mmol, 212 mg, 204 μL), octylamine (**2b**) (2 mmol, 258 mg, 330 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 60 °C for 5 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite

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pad. The filtrate was concentrated and purified on flash column chromatography (eluent 7 hexane/3 ethyl acetate) to obtain 4-nitro-1-octyl-5-phenylpyrrolidin-2-one (**9**) as a white solid. (501 mg, 79%). TLC Rf (7 hexane/3 ethyl acetate) = 0.26. M.p. = 91−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.863 (t, J = 6.9 Hz, 3H), 1.23 (m, 10H), 1.45 (m, 2 H), 2.63 (dt, J = 13.7; 6.7, 1H), 3.03 (dd, J = 18.2; 8.2 Hz, 1H), 3.14 (dd, J = 18.2; 2.8 Hz, 1H), 3.78 (dt, J = 13.7; 7.9 Hz, 1H), 4.87 (m, 1H), 5.15 (d, J = 1.5 Hz, 1H), 7.21 (m, 2H), 7.44 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 22.5, 26.5, 26.7, 29.03, 29.06, 31.7, 34.6, 40.9, 65.9, 84.5, 126.2, 129.4, 129.6, 136.4, 169.9. GC-EIMS (*m*/*z*, %): 91 (45), 104 (10), 115 (32), 116 (11), 117 (53), 118 (28), 144 (18), 159 (14), 160 (15), 172 (37), 173 (29), 174 (15), 270 (20), 271 (29), 272 (100), 273 (19). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.87; H, 8.19; N, 8.85. FT-IR (KBr, cm^{-1}): 1690, 1556, 1430, 1401.

*(±)-5-(4-Chlorophenyl)-4-nitro-1-octylpyrrolidin-2-one (**10**).* In a 2 mL vial equipped with a magnetic stirrer, 4-chlorobenzaldehyde (**1b**) (2 mmol, 242 mg), octylamine (**2b**) (2 mmol, 258 mg, 330 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 60 °C for 5 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated and purified on flash column chromatography (eluent 7 hexane/3 ethyl acetate) to obtain 5-(4-chlorophenyl)-4-nitro-1-octylpyrrolidin-2-one (**10**) as white solid crystallized in diethyl ether and petroleum ether. (548 mg, 78%). TLC Rf (7 hexane/3 ethyl acetate) = 0.29. M.p. = 74−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J = 6.6 Hz, 3H), 1.23 (m, 10H), 1.44 (m, 2H), 2.60 (dt, J = 13.8; 6.7, 1H) 3.02 (dd, J = 18.4; 8.3 Hz, 1H), 3.16 (dd, J = 18.4; 3.2 Hz, 1H), 3.77 (dt, J = 13.8; 7.9 Hz, 1H), 4.83 (m, 1H), 5.13 (d, J = 2.1 Hz, 1H), 7.17 (m, 2H), 7.43 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.6, 26.7, 29.0, 31.7, 34.4, 40.9, 65.3, 84.7, 127.6, 129.9, 134.9, 135.5, 169.8. GC-EIMS (*m*/*z*, %): 91 (28), 115 (57), 116 (19), 117 (39), 118 (18), 145 (100), 147 (30), 161 (36), 162 (100), 218 (41). Anal. Calcd for: $C_{18}H_{25}ClN_2O_3$: C, 61.27; H, 7.14; N, 7.94. Found: C, 61.21; H, 7.18; N, 7.89. FT-IR (KBr, cm^{-1}): 1692, 1549, 1491, 1455, 1404.

*(±)-5-(3-Chlorophenyl)-4-nitro-1-octylpyrrolidin-2-one (**11**).* In a 2 mL vial equipped with a magnetic stirrer, 3-chlorobenzaldehyde (**1d**) (2 mmol, 242 mg, 226 μL), octylamine (**2b**) (2 mmol, 258 mg, 330 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 60 °C for 5 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated and purified on flash column chromatography (eluent 7 hexane/3 ethyl acetate) to obtain 5-(3-chlorophenyl)-4-nitro-1-octylpyrrolidin-2-one (**11**) as a yellow oil. (540 mg, 77%). TLC Rf (7 hexane/3 ethyl acetate) = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, J = 6.6 Hz, 3H), 1.23 (m, 10H), 1.46 (m, 2H), 2.62 (dt, J = 14.0; 6.7), 3.04 (d, J = 18.3; 8.7 Hz, 1H), 3.16 (dd, J = 18.3; 3.0 Hz, 1H), 3.79 (m, 1H), 4.85 (m, 1H), 5.13 (d, J = 1.86 Hz, 1H), 7.11 (m, 1H), 7.21 (s, 1H), 7.39 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.5, 26.7, 29.0, 31.7, 34.4, 41.0, 65.3, 84.5, 124.4, 126.4, 129.7, 131.0, 135.8. 138.5, 169.8. GC-EIMS (*m*/*z*, %): 115 (27), 116 (18), 125 (22), 151 (22), 152 (14), 178 (12), 193 (13), 194 (13), 206 (26), 207 (14), 208 (19), 305 (20), 306 (100), 307 (26), 308 (34). Anal. Calcd for: $C_{18}H_{25}ClN_2O_3$: C, 61.27; H, 7.14; N, 7.94. Found: C, 61.21; H, 7.18; N, 7.89. FT-IR (cm^{-1}): 1696, 1554, 1413, 1366.

*(±)-5-Cyclohexyl-4-nitro-1-octylpyrrolidin-2-one (**12**).* In a 2 mL vial equipped with a magnetic stirrer, cycloexanecarboxyaldehyde (**1f**) (2 mmol, 224 mg, 282 μL), octylamine (**2b**) (2 mmol, 258 mg, 330 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 60 °C for 5 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated and purified on flash column chromatography (eluent 7 hexane/3 ethyl acetate) to obtain 5-cyclohexyl-4-nitro-1-octylpyrrolidin-2-one (**12**) as a yellow oil. (612 mg, 95%). TLC Rf (6 hexane/4 ethyl acetate) = 0.39. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.73 (m, 1H), 0.88 (t, J = 6.2 Hz, 3H), 1.26 (m, 13H), 1.54 (m, 3H), 1.78 (m, 6H), 2.82 (m, 2H), 3.02 (dd, J = 18.3, 1.88 Hz, 1H), 3.74 (m, 1H), 3.93 (d, J = 2.15 Hz, 1H), 4.89 (d, J =, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 25.7, 25.9, 26.0, 26.1, 26.6, 26.7, 28.9, 29.09, 29.13, 31.68, 35.8, 38.5, 40.6, 67.2, 79.4, 169.8. GC-EIMS (*m*/*z*, %): 55 (13), 68 (11), 96 (16), 97 (13), 124 (10), 138 (11), 143 (10), 166 (11), 194 (13), 195 (100), 196 (48), 222 (15), 241 (74), 242 (11), 277 (10), 278 (38). Anal. Calcd for: $C_{18}H_{32}N_2O_3$:C, 66.63; H, 9.94; N, 8.63. Found: C, 66.68; H, 9.90; N, 8.59.FT-IR (cm^{-1}): 1690, 1553, 1451, 1366.

*(±)-1-Benzyl-5-cyclohexyl-4-nitropyrrolidin-2-one (**13**).* In a 2 mL vial equipped with a magnetic stirrer, cycloexanecarboxyaldehyde (**1f**) (2 mmol, 224 mg, 282 μL), benzylamine (**2a**) (2 mmol, 214 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 5 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated to obtain 1-benzyl-5-cyclohexyl-4-nitropyrrolidin-2-one (**13**) as a yellow oil. (527 mg, 87%). TLC Rf (6 hexane/4 ethyl acetate) = 0.34. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.75 (m, 1H), 1.10−1.80 (m, 10H), 2.86 (dd, J = 18.8, 8.3 Hz, 1H), 3.11(dd, J = 18.8, 1.7 Hz, 1H), 3.71 (m, 1H), 3.96 (d, J = 15.2 Hz, 1H), 4.89 (m, 1H), 5.07 (d, J = 15.2 Hz, 1H), 7.29 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 25.6, 25.8, 25.9, 26.1, 35.7, 38.2, 44.6, 67.0, 79.2, 127.9, 180.0, 127.9, 127.9, 128.9, 135.0, 170.2. GC-EIMS (*m*/*z*, %): 91 (100), 173 (83), 174 (29), 219 (22), 256 (16), 302 (23). Anal. Calcd for: $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.57; H, 7.29; N, 9.20. FT-IR (cm^{-1}): 1690, 1553, 1440, 1364.

*(±)-1-Benzyl-5-isobutyl-4-nitropyrrolidin-2-one (**14**).* In a 2 mL vial equipped with a magnetic stirrer, isovaleraldehyde (**1g**) (2 mmol, 172 mg, 220 μL), benzylamine (**2a**) (2 mmol, 214 mg, 218 μL), methyl 3-nitropropionate (**3**) (2 mmol, 266 mg), and the catalyst Aquivion PW65-S (10 mol %, 131 mg) were consecutively added. The mixture was left under stirring at 40 °C for 24 h. Then it was diluted and washed with ethyl acetate (12 mL), and the catalyst filtered off using a Celite pad. The filtrate was concentrated and purified on flash column chromatography (eluent 7 hexane/3 ethyl acetate) to obtain 1-benzyl-5-isobutyl-4-nitropyrrolidin-2-one (**14**) as a yellow oil. (386 mg, 70%). TLC Rf (6 hexane/4 ethyl acetate) = 0.27. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.803 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.50 Hz, 3H), 1.30 (m, 1H), 1.57 (m, 1H), 1.68 (m, 1H), 2.96 (dd, J = 18.0, 7.99 Hz, 1H), 3.13 (dd, J=18.0, 1.8 Hz, 1H), 3.78 (m, 1H), 3.90 (d, J = 15.0 Hz, 1H), 4.80 (m, 1H), 5.10 (d, J = 15.0 Hz), 7.27 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.3, 23.5, 24.7, 34.4, 40.2, 44.3, 60.7, 82.1, 128.0, 128.9, 134.9, 169.5. GC-EIMS (*m*/*z*, %): 91 (100), 106 (23), 132 (10), 173 (49), 174 (45), 187 (11), 230 (29), 276 (11). Anal. Calcd for: $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.16; H, 7.33; N, 10.10. FT- IR (cm^{-1}): 1692, 1550, 1433, 1363.

RESULTS AND DISCUSSION

Our research is directed to the definition of novel catalytic systems and to test their efficiency to set reliable and sustainable procedures.[26−31] In our studies toward the tailoring of novel solid acid catalytic systems useful for the synthesis of target fine chemicals, we have decided to test the catalytic performance of Aquivion PFSA (that can be prepared in different grades, e.g., pellet or powder) in more challenging and more widely interesting organic transformations.

We have been attracted by the synthesis of 2-pyrrolidin-2-ones by nitro-Mannich/Lactamization cascade considering that it is both synthetically very useful and interesting and also that it has been very rarely investigated with the exception of a few contributions.[22−25] We envisaged the possibility of improving this protocol in terms of sustainability by employing catalytic amounts of a supported acidic catalyst in solvent free (SolFC) or concentrated conditions and flow (Table 1).

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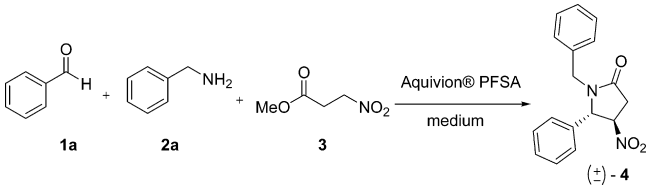
Table 1. Opmization of Conditions for Aquivion PFSA Catalyzed Nitro-Mannich/Lactamization Cascade[a]

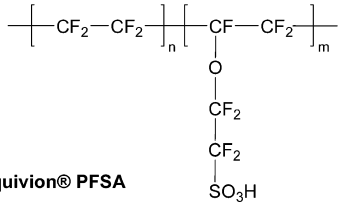


entry	catalyst	medium	T (°C)	t (h)	C (%)[b]	yield (%)[c]
1	PW65-S (10 mol %)	–	60	5	99	64
2	PW65-S (5 mol %)	–	60	5	99	61
3	PW65-S (5 mol %)	–	40	24	86	72
4	PW65-S (10 mol %)	–	40	24	98	89
5	PW98 (10 mol %)	–	60	5	99	59
6	PW98 (5 mol %)	–	60	5	99	60
7	PW98 (10 mol %)	–	40	24	95	87
8	P98 (10 mol %)	–	40	24	96	83
9	PW65-S (10 mol %)	AcOEt	40	24	75	-
10	PW65-S (10 mol %)	CPME	40	24	64	-
11	PW65-S (10 mol %)	2-Me-THF	40	24	62	-
12	PW65-S (10 mol %)	toluene	40	24	70	-

[a]Reaction conditions: benzaldehyde **1a** (1.0 mmol), benzylamine **2a** (1.0 mmol), methyl 3-nitropropanoate **3** (1.0 mmol), when indicated medium was used in 2 mL/mmol. Please notice that no conversion was observed in the absence of catalyst. [b]Conversion to **4** determined by ^{1}H NMR analysis. [c]Yield of isolated pure product **4** by recrystallization of the crude reaction mixture.

Three different grades of Aquivion PFSA have been tested to catalyze the above-described reaction, namely, PW65-S, PW98, and P98. These materials have recently become commercially available from Solvay Specialty Polymers S.p.A. All the catalysts are based on Aquivion PFSA but differ in form (powder vs cylindric pellets of about 2.5 mm × 2.5 mm), acid loading (1.5 vs 1.0 $mmol_{SO3H}/g_{resin}$), and stabilization treatment (Scheme 1). The stabilization treatment, carried out in the presence of gaseous fluorine at high temperature, is aimed to end-cap the carboxylic acid groups (installed on the polymer backbone through a well-known side reaction during polymerization[32]) by transformation into $-CF_3$ groups.[33]

Scheme 1. Different Grades of Aquivion PFSA Used in This Study



Form Name	Form	EW (g/mol)	Acid Loading (mmol/g)	Stabilization
PW65-S	Powder	650	1.5	Yes
PW98	Powder	980	1.0	No
P98	Pellet	980	1.0	No

In Table 1, the optimization study by employing benzaldehyde **1a**, benzylamine **2a**, and methyl 3-nitropropanoate **3** as reactants is reported. When PW65-S catalyst was used at 60 °C in 5–10 mol %, excellent conversion values but only moderate yield were obtained after 5 h due to the decomposition of the product (Table 1, entries 1 and 2). Lowering the temperature to 40 °C and increasing the reaction time led to the best experimental conditions with a 89% isolated yield from crystallization (Table 1, entry 4). The PW98 catalyst possesses a lower acidic loading than PW65-S but in all the experimental conditions employed gave the desired product in comparable yields (Table 1, entries 5–7).

When the P98 pellet form of Aquivion PFSA was used, isolated yield of **4** was slightly poorer (Table 1, entry 8), and this result is ascribable to the difficulties encountered in the isolation of the reaction mixture. In fact, due to the larger dimension of the pellet (ca. 3 mm), stirring of the reactants and isolation of the product is difficult. However, this form of Aquivion PFSA is expectedly more useful for larger scale protocol, especially in view of our final set of a flow procedure.

Finally, the reaction between **1a**, **2a**, and **3** was also performed in representative organic media (2 mL/mmol). It is evident how the reaction is much slower (Table 1, entries 9–12), and complete conversion is not reached even after much longer time.

The Aquivion PFSA catalyzed reaction resulted to be stereoselective as the *trans*-isomer of the pyrrolidin-2-one **4** has been obtained as the major product and only traces of the *cis*-isomer were detected (always equal or less than 4%, see Table 2 for details).

The scope of the new protocol has been tested using a variety of either aromatic/aliphatic aldehydes or benzylic/aliphatic amines as reported in Table 2. When aromatic aldehydes bearing electron-withdrawing or electron-donating groups **1b–e** were allowed to react with benzylamine **2a** and methyl 3-nitropropanoate **3** in equimolar ratios, excellent results were obtained as the desired products **5–8** were isolated from reaction mixture by simple filtration on a Celite pad (Table 2, entries 2–5). Shorter reaction times but higher temperature (60 °C) were required when octylamine **2b** was employed in place of benzylamine **2a** to yield pyrrolidin-2-ones **9–11** (Table 2, entries 6–8). Aliphatic aldehydes such as cyclohexanecarboxyaldehyde **1f** and isovaleraldehyde **1g** reacted smoothly with either benzylamine **2a** and octylamine **2b** and methyl 3-nitropropanoate **3** to yield the corresponding products **12–14** (Table 2, entries 9–11).

We have also investigated the reuse of PW65-S catalyst. While initial experiments proved that the acidic efficiency of the system is unvaried, the recovery of the catalyst is actually tedious, and recovered material was difficult to handle compared to the original catalyst. In fact, inclusion of the product into the solid acid was evident, and large volumes of solvents were required to completely wash it. This issue is closely related to the physical properties of the products, which are highly viscous oils with limited solubility in the solvent used such as ethyl acetate.

Finally, we have also explored the possibility to improve the efficiency of the process, simplify the isolation procedure, and improve the reusability of the catalytic system by replacing classic stirring (magnetic bar) with flow. In fact, we have proved in several occasions[34−38] that adoption of flow conditions may significantly help to enlarge the scale of a batch protocol and at the same time allow preservation of the physical integrity of the catalytic system. With this aim, we have set a flow reactor system based on a column packed with pellet form catalyst Aquivion PFSA P98 and representatively running the reaction between **1a**, **2a**, and **3** (Scheme 2).

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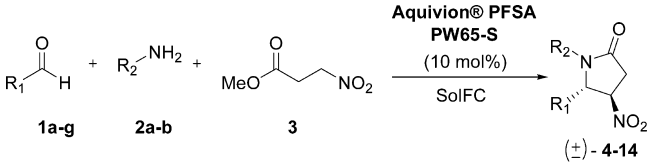
Table 2. Substrate Scope of Aquivion PFSA-Catalyzed Synthesis of 2-Pyrrolidin-2-ones 4−14 in Batch Conditions[a]



equimolar amounts

Entry	R_1	R_2	T (°C)	time (h)	yield (%)	product	dr[b]
1	1a	2a	40	24	89	**4**	96:4
2	1b	2a	40	72	81	**5**	98:2
3	1c	2a	40	48	92	**6**	96:4
4	1d	2a	40	24	95	**7**	96:4
5	1e	2a	40	48	93	**8**	99:1
6	1a	2b	60	5	79	**9**	99:1
7	1b	2b	60	5	78	**10**	99:1
8	1d	2b	60	5	77	**11**	97:3
9	1f	2b	60	5	95	**12**	99:1
10	1f	2a	40	5	89	**13**	99:1
11	1g	2a	40	5	70	**14**	98:2

[a]Reaction conditions: aldehyde **1a−g** (2.0 mmol), amine **2a−b** (2.0 mmol), methyl 3-nitropropanoate **3** catalyst (10 mol %). [b]*dr* values are based on the crude ^{1}H NMR analysis.

An immediate issue encountered moving to flow and larger scale (30 mmol) is related to the clogging of the pump due to the highly viscosity of **4**. Therefore, some organic solvent needed to be added, and expectedly, the reaction was slower. In fact, using 0.05 mL/mmol of ethyl acetate reaction was only slightly slower, but going over 90% conversion, the mixture became so viscous that the pump clogged. To achieve the sufficient solubility of the reaction mixture, 1.0 mL/mmol of ethyl acetate was needed, and a 97% conversion into **4** was achieved after 68 h at 40 °C.

The flow protocol allowed for performing three consecutive runs without observing any decrease in the reactivity of Aquivion P98 catalysts, and **4** was isolated pure after recrystallization in excellent yields (91−94%). In a similar fashion, the batch protocol for the synthesis of **5** (50 mmol scale) has been applied to flow conditions with an increase in yield of 5%.

The recovered catalyst has been analyzed after each run, and EDS (energy dispersive X-ray spectrometry) and SEM (scanning electron microscopy) analyses showed that recovered material preserved its physical structure, but formation of a superficial encrustation on the pellets surface is observed. Considering the high content of carbon and the absence of fluorine and sulfur in the entrustment, this is ascribable to the product deposition on the surface of the catalyst. The encrustation does significantly increase over the runs, and this may be reasonable due to the insolubility of the product, which basically results in the precipitation of a constant amount of product over time (see Figures 1 and 2 for representative EDS and SEM images and the Supporting Information).

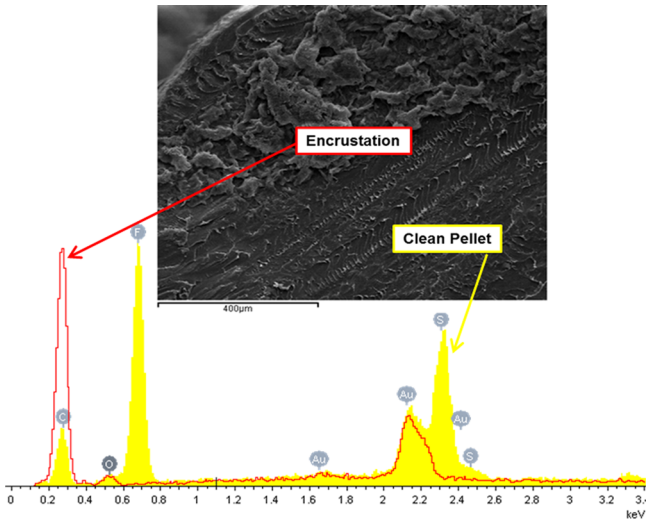
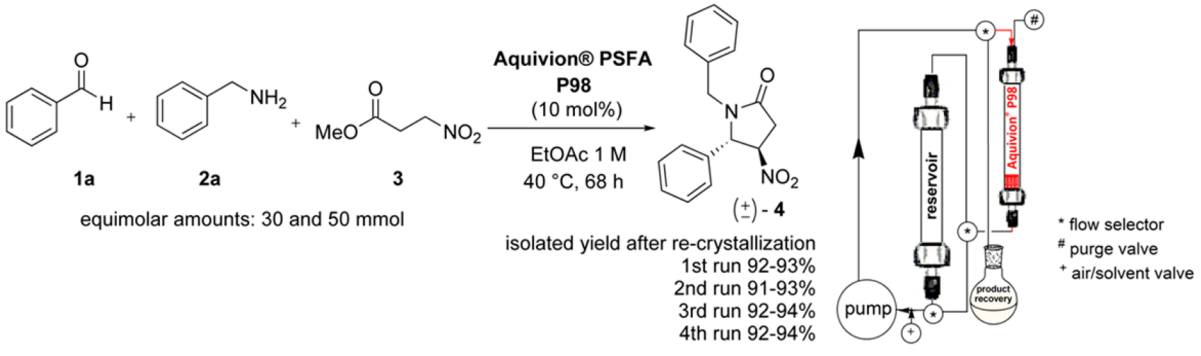


Figure 1. EDS images of starting and recovered Aquivion PFSA P98.

In order to evaluate the efficiency of our synthetic strategy and according to Andraos algorithm,[39] we have calculated some parameters of green metrics, i.e., E-factors,[40] and process mass

Scheme 2. Flow Reactor for Aquivion PFSA P98 Catalyzed Synthesis of 4



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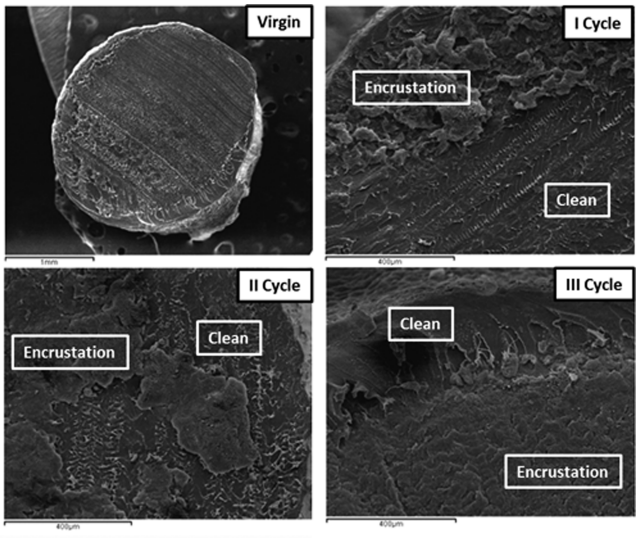

Figure 2. SEM images of starting and recovered Aquivion PFSA P98.

intensity PMI.[41] The overall E-factor (E_{tot}) has been divided into its components arising from byproducts, side products, and unreacted starting materials (E_{kernel}), excess reagent consumption (E_{excess}), and auxiliary material consumption arising from reaction solvent, catalysts, all workup materials, and all purification materials (E_{aux}).

As shown in Table 3, in the batch protocol, the E-total value for the preparation of 2-pyrrolidin-2-one **4** was 29.42, whereas the flow procedure features an E_{tot} value of ca. 6 without considering the solvent recovery and an E_{tot} value of ca. 2 taking into account the solvent recovery, with 80% and 93% reduction of waste, respectively.

Table 3. Green Metrics Calculation for Synthesis of 2-Pyrrolidin-2-ones 4 and 5 in Batch and Flow Conditions[a]

entry	product	yield (%)[a]	E_{kernel}	E_{aux}	E_{tot}	PMI
1[b]	**4**	89	0.32	29.1	29.42	30.42
2[c]	**4**	93	0.26	5.88	6.14	7.14
3[d]	**4**	93	0.26	1.72	1.98	2.98
4[b]	**5**	81	0.42	136.91	137.33	138.33
5[c]	**5**	86	0.35	5.73	6.08	7.08
6[d]	**5**	86	0.35	1.67	2.02	3.02

[a]E_{excess} is omitted as it does not contribute to the E-factor because the reactants were used in equimolar amounts. [b]Batch conditions. [c]Flow conditions; no solvent recovery. [d]Flow conditions; solvent recovery.

In the case of product **5**, the reduction of waste for the procedure in flow is 95.6% without considering the solvent recovery and 98.5% considering the solvent recovery. It is noteworthy that in the batch, the pure product **5** was obtained after purification by flash chromatography and recrystallization, while in flow, only recrystallization was sufficient with a further reduction of auxiliary material consumption. The largest contribution is E_{aux}; in flow condition, the minimal use of organic solvent to recover the final product allowed us to reduce the reaction's waste, thus minimizing E_{aux} and E_{tot}.

To compare our synthetic strategy to those of already published protocols,[23−25] we have calculated the parameters of green metrics also for literature procedures[23−25] (Table 4). In these procedures, the auxiliary material consumption was not disclosed; however, we have calculated E_{tot} considering the minimal amounts of workup and purification step materials.

Therefore, E_{tot} and PMI values appear as lower limits in the table, i.e., values appear with a "greater than" inequality sign (>). The proposed protocol showed great improvements in the sustainability of the reaction as evident by comparison of Table 3 with Table 4. In fact, the experimental literature conditions have not been optimized on the sustainability point of views, and this mean values of E_{tot} greater than 300 in all cases, with a consequent reduction of wastes for our optimized flow protocol greater than 99%.

CONCLUSION

In conclusion, a new convenient protocol for the solventless synthesis of 2-pyrrolidin-2-ones have been proposed based on the use of Aquivion PFSA as catalyst in different forms. Powdered PW65 Aquivion PFSA gave optimal and excellent results in catalyzing the nitro-Mannich/lactamization cascade reaction of aliphatic and aromatic aldehydes with benzylamine or octylamine and methyl 3-nitropropanoate in batch conditions.

The processes were highly diasteroselective with the *trans* isomer being almost the exclusive product. The recovery and reuse of the catalyst was optimized in flow conditions where the most appropriate form proved to be Aquivion PFSA pellet P98. Recovery and reuse has been representatively proven for the synthesis of **4** and **5**; although a bit slower due to the needed presence of an organic reaction medium, the final products were obtained on a 30 or 50 mmol scale with excellent yields.

In general, the protocol here presented is very convenient both in terms of sustainability and of efficiency; in fact, little amount of catalyst was employed, equimolar amounts of reactants were used, and the procedure to isolate the products was straightforward. The adoption of flow technology as an alternative to classic mechanical stirring has allowed the effective minimization of waste production and the recovery and reuse of the catalyst. Green metrics calculations have confirmed the significant contribution and improvements of the protocol among other literature reports on this topic.

ASSOCIATED CONTENT

Supporting Information

Full characterization of compounds **4**−**14** and copies of the ^{1}H and ^{13}C NMR spectra. The Supporting Information is available

Table 4. Green Metrics Calculation for Literature Synthetic Approach to 2-Pyrrolidin-2-ones

reference	yield (%)[a]	E_{kernel}	E_{excess}	E_{aux}	E_{tot}
Dixon et al. (2009)[25a]	52−87	0.4−0.7	1.3−1.7	>300−400	>300−400
Dixon et al. (2011)[24a]	55−82	0.2−0.5	1.5−1.7	>490−570	>490−570
Anderson et al. (2012)[23a]	33−84	0.5−2.8	4.1−9.3	>300−650	>300−660

[a]It should be noted that these studies were not optimized in the context of waste minimization; in particular, Dixon's study was driven by new reactivity and methods development.

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Notes

The authors declare no competing financial interest.

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