Three-Component Domino Reaction in PPG: An Easy Access to 4-Thiazolidinone Derivatives

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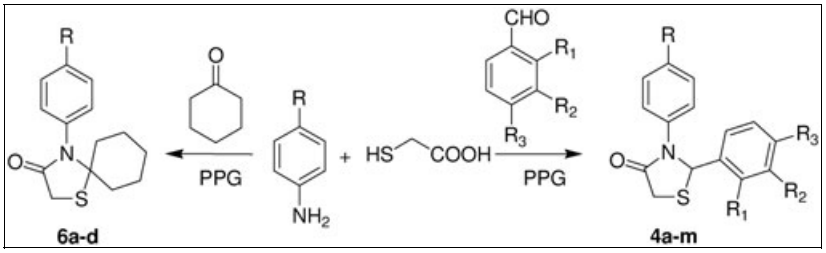

A simple, economical, and convenient synthesis of a new series of 4-thiazolidinone derivatives using one-pot three-component condensation of aromatic amines, thioglycolic acid and aromatic aldehydes or cyclohexanone in polypropylene glycol (PPG), a recyclable and inexpensive solvent medium is reported. All the reactions are carried out at 110°C without using catalyst or additives. The products are obtained in good to excellent yields (60–97%) after easy workup and purification.

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INTRODUCTION

The use of multi-component domino reactions for the construction of complex organic structures from simple and easily available precursors has received considerable attention in recent years [1]. In comparison to conventional chemical reactions, these processes avoid multi-step synthetic protocols and offer an easy access to a variety of pharmaceutically useful heterocyclic molecules [2].

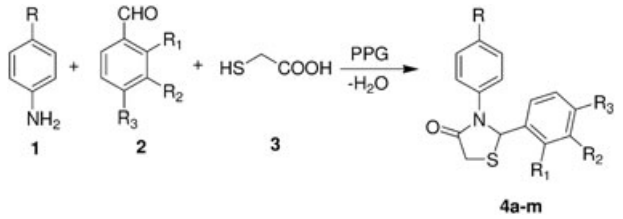
4-Thiazolidinones are an important class of five membered heterocycles and occupy a unique place in therapeutic and medicinal fields because of their pharmacological profiles as anticonvulsant [3], anti-HIV [4], antifungal [5], antibacterial [6], COX-1 inhibitors [7], and nematicidal agents [8]. Although a number of methods are reported in the literature employing either a two step or an one step procedure to afford 4-thiazolidinones by a condensation cyclization reaction between amine, carbonyl compound (ketone or an aldehyde) and thioglycolic acid but the design of simple, economical, and efficient synthetic routes for the synthesis of these biologically active molecules is highly desired.

Thorough literature search revealed that the reaction proceeds via initial formation of a Schiff base intermediate, which undergoes attack by sulfur nucleophile followed by intramolecular cyclization with the expulsion of water to form the cyclized product [9]. It is generally believed that the last step, that is, removal of water molecule is the rate determining and seems to be critical for obtaining 4-thiazolidinones in better yields. The most common approach to remove water from the reaction medium is by azeotropic distillation using Dean Stark trap [10]. Besides this, various dehydrating agents such as Na_2SO_4 [11], molecular sieves [10(a)], DCC [12], HBTU [13], and Lewis acid catalysts such as anhydrous $ZnCl_2$ [14] and $SnCl_2$ [15] have also been used to improve the yield of the desired product.

In view of enormous pharmacological potential of 4-thiazolidinone class of compounds, we hereby report a simple, economical, and robust one-pot three-component synthesis of these heterocycles in good to excellent yields using polypropylene glycol (PPG) as a solvent medium (Scheme 1).

To the best of our knowledge, PPG has not been used previously as a solvent medium for the construction of 4-thiazolidinone derivatives. We have chosen PPG as a solvent because it is immiscible with water and hence can easily facilitate the reaction rate by eliminating water molecules from the reaction medium. Furthermore, PPG is an environmentally benign solvent and also offers many advantages like low cost, less toxicity, recyclability, easy work-up, and miscibility with a wide range of organic solvents. In comparison to reported one-pot methods [10 (a),12,13,16], our synthetic protocol does not require any catalyst or additives and products were obtained in good to excellent yields at 110°C in 4–11 h.

Scheme 1



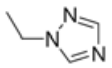
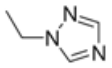
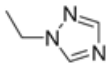
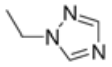
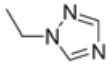
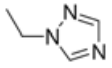
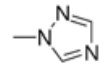
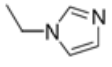
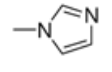
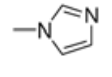
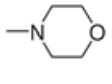
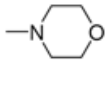
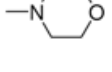
RESULTS AND DISCUSSION

For the synthesis of a novel series of 4-thiazolidinones (**4a-m** and **6a-d**), various aromatic amines (**1**) were prepared according to the literature procedure [17]. The synthesis of 3-(4-((1*H*-1,2,4-triazol-1-yl)methyl)phenyl)-2-phenylthiazolidin-4-one (**4a**) was attempted by reacting 4-((1*H*-1,2,4-triazol-1-yl)methyl)aniline with benzaldehyde and thioglycolic acid in PPG at 110°C for 7 h. After completion of the reaction, as indicated by TLC, the mixture was allowed to cool at 25°C and diluted with hexane. The precipitated crude product was filtered, washed well with hexane, and chromatographed over silica gel to afford pure compound in 81% yield. The filtrate (hexane layer) was evaporated under reduced pressure to recover PPG which can be reused. To optimize the reaction conditions, a number of reactions were carried out with varying amounts of the reactants and it was noticed that the reaction proceeds quantitatively by using amine, aldehyde, and thioglycolic acid in 1:2:3 ratio, respectively. Encouraged by this result and to gain insight into the reaction, a library of novel 4-thiazolidinones (**4b-m**) has been synthesized by condensing the corresponding aromatic amines with different aromatic aldehydes and thioglycolic acid in PPG at 110°C for 4–11 h. In general, the reaction proceeds well with aromatic aldehydes having electron withdrawing substituents such as CF_3 (Table 1, Entries 2, 8, and 13) while aldehydes having electron donating substituents such as CH_3 on the aromatic ring (Table 1, Entry 3) retards the rate of reaction. In addition, the position of substituents viz. *o*-, *m*-, or *p*- (Table 1, Entries 4, 5, and 6) with respect to carbonyl group does not have any influence on the reaction rate. Similarly, the reaction is merely affected by the nature of "R" group of aromatic amines as evident from Table 1.

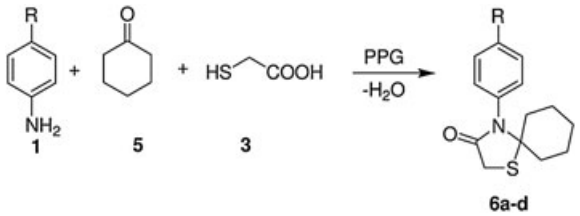
All the synthesized compounds (**4a-m**) have been characterized by IR, mass, NMR, and elemental analysis. The infrared absorption spectrum of novel 3-(4-((1*H*-1,2,4-triazol-1-yl)methyl)phenyl)-2-phenylthiazolidin-4-one (**4a**) exhibited characteristic strong absorption band at 1662 cm^{-1} due to stretching of C=O bond. The presence of thiazolidinone moiety in the molecule was confirmed by NMR spectroscopy. ^1H NMR spectrum of **4a** in $CDCl_3$

Table 1

One-pot three-component synthesis of 4-thiazolidinones (**4a-m**) in PPG.

Entry	R	R_1	R_2	R_3	Time (h)	Yield (%)	Product
1		H	H	H	7	81	**4a**
2		H	H	CF_3	4	97	**4b**
3		H	H	CH_3	11	80	**4c**
4		H	H	Cl	7	79	**4d**
5		H	Cl	H	7	78	**4e**
6		Cl	H	H	7	76	**4f**
7		H	H	Br	6	84	**4g**
8		CF_3	H	H	4	91	**4h**
9		H	H	H	7	80	**4i**
10		H	H	Br	6	86	**4j**
11		H	H	H	7	86	**4k**
12		H	H	F	4	88	**4l**
13		CF_3	H	H	4	92	**4m**

Scheme 2



showed a characteristic singlet at 6.08 ppm for one proton corresponds to N—CH—S with additional doublets at 3.85 and 3.98 ppm due to coupling between two geminal protons of SCH_2CO group of the thiazolidinone ring.

To test the versatility of this procedure, synthesis of novel spiro-thiazolidinones (**6a-d**) has also been carried out under standardized reaction conditions through one-pot condensation of corresponding aromatic amine with cyclohexanone and thioglycolic acid in PPG at 110°C for 11 h (Scheme 2).

Over all, the reaction of amine (**1**) with cyclohexanone and thioglycolic acid was found to be sluggish and produced desired products (**6a-d**) in moderate yields. Surprisingly, the substituent "R" of aromatic amine does not have any significant influence on the reaction rate within the series (Table 2). The spectral and analytical data of these compounds were found in full agreement with the proposed structures and are presented in the experimental section.

Additionally, we have investigated the recyclability of PPG for the synthesis of 2-(4-fluorophenyl)-3-(4-morpholinophenyl)thiazolidin-4-one (**4l**). After each run, the PPG was extracted with hexane and reused after the removal of solvent by vacuum. The good yields were obtained in all four runs (Table 3).

Table 2

One-pot three-component synthesis of spiro-thiazolidinones (**6a-d**) in PPG.

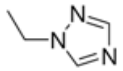
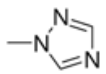
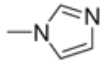
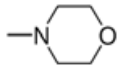
Entry	R	Time (h)	Yield (%)	Product
1		11	60	**6a**
2		11	62	**6b**
3		11	61	**6c**
4		11	62	**6d**

Table 3

PPG recycle for the one-pot condensation reaction of 4-morpholinoaniline, thioglycolic acid, and 4-fluorobenzaldehyde at 110°C.

Entry	Run	Time (h)	Yield (%)[a]
1	1	4	90
2	2	4	89
3	3	4	89
4	4	4	89

[a]Isolated yields for product (**4l**) after each cycle.

EXPERIMENTAL

All the chemicals were purchased from Aldrich and used without further purification. Thin layer chromatography (TLC) was performed using silica gel 60 F254 (pre-coated aluminium sheets) from Merck. Reactions were monitored by TLC and products were purified by column chromatography using silica gel (60–120 mesh size). ^{1}H NMR spectra were obtained in $CDCl_3$, using a Bruker 300 MHz and Jeol ECX 400 MHz NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane (TMS; 0 ppm) as an internal standard. Coupling constants (*J*) are reported in hertz (Hz). Infrared spectra were recorded on Perkin Elmer IR spectrometer and absorption maxima (υ_{max}) are given in cm^{-1}. Mass spectra were recorded on ESI-MS (micromass LCT, waters) mass spectrometer.

General procedure for the synthesis of 4-thiazolidinones (4a-m and 6a-d). To a mixture of aromatic amine (1.0 mmol) and aromatic aldehyde or cyclohexanone (2.0 mmol) in PPG-2000 (3.0 mL), thioglycolic acid (3.0 mmol) was added. The reaction mixture was heated at 110°C for 4–11 h. Then, the mixture was cooled to room temperature and PPG was extracted with hexane (10 mL × 3 times). After complete removal of PPG, the residue was dissolved in ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ solution (15 mL × 3 times) followed by water (15 mL × 3 times). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography over silica gel (60 mesh size) using 2–4% MeOH in benzene as eluent. PPG was recovered quantitatively after the evaporation of hexane under vacuum and can be recycled.

3-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-2-phenylthiazolidin-4-one (4a). Yellow solid; m.p. 126°C. IR (Nujol): υ = 1662, 1508, 1457, 1390, 1344, 1267, 1139, 1018, 956, 801, 767, 721, 693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1 H, ArH), 7.94 (s, 1H, ArH), 7.36–7.14 (m, 9H, ArH), 6.08 (s, 1H, CH), 5.25 (s, 2H, CH_2), 3.98 (d, *J* = 16.2 Hz, 1H, CH_2), 3.85 (d, *J* = 15.9 Hz, 1H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.12, 151.19, 142.08, 138.23, 136.86, 132.15, 128.00, 127.53, 125.72, 124.77, 122.68, 64.30, 51.82, 32.38 ppm; MS (ESI): *m/z* 337 $[M+H]^+$.

3-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-2-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (4b). Light yellow solid; m.p. 174°C. IR (Nujol): υ = 1687, 1514, 1458, 1373, 1319,

1111, 1063, 1012, 855, 754, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H, ArH), 7.95 (s, 1H, ArH), 7.57 (d, *J* = 8.4 Hz, 2H, ArH), 7.40 (d, *J* = 8.1 Hz, 2H, ArH), 7.26–7.16 (m, 4H, ArH), 6.14 (s, 1H, CH), 5.27 (s, 2H, CH_2), 3.98 (dd, J_1 = 16.0 Hz, J_2 = 0.9 Hz, 1H, CH_2), 3.87 (d, *J* = 15.9 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.85, 152.04, 143.29, 143.08, 137.32, 133.48, 128.52, 126.93, 125.98, 125.95, 125.38, 124.88, 64.27, 52.55, 33.13 ppm; MS(ESI): *m/z* 405 $[M+H]^+$; Anal. calcd for $C_{19}H_{15}F_3N_4OS.H_2O.0.4C_6H_6$: C, 56.66; H, 4.31; N, 12.35; S, 7.07. Found: C, 56.43; H, 4.39; N, 12.35; S, 7.43.

3-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-2-*p*-tolylthiazolidin-4-one (4c). Light yellow solid; m.p. 138°C. IR (Nujol): υ = 1686, 1610, 1560, 1513, 1426, 1414, 1376, 1336, 1301, 1272, 1214, 1180, 1137, 1017, 957, 900, 829, 752, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, ArH), 7.93 (s, 1H, ArH), 7.18–7.09 (m, 8H, ArH), 6.06 (s, 1H, CH), 5.23 (s, 2H, CH_2), 3.95 (d, *J* = 15.9 Hz, 1H, CH_2), 3.82 (d, *J* = 15.3 Hz, 1H, CH_2), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.03, 151.91, 143.02, 138.82, 137.66, 135.97, 133.00, 129.50, 128.32, 126.52, 125.66, 64.99, 52.60, 33.27, 21.02 ppm; MS (ESI): *m/z* 351 $[M+H]^+$.

3-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-2-(4-chlorophenyl)thiazolidin-4-one (4d). Yellow solid; m.p. 164°C. IR (Nujol): υ = 1686, 1514, 1491, 1376, 1272, 1216, 1137, 1089, 1015, 957, 844, 798, 752, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, ArH), 7.94 (s, 1H, ArH), 7.25–7.17 (m, 8H, ArH), 6.07 (s, 1H, CH), 5.27 (s, 2H, CH_2), 3.96 (d, *J* = 15.9 Hz, 1H, CH_2), 3.85 (d, *J* = 15.6 Hz, 1H, CH_2) ppm; MS (ESI): *m/z* 371 $[M+H]^+$.

3-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-2-(3-chlorophenyl)thiazolidin-4-one (4e). White solid; m.p. 148°C. IR (Nujol): υ = 1690, 1513, 1477, 1432, 1375, 1328, 1273, 1244, 1199, 1137, 1078, 1017, 999, 957, 883, 855, 798, 750, 700, 680, 665, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, ArH), 7.95 (s, 1H, ArH), 7.27–7.13 (m, 8H, ArH), 6.04 (s, 1H, CH), 5.27 (s, 2H, CH_2), 3.98 (dd, J_1 = 16.0 Hz, J_2 = 1.37 Hz, 1H, CH_2), 3.85 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.02, 152.26, 143.32, 141.57, 137.54, 134.89, 133.66, 130.41, 129.29, 128.69, 126.95, 125.76, 124.99, 64.56, 52.73, 33.35 ppm; MS (ESI): *m/z* 371 $[M+H]^+$; Anal. calcd for $C_{18}H_{15}ClN_4OS.0.25H_2O$: C, 57.60; H, 4.16; N, 14.93; S, 8.54. Found: C, 57.68; H, 4.10; N, 14.79; S, 8.74.

3-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-2-(2-chlorophenyl)thiazolidin-4-one (4f). White solid; m.p. 142°C. IR (Nujol): υ = 1693, 1514, 1473, 1445, 1376, 1339, 1304, 1272, 1218, 1138, 1047, 1017, 957, 852, 800, 749, 698, 679, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1 H, ArH), 7.94 (s, 1H, ArH), 7.38–7.18 (m, 8H, ArH), 6.53 (s, 1H, CH), 5.27 (s, 2H, CH_2), 3.92 (dd, J_1 = 16.0 Hz, J_2 = 1.37 Hz, 1H, CH_2), 3.79 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.42, 152.24, 143.19, 137.88, 136.79, 132.91, 132.41, 130.38, 129.89, 128.68, 127.62, 126.91, 124.29, 61.61, 52.82, 32.98 ppm; MS (ESI): *m/z* 371 $[M+H]^+$; Anal. calcd for $C_{18}H_{15}ClN_4OS.0.2H_2O$: C, 57.73; H, 4.15; N, 14.96; S, 8.56. Found: C, 57.92; H, 4.43; N, 14.61, S, 8.54.

3-(4-(1*H*-1,2,4-Triazol-1-yl)phenyl)-2-(4-bromophenyl)thiazolidin-4-one (4g). Yellow solid; m. p. 128°C. IR ($CHCl_3$): υ = 1686, 1521, 1489, 1375, 1278, 1144, 1071, 1051, 1009, 982, 954, 835, 771, 673, 567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H, ArH), 8.07 (s, 1H, ArH), 7.62 (dd, J_1 = 6.88 Hz, J_2 = 2.28 Hz, 2H, ArH), 7.44 (dd, J_1 = 6.64 Hz, J_2 = 2.08 Hz, 2H, ArH), 7.33 (dd, J_1 = 6.88 Hz, J_2 = 2.08 Hz, 2H, ArH), 7.19 (dd, J_1 = 6.63 Hz, J_2 = 1.84 Hz, 2H, ArH), 6.12 (s, 1H, CH), 3.98 (dd, J_1 = 15.9 Hz, J_2 = 1.6 Hz, 1H, CH_2), 3.90 (dd, J_1 = 15.8 Hz, J_2 = 0.68 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.03, 152.72, 140.99, 137.97, 136.97, 135.24, 132.31, 128.77, 126.63, 123.25, 120.60, 64.65, 35.51 ppm; MS (ESI): *m/z* 401 $[M]^+$; Anal. calcd for $C_{17}H_{13}BrN_4OS.0.51H_2O$: C, 49.74; H, 3.44; N, 13.65; S, 7.81. Found: C, 50.11; H, 3.66; N, 13.25; S, 7.63.

3-(4-((1*H*-Imidazol-1-yl)methyl)phenyl)-2-(2-(trifluoromethyl)phenyl)thiazolidin-4-one (4h). Gummy yellow solid; IR ($CHCl_3$): υ = 1693, 1608, 1515, 1455, 1392, 1313, 1271, 1232, 1165, 1118, 1059, 1038, 906, 816, 761, 724, 662, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.04 Hz, 1H, ArH), 7.56–7.54 (m, 2H, ArH), 7.47 (s, 1H, ArH), 7.38–7.37 (m, 1H, ArH), 7.27–7.25 (m, 2H, ArH), 7.06–7.04 (m, 3H, ArH), 6.83 (s, 1H, ArH), 6.55 (s, 1H, CH), 5.03 (s, 2H, CH_2), 3.99 (dd, J_1 = 16.1 Hz, J_2 = 1.32 Hz, 1H, CH_2), 3.86 (d, *J* = 16.1 Hz, 1H, CH_2) ppm; MS (ESI): *m/z* 404 $[M+H]^+$.

3-(4-(1*H*-Imidazol-1-yl)phenyl)-2-phenylthiazolidin-4-one (4i). Yellow solid; m.p. 136°C. IR ($CHCl_3$): υ = 1688, 1682, 1607, 1520, 1490, 1456, 1431, 1382, 1344, 1303, 1265, 1247, 1219, 1178, 1131, 1111, 1074, 1056, 1029, 964, 904, 838, 816, 743, 700, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1H, ArH), 7.32–7.30 (m, 9H, ArH), 7.17 (d, *J* = 8.24 Hz, 2H, ArH), 6.12 (s, 1H, CH), 4.00 (dd, J_1 = 15.91 Hz, J_2 = 1.37 Hz, 1H, CH_2), 3.89 (dd, J_1 = 15.9 Hz, J_2 = 0.69 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.69, 138.61, 136.08, 134.93, 130.01, 128.68, 128.60, 126.50, 126.30, 121.25, 117.55, 64.73, 32.98 ppm; MS (ESI): *m/z* 322 $[M+H]^+$; Anal calcd for $C_{18}H_{15}N_3OS.0.25H_2O$: C, 66.34; H, 4.79; N, 12.89; S, 9.84. Found: C, 66.55; H, 4.75; N, 12.73; S, 10.13.

3-(4-(1*H*-Imidazol-1-yl)phenyl)-2-(4-bromophenyl)thiazolidin-4-one (4j). Light yellow solid; m.p. 126°C. IR ($CHCl_3$): υ = 1688, 1520, 1488, 1409, 1379, 1303, 1263, 1247, 1218, 1111, 1071, 1056, 1010, 964, 904, 834, 799, 756, 681, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1H, ArH), 7.45 (dd, J_1 = 6.53 Hz, J_2 = 1.83 Hz, 2H, ArH), 7.33–7.28 (m, 4H, ArH), 7.21–7.17 (m, 4H, ArH), 6.10 (s, 1H, CH), 3.98 (dd, J_1 = 15.9 Hz, J_2 = 1.37 Hz, 1H, CH_2), 3.89 (dd, J_1 = 16.0 Hz, J_2 = 0.69 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.87, 137.86, 136.18, 135.56, 135.27, 132.11, 130.37, 128.52, 126.65, 123.02, 121.89, 117.92, 64.50, 33.24 ppm; MS (ESI): *m/z* 400 $[M]^+$; Anal calcd for $C_{18}H_{14}BrN_3OS.0.4H_2O$: C, 53.05; H, 3.66; N, 10.31; S, 7.87. Found: C, 53.10; H, 3.68; N, 9.98; S, 7.89.

3-(4-Morpholinophenyl)-2-phenylthiazolidin-4-one (4k). Pale yellow solid; m. p. 186°C. IR ($CHCl_3$): υ = 1682, 1608, 1516, 1450, 1379, 1341, 1303, 1263, 1234, 1176, 1121, 1072, 1051, 1029, 930, 826, 805, 786, 752, 705, 697, 657, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 5H, ArH), 7.01 (dd, J_1 = 6.88 Hz, J_2 = 1.84 Hz, 2H, ArH), 6.77 (dd, J_1 = 7.09 Hz, J_2 = 1.84 Hz, 2H, ArH), 5.98 (d, *J* = 1.84 Hz, 1H, CH), 3.99 (dd, J_1 = 16.0 Hz, J_2 = 1.84 Hz, 1H, CH_2), 3.86(d, *J* = 16.0 Hz, 1H, CH_2), 3.79 (t, *J* = 5.0 Hz, 4H, morpholine), 3.08 (t, *J* = 5.0 Hz, 4H, morpholine) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.19, 150.09, 129.26, 128.97, 127.08, 126.96, 115.79, 66.83, 65.99, 65.83, 48.90, 33.44

ppm; MS (ESI): *m/z* 341 $[M+H]^+$; Anal. calcd for $C_{19}H_{20}N_2O_2S.0.15H_2O$: C, 66.50; H, 5.96; N, 8.16; S, 9.34. Found: C, 66.26; H, 5.75; N, 7.96; S, 9.83.

2-(4-Fluorophenyl)-3-(4-morpholinophenyl)thiazolidin-4-one (4l). Yellow solid; m.p. 132°C. IR ($CHCl_3$): υ = 1684, 1605, 1515, 1450, 1428, 1378, 1334, 1304, 1263, 1234, 1176, 1157, 1121, 1095, 1070, 1051, 1030, 1013, 930, 846, 826, 790, 754, 695, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2H, ArH), 6.99–6.94 (m, 4H, ArH), 6.77 (dd, J_1 = 6.87 Hz, J_2 = 2.29 Hz, 2H, ArH), 5.97 (d, *J* = 1.37 Hz, 1H, CH), 3.96 (dd, J_1 = 15.8 Hz, J_2 = 1.83 Hz, 1H, CH_2), 3.87 (d, *J* = 15.8 Hz, 1H, CH_2), 3.80 (t, *J* = 4.58 Hz, 4H, morpholine), 3.09 (t, *J* = 4.81 Hz, 4H, morpholine) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.82, 149.99, 129.11, 129.03, 128.66, 126.97, 115.77, 115.6, 115.55, 65.59, 65.06, 48.60, 33.24 ppm; MS (ESI): *m/z* 359 $[M+H]^+$; Anal. calcd for $C_{19}H_{19}FN_2O_2S$: C, 63.66; H, 5.31; N, 7.62; S, 8.68. Found: C, 63.67; H, 5.34; N, 7.82; S, 8.95.

3-(4-Morpholinophenyl)-2-(2-(trifluoromethyl)phenyl)thiazolidin-4-one (4m). White solid; m.p. 206°C. IR ($CHCl_3$): υ = 1690, 1608, 1516, 1451, 1382, 1337, 1313, 1264, 1234, 1165, 1118, 1059, 1038, 931, 826, 805, 790, 765, 654, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.72 Hz, 1H, ArH), 7.57 (d, *J* = 7.72 Hz, 2H, ArH), 7.37–7.33 (m, 1H, ArH), 7.12 (dd, J_1 = 6.72 Hz, J_2 = 2.01 Hz, 2H, ArH), 6.78 (dd, J_1 = 6.72 Hz, J_2 = 2.01 Hz, 2H, ArH), 6.49 (s, 1H, CH), 3.99 (dd, J_1 = 15.7 Hz, J_2 = 1.68 Hz, 1H, CH_2), 3.86 (d, *J* = 15.7 Hz, 1H, CH_2), 3.79 (t, *J* = 4.70 Hz, 4H, morpholine), 3.08 (t, *J* = 4.70 Hz, 4H, morpholine) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.16, 149.86, 139.38, 132.75, 128.75, 128.47, 127.60, 127.26, 126.97, 126.26, 125.94, 115.62, 66.70, 60.20, 48.68, 32.97 ppm; MS (ESI): *m/z* 409 $[M+H]^+$; Anal. calcd for $C_{20}H_{19}F_3N_2O_2S$. $0.3H_2O$: C, 58.04; H, 4.77; N, 6.77; S, 7.75. Found: C, 57.94; H, 4.48; N, 6.54; S, 7.69.

4-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (6a). Gummy brown matter; IR ($CHCl_3$): υ = 1679, 1609, 1512, 1447, 1418, 1377, 1338, 1270, 1224, 1136, 1016, 956, 906, 854, 746, 698, 677, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H, ArH), 8.00 (s, 1H, ArH), 7.32 (dd, J_1 = 6.41 Hz, J_2 = 2.06 Hz, 2H, ArH), 7.16 (dd, J_1 = 6.41 Hz, J_2 = 2.06 Hz, 2H, ArH), 5.39 (s, 2H, CH_2-Ph), 3.67 (s, 2H, CH_2), 1.98–1.95 (m, 2H, cyclohexane), 1.73–1.56 (m, 8H, cyclohexane) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.92, 152.13, 143.27, 136.52, 135.42, 130.86, 128.61, 74.08, 52.63, 38.92, 31.43, 23.98, 23.25 ppm; MS (ESI): *m/z* 328 $[M]^+$.

4-(4(1*H*-1,2,4-Triazol-1-yl)phenyl)-1-thia-4-azaspiro[4.5]-decan-3-one (6b). Light brown solid; m.p. 132°C. IR ($CHCl_3$): υ = 1681, 1607, 1521, 1450, 1380, 1335, 1278, 1216, 1145, 1050, 1011, 982, 954, 843, 794, 754, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H, ArH), 8.13 (s, 1H, ArH), 7.78 (dd, J_1 = 6.64 Hz, J_2 = 2.06 Hz, 2H, ArH), 7.32 (dd, J_1 = 6.64 Hz, J_2 = 2.06 Hz, 2H, ArH), 3.70 (s, 2H, CH_2), 2.03–2.01 (m, 2H, cyclohexane), 1.77–1.59 (m, 8H, cyclohexane) ppm; MS (ESI): *m/z* 315 $[M+H]^+$.

4-(4-(1*H*-Imidazol-1-yl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (6c). Gummy brown matter; IR ($CHCl_3$): υ = 1677, 1605, 1542, 1521, 1449, 1382, 1335, 1305, 1247, 1128, 1057, 1011, 963, 904, 842, 752, 659, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 0.69 Hz, 1H, ArH), 7.49 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.30–7.28 (m, 3H, ArH), 7.23 (d, *J* = 0.92, 1H, ArH), 3.70 (s, 2H, CH_2), 2.03–2.01 (m, 2H, cyclohexane), 1.78–1.60 (m, 8H, cyclohexane) ppm; MS (ESI): *m/z* 313 $[M]^+$.

4-(4-Morpholinophenyl)-1-thia-4-azaspiro[4.5]-decan-3-one (6d). White solid; m. p. 190°C. IR ($CHCl_3$): υ = 1682, 1607, 1515, 1449, 1377, 1334, 1303, 1261, 1230, 1122, 1069, 1052, 930, 904, 822, 753, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 9.08 Hz, 2H, ArH), 6.93 (d, *J* = 9.08 Hz, 2H, ArH), 3.85 (t, *J* = 4.7 Hz, 4H, morpholine), 3.66 (s, 2H, CH_2), 3.20 (t, *J* = 5.0 Hz, 4H, morpholine), 1.96–1.93 (m, 2H, cyclohexane), 1.74–1.58 (m, 8H, cyclohexane) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.11, 151.21, 131.02, 127.64, 115.75, 74.20, 66.87, 48.76, 39.15, 31.60, 24.37, 23.53 ppm; MS (ESI) *m/z* 333 $[M+H]^+$; Anal calcd for $C_{18}H_{24}N_2O_2S.0.1H_2O$: C, 64.68; H, 7.30; N, 8.38; S, 9.59. Found: C, 64.37; H, 6.94; N, 8.22; S, 9.96.

CONCLUSION

In conclusion, we have developed a simple, convenient, and inexpensive procedure for the synthesis of novel 4-thiazolidinones in good to excellent yields via three-component domino reaction using PPG as a solvent medium. It is important to mention that this methodology does not require any catalyst and other additives.

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