The First One-Pot, Solvent-Free, Microwave-Accelerated, Three-Component Synthesis of Spirothiazolidin-4-ones *via Staudinger*/Aza-*Wittig* Coupling/Cyclization

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An efficient and rapid, solvent-free, microwave-accelerated, one-pot, three-component protocol for the synthesis of spirothiazolidin-4-ones from organic azides is reported for the first time *via Staudinger*/aza-*Wittig* coupling/cyclization. The solvent-free approach overcomes the limitations associated with the prevailing solution-phase methodologies in the case of amines. In particular, its novelty is that it eradicates the vital limitation, *i.e.*, the accumulation of H_2O (by-product), which is known to affect the yield and rate of the reaction, thus affording the spirothiazolidin-4-ones in short reaction times in excellent yields.

Introduction. – Spirocyclic compounds are of recent interest due to their interesting bioactivity profiles [1–4]. On the other hand, syntheses of spirothiazolidinones have received interest and attention from a large number of organic chemists, pharmacologists, and biologists, due to their significant biological activities associated with the thiazolidinone nucleus [5]. Consequently, focus is directed towards the development of elegant and environmentally friendly protocols for the synthesis of spirothiazolidinones.

Of the most frequently used methodologies for the synthesis of spirothiazolidin-4-ones, the well-documented solution-phase protocol [6–10], involves the three-component reactions of an amine, a ketone, and 2-sulfanylacetic acid, wherein condensation of the amine with the ketone affords the imine, which reacts with 2-sulfanylacetic acid to give the desired product. The solution-phase methodologies are not environmentally benign as they are associated with the hazards due to the organic solvents. The vital drawback in the solution phase protocol of the synthesis of thiazolidin-4-ones is the accumulation of H_2O (formed as by-product), which is known to affect the rate of the reaction and yield of the product; hence, the azeotropic removal of H_2O is required.

Thus, the azeotropic removal of H_2O has been reported to be crucial for obtaining high yields of thiazolidin-4-ones starting from amines. Alternatively, desiccants such as molecular sieves, anhydrous $ZnCl_2$ [11], Na_2SO_4 [12], *N*,*N*-dicyclohexylcarbodiimide (DCC) [6], or 2-(1*H*-benzotriazoyl)-1,1,3,3-tetramethyl uronium hexafluorophospate (HBTU) [13] have been used to accelerate the reaction. Additionally, use of condensation agents [6][14], microwave irradiation [15], *Lewis* acids or bases [9],

and ionic liquids [16] had resulted in improved yields of thiazolidin-4-ones. Consequently, search for a protocol, which would overcome the above mentioned limitations, is desirable.

Results and Discussion. – It was planned to elaborate an environmentally friendly solvent-free synthesis of spirothiazolidin-4-ones *via Staudinger*/aza-*Wittig* reaction, which is known to be a powerful tool in synthetic strategies towards *N*-containing heterocycles [17], wherein azides are used as nitrogen source instead of amines. So far, no report is known involving azides as starting material towards the synthesis of spirothiazolidin-4-ones.

Recently, we have also reported the advantages of switching from a solution-phase to a solvent-free methodology to achieve efficient and rapid syntheses of amides [18], thioamides [19], and cyclic imides [20] under solvent-free conditions. In continuation of this, we attempted at the three-component synthesis of spirothiazolidin-4-ones under solvent-free conditions, which would decrease the accumulation of H_2O (eliminated during the course of the reaction) in two ways *viz*. *i*) no azeotrope formation and *ii*) the microwave heating resulting in spontaneous vaporization of H_2O.

At the outset, the one-pot, three-component synthesis of spirothiazolidin-4-one was attempted (*Scheme 1*) in various solvents and under solvent-free conditions. A mixture of (azidomethyl)benzene (**1a**; 1 equiv.), Ph_3P (1.1 equiv.), cyclohexanone (**2a**; 1.0 equiv.), and 2-sulfanylacetic acid (**3**; 1.1 equiv.) was heated to reflux in various solvents, which took around 3–7 h (*Table 1*, *Entries 1–5*) for completion to afford 60–84% of spirothiazolidin-4-one **4a**.

Scheme 1. *Synthesis of Spirothiazolidin-4-one* **4a**

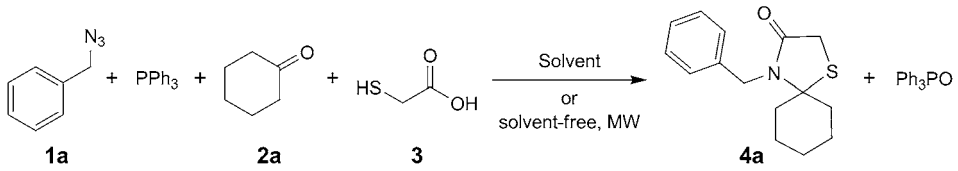


Table 1. *Optimization for the Synthesis of Spirothiazolidin-4-one* **4a**

Entry	Solvent	Reaction conditions	
		Time [h]	Yield[a]) [%]
1	THF	7	60
2	MeCN	6	72
3	Benzene	6	80
4	Toluene	4	82
5	Xylene	3	84
6	Solvent-free	15 min[b])	96

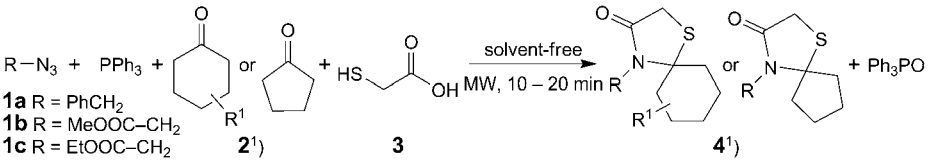
[a]) Yield of isolated product. [b]) Microwave irradiation (150°, 80 W).

From solvent screening, it is evident that in high-boiling solvents with relatively low polarity, *viz*. toluene and xylene (*Table 1*, *Entries 4* and *5*), the reaction was rapid and completed within 3–4 h. Based on this, it was envisaged that higher reaction

temperatures could be obtained in absence of solvent, and the reaction rate may be further accelerated by using microwave irradiation. Indeed, under microwave-assisted solvent-free condition resulted in a prominent increase in the rate of the reaction and **4a** was obtained in an excellent yield (96%) in just 15 min (*Table 1*, *Entry 6*).

Having optimized the reaction conditions, this convenient synthesis was used to prepare a library of compounds **4** (*Scheme 2*). The synthesis involves the *in situ* formation of imines *via* aza-*Wittig* reaction of nascent phosphazenes with cyclic ketones **2**, followed by the instantaneous reaction of the imine with 2-sulfanylacetic acid (**3**) to afford **4a**–**4l** in excellent yields (92–96%; *Table 2*[1]).

Scheme 2. *Synthesis of Spirothiazolidin-4-ones* **4**



The synthesized spirothiazolidin-4-ones **4a**–**4l** were characterized by IR, NMR (1D and 2D), and mass-spectral techniques. The ^{1}H-NMR spectrum of the representative compound **4d** showed a *singlet* at 4.62 ppm for two benzylic H-atoms (NCH_2Ph), and a *singlet* at 3.67 ppm for the SCH_2 and a *multiplet* at *ca.* 2.40 ppm for a CH group. In the ^{13}C-NMR spectrum of **4d**, the signal of a C=O group appeared at 171.7 ppm, those of two CH_2 C-atoms appeared at 45.2 ppm (NCH_2) and 31.3 ppm (SCH_2), respectively, four CH_2 groups absorbed at 30.9 and 38.3 ppm, and the signals of the CH group and of the quaternary C-atom appeared at 38.3 and 73.7 ppm, respectively. The IR spectrum showed the C=O band at 1662 cm^{-1}, and the HR-MS spectrum of **4d** exhibited the $[M+H]^+$ peak at m/z 338.1512.

Conclusions. – In conclusion, we have described the solvent-free synthesis of spirothiazolidin-4-ones by a microwave-accelerated, one-pot, three-component strategy *via Staudinger*/aza-*Wittig* coupling/cyclization, which is efficient, rapid, and environmentally benign. This protocol overcomes most of the limitations associated with the solution-phase methods.

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Experimental Part

General. All chemicals and solvents were of commercially high-purity grade purchased from *Avra Synthesis Pvt. Ltd.* and *Merck Pvt. Ltd.*, India. The org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. Column chromatography (CC): SiO_2 (60–120 mesh). ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$ on a *Bruker Avance 300* spectrometer; the chemical shifts (δ) in ppm

[1]) For R^1, see *Table 2*.

Table 2. *Microwave-Accelerated, Solvent-Free Synthesis of the Spirothiazolidin-4-ones* **4a** – **4l**

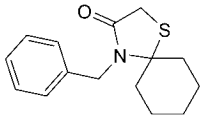
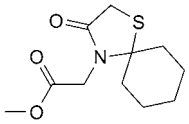
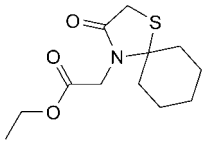
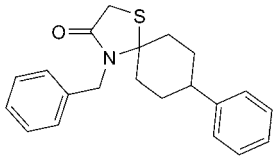
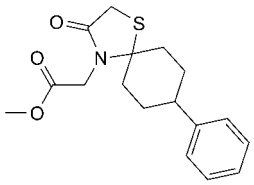
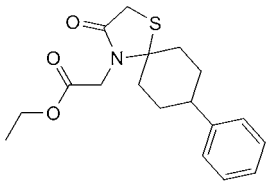
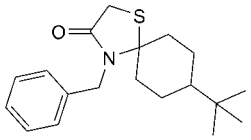
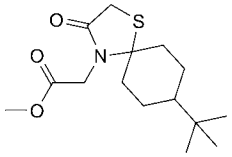
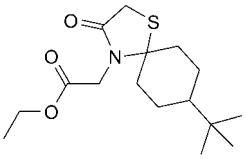
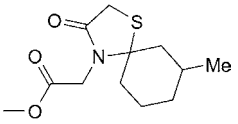
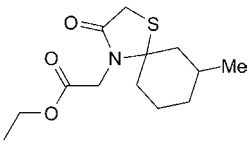
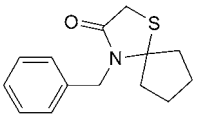
Entry	Azido compound	Ketone	Spirothiazolidin-4-ones	MW-Irradiation		
				Temp. [°]	Time [min]	Yield[a]) [%]
1	**1a**	Cyclohexanone (**2a**)	**4a** [6] 	150	10	96
2	**1b**	**2a**	**4b** 	150	15	96
3	**1c**	**2a**	**4c** 	150	20	96
4	**1a**	4-Phenylcyclohexanone (**2b**)	**4d** 	160	20	95
5	**1b**	**2b**	**4e** 	160	20	94
6	**1c**	**2b**	**4f** 	160	20	95
7	**1a**	4-(*tert*-Butyl)cyclohexanone (**2c**)	**4g** 	140	10	95
8	**1b**	**2c**	**4h** 	140	10	95

Table 2 (cont.)

Entry	Azido compound	Ketone	Spirothiazolidin-4-ones		MW-Irradiation		
					Temp. [°]	Time [min]	Yield[a]) [%]
9	**1c**	**2c**	**4i**		140	10	93
10	**1b**	3-Methylcyclohexanone (**2d**)	**4j**		160	20	94
11	**1c**	**2d**	**4k**		160	20	94
12	**1a**	Cyclopentanone (**2e**)	**4l** [21]		150	15	92

[a]) Yield of the isolated product.

rel. to TMS, *J* in Hz; ^{13}C-NMR data with respect to the solvent peak (δ ($CDCl_3$), 77.0 ppm) as the internal standard. HR-MS: *Bruker Maxis* instrument.

Preparation of Organic Azides. Azido compounds **1a** [22], **1b** [23], and **1c** [24] were prepared according to the previously reported procedures.

General Procedure for the Synthesis of Spirothiazolidin-4-ones **4a**–**4l**. To a well ground intimate mixture of Ph_3P (1.1 equiv.) and ketone **2** (1.0 equiv.) in a microwave vial (10 ml), equipped with a magnetic stirring bar, the azido compound **1** (0.2 g, 1.0 equiv.) was added dropwise while stirring. Stirring was continued until liberation of N_2 ceased, and *2-sulfanylacetic acid* (**3**; 1.1 equiv.) was added to the above mixture, and the reaction vessel was sealed with a septum. It was then placed into the cavity of a focused monomode microwave reactor (*CEM Discover Bench Mate*) and operated at 120–140° (temp. monitored by a built-in IR sensor); power, 80 W for 10–20 min. The reaction temp. was maintained by modulating the power level of the reactor. Then, the mixture was allowed to stand at r.t., and the residue was purified by CC (SiO_2; petroleum ether/AcOEt 97:3) to afford **4a**–**4l** in 92–96% yield. Compounds **4a** [6] and **4l** [21] are known.

Methyl 2-(3-Oxo-1-thia-4-azaspiro[4.5]dec-4-yl)acetate (**4b**). Yield: 0.40 g (96%). Gummy matter. IR (KBr): 1751 (O–C=O), 1683 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18–1.96 (*m*, 10 H); 3.50 (*s*, 2 H); 3.67 (*s*, 3 H); 3.96 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.3; 168.8; 73.0; 52.2; 42.8; 38.0; 30.8; 24.3; 23.1. HR-MS: 244.0935 ($[M+H]^+$, $C_{11}H_{18}NO_3S^+$; calc. 244.0912).

Ethyl 2-(3-Oxo-1-thia-4-azaspiro[4.5]dec-4-yl)acetate (**4c**). Yield: 0.38 g (96%). Gummy matter. IR (KBr): 1751 (O–C=O), 1693 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23 (*t*, $J = 6.9$, 3 H); 1.53–1.87 (*m*, 10 H); 3.96 (*s*, 2 H); 3.52 (*s*, 2 H); 4.14 (*q*, $J = 6.9$, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4; 168.3; 73.1; 61.4; 43.0; 38.0; 30.8; 24.3; 23.1; 14.0. HR-MS: 258.1097 ($[M+H]^+$, $C_{12}H_{20}NO_3S^+$; calc. 258.1086).

4-Benzyl-8-phenyl-1-thia-4-azaspiro[4.5]decan-3-one (**4d**). Yield: 0.48 g (95%). White solid. M.p. 130–131°. IR (KBr): 1662 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.94–2.03 (*m*, 8 H); 3.67 (*s*, 2 H); 2.30–2.55 (*m*, 1 H); 4.62 (*s*, 2 H); 7.12–7.30 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.7; 145.5; 137.9; 128.5; 128.4; 127.3; 127.0; 126.6; 126.3; 73.7; 45.2; 42.6; 38.3; 31.3; 30.9. HR-MS: 338.1512 ($[M+H]^+$, $C_{21}H_{24}NOS^+$; calc. 338.1500).

Methyl 2-(3-Oxo-8-phenyl-1-thia-4-azaspiro[4.5]dec-4-yl)acetate (**4e**). Yield: 0.52 g (94%). White solid. M.p. 160–161°. IR (KBr): 1765 (O–C=O), 1683 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.85–2.02 (*m*, 8 H); 3.63 (*s*, 2 H); 2.35–2.55 (*m*, 1 H); 3.77 (*s*, 3 H); 4.08 (*s*, 2 H); 7.22–7.33 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4; 168.9; 145.3; 128.4; 126.6; 126.4; 72.5; 52.4; 42.9; 42.6; 38.1; 31.0; 30.7. HR-MS: 320.1221 ($[M+H]^+$, $C_{17}H_{28}NOS^+$; calc. 320.1242).

Ethyl 2-(3-Oxo-8-phenyl-1-thia-4-azaspiro[4.5]dec-4-yl)acetate (**4f**). Yield: 0.46 g (95%). White solid. M.p. 109–110°. IR (KBr): 1762 (O–C=O), 1677 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29 (*t*, $J = 6.9$, 3 H); 1.85–2.02 (*m*, 8 H); 2.35–2.65 (*m*, 1 H); 3.63 (*s*, 2 H); 4.06 (*s*, 2 H); 4.14 (*q*, $J = 6.9$, 2 H); 7.22–7.35 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4; 168.4; 145.4; 128.5; 126.7; 126.4; 72.6; 61.6; 43.1; 42.6; 38.2; 31.0; 30.8; 14.1. HR-MS: 334.1409 ($[M+H]^+$, $C_{18}H_{24}NO_3S^+$; calc. 334.1399).

*4-Benzyl-8-(*tert*-butyl)-1-thia-4-azaspiro[4.5]decan-3-one* (**4g**). Yield: 0.53 g (95%). Gummy matter. IR (KBr): 1660 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83 (*s*, 9 H); 1.32–1.80 (*m*, 8 H); 3.62 (*s*, 2 H); 4.56 (*s*, 2 H); 7.26–7.33 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.8; 138.0; 128.5; 127.2; 127.0; 74.3; 46.6; 45.1; 38.4; 32.2; 31.3; 27.4; 24.3. HR-MS: 318.1842 ($[M+H]^+$, $C_{19}H_{22}NOS^+$; calc. 318.1813).

*Methyl 2-[8-(*tert*-Butyl)-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl]acetate* (**4h**). Yield: 0.49 g (95%). Gummy matter. IR (KBr): 1762 (O–C=O), 1677 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86 (*s*, 9 H); 1.25–1.96 (*m*, 9 H); 3.58 (*s*, 2 H); 3.75 (*s*, 3 H); 4.02 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.5; 169.0; 73.1; 52.4; 46.6; 42.9; 38.3; 32.3; 31.0; 27.5; 24.2. HR-MS: 300.1572 ($[M+H]^+$, $C_{15}H_{26}NO_3S^+$; calc. 300.1555).

*Ethyl 2-[8-(*tert*-Butyl)-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl]acetate* (**4i**). Yield: 0.39 g (93%). Gummy matter. IR (KBr): 1760 (O–C=O), 1671 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.87 (*s*, 9 H); 1.28 (*t*, $J = 7.2$, 3 H); 1.33–1.97 (*m*, 8 H); 3.58 (*s*, 2 H); 4.00 (*s*, 2 H); 4.20 (*q*, $J = 7.2$, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4; 168.3; 73.1; 61.3; 46.4; 42.9; 38.2; 32.1; 30.8; 27.3; 24.0; 14.0. HR-MS: 314.1728 ($[M+H]^+$, $C_{16}H_{28}NO_3S^+$; calc. 314.1712).

Methyl 2-(7-Methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)acetate (**4j**). Yield: 0.42 g (94%). Gummy matter. IR (KBr): 1760 (O–C=O), 1665 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, $J = 6.3$, 3 H); 1.25–1.90 (*m*, 9 H); 3.58 (*s*, 2 H); 3.75 (*s*, 3 H); 4.02 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4; 168.9; 73.1; 52.3; 46.3; 42.8; 37.5; 33.2; 30.2; 29.8; 22.7; 22.0. HR-MS: 258.1121 ($[M+H]^+$, $C_{12}H_{20}NO_3S^+$; calc. 258.1086).

Ethyl 2-(7-Methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)acetate (**4k**). Yield: 0.35 g (94%). Gummy matter. IR (KBr): 1768 (O–C=O), 1663 (N–C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93 (*d*, $J = 6.6$, 3 H); 1.28 (*t*, $J = 6.9$, 3 H); 1.59–1.90 (*m*, 9 H); 3.58 (*s*, 2 H); 4.00 (*s*, 2 H); 4.20 (*q*, $J = 6.9$, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.1; 168.1; 72.9; 61.1; 46.1; 42.8; 37.3; 32.1; 30.9; 27.3; 22.5; 21.8; 13.8. HR-MS: 272.1228 ($[M+H]^+$, $C_{13}H_{22}NO_3S^+$; calc. 272.1242).

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