Three-component solvent-free diastereoselective formation of oxo-thiazolidinylthiazoles under microwave irradiation

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The one-pot diastereoselective cyclisation of 4,4'-bis(2"-aminothiazol-4"-yl)bibenzyl to 4,4'-bis[2"-(2"'-aryl-5"'-methyl/carboxymethyl-4"'-thiazolidinon-3"'-yl)thiazol-4"-yl]bibenzyls, in high yields (85-96%) under the influence of microwave radiation, is described.

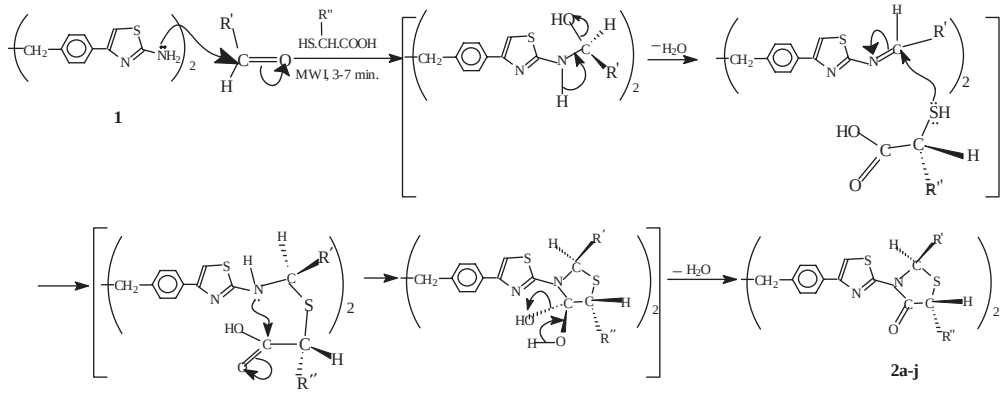
Keywords: thiazolidin-4-ones, thiazoles, bibenzyls

Thiazole,[1] thiazolidinone[2] and bibenzyl[3] analogues are of interest because of their biological activities. These compounds have been synthesised by different methods using a variety of reagents.[4] Most of these processes suffer from drawbacks such as extended reaction times, and the use of toxic solvents and corrosive substances that generate undesirable waste materials. Consequently, there is a need for the development of a manipulatively easy, high yielding and environmentally benign solvent-free protocol for organic synthesis. One-pot organic reactions assisted by microwave, especially under solvent-free conditions, have attracted attention recently because of their association with milder reaction conditions, enhanced yields, reduction in reaction times[5] and ease of manipulation and being environmentally benign.

Rational approaches involving the consolidation of multi-step procedures into a one-pot, single-step process has environmental advantage because it decreases or eliminates the generation of hazardous substances. *In situ* generation followed by consumption of toxic intermediates which may be formed in the process enables their complete isolation from the environment.

In continuation of our work on the synthesis of bibenzyl analogues,[6] we report herein a one-pot, microwave-assisted, solvent-free, diastereoselective synthesis of 4-oxothiazolidine-5-acetic acids and thiazolidin-4-ones. After some preliminary experimentation it was found that the synthesis of 4,4′-bis[2"-(2"'-aryl-5"'-methyl/carboxymethyl-4"'-oxothiazolidin-3"'-yl) thiazol-4"-yl]bibenzyls **2a–j** under microwave irradiation was successful in high yields (85–96%) (Scheme 1). A mixture of the bis-aminothiazole **1**, an aromatic aldehyde (benzaldehyde/anisaldehyde/veratraldehyde/*p*-chlorobenzaldehyde/*p*-nitrobenzaldehyde) and 2-mercaptopropionic acid/2-mercaptosuccinic acid in one-pot was irradiated for 3–7 min. Nucleophilic addition of **1** on carbonyl carbon followed by dehydration produced Schiff base *in situ* which on nucleophilic addition on carbon of C=N bond with the –SH group of 2-mercaptopropionic acid or 2-mercaptosuccinic acid, followed by intramolecular amide formation onto the carboxylic group of the thioacid yielded **2a–j**. Although the resulting product could have been formed as diastereomeric pairs we could not separate the products into diastereomers. It seems that *cis*-isomers, if formed, probably isomerised into more stable *trans*-products. The ^{1}H NMR spectra of the products showed distinct doublets at *ca* δ 1.50 (d, 6H, *J* = 8 Hz) for $C_{5'''}$-CH_3 (**2a–e**) and distinct doublets at *ca* δ 2.72 (d, 4H, *J* = 7 Hz) for $C_{5'''}$-CH_2COOH (**2f–j**) of thiazolidinone ring, and singlets at *ca* δ 3.10 for $C_{2'''}$-H, so the diastereomers obtained were assigned the *trans* configuration.[6-8]

An integrated chemical process has proved to be effective for realising a multi-step one-pot, solvent-free synthesis enabling isolation of an intermediate from the environment through *in situ* generation followed by consumption. In summary, we have devised a method for one-pot expeditious, diastereoselective synthesis of heteryl analogues of fungitoxic bibenzyls employing microwave technique in solvent-free conditions, which may find application in organic syntheses.



Compd.	R'	R"	Compd.	R'	R"
2a	C_6H_5	CH_3	**2f**	C_6H_5	CH_2COOH
2b	4-$CH_3OC_6H_4$	CH_3	**2g**	4-$CH_3OC_6H_4$	CH_2COOH
2c	3,4-$(CH_3O)_2C_6H_4$	CH_3	**2h**	3,4-$(CH_3O)_2C_6H_4$	CH_2COOH
2d	4-ClC_6H_4	CH_3	**2i**	4-ClC_6H_4	CH_2COOH
2e	4-$O_2NC_6H_4$	CH_3	**2j**	4-$O_2NC_6H_4$	CH_2COOH

Scheme 1 One-pot diastereoselective synthesis of 2-(4-oxothiazolidin-3-yl)thiazoles **2a–j**.

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Experimental

All commercially available reagents were used without further purification. ^{1}H NMR spectra were recorded on a Bruker WM-40C (400 MHz) FT spectrometer in $CDCl_3$ using TMS as an internal reference. Mass-spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were performed by a Perkin-Elmer series C, H, N, S analyzer 2400.

The antifungal activity of the compounds of the type **2a–j** were determined against *Fusarium oxysporum* and *Penicillium citrinum* at 1000, 100 and 10 ppm concentration by agar-growth technique[9] using Czapek's agar medium as described.[6,10] The number of replicate assays in each were three, and six replicate controls were used. A standard commercial fungicide, Dithane M-45 [a mixed Mn^{2+} and zinc salt of *N,N*-ethylenebis(dithiocarbamic acid)] was also tested under similar conditions. All the tested compounds were found to be active antifungals but amongst them **2d**, **2e** and **2j** were most active, showing antifungal activity comparable with Dithane M-45.

4,4′-Bis(2"-aminothiazol-4"-yl)bibenzyl (**1**): 4,4′-Diacetylbibenzyl (13.3 g, 50 mmole), thiourea (6.2 g, 100 mmole) and iodine (25.4 g, 100 mmole) were mixed with a few drops of 1,4-dioxan and heated on a water bath for 3 h. The mass obtained was washed with ice-cold water, extracted with hot water and filtered. The filtrate was treated with dilute ammonia to give **1**, which is filtered off and crystallised with ethanol to furnish analytically pure **1** (16.0 g, 85%), m.p. 191 °C. MS: *m/z* 378 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.85 (s, 4H, acyclic CH_2CH_2), 7.2–8.0 (m, 10H, ArH, aryl and thiazole), 5.24 (4H, s, NH_2); Anal. Calc. for $C_{20}H_{18}N_4S_2$: C, 63.46; H, 4.79; N, 14.80; S, 16.94; Found: C, 63.39; H, 4.77; N, 14.82; S, 16.90 %.

4,4′-Bis[2"-(2"'-aryl-5"'-methyl/carboxymethyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2a–j**): Compound **1** (5.0 mmol) aromatic aldehyde (10.0 mmol) (benzaldehyde/anisaldehyde/veratraldehyde/*p*-chlorobenzaldehyde/*p*-nitrobenzaldehyde) and 2-mercaptopropionic acid/2-mercaptosuccinic acid (10.0 mmol) were adsorbed on neutral alumina support (150 mesh) and exposed to microwave irradiation operating at medium power (600 W). After every 30 sec. the heating was stopped and the reaction was monitored by TLC; it was found to be complete after 3–7 min. The reaction mixture was cooled to room temperature and eluted with methanol (3×10ml). The eluate was evaporated to dryness and washed with $NaHCO_3$ (3.0% w/v) and finally with cold H_2O, dried with anhyd. $MgSO_4$. The solvent (left in traces during drying) was removed under reduced pressure to obtain the crude product. The residue on purification by silica gel column chromatography (hexane–EtOAc, 8 : 2 v/v) furnished analytically pure compound **2**.

4,4′-Bis[2"-(2"'-phenyl-5"'-methyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2a**): m.p. 198 °C. MS *m/z* 730 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50 (d, *J* = 8 Hz, 6H, CH_3), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (q, *J* = 8 Hz, 2H, CO–CH–S), 7.22–8.01 (m, 20H, ArH, aryl and thiazole); Anal: calc. for $C_{40}H_{34}N_4O_2S_4$: C, 65.72; H, 4.68, N, 7.66; S, 17.54; Found: C, 65.70; H, 4.60; N, 7.65; S, 17.55 %.

4,4′-Bis[2"-(2"'-p-methoxyphenyl-5"'-methyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2b**): m.p. 225 °C. MS, *m/z*: 790 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50 (d, *J* = 8 Hz, 6H, CH_3), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (q, *J*=8 Hz, 2H, CO–CH–S), 4.13 (s, 6H, OCH_3), 7.22–8.01 (m, 18H, ArH, aryl and thiazole); Anal. Calc. for $C_{42}H_{38}N_4O_4S_4$: C, 63.77; H, 4.84; N, 7.08; S, 16.21; Found: C, 63.71; H, 4.81; N, 7.10; S, 16.18 %.

4,4′-Bis[2"-(2"'-(3,4-dimethoxyphenyl-5"'-methyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2c**): m.p. 229 °C. MS, *m/z*: 850 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50 (d, *J* = 8 Hz, 6H, CH_3), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (q, *J* = 8 Hz, 2H, CO–CH–S), 4.13 (s, 6H, OCH_3), 4.15 (s, 6H, OCH_3), 7.22–8.01 (m, 16H, ArH, aryl and thiazole). Anal. Calc. for $C_{44}H_{42}N_4O_6S_4$: C, 62.09; H, 4.97; N, 6.58; S, 15.07; Found: C, 62.10; H, 4.98; N, 6.61; S, 15.12 %.

4,4′-Bis[2"-(2"'-p-chlorophenyl-5"'-methyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2d**): m.p. 210 °C. MS, *m/z*: 798 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50 (d, *J* = 8 Hz, 6H, CH_3), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (q, *J* = 8 Hz, 2H, CO-CH-S), 7.22–8.01 (m, 18H, ArH, aryl and thiazole); Anal. Calc. for $C_{40}H_{32}Cl_2N_4O_2S_4$: C, 60.06; H, 4.01; N, 7.00; S, 16.03; Found: C, 60.01; H, 4.00; N, 6.99; S, 15.91 %.

4,4′-Bis[2"-(2"'-p-nitrophenyl-5"'-methyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2e**): m.p. 199 °C. MS, *m/z*: 820 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50 (d, *J*=8 Hz, 6H, CH_3), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (q, *J* = 8 Hz, 2H, CO–CH–S), 7.22–8.01 (m, 18H, ArH, aryl and thiazole); Anal. Calc. for $C_{40}H_{32}N_6O_6S_4$: C, 58.51; H, 3.92; N, 10.23; S, 15.62; Found: C, 58.58; H, 3.90; N, 10.27; S, 15.59 %.

4,4′-Bis[2"-(2"'-phenyl-5"'-carboxymethyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2f**) m.p. 213 °C. MS, *m/z*: 818 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.72 (d, *J* = 7 Hz, 4H, CH_2COOH), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (t, *J* = 7 Hz, 2H, CO–CH–S), 7.22–8.01 (m, 20H, ArH, aryl and thiazole), 12.81 (s, 2H, COOH); Anal. Calc. for $C_{42}H_{34}N_4O_6S_4$: C, 61.59; H, 4.18; N, 6.84; S, 15.66; Found: C, 61.56; H, 4.10; N, 6.80; S, 15.69 %.

4,4′-Bis[2"-(2"'-p-methoxyphenyl-5"'-carboxymethyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2g**)**:** m.p. 232 °C. MS, *m/z*: 878 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.72 (d, *J* = 7 Hz, 4H, CH_2COOH), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (t, *J* = 7 Hz, 2H, CO–CH–S), 4.13 (s, 6H, OCH_3), 7.22–8.01 (m, 18H, ArH, aryl and thiazole), 12.81 (s, 2H, COOH); Anal. Calc. for $C_{44}H_{38}N_4O_8S_4$: C, 60.11; H, 4.35; N, 6.37; S, 14.59; Found: C, 60.12; H, 4.31; N, 6.36; S, 14.58 %.

4,4′-Bis[2"-(2"'-m,p-dimethoxyphenyl-5"'-carboxymethyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2h**): m.p.: 211 °C. MS, *m/z:* 938 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.72 (d, *J*=7 Hz, 4H, CH_2COOH), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (t, *J*=7 Hz, 2H, CO–CH–S), 4.13 (s, 6H, OCH_3), 4.15 (s, 6H, OCH_3), 7.22–8.01 (m, 16H, ArH, aryl and thiazole), 12.81 (s, 2H, COOH); Anal. Calc. for $C_{46}H_{42}N_4O_{10}S_4$: C, 58.83; H, 4.50; N, 5.96; S, 13.65; Found: 58.81; H, 4.52; N, 5.94; S, 13.63 %.

4,4′-Bis[2"-(2"'-p-chlorophenyl-5"'-carboxymethyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2i**): m.p. 218 °C. MS, *m/z*: 886 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.72 (d, 4H, *J*=7 Hz, CH_2COOH), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (t, *J*=7 Hz, 2H, CO–CH–S), 7.22–8.01 (m, 18H, ArH, aryl and thiazole), 12.81 (s, 2H, COOH); Anal. Calc. for $C_{42}H_{32}Cl_2N_4O_6S_4$: C, 56.81; H, 3.62; N, 6.30; S, 14.44; Found: C, 56.80; H, 3.63; N, 6.27; S, 14.42 %.

4,4′-Bis[2"-(2"'-p-nitrophenyl-5"'-carboxymethyl-4"'-oxothiazolidin-3"'-yl)thiazol-4"-yl]bibenzyl (**2j**): m.p. 205 °C. MS, *m/z*: 908 (M^+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.72 (d, *J* = 7 Hz, 4H, CH_2COOH), 2.85 (s, 4H, CH_2CH_2), 3.10 (s, 2H, Ar–C–H), 3.94 (t, *J* = 7 Hz, 2H, CO–CH–S), 7.22–8.01 (m, 18H, ArH, aryl and thiazole), 12.81 (s, 2H, COOH); Anal. Calc. for $C_{42}H_{32}N_6O_{10}S_4$: C, 55.49; H, 3.54; N, 9.24; S, 14.11; Found: C, 55.45; H, 3.55; N, 9.21; S, 14.10 %.

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