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Sulfamic acid-catalyzed, environmentally benign synthesis of bis-tetronic acids at ambient temperature

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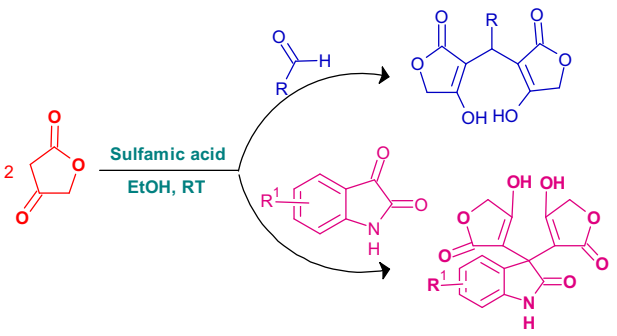
Abstract An enviro-economic protocol has been described for the synthesis of bis-tetronic acids by pseudo-three-component condensation between aldehydes/isatins and tetronic acid using sulfamic acid as a solid acid catalyst. Easy commercial availability of the catalyst at extremely low cost, excellent yields and avoidance of conventional purification procedures are the main merits of this energy efficient protocol.

Graphical Abstract



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Introduction

The main issue in the synthesis of complex organic molecules is currently aimed at improving efficiency, avoidance of toxic agents, reduction in waste and responsible utilization of natural sources [1–4]. In this context, the use of multicomponent reactions involving the participation of three or more substrates is of relevance from both economic and ecological points of view [5–9]. Like multicomponent reactions, domino reactions also constitute a powerful synthetic strategy to introduce chemical and structural complexity. Among domino reactions, Knoevenagel–Michael reactions have emerged as a powerful strategy in the synthesis of various oxa- as well as aza-heterocycles [10–13].

It is well known that Knoevenagel-initiated Domino reactions of aldehydes with active methylene compounds like dimedone, cyclohexane-1,3-dione, 4-hydroxycoumarin, Meldrum's acid, barbituric acid, pyrazolone, tetronic acid, etc., furnish biologically active organic compounds. For instance, 1-oxo-hexahydroxanthenes (Fig. 1A) results from the reaction between salicylaldehydes with two equivalents of cyclic-1,3-diones [14–20], while tetraketones (Fig. 1B) result from the reaction between the same diketones with aromatic aldehydes, devoid of the ortho-hydroxyl group [21–24]. Among these, 1-oxo-hexahydroxanthenes are known for their important pharmacological properties, such as anti-estrogenic, antimicrobial, hypoglycaemic, antibacterial and thrombin inhibitory activities and serve as

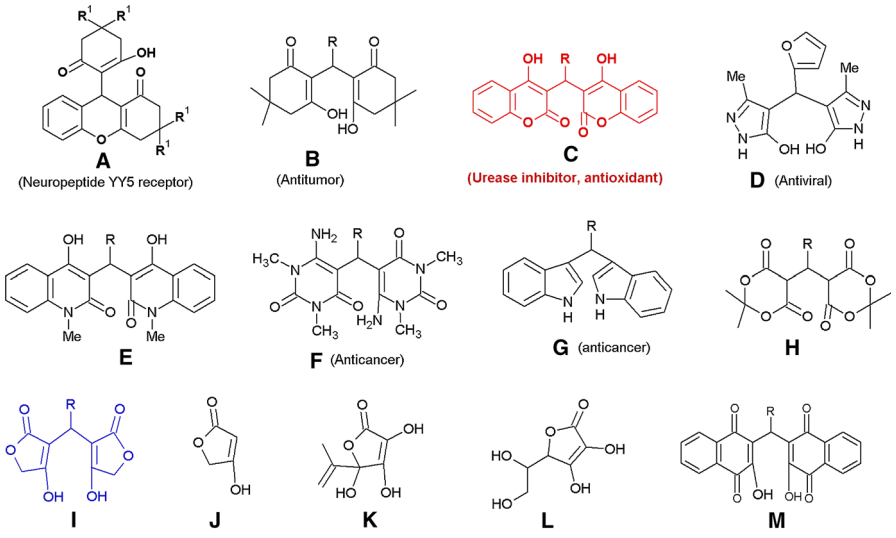


Fig. 1 Structures of representative biologically active molecules (**A**–**M**) of synthetic and natural origin

neuropeptide YY5 receptor antagonists [25–28], while tetraketones are known to possess antitumor activity [29–32]. On the other hand, bis-coumarins (Fig. 1C), which result from the reaction between aldehydes with two equivalents of 4-hydroxycoumarin, are known to act as urease inhibitor, anti-oxidant, polymerase β-lyase inhibitor, anticoagulant and snake venom NPP1 inhibitor [33–39], while bis-pyrazoles (Fig. 1D) are known to exhibit antibacterial, antidepressant and antifilarial activities [40–42]. The molecules containing quinolone as well as uracil as the structural motif are known to exhibit important biological activities. For instance, bis-*N*-methyl-4-hydroxyquinolones (Fig. 1E) and bis-uracils (Fig. 1F) are known to exhibit antibacterial as well as anticancer activities [43–47]. Indoles are conventionally not regarded as active methylene compounds. However, they can also undergo reactions with aldehydes to furnish bis-indolylalkanes, among which Vibrindole-A, (Fig. 1G) is known to have anticancer activity [48–50]. Among various active substrates employed for the synthesis of bis-derivatives, our attention has been focused on relatively less explored tetronic acid (Fig. 1J).

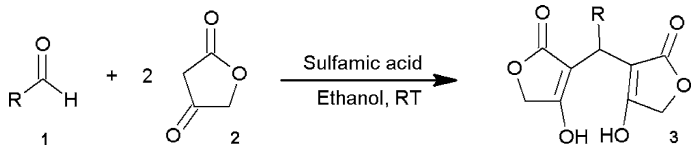
It is well known that tetronic acid (Fig. 1J) constitutes a subclass of β-hydroxy butenolides, and two important members belonging to this class are pennicillic acid (Fig. 1K) and ascorbic acid (Fig. 1L). A great number of compounds belonging to this class are found in many natural products which exhibit a wide array of biological properties [51–53]. In addition, many heterocycles containing tetronic acid as a structural motif are known to exhibit important biological activities. [54].

A literature survey within the framework on the use of tetronic acid in the synthesis of corresponding bis derivatives revealed that, to the best of our knowledge, there are only two reports on the synthesis of bis-tetronic acids [55–57]. Zhang et al. [55] reported the synthesis of bis-tetronic acids using aldehydes as starting compounds and diethylamine as well as an electrochemically generated base (EGB) as the catalysts. The EGB-promoted protocol is operable at 0 °C while the diethylamine-catalyzed protocol requires more than a stoichiometric amount of the catalyst, reflux conditions and very long reaction times, and furnishes the desired bis-tetronic acid in low yield. On the other hand, Daribi et al. [56] have reported the synthesis of bis-tetronic acids using isatins as starting compounds. This protocol also suffers from drawbacks such as the use of elevated temperature and the necessity for ultrasonic activation. Keeping all these facts in mind, we envisaged that there certainly exists scope for the development of a practically simple protocol for the synthesis of bis-tetronic acids. Here, we report a sulfamic acid-catalyzed protocol for the synthesis of bis-tetronic acids (Scheme 1).

Experimental

General experimental procedure for 3/5

To a well-stirred solution of aldehyde **1** or isatin **4** (2 mmol) and tetronic acid **2** (4 mmol) in ethanol (5 mL) was added sulfamic acid (20 mol%) with continuous stirring. With the progress of the reaction, a yellowish solid separated out. Upon completion of the reaction (TLC), the resultant solid was filtered, washed with



Scheme 1 Sulfamic acid-catalyzed synthesis of bis-tetronic acids

ethanol and dried. The resultant bis-tetronic acid **3/5** was found to be pure and did not require any further purification.
The spectral data of new compounds is summarized below.

3-((2,5-Dihydro-4-hydroxy-2-oxofuran-3-yl)(4-isopropylphenyl)methyl)-4-hydroxyfuran-2(5H)-one, ***3f*** Solid; M. P.: 186–189 °C; IR (KBr): 3347, 1710, 1645, 1488, 1419, 1223, 1087 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 1.15 (s, 3H), 1.17 (s, 3H), 2.76–2.86 (m, 1H), 4.60–4.66 (m, 4H), 4.87 (s, 1H), 7.07 (s, 1H); ^{13}C-NMR: (75 MHz, DMSO-d_6,); δ 24.20, 31.38, 33.47, 67.60, 100.66, 126.43, 127.35, 137.44, 146.78, 175.72, 176.99 ppm, LC–MS/MS: mass calculated for $[C_{18}H_{18}O_6]$: 331.1181 $[M + H]^+$; Obs. mass: 331.1175 $[M + H]^+$.

3-((4-Chlorophenyl)(2,5-dihydro-4-hydroxy-2-oxofuran-3-yl)methyl)-4-hydroxyfuran-2-(5H)-one, ***3g*** Solid; M. P.: 210–212 °C; IR (KBr): 3429, 1714, 1645, 1482, 1414, 1125, 1012 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.51–4.66 (m, 4H), 4.86–4.98 (m, 1H), 7.15 (s, 4H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 31.47, 67.56, 100.10, 128.32, 129.12, 131.79, 138.73, 175.67, 176.60 ppm; LC–MS/MS: mass calculated for $[C_{15}H_{11}ClO_6]$: 323.0322 $[M + H]^+$; Obs. mass: 323.0320 $[M + H]^+$.

3-((2,5-Dihydro-4-hydroxy-2-oxofuran-3-yl)(3,4-dimethylphenyl)methyl)-4-hydroxyfuran-2(5H)-one, ***3j*** Solid; M. P.: 175–178 °C; IR (KBr): 3447, 1743, 1676, 1499, 1401, 1155, 1054 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.15 (s, 6H), 4.59–4.66 (m, 4H), 4.71 (s, 1H), 6.90 (d, 2H, $J = 3.2$ Hz), 6.99 (d, 1H, $J = 7.6$ Hz), 7.93 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 19.37, 20.03, 32.24, 67.41, 99.10,125.18, 128.91, 129.56, 134.25, 135.98, 138.33, 176.14, 176.20 ppm; LC–MS/MS: mass calculated for $[C_{17}H_{16}O_6]$: 317.1025 $[M + H]^+$ and 339.0845 $[M + Na]^+$; Obs. mass: 317.1019 $[M + H]^+$ and 339.0837 $[M + Na]^+$.

3-((2,5-Dihydro-4-hydroxy-2-oxofuran-3-yl)(2,5-dimethylphenyl)methyl)-4-hydroxyfuran-2(5H)-one, ***3k*** Solid; M. P.: 206–208 °C; IR (KBr): 3432, 1721, 1632, 1531, 1434, 1369, 1127, 1087, 834 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.21 (s, 3H), 4.51–4.63 (m, 4H), 4.88 (s, 1H), 6.83 (d, 1H, $J = 7.4$ Hz), 6.91 (d, 1H, $J = 7.6$ Hz), 7.04 (s, 1H), 10.15 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 19.26, 21.38, 29.99, 67.21, 100.13, 127.26, 128.77, 130.32, 132.80, 134.56, 138.00, 174.84, 176.27 ppm, LC–MS/MS: mass calculated for $[C_{17}H_{16}O_6]$: 317.1025 $[M + H]^+$ and 339.0845 $[M + Na]^+$; Obs. mass: 317.1019 $[M + H]^+$ and 339.0837 $[M + Na]^+$.

3-((2,5-Dihydro-4-hydroxy-2-oxofuran-3-yl)(5-nitrobenzo[d][1, 3]dioxol-6-yl)methyl)-4-hydroxyfuran-2(5H)-one, ***3l*** Solid; M. P.: 192–195 °C; IR (KBr): 3427, 1720,

1643, 1522, 1510, 1412, 1365, 1110, 1042, 842 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.51 (s, 4H), 5.26 (s,1H), 6.10 (s, 2H), 6.95 (s, 1H), 7.37 (d, 1H, $J = 7.4$ Hz), 11.16 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 30.67, 66.74, 98.32, 103.15, 105.04, 110.56, 131.95, 142.81, 146.55, 151.17, 174.19, 174.38 ppm; LC–MS/MS: mass calculated for [$C_{16}H_{11}NO_{10}$]: 378.0461 $[M + H]^+$; Obs. mass: 378.0820 $[M + H]^+$.

3-((2,5-Dihydro-4-hydroxy-2-oxofuran-3-yl)(3-methylthiophen-2-yl)methyl)-4-hydroxyfuran-2(5H)-one, ***3m*** Solid; M. P.: 158–161 °C; IR (KBr): 3442, 1723, 1655, 1503, 1413, 1126, 1053, 865 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.06 (s, 3H), 4.56–4.68 (m, 4H), 4.90 (s, 1H), 6.74 (d, 1H, $J = 5.1$ Hz), 7.12 (d, 1H, $J = 5.0$ Hz), 8.69 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 13.91, 26.85, 67.32, 99.32, 122.08, 130.22, 132.72, 138.69, 175.59, 176.19 ppm; LC–MS/MS: mass calculated for [$C_{14}H_{12}O_6S$]: 331.0253 $[M + Na]^+$; Obs. mass: 331.0250 $[M + Na]^+$.

3,3′-(Pyridin-3-ylmethanediyl)bis(4-hydroxyfuran-2(5H)-one), ***3o*** Solid; M. P.: 188–190 °C; IR (KBr): 3465, 1711, 1665, 1577, 1400, 1116, 1087, 965 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.45 (s, 4H), 4.65 (s, 1H), 7.87–7.91 (m, 1H), 8.28 (d, 1H, $J = 7.6$ Hz), 8.60 (s, 2H), 8.68 (d, 1H, $J = 4.78$ Hz), 10.45 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 30.83, 68.31, 96.53, 127.10, 141.29, 141.57, 143.34, 143.71, 176.30, 181.43 ppm; LC–MS/MS: mass calculated for [$C_{14}H_{11}NO_6$]: 290.2481 $[M + H]^+$; Obs. mass: 290.0635 $[M + H].^+$

3,3-Bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,3-dihydro-2H-indol-2-one, ***5a*** Solid; M. P.: 164–167 °C; IR (KBr): 3420, 3152, 3056, 1766, 1565, 1315, 916, 719 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.50 (s, 4H), 6.77 (d, 1H, $J = 7.8$ Hz), 6.85 (t, 1H, $J = 7.6$ Hz), 7.09 (t, 1H, $J = 7.5$ Hz), 7.43 (d, 1H, $J = 7.5$ Hz), 10.73 (s, 1H), 10.80 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 48.79, 66.49, 109.72, 121.71, 126.94, 128.15, 130.57, 141.84, 172.36, 174.57, 178.60 ppm; LC–MS/MS: mass calculated for [$C_{16}H_{11}NO_7$]: 330.0614 $[M + H]^+$ and 352.0434 $[M + Na]^+$; Obs. mass: 330.0802 $[M + H]^+$ and 352.0601 $[M + Na]^+$.

3,3-Bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-5-nitro-1,3-dihydro-2H-indol-2-one, ***5b*** Solid; M. P.: 175–178 °C; IR (KBr): 3440, 3122, 3067, 1772, 1580, 1340, 951, 715 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.68 (s, 4H), 6.97(d, 1H, $J = 9.3$ Hz), 8.13 (s, 2H), 11.13 (s, 1H), 11.93 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 47.62, 66.90, 95.79, 109.66, 120.20, 125.73, 133.31, 142.29, 148.97, 172.73, 174.73, 176.34 ppm; LC–MS/MS: mass calculated for [$C_{16}H_{10}N_2O_9$]: 375.0464 $[M + H]^+$; Obs. mass: 375.0597 $[M + H]^+$.

5-Bromo-3,3-bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,3-dihydro-2H-indol-2-one, ***5c*** Solid; M. P.: 182–184 °C; IR (KBr): 3445, 3130, 3054, 1757, 1558, 1340, 975, 819 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.60 (s, 4H), 6.73 (d, 1H, $J = 7.8$ Hz), 7.30 (d, 1H, $J = 7.1$ Hz), 7.41 (s, 1H), 10.58 (s, 1H), 11.97 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 48.02, 66.72, 111.46, 113.18, 127.67, 130.85,

134.61, 141.62, 172.71, 174.26, 175.97 ppm; LC–MS/MS: mass calculated for $[C_{16}H_{10}BrNO_7]$: 407.9716 $[M + H]^+$; Obs. mass: 407.9734 $[M + H]^+$.

3,3-Bis-(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1-methyl-1,3-dihydro-2H-indol-2-one, ***5d*** Solid; M. P.: 158–161 °C; IR (KBr): 3435, 3101, 2999, 1774, 1563, 965, 689 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 3.12 (s, 3H), 4.56 (s, 4H), 6.92 (t, 2H, $J = 7.4$ Hz), 7.21 (t, 1H, $J = 7.2$ Hz), 7.33 (d, 1H, $J = 7.6$ Hz), 11.91 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 26.85, 47.50, 66.60, 96.81, 108.45, 122.31, 124.83, 128.24, 131.32, 143.59, 172.57, 174.06, 175.01 ppm; LC–MS/MS: mass calculated for $[C_{17}H_{11}NO_7]$: 344.0770 $[M + H]^+$; Obs. mass: 344.0871 $[M + H]^+$.

3,3-Bis-(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-5-methyl-1,3-dihydro-2H-indol-2-one, ***5e*** Solid; M. P.: 162–164 °C; IR (KBr): 3467, 3092, 2918, 1754, 1545, 1313, 868, 777 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.18 (s, 3H), 4.57 (s, 4H), 6.65 (d, 1H, $J = 7.8$ Hz), 6.92 (d, 1H, $J = 7.5$ Hz), 7.16 (s, 1H),10.42 (s, 1H), 11.83 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 21.23, 48.21, 66.53, 96.97, 109.27, 126.15, 128.44, 130.22, 132.08, 139.71, 172.65, 173.92, 176.95 ppm; LC–MS/MS: mass calculated for $[C_{17}H_{13}NO_7]$: 344.0770 $[M + H]^+$; Obs. mass: 344.0871 $[M + H]^+$.

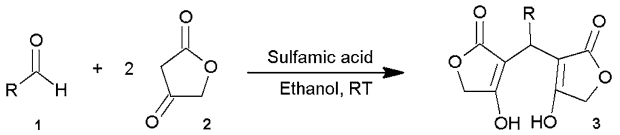
5-Chloro-3,3-bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,3-dihydro-2H-indol-2-one, ***5f*** Solid; M. P.: 177–179 °C; IR (KBr): 3498, 3153, 2976, 1768, 1554, 1322, 977, 788 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.61 (s, 4H), 6.78 (d, 1H, $J = 7.6$ Hz), 7.17 (d, 1H, $J = 6.9$ Hz), 7.29 (s, 1H), 10.58 (s, 1H), 11.89 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 48.07, 66.72, 96.32, 110.32, 125.00, 125.48, 128.03, 134.20, 141.18, 172.72, 174.26, 176.12 ppm; LC–MS/MS: mass calculated for $[C_{16}H_{10}ClNO_7]$: 364.0224 $[M + H]^+$; Obs. Mass: 364.0281 $[M + H]^+$.

7-Chloro-3,3-bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,3-dihydro-2H-indol-2-one, ***5g*** Solid; M. P.: 184–187 °C; IR (KBr): 3484, 3155, 3012, 1770, 1561, 1358, 866, 777 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.58 (s, 4H), 6.86 (t, 1H, $J = 7.9$ Hz), 7.16 (d, 1H, $J = 8.00$ Hz), 7.24 (d, 1H, $J = 7.4$ Hz), 10.81 (s, 1H), 11.88 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 48.63, 66.68, 96.57, 113.52, 122.86, 123.50, 128.15, 134.18, 139.98, 172.63, 174.10, 176.09 ppm; LC–MS/MS: mass calculated for $[C_{16}H_{10}ClNO_7]$: 364.0224 $[M + H]^+$; Obs. Mass: 364.0281 $[M + H]^+$.

Results and discussion

It is well known that Knoevenagel condensation as well as Michael addition reactions are typically base catalyzed reactions. Logically, with the choice of an appropriate base, Knoevenagel–Michael Domino reactions could also be effected. Based upon this philosophy, recently we have reported the synthesis of 1-oxo-hexahydroxanthenes and bis-coumarins using diethylamine as the catalyst [18]. As the synthesis of bis-tetronic acids is also delineated to proceed by the Knoevenagel–

Table 1 Screening of catalyst for the optimum yield of bis-tetronic acid **3a** at ambient temperature



Entry	Catalyst (20 mol%)	Time (h)	Yield (%)[a]
1	THAM	12	NR
2	Triethylamine	12	40[b]
3	Piperidine	12	50
4	Dimethylaminopyridine	12	50[b]
5	DBU	12	60
6	DABCO	12	52
7	Potassium phosphate	24	45[b]
8	Potassium carbonate	24	45[b]
9	Imidazole	24	30[b]
10	Urea	12	35[b]
11	Sulfamic acid	4	91
12	Sulfamic acid[c]	8	76
13	Sulfamic acid[d]	12	64
14	Oxalic acid	6	70
15	*p*-Toluenesulfonic acid	6	77

Reaction conditions: anisaldehyde (1 mmol), tetronic acid (2 mmol), catalyst (20 mol%), EtOH (5 mL), RT. The combination with the best yield is shown in bold.

NR No reaction

[a] Isolated yield

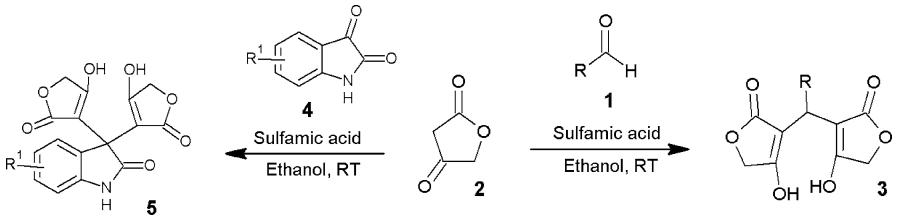
[b] Yield refers to Knoevenagel condensation product

[c, d] Sulfamic acid (15 and 10 mol%, respectively)

Michael Domino pathway, we planned to screen the suitability of a basic catalyst in the synthesis of bis-tetronic acids.

To begin with, a few model reactions were performed at ambient temperature using anisaldehyde **1a** and tetronic acid **2** as the substrates (1:2 equiv.), ethanol as the reaction medium and triethylamine, piperidine, DBU, DABCO, dimethylaminopyridine, Imidazole, Tris-hydroxymethylaminomethane (THAM), urea, potassium phosphate and potassium carbonate (20 mol%) as the catalysts. The results are summarized in Table 1. It was noticed that, with the choice of most of these catalysts, the reaction remained arrested at the Knoevenagel condensation stage, while, with the choice of piperidine, DBU and DABCO, the reactions furnished the desired bis-tetronic acid **3a** in very low yield. Next, we planned to screen a few Brønsted acid catalysts for the synthesis of bis-tetronic acids. The choice of an acid catalyst was based upon the parameters of easy commercial availability, cost, ease of handling and its environmental compatibility. The model

Table 2 Sulfamic acid-catalyzed synthesis of the bis-tetronic acids, **3/5**



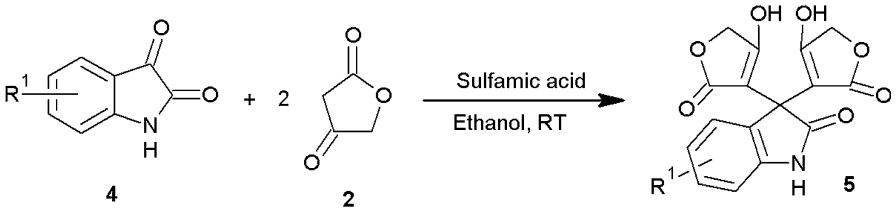
Product	Aldehyde	Time (h)	Yield[a] (%)	Melting point (°C)	
				Obs.	Lit. [Ref.]
3a	4-Methoxybenzaldehyde	4.0	91	174–178	174–176 [55]
3b	2-Nitrobenzaldehyde	3.5	82	224–226	227–229 [55]
3c	3-Nitrobenzaldehyde	3.0	88	235–237	236–238 [55]
3d	4-Nitrobenzaldehyde	4.0	84	230–232	232–234 [55]
3e	4-Methylbenzaldehyde	4.5	85	190–192	187–189 [55]
3f	4-Isopropylbenzaldehyde	4.5	91	186–189	–
3g	4-Chlorobenzaldehyde	4.0	85	210–212	–
3h	4-Bromobenzaldehyde	4.0	84	187–190	192–194 [55]
3i	Benzaldehyde	4.5	89	132–135	125–127 [55]
3j	3,4-Dimethylbenzaldehyde	4.0	87	175–178	–
3k	2,5-Dimethylbenzaldehyde	4.5	85	206–208	–
3l	6-Nitropiperonal	3.5	88	192–195	–
3m	3-Methyl-2-thiophenecarbaldehyde	4.0	86	158–161	–
3n	*n*-Butyraldehyde	12.0	NR	–	–
3o	Pyridine-3-carbaldehyde	4.5	69	188–190	–
3p	Furfural	12	NR[b]	–	–
5a	Isatin	6.0	86	164–167	168–170 [56]
5b	5-Nitroisatin	5.5	85	175–178	178–180 [56]
5c	5-Bromoisatin	6.0	83	182–184	181–183 [56]
5d	1-Methylisatin	6.0	82	158–161	–
5e	5-Methylisatin	6.0	85	162–164	163–165 [56]
5f	5-Chloroisatin	6.0	84	177–179	–
5g	7-Chloroisatin	6.0	82	184–187	–

Reaction conditions: aldehyde/isatin (1 mmol), tetronic acid (2 mmol), SA (20 mol%), Ethanol (5 mL), RT

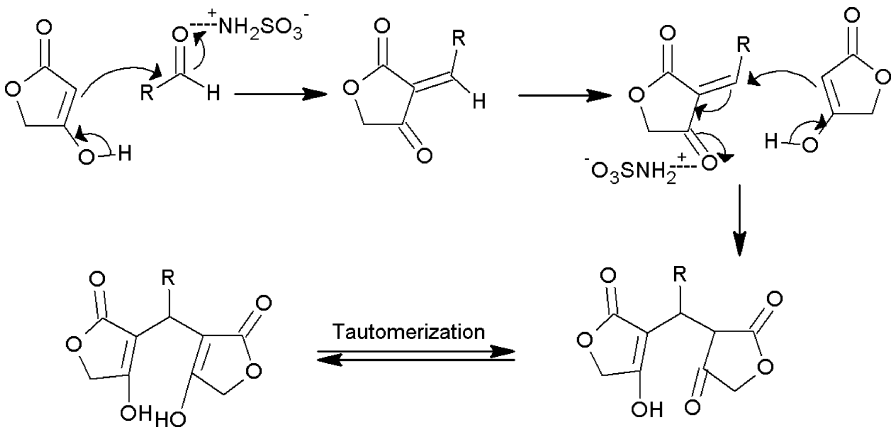
NR No reaction

[a] Isolated yield

[b] Dark brown gummy solid



Scheme 2 Sulfamic acid catalyzed synthesis of spirocyclic bis-tetronic acids **5**



Scheme 3 Plausible mechanism of sulfamic acid-catalyzed synthesis of bis-tetronic acids

reaction between anisaldehyde **1a** and tetronic acid **2** was then repeated in the presence of three acid catalysts, i.e., oxalic acid, sulfamic acid and *p*-toluenesulfonic acid, which fulfil the aforementioned requirements. During monitoring of the reactions, it was noticed that, with the use of all these acids, a pale yellow colored solid separates out during the reactions. Upon completion of the reaction (TLC), the resultant solid in each reaction flask was filtered, washed with water and dried. On the basis of physical as well as spectroscopic data, the resulting product was identified to be the desired bis-tetronic acid **3a**. Most interestingly, with the choice of sulfamic acid (20 mol%), the desired bis-tetronic acid was obtained as a sole product and in excellent yield (91 %), while, with the choice of oxalic acid as well as *p*-toluenesulfonic acid as catalyst, the desired **3a** was obtained in lower yield.

The use of sulfamic acid as an organo-acid catalyst is well documented [58]. Earlier, we have demonstrated the use of sulfamic acid as an organo-catalyst in the multicomponent synthesis of α-aminophosphonates, α-aminonitriles, 1-oxo-hexahydroxanthenes and α-trimethylsilyloxy phosphonates [59–62]. On the other hand, there are also reports on sulfamic acid-catalyzed synthesis of bis-indolylalkanes and bis-pyrazoles [63, 64], and when the current work on the synthesis of bis-tetronic acid was complete, there appeared a report on the application of sulfamic acid in the synthesis of bis-Lawsome (Fig. 1M) derivatives [65]. However, to the best of our knowledge, there are no reports on the use of sulfamic acid in the synthesis of bis-

tetronic acids. Hence, we planned to explore the use of sulfamic acid in the synthesis of bis-tetronic acids.

Employing the reaction conditions established for the synthesis of **3a**, a variety of aromatic as well as heteroaromatic aldehydes were allowed to react with tetronic acid (2 equiv.). It was observed that, irrespective of the presence of electron-withdrawing or electron-donating groups, all the aromatic aldehydes furnished corresponding the bis-tetronic acids **3b–m** in excellent yield (Table 2). However, under the same reaction conditions, n-butyraldehyde, a representative aliphatic aldehyde, failed to furnish the corresponding bis-tetronic acid. Modification of the reaction conditions as regards change in solvent, increase in the amount of catalyst, and reaction temperature did not obtain the corresponding bis-tetronic acid in acceptable yield. To expand the scope of the present protocol, we next planned to replace the aldehyde component from the reactions with isatins (Scheme 2). We are indeed happy to disclose that, under the reaction conditions, various isatins also underwent smooth condensation with tetronic acid to furnish the corresponding bis-tetronic acids **5a–g** in excellent yields (Table 2). A plausible mechanism of sulfamic acid-catalyzed synthesis of bis-tetronic acids is depicted in Scheme 3. Based upon the analogy between the structures of bis-coumarins (Fig. 1C) and bis-tetronic acids (Fig. 1I), we anticipate that, similar to bis-coumarins, bis-tetronic acids may also exhibit urease inhibitor, anti-oxidant and anticoagulant activities. Currently, these studies are being pursued in our laboratory.

Conclusion

In summary, we have developed an extremely simple and environmentally benign protocol for the synthesis of bis-tetronic acids using sulfamic acid as the catalyst. Commercial availability of the catalyst at extremely low cost, ambient reaction conditions, excellent yields and avoidance of conventional work-up, as well as purification procedures, are the notable advantages of this energy-efficient protocol.

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References

1. P. Tundo, P.T. Anastas, *Green Chemistry: Theory and Practice*, 1st edn. (Oxford University Press, Oxford, 1998)
2. J.H. Clark, J.D. Macquarrie, *Handbook of Green Chemistry and Technology* (Wiley, London, 2002), p. 564
3. Y.L. Gu, Green Chem. **14**, 2091 (2012)
4. C.J. Li, P.T. Anastas, Chem. Soc. Rev. **41**, 1413 (2012)
5. J. Zhu, H. Bienayme, *Multicomponent Reactions* (Wiley-VCH, Wienheim, 2003)
6. R.V.A. Orru, E. Ruijter, in *Topics in Heterocyclic Chemistry, Synthesis of Heterocycles Via Multicomponent Reactions*, ed. by R.V.A. Orru, E. Ruijter (Springer, Berlin, 2010), p. 280
7. M.S. Singh, S. Singh, RSC Adv. **2**, 4547 (2012)

8. L.F. Tietze, H.P. Bell, G. Brasche, *Domino Reactions in Organic Synthesis* (Wiley-VCH, Weinheim, 1996), p. 631
9. C.M.R. Volla, I. Atodiresei, M. Rueping, Chem. Rev. **34**, 2390 (2014)
10. H. Yi-Fang, M. Xia, Curr. Org. Chem. **14**, 379 (2010)
11. N. Parmar, *Efficient Methods for Pyran-Heterocycles Via Domino Reaction* (Scholar's Press, Germany 2014), pp. 1–100
12. L.G. Voskressensky, A.A. Festa, A.V. Varlamov, Tetrahedron **70**, 551 (2014)
13. K.S. Pandit, P.V. Chavan, U.V. Desai, M.A. Kulkarni, P.P. Wadgaonkar, New J. Chem. **39**, 4452 (2015)
14. P. Zhang, Y.D. Yu, Z.H. Zhang, Synth. Commun. **38**, 4474 (2008)
15. D. Prasad, A. Preetam, M. Nath, C. R. Chim. **16**, 353 (2013)
16. G. Sabitha, K. Arundhathi, K. Sudhakar, S. Sastry, J.S. Yadav, Synth. Commun. **38**, 3439 (2008)
17. F. He, P. Li, Y. Gu, G. Li, Green Chem. **3**, 1767 (2009)
18. R.V. Kupwade, K.S. Pandit, U.V. Desai, M.A. Kulkarni, P.P. Wadgaonkar, Res. Chem. Intermed. (2016). doi:10.1007/s11164-016-2464-4
19. D. Shi, Y. Wang, Z. Lu, G. Dai, Synth. Commun. **30**, 713 (2000)
20. X.S. Wang, D.Q. Shi, Y.L. Li, H. Chen, X.Y. Wei, Z.M. Zong, Synth. Commun. **35**, 97 (2005)
21. J.-J. Yu, L.-M. Wang, J.-Q. Liu, F.-L. Guo, Y. Liu, N. Jiao, Green Chem. **12**, 216 (2010)
22. D.B. Ramachary, M. Kishor, J. Org. Chem. **72**, 5056 (2007)
23. N. Azizi, S. Dezfooli, M.M. Hashemi, C. R. Chim. **16**, 997 (2013)
24. F.-M. Wang, D. Bao, B.-X. Hu, Z.-Y. Zhou, D.-D. Huang, L.-Z. Chen, Y.-M. Liu, J. Chem. Res. **39**, 445 (2015)
25. K. Hajela, R.S. Kapil, Eur. J. Med. Chem. **32**, 55 (1997)
26. S.P. Chaudhari, N.R. Pai, J. Heterocycl. Chem. **17**, 149 (2007)
27. H.M. El-Shaaer, P. Foltinova, M. Lacova, J. Chovancova, H. Stankovicova, Farmaco **33**, 224 (1998)
28. L. Tang, Y. Yang, R. Ji, Yaoxue Xuebao **43**, 162 (2008)
29. R. Frederick, S. Robert, C. Charlier, J. Wouters, B. Masereel, L. Pochet, J. Med. Chem. **30**, 3645 (2007)
30. N. Sato, M. Jitsuoka, H. Takunobu, K. Nonoshita, M. Moriya, Y. Haga, A. Sakurba, M. Ando, T. Ohe, I. Tomoyuki, H. Waasa, H.A. Gomori, A. Ishihara, A. Kanatani, T. Fukami, J. Med. Chem. **51**, 4765 (2008)
31. T. Futagoishi, M. Murata, A. Wakamiya, T. Sasamori, Y. Murata, Org. Lett. **15**, 2750 (2005)
32. R. Zhang, T. Futagoishi, M. Murata, A. Wakamiya, Y. Murata, J. Am. Chem. Soc. **56**, 8193 (2014)
33. Z.U. Haq, M.A. Lodhi, A.S. Nawaz, S. Iqbal, K.M. Khan, B.M. Rode, A.U. Rahman, M.I. Choudhary, Bioorg. Med. Chem. **16**, 3456 (2008)
34. I. Manolov, C.M. Moessmer, N.D. Danchev, Eur. J. Med. Chem. **41**, 882 (2006)
35. M.I. Choudhary, N. Fatima, K.M. Khan, S. Jalil, I. Sajjid, A.U. Rahman, Bioorg. Med. Chem. **14**, 8066 (2006)
36. S.S. Li, Z. Gao, X. Feng, S.M. Hecht, J. Nat. Prod. **67**, 1608 (2004)
37. K.M. Khan, S. Iqbal, M.A. Lodhi, M.G. Maharvi, Z. Ullah, M.I. Choudhary, A.U. Rahman, Bioorg. Med. Chem. **12**, 1963 (2004)
38. S. Han, F.-F. Zhang, H.-Y. Oian, L.-L. Chen, J.-B. Pu, X. Xie, J.-Z. Chen, Eur. J. Med. Chem. **93**, 16 (2015)
39. J. Li, X.-Y. Xue, X. Li, Z. Hou, X.-Y. Yang, D. Qu, Y. Zhou, Z.-D. Zhang, X.-X. Luo, J.-J. Li, M.-K. Li, Arch. Pharm. Res. (2015). doi:10.1007/s12272-015-0614-7
40. D.M. Bailey, P.E. Hansen, A.G. Hlavac, E.R. Baizman, J. Pearl, A.F. Defelice, M.E. Feigenson, J. Med. Chem. **28**, 256 (1985)
41. R.N. Mahajan, F.H. Havaldar, P.S. Fernandes, J. Indian Chem. Soc. **68**, 245 (1991)
42. P.M.S. Chauhan, S. Singh, R.K. Chatterjee, Indian J. Chem. **32**, 858 (1993)
43. R.P. Singh, O.P. Malik, V. Rao, M. Darbarwar, Indian J. Pharm. Sci. **49**, 192 (1987)
44. S. Das, A.J. Thakur, Eur. J. Org. Chem. **12**, 2301 (2011)
45. T. Lundqvist, S.L. Fisher, G. Kern, R.H.A. Folmer, Y.F. Xue, D.T. Newton, T.A. Keating, R.A. Alm, B.L.M. De-Jonge, Nature **447**, 817 (2007)
46. J.B. Parker, M.A. Bianchet, D.J. Krosky, J.I. Friedman, L.M. Amzel, J.T. Stivers, Nature **449**, 433 (2007)
47. A.R. Dinner, G.M. Blackburn, M. Karplus, Nature **413**, 752 (2001)
48. M. Karthik, A.K. Tripathi, N.M. Gupta, M. Palanichamy, V. Murugeson, Catal. Commun. **5**, 371 (2004)

49. M. Chakrabarty, R. Basak, Y. Harigaya, N. Ghosh, Tetrahedron Lett. **43**, 4075 (2002)
50. E. Koukabi, M.M. Hosseini, J. Mol. Catal. A Chem. **397**, 68 (2015)
51. L.J. Haynes, J.R.Q. Plimmer, Rev. Chem. Soc. **14**, 292 (1960)
52. M. Sodeoka, R. Sampe, S. Kojima, Y. Baba, T. Usui, K. Ueda, H. Osada, J. Med. Chem. **44**, 3216 (2001)
53. H. Buhler, A. Bayer, F. Effenberg, Chem. Eur. J. **6**, 2564 (2000) **(and references therein)**
54. S.A. Savina, V.M. Lyubchanskaya, L.M. Alekseeva, A.S. Shashkov, V.G. Granika, Russ. Chem. B. **56**, 2298 (2007)
55. Z.Z. Zhang, H. Zhang, W.Z.-Q. Li, C.-C. Zeng, R.-G. Zhong, Y.-B. She, RSC Adv. **1**, 583 (2011)
56. M. Dabiri, Z.N. Tisseh, M. Bahramnejad, A. Bazgir, Ultrason. Sonochem. **18**, 353 (2011)
57. K. Goelitzer, J. Trttmacher, U. Bartke, Pharmazie **57**, 606 (2002)
58. M.M. Heravi, B. Baghernejad, H.A. Oskooie, Curr. Org. Chem. **13**, 1002 (2009)
59. S.D. Mitragotri, D.M. Pore, U.V. Desai, P.P. Wadgaonkar, Catal. Commun. **9**, 1822 (2008)
60. Unpublished work from Ph.D. Thesis of Dr. T. S. Thopate, Shivaji University, Kolhapur, Sulfamic acid catalyzed synthesis of α-aminonitriles (2007)
61. Unpublished work from Ph.D. Thesis of Mr. K. S. Pandit, Shivaji University, Kolhapur, Sulfamic acid catalyzed synthesis the 1-oxo-hexahydroxanthenes (2015)
62. Unpublished work from Ph.D. Thesis of Dr. S. D. Mitragotri, Shivaji University, Kolhapur Sulfamic acid catalyzed synthesis of α-trimethylsilyloxy phosphonates (2009)
63. W.-J. Li, X.-F. Lin, J. Wang, G.-L. Li, Y.-G. Wang, Synth. Commun. **35**, 2765 (2010)
64. S. Tayebi, K. Niknam, Iran. J. Catal. **2**, 69 (2012)
65. G. Brahmachari, ACS Sustain. Chem. Eng. **3**, 2058 (2015)