REVIEW

Advancements in tetronic acid chemistry. Part 1: Synthesis and reactions

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Abstract The preparation and the properties of the elusive tetronic acid are reviewed, including its synthesis, chemical reactivity and reactions.

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1. Introduction

Tetronic acids, 4-hydroxy-2(5H)-furanones, were discovered in 1896 by Wolfe and Schwabe (1896). They are a structural fragment of a series of natural compounds, such as acetogenins, muconolactones, leptosfaerin, and strigol (Cain et al., 1989; De Guzman and Schnutz, 1990; Iida et al., 1997; Miller and Hagedus, 1993; Miller et al., 1998; Ribbons and Sutherland, 1994; Rupprecht et al., 1990; Schiehser et al., 1986; Tejedor and García-Tellado, 2004; Zografos and Georgiadis, 2006). They represent an interesting template for medicinal chemistry because of their antibiotic (Brodersen and Kjaer, 1946; Capon and MacLeod, 1987; Haynes and Plimmer, 1960; Ley et al., 1991; Matsumoto et al., 1990; Vanwagenen and Cardellina, 1986; Vieveg et al., 2014), HIV-1 protease inhibitors (Roggo et al., 1994), anticoagulant (Rehse and Emisch, 1983; Rehse and Rothe, 1982; Rehse et al., 1978; Witàk et al., 1982), antiepileptic (Zhang et al., 1992), antibacterial (Murray et al., 2014), antifungal (Luk and Readshaw, 1987; Vishwakarma et al., 1987; Hu et al., 2014), insecticidal (Ibi et al., 1979), analgesic (Dal Pozzo et al., 1974) and anti-inflammatory activities (Foden et al., 1975). Recently, these compounds have also been reported as anticancer agents (Andreoli et al., 2014; Han et al., 2014; kamal et al., 2014a, 2014b).

In continuation of our studies in exploring the utilization of cyclic 1,3-dicarbonyl compounds as versatile precursors for synthesis of organic compounds (Abdou et al., 2015a, 2015b; Abdou, 2014a, 2014b, 2013; Metwally et al., 2013a, 2013b, 2012a, 2012b, 2012c, 2012d, 2012e). The aim of this review was to give an account of the principal literature on methods of synthesis and the reactivity of tetronic acid (without any substituents attached). The discussion is supported by numerous lucid diagrams and the extensive reaction schemes are supported by relevant and up-to-date references from the original literature.

2. Tautomeric structure(s)

Tetronic acid can exist in either the keto- or enol-form (Fig. 1). These four possible prototropic transformations have been intensively examined by various chemical reactivity, spectral, thermochemical, and computational methods (Ballantine et al., 1968; Duncanson, 1953; Edsall and Sagall, 1943; Haynes et al., 1968; Jurd, 1996; Martoglio and Katon, 1993; Pollet et al., 1984; Zimmer et al., 1978).

3. Synthesis

The syntheses of tetronic acid are reported throughout the literature (Allan et al., 1983; Bloomer and Kappler, 1976; Greenhill et al., 1975; Greenhill and Tomassini, 1974; Haynes and Plimmer, 1960; Pollet and Gelin, 1978; Schmidt and Zimmer, 1981; Svendsen and Boll, 1973; Zimmer et al., 1978), although very little has been done to concentrate the wide range of syntheses into a single report.

3.1. Using 1,3-dioxin-4-one

Sato et al. (1990) disclosed a simple and inexpensive synthesis of tetronic acid 1 in 78% yield via refluxing of 6-(hydroxymethyl)-dioxin-4-one 2 in toluene (Scheme 1).

![Scheme 1](image1)

3.2. Using 1,3-dicarbonyl compounds

Sato et al. (1990) disclosed a simple and inexpensive synthesis of tetronic acid 1 in 78% yield via refluxing of 6-(hydroxymethyl)-dioxin-4-one 2 in toluene (Scheme 1).

![Scheme 2](image2)

3.3. Using other precursors

Sato et al. (1990) disclosed a simple and inexpensive synthesis of tetronic acid 1 in 78% yield via refluxing of 6-(hydroxymethyl)-dioxin-4-one 2 in toluene (Scheme 1).

![Scheme 3](image3)

Figure 1 Possible tautomeric structures of tetronic acid 1 (A–D).
3.2. Using lactonization of γ-acetoxy-β-keto esters

Gelin and Pallet (1980) reported that the desired tetronic acid 1 could be obtained by lactonization of γ-acetoxy-β-keto ester 3 in refluxing toluene (Scheme 2).

3.3. Debromination of α-bromotetronic

A catalytic debromination of α-bromotetronic 4 with palladium on carbon, under approximately 40 lbs of hydrogen pressure, results in 90% yield of 1 (Schmidt and Zimmer, 1981) (Scheme 3).

4. Chemical reactions

In this section, all the reactions with participation of tetronic acid on the basis of the new bond formed.

4.1. Reactions involving carbon–carbon bond formation

4.1.1. C–C bond formation reactions

4.1.1.1. C₃-alkylation. Ramachary and Kishor (2010) observed that the reaction of tetronic acid 1 with benzaldehyde 6 and diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 7 under proline catalysis in dichloromethane gave 3-benzyl-tetronic acid 8 (Scheme 4).

Michael addition reactions of 1 to β-nitroalkenes 9 afforded 3-(1-substituted-2-nitro-ethyl)-furan-2,4-diones 10. This reaction requires a basic catalyst in organic solvents, as well as long reaction times, which may lead to environmentally hazardous residues and undesirable by-products (Iwata et al., 1993). Recently, an environmentally benign, fast and convenient protocol for this reaction by a grinding method under catalyst and solvent-free conditions was reported (Xie et al., 2012) (Scheme 5).

The double alkylation of tetronic acid 1 with 1,1-disubstituted alkenes 11 in the presence of manganese(III) acetate in acetic acid at room temperature afforded the diethyl- and/or ethenyl-ethyl-substituted tetronic acids 12 and/or 13 along with peroxypropellane 14 (Haque and Nishino, 2011) (Scheme 6).

4.1.1.2. C₃-allylation reaction. The allylation of 1 is an important strategy for the formation of C–C bonds in organic synthesis. Activator-free and one-pot C-allylation of 1 by simple palladium catalyst in water using cinnamyl alcohol 15 and heating gave the corresponding C-allylated product 16 (Gan et al., 2008; Shue and Yang, 2012) (Scheme 7).

Prat et al. (1988) reported that tetronic acid 1 is efficiently alkylated with cinnamyl acetate 17 to afford 16 (38%) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), palladium(II) 2,4-pentanedionate, triphenylphosphine as catalyst in tetrahydrofuran (Scheme 8).

The above methodology (Moreno-Manas et al., 1988; Prat et al., 1988) was successfully applied for the alkylation by using 2-cyclohexenyl acetate 18. This reaction proceeds smoothly to give the corresponding monoalkylated lactone 19 (57%) although minor amounts of the dialkylated butanolide 20 were also isolated (Scheme 9).
Tetronic acid 1 was dialkenylated with allyl bromide 21 under the phase-transfer catalyst [e.g., benzyltriethylammonium chloride (Kotha and Deb, 2008) or tetra(n-butyl)ammonium hydrogensulfate (Kotha et al., 2005)] to give a mixture of C-diallylated tetronic acid 22 and O-allylated isomer 23 (Scheme 10).

4.1.1.3. C₃-benzylaion. Jurd (1997, 1996) reported that the reaction of tetronic acid 1 with Mannich bases 24 in acetic acid furnished benzyl lactones 25 (Scheme 11).

4.1.1.4. Arylation. An efficient palladium-catalyzed cross-coupling reaction of tetronic acid 1 with arylboronic acid 26 in the presence of palladium dichloride in tetrahydrofuran at
60 °C afforded 2(5H)-furanones 27 in good yields (Hu et al., 2011) (Scheme 12).

4.1.1.5. Olefination. A most frequently used method for constructing 3-arylmethylenetetrahydrofuran-2,4-diones 29 is the Knoevenagel condensation between tetronic acid 1 and several substituted benzaldehydes 28 under reflux (Chen et al., 2011; Kozlov et al., 2008; Pashkovskii et al., 2008) (Scheme 13). The microwave assisted condensation reaction of aldehydes 28 with tetronic acid 1 on acidic Montmorillonite KSF gave efficiently 3-(arylmethylene)-2,4-(3H,5H)furanidiones 30 (Villemin and Labiad, 1990) (Scheme 14).

Heating tetronic acid 1 and triethyl orthoformate 31 for two hours gave 3-ethoxymethylene-3H-2,4-dione 32 in 60% yield (Otto, 1987) (Scheme 15).

4.1.1.6. Allylation. Yonemitsu-type trimolecular condensation of 1 with indole 33 and propanal 34 was promoted by TiCl4, afforded 2-(indol-3-yl)-2-(2-propyl)tetronic acid 35 (Gérard et al., 2010) (Scheme 16). Colombo et al. (2008) developed a three-component domino allylation reaction of 1H-indole-3-carbaldehyde 36 with allyl bromide 37 and 1 in the presence of indium metal in a mixture of tetrahydrofuran and water (1:1) afforded the desired adduct 38 (Scheme 17).

4.1.1.7. Acetylation reaction. C-acylation of tetronic acid 1 with aliphatic carboxylic acids 39 in the presence of N,N0-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane gave 3-acyltetrahydrofuran-2,4-diones 40 (Baati et al., 2011, 2010; Nomura et al., 1986; Pashkovskii et al., 2003; Rouleau et al., 2013; Murray et al., 2014) (Scheme 18).

4.2. Reactions involving carbon–heteroatom bond formation

4.2.1. C–N bond formation

4.2.1.1. Coupling reactions. 3-Arylazotetronic acids 42 were prepared by coupling of 1 with diazotized arylamines 41 in aqueous sodium hydroxide solution (Tanaka et al., 1984) (Scheme 19).

4.2.1.2. Nitration reaction. Nitration of 1 with concentrated nitric acid in diethyl ether afforded 3-nitrotetronic acid 43 (Pollet et al., 1984) (Scheme 20).

4.2.1.3. Amination reaction. Reaction of tetronic acid 1 with an equimolar amount of various anilines 44 produced the corresponding 3-anilinolactones 45 in excellent yields (Cole et al., 2002; Cook et al., 1994; Darwish et al., 2004; Ghahremanzadeh et al., 2013; Jeedimalla et al., 2013; Madec et al., 2008; Momose et al., 1988; Paulvannan and Stille, 1994; Savina et al., 2007; Shaabani et al., 2010) (Scheme 21).

The condensation reaction of tetronic acid 1 with o-phenylenediamines 46 at different reaction conditions (YCl3, AcOH, EtOH) gave 4-(2-aminophenylamino)furan-2(5H)-ones 47 (Amari et al., 2002; Bentarzi et al., 2009; Cai et al., 2011; Cheng et al., 2011; Kaoua et al., 2013) (Scheme 22).

4.2.1.4. Diazotization reactions. Regitz reaction using p-toluenesulfonyl azide (TsN3) as the diazo transfer reagent remains the most efficient approach despite it is hampered by potential hazard and purification problems to remove the p-tosylamide co-product (Chapman et al., 1987; Geraghty et al., 2000). Even, 2-azido-3-ethylbenzthiazolium tetrafluoroborate was revealed as an effective diazo transfer reagent for the transformation of 1 into 3-diazotetrahydrofuran-2,4-dione 48 (Stachel et al., 1994) (Scheme 23).
4.2.2. C–S bond formation
4.2.2.1. Sulfonation reaction. Combs et al. (2005) showed that sulfonation of 1 with sodium hydrogensulfite in ethanol resulted in the formation of the corresponding sulfonic acid 49 (Scheme 24).

4.2.2.2. Thionation reaction. Treatment of 1 with Lawesson’s reagent 50 in boiling toluene afforded the regioselective thiolotetronic acid 51 in 70% yield (Desbene-Finck et al., 2006) (Scheme 25).

Goddard et al. (2010) have reported that treatment of 1 with Martin’s sulfurane 52, in diethyl ether afforded the corresponding sulfur ylide 53 in 73% yield (Scheme 26).

4.2.3. C–O bond formation
4.2.3.1. Esterification. Radical precursors, enol esters 55, were prepared by coupling of 2-bromobenzoic acids 54 with tetronic acid 1 in the presence of 2-chloro-1-methylpyridinium iodide and triethylamine in THF at room temperature (Pugh et al., 2003; Zhang, 2000) (Scheme 27).

In addition, O-acylation of tetronic acid 1 with pivaloyl chloride 56 in the presence of 4-dimethylaminopyridine (DMAP) (Axelrod et al., 2013) or 4-pyrrolidinopyridine (Balthazor, 1992) afforded 2,2-dimethyl-2,5-dihydro-5-oxo-3-furanyl ester 57 (Scheme 28).

4.2.3.2. O-alkylation reaction. O-alkyl tetronic acids are compounds of interest, being useful starting materials for natural product synthesis (Hamada and Shiori, 1984; Kametani et al., 1987, 1986; Schmidt et al., 1983). Many methods for the O-alkylation of tetronic acid 1 were reported in the literature. However, most of the reported methods are restricted to form the methyl and ethyl tetronates using alkylating agents such as dimethyl or diethyl sulfate (Wegner et al., 1979), trimethylxonium tetrafuoroborate (Wegner et al., 1979) and diazomethane (Ley and Wadsworth, 1989). The Fischer etherification method (Gelin and Pallet, 1980) was used successfully for the preparation of methyl and ethyl tetronates.
Zimmer et al. (1988) studied the preparation of alkyl tetroates by treatment of primary or secondary alcohols and tetronic acid with conc. H₂SO₄. Although this procedure allows for preparation of various alkyl ethers, it has some serious limitations.

Hoffmann et al. (1989) have reported a modification of Zimmer’s method which replaces the excess of conc. H₂SO₄ with a catalytic amount of p-toluenesulfonic acid. While this modification works well with primary alcohols, secondary alcohols gave poor yields of the alkyl tetroate.

Treatment of tetronic acid 1 with an alkyl bromides or with alcohols 58 under Mitsunobu conditions [disopropyl diazenedicarboxylate (DIAID) (Bach and Kemmler, 2003; Bajwa and Anderson, 1990; Billaud et al., 2007) represents a general method for the regio-specific O-alkylation of tetronic acid 59 in high yields. Alternatively, cesium fluoride (CsF) in dimethylformamide (DMF) has been reported to be an efficient agent for the O-alkylation of tetronic acid (method B) (Bach et al., 2004) (Scheme 29).

4.2.3. Sulfonates ether formation. Several groups have developed general methodology for the one step formation of 61 via tosylation reaction of tetronic acid 1 with tosyl chloride 60 in the presence of triethylamine at room temperature (Blanc et al., 2013; Sun et al., 2005; Wang et al., 2003) (Scheme 30).

The compound 1 was readily converted to the corresponding triflates 63 in 66% yield by treatment with triflic anhydride 62 in methylene chloride in the presence of N,N-disopropylethylamine (DIPEA) (Grigg et al., 1997, 1994) (Scheme 31).

4.2.4. Carbon–halogen bond formation

Halogenoheteroarenes are useful intermediates for the syntheses of bioactive natural products and pharmaceutical drugs.

4.2.4.1. Bromination. Bromination of tetronic acid 1 with oxalyl bromide in dichloromethane and DMF at room temperature yielded 4-bromo-5H-2-furanone 66 (Boukouvalas and Albert, 2011; Bach et al., 2012; Barrett

\[
\begin{align*}
\text{Conditions} \\
\text{A: Ytterbium trichloride in ethanol, Time = 24h, T= 20 °C.} \\
\text{B: Acetic acid in water, Time = 0.25h.} \\
\text{C: Ethanol, Time = 0.5h, Heating.}
\end{align*}
\]

Scheme 22

\[
\begin{align*}
\text{Scheme 23}
\end{align*}
\]

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\begin{align*}
\text{Scheme 24}
\end{align*}
\]
Scheme 27

Scheme 28

Scheme 29

Scheme 30

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When the bromination of 1 is carried out using N-bromosuccinimide (NBS) as effective promoters in ethanol at room temperature, it afforded 2-bromotetronic acid 184 (Ge and Kirk, 1997) (Scheme 33).

5. Conclusion

We hope to have conveyed to the readers of this review the current interest of the synthetic community in the synthesis, and chemical reactivity of tetrone acid. It seems likely that this review will serve as a useful reference for chemists interested in discovering new types of reactions and synthesis of tetrone acid.

References


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