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NEW APPLICATION OF TRIPHOSGENE IN A CONVENIENT SYNTHESIS OF 3-ARYL-1,3-BENZOXAZINE-2,4-DIONES FROM ANACARDIC ACIDS

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Abstract – In conjunction with a search program focused on utilization of cashew (*Anacardium occidentale*) nut shell liquid (CNSL) as starting material for the preparation of useful compounds, a convenient synthesis of novel series of 3-aryl-1,3-benzoxazine-2,4-diones was prepared from anacardic acids by using of the triphosgene.

INTRODUCTION

Benzoxazines, an important class of heterocyclic compounds which exhibit a wide range of biological activity, have attracted the attention of many researchers. On the other hand, 1,3-benzoxazine-2,4-diones, which exhibit promising antimycobacterial[1] and antifungal[2] properties, no considerable synthetic pathway have been described to them. The preparation of the 3-aryl-1,3-benzoxazine-2,4-diones was primarily reported in 1960s from salicylanilide and ethyl chloroformate.[3] Others synthetic procedures to construction of this class of compounds include cyclization of salicylamide with 1,1'-carbonyldiimidazole[4] and 2-hydroxybenzonitrile with phenylisocyanate, followed by hydrolytic cleavage.[5]

In the past ten years, the preparation of several substituted 3-phenylbenzoxazine-2,4-diones thioxo analogues by using ethyl chloroformate as synthetic tool for insertion of C-O unit have been described.[1,6] Structure-activity relationship studies based in activity against atypical strains including *M. tuberculosis* have showed that the antimycobacterial activity increases with electron-accepting ability and hydrophobicity of the substituents on the phenyl ring,[1] where the *in vitro* activity of some of them exceeds that of commercial tuberculostactics used as standards.[7] Nowadays, bis(trichloromethyl)carbonate (triphosgene) is recognized not only as synthetic auxiliary[8] but also for insertion of C=O moiety.[9] Recently, it was successfully

employed for one-step cycloaddition reactions of spiro 1,3-benzoxazine dimers[10] and 4-methylene-1,3-benzoxazinones from arylhidrazones.[11] This latter prompted us to speculate the application of triphosgene in the direct construction of 3-aryl-1,3-benzoxazine-2,4-dione system.

In connection with our ongoing program aiming to the development of bioactive heterocyclic compounds using as starting material non-isoprenoid phenolic lipids from *Anacardium occidentale* we became interested in the preparation of new substituted 5-pentadecyl-3-phenyl-1,3-benzoxazine-2,4-diones (**1**) from anacardic acids (**2**), the major component of natural CNSL,[12] an inexpensive Brazilian starting material (Figure 1).

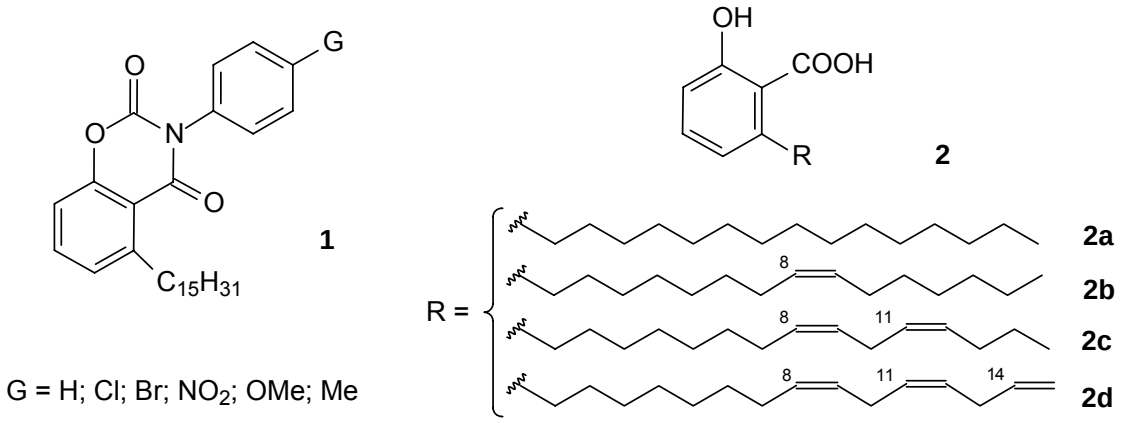
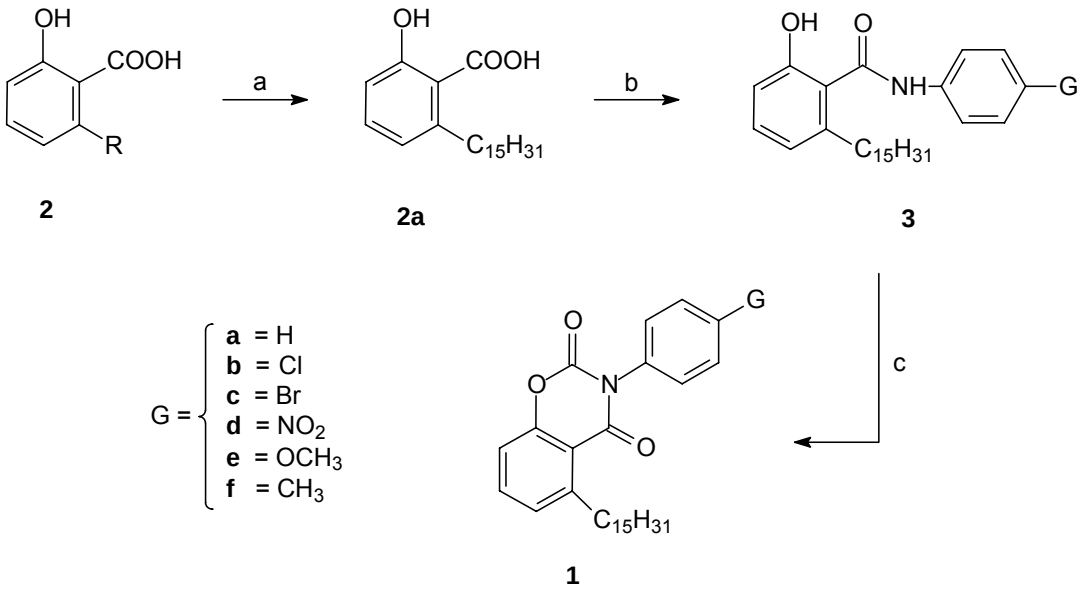


Figure 1. 5-Pentadecyl-3-aryl-1,3-benzoxazine-2,4-diones (**1**) and anacardic acids (**2**).

Apart from industrial use, anacardic acids have been described as potent fungicide[13] and bactericide.[14] Several analogues of well-known drugs have been prepared using **2a** and suggested fields of application are given based on their prototype currently in use.[15] These novel 3-phenyl-1,3-benzoxazine-2,4-diones (**1**) were structurally planned by maintenance of the 1,3-benzoxazine-2,4-diones subunit, a chemically hydrophilic moiety, which would retain high intrinsic activity of the well-known prototypes having no long alkyl side chain. The second structural feature consists in the presence of a C15 side chain group, which provide a hydrophobic character to the new compounds, so that would play an important role to bioactivity. Further structural modifications were replacement of the hydrogen atom at the G-position, for electron-withdrawing groups *e.g.* chlorine, bromine, nitro, as well as electron-donating groups *e.g.* methyl and methoxy, both elected in order to investigate the eventual electronic and hydrophobic contribution in assisting the enhanced activities of the analogues with long side chain.

RESULTS AND DISCUSSION

As outlined in Scheme 1, our approach for the synthesis of the title compounds involves the use of inexpensive anacardic acids (**2**) and features the use of triphosgene for one-step cycloaddition. Initially, the heterogeneous mixture of anacardic acids was quantitatively converted by conventionally catalytic hydrogenation into saturated anacardic acid (**2a**). This was converted to the corresponding anilides (**3a**-**f**) by heating with PCl_3 followed by treatment with appropriated anilines according to standard.[16] In this step the yields were very much influenced by the pureness of the commercially available anilines.



Scheme 1 - a) H_2, 10 % Pd-C, EtOH, 60 psi, rt, 2 h, 86%; b) PCl_3, PhCl, reflux, appropriated aniline, 40-80%; c) triphosgene, pyridine, CH_2Cl_2, rt, 12 h or overnight, 85-91%.

By analogy with the previous method for preparation of 3-phenyl-1,3-benzoxazines-1,4-dione which characterised by using of salicylanilide and ethyl chloroformate as synthetic tool for insertion of C=O unit, we decided that such a direct transformation could be possible by replacing the chloroformate reagent by triphosgene, a solid safe and convenient phosgene.[18] In this way, salicycilic acid was used primarily as model study and triphosgene as a reagent for one-pot preparation of the 3-phenyl-1,3-benzoxazine-2,4-dione in 81% yield. Attempts to promote the ring closure of the salicylanilide with ethyl chloroformate instead of triphosgene led to the 3-phenyl-1,3-benzoxazine-2,4-dione in 70% yield. Furthermore, by using triphogene was found simplicity of the work-up procedure. In light of the above experiments, the present methodology was applied for preparation of the 5-pentadecyl-3-phenyl-1,3-benzoxazine-2,4-diones (**1a**-**f**) from the corresponding anilides. The ring closure was smoothly promoted by

triphosgene in presence of pyridine, under very mild reaction conditions (Scheme 1). In the most cases the target compounds were obtained in high yield *ca.* 90%.

Interestingly, the presence of the alkyl side chain did not affect the reactivity of the anilides in the cyclization step, since **1a** was obtained in 81% from the **3a** similar to the model study. According to our current investigation, no influence related to the electronic effects of both electron-withdrawing and electron-donating groups was observed.

In conclusion, we have shown that triphosgene can be used for direct and mild conversion of salicylanilide into the 3-phenyl-1,3-benzoxazine-2,4-dione. The reaction also proved to be successful for preparation of novel substituted 3-phenyl-1,3-benzoxazine-2,4-diones from anacardic acids. This procedure can be used to promote cycloaddition in both electron-rich and electron-deficient with comparable very high yields. Noteworthy, we register here of the high efficiency and ready availability of the starting material, allied the structural features and potential activity of the title compounds.

EXPERIMENTAL

General Procedures. IR spectra were recorded on a Bomem Hartmann & Braun (MB – 100) spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on Varian Gemini and Mercury plus spectrophotometers (300 MHz) using $CDCl_3$/TMS. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS. The assignments of some ^{13}C-NMR signals were made with the aid of APT experiments. HRMS were obtained by electronic ionization (IE). Analytical TLC was performed on silica gel plates Merck ($60F_{254}$/0.2 mm), using 5% ethanolic phosphomolybidic acid or iodine vapors to visualize the spots. Melting points were obtained on a Köffler apparatus.

Preparation of 3-phenyl-1,3-benzoxazine-2,4-diones. A solution of the appropriated salicylanilide (0.5 mmol) in methylene chloride (15 mL), were added pyridine (0.15 mL) and triphosgene (250 mg; 1.0 mmol). The cloudy reaction mixture was stirred overnight at rt, under argon atmosphere. The reaction was diluted with ethyl acetate (20 mL) then, washed with brine. The organic phase was dried with sodium sulfate and the solvent was removed to furnish a solid, which was recrystallized from hexane-acetone to afford the corresponding benzoxazines (85-91%) as white or pale yellow crystals.

Physical Data

5-Pentadecyl-3-phenyl-1,3-benzoxazine-2,4-dione (**1a**): Yield 90%; R_f = 0.48 (4:1, hexane:ethyl acetate); mp 123-124°C (hexane-acetone); IR (KBr) cm^{-1}: 1764, 1696. ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.4 Hz, CH_3), 1.18-1.40 (24H, m, CH_2), 1.53-1.63 (2H, m, CH_2), 3.13-3.17 (2H, m, CH_2), 7.21 (2H, d, J = 7.8 Hz, Ar-H), 7.31 (2H, d, J = 7.0 Hz, Ar-H'), 7.47-7.58 (3H, m, Ar-H'), 7.62 (1H, t, J = 7.9 Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_3), 22.7 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 31.2 (CH_2), 31.9 (CH_2), 34.5 (CH_2), 112.0 (C), 114.7 (CH), 128.1 (CH), 128.2 (CH), 129.3 (CH), 129.6 (CH), 134.5 (C), 135.3 (CH), 148.1 (C), 154.0 (C), 160.8 (C). HRMS-IE *m/z* = 449.2930 (Calcd 449.2929). *Anal*. Calcd for $C_{29}H_{39}NO_3$: C, 77.47; H, 8.74; N, 3.12. Found: C, 77.52; H, 8.60; N, 3.03.

3-(4-Chlorophenyl)-5-pentadecyl-1,3-benzoxazine-2,4-dione (**1b**): Yield 89%; R_f = 0.51 (4:1, hexane:ethyl acetate); mp 115-116°C (hexane-acetone); IR (KBr) cm^{-1}: 1762, 1698. ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.6 Hz, CH_3), 1.20-1.35 (24H, m, CH_2), 1.47-1.62 (2H, m, CH_2), 3.14 (2H, t, J = 7.7 Hz, CH_2), 7.20 (2H, d, J = 8.2 Hz, Ar-H'), 7.25 (2H, d, J = 8.8 Hz, Ar-H), 7.51 (2H, d, J = 8.5, Ar-H'), 7.61 (1H, t, J = 8.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 14.4 (CH_3), 22.9 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 31.4 (CH_2), 32.1 (CH_2), 34.8 (CH_2), 112.0 (C), 114.8 (CH), 129.3 (CH), 129.8 (CH), 130.0 (CH), 133.1(C), 135.5 (C), 135.6 (CH), 147.8 (C), 148.4 (C), 154.2 (C), 160.3 (C). HRMS-EI: *m/z* = 483.2540 (Calcd 483.2540). *Anal*. Calcd for $C_{29}H_{38}NO_3Cl$: C, 71.96; H, 7.32; N, 2.89. Found: C, 69.39; H, 7.59; N, 2.73.

3-(4-Bromophenyl)-5-pentadecyl-3-phenyl-1,3-benzoxazine-2,4-dione (**1c**): Yield 91%; R_f = 0.51 (4:1, hexane:ethyl acetate); mp 103-104°C (hexane-acetone); IR (KBr) cm^{-1}: 1763, 1698. ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.6 Hz, CH_3), 1.20-1.40 (24H, m, CH_2), 1.50-1.62 (2H, m, CH_2), 3.11-3.20 (2H, m, J = 7.8 Hz, CH_2), 7.18-7.21 (4H, m, Ar-H'), 7.60-7.68 (3H, m, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_3), 22.7 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 31.1 (CH_2), 31.9 (CH_2), 34.5 (CH_2), 111.8 (C), 114.7 (CH), 123.4 (CH), 128.0 (CH), 130.0 (CH), 133.3 (C), 135.5 (C), 147.6 (C), 148.2 (C), 154.0 (C), 160.5 (C). HRMS-EI: *m/z* = 529.2020 (M+2) (Calcd 527.2035). *Anal*. Calcd for $C_{29}H_{38}NO_3Br$: C, 65.90; H, 7.25; N, 2.65. Found: C, 65.76; H, 7.18; N, 2.43.

3-(4-Nitrophenyl)-5-pentadecyl-1,3-benzoxazine-2,4-dione (**1d**): Yield 95%; R_f = 0.36 (4:1, hexane:ethyl acetate); mp 126-127°C (hexane-acetone); IR (KBr) cm^{-1}: 1767, 1698, 1521, 1350; ^1H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 6.6 Hz, CH_3), 1.40-1.60 (24H, m, CH_2), 1.72-1.82 (2H, m,

CH_2), 3.33 (2H, t, J = 7.7 Hz, CH_2), 7.43 (2H, d, J = 8.2 Hz, Ar-H), 7.73 (2H, d, J = 9.0 Hz, Ar-H'), 7.84 (1H, t, J = 8.0, Ar-H), 8.60 (2H, d, J = 8.8 Hz, Ar-H'); ^{13}C NMR ($CDCl_3$) δ: 14.3 (CH_3), 22.9 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.3 (CH_2), 32.1 (CH_2), 34.7 (CH_2), 111.8 (C), 115.0 (CH), 125.0 (CH), 128.5 (CH), 130.0 (CH), 135.9 (CH), 140.2 (C), 147.3 (C), 148.1 (C), 148.5 (C), 154.2 (C), 160.4 (C). HRMS: *m/z* = 495.2859 (M+1) (Calcd 494.2781). *Anal*. Calcd for $C_{29}H_{38}N_2O_5$: C, 70.42; H, 7.74; N, 5.66. Found: C, 70.86; H, 7.66; N, 5.88.

3-(4-Methylphenyl)-5-pentadecyl-1,3-benzoxazine-2,4-dione (**1e**): Yield 90%; R_f = 0.48 (4:1, hexane:ethyl acetate); mp 129-130 °C (hexane-acetone); IR (KBr) cm^{-1}: 1767, 1688; ^{1}H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.3 Hz, CH_3), 0.95-1.41(24H, m, CH_2), 1.43-1.66 (2H, m, CH_2), 2.42 (3H, s, $ArCH_3$), 3.14 (2H, t, J=7.5, $ArCH_3$), 7.18 (4H, d, J = 8.4, ArH'), 7.34 (2H, d, J = 8.4 Hz, Ar-H), 7.59 (1H, t, J = 7.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 14.1(CH_3), 21.2 (CH_3), 22.6 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 31.8 (CH_2), 34.5 (CH_2), 111.9 (C), 114.5 (CH), 127.7 (CH), 127.8 (CH), 130.3 (CH), 131.8 (C), 135.5 (CH), 135.1 (CH), 139.2 (C), 147.9 (C), 148.0 (C), 153.9 (C), 160.7 (C); HRMS: *m/z* = 463.3079 (Calcd 463.3086). *Anal*. Calcd for $C_{30}H_{41}NO_3$: C, 77.71; H, 8.91; N, 3.02. Found: C, 77.68; H, 8.68; N, 3.19.

3-(4-Methoxyphenyl)-5-pentadecyl-1,3-benzoxazine-2,4-dione (**1f**): Yield 85%; R_f = 0.40 (4:1, hexane:ethyl acetate); mp 132-133 °C (hexane-acetone); IR (KBr) cm^{-1}: 1773, 1688. ^{1}H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.3 Hz, CH_3), 0.93-142 (24H, m, CH_2), 1.58 (2H, q, J =7.5, CH_2), 3.15 (2H, t, J = 7.5 Hz, CH_2), 3.85 (3H, s, OCH_3), 7.05 (2H, d, J = 9.0 Hz, Ar-H'), 7.18 (2H, d, J = 8.7, Ar-H'), 7.22 (2H, d, J = 9.0 Hz, Ar-H), 7.61 (1H, t, J = 8.1 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_3), 22.6 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 32.9 (CH_2), 34.5 (CH_2), 55.5 (OCH_3), 111.9 (C), 114.2 (CH), 114.6 (CH), 114.9 (CH), 126.9 (C), 127.9 (CH), 129.1 (CH), 135.1(CH), 148.1 (C), 154.0 (C), 159.9 (C), 160.9 (C); HRMS: *m/z* = 479.3033 (Calcd 479.3039). *Anal*. Calcd for $C_{30}H_{41}NO_4$: C, 75.12; H, 8.62; N, 2.92. Found: C, 74.83; H,8.5 8.53; N, 3.13.

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