Synthetic Applications of 3,4-Dihalo-2(5*H*)-furanones: A Formal Total Synthesis of Nostoclides I and II

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Received 12 September 2002; revised 21 September 2002

Abstract: 3-Benzyl-4-isopropyl-2(5*H*)-furanone, which is a precursor to two naturally-occurring cytotoxic (*Z*)-5-ylidene-2(5*H*)-furanone derivatives, has been conveniently prepared from 3,4-dibromo-2(5*H*)-furanone by a three-step procedure involving two Pd-catalyzed cross-coupling reactions and a Rh(I)-catalyzed hydrogenation.

Key words: 2(5*H*)-furanones, cross-coupling, regioselectivity, Stille reaction, benzylation

We have previously described convenient and efficient methods for the synthesis of 3,4-dihalo-2(5*H*)-furanones **1**[1] and **2**[2] and the use of these flexible synthetic species to prepare natural and synthetic products containing the 2(5*H*)-furanone subunit.[1–4] In particular, we reported that 4-aryl-3-bromo-2(5*H*)-furanones **3** can be selectively synthesized in satisfactory yields by either Stille-type reactions with aryl(trialkyl)stannanes[1,3] or Suzuki-type reactions with arylboronic acids.[3] Bromides **3** proved to be useful precursors to 3,4-diaryl-2(5*H*)-furanones **4**,[1] including Rofecoxib (**4a**) which is an antiinflammatory drug launched by Merck and approved by FDA, 4-aryl-3-methyl-2(5*H*)-furanones **5**,[1] 4-aryl-2(5*H*)-furanones **6**,[1] and (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-bromo-2(5*H*)-furanones **7**,[3] including the compound with the structure corresponding to that reported for rubrolide N (**7a**), which is a natural product isolated from *Synoicum blochmanni*[5] (Figure 1).

Further investigations allowed us to find that dibromide **1** is able to undergo regioselective reaction with a variety of primary alkylboronic acids in the presence of catalytic amounts of $PdCl_2(MeCN)_2$ and Ph_3As and a molar excess of Ag_2O to provide the corresponding 4-alkyl-3-bromo-2(5*H*)-furanones **8** in satisfactory yields.[4] These last compounds proved to be useful precursors to unsymmetrically 3,4-dialkyl substituted 2(5*H*)-furanones **9**,[4] including the racemic form of seiridin (**9a**), which is a naturally occurring homochiral compound isolated from *Seiridium cardinale*.[6]

Recently, we also reported that 3-aryl-4-chloro-2(5*H*)-furanones **10** can be regioselectively prepared in satisfactory yields by the reaction of dichloride **2** with either arylboronic acids in toluene at 85 °C in the presence of KF and catalytic amounts of $Pd_2(dba)_3$ and (*o*-Tolyl)$_3$P or aryl(tributyl)stannanes in 1-methyl-2-pyrrolidinone (NMP) at 85 °C in the presence of catalytic amounts of $Pd_2(dba)_3$ and (*o*-Tolyl)$_3$P.[2] We then used compounds **10** as precursors to some cytotoxic (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones **11**[2] including rubrolide M (**11a**), which is another compound isolated from the red colonial tunicate *S. blochmanni*[5,7] (Figure 2).

More recently, as part of an effort to explore the use of compounds **1** and **2** for the selective synthesis of natural and synthetic substances which are potentially cytotoxic against human tumor cell lines,[2,3,8] we began an investigation on the synthesis of either nostoclides I (**12**) and II (**13**), which are a pair of cytotoxic 2(5*H*)-furanone derivatives produced by a cyanobacterium,[9] or some congeners of these natural products starting from the dibromide **1**. Herein, we report a formal total synthesis of **12** and **13**, which involves a convenient and concise preparation of 4-benzyl-3-isopropyl-2(5*H*)-furanone (**14**), a compound which Boukovalas and co-workers synthesized in five steps from 2(5*H*)-furanone (**15**) in 19–23% overall yield

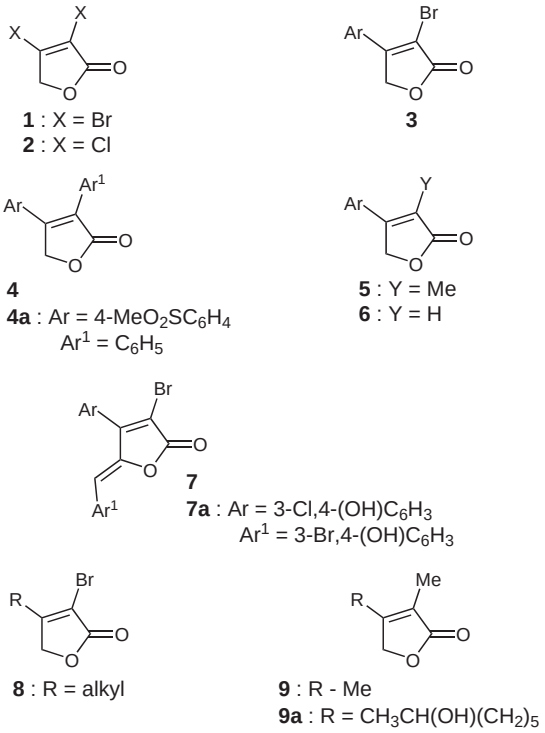


Figure 1 The structures of compounds **1**–**9**

Synthesis 2002, No. 18, Print: 19 12 2002.
Art Id.1437-210X,E;2002,0,18,2729,2732,ftx,en;Z12302SS.pdf.

ISSN 0039-7881

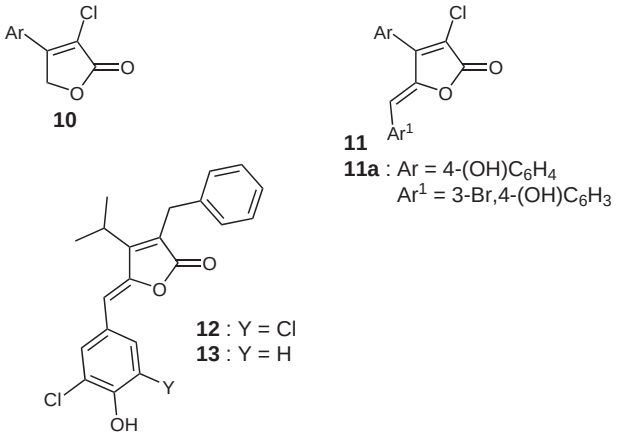


Figure 2 The structures of compounds **10**–**13**

and used as precursor to **12** and **13** in the first total synthesis of these natural products[10] (Figure 3).

Initially, we planned to prepare **14** in two steps by Pd-catalyzed regioselective alkylation of **1** with isopropylboronic acid (**16**)[11] followed by a Pd-catalyzed benzylation reaction of the resulting monobromide **8a**. However, when we attempted to prepare **8a** by treatment of **1** with 1.1 equivalents of **16** in THF under reflux for 39 hours in the presence of 3 equivalents of Ag_2O and 5 mol% $PdCl_2(MeCN)_2$, i.e. using the reaction conditions which we previously developed and employed to prepare a variety of compounds of general formula **8**,[4] we observed that the reaction did not occur at all. We also found that when **1** was reacted with **16** in toluene at 80 °C for 18 hours in the presence of 2.5 mol% of $Pd_2(dba)_3$, 10 mol% of (*o*-Tolyl)$_3$P and 3.0 equivalents of KF, dibromide **1** was completely consumed but the reaction did not produce any trace of **8a** at all. Moreover, a negative result was obtained when **1** was reacted with isopropylmagnesium bromide (**17**) in THF at –70 °C in the presence of 2.5 mol% of $PdCl_2(Ph_3P)_2$.[12] Nevertheless, we succeeded to prepare **8a** in two steps from **1** in 74% overall yield (Scheme 1). In fact, reaction of **1** with 1.1 equivalents of isopropenyltributyltin (**18**) in NMP at room temperature for 5 days in the presence of 5 mol% $PdCl_2(PhCN)_2$ and 10 mol% Ph_3As gave **19** in 78% yield.[1] Subsequent hydrogenation

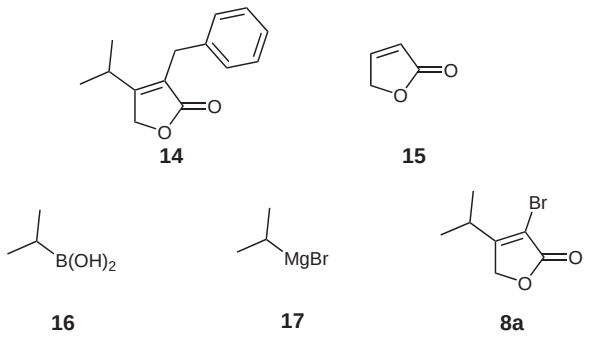
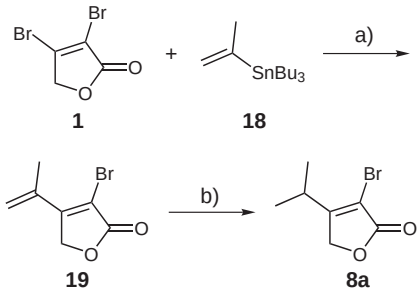


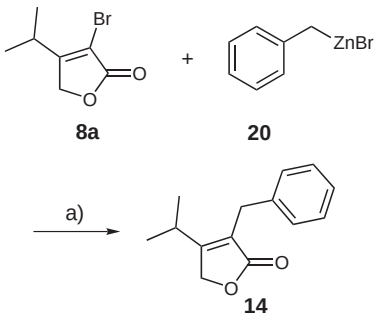
Figure 3 The structures of compounds **8a** and **14**–**17**

of this compound in benzene solution in the presence of 3 mol% $RhCl(PPh_3)_3$ furnished **8a** in 95% yield[13] (Scheme 1).



Scheme 1 a) **18** (1.1 equiv), $PdCl_2(PhCN)_2$ (5 mol%), Ph_3As (10 mol%), NMP, r.t., 5 d, 78%; b) $RhCl(Ph_3P)_3$ (3 mol%), H_2 (1 atm), benzene, r.t., 95%

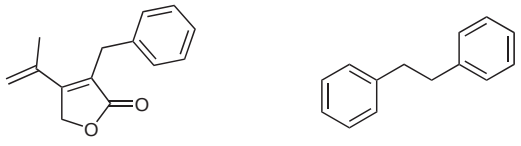
Finally, we examined the preparation of **14** by Pd-catalyzed benzylation of **8a** and found that treatment of this bromide with 1.2 equivalent of benzylzinc bromide (**20**) in a 1: 1 mixture of DMF and THF at 60 °C for 5 hours, in the presence of 5 mol% $PdCl_2[(o\text{-Tolyl})_3P]_2$[14] gave compound **14** in 36% yield (Scheme 2).[15,16] The physical and spectral properties of this compound were in agreement with those previously reported.[10]



Scheme 2 a) **20** (1.2 equiv), DMF/THF (1:1), $PdCl_2[(o\text{-Tolyl})_3P]_2$ (5 mol%), 60 °C, 5 h, 36%

It is worth mentioning that we attempted to prepare **14** in a higher yield via Pd-catalyzed benzylation of **19** followed by selective hydrogenation of the resulting 3-benzyl-4-isopropenyl-2(5*H*)-furanone (**21**). However, we did not succeed to prepare this compound using a protocol similar to that employed for the synthesis **14**. In fact, treatment of **19** with **20** in DMF and THF at 60 °C in the presence of 5 mol% $PdCl_2[(o\text{-Tolyl})_3P]_2$ afforded a reaction mixture in which we observed only the presence of 1,2-diphenylethane (**22**), the dimeric product of benzylzinc bromide (Figure 4). We also found that compound **19** was completely consumed.

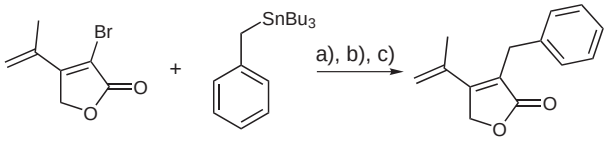
Finally, after a considerable experimentation as regards the catalyst system and the experimental conditions of the Stille reaction between **19** and benzyltributyltin (**23**), we found that treatment of **19** with 1.3 equivalents of **23** in NMP at 80 °C for 45 hours, in the presence of 2.5 mol%



21 **22**

Figure 4 The structures of compounds **21** and **22**

$Pd_2(dba)_3$, 10 mol% (2-furyl)$_3$P and 10 mol% CuI, provided compound **21** in 22% yield (Scheme 3).[17]



19 **23** **21**

Scheme 3 a) **23** (1.3 equiv), $Pd_2(dba)_3$ (2.5 mol%), (2-furyl)$_3$P (10 mol%), CuI (10 mol%), NMP, 80 °C, 45 h; b) KF, Et_2O, H_2O; c) MPLC on silica gel, 22%

However, the low yield of **21** prompted us to drop the idea to prepare **14** via the route involving synthesis and selective hydrogenation of this 4-alkenyl-2(5*H*)-furanone derivative.

In conclusion, we developed a new and concise method for the synthesis of 4-benzyl-3-isopropyl-2(5*H*)-furanone (**14**), which is a precursor to nostoclides I (**12**) and II (**13**).[10] This method, which allows compound **14** to be prepared in three steps and in 27% overall yield starting from dibromide **1**, represents an attractive alternative to the previously established procedure.[10] We are currently investigating the use of **14** for the synthesis of some congeners of naturally occurring **12** and **13**.

Melting points are uncorrected. Precoated aluminum silica gel sheets Merck 60 F_{254} were used for TLC analyses. GC analyses were performed on a DANI GC 1000 instrument with PTV injectors, which were equipped with a DANI data station DS-1000. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m × 0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by MPLC on silica gel (Merck silica gel 60, particle size 0.015–0.040mm) were performed on a Büchi B-680 system using a Knauer differential refractometer as detector. GC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer gas chromatograph. IR spectra were recorded on a Perkin–Elmer 1725 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Varian Gemini 200 spectrometer using TMS as an internal standard. All reactions of air and water sensitive materials were performed in flame dried glassware under argon using standard syringe, cannula and septum techniques. Solvents were dried and distilled before use. Petroleum ether used had bp 40–60 °C. The following compounds were prepared by published procedures: 3,4-dibromo-2(5*H*)-furanone (**1**),[3] isopropenyltributyltin (**17**),[17] benzyltributyltin (**22**).[18] $PdCl_2(PhCN)_2$, Ph_3As, $RhCl(Ph_3P)_3$, $PdCl_2[(o\text{-Tol})_3P]_2$, CuI, benzylzinc bromide (0.5 M solution in THF) were obtained from Aldrich and used as received.

3-Bromo-4-isopropenyl-2(5*H*)-furanone (19)

To a solution of 3,4-dibromo-2(5*H*)-furanone (**1**; 7.26 g, 30.0 mmol), $PdCl_2(PhCN)_2$ (0.58 g, 1.5 mmol) and Ph_3As (0.92 g, 3.0 mmol) in NMP (50 mL) was added a solution of isopropenyltributyltin (**18**; 10.93 g, 33.0 mmol) in NMP (10 mL), and the resulting red colored solution was stirred at r.t. for 5 d. The mixture was then poured into a sat. aq NH_4Cl solution (300 mL) and extracted with EtOAc (4 × 100 mL). The combined organic extracts were stirred for 5 h at r.t. with an aq 50% KF solution (400 mL), filtered over Celite and the filtrate was extracted with EtOAc (4 × 80 mL). The combined organic extracts were washed with H_2O (4 × 100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to furnish a brown solid, which was purified by MPLC on silica gel with $CHCl_3$–petroleum ether (70:30 + 1% EtOAc) as eluent. The chromatographic fractions containing the required compound were concentrated under reduced pressure to give pure **19** as a pale yellow solid; yield 4.75 g (78%, 99% purity by GC); mp 56–58 °C.

IR (KBr): 1753, 1616, 1584, 1456, 1038, 985, 926 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.22 (m, 3 H), 4.93 (s, 2 H), 5.49 (q, 1 H, *J* = 1.5 Hz), 5.59 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 21.1, 71.6, 107.2, 122.1, 135.1, 156.6, 169.7.

MS: *m*/*z* (%) = 204 (30), 202 (31), 175 (53), 173 (56), 147 (41), 145 (41), 65 (100).

Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.48. Found: C, 41.65; H, 3.38.

3-Bromo-4-isopropyl-2(5*H*)-furanone (8a)

A solution of 3-bromo-4-isopropenyl-2(5*H*)-furanone (**19**; 2.03 g, 10.0 mmol) in benzene (20 mL) was added to a solution of $RhCl(Ph_3P)_3$ (0.28 g, 0.3 mmol) in benzene (30 mL). The mixture was vigorously stirred under an H_2 atmosphere at r.t. and the uptake of gas was monitored. After 5 h, the uptake had ceased and the mixture was diluted with benzene (10 mL) and concentrated under reduced pressure. The residue was purified by MPLC on silica gel with CH_2Cl_2–hexane (60:40 + 1% EtOAc) as eluent. The chromatographic fractions containing the required compound were concentrated under reduced pressure to give pure **8a** as a pale yellow liquid; yield 1.94 g (95%, 99% purity by GC).

IR (film): 1768, 1636, 1347, 1179, 1015, 985, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 7.0 Hz, 6 H), 3.09 (hept, 1 H, *J* = 7.0 Hz), 4.82 (d, 2 H, *J* = 0.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 19.8, 28.9, 70.5, 106.8, 169.1, 169.4.

MS: *m*/*z* (%) = 206 (17), 204 (18), 164 (97), 162 (100), 125 (47), 97 (32), 67 (59).

Anal. Calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.42. Found: C, 41.09; H, 4.36.

3-Benzyl-4-isopropyl-2(5*H*)-furanone (14)

To a solution of 3-bromo-4-isopropyl-2(5*H*)-furanone (**8a**; 1.03 g, 5.0 mmol) and $PdCl_2[(o\text{-Tol})_3P]_2$ (0.20 g, 0.25 mmol) in DMF (25 mL) and THF (13 mL), which was warmed up to 60 °C, was added a 0.5 M solution of benzylzinc bromide in THF (**20**; 12 mL, 6.0 mmol). The red colored reaction mixture was stirred for 5 h at 60 °C, then cooled to r.t., poured into a sat. aq NH_4Cl solution (200 mL) and extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with H_2O (6 × 50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to furnish a brown solid, which was purified by MPLC on silica gel with CH_2Cl_2–hexane (60:40 + 1% EtOAc) as eluent. The chromatographic fractions containing the required compound were concentrated under reduced pressure to give pure **14** as a pale yellow solid; yield: 0.39 g (36%, 98% purity by GC); mp 55–56 °C (Lit.[10] mp 55–56 °C).

IR (KBr): 1750, 1660, 1452, 1338, 1169, 1073, 1054, 1007 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.10 (d, 6 H, *J* = 7.0 Hz), 3.06 (hept, 1 H, *J* = 7.0 Hz), 3.62 (s, 2 H), 4.71 (s, 2 H), 7.21 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 20.9 (2 C), 27.2, 29.4, 68.7, 124.3, 126.3, 128.3 (2 C), 128.4 (2 C), 138.1, 166.8, 174.9.

MS: *m*/*z* (%) = 216 (14), 173 (37), 155 (16), 129 (100), 128 (23), 115 (21), 91 (30).

3-Benzyl-4-isopropenyl-2(5*H*)-furanone (21)

To a solution of 3-bromo-4-isopropenyl-2(5*H*)-furanone (**19**; 0.30 g, 1.5 mmol), $Pd_2(Pdba)_3$ (0.03 g, 0.04 mmol), $(2\text{-furyl})_3P$ (0.04 g, 0.15 mmol) and CuI (0.03 g, 0.15 mmol) in NMP (5 mL) was added a solution of benzyltributyltin (**23**; 0.73 g, 1.92 mmol) in NMP (2 mL), and the resulting mixture was refluxed for 45 h. The mixture was poured into a sat. aq NH_4Cl solution (100 mL) and extracted with EtOAc (4 × 20 mL). The combined organic extracts were then stirred for 6 h at r.t. with an aq 50% KF solution (100 mL), filtered over Celite and the filtrate was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (4 × 30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to furnish a reddish viscous oil, which was purified by MPLC on silica gel with CH_2Cl_2–petroleum ether (60:40 + 1% EtOAc) as eluent. The chromatographic fractions containing the required compound were concentrated under reduced pressure to give pure **21** as an orange oil; yield 0.07 g (22%, 95% purity by GC).

^1H NMR ($CDCl_3$): δ = 2.04 (m, 3 H), 3.83 (s, 2 H), 4.87 (s, 2 H), 5.24 (m, 1 H), 5.30 (m, 1 H), 7.21 (m 5 H).

^{13}C NMR ($CDCl_3$): δ = 21.6, 30.1, 74.5, 120.0, 125.5, 126.3, 128.1 (2 C), 128.5 (2 C), 136.0, 138.0, 157.0, 175.1.

MS: *m*/*z* (%) = 214 (80), 169 (100), 153 (40), 141 (76), 129 (78), 115 (51), 91 (68).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.63; H, 6.65.

Acknowledgment

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) and the University of Pisa.

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(13) It should be noted that when we attempted to prepare **8a** by hydrogenation of **18** in toluene at r.t. in the presence of 10 mol% Pd on $BaSO_4$, the reaction provided significant amounts of a compound which had a MS spectrum corresponding to that of 4-isopropyl-2(5*H*)-furanone.
(14) The catalyst precursor constiting of $Pd_2(dba)_3$ (2.5 mol%)/$(o\text{-Tol})_3P$ (10 mol%) gave a similar yield, while the use of $Pd_2(dba)_3$ (2.5 mol%)/Ph_3As (10 mol%) or $Pd(PPh_3)_4$ (5 mol%) as catalyst precursors gave less satisfactory results.
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(16) It should be noted that the crude product, derived from the Pd-catalyzed reaction of **8a** with **20**, contained compound **14** and significant amounts of 1,2-diphenylethane (**22**) and a compound which had a MS spectrum in agreement with that of 3,5-dibenzyl-4-isopropyl-2(5*H*)-furanone.
The use of $PdCl_2[(o\text{-Tol})_3P]_2$ (5 mol%)/CuI (10 mol%), $Pd_2(dba)_3$ (2.5 mol%)/Ph_3As (10 mol%)/CuI (10 mol%) or $Pd_2(dba)_3$ (2.5 mol%)/*t*-Bu_3P (10 mol%)/CuI (10 mol%) as catalyst precursors in NMP at 85 °C gave less satisfactory results, while employing $Pd_2(dba)_3$ (2.5 mol%)/*t*-Bu_3P (10 mol%) as a catalyst precursor in dioxane at reflux and in the presence of 3 equiv of KF no product was obtained.
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