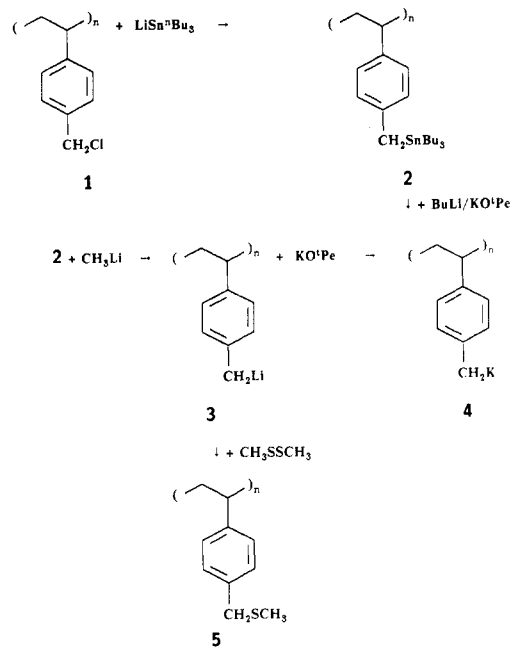
Scheme I



The two major routes[3] to organolithium reagents from chlorides, direct reaction with the metal and metal–halogen exchange with alkyllithiums, are not applicable to polymer-bound CH_2Cl groups. The former fails because both reagents are insoluble and the latter because Wurtz coupling is very effective in polymer systems. However, metal–metal exchange is also a valuable route to organolithium reagents[3] and can be applied successfully to chloromethylated polystyrenes by first substituting the polymer in a Wurtz-type step and then performing the metal–metal exchange reaction.

If a commercial Merrifield resin (**1**) is allowed to swell in THF and then reacted with LiSn-*n*-Bu_3 at 15 °C for 24 h, the reaction solution filtered off, and the polymer washed several times with THF, a slightly yellow tributyltin-substituted polymer (**2**) is obtained. This polymer is not only a valuable intermediate for organometallically substituted polymers but may also have considerable potential as a precursor for radical centers on the polymer. Polymer **2** is stable indefinitely under normal conditions and can therefore be made in large batches and stored for further use. The benzylic carbon–tin bond can be cleaved by a variety of reagents. For instance, reaction with methyllithium in THF at 20 °C for 3 h yields the benzyllithium derivative of the polymer (**3**) in quantitative yield (based on acid/base titration with standard alcohol[4] using the red color of the polymer as indicator and on microanalyses for Cl and Sn on the hydrolyzed polymer and for S on samples quenched with MeSSMe). Similarly, the potassium derivative **4** may be produced by direct cleavage of the tin polymer with butylpotassium (made by metal–metal exchange between butyllithium and potassium *tert*-pentanolate[5]) at −78 °C to prevent reaction of the butylpotassium with THF, but the conversion is not complete at this temperature. A better procedure is to perform the corresponding metal–metal exchange on the lithiated polymer (see Scheme I).

Experimental Section

Typical experimental procedures are as follows (all operations were carried out under an argon atmosphere):

(Tri-*n*-butylstannyl)lithium[6] was prepared by adding 40.8 mL (150 mmol) of tri-*n*-butyltin chloride to a suspension of 4.9 g (707 mmol) of lithium sand in 180 mL of THF (distilled from benzophenone/potassium) at 15 °C over 2 h. The suspension was stirred for 6 h, and the dark green solution was then filtered from the solids and stored under argon at 0 °C. The yield of (tri-*n*-butylstannyl)lithium was estimated by acid–base titration. Some hexa-*n*-butylditin is formed as a byproduct, but does not interfere with the subsequent reaction.

Poly[4-[(tri-*n*-butylstannyl)methyl]styrene] (2) was prepared by stirring 50 g of resin **1** [130 mequiv of CH_2Cl, prepared by chloromethylation[7] of 3% cross-linked polystyrene beads (Janssen)], swollen in 100 mL of THF with LiSn-*n*-Bu_3 (200 mmol) for 1 h at 15 °C. The mixture was allowed to stand in the refrigerator for 24 h and then stirred at 40 °C for 2 h. The polymer was filtered off, washed with THF, water, methanol, and ether, and dried under vacuum for 24 h to give 56.5 g of **2**. Analyses for chlorine and tin gave 98% elimination of the former from the original polymer and 96% incorporation of tin. Commercial polymer **1** [1.5 mequiv of Cl/g, 2% cross-linked (Merck-Schuchardt)] gave the same results.

Poly[4-(lithiomethyl)styrene] (3) was obtained by adding 1.0 mL of 1.5 N methyllithium in ether at −78 °C to 500 mg (0.76 mmol of Sn-*n*-Bu_3) of resin **2** in 20 mL of THF. The mixture was allowed to warm to room temperature with stirring over 3 h to give orange-red polymer beads which were washed with precooled (0 °C) THF (2 × 10 mL). Analysis by direct titration with a standard 2-butanol solution in toluene[4] until the red color disappeared or by adding excess CH_3SSCH_3 to the polymer at −78 °C and warming to room temperature to give a colorless CH_2SCH_3-substituted polymer (**5**) followed by microanalysis for tin and sulfur indicated quantitative conversion of **2** to **3**.

Poly[4-(potassiomethyl)styrene] (4). Method A. Polymer **3** (prepared and washed as above) was stirred in THF with 2 equiv of 1.6 M potassium *tert*-pentanolate in hexane for 2 h at 20 °C. The color of the polymer beads changes from orange-red to dark red.

Method B. Polymer **2**, swollen in THF at room temperature, was cooled to −78 °C and stirred with an excess of a 1:1 mixture of 1.6 M *n*-butyllithium and 1.6 M potassium *tert*-pentanolate (both in hexane). Even for large excesses of the base and long reaction times, the percentage conversion was never higher than 90% (analysis as above).

Registry No. CH_3Li, 917-54-4; BuK, 6231-20-5.

(3) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974.
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A New Isocyanide from a Sponge. Is the Formamide a Natural Product?

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Isocyanide metabolites have been isolated from several species of marine sponges.[1] In almost all cases, the isocyanide is accompanied by the corresponding isothio-

(1) For example: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551–598; **1986**, *3*, 1–33.

0022-3263/88/1953-3366$01.50/0

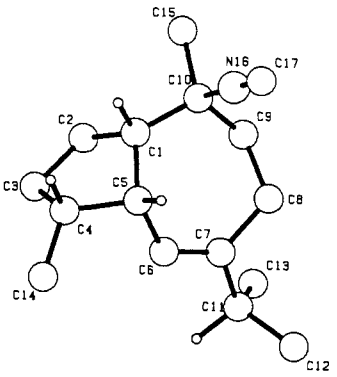
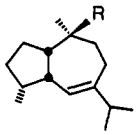


Figure 1. Perspective view of 1. Hydrogen atoms of methyl and methylene groups were omitted for clarity, and no absolute configuration is implied.

cyanate and formamide. Here we describe a guai-6-ene isocyanide–isothiocyanate–formamide series from an unidentified sponge.[2]

Extraction of the frozen sponge by dichloromethane followed by group separation of the extract on an ODS column gave a sesquiterpene fraction, which was subjected to silica gel chromatography to give a crude isocyanide fraction. Recrystallization of this fraction yielded pure and highly crystalline isocyanide 1: mp 57–59 °C; $[\alpha]_D$ –60.1°



1 : R=NC
2 : R=NHCHO
3 : R=NCS

(*c*, 0.4 $CHCl_3$); $C_{16}H_{25}N$ (from elemental analysis[3] and mass spectrum). The IR spectrum (2120 cm^{-1}) coupled with MS data [*m/z* 231 (M^+), 205 (base peak, M^+ – NC), 188 (M^+ – isopropyl)] indicated that 1 was sesquiterpene isocyanide. As the ^1H NMR spectrum [δ 0.97, 0.98, 2.26 (*i*-Pr), 1.06 (*sec*-Me), 1.36 ($<^{Me}_{NC}$), 5.17 ($>=<_H$)] and the ^{13}C NMR spectrum (Me × 4, CH_2 × 4, CH × 4, C × 1, C=C, NC) were complex, the structure of 1 was determined by X-ray analysis as shown in Figure 1.

Isocyanide 1 represents the first isolation of the guai-6-ene skeleton from nature. The compound showed potent cytotoxic activity in vitro: ED_{50} = 0.19 μg/mL for L-1210 cells and ED_{50} = 0.27 μg/mL for HeLa cells.[4]

The fraction eluting after the isocyanide was further purified by preparative RPHPLC using ODS and CN columns successively to obtain formamide 2: mp 162–165 °C; IR (KBr) 3330, 3250, 1675, 1625 cm^{-1}; MS, *m/z* 204 (M^+ – NH_2CHO), 161 (base peak, 204 – isopropyl); ^1H NMR ($CDCl_3$) δ 8.33 and 8.14 (CHO), 5.90 and 5.32 (NH), and 1.38 and 1.31 ($<^{Me}_{NHCHO}$) (these doublets became singlets at 140 °C).

Another fraction eluting after the isocyanide fraction was subjected to ODS chromatography and yielded isothiocyanate 3: IR ($CHCl_3$) 2100 cm^{-1}; MS, *m/z* 263 (M^+, base peak), 205 (M^+ – NCS), 204 (M^+ – HNCS), 161 (204 – isopropyl); ^1H NMR ($CDCl_3$) δ 5.17 ($>=<_H$), 1.33 ($<^{Me}_{NCS}$), 1.06 (*sec*-Me), 0.96, 0.97 (*i*-Pr).

When pure isocyanide 1 was examined on a TLC plate (SiO_2, RP-18, and CN), a small polar spot was always observed. Compound 1 was completely converted to the polar material if a plate spotted with 1 was left overnight. For preparative purposes, a solution of isocyanide 1 was mixed with the pulverized support of RPTLC plate and left standing for 2 days. Extraction of the support with dichloromethane afforded formamide 2. This conversion could also be achieved by passing 1 through an ion-exchange resin (H^+ form) column. Since isocyanides are known to be converted to formamides by acid, conversion of 1 to 2 on a TLC plate may be due to hydration catalyzed by silanol or by a trace of acid adsorbed on the support of the TLC plate.[5]

We concluded that our formamide 2 may have been derived from the isocyanide 1 during the separation by column chromatography.[5,6] Although formamides may be natural products,[7] isocyanides may be converted into formamides during chromatography, suggesting that the formamide is not always a natural product but may be an artifact.

Experimental Section

Isolation. The frozen sponge material[2] was directly immersed in dichloromethane for simultaneous defrosting and extraction. The organic layer gave a lipophilic extract (680 mg), which was chromatographed on ODS (YMC-ODS, 105–125 μm, MeOH) for group separation. The second fraction (246 mg) was then rechromatographed on silica gel (Merck, 63–85 μm), and *n*-hexane eluate (165 mg) was recrystallized from aqueous EtOH to yield pure isocyanide 1 (63 mg). The following dichloromethane eluate (49 mg) was applied to an ODS column [Develosil ODS, 7 μm, packed in a heavy-wall glass column 10 (i.d.) × 250 mm, MeOH–H_2O (9:1)], and the formamide fraction (12 mg) was rechromatographed on a CN column [YMC-CN, 10 μm, packed in a heavy-wall glass column 14 (i.d.) × 250 mm, hexane–CH_2Cl_2 (3:2)], giving pure formamide 2 (2 mg). The third fraction (75 mg) of the group separation was rechromatographed on Develosil ODS, which gave isothiocyanate 3 (5 mg).

Conversion of Isocyanide 1 to Formamide 2. (a) A solution of 1 was spotted on a TLC plate (Merck), which was tightly covered with a glass plate and left standing overnight. Complete conversion was observed after development of the plate: SiO_2, R_f 0.37, hexane–CH_2Cl_2 (1:1) → R_f 0.32, CH_2Cl_2–MeCN (9:1); RP-18, R_f 0.49 → R_f 0.57, MeOH; CN, R_f 0.63 → R_f 0.36, MeCN–H_2O (3:1). (b) To a solution of 1 (10 mg) was added the support material stripped off from an RPTLC plate (Merck). After evaporation of the solvent in vacuo, the RP support was left for 2 days. Extraction with CH_2Cl_2 gave a white solid (9 mg), which proved to be identical with 2 (IR, MS, and ^1H NMR). (c) A solution of 1 (10 mg) in 80% aqueous MeOH was passed through a column of Dowex 50W × 8 (H^+ form). Evaporation of the eluate gave a residue, which was identical with 2 (IR and ^1H NMR).

X-ray Diffraction Analysis Data. Crystal data: monoclinic, *C*2, *a* = 24.966 (5) Å, *b* = 6.666 (1) Å, *c* = 13.679 (4) Å, β = 138.75 (1)°, *Z* = 4, *V* = 1501.0 (6) Å^3, D_{calcd} = 1.024 g/cm^3. Intensity data of 1231 unique reflections with $2\theta \leq 120°$ were collected on a Rigaku diffractometer using Cu Kα radiation. The structure was solved by direct methods and refined by a block-diagonal least-squares technique to R = 0.045 for 1107 observed reflections with $|F_o| > 3\sigma(F_o)$. Additional crystallographic details are available as supplementary material.

(2) The specimen has been retained pending identification (class Demospongia). The sponge material was obtained at Wakayama Prefecture (30-m depth) with a dragnet and was extracted before identification. The material was so badly damaged that it could not be identified despite the efforts of Dr. T. Hoshino of Hiroshima University. We thank him for trying to find its scientific name.

(3) Calculated for $C_{16}H_{25}N$: C, 83.05; H, 10.89; N, 6.05. Found: C, 82.51; H, 10.85; N, 6.00.

(4) Krebs, H. Chr. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: Wien, 1986; Vol. 49, pp 151–363.

(5) If ODS is manufactured by using alkylsilyl chloride, a trace of acid may often remain in the packing material, even after exhaustive washings.

(6) We have encountered a conversion catalyzed by packing materials during the isolation of dialdehydic metabolites on an ODS column, which gave a bishemiacetal: Yasuda, F.; Tada, H. *Experientia* **1981**, *37*, 110–111.

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Supplementary Material Available: Tables of atomic positional parameters, bond lengths, and bond angles for 1 (3 pages). Ordering information is given on any current masthead page.

On the Synthesis of 4-Alkoxy-2(5*H*)-furanones

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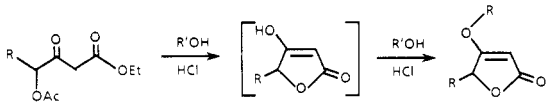
Enol ethers of β-tetronic acid represent useful synthons for the synthesis of natural products derived from β-tetronic acid (4-hydroxy-2(5*H*)-furanone, **1**).[2] As a continuation of our interest in the chemistry of **1**[3a–c] we became interested in finding a simple and convenient method for the preparation of alkyl ethers of **1**.

There exists a sizeable literature on the synthesis of these compounds. Virtually all of such reports, however, are restricted to methyl and ethyl ethers of **1** formed by using a number of different alkylating agents.[4–10]

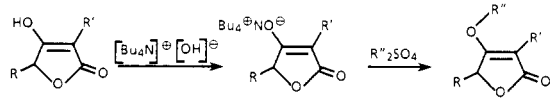
Recently, a novel route to these compounds was introduced by Gelin,[11] reporting that the desired compounds could be obtained by lactonization of γ-acetoxy-β-keto esters in the presence of 1% hydrochloric acid in methanol or ethanol (eq 1).



(1)

The benzyl ether was obtained more conveniently by refluxing **1** in benzene in the presence of benzyl alcohol and a catalytic amount of *p*-toluenesulfonic acid.[11] Boll and co-workers questioned these results.[12] They reported difficulties in repeating the procedures of the French group.[11] They also doubted the structural assignments and stated that isomeric 2-alkoxy-4(5*H*)-furanones could have been formed as well under the cited reaction condition.

Boll et al.[12] showed that 4-methoxy- and 4-ethoxy-2(5*H*)-furanones could be obtained reproducibly by stirring tetrabutylammonium tetronate with dimethyl or diethyl sulfate for 1 or 10 h, respectively (eq 2). For the preparation of 4-*O*-methyl-**1**, a second method was given. It could be obtained by alkylating **1** directly with trimethyloxonium tetrafluoroborate.



(2)

(1) On leave from Faculty of Science, Alexandria University, Egypt.
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(3) (a) Schmidt, D. G.; Zimmer, H. *J. Org. Chem.* **1983**, *48*, 4367. (b) Schmidt, D. G.; Zimmer, H. *J. Heterocycl. Chem.* **1983**, *20*, 787. (c) Schmidt, D. G.; Zimmer, H. *Synth. Commun.* **1981**, *11*, 385. (d) Zimmer, H.; Hillstrom, W. W.; Schmidt, J. C.; Seemuth, P. D.; Vögeli, R. *J. Org. Chem.* **1978**, *43*, 1541.
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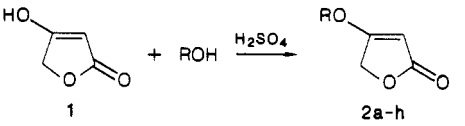
(7) Kumler, W. D. *J. Am. Chem. Soc.* **1938**, *60*, 2532.
(8) Calam, C. T.; Todd, A. R.; Waring, W. S. *Biochem. J.* **1949**, *45*, 520.
(9) Pelizzoni, F.; Tommi, G. *Gazz. Chim. Ital.* **1959**, *89*, 1894.
(10) DeGraw, I. *Tetrahedron* **1972**, *28*, 967.
(11) Pollet, P.; Gelin, S. *Tetrahedron* **1978**, *34*, 1453.
(12) Wegnel, A. S.; Reffstrup, T.; Boll, P. M. *Tetrahedron* **1979**, *35*, 2181.

Table I. 4-Alkoxy-2(5*H*)-furanones 2 from 1



1 2a-h

no.	R	yield,[a] %
2a	methyl	44
2b	ethyl	56
2c	*n*-propyl	56
2d	1-methyleth-1-yl	65
2e	*n*-hexyl	55
2f	2,2-dimethylprop-1-yl	22
2g	cyclopentyl	40
2h	benzyl	11

[a] Yields which are not optimized are based on the molar amount of tetronic acid charged to the reaction.

Immediately after the appearance of this paper,[12] Gelin and Pollet reconfirmed the results of their initial publication.[13] By a slightly changed procedure, they reported the syntheses of 4-*O*-methyl-**1** and 4-*O*-ethyl-**1** by refluxing a solution of **1** with acetyl chloride in excess methanol or ethanol, respectively. For the preparation of *O*-benzyl-**1** a different method, namely, heating benzyl alcohol with **1** in the presence of *p*-toluenesulfonic acid, was reported. Moreover, in this paper no procedures involving 2°, 3°, or alicyclic alcohols were given. An attempt by us to use the modified Fischer Method (as these authors call it) for the preparation of a long-chain alkyl ether of **1** was unsatisfactory.

The alkylation procedure of Boll[12] employs tetrabutylammonium tetronate and a dialkyl sulfate as an alkylating agent. Thus, since only dimethyl and diethyl sulfates are readily available, this method is not a general one. The procedure for obtaining 4-alkoxy-2(5*H*)-furanones introduced by Gelin depends on ethyl 4-acetoxy-3-keto esters as starting materials; these compounds again are not readily available. Lastly, the most simple preparation for 4-methoxy-2(5*H*)-furanones, namely, the reaction of **1** with diazomethane, due to the unavailability of higher diazoalkanes as convenient starting materials, is of very limited use for the synthesis of analogues of the 4-methyl ether of **1**.

Due to the above-cited ambiguities, the restrictions, and the cumbersome nature of these and the older methods, we concluded an improved synthesis method was needed. We decided to develop a simple way to prepare the desired 4-*O*-alkyl-**1** compounds that would be versatile enough to synthesize a wide range of different 4-alkoxy derivatives of **1**, not only just its methyl or ethyl ethers.

Results and Discussion

We found that **1** reacts with alcohols in concentrated H_2SO_4 medium in different ways depending on the nature of the alcohol. Thus, 1° or 2° alcohols reacted smoothly with **1** to give the desired 4-alkoxy-2(5*H*)-furanones **2a–h** in yields up to 65% (isolated but not optimized) (Table I). In the case of 3° alcohols, **3a–c**, the reaction products were the isomeric C-alkylated 3-alkyl-4-hydroxy-2(5*H*)-furanones **4a–c**, and not the O-alkylated **1**.

From an analysis of the reaction mixtures by TLC, GC-MS, and ^1H NMR spectroscopy, it became evident that a competing reaction, namely, polymerization of these alcohols by the action of concentrated H_2SO_4, took place.[14–18] The ratio of the rate of polymerization to the

(13) Gelin, S.; Pollet, P. *Synth. Commun.* **1980**, *10*, 805.

0022-3263/88/1953-3368$01.50/0