Table III. Competitive Bromination Reactions[a] with 1 and 2

halogenating agent	conditions, rctn time, added matl	% yield[b] benzyl bromide	% yield[b] benzhydryl bromide
NBSac	80 °C, 150-W lamp, 45 min, PhC(O)OO(O)CPh (5%)	34.25	65.75
NBS		35.00	65.00

[a] NBSac or NBS, 0.0015 mol; 1, 0.002 mol; 2, 0.001 mol in 10 mL of dry CCl_4. [b] Evaluated by ^1H NMR spectroscopy from crude reactions.

radical initiator, but it was increased dramatically by means of visible or ultraviolet irradiation or in the prescence of a radical initiator [azobis(isobutyronitrile), benzoyl peroxide] and was negligible again in the presence of a radical scavenger (*p*-quinone). These observations clearly indicate that the substitution product is formed by a chain sequence. We believe that this process involves the bromine molecule like the Goldfinger[7] mechanism.

$$Br\cdot + RH \rightarrow BrH + R\cdot \quad (1)$$

$$BrH + NBSac \rightarrow Br_2 + HNSac \quad (2)$$

$$Br_2 + R\cdot \rightarrow BrR + Br\cdot \quad (3)$$

This is supported by the following: (a) free bromine formation was observed after several minutes of reaction, which was evident by both its typical red-yellow color and a weak absorption at 406 nm in the UV spectra, (b) inhibition of the reaction by addition of silver acetate.[8] This salt reacts with the hydrogen bromide formed in the abstraction step (1) blocking the subsequent bromine molecule formation (2). This was proved by the appearance in the ^1H NMR spectra of the acetic acid proton absorption. It was shown that this acid was not formed by the acid–base reaction of silver acetate and insoluble saccharin since a mixture of these two compounds boiled together in carbon tetrachloride and irradiated with a 100-W lamp for 6 h did not form acetic acid as measured by ^1H NMR. It might be thought that the inhibition of the reaction was due to the consumption of the NBSac by the silver acetate, but we observed that they did not react under our experimental conditions. In addition, competitive reactions between NBSac and NBS with a mixture of toluene and diphenylmethane gave similar results. This would also suggest that both reactions take place by the same mechanism (Table III).

In general, NBSac showed to be an excellent brominating agent in both benzylic and α-carbonylic positions. As it is shown in Tables I and II, NBS produces slightly lower yields than NBSac only with the carbonylic compounds. Besides, a few comparable results were obtained by using NBS in this type of bromination.[9]

Experimental Section

General Procedures. The ^1H NMR spectra were recorded with a Varian T-60 spectrometer with Me_4Si as an internal standard. The IR spectra were recorded on a Beckman IR-8 spectrophotometer and the UV spectra on a Beckman DBG spectrophotometer. Thin-layer chromatography was carried out on silica gel G with $CHCl_3$ as eluent. Gas chromatographic analyses were performed on a Hewlett-Packard F&M 776 equipped with a flame-ionization detector and a 5 ft × 6 mm o.d. stainless-steel column packed with 10% Apiezon "L" on Chrom CLA (100/200 mesh). The sunlamp was a Philips UV 300 W (low limit, 280 nm) placed 10 cm from the reaction vessel.

General Bromination Procedure. The substrate was added to a suspension of dry crude NBSac in 10 mL of dry CCl_4 as solvent, generally the concentration of NBSac was 0.1 M and the molar ratio NBSac/reactant was 1:1. The reactions were carried out under nitrogen and stirred with a magnetic stirrer. Their progress was monitored with potassium iodide–starch paper test and/or iodometry. Then they were cooled, and the insoluble saccharin was filtered off with suction (95% recovery). The crude solutions were analyzed by thin-layer or gas chromatography and directly evaluated by ^1H NMR spectroscopy. The products of the more representative reactions were separated by vacuum fractional distillation or by preparative thin-layer chromatography. The yields of the products so obtained are shown in parentheses in Tables I and II. Their structures were determined by spectroscopic comparisons of their spectra with those of authentic samples. Experimental conditions are indicated in the tables.

Acknowledgment. Part of this investigation was made possible by Grant 7161/75 from the National Council of Scientific and Technical Research.

Registry No. 1, 108-88-3; 2, 101-81-5; 3, 91-57-6; 4, 108-94-1; 5, 451-40-1; 6, 98-86-2; benzyl bromide, 100-39-0; α,α-dibromotoluene, 618-31-5; benzhydryl bromide, 776-74-9; 2-(bromomethyl)-naphthalene, 939-26-4; 1-bromo-2-methylnaphthalene, 2586-62-1; 2-bromocyclohexanone, 822-85-5; 2-cyclohexenone, 930-68-7; α-phenylphenacyl bromide, 1484-50-0; phenacyl bromide, 70-11-1; *N*-bromosaccharin, 35812-01-2.

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Regiospecific Synthesis of Arylfurans Employing a Nickel(II)–Phosphine Complex as a Catalyst in the Homolytic Cross-Coupling of Grignard Reagents to Halofurans[1]

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Received November 17, 1981

In developing a new pyridazine antihypertensive,[2] we required a general regiospecific synthesis of 2-(*o*-alkoxyphenyl)furans. The commonly reported syntheses of arylfurans (i.e., **3a–f**) require generation of aryl radicals in the presence of furan. These radicals may be generated by aprotic diazotization of aromatic amines with alkyl-nitrites[3] or by decomposition of *N*-nitrosoacetanilides,[5,7c] (phenylazo)triphenylmethane,[6] or aromatic diazonium

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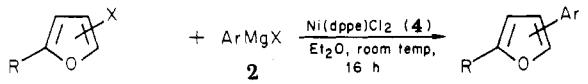
0022-3263/82/1947-1590$01.25/0

Table I. [1,2-Bis(diphenylphosphino)ethane]nickel(II) Dichloride (4) Catalyzed Coupling of Aryl Grignards to Halofurans 1[a]

			compd 3		
entry	1	Ar of ArMgX (2)	substituents	mp or bp, °C (torr)	% yield[b]
1	a	Ph	a, 2-Ph	40 (0.4)[c]	82
2	a	4-CH_3Ph	b, 2-(4-CH_3Ph)	68 (0.75)[d]	85
3	a	3,4-$(CH_3)_2$Ph	c, 2-[3,4-$(CH_3)_2$Ph]	71 (0.05)	98
4	b	3-CH_3Ph	d, 3-(3-CH_3Ph)	70 (0.5)	93
5	a	4-(CH_3CH_2)Ph	e, 2-[4-(CH_3CH_2)Ph]	60 (0.05)	97
6	b	Ph	f, 3-Ph	58-60[e]	93
7	b	2-CH_3Ph	g, 3-(2-CH_3Ph)		23[f]
8	b	$CH_2CH_2CH_3$	h, 3-$CH_2CH_2CH_3$	50 (5)	38
9	c	Ph	i, 2-Ph, 5-$CH_2CH_2CH_2CH_3$	95 (0.3)	90

[a] All the reactions were carried out in ether for 16 h at room temperature. A molar ratio of 0.011/1.0 (catalyst 4 to furan 1) was used. [b] Isolated distilled yield except where indicated. [c] Lit.[7c] 92-95 °C (10 torr). [d] Lit.[3b] bp 56 °C (0.5 torr). [e] Lit.[12a] mp 58.5-59 °C.

Scheme I



1a, 2-Br; R = H
b, 3-Br; R = H
c, 2-SCH_3; R = 5-*n*-Bu

3a-i[a]

[a] See Table I.

salts[4] (including Gomberg reaction conditions[7]). In all of these cases the yields are at best moderate. Other multistep syntheses of 2-arylfurans are also available, e.g., photochemically induced cyclization of acetylenic ketones (20% yield),[8] acid-catalyzed cyclization of 3-tosylpropanol ethylene acetal,[9a,b] degradation of 3,4-diazacyclopentadienone derivatives,[10] and acid-catalyzed cyclization of 4-hydroxy-1-phenylbut-2-en-1-one.[11] None of the methods above produce 3-arylfurans which are also only accessible through lengthy and inefficient routes.[12]

We have previously shown how transition metal–phosphine complexes may be used to catalyze cross-coupling of Grignard reagents to haloheterocycles to form the corresponding aryl or arylalkyl heterocycles.[13,14] This Grignard cross-coupling reaction, surprisingly, has not been extended to include furans, which are important organic synthons.[15] However, we now have been able to prepare 2- and 3-arylfurans **3a–f** (Scheme I) in excellent yields regiospecifically by cross-coupling the appropriate furan **1** and aryl Grignard reagent **2** and using [1,2-bis(diphenylphosphino)ethane]nickel(II) dichloride (**4**) as a catalyst.[16,17] Table I shows our results.

To complement halofurans as starting materials, we successfully employed the 2-(methylthio)furan **1c** as our substrate to prepare 2-phenyl-5-*n*-butylfuran (**3i**) in excellent yield.[18] (Alkylthio)furans are readily available from lithiofurans,[19] as are alkylfurans (vide infra).

The limitations encountered in this cross-coupling reaction, other than the obvious ones imposed by the presence of a Grignard reagent, were (1) the inability of ortho-substituted Grignards to couple to 1 as demonstrated by entry 7 (we were also unable to obtain satisfactory results with *o*-anisylmagnesium bromide)[20] and (2) the relu ctance of *n*-propyl Grignard (and, by analogy, other reducing Grignards) to efficiently undergo this cross-coupling reaction (entry 8). It has been observed that Grignards with β-hydrogens in the presence of nickel transition metal–phosphine complexes can eliminate to form olefins rather than cross-couple with aryl or olefinic halides.[17] Alternatively, alkyl furans are generally obtainable from lithiofurans[19] and from 3-tosylpropanal ethylene acetals.[9c] Overall, this cross-coupling reaction of aryl Grignards to halo- and (methylthio)furans represents a vast improvement over existing syntheses of arylfurans.

Experimental Section

^1H NMR spectra were obtained on a Perkin-Elmer R-600 or R-24 with Me_4Si as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 283 spectrometer. Mass spectra (EI) were obtained on a Hitachi Perkin-Elmer RMU-6E by direct insertion. GC data were obtained on a Finnigan 3600 by using a 4 ft × 0.078 in. column filled with 3% OV-17 on Chromasorb WHP. Grignard reagents were titrated by the method of Bergbreiter and Pendergrass.[21]

General Procedure. 3-(3-Methylphenyl)furan (3d). A 100-mL three-necked flask containing a stirring bar was fitted with gas inlet and gas outlet tubes, heated, and swept with ni-

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trogen. After the flask cooled, 45 mg (8.5×10^{-2} mmol) of $NiCl_2$(dppe) (4) and 1.0 g (7.6 mmol) of 3-bromofuran (**1b**)[22b] [2-bromofuran(**1a**)[22a] was prepared by decarboxylation of 5-bromofuroic acid[22b] by using the procedure of Burness[22c] for the synthesis of 3-methylfuran] were added to 75 mL of dry ether. The flask was fitted with a neoprene septum, and *m*-tolylmagnesium bromide (1.2 equiv) was added under positive nitrogen pressure via syringe. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 16 h and then poured onto 50 mL of aqueous ammonium chloride. The organic layer was removed and the aqueous layer extracted several times with ether. The combined and dried ($MgSO_4$) ether layers were concentrated to an oil which was distilled to yield **3d**: 1.1 g (7.06 mmol, 93%); IR (film) 3040, 2920, 1610, 1510, 1170, 1055, 1020, 870, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (m, 1 H), 7.5–7.0 (m, 5 H), 6.65 (m, 1 H), 2.4 (s, 3 H); mass spectrum, *m/e* 158 (parent peak).

Anal. Calcd for $C_{11}H_{10}O$: C, 83.52; H, 6.37. Found: C, 83.26; H, 6.20.

2-(3,4-Dimethylphenyl)furan (3c) was prepared as described above: IR (film) 2925, 1480, 1450, 1010, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–6.9 (m, 4 H), 6.55 (q, 2 H), 2.32 (s, 6 H); high-resolution mass spectrum, *m/e* 172.090 (M^+; $C_{12}H_{12}O$ requires 172.089).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.19; H, 7.06.

2-(4-Ethylphenyl)furan (3e) was prepared as described above: IR (film) 2970, 1520, 1485, 1005, 835, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (m, 1 H), 7.41 (q, 4 H), 6.55 (q, 2 H), 2.7 (q, 2 H), 1.25 (t, 3 H); mass spectrum, *m/e* 172 (parent peak).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.56; H, 7.38.

3-(*n*-Propyl)furan (3h) was prepared as described above: IR (film) 2950, 1500, 1160, 1020, 870, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (d, 2 H), 6.3 (s, 1 H), 2.4 (t, 2 H), 1.5 (sextet, 2 H), 0.9 (t, 3 H); high-resolution mass spectrum, *m/e* 110.072 (M^+; $C_7H_{10}O$ requires 110.073).

2-Phenyl-5-*n*-butylfuran (3i) was prepared as described above but by using **1c**:[23] IR (film) 2620, 1540, 910, 750, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (m, 5 H), 6.55 (d, 1 H), 6.05 (d, 1 H), 2.7 (t, 2 H), 1.55 (m, 4 H), 1.0 (m, 3 H); high-resolution mass spectrum, *m/e* 200.119 (M^+; $C_{14}H_{16}O$ requires 200.120).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.17; H, 8.02.

Registry No. **1a**, 584-12-3; **1b**, 22037-28-1; **1c**, 80866-21-3; **3a**, 17113-33-6; **3b**, 17113-32-5; **3c**, 80866-22-4; **3d**, 80866-23-5; **3e**, 80866-24-6; **3f**, 13679-41-9; **3g**, 80866-25-7; **3h**, 42908-61-2; **3i**, 80866-26-8; **4**, 38754-20-0.

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(23) Furan **1c** as prepared by using the procedure of Cohen.[19a] NMR, IR, and mass spectral data are satisfactory.

A Simple Stereospecific Synthesis of 14-Hydroxymorphinans

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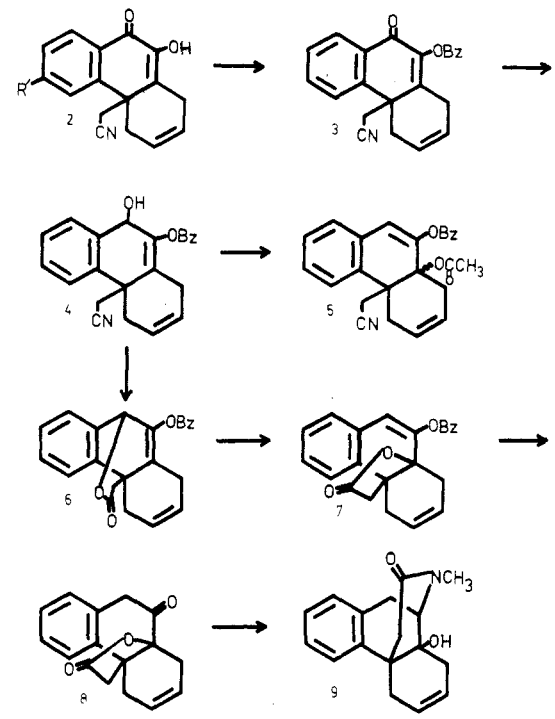
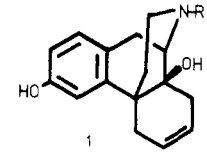
Received July 8, 1980 (Revised Manuscript Received January 12, 1982)

The 3,14-dihydroxymorphinan N-substituted derivatives (**1**, R = allyl, cyclopropylmethyl, cyclobutylmethyl) have interesting pharmacological properties.[1] We report herein a new method for the synthesis of the 14-hydroxymorphinan system that is short, efficient, and adaptable to a wide variety of derivatives.

Scheme I





In this synthesis the (cyanomethyl)hydrophenanthrene system **2** (R = H) of years past[2] once again serves as starting material for a morphinan, this time with a hydroxyl group stereospecifically placed in the 14-position. The method employed is first to fix the oxidation state at C_9 by alkylation to give the enol ether **3**, which is then reduced (sodium borohydride, methanol) to the benzylic alcohol **4** (Scheme I). This benzylic alcohol or its acetate can be rearranged in very high yield (*p*-toluenesulfonic acid (PTSA), acetic acid, acetic anhydride) to a mixture of the C_{14} acetoxy epimers of **5**. The conditions for this rearrangement are similar to those reported by Babler for the rearrangement of allylic alcohols and acetates under acidic conditions.[3] When the lactone **6**, produced by hydrolysis of the nitrile **4**, is similarly rearranged, the lactone **7** of defined stereochemistry is obtained in 80% overall yield from **3**.[4]

Hydrolysis of the enol ether of **7** (HCl, acetic acid, H_2O) gives the ketone **8**. Reductive amination of **8** ($NaCNBH_3$, CH_3NH_2) yields the morphinan lactone **9** (40% overall from **7**). Consistent with this structure, the morphinan lactam is reduced with lithium aluminum hydride in high

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(4) The generality of this rearrangement will be reported elsewhere.

0022-3263/82/1947-1592$01.25/0