ORGANIC LETTERS

1999
Vol. 1, No. 11
1815−1818

Consequences of Acid Catalysis in Concurrent Ring Opening and Halogenation of Spiroketals[1]

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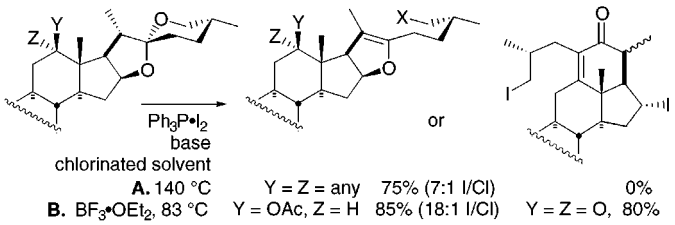
Received September 22, 1999

ABSTRACT



Lewis and/or Bronsted acid additives permit ring opening and halogenation of spiroketals at substantially reduced temperatures to produce ω-iodo enol ethers in improved yield and purity, which can undergo further reaction in the presence of distal electrophilic centers to give new steroid skeletons.

The derivation of structurally or biologically interesting molecules from common steroids is of continued interest to the synthetic community.[2] As part of our ongoing program occasioned by the structural challenges and extreme antitumor activity of cephalostatin bis-steroidal marine products, we have sought the efficient construction of all of the subunits of these antineoplastics from commercially available hecogenin acetate **1**.[3] Selective functionalization of the E−F rings and reorganization of the spiroketal fusion is fundamental to this goal.

In a previous communication,we reported one-step access to intermediates such as **2** by treatment of **1** or other steroidal spiroketals with $Ph_3P{\cdot}X_2$/base in chlorocarbon solvent under essentially neutral conditions (Scheme 1).[1] In the case of iodides such as **2a**, we noted that minimizing the amount of base enhanced both the rate of reaction and the ratio of iodide to chloride products. The latter is of practical consequence to our purposes since conversion of 26-chlorides to the requisite terminal alkenes has proved unrewarding under a wide variety of protocols.[4] Although the temperature requirements of this system for opening the hindered, stable spiroketal moiety of *iso*-sapogenins such as hecogenin acetate **1** was also improved (130−140 °C) in relation to that of previous methods (180−240 °C),[5] we were hopeful that other Lewis or Bronsted acid catalysis might offer further amelioration[5d] in order to extend the reaction to highly

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(3) (a) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692. (b) Kim, S.; Sutton, S. C.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc*. **1999**, *121*, 2056. (c) Jeong, J. U.; Guo, C.; Fuchs, P. L. *J. Am. Chem. Soc*. **1999**, *121*, 2071.

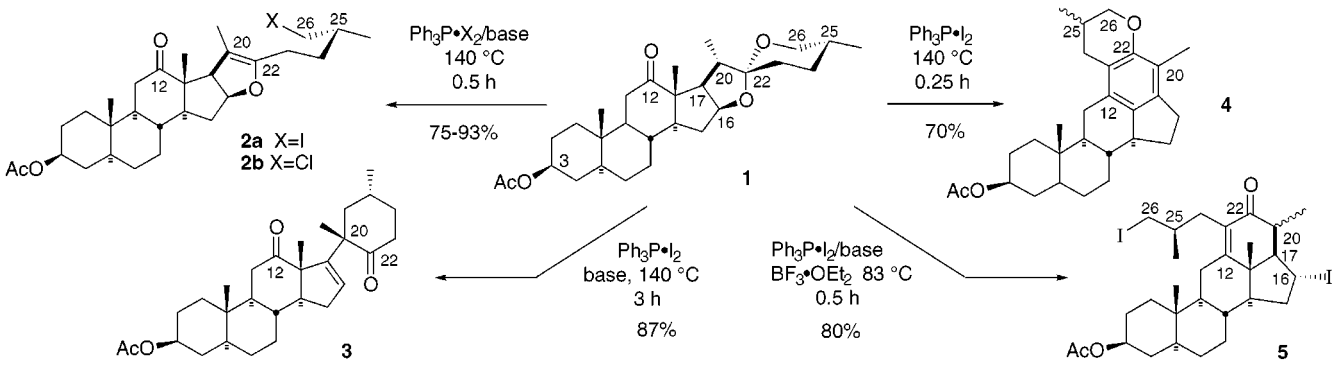
(4) (a) DBU, KOtBu, Ag_2O, etc. gave substitution byproducts, as did TIPSOK: Soderquist, J. A.; Vaquer, J.; Diaz, M. J.; Rane, A. M.; Bordwell, F. G.; Zhang, S. *Tetrahedron Lett.* **1996**, *37*, 2561. (b) Exchange was sluggish (e.g. NaI/3-pentanone/105 °C) and degraded **2a**.

(5) (a) Dauben, W. C.; Fonken, G. J. *J. Am. Chem. Soc.* **1954**, *76*, 4618. (b) Cameron, A. F. B.; Evans, R. M.; Hamlet, J. C.; Hunt, J. S.; Jones, P. G.; Long, A. G. *J. Chem. Soc.* **1955**, 2807. (c) Jeong, J. U.; Fuchs, P. L., *J. Am. Chem. Soc*. **1994**, *116*, 773. (d) Reaction with Ac_2O, for example, required ∼240 °C, but use of a catalyst (e.g., $AlCl_3$, pyr·HCl) permitted complete reaction at 180 °C (refs a−c and references therein).

(6) All new compounds gave satisfactory NMR, MS, and HRMS or combustion analysis. X-ray data for **4** (needles from EtOAc, mp 70−73 °C, 2:1 NMR ratio of epimers) Cambridge Crystallographic Data Centre [CCDC 136164] $C_{28}H_{38}O_3$; unit cell parameters *a* 13.4662 (18), *b* 12.613 (3), and *c* 14.726 (2) Å, *β* 105.497 (13)°, space group *P*21. Halides **2/10** prepared in this work were identical by NMR and TLC to that in ref 1 except for chloride content.

10.1021/ol991078r CCC: $18.00
Published on Web 10/28/1999

Scheme 1



functionalized or sensitive substrates. In this Letter, we describe the effects of such acids and of added or alternate sources of iodide on the course of concurrent spiroketal opening and halogenation.

Reactions of **1** with $Ph_3P{\cdot}I_2$ using less than a minimum (0.8 equiv)[1] of soluble nonnucleophilic amine (imidazole, 2,6-lutidine, DBMP) evidenced new high R_f compounds whose proportion increased rapidly with the decrease in available base (entries 1−5, Table 1). We ascribe this diversion to the presence of free HI, which was evident in the vapor above the reaction mixture. Insoluble bases such as PVP, lithium or sodium hydrides, and all alkali metal carbonates led to similar results. We have identified the majority of these products as new aromatic steriods **4**[6] (a 2:1 ratio of C25 epimers), which can obtained in good yield by foregoing the use of base altogether (entry 5). Single-crystal X-ray analysis confirmed that **4** resulted from a deep-seated backbone rearrangement. This skeleton is suggestive of the South units in cephalostatins 5 and 6,[7] which have likewise sacrificed C18 to achieve aromaticity.

The presence of other acids did permit lower reaction temperatures, but **2a** was not cleanly produced. Various additives were examined in catalytic and stoichiometric or excess quantities. For example, $TiCl_4$ at 0 °C induced no reaction, but several products including traces of **2a** formed at 25−37 °C (entries 6 and 7). No reaction occurred with excess $BF_3{\cdot}OEt_2$ at 25 °C, but **1** was smoothly converted at 85 °C to new products **5** (entry 8).[6,8]

In each of these cases, formation of both **3** and chloride **2b** was reduced. Minimizing **2b** by including sources of additional iodide afforded mainly Pyhrric victories. Excess LiI (10 equiv) permitted, for the first time, complete reaction with stoichiometric $Ph_3P{\cdot}I_2$/base, but afforded **2a**, **3**, **4**, and several unidentified compounds (entry 9). Less LiI led to fewer side products but increased amounts of **2b**. Similar results were obtained with NaI or $LiClO_4$, indicating the role of alkali metal counterion as Lewis acid. Surprisingly, addition of non-Lewis acidic tetrabutylammonium iodide enhanced the rate but gave exclusively **2b** in excellent yield (entry 10). Use of a 20% excess of I_2 offered a slightly

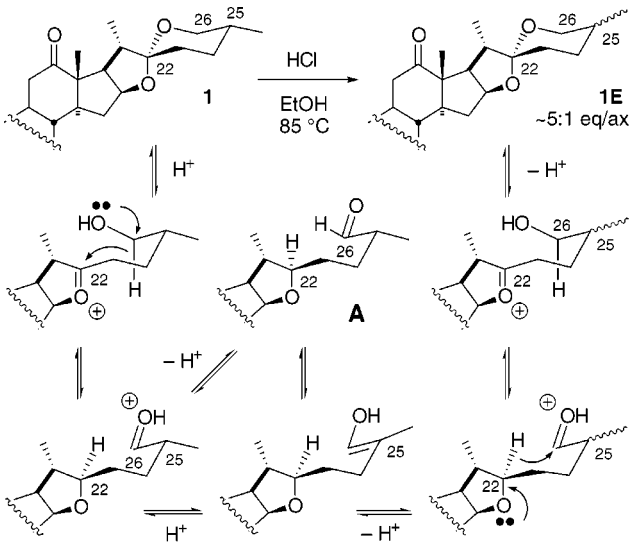
Table 1. Conditions for Reaction of **1** To Give Products **2**−**5**

entry	equiv of $Ph_3P{\cdot}I_2$/base[a]	additive	solvent[a]	temp, °C[a]	time	**2** (I/Cl ratio)[b]	**3**[b]	**4**[b]	**5**[b]
1	2.0/2.0 lutidine		TCE	140	1 h	67% (5:1 **a**/**b**)	25%		
2	2.0/0.8 lutidine		TCE	140	0.5 h	75% (7:1 **a**/**b**)	18%		
3	2.0/0.8 lutidine		TCE	140	3 h	8% (**b** only)	87%		
4	2.0/0.5 lutidine		TCE	140	20 min	15% (**a** only)[c]	20%[c]	40%[c]	
5	1.1/none		TCE	140	10 min	50% (**a** only)[c]	5%[c]	10%[c]	trace
					15 min	trace (**a** only)	10%	70%	trace
6	2.0/1.0 DBMP	1 equiv of $TiCl_4$	DCM	25	24 h	trace (**a** only)			
7	2.0/1.0 DBMP	1.7 equiv of $TiCl_4$	DCM	37	24 h	trace (**a** only)		20%[c]	40%[c]
8	2.0/1.0 DBMP	4 equiv of $BF_3{\cdot}OEt_2$	DCE	85	0.5 h	trace (**a** only)	trace	trace	80%
9	1.1/1.0 lutidine	10 equiv of LiI	TCE	140	2.0 h	23% (**a** only)	22%	28%	trace
10	2.0/2.0 lutidine	10 equiv of Bu_4NI	TCE	140	0.5 h	93% (**b** only)	6%		
11	2.0/0.8 lutidine	0.2 equiv of I_2	TCE	140	1 h	82% (8:1 **a**/**b**)	11%		
12	none	10 equiv of HI	DCM	42	2 d	trace (**a** only + 70% sm)[c]		5%[c]	15%[c]
13	none	2 equiv of HBF_4/ 10 equiv of LiI	DCM/CH_3CN	25	2 d	6% (**a** only)			78%

[a] DBMP = 2,6-di-*tert*-butyl-4-methylpyridine; TCE = 1,1,2,2-tetrachloroethane; DCM = dichloromethane; DCE = 1,2-dichloroethane. All reactions are 0.1 M in **1** and use preheated baths. [b] Isolated yields unless noted; halide ratios determined by NMR. [c] Yields estimated by NMR.

improved yield and **2a/b** ratio but required extra time (a 20 min induction period was noted, entry 11). Reaction of **1** with HI alone proved very sluggish even at 42 °C, but **5** formed slowly at 25 °C using LiI/HBF_4 (entries 12 and 13).[6] Similar results were obtained with LiI/BF_3·OEt_2. Thus, judicious choice of reaction parameters induced **1** to provide any of compounds **2**−**5** in good to excellent yield.

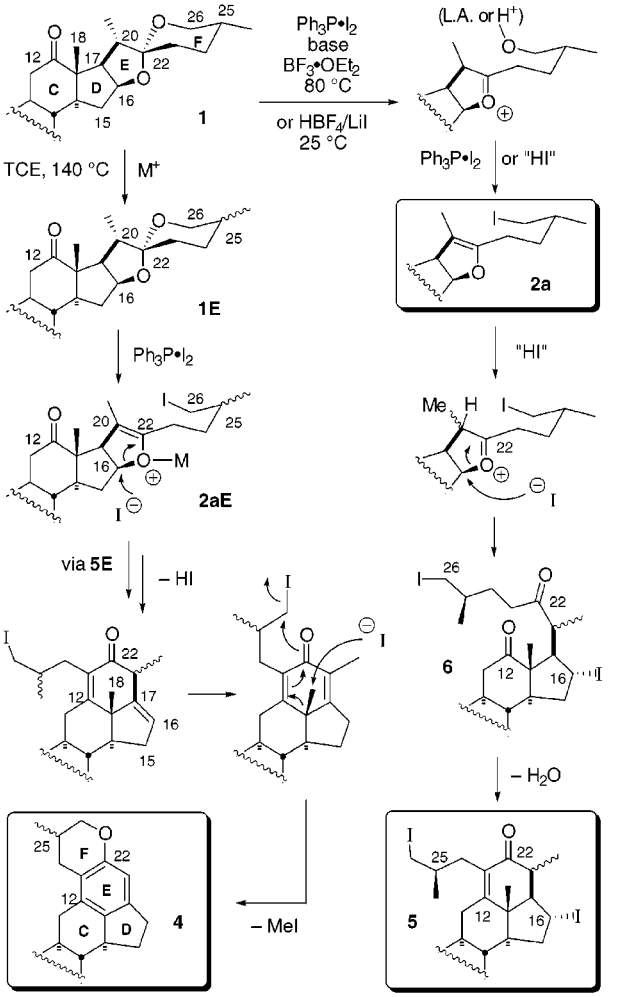
The acid promoters herein likely encourage first-step C22−O26 cleavage rather than the prior C26 iodide attack (C26−O26 cleavage) postulated for neutral conditions.[1] Strong mineral acids have been considered unsuitable as catalysts for opening steroidal spiroketals due to internal redox-mediated C25 epimerization in polar solvent.[9] A 1,5 hydride transfer from the initial oxacarbenium ion affords enolizable aldehyde **A**, from which the diastereomeric spiroketals derive. This reversible hydride transfer forms the basis of stereoselective Lewis acid promoted spiroketal reductions which trap **A** upon formation.[10]



In chlorocarbon solvent, we likewise observed loss of stereochemical integrity at 140 °C, but epimerization of **1** appears suppressed at 85 °C in the presence of the iodinating reagent,[8] which may trap the protonated or Lewis acid complexed alkoxy moiety faster than hydride transfer occurs. Exposure of **1** at 25 °C to any of a variety of acids (HI, HBF_4, CSA) induced epimerization in neither CH_3CN nor chlorinated solvents. Previous investigations have demonstrated that C25 integrity is also retained at 25 °C with HBr in AcOH.[11]

A plausible mechanism for the production of **4** and **5** is outlined in Scheme 2. The ω-halo enol ether **2** is the first

Scheme 2



product detected in all these reactions. Bronsted or Lewis acid activation of **2a** permits C16 substitution with E-ring opening, leading to products derived from ω,ω'-diiodo-22-ketone **6** when an aldol acceptor functionality (e.g., the C12 ketone) is available. At lower temperatures, the reaction halts at diiodo enone **5**. Prior C25 epimerization of **1** leads to the corresponding **2aE** and **5E** diastereomeric mixtures. High temperatures apparently provide sufficient energy for elimination of the 16-iodide from **5E**, migration of the resulting Δ^{15} or Δ^{16} bond, and loss of C18 (probably as MeI) to achieve aromaticity in **4**.

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(8) (a) **5** was obtained as a 3:1 mixture (NMR) of diastereomers. ^1H and ^{13}C NMR are consistent with C20 epimers: positions 11, 18, 19−21, 26, and 27 all show minor peaks [e.g., ^1H NMR ($CDCl_3$, 300 MHz) δ major (3.15, dd, J = 9.6, 5.3, H_{26b}; 2.72, dd, J = 12, 4.4, $H_{11\alpha}$; 0.87, d, J = 6, H_{27}), minor (3.09, dd, J = 9.6, 5, H_{26b}; 2.82, dd, J = 13, 4.6, $H_{11\alpha}$; 0.85, d, J = 6, H_{27})] in similar ratios. 25(*R*) iodides prepared under neutral conditions in (ref 1) such as **2a** [3.24, dd, J = 9.6, 4.3, H_{26a}; 3.14, dd, J = 9.6, 5.7, H_{26b}; 2.22, dd, J = 13.6, 5, $H_{11\alpha}$; 0.99, d, J = 6.2, H_{27}] and **10a** [3.24, dd, J = 9.6, 4.2, H_{26a}; 3.14, dd, J = 9.6, 5.5, H_{26b}; 1.00, d, J = 6.5, H_{27}] are distinguishable from 25(*S*) iodides, e.g., from sarsasapogenin (ref 1 **13a** [3.20, dd, J = 9.7, 4.0, H_{26a}; 3.14, dd, J = 9.7, 5.9, H_{26b}; 0.96, d, J = 5.4, H_{27}]), and none showed minor peaks as in **5**. **2a** from entry 8, Table 1, appears to be >98% diastereomerically pure as judged by conversion to **3** and comparison to **3** prepared in ref 1.

(9) (a) Callow, R. K.; James, V. H. T. *J. Chem. Soc.* **1955**, 1671. (b) Wall, M. E.; Serota, S.; Witnauer, L. P. *J. Am. Chem. Soc.* **1955**, *77*, 3086. (c) Woodward, R. B.; Sondheimer, F.; Mazur, Y. *J. Am. Chem. Soc.* **1958**, *80*, 6693. (d) Deslongchamps, P.; Rowan, D. D.; Pothier, N. *Can. J. Chem.* **1981**, *59*, 2787.

(10) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484 and references therein.

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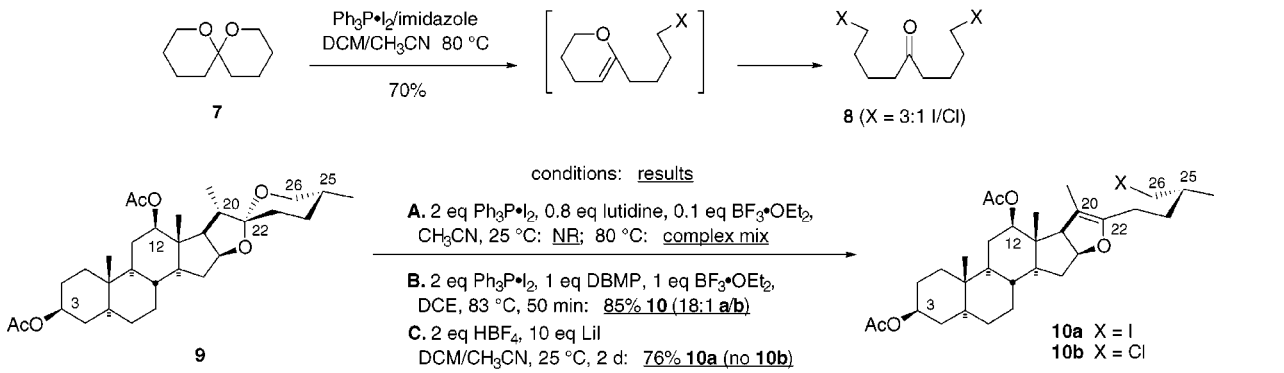
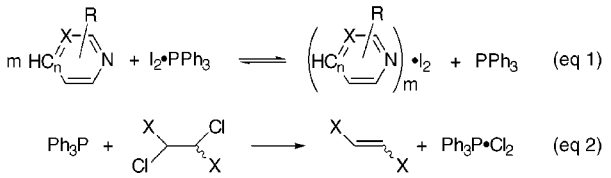
Scheme 3



Although the putative diketone **6** was not observed, the reaction of the simple 6,6-spiroketal **7** helped illuminate structural influences on the course of these reactions (Scheme 3). No reaction of **7** with the $Ph_3P{\cdot}I_2$/base reagent occurred at 25 °C, and only slow conversion was noted in DCM/CH_3-CN at 60 °C. However, complete consumption of **7** proceeds smoothly at 80 °C to afford a 70% yield of unexpected products **8**.[6] Presumably, the unhindered ω-halo enol ether products derived from **7** undergo subsequent reaction to give ω,ω'-dihalo ketones **8**. In the absence of reactive distal functionality, such a product is isolable.

The absence of a C12 electrophilic center in rockogenin diacetate **9** was expected to render the substrate compatible with acid catalysis. In the event, reaction of **9** with $Ph_3P{\cdot}I_2$/base alone in TCE required 130−140 °C,[1] but addition of stoichiometric $BF_3{\cdot}OEt_2$ permitted smooth conversion to **10a/b**[6] in high yield at 85 °C (refluxing DCE, Scheme 3, reaction B). Use of nonchlorinated solvent (CH_3CN, reaction A) to avoid formation of chloride **10b** gave multiple products with even catalytic $BF_3{\cdot}OEt_2$, and further solvent studies were rendered superfluous by the near absence of **10b** (5%) in the DCE reaction.[12] We note that the mixing order in A−C (Ph_3P added to a solution of **9** followed by iodine, base, then Lewis acid) differs from that adopted for "neutral" conditions (substrate, Ph_3P, base, I_2).[1] With base already present, mixtures were nearly colorless until complete dissolution of I_2, when a pale orange color arose which became deep red on heating. Deferred introduction of base provided visible evidence for the postulated origin of chlorides **2b/10b**:[1] the red solution obtained on total dissolution of I_2 (1% excess) lightened to pale orange on addition of imidazole, 2,6-lutidine, or DBMP but returned to a deep red on either heating or on addition of Lewis acid. We infer some competition by nitrogenous base for I_2 complexation,[13] freeing Ph_3P to form $Ph_3P{\cdot}Cl_2$ by reaction with chlorinated solvent (eqs 1 and 2). Acid (or excess I_2) may suppress such competition and maximize the effective "$Ph_3P{\cdot}I_2$" (or $Ph_3PI^+I_3^-$, or base$\cdot Ph_3P{\cdot}I_2$,[14] the actual form of the reagent is not clear).



No diidoketone analogous to **6** (Scheme 1) or **8** (Scheme 3) was confirmed from **9** under conditions (excess $BF_3{\cdot}OEt_2$ as in entry 9, Table 1) which gave **5** from **1**, although several as yet unidentified products were observed in addition to **10a** (30%, no **10b**). For **9**, and likely for any steroid without additional acid-labile moieties, spiroketal conversion to ω-iodo enol ethers such as **10a** which are wholly free of chlorides can also be accomplished (slowly) at 25 °C in good yield under the influence of combined Bronsted and Lewis acid catalysis (HBF_4/LiI, reaction C). It should be noted that HI alone or HI with added LiI gave extremely sluggish reaction with **9**, as had been seen for **1**.

In conclusion, Lewis and/or Bronsted acid promotion of concurrent ring opening and halogenation of spiroketals permits lower reaction temperature than is required under neutral conditions and minimizes diversion to chloride and cyclohexanone side products. Substrates such as **9** without a C12 ketone appear amenable under these conditions to clean production of stable ω-iodo enol ethers, whereas **1** gives iodo enol ether **2a** which can react to furnish new steroid skeletons. Further experiments along these lines are in progress which we hope will identify a lower temperature protocol compatible with acid-sensitive substrates such as **1**.

Acknowledgment. We thank the Indiana Elks/Purdue Cancer Center and Proctor and Gamble (T.G.L. fellowships) and the NIH (CA 60548) for funding, Arlene Rothwell for MS data, and Phil Fanwick for X-ray analysis.

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(12) Rapid heating (immersion into a preheated bath as in ref 1 and Table 1) gave maximal iodide production. Slow heating (25 min to achieve 90 °C) of an identical mixture gave a 90% yield of **10a/b** (4:1).

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