Tetrahedron Letters, Vol. 34, No. 18, pp. 2875-2878, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Synthesis of 2-Aryl-3-hydroxybenzothiophenes and Analogs by the Base Promoted Cyclization of N-Phenyl-2-(benzylthio)benzamides

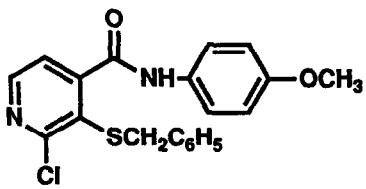
Stephen W. Wright* and Ronald L. Corbett

The Du Pont Merck Pharmaceutical Company, Du Pont Experimental Station, Wilmington, Delaware 19880-0353

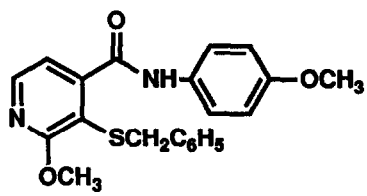
Key Words: thiophene, cyclization, benzyl sulfide, selenophene, benzyl selenide, potassium t-butoxide

Abstract: A new methodology is described for the synthesis of 3-hydroxybenzothiophenes, 3-hydroxypyridothiophenes, and the corresponding selenophene analogs by the base promoted cyclization of corresponding 2-(benzylthio)arenecarboxanilides. The starting materials are readily prepared using directed metalation of the corresponding arenecarboxanilides.

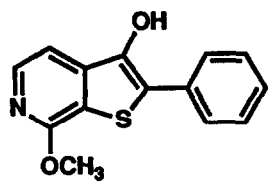
During the course of an attempted conversion of N-(4-methoxyphenyl)-2-chloro-3-(benzylthio)-isonicotinamide (**1**) to N-(4-methoxyphenyl)-2-methoxy-3-(benzylthio)-isonicotinamide (**2**) by the displacement of chloride with 5 equivalents of sodium methoxide in DMF at 100°, we obtained instead as the principal reaction product (65% yield) the 3-hydroxypyridothiophene **3a**. The identity of **3a** was confirmed by ^{1}H NMR, MS, IR, and elemental analysis.[1] The formation of **3a** under these conditions was remarkable as it apparently occurred by the deprotonation of an unactivated SCH_2Ph methylene group by a relatively weak base ($NaOCH_3$), followed by nucleophilic attack of the thiobenzyl anion on the secondary amide (which may be expected to be largely deprotonated under these conditions) and elimination of p-anisidine.[2]



1



2



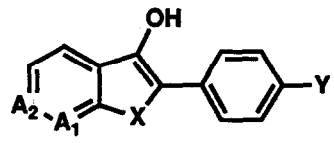
3a

This unexpected result prompted us to extend this methodology to other substrates, and to examine the potential scope of this transformation. Indeed, we found that this reaction was successful for a wide variety of substrates (Table 1), and that this methodology could be extended to the preparation of 2-aryl-3-hydroxybenzoselenophenes as well.[3]

A representative procedure is as follows: To 1.4 g (3.6 mmol) of **1**[4] in 30 mL of dry DMF under nitrogen was added 0.98 g (18 mmol, 5 eq) of sodium methoxide. The reaction mixture was heated at 100° until complete disappearance of **1** by tlc analysis (*ca.* 3 h), then cooled and poured into water (150 mL), acidified with 3 M HCl,

and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with water (5 x 30 mL), brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica (1:1 hexanes:ethyl acetate) to give 0.60 g (65%) of **3a**, mp 141° - 143° (1-chlorobutane). ^1H NMR ($CDCl_3$): δ = 8.07 (d, 1 H); 7.73 (d, 2 H); 7.51 (m, 2 H); 7.40 (m, 1 H); 7.23 (d, 1 H); 4.12 (s, 3 H); 1.62 (br s, 1 H). MS (NH_3 CI): *m/z* = 258 ($M + H^+$, 100%). IR (KBr pellet): 3600 - 3200 (br, OH); 1596 (s, Ar); 1526 (s, C=C) cm^{-1}. Analysis: Calc'd for $C_{14}H_{11}NO_2S$: C 65.35%; H 4.31%, N 5.44%; Found: C 65.00%; H 4.18%; N 5.26%.

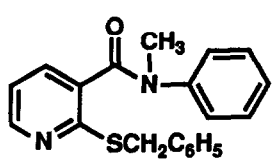
Table 1



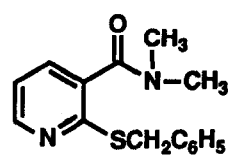
Entry	A_1	A_2	X	Y	Yield[a]	mp, °C	Base
3a	$C(OCH_3)$	N	S	H	65%	56° - 58°	$NaOCH_3$
3b	CH	CH	Se	H	39%	85° - 88°	KO-*t*-Bu[b]
3c	CCl	N	S	H	46%	173° - 175°	$NaOCH_3$
3d	CH	CH	Se	CCF_3	68%	118° - 120°	$NaOCH_3$
3e	CH	CH	S	H	33%	106° - 108°[c]	KO-*t*-Bu
3f	N	CH	S	H	57%	230° - 232°[d]	KO-*t*-Bu[b]
3g	$C(OCH_3)$	CH	Se	H	48%	91° - 93°	$NaOCH_3$
3h	N	CH	Se	H	63%	186° - 188°	KO-*t*-Bu[b]

[a] All yields are for purified products. All products gave satisfactory ^1H NMR, MS and IR spectral data and elemental analyses. [b] No reaction was observed with $NaOCH_3$. [c] Lit. mp 103° - 104°.[5] [d] Lit. mp 234° - 235°.[6]

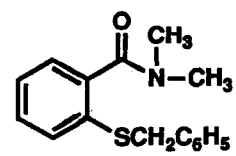
We examined the use of tertiary 2-(benzylthio)benzamides as substrates for this reaction, to determine whether the amide anion that is initially generated *ortho* to the benzyl sulfide upon the addition of potassium *t*-butoxide to the secondary amide assists in the deprotonation of the benzylic methylene group. We found that the reaction occurs much faster, in higher yields, and at lower temperatures with a tertiary amide substrate under the same conditions. For example, both *N*-methyl-*N*-phenyl-2-(benzylthio)nicotinamide **4** and *N,N*-dimethyl-2-(benzylthio)nicotinamide **5** gave **3f** in 77% and 80% isolated yield, respectively, upon treatment with 5 equivalents of potassium *t*-butoxide in DMF at 25° for 15 minutes. Likewise, **6** gave **3e** in 84% yield under the same conditions. These results suggest that the amide group is not involved in the deprotonation of the SCH_2Ph methylene group, and that potassium *t*-butoxide is sufficiently basic to rapidly metalate the benzyl group under these conditions.[7]



4

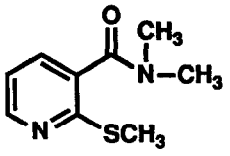


5

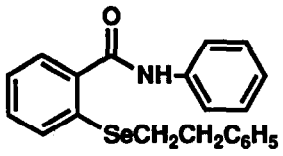


6

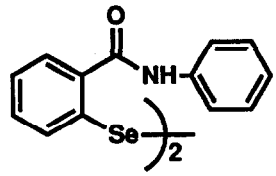
As expected, only benzyl sulfides and benzyl selenides underwent this transformation. Other alkyl sulfides and alkyl selenides did not afford cyclized products. For example, *N,N*-dimethyl 2-(methylthio)nicotinamide (7) failed to afford any cyclized products under these conditions, while the phenethyl selenide **8** underwent elimination to give exclusively the diselenide bis-amide **9**[8] in 96% yield under these conditions.[9] We examined the use of various bases to effect this transformation, including sodium methoxide, potassium *t*-butoxide, and sodium hydride. Of these, potassium *t*-butoxide was found to be the most useful (Table 1).



7



8



9

Attempts to extend this methodology to the preparation of 2-aryl-3-hydroxybenzotellurophenes from *N*-phenyl-2-(benzyltelluro)benzamides or *N,N*-dimethyl-2-(benzyltelluro)benzamides were unsuccessful.[10,11] Not surprisingly, attempts to prepare 2-aryl-3-hydroxybenzofurans (2-aryl coumaranones) from *N*-phenyl-2-(benzyloxy)benzamides or *N,N*-dimethyl-2-(benzyloxy)benzamides were also unsuccessful.[12]

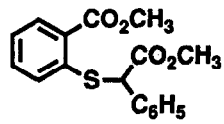
The utility of this transformation is further enhanced by the availability of the appropriate benzyl sulfides and benzyl selenides, which may be readily prepared from the corresponding *N*-phenyl-(substituted)benzamides by *ortho*-metalation (taking advantage of the excellent directed metalation properties of anilides),[13] followed by sequential treatment with sulfur (or selenium) and the desired (substituted)benzyl bromide.

In summary, we have found that 2-(benzylthio)arenecarboxamides and 2-(benzylseleno)arene-carboxamides are rapidly cyclized to 2-aryl-3-hydroxybenzothiophenes and 2-aryl-3-hydroxybenzoselenophenes upon treatment with alkoxide bases in DMF. The success of this reaction appears to be due to the enhanced basicity of the alkoxide in this solvent. Tertiary 2-(benzylthio)arenecarboxamides are the most synthetically useful substrates, undergoing cyclization rapidly at 25° with potassium *t*-butoxide to give good yields of products.

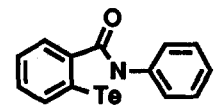
References and Notes

1. Also, compounds **3a-h** react with potassium *t*-butoxide and dimethyl sulfate in DMF to give the expected O-methyl derivatives in high yield (Lantz, R., Hornfeldt, A. B. *Chemica Scripta* **1976**, *10*, 126-132).
2. Conventional methods for the synthesis of 2-aryl-3-hydroxybenzothiophenes typically proceed by the base catalyzed cyclization of a suitable methyl 2-((2-phenyl)carbomethoxymethylthio)benzoate (**10**) by sodium methoxide, followed by decarboxylation. In this case the $SCH(CO_2CH_3)Ph$ methine group is more activated than in the present reaction (as a phenylacetate), and the anion condenses with more electrophilic carbonyl group (an ester). See, for example, Sauter, F. *Fr. Demande 2,447,914* (29 August 1980)
3. These compounds are the subject of a recent U.S. patent application.

4. Prepared from N-(4-methoxyphenyl)-2-chloroisonicotinamide by directed metalation with n-butyllithium and TMEDA in THF and treatment with powdered sulfur, followed by BzCl, see: Epsztajn, J.; Bieniek, A.; Kowalska, J. A. *Tetrahedron* **1991**, *47*, 1697 - 1706.
5. Baker, R. K.; Rupprecht, K. M.; Pessolano, A. A.; Durette, P. L. *U.S. Patent 4,767,766* (30 August 1988).
6. Stridsberg, B.; Allenmark, S. *Chemica Scripta* **1976**, *9*, 216 - 219.
7. It has been shown that the basicity of metal alkoxides is substantially enhanced in dipolar aprotic solvents such as DMSO. The pKa of t-BuOH under these conditions is estimated to be 32.3, that of MeOH is estimated to be 29.0. See Bordwell, F. G.; Margolin, Z.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3295-3299.
8. Engman, L.; Hallberg, A. *J. Org. Chem.*, **1989**, *54*, 2964-2966.
9. Styrene was detected as a by-product.
10. These were prepared by directed metalation of the amide with n-BuLi in THF, followed by sequential treatment of the reaction mixture with tellurium and an appropriate benzyl halide.
11. The benzyl tellurides underwent extensive decomposition with precipitation of elemental tellurium under these reaction conditions. The principal product that could be identified by mass spectroscopy was the parent benzamide (lacking any tellurium or benzyl substituent). The reaction of *N*-phenyl-2-(benzyltelluro)benzamides with KO-*t*-Bu in DMF also afforded some 2-phenyl benzisotellurazol-3-one (**11**), which may arise from fragmentation of the corresponding ditelluride bis-anilide.
12. The expected 2H-benzofuran-3-one could be detected by mass spectroscopy, but was not isolated in a acceptable degree of purity. 2H-Benzofuran-3-ones which are not 2,2-disubstituted are unstable compounds that dimerize upon exposure to base and are readily oxidized to resinous products by air (Mustafa, A. in *The Chemistry of Heterocyclic Compounds, Vol. 29* [Weissberger, A., Taylor, E. C. eds. New York: Wiley, 1974] p. 226-227). See also, for example, Dean, F. M., Manunapichu, K. *J. Chem. Soc.* **1957**, 3112-3123.
13. Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1 - 360.



10



11

(Received in USA 4 December 1992)