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Solution-Phase Synthesis of Diaryl Selenides Using Polymer-Supported Borohydride

Corinne Millois and Philippe Diaz*

GALDERMA R&D, 635 route des Lucioles BP87, F06902 Sophia-Antipolis Cedex, France

philippe.diaz@galderma.com

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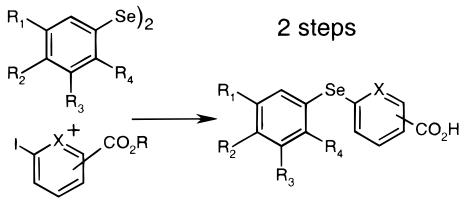
ABSTRACT



A new series of selenium-containing diaryl retinoids have been prepared by a new direct nickel(II)-catalyzed coupling of a diselenide with an iodoaryl in the presence of polymer-supported borohydride.

Retinoids (Figure 1), synthetic[1] and natural analogues of *all-trans* or 9-*cis*-retinoic acid, exert profound effects on cell differentiation and proliferation.[2] These biological properties are indicative of a high potential for the treatment of hyperproliferative disorders such as psoriasis or cancer. Many of their biological effects are mediated by activation of nuclear receptors. There are two known types of retinoic acid receptors, RAR (α, *β*, and *γ*)[3] and RXR (α, *β*, and *γ*),[4] located in the cell nucleus. In the presence of ligand, these receptors form dimers which bind to DNA through distinct response elements.

Others[5] and us[6] were interested in the synthesis of RXRs selective diaryl sulfide compounds (**CD2809**). Recently we reported the synthesis of a new series of selenium-containing retinoids[7] (**CD3386**) with potent RAR affinities. In regard to the similarities between sulfur and selenium (structural, potentially oxidable ...), we decided to synthesize a new series of diarylselenium-containing RXR compounds.

A variety of synthetic routes to unsymmetrical diaryl selenides have been described.[8] Among them, the nickel-(II)-catalyzed substitution of aryl halides by aryl selenolates[9] is compatible with many functional groups. The method used requires previous preparation of the anion from the corresponding diselenide using sodium borohydride. We were troubled with the foul smell of byproducts and by the rapid conversion of the anion to the corresponding diselenide in the presence of air. On the other hand, it has been shown

(1) (a) Charpentier, B.; Bernardon, J. M.; Eustache, J.; Millois, C.; Martin, C.; Michel, S; Shroot, B. *J. Med. Chem.* **1995**, *38*, 4993−5006. (b) Diaz, P.; Michel, S.; Stella, L.; Charpentier, B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2289−2294. (c) Diaz, P.; Gendre, F.; Stella, L.; Charpentier, B. *Tetrahedron* **1998**, *54*, 4579−4590.

(2) Sporn, M.; Roberts, A. B.; Goodman, D. S. In *The Retinoids: Biology, Chemistry, and Medecine*; Raven Press: New York, 1994.

(3) (a) Guiguere, V.; Ong, E. S.; Segui, P.; Evans, R. M. *Nature* **1987**, *330*, 624−629. (b) Brand, N.; Petkovitch, M.; Krust, A.; Chambon, P.; de Thé, H.; Marchio, A.; Tiollais, P.; Dejean, A. *Nature* **1988**, *332*, 850−853. (c) Krust, A.; Kastner, P.; Petkovitch, M.; Zelent, A.; Chambon, P. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 5310−5314.

(4) (a) Mangelsdorf, D.; Ong, E.; Dyck, J.; Evans, R. *Nature* **1990**, *345*, 224−229. (b) Mangelsdorf, D.; Borgmeyer, U.; Heyman, R.; Zhou, J.; Ong, E.; Oro, A.; Kakizuka, A.; Evans, R. *Genes Dev.* **1992**, *6*, 329−344.

(5) Beard R. L.; Colon D. F.; Song T. K.; Davies P. J. A.; Kochhar D. M.; Chandraratna R. A. S., *J. Med. Chem.* **1996**, *39*, 3556−1563.

(6) Bernardon J. M., C.I.R.D. GALDERMA, EP 0679630-A1, 1995; *Chem. Abstr.* **1996**, *124*, 145647e.

(7) Diaz, P.; Gendre, F.; Bernardon, J. M. *Tetrahedron Lett.* **1998**, *39*, 9003−9006.

(8) (a) Pierini, A. B.; Rossi, R. A. *J. Org. Chem.* **1979**, *44*, 4667−4673. (b) Gassman, P. G.; Miura, A.; Miura, T. *J. Org. Chem.* **1982**, *47*, 951−954. (c) Osuka, A.; Ohmasa, N.; Susuki, H., *Synthesis* **1982**, 857−858. (d) Sindelar, K.; Svatek, E.; Metysova, J.; Metys, J.; Provita, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3792−3800.

(9) Cristau, H. J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *Organometallics* **1985**, *4*, 657−661.

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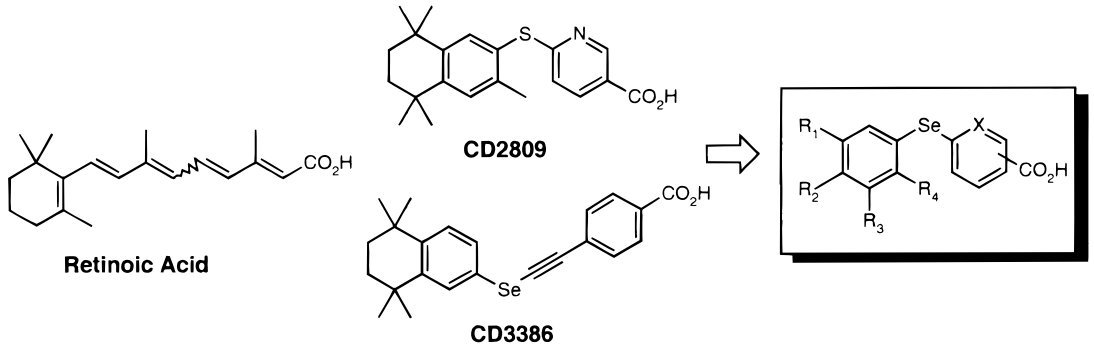
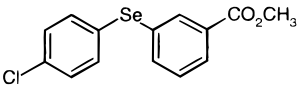
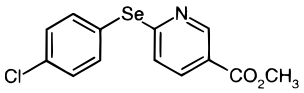


Figure 1.

that diphenyl diselenide can be readily converted to the corresponding phenylselenolate anion by polymer-supported borohydride.[10] Therefore, we were interested in developing a new practical methodology which avoided the preformation of the selenolate mixing polymer-supported borohydride, the catalyst, the iodide compound, and the diselenide compound.

This paper describes the development of this new synthesis by direct nickel(II)-catalyzed coupling of a diselenide with an iodoaryl in the presence of polymer-supported borohydride. The effect of the catalyst was examined (Table 1).

Table 1. Effect of Catalyst on the Coupling Reaction[a]

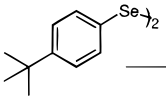
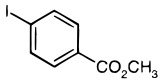
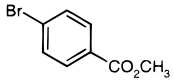
Entry	Structure	Catalyst	Yield
1		$Pd(PPh_3)_4$	60 %
		$(bpy)_2NiBr_2$	84 %
2		$Pd(PPh_3)_4$	90 %
		$(bpy)_2NiBr_2$	100 %

[a] For the typical procedure for the coupling reaction, see ref 11. Methanol was used as solvent. Temperature 60 °C.

Palladium catalyst was first assessed due to its commercial availability, although to our knowledge there is no example in the literature. The coupling of bis(4-chlorophenyl) diselenide with methyl 3-iodobenzoate and methyl 6-iodonicotinate affords respectively products **1** and **2** with nickel[9] or palladium catalyst. In both cases, the yields are better with the nickel catalyst. The reactions are very clean as the impurities are the starting materials.

The effects of temperature and halogenide were then examined (Table 2). Bis(4-*tert*-butyl) diselenide was coupled with methyl bromo- and iodobenzoate. The esters resulting from transesterification with the alcohol used as solvent were recovered. The lack of reactivity of the bromide compound as compared to that with the iodide compound dramatically reduced the rate of coupling. Ethanol, which is more easily removed than butanol, gave the same yield in the case of an aryl iodide.

Table 2. Effects of the Temperature and the Aryl Halogenide on the Coupling Reaction[a]

Selenide	Aryl halogenide	Conditions	Coupling (^1H NMR)
		MeOH/60°C	91 %
		EtOH/70°C	100 %
		n-BuOH/105°C	100 %
		EtOH/70°C	17 %
		n-BuOH/105°C	50 %

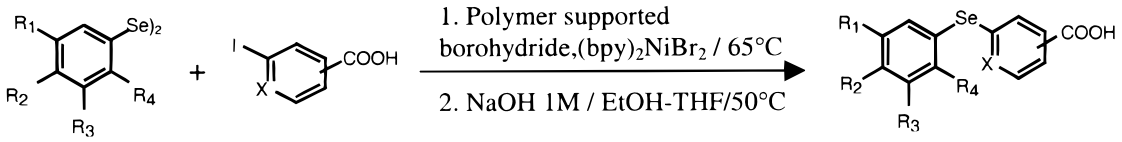
[a] For the typical procedure for the coupling reaction, see ref 11.

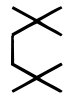
The optimal procedure[11,12] was used to synthesize a library (Table 3): $(bpy)_2NiBr_2$ as catalyst; ethanol and THF (4/1) to improve solubility, as solvent, at 65 °C during 16 h. The resulting esters were saponified, providing the corresponding carboxylic acids. Diselenide compounds were obtained from the action of *tert*-butyllithium or -magnesium followed by selenium.[13] Final products were isolated by crystallization, which explains the variability in the yields. Coupling of ethyl 2-iodonicotinate (entries **6**, **17**, **21**, and **37**) afforded ethyl nicotinate as the major impurity, resulting from reduction of iodine.

(10) Gibson, H.; Courtney Bailey, F. *J. Chem. Soc., Chem. Commun.* **1977**, 815.

(11) **Typical procedure for coupling reaction:** a mixture of diselenide (0.3 mmol), iodide (0.4 mmol), catalyst (10 μmol), and resin (480 mg, 1.2 mmol) (Aldrich 32,864-2) in alcohol (4 mL) and THF (1 mL) was stirred for 16 h at 65 °C under N_2. Reaction mixture was concentrated, diluted with water, and extracted twice with diethyl ether in cartridges (Whatman phase separation cartridge). The organic layer was dried with Na_2SO_4 (sample drying device, Whatman), concentrated, purified using SPE cartridges (Supelco, 20 mL, 5 g LC silica packing), and concentrated. **Ethyl ester of 29:** mp 108 °C. ESMS *m*/*z* 432 $(m + H)^+$.^1H NMR ($CDCl_3$) δ: 1.25 (6H, s), 1.31 (6H, s), 1.37 (3H, t, $J = 7.1$ Hz), 1.69 (4H, s), 2.37 (3H, s), 4.37 (2H, q, $J = 7.1$ Hz), 6.86 (1H, d, $J = 8.3$ Hz), 7.28 (1H, s), 7.65 (1H, s), 7.94 (1H, dd, $J = 8.3$ Hz, $J' = 2.2$ Hz), 8.99 (1H, d, $J = 2$, 2 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.3, 31.5, 31.6, 33.8, 34.0, 34.7, 61.0, 122.0, 122.3, 124.3, 128.6, 136.2, 136.7, 139.0, 144.1, 147.1, 150.6, 165.2, 166.1.

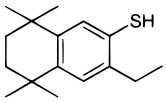
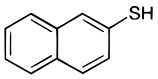
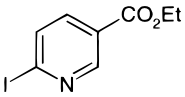
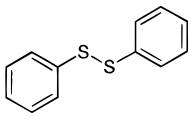
Table 3. Diaryl Selenides Prepared According to the Optimized Procedure[11,12]



R_1	R_2	R_3	R_4	X	COOH position Vs selenium	Entry	HPLC Purity %	Yield %
H	H	H	H	CH	*Para*	**3**	96	77
H	H	H	H	CH	*Meta*	**4**	95	10
H	H	H	H	N	*Para*	**5**	95	10
H	Cl	H	H	N	*Ortho*	**6**	98	27
H	Cl	H	H	N	*Para*	**7**	80	30
H	Cl	H	H	CH	*Para*	**8**	99	14
H	Cl	H	H	CH	*Meta*	**9**	77	14
H	CH_3	H	H	CH	*Meta*	**10**	97	79
H	CH_3	H	H	CH	*Para*	**11**	75	72
H	CH_3	H	H	N	*Para*	**12**	98	85
tBu	OCH_3	H	H	N	*Para*	**13**	99	69
H	tBu	H	H	CH	*Meta*	**14**	96	69
H	tBu	H	H	CH	*Para*	**15**	100	55
H	tBu	H	H	N	*Para*	**16**	98	48
H	tBu	H	H	N	*Ortho*	**17**	99	16
tBu	H	tBu	OMOM	CH	*Para*	**18**	98	25
tBu	H	tBu	OMOM	CH	*Meta*	**19**	98	29
tBu	H	tBu	OMOM	N	*Para*	**20**	98	23
tBu	H	tBu	OMOM	N	*Ortho*	**21**	86	19
tBu	H	tBu	OBn	N	*Para*	**22**	99	43
H	H			CH	*Para*	**23**	97	20
H	H			CH	*Meta*	**24**	98	9
H	H			N	*Para*	**25**	98	43
		H	H	CH	*Para*	**26**	91	10
		H	H	CH	*Meta*	**27**	95	35
		H	H	N	*Para*	**28**	94	52
		H	CH_3	N	*Para*	**29**	98	88
		OMEM	H	CH	*Meta*	**30**	98	52
		OMEM	H	N	*Para*	**31**	95	26
		OMEM	H	$C(OCH_3)$	*Para*	**32**	98	31
		OMEM	H	$C(OCH_3)$	*Meta*	**33**	79	72
		H	OMEM	CH	*Para*	**34**	99	43
		H	OMEM	CH	*Meta*	**35**	98	42
		H	OMEM	N	*Para*	**36**	99	20
		H	OMEM	N	*Ortho*	**37**	99	30
		OMOM	H	N	*Para*	**38**	96	14
		H	OBn	N	*Para*	**39**	97	55
		H	OBn	$C(OCH_3)$	*Para*	**40**	98	54
		OBn	H	CH	*Para*	**41**	97	71
		OBn	H	N	*Para*	**42**	99	63
		OBn	H	$C(OCH_3)$	*Para*	**43**	97	45
		OC_6H_{13}	H	N	*Para*	**44**	98	43
		OC_6H_{13}	H	$C(OCH_3)$	*Para*	**45**	98	58
	OMEM	H	CH_3	CH	*Para*	**46**	96	71
	OMEM	H	CH_3	CH	*Meta*	**47**	94	14
	OBn	H	CH_3	N	*Para*	**48**	100	73
	OBn	H	CH_3	$C(OCH_3)$	*Para*	**49**	98	14
OBn		H	H	N	*Para*	**50**	96	46

Thiophenol and disulfide were also submitted to the same procedure. Comparable results were obtained (Table 4).

Table 4. Diaryl Sulfides Prepared According to the Optimized Procedure[11]

Sulfur derivatives	Iodide	HPLC Purity	Yield
		99.5 %	69 %
		99.8 %	40 %
		95 %	43 %

In conclusion, the mildness and operational simplicity of this new protocol allowed the preparation of a library of diaryl selenides. Furthermore, the protocol was applied to sulfur derivatives with success.

Various interesting products were obtained in this library. Among them, new RXR antagonists were found. Compound **29** is 10 times more potent as an RXR agonist than its sulfur analogue.

Acknowledgment. We thank J. M. Bernardon for his constant interest in this program. The help of C. Raffin and F. Gendre is also acknowledged.

Supporting Information Available: ^{1}H NMR spectra for compounds **3**−**50** and sulfur derivatives. This material is available free of charge via Internet at http://pubs.acs.org.

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(12) **Typical procedure for saponification:** the ester was stirred at 50 °C for 24 h in a 1 M solution of sodium hydroxide/EtOH−THF (1:1). The reaction mixture was concentrated, diluted with water, acidified with HCl 1 N, and extracted with diethyl ether in cartridges (Whatman phase separation cartridge). The organic layer was dried with Na_2SO_4 (sample drying device, Whatman), concentrated, and isolated by crystallization in heptane or heptane/CH_2Cl_2. **6-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylselanyl)nicotinic acid (29):** mp 258 °C. ESMS *m*/*z* 402 (m − H)$^-$. ^{1}H NMR (DMSO) δ: 1.06 (6H, s), 1.11 (6H, s), 1.49 (4H, s), 2.14 (3H, s), 6.81 (1H, d, J = 8.3 Hz), 7.24 (1H, s), 7.45 (1H, s), 7.86 (1H, dd, J = 8.3 Hz, J' = 2.2 Hz), 8.70 (1H, d, J = 2.2 Hz), 13.12 (1H, s). ^{13}C NMR (DMSO) δ: 22.2, 31.6, 33.8, 34.0, 34.6, 122.5, 123.4, 124.3, 128.9, 135.6, 137.7, 138.9, 143.9, 146.9, 150.7, 164.2, 166.2. IR (cm^{-1}): 1081, 1140, 1294, 1416, 1460, 1579, 1679, 2862, 2924, 2962.

(13) Diaz P. C.I.R.D. GALDERMA, WO 9965872-A1, 1999; *Chem. Abstr.* **2000**, *132*(4), 35910t.