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New Selenium-Containing Acetylenic Retinoids by Direct Coupling of Alkynylsilanes with Selenylhalides.

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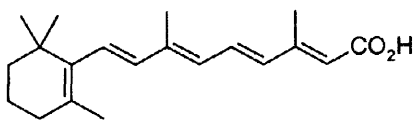
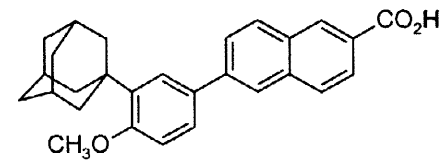
Abstract: A new series of alkynylselenide-containing retinoids has been synthesized by reacting phenylchalcogenyl halides with trimethylsilylalkynes in the presence of copper iodide.

Retinoids (Scheme 1), both synthetic (Adapalene[1]) and natural analogues of all-*trans*-retinoic acid (AtRA), exert marked effects on cell differentiation and proliferation[2]. Many of their biological effects are mediated by interaction with specific nuclear receptor (RARs) which can induce transcriptional activation through response elements[3] and/or which affect the activity of the transcription factor AP1[4].



All-*trans*-retinoic acid



Adapalene

Selenium is an antioxidant and may play a crucial role in diseases as diverse as cancer, heart disease, inflammation[5], arthritis and UV induced skin damage[6] because of its involvement in enzymatic processes. On the other hand, interaction between organoselenium compounds (Se-cystine or Se-cystamine) and sulfhydryl groups in functional proteins may lead to high toxicity[7]. So far, the majority of seleno-organic compounds reported in the literature have been direct analogues of oxygen- or sulfur-containing compounds but without therapeutic advantages. However, the benzoisoselenazol derivative ebselen[8] and more recently phenylamino selenide compounds[9] show biological activities as a consequence of the presence of selenium, with relatively low toxicity.

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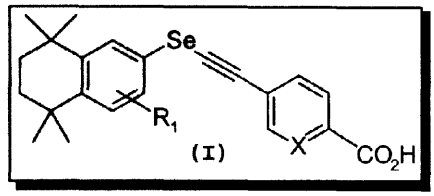
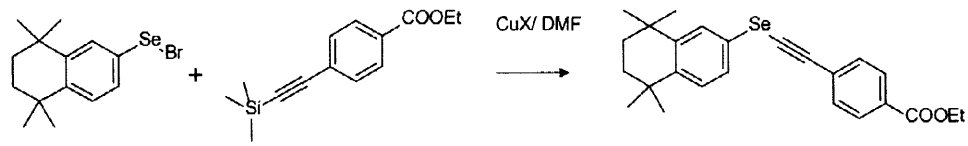
Therefore, we sought to obtain a new series of selenium-containing acetylenic retinoids (general structure (**I**)).



Scheme 1

Copper (I) iodide assisted reaction of chalcogenyl halides or diselenides with terminal alkynes or alkynyl bromides provide alkynyl selenides in good yields[10,11]. Syntheses of alkynylcopper reagents have recently been described by direct alkynyl group transfer from silicon to copper using copper (I) chloride[12,13,14]. We first investigated the reaction conditions. Treatment of the corresponding trimethylsilylalkyne with 1 eq. of CuCl at 80°C (Table 1) afforded a complex mixture containing the target product. The same conditions in the presence of NaI gave comparable results. Use of CuI instead of CuCl yielded the alkynyl selenide (41%). Increasing the quantity of CuI afforded the alkynyl selenide in good yield. This demonstrates the important role of CuI in this reaction.

Table 1. Effect of copper salts on the coupling reaction yield.



The selenyl bromides were obtained by action of bromine on the corresponding diselenides

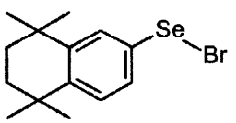
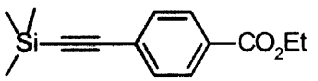
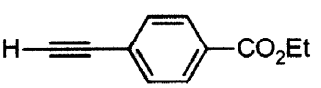
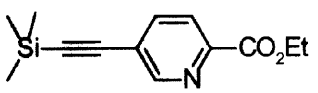
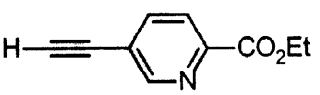
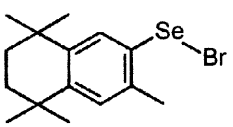
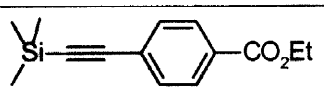
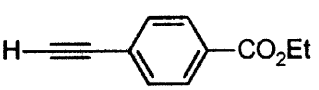
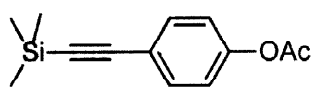
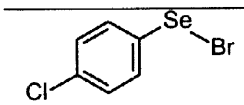
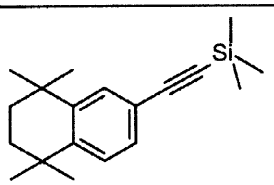
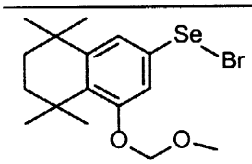
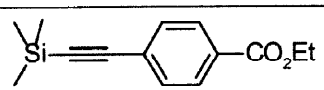
CuX	Yield
CuCl : 0.9 mol equiv	Complex mixture containing coupling product
CuCl : 0.9 mol equiv; NaI : 1 mol equiv	Complex mixture containing coupling product
CuI : 1 mol equiv	41 %
CuI : 2 mol equiv	90 %

Typical coupling procedure : a mixture of bromo selenide, trimethylsilylalkyne (1eq.) and CuX in DMF was stirred for 8h at 80°C under N_2. The reaction mixture was diluted with diethylether, washed with aqueous NH_4OH, with water and then dried. After concentration the residue was purified by silica gel chromatography.

Various analogues were synthesized using the same procedure. Isolated yields have been compared to prove the efficiency of the direct coupling method (Table 2). All the compounds were obtained in similar or better yields than by the classical terminal alkyne coupling reaction. The introduction of a methyl group *ortho* relative to the selenium atom, or the

presence of a pyridine ring in the alkyne fragment had almost no influence on the outcome of the reaction nor did the presence of electron withdrawing or electron donating groups (Entries **4** and **5**).

Table 2. Alkynyl selenides prepared according to the optimized procedure.

Bromo selenide	Alkyne	Entry	Isolated yield[a]
		**1a**	90%
		**1b**	75%
		**2a**	63%
		**2b**	32%
		**3a**	71%
		**3b**	70%
		**4**	98%
		**5**	39%
		**6**	31%[b]

[a]Typical coupling procedure : a mixture of bromo selenide, trimethylsilylalkyne (1eq.) and CuI (2eq.) in DMF was stirred for 8h at 80°C under N_2. The reaction mixture was diluted with diethylether, washed with aqueous NH_4OH, with water and then dried. After concentration the residue was purified by silica gel chromatography. [b] The phenol derivative resulting from the coupling and cleavage of the MOM ether was obtained in 16% yield.

After saponification of the esters, all the compounds were tested for RAR agonist activity. The carboxylic acid derivative resulting from the ester **1** displayed a transcriptional activity as good as that of *all-trans*-Retinoic Acid.

In summary, new selenium-containing alkynyl retinoids were obtained *via* transmetalation of an alkynyl silane under copper (I) iodide catalysis. Efficiency of this new methodology for coupling selenium halides has been demonstrated; cleavage of the trimethylsilyl protecting group from the alkynes is no longer required. Furthermore this new series of compounds seems to possess interesting biological activities.

References and Notes.

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